UNIVERSITY OF SOUTHAMPTON

Towards the Total Synthesis of the Pseudopterosins

By

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Doctor of Philosophy

Faculty of Science

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ABSTRACT

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A synthetic approach to the pseudopterosins, a family of marine natural products shown to be potent anti-inflammatory and analgesic agents has been investigated. The key steps in this approach involve either a Lewis acid mediated Friedel-Crafts alkylation of an epoxide tethered to an arene to give a bicyclic precursor to pseudopterosin or a Brønstead-Lowry acid mediated alkylation reaction of a γ-methylene-γ-butyrolactone to give a benzylic spirofuranone. Hydrogenation then exposure to a Brønstead-Lowry acid gives a phenalene skeleton related to pseudopterosin. The scope and limitation of the reactions has been investigated in several model systems.

This work has demonstrated that the intramolecular alkylation of an arene with a γ-methylene-γ-butyrolactone proceeds with a remarkable degree of diastereoselectivity. This has been attributed to an axially orientated methyl group at C7 in the precursor. Also notable is the control of relative stereochemistry of the C3 and C4 centres *via* the stereorelay C7→C4→C3.

Previous syntheses of the pseudopterosins including synthetic approaches towards the tricyclic aglycone are reviewed in Chapter 1.

Contents

Preface

The research described in this thesis was carried out at the University of Southampton between October 1997 and October 2000. No part of this thesis has previously been submitted for a degree at this or any other institution except where specific acknowledgement has been made.

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Abbreviations

Ac	Acetate
acac	acetylacetonate
AIBN	azo-*iso*-butyronitrile
APCI	atmospheric pressure chemical ionisation
approx.	approximately
Bn	benzyl
Bu	*n*butyl
Bz	benzoate
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
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	3,4-dihydro-2*H*-pyran
DIBAL-H	di-*iso*-butylaluminium hydride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
de	diastereoisomeric excess
dr	diastereoisomeric ratio
EI	electron impact
ee	enantiomeric excess
eq.	equivalents
ES	electrospray
Et	ethyl
FT	Fourier transform
h	hours
HMDS	1,1,1,3,3,3-hexamethyldisilazide

HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
IR	infra red
LA	Lewis acid
LAH	lithium aluminium hydride
LDA	lithium di-*iso*-propylamide
LHMDS	lithium hexamethyldisilazide
lit.	literature
LiTMP	lithium tetramethylpyrrolidine
***m*CPBA**	*meta*-chloroperoxy benzoic acid
Me	methyl
min	minutes
MP	melting point
Ms	methanesulphonyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
n.*O*.e	nuclear Overhauser effect
P.	*pseudopterogorgia*
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
PNB	*para*-nitrobenzyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *para*-toluenesulphonate
Ps.	pseudopterosin
psi	pounds per square inch
Py	pyridine
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
TLC	thin layer chromatography

TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulphonyl
UV	ultra violet
Vis	visible
X	halide (unless otherwise stated)
xs.	excess

Chapter 1

Introduction

Introduction

Biological and Commercial Significance of the Pseudopterosins

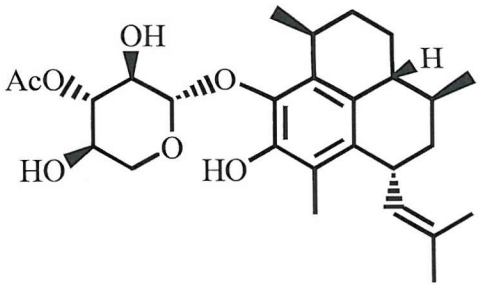
One quarter of the worlds drugs originate from natural sources, primarily microorganisms and rainforest plants. As terrestrial resources become over exploited, attention has turned (particularly in the last two decades) to the marine environment as an alternative source of novel bioactive metabolites.

The marine environment offers a number of advantages in the search for new drugs compared to the terrestrial environment. Firstly the seas contain a large diversity of organisms and harbouring more than 80% of all life on earth, remains our greatest untapped natural resource. Secondly marine life offers new dimensions to the search for bioactive compounds since there are major differences between the types of compounds produced by marine and terrestrial organisms (where most medicinal compounds currently originate).

Despite an explosive growth in the number of marine natural products isolated and characterised in the last twenty years very few have shown therapeutically significant biological activity. A striking exception to this appears to be a group of polar metabolites isolated from the Caribbean sea plume *pseudopterogorgia elisabethae* (**Figure 1**) and known as the *pseudopterosins*.

Figure 1. The Caribbean Sea Whip *Pseudopterogorgia elisabethae.* Isolated from the Florida Keys.

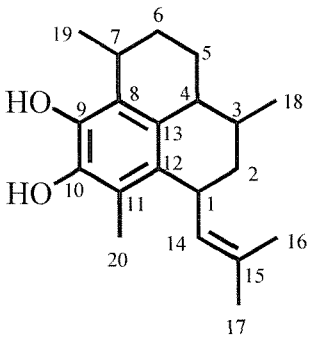
P. elisabethae is an abundant species of octocoral found in the reef and deeper water (below 50 m) habitats of the West Indian region.[1] To date twelve pseudopterosins (A-L) have been isolated and constitute a new class of chemically novel diterpenoids. This class of compounds have become the focus of much commercial interest in recent years due to their potent anti-inflammatory and analgesic properties which vastly exceed (up to fifty times) the potency of existing drugs such as indomethacin (the industry standard).[2] Currently most commercial interest is focused on pseudopterosin C **1** which is the active component in the anti ageing skin cream *Resilience* marketed by Estée Lauder.[3]



Pseudopterosin C **1**

Nomenclature of the Pseudopterosins

The system of nomenclature for the pseudopterosins is depicted in **Figure 2**. Within the text this nomenclature has been used to aid the description of stereogenic centres. The *seco*-pseudopterosins, *vide infra*, are treated similarly (**Figure 2**). In the experimental section the nomenclature used is systematic.



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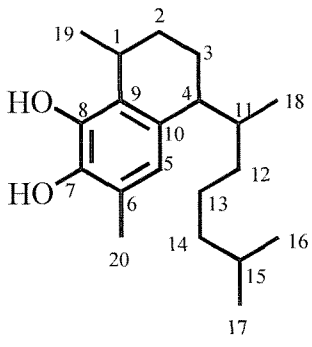

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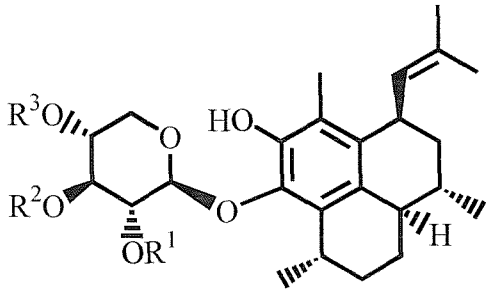
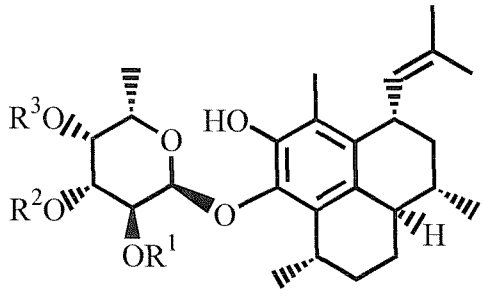
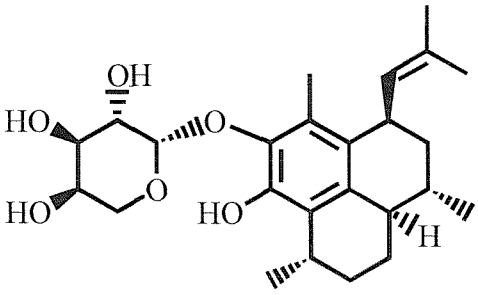


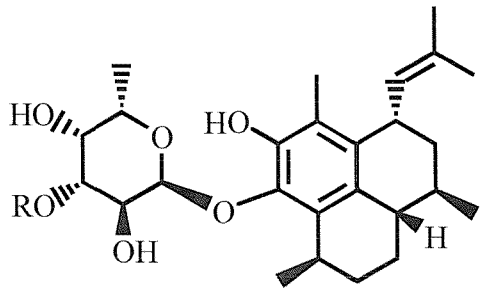


4	Ps. A, $R^1 = R^2 = R^3 = H$	**8**	Ps. G, $R^1 = R^2 = R^3 = H$
5	Ps. B, $R^1 = Ac$, $R^2 = R^3 = H$	**9**	Ps. H, $R^1 = Ac$, $R^2 = R^3 = H$
6	Ps. C, $R^1 = R^3 = H$, $R^2 = Ac$	**10**	Ps. I, $R^1 = R^3 = H$, $R^1 = Ac$
7	Ps. D, $R^1 = R^2 = H$, $R^3 = Ac$	**11**	Ps. J, $R^1 = R^2 = H$, $R^3 = Ac$

Figure 2 Nomenclature of the pseudopterosins

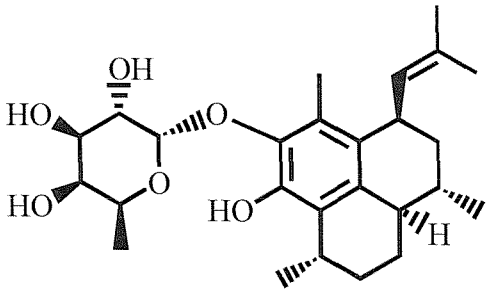


12 Ps. F



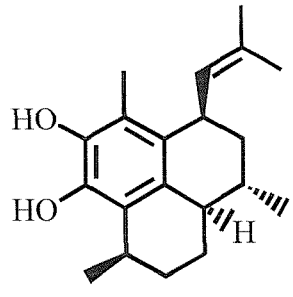
13 Ps. K, R = H

14 Ps. L, R = Ac



15 Ps. E

It should be noted that since their isolation the stereochemical profile of the pseudopterosin G-J aglycone has been revised. Originally assigned as **16** a number of groups have successfully targeted this structure believing it to be one of the pseudopterosins. Corey *et al.* reassigned the stereochemistry of the pseudopterosin G-J aglycone after synthetic work showed the true structures of the pseudopterosin G-J aglycone were in fact **8-11**.[4]



16

The potent antiinflammatory properties of the pseudopterosins mean that they have potential applications in treating various conditions such as arthritis, gout, psoriasis, and chemically induced oedemas. Inflammation is often associated with swelling and pain in and around the epidermal tissue and, although not life threatening, is a source of much discomfort to sufferers. It is caused by either increased blood flow or an accumulation of various plasma constituents. The inflammatory response is triggered by an increased cellular production of prostaglandins, thromboxanes, eicosonoids or leukotrienes resulting from the biosynthesis of arachidonic acid (which is released when phospholipase A_2 (PLA_2) catalyses the hydrolysis of the ester at the *sn*-2 position of membrane phospholipids.[5]

The pseudopterosins are particularly attractive as antiinflammatory drugs since they appear to act by a novel mechanism. In cell studies using human neutrophils, they have been shown to inhibit the synthesis of leukotrienes, suggesting that the pseudopterosins are antagonists of lipooxygenases or enzymes higher in the arachidonic acid cascade. Of the series, pseudopterosin E possesses superior antiinflammatory and analgesic properties, and was non toxic at levels in excess of 300 mg kg^{-1} in mice.

Isolation and Characterisation of the Pseudopterosins[6]

Pseudopterogorgia elisabethae was collected in 1982 in shallow waters near Crooked Island in the Bahamas. The organisms were frozen and then extracted with chloroform and ethyl acetate. Rapid elution chromatography and HPLC provided pseudopterosins A-D. Of these four, pseudopterosin C was the most abundant comprising 7.5% of the lipid extract compared to A, B and D which accounted for no more than 1% of the organic extract.

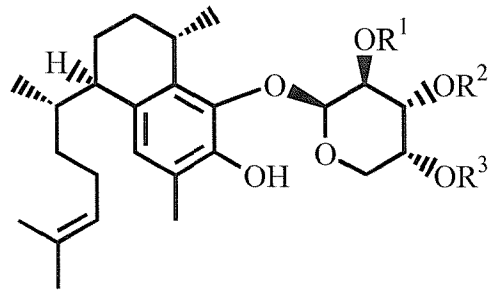
A bioassay of these compounds revealed promising anti-inflammatory activity. This initiated a comprehensive study of *P. elisabethae* from numerous regions in the Carribean. Collections made in the Bermuda region revealed six new metabolites, pseudopterosins E – J which were

accompanied by traces of the less polar pseudopterosins A – D. Interestingly, sea whips collected from the waters around Abaco Island in the Bahamas were found to contain only pseudopterosins K and L.

Related Natural Products

(i) The *Seco*-Pseudopterosins[7]

Four new bicyclic diterpenoid glycosides related to the pseudopterosins have been isolated from the gorgonian coral *pseudopterogorgia kallos,* collected in the Florida Keys. The *seco*-pseudopterosins (A-D), in common with the pseudopterosins are potent anti-inflammatory and analgesic agents. They represent a chemotaxonomically distinct *pseudopterogorgia* species. In addition to their analgesic activity this group of metabolites also posess antimicrobial activities against a wide range of bacterial and fungal pathogens.



17 Seco Ps. A, $R^1 = R^2 = R^3 = H$

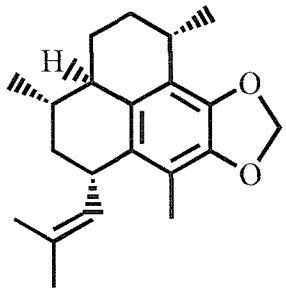
18 Seco Ps. B, $R^1 = Ac$, $R^2 = R^3 = H$

19 Seco Ps. C, $R^1 = R^3 = H$, $R^2 = Ac$

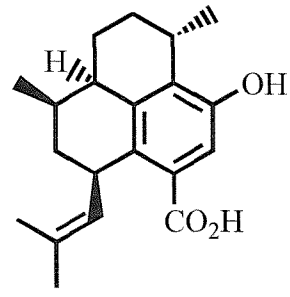
20 Seco Ps. D, $R^1 = R^2 = H$, $R^3 = Ac$

(ii) Helioporin E[8] and Eremophillin[9]

Two further natural products bearing structural resemblance to the pseudopterosins are helioporin E **21** and eremophillin **22**. The helioporins are a group of bioactive diterpenoids isolated from the blue coral *Heliopora coerulea*. The tricyclic core of helioporin E (which posesses cytotoxic activity) resembles the aglycones of pseudopterosins G-J and its original stereochemical assignment has also been shown to be incorrect. Eremophillin has a similar structure to the pseudopterosins but with a unique stereochemical profile.



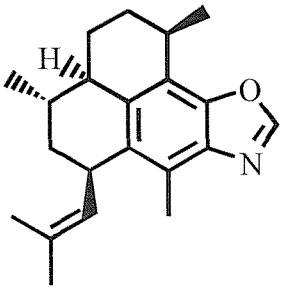
Helioporin E **21**



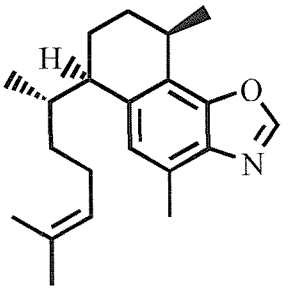
Eremophilin **22**

(iii) Pseudopteroxazole and *seco*-Pseudopteroxazole[10]

In 1999 Rodriguez *et al.* conducted a search for marine natural products with activity against tuberculosis. Two active diterpenoid benzoxazole alkaloids were isolated from *pseudopterogorgia elisabethae* which they named pseudopteroxazole **23** and *seco*-pseudopteroxazole **24**.



Pseudopteroxazole **23**



seco-Pseudopteroxazole **24**

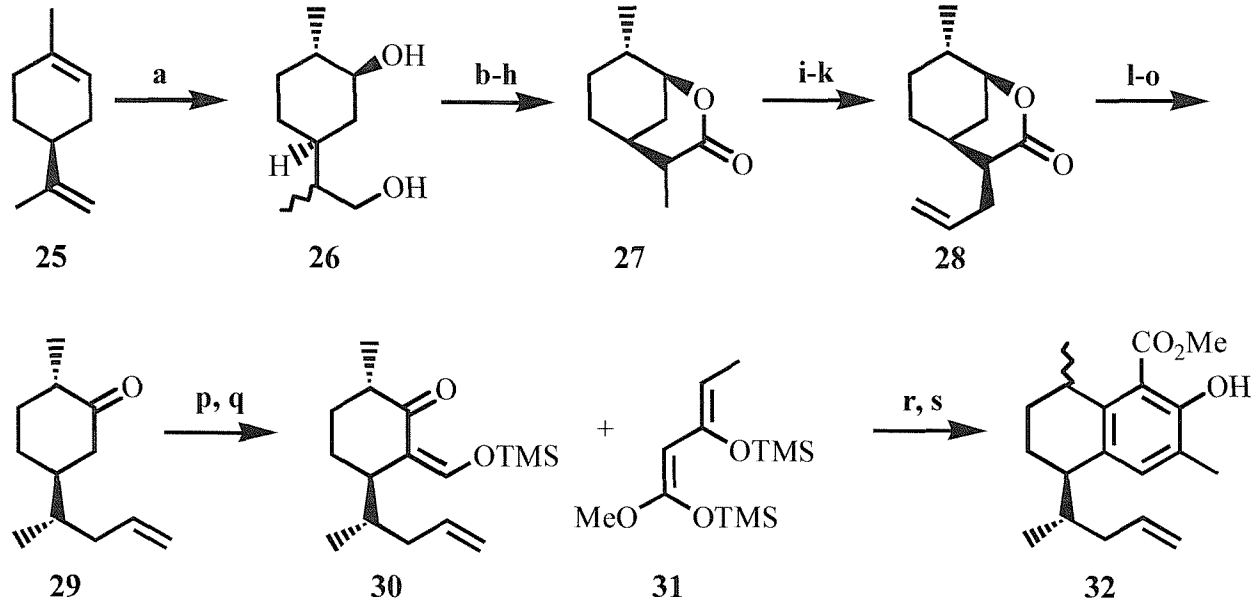
The structures of these two natural products are closely related to the pseudopterosins and posses the stereochemical profiles originally attributed to pseudopterosin G (and so may be in error). Biological screening studies have indicated that pseudopteroxazole is a potent growth inhibitor of *mycobacterium tuberculosis* H37Rv and *seco*-pseudopteroxazole shows moderate to strong inhibitorial activity.

A variety of other novel metabolites have been isolated from *pseudopterogorgia elisabethae* whose carbon framework does not directly mirror that of pseudopterosin. These have included colombiassin,[11] and the sandresolides.[12] The biological and therapeutic significance of these compounds remains to be fully investigated.

The Total Synthesis of Pseudopterosins

The Broka Synthesis[13]

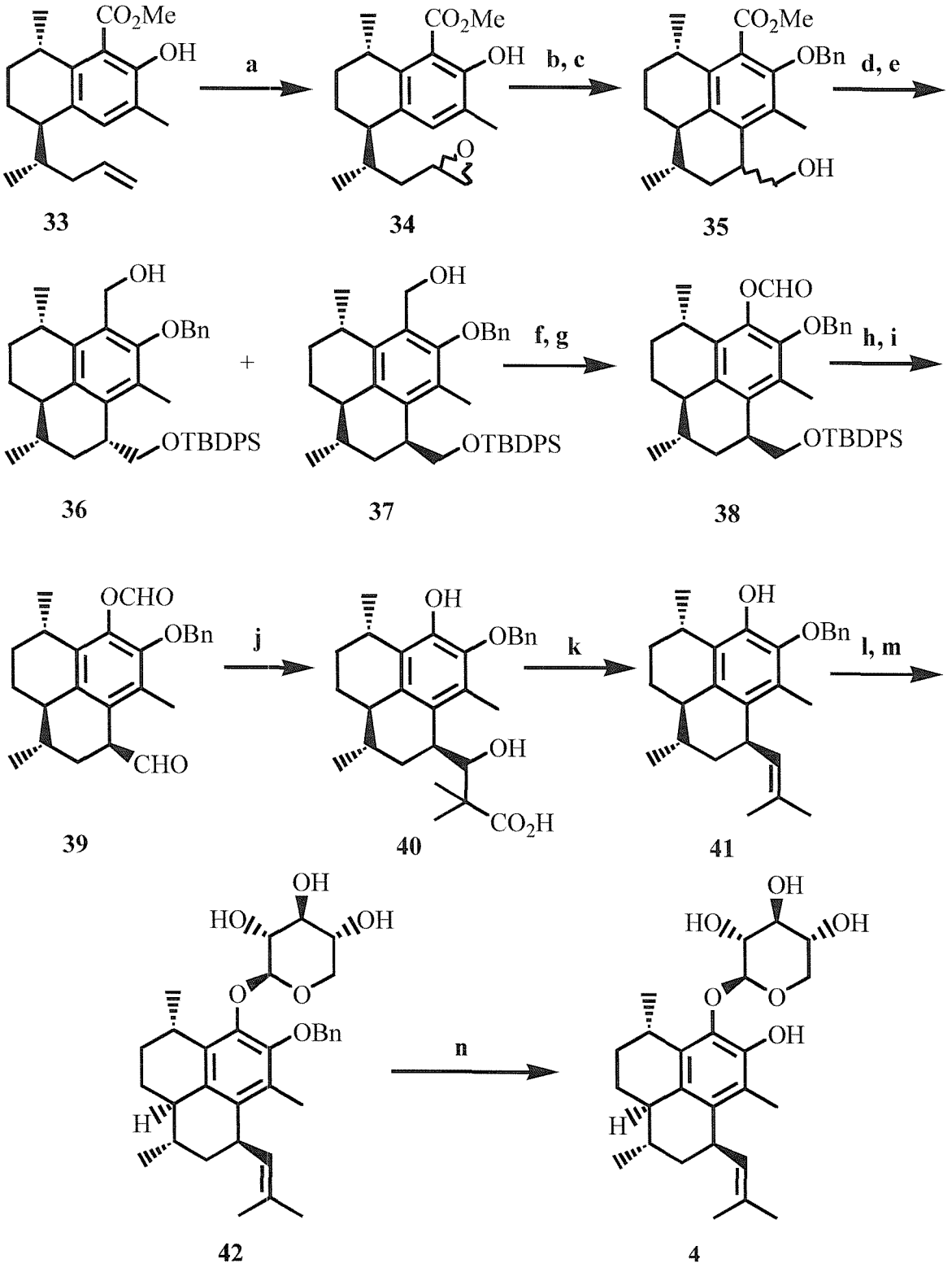
Various approaches have been employed to synthesise the pseudopterosin aglycone skeleton. The first workers to complete a total synthesis of pseudopterosin A were Broka *et al.* in 1988. Their route began with (*S*)-limonene **25**, which was converted in 17 steps into an epimeric (1 : 1) mixture of enol ethers **30**. A Lewis acid mediated cyclisation with diene **31** followed by exposure to base, then allowed construction of the aromatic ring to yield phenols **32** as a 3 : 2 mixture of diastereoisomers, which favoured the undesired C7 epimer. These were easily separated by preparative thin layer chromatography (**Scheme 1**).



Reagents & Conditions: a. Thexylborane, NaOH, H_2O_2. **b.** Piv-Cl, Py. **c.** DHP, PPTS. **d.** KOH. **e.** PCC, NaOAc. **f.** $NaClO_2$, *t*BuOH. **g.** AcOH. **h.** TsOH, PhH, reflux. **i.** LDA, PhSeCl. **j.** H_2O_2. **k.** Vinylmagnesium bromide, CuI, TMSCl. **l.** LAH, THF. **m.** $PhSO_2Cl$. **n.** $LiBHEt_3$, THF. **o.** PCC. **p.** HCO_2Et, NaH, dioxane. **q.** TMSCl, NEt_3. **r.** $TiCl_4$, DCM. **s.** NaOMe, MeOH.

Scheme 1

Peracid oxidation of **33** gave the epoxides **34** as an inseperable mixture. Closure of the final ring of the amphilectane was then achieved by an intramolecular Friedel-Crafts alkylation mediated by the Lewis acid tin(IV) chloride. Selective benzylation of the phenolic moiety gave **35** once again as a mixture of epimers. Reduction of the ester followed by silyl protection of the alcohol gave the epimers **36** and **37** which could be separated by preparative TLC. Oxidation of **37** to the corresponding aldehyde followed by Bayer-Villiger oxidation gave formate ester **38**. Desilylation of **38** with TBAF was achieved without simultaneous hydrolysis of the formyl unit by adjusting the pH of the solution to ~7. Swern oxidation of the resulting alcohol gave **39** without detectable aldehyde epimerisation. Treatment of **39** with the dianion of isobutyric acid furnished the expected hydroxy acid **40** with simultaneous removal of the formate ester. Decarboxylation and alcohol elimination was then achieved by treatment with excess *N*,*N*-dimethylformaldehyde dineopentyl acetal. The total synthesis was then completed by sequential treatment with excess 1-α-bromo-2,3,4-triacetyl-D-xylose, hydrolysis of the acetyl groups with sodium hydroxide then deprotection of the benzyl moiety with Li/NH_3 (**Scheme 2**).



Reagents & Conditions: **a.** mCPBA, DCM. **b.** $SnCl_4$, DCM. **c.** BnBr, DMSO, K_2CO_3, **d.** TBDPSCl, imidazole, DMF. **e.** DIBAL-H, DCM. **f.** PCC, DCM. **g.** *m*CPBA, K_2HPO_4, $CHCl_3$. **h.** TBAF, AcOH, THF. **i.** $(COCl)_2$, DMSO, DCM. **j.** Me_2CLiCO_2Li, THF. **k.** *N,N*-dimethylformaldehyde dineopentyl acetal, 4,4'-methylenebis(2,6 di-t-butylphenol). **l.** 1-α-bromo-2,3,4-triacetyl-D-xylose (5.0 eq.). **m.** NaOH. **n.** Li/NH_3, tBuOH.

Scheme 2

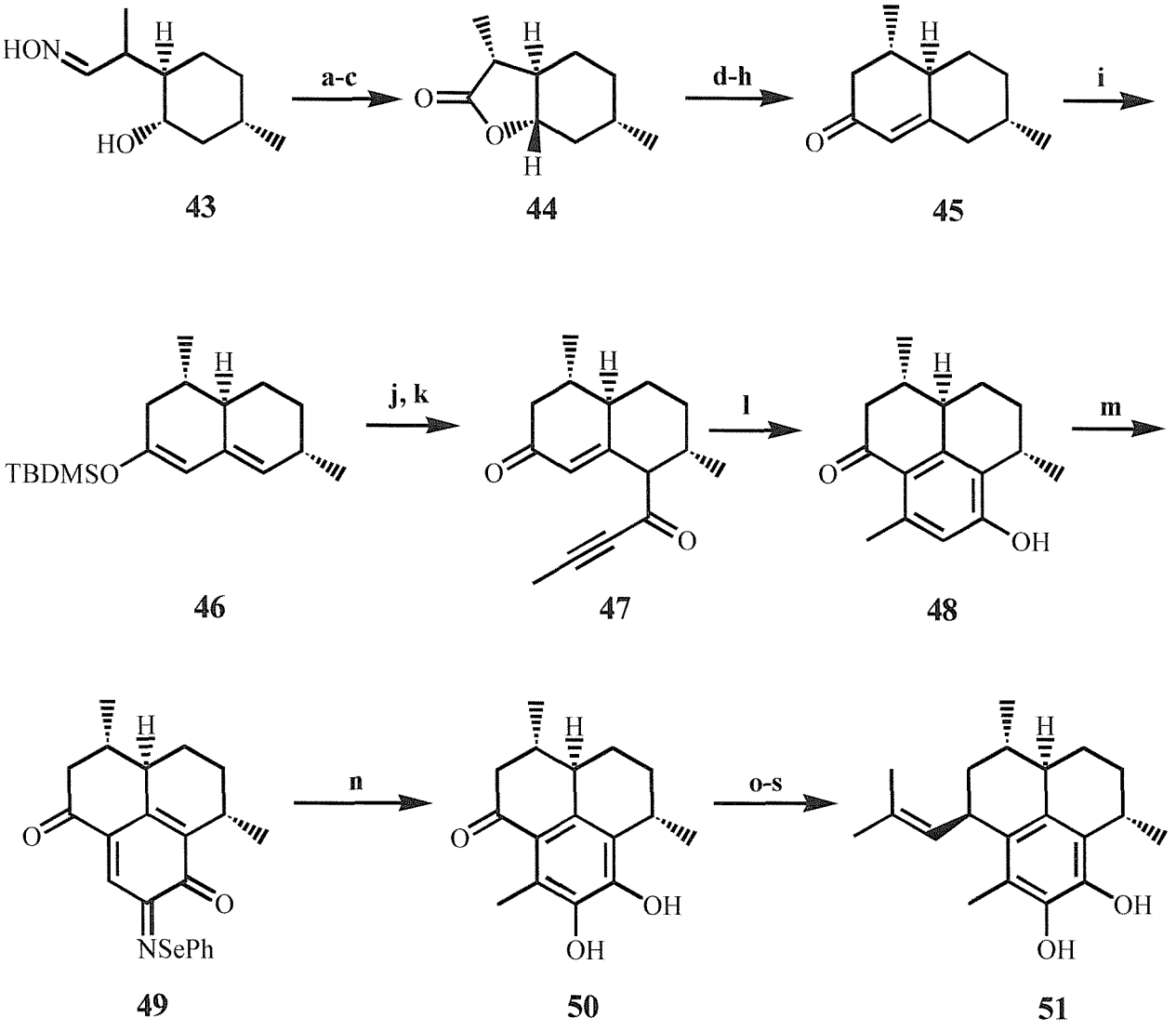
The First Corey Synthesis[14]

Corey and Carpino were next to publish a total synthesis of pseudopterosin A. Their synthesis began with **43**, the stereogenic centres in this molecule corresponding to the C3, C4, and C7 centres in the pseudopterosin aglycone. Elaboration of **43** to ynone **47** was accomplished in eleven steps

Construction of the tricyclic nucleus was then achieved by the reaction of **47** with KH in THF which induced an unprecedented cyclisation to phenol **48**. *Ortho*-hydroxylation of **48** to give **50** was achieved *via* oxidation with benzene selenic anhydride and hexamethyldisilazane, to *N*-(phenylselenyl)-*o*-quinone imine **49** which was then hydrolysed and reduced to give catechol **50**.

To complete the synthesis of the aglycone an *iso*-butyl substituent needed to be introduced at the C1 position. The catechol was therefore protected as an *iso*-propylidene acetal and the ketone converted to an epoxide. Rearrangement to the aldehyde followed by a Wittig reaction and deprotection of the catechol gave the pseudopterosin aglycone **51**.

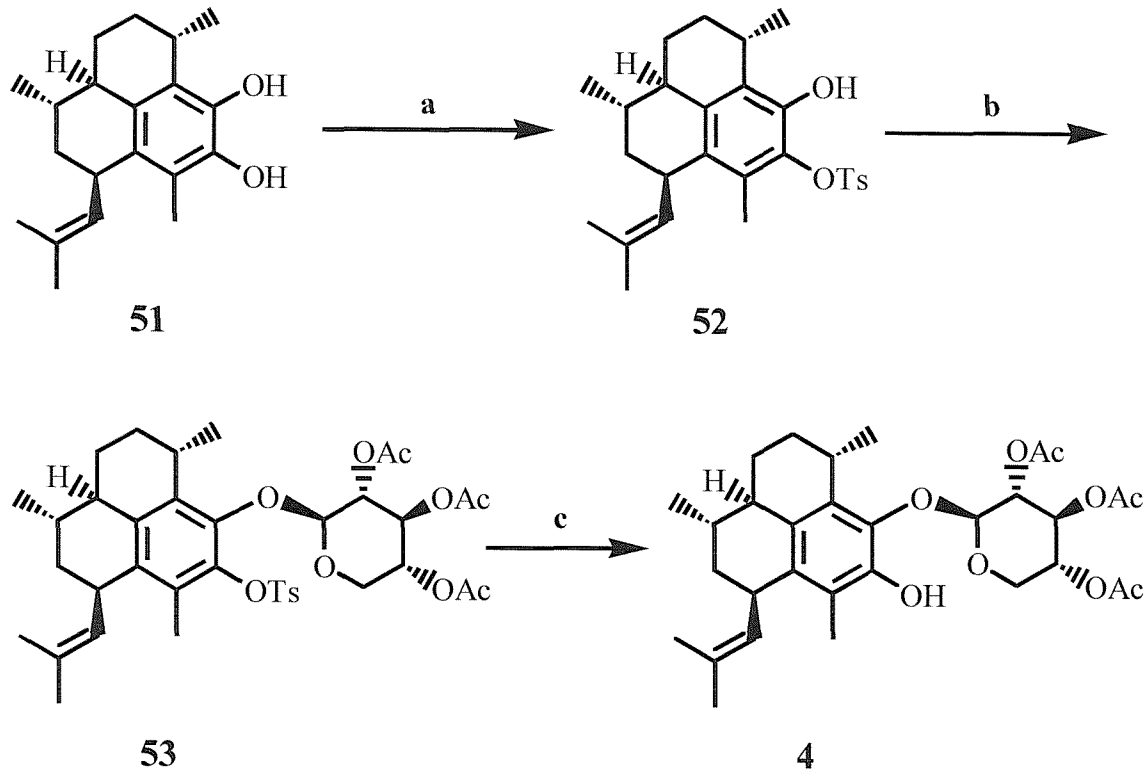
(Scheme 3).



Reagents & Conditions: **a.** $KHSO_3$, H_2O. **b.** Br_2, H_2O, $CaCO_3$. **c.** LDA, THF then H_2O. **d.** DIBAL-H, DCM, **e.** $Ph_3P{=}C(CH_3)SEt$, DMSO. **f.** Swern. **g.** $HgCl_2$, MeCN-H_2O. **h.** NaOMe, MeOH. **i.** NaH, TBDMSCl. **j.** 2-butynal, TMSOTf. **k.** PCC, DCM. **l.** KH, THF. **m.** C_6H_6-$[C_6H_5Se(O)]_2O$, HMDS, **n.** aq. AcOH, cat. $HClO_4$, $KHSO_3$. **o.** $(CH_3)_2C(OCH_3)_2$, PPTS. **p.** $(CH_3)_3S^+Cl^-$, *n*BuLi. **q.** $BF_3.OEt_2$, DCM .**r.** $(CH_3)_2C{=}PPh_3$. **s.** 10% aq. HCl.

Scheme 3

To convert the aglycone into pseudopterosins A and E, a means of distinguishing the two phenolic hydroxy groups was required. This was achieved by monotosylation of the C10 hydroxyl group to give **52**. Reaction with 2,3,4-triacetyl-α-D-xylopyranosyl bromide gave **53**, and deprotection of the hydroxyl group then provided pseudopterosin A **4** (**Scheme 4**).



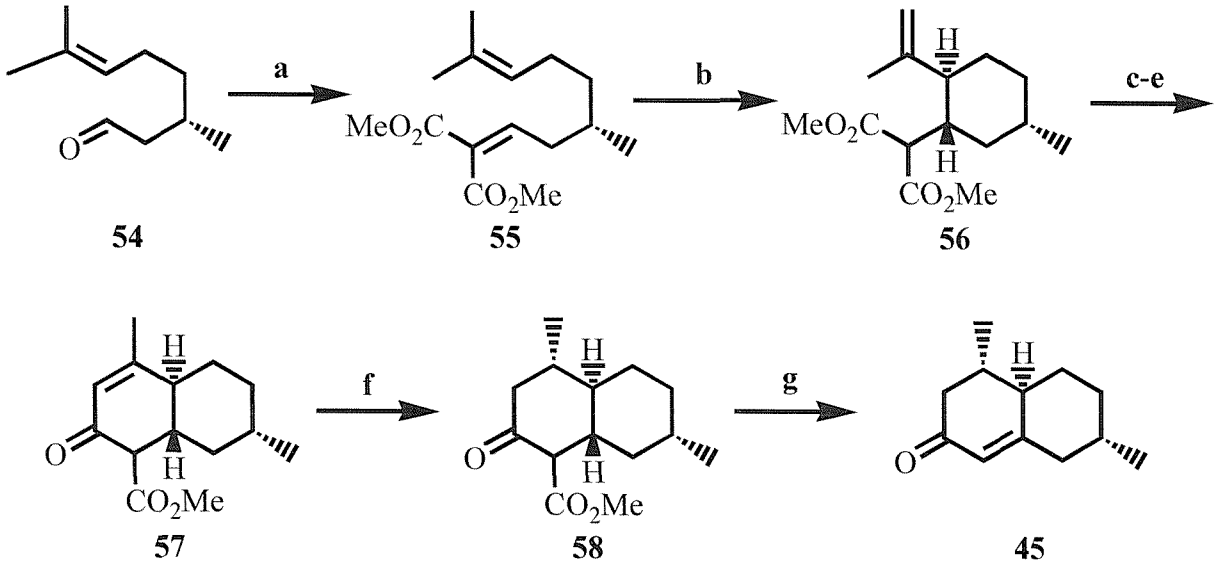
Reagents & Conditions: a. TsCl, NEt_3, DCM. **b.** NaH, MeCN, 2, 3, 4-triacetyl α -D-xylopyranosyl bromide. **c.** KOH, MeOH-H_2O, 6% Na/Hg, 23°C.

Scheme 4

Coreys Modified Synthesis[15]

One year after their original publication, Corey and Carpino published a modification of their approach to pseudopterosin which involved a more direct and efficient synthesis of the ketones **45** and **50**, key intermediates in the original approach. The modified approach commenced with *(S)*-citronellal **54**, which underwent a Knoevanagel type condensation with dimethyl malonate. The unsaturated diester **55** was then exposed to $FeCl_3$ giving the cyclic diester **56** as a 97 : 3 mixture of diastereoisomers. The diester **56** was hydrolysed to give the monoacid by treatment with LiOH in methanol. The acid was then converted to the acyl chloride which, on exposure to diethyl aluminium chloride, gave the bicyclic enone **57**. Reduction of the enone unit was effected by Li/NH_3, yielding the saturated product **58**. This

was then converted to the enone **45** by deprotonation with sodium hydride followed by quenching of the anion with bromine. Heating the crude product with lithium chloride in DMF gave the bicyclic enone **45**, identical to the previously synthesised material (**Scheme 5**).



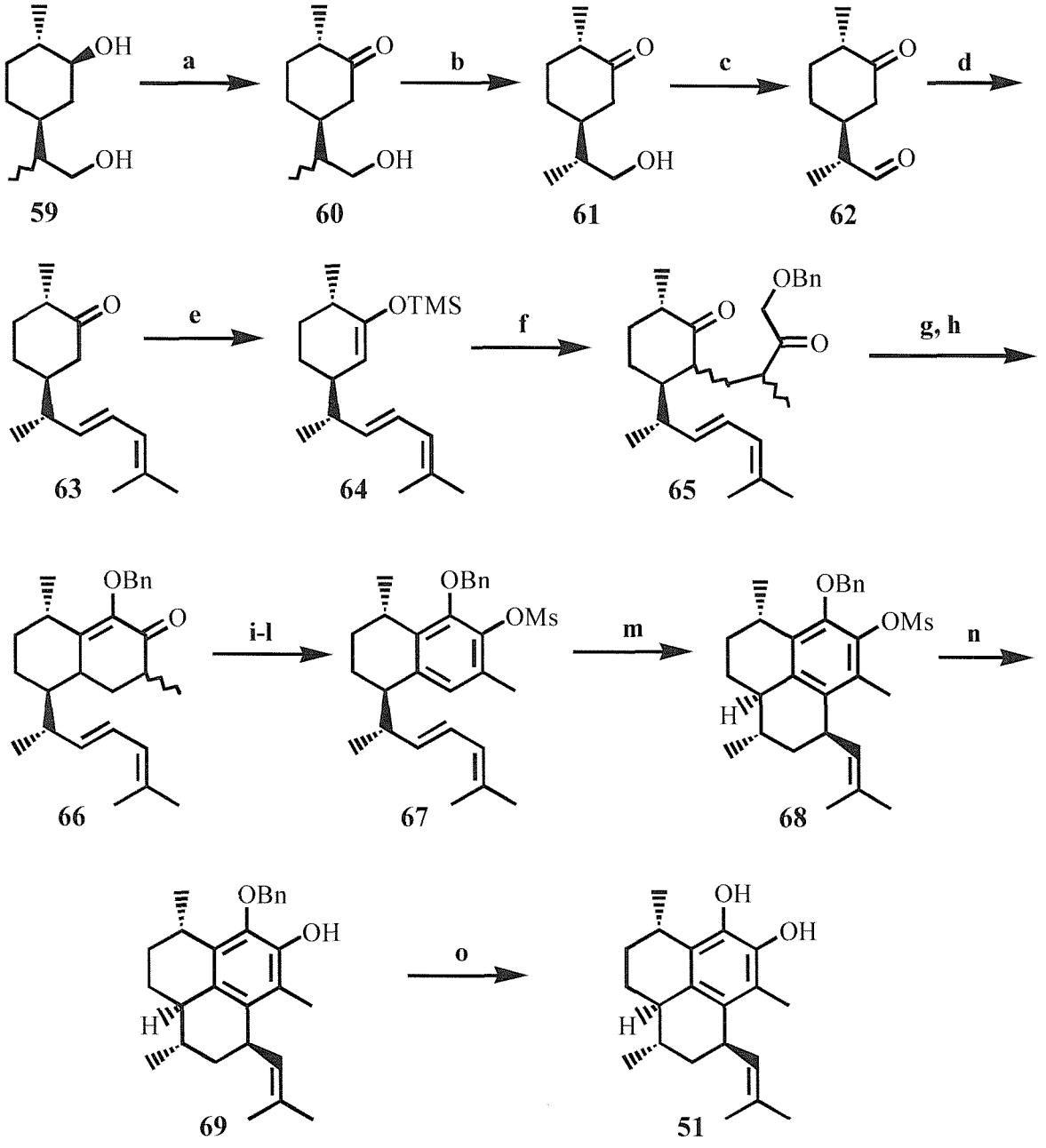
Reagents & Conditions: a. $CH_2(CO_2Me)_2$, piperidinium acetate. **b.** $FeCl_3$, DCM. **c.** LiOH, MeOH. **d.** $(COCl)_2$, cat. DMF, DCM. **e.** Et_2AlCl (3 eq.), DCM. **f.** Li/NH_3, -78°C. **g.** (i) NaH,THF, 2h then Br_2. (ii) 6% LiCl, DMF, 80-125°C.

Scheme 5

Corey's Third Approach[16]

Recently a new synthesis of the pseudopterosin aglycone has been described by Corey who claimed it to have the advantages of simplicity, directness and practicality; features apparently lacking in the approaches of others. The starting material for this synthesis was diol mixture **59** obtained from *(S)*-(-)-limonene **25** *via* oxidative hydroboration. Exposure of **59** to sodium hypochlorite gave selective oxidation at C2 to form the diastereomeric mixture of ketones **60**. Exposure of this mixture to isopropenyl acetate using amano PS lipase as the catalyst resulted in selective acetylation of the (8*S*)-hydroxy ketone which could be separated from the desired

(8*R*)-enantiomer *via* chromatography. A series of standard transformations then gave the diketone **65** which on treatment with base and subsequent elimination gave the cyclised product **66**. Silylation of the ketone then manganese dioxide mediated oxidation established the aromatic nucleus. Protecting group exchange followed by a Friedel-Crafts cyclisation under surprisingly mild conditions afforded the tricycle **68** with excellent diastereoselectivity. Deprotection of the phenol then furnished the pseudopterosin A-F aglycone **51** (**Scheme 6**).

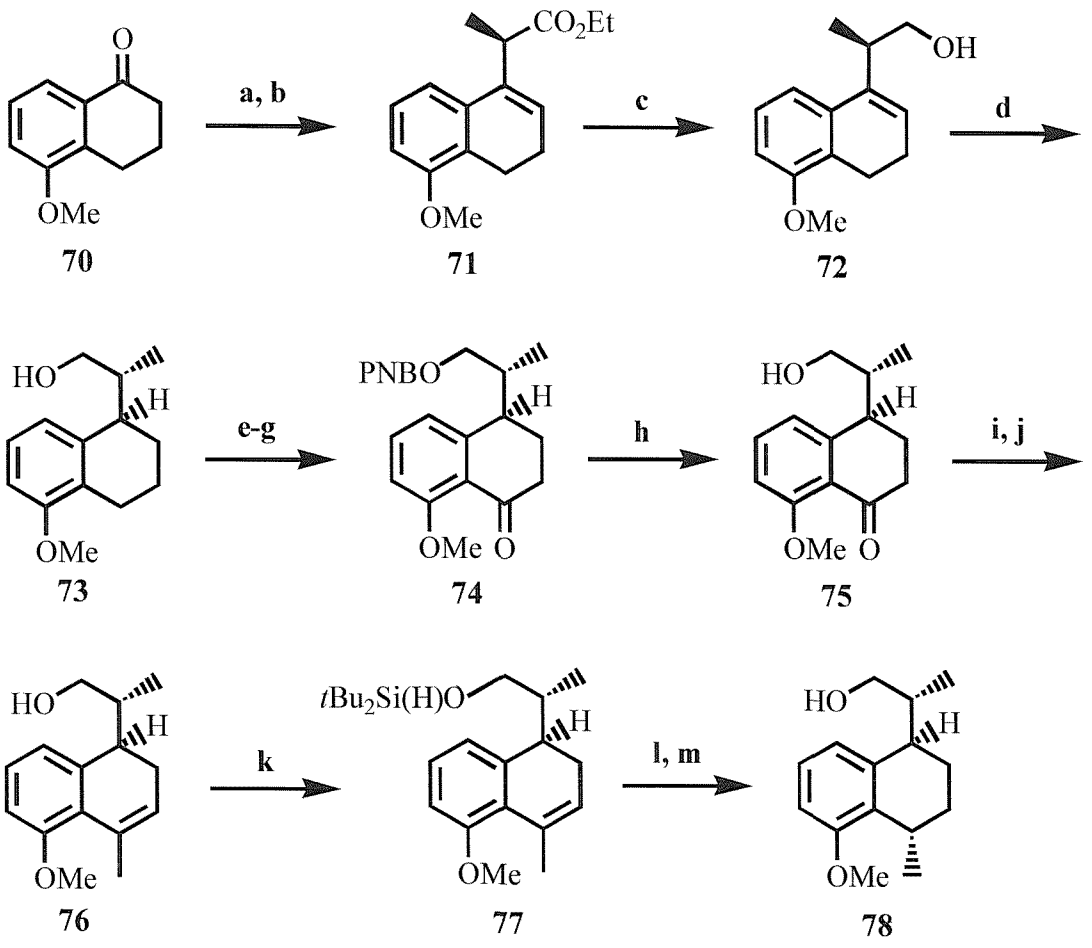


Reagents & Conditions: a. NaOCl. **b.** Isopropenyl acetate, Amano PS lipase (+ (*S*)-acetate). **c.** NaOCl. **d.** $Ph_2P^+(CH_2CH{=}C(CH_3)_2)_2\ Br^-$, KO*t*Bu. **e.** LDA, THF, TMSCl. **f.** $CH_3C(=CH_2)COCH_2OBn$, $SnCl_4$ **g.** KOH. **h.** $SOCl_2$. **i.** LDA, TBSOTf. **j.** MnO_2. **k.** TBAF. **l.** MsCl. **m.** MsOH, DCM. **n.** MeMgBr. **o.** BBr_3.

Scheme 6

The McCombie Approach[17]

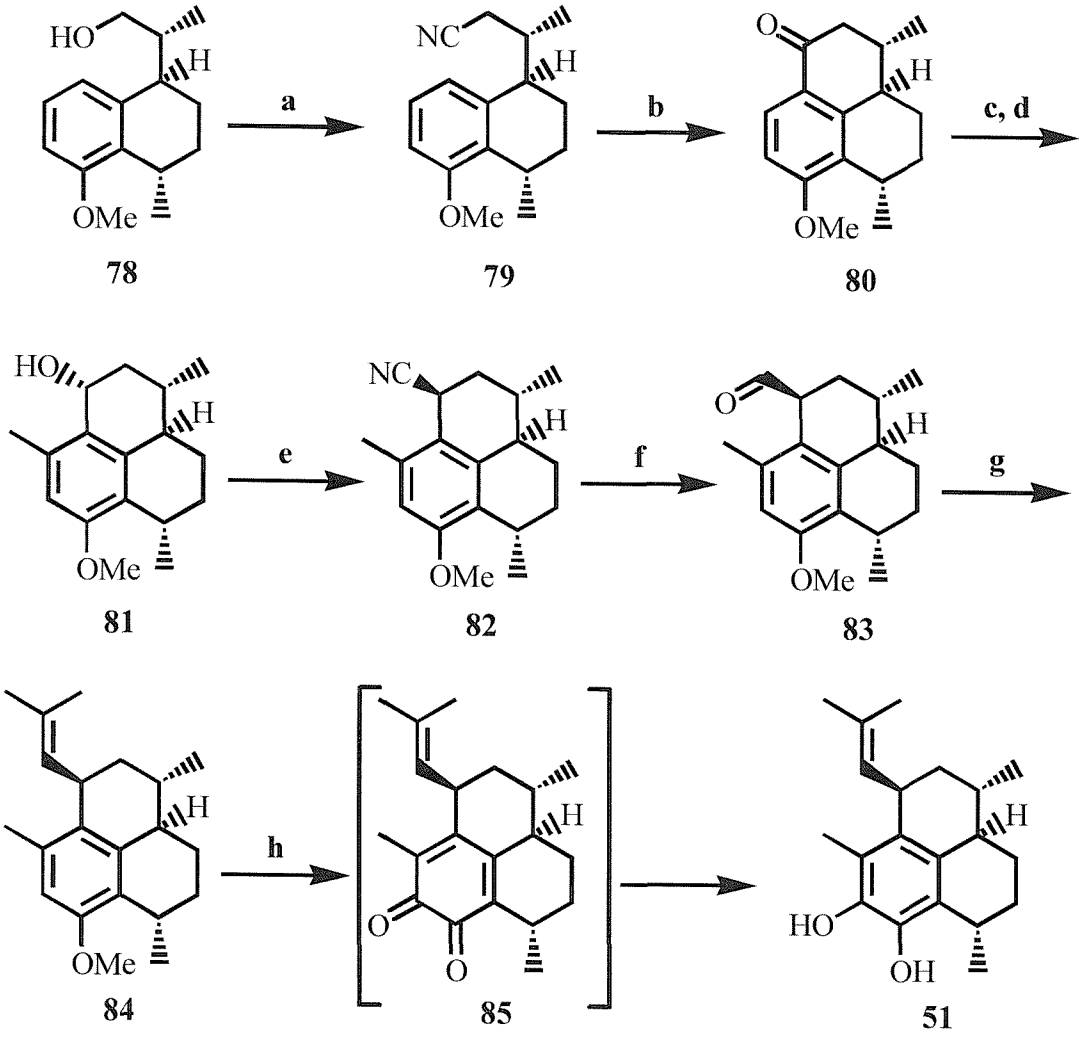
In 1992 McCombie *et al.* published a racemic synthesis of the pseudopterosin A-F aglycone demonstrating the intramolecular ionic hydrogenation methodology developed in that group. The synthesis began with the commercially available 5-methoxy-1-tetralone **70** which, after a Reformatsky reaction with ethyl 2-bromopropionate and dehydration, gave the styrene **71**. Reduction of the ester functionality gave the primary alcohol **72** which underwent a highly diastereoselective hydrogenation with Wilkinsons catalyst (with the inclusion of base to promote attachment to the metal centre). Protection of the alcohol, persulphate induced benzylic oxidation *ortho* to the aromatic methoxy group and PCC oxidation gave tetralin **74**. Deprotection of the alcohol followed by addition of methyl cerium dichloride and dehydrogenation furnished the styrene **76** now with the C1 methyl group installed. Direct catalytic hydrogenation of the double bond resulted in an 'unnatural isomer' being obtained with excellent stereocontrol. By contrast hydrosilylation of the alcohol followed by an intramolecular hydride delivery *via* TFA protonation of the olefin gave the key alcohol **78** (**Scheme 7**).



Reagents & Conditions: **a.** $MeCHBrCO_2Et$, Zn, THF. **b.** TsOH. **c.** Red-Al. **d.** H_2, $ClRh(PPh_3)_3$, KO*t*Bu, THF. **e.** PNBCl, pyridine. **f.** $K_2S_2O_8$, $CuSO_4$, $MeCN\text{-}H_2O$. **g.** PCC, DCM. **h.** aq. KOH. **i.** $MeCeCl_2$. **j.** TsOH. **k.** tBu_2SiHCl, imidazole. **l.** TFA, DCM. **m.** Bu_4NF, THF.

Scheme 7

The alcohol **78** was converted into the nitrile **79** *via* tosylation and S_N2 displacement with cyanide. A Friedel-Crafts reaction then gave the tricyclic ketone **80** which was converted into the nitrile **82** by standard chemistry. Reduction of the nitrile to the imine followed by acid hydrolysis then gave the aldehyde **83**. The isobutenyl sidechain of pseudopterosin was then introduced *via* a Julia olefination reaction. Deprotection of the phenolic moiety followed by oxidation of the aromatic nucleus utilising Fremys reagent gave the *ortho*-quinone **85** which was reduced *in situ* to pseudopterosin A-F aglycone **51** (**Scheme 8**).

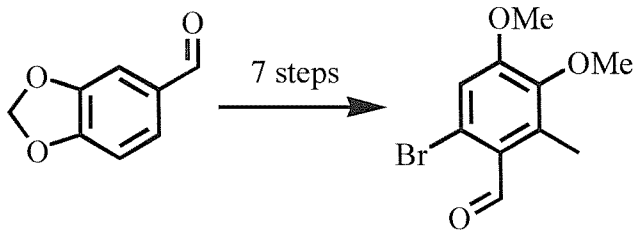


Reagents & Conditions: **a.** TsCl, py, NaCN. **b.** MsOH, $(CH_2Cl)_2$. **c.** $NaBH_4$. **d.** *t*BuLi, MeI. **e.** Et_2AlCN, $SnCl_4$. **f.** DIBAL-H then aq. HCl. **g.** $PhSO_2C(Li)Me_2$, Na/Hg, K_2HPO_4. **h.** BBr_3, 2,6-dibutylpyridine, $ON(SO_3K)_2$, KH_2PO_4, $Na_2S_2O_4$.

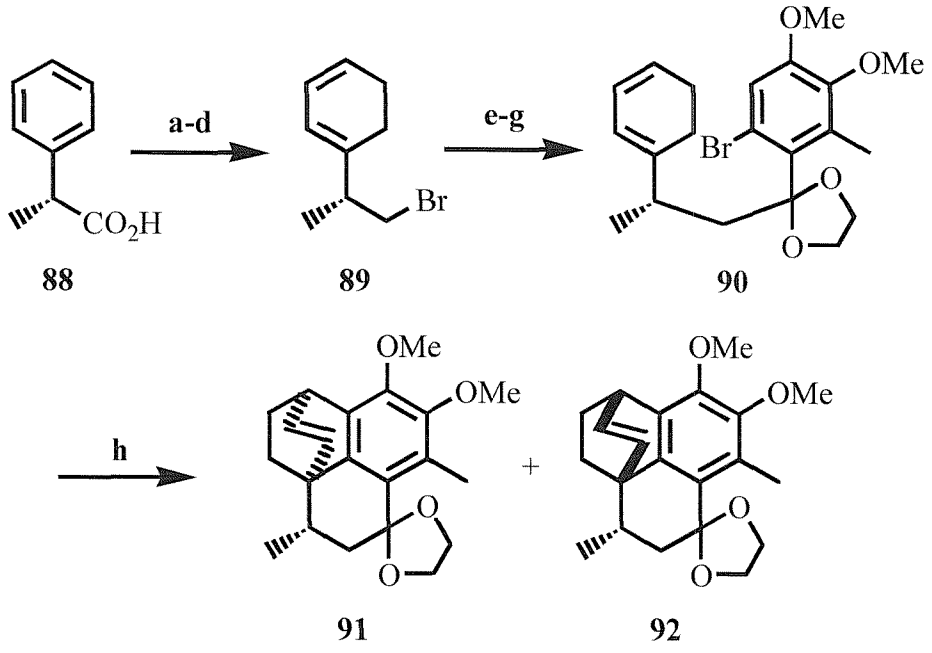
Scheme 8

The Buszek Synthesis[18]

Buszek and Bixby were the next to report a total synthesis of the pseudopterosin A-F aglycone. Their synthesis began with commercially available *(R)*-(-)-2-phenylpropionic acid **88**. Reduction of the carboxylic acid with excess LAH afforded the corresponding alcohol. Birch reduction followed by base induced isomerisation gave the 1-substituted cyclohexadiene. The alcohol was brominated using NBS/PPh_3 to furnish **89**. The Grignard reagent derived from **89** was added to the benzaldehyde **87** (derived from piperonal in seven steps) to give a diastereomeric mixture of benzylic alcohols. These were oxidised using the Swern procedure to a ketone which was protected as its cyclic ketal **90**. Treatment of the precursor with LDA in THF then generated a reactive benzyne which immediately underwent an intramolecular Diels-Alder cycloaddition reaction to give a 58 : 42 mixture of the diastereoisomers **91** and **92** (**Scheme 9**).



86 **87**



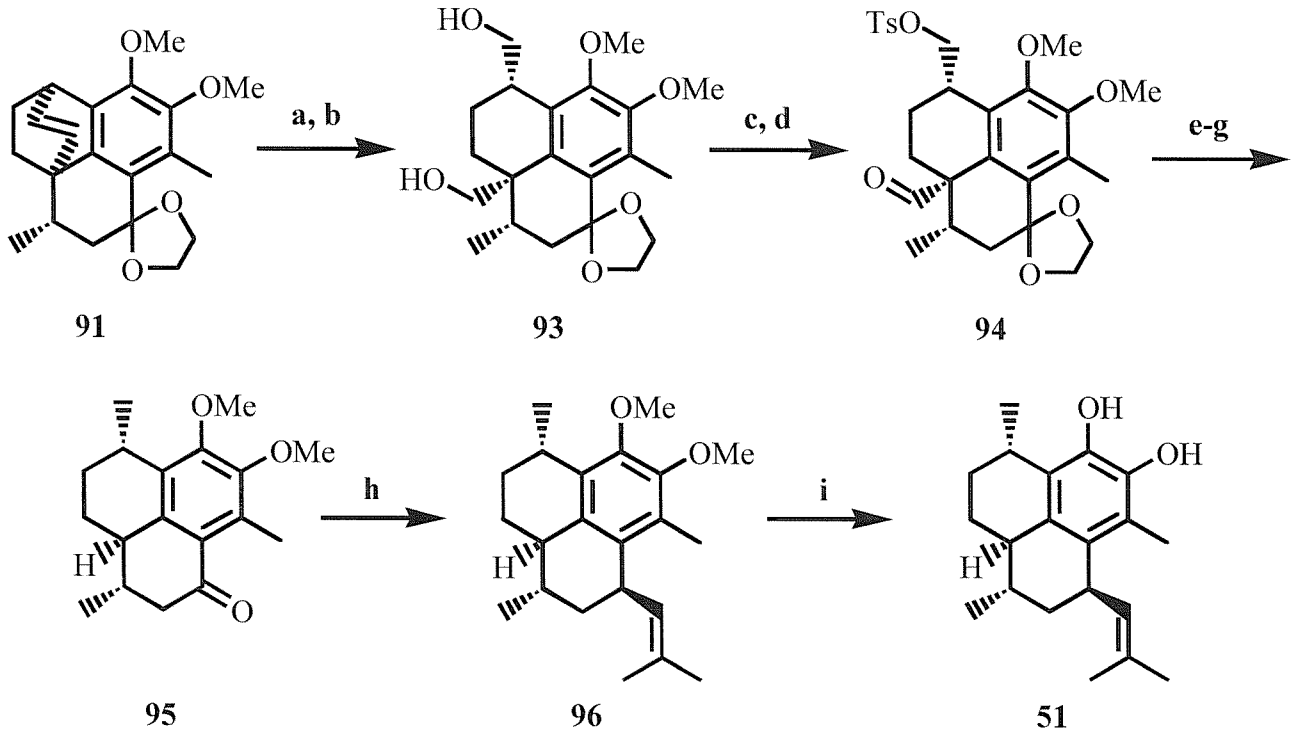
88 89 90

91 92

Reagents & Conditions: a. $LiALH_4$, THF. **b.** Na/NH_3, EtOH. **c.** KO*t*Bu, DMSO, 65°C. **d.** NBS, PPh_3. **e.** Mg, then **87**. **f.** $(COCl)_2$, DMSO, NEt_3, DCM. **g.** $(CH_2OH)_2$, THF, cat. TsOH. **h.** LDA, THF, -78°C-RT, 12h.

Scheme 9

The unwanted diastereoisomer **92** was then separated by chromatography. Oxidative cleavage of the ethylene bridge in **92** first afforded a dialdehyde which was then reduced to the diol **93**. Selective protection as the tosylate of the less hindered alcohol at C19 was followed by oxidation of the remaining hydroxyl giving the aldehyde **94** which, on decarbonylation with Wilkinsons catalyst and nucleophillic hydride displacement of the tosylate established the methyl group at C19 as a single diastereoisomer. Deketalisation with PPTS in aqueous acetone gave the tricyclic ketone **95**, directly analogous to the tricyclic ketone prepared by Corey. Finally the isobutenyl side chain was introduced by the method of Corey and the methyl ethers deprotected by the use of TMS iodide to give the aglycone **51** (**Scheme 10**).

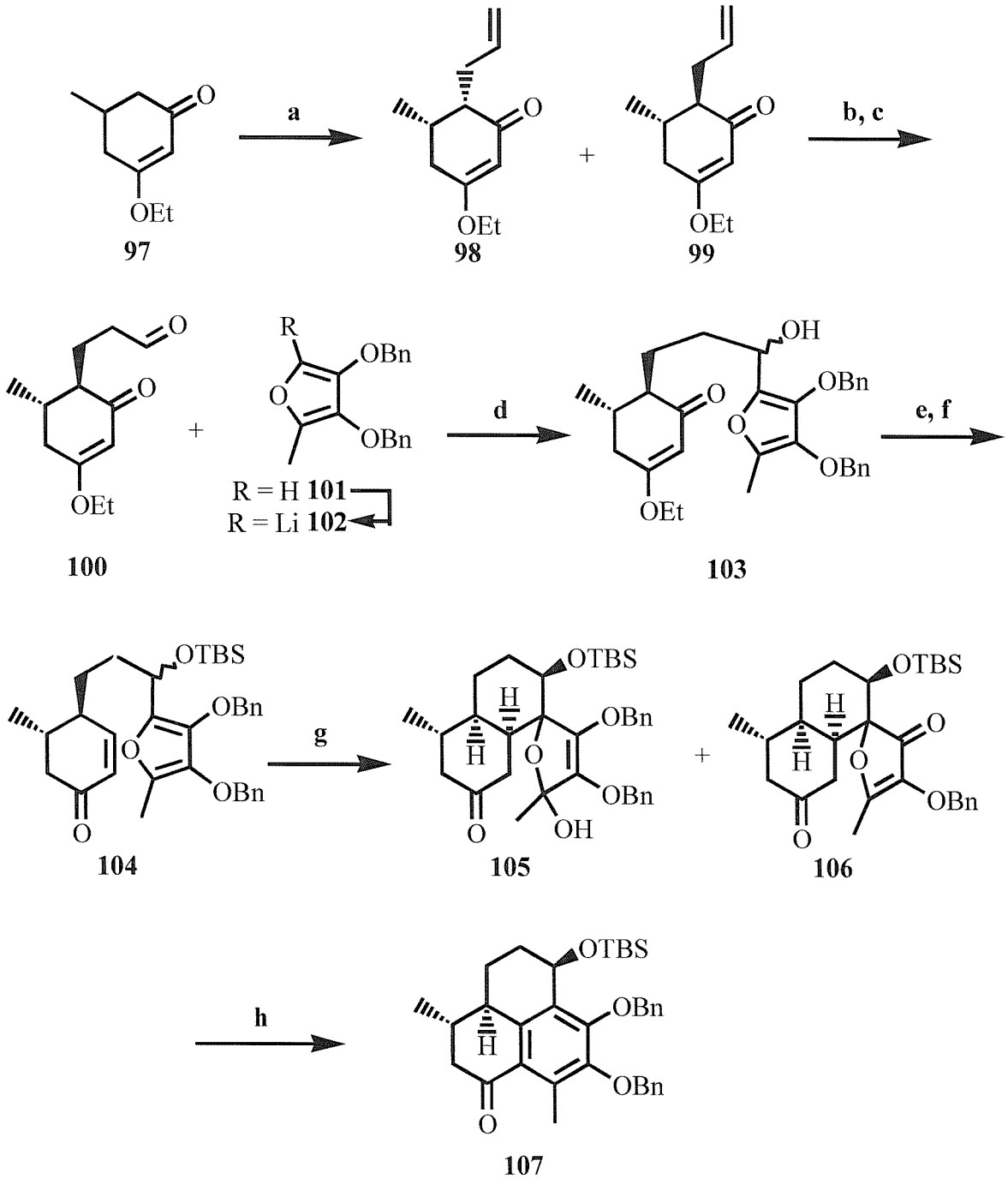


Reagents & Conditions: a. NMO, cat. OsO_4. **b.** KIO_4, THF-H_2O then $NaBH_4$. **c.** TsCl, py. **d.** Dess-Martin. **e.** $(PPh_3)_3RhCl$, PhCN. **f.** $LiAlH_4$, THF. **g.** PPTS, $(CH_3)_2CO$, H_2O. **h.** (i) $(CH_3)_3S^+Cl^-$, *n*BuLi. (ii) $BF_3.OEt_2$, DCM. **i.** TMSI, $CHCl_3$, 35°C.

Scheme 10

The Jung Approach[19]

A late tricyclic intermediate for the synthesis of the pseudopterosin aglycone has been described by Jung and Siedem. Their approach begins with the vinyl ether **97** which can be alkylated with allyl bromide to give a 7.5 : 1 mixture of diastereoisomers favouring the desired *trans* product **99**. Hydroboration of the alkene, oxidation to the alcohol and Swern oxidation to the aldehyde **100** was followed by addition of organolithium **102** (generated from the known furan **101** *via* deprotonation with *n*-butyllithium) giving a 1 : 1 mixture of alcohols **103**. Protection as the silyl ether and conversion of the β-ethoxyenone into the transposed enone by reduction with DIBAL-H followed by elimination on silica gel provided enone **104** with simultaneous epimerisation of the C9 centre. Exposure of **104** to $SnCl_4$ unexpectedly gave rather than the products derived from a Diels-Alder cycloaddition the intramolecular Michael adducts **105** and the debenzylated product **106**. Treatment of **105** with potassium *tert*-butoxide in *t*BuOH then gave **107** and its desilylated analogue (**Scheme 11**).

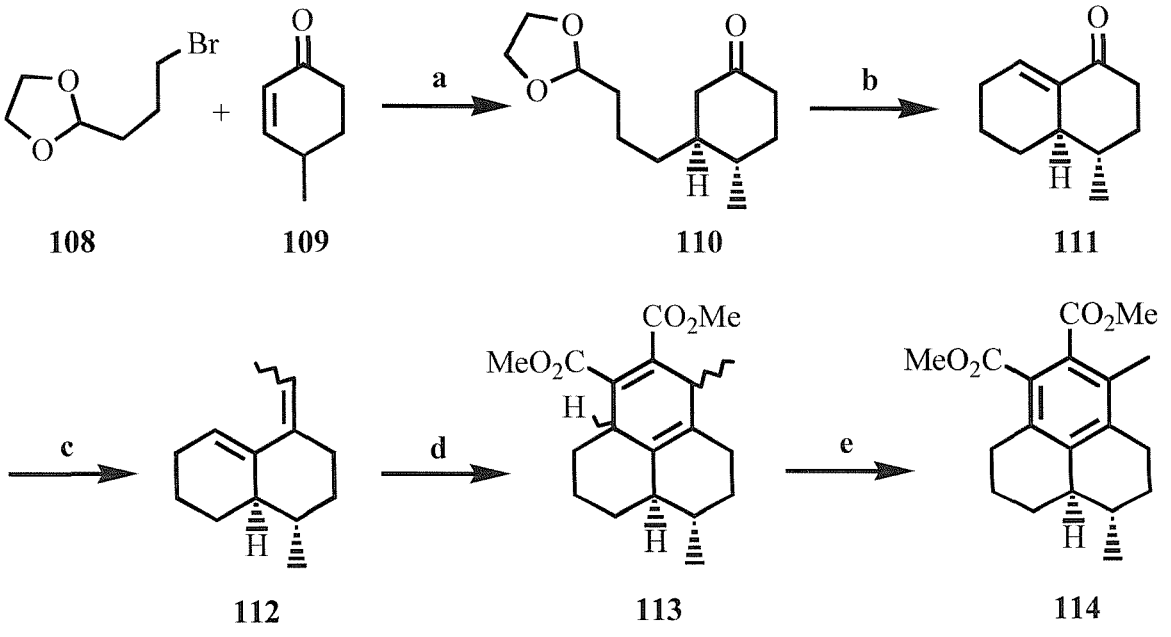


Reagents & Conditions: **a.** LDA, THF, allyl bromide. **b.** Sia_2BH, H_2O_2, NaOH. **c.** DMSO, $(COCl)_2$, NEt_3. **d.** *t*BuLi, THF. **e.** TBSCl, imidazole, DMF. **f.** DIBAL-H, PhMe, then SiO_2. **g.** $SnCl_4$, DCM. **h.** KO*t*Bu, *t*BuOH, TBSCl.

Scheme 11

The Frejd Approach[20]

Frejd *et al.* have described a synthetic route to the tricyclic hexahydrophenalene nucleus of the pseudopterosin aglycone. Cuprate addition of the protected bromoaldehyde **108** to 4-methyl cyclohexene **109** affords the protected keto aldehyde **110** as a 97 : 3 mixture of diastereoisomers in favour of the *trans* isomer. Subsequent acidic hydrolysis of the acetal functionality also induced an intramolecular aldol condensation to give the methyloctalone **111**. Treatment of the ketone with ethylphosphorane afforded the diene **112** as a mixture of *(E)* and *(Z)* isomers both of which underwent Diels-Alder cycloaddition reactions with dimethyl acetylenedicarboxylate to yield diester **113**. Aromatisation with DDQ provided tricyclic precursor **114** (**Scheme 12**). Despite being one of the most rapid entries to the tricyclic framework of pseudopterosin, the approach suffers from the fact that the aromatic ring is at the wrong oxidation level and also fails to introduce the substituents at the C1 and C7 centres.



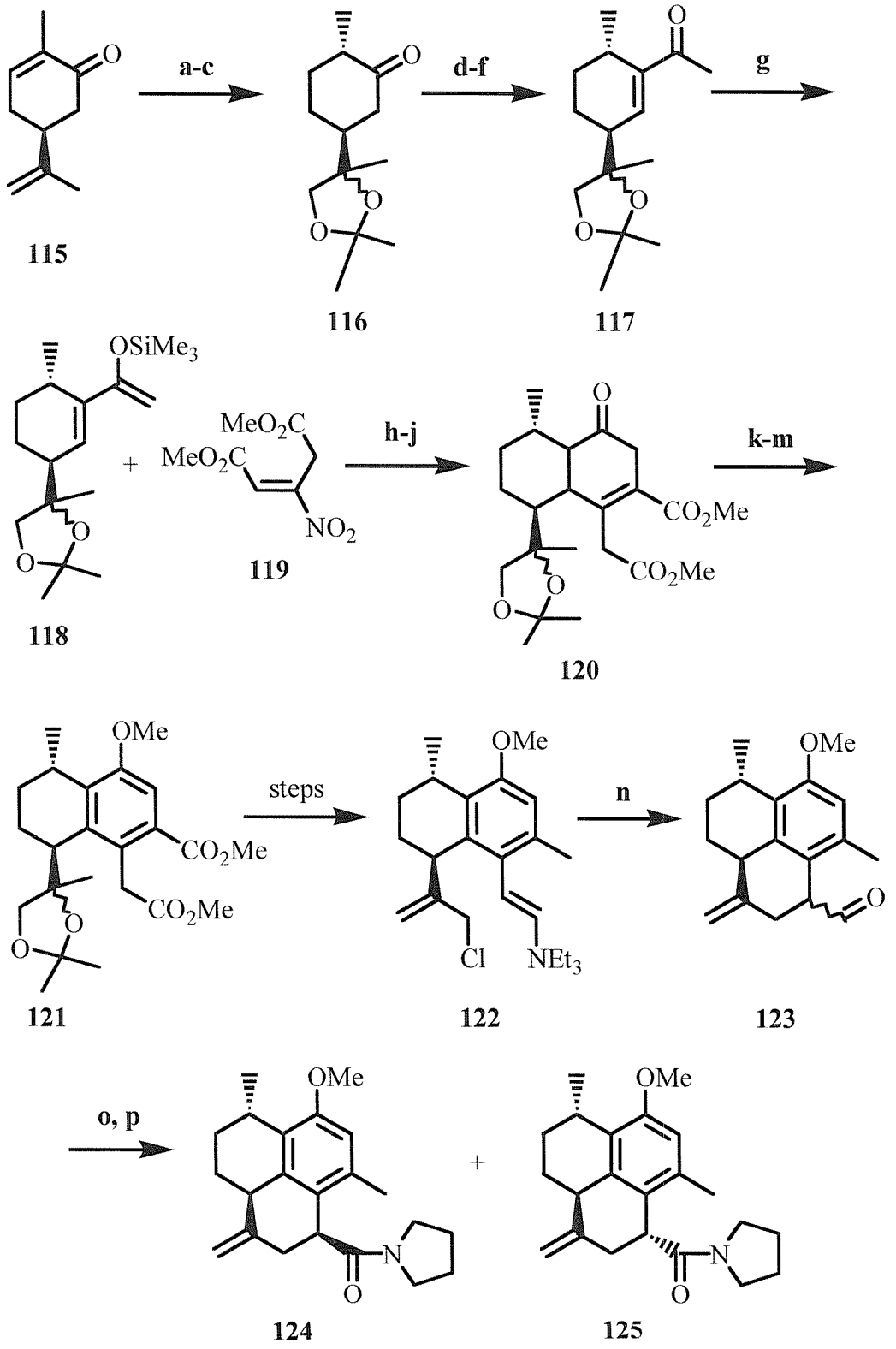
108 **109** **110** **111** **112** **113** **114**

Reagents & Conditions: a. Mg, $CuBr.SMe_2$. **b.** aq. HCl, THF. **c.** $Ph_3P{=}CHMe$. **d.** DMAD, $AlCl_3$. **e.** DDQ.

Scheme 12

The Kozikowski Approach[21]

An alternative approach for the construction of the tricyclic skeleton of the pseudopterosins has been reported by Kozikowski and Wu. Their approach began with an eight step sequence to transform *(S)*-carvone **115** into the diene **118**. Union with the dienophile **119** then gave decalin **120** after hydrolysis and elimination. The unsaturated enone **120** was next converted into the tetralin **121** *via* DDQ oxidation of its silyl enol ether. An extensive series of transformations then afforded the chloride **122** which underwent cyclisation to give an inseparable mixture of aldehydes **123**. These were transformed into the pyrrolidine amides **124** and **125** which were separable by chromatography (**Scheme 13**).

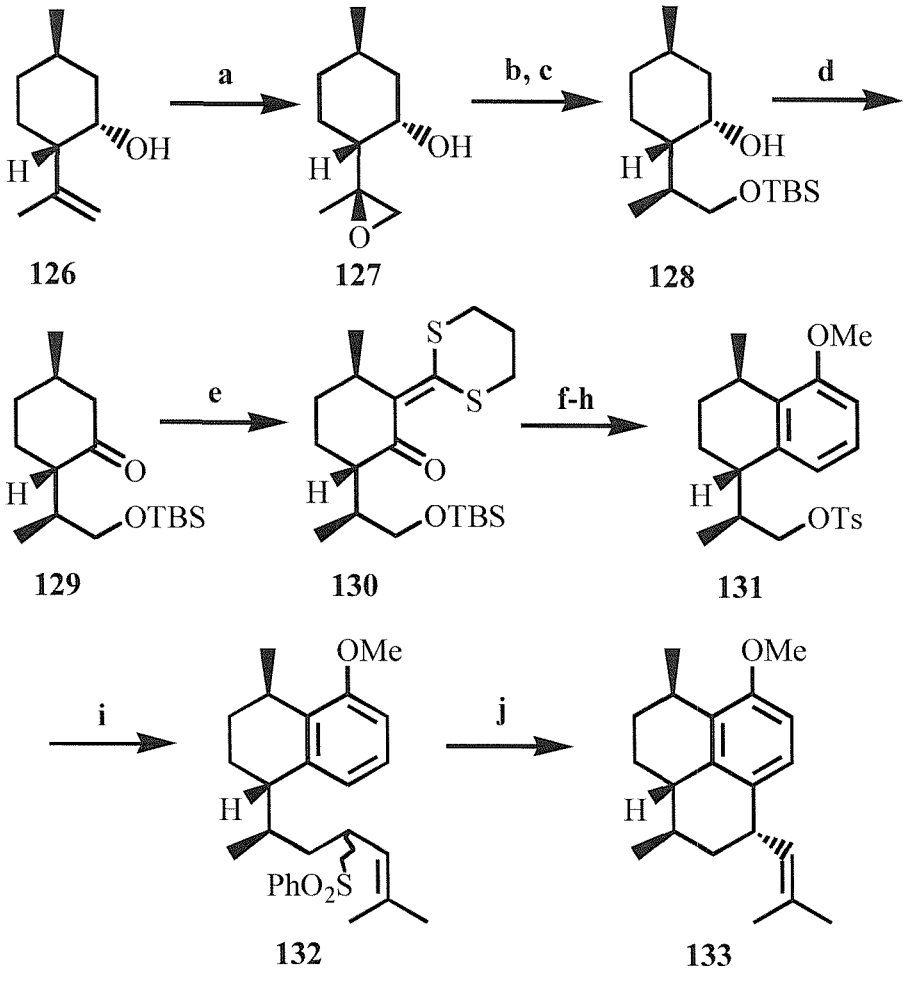


Reagents & Conditions: **a.** Li/NH_3, *t*BuOH, THF. **b.** NMO, cat. OsO_4, *t*BuOH-THF-H_2O. **c.** $Me_2C(OMe)_2$, PPTS, DCM. **d.** TrisNHNH$_2$, MeOH. **e.** *n*BuLi, MeCHO. **f.** PDC, DCM. **g.** LiHMDS, THF, TMSCl. **h.** 3,5-di-*t*butylcatechol, 0°C. **i.** aq. HCl, THF. **j.** DBU. **k.** TMSI, HMDS, NEt_3, DCE. **l.** DDQ, PhH. **m.** K_2CO_3, Me_2SO_4, acetone. **n.** NaI, EtOH, reflux. **o.** $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*BuOH. **p.** Pyrrolidine, NEt_3, 2-chloro-1-methylpyridinium iodide.

Scheme 13

The Kocienski Approach[22]

A general approach to the pseudopterosin aglycone has been described by Kocienski *et al.* The synthesis began with a stereoselective directed epoxidation reaction of (1*S*,2*S*,5*R*)-neoisopulegol **126** which is readily available from commercial (1*R*,2*S*,5*R*)-neoisopulegol. The oxirane was cleaved with inversion of stereochemistry using sodium cyanoborohydride in the presence of $BF_3.OEt_2$. The resulting diol was obtained as a single diastereoisomer. Protection of the more reactive primary hydroxyl and Swern oxidation of the remaining secondary alcohol gave ketone **129**. Kinetic deprotonation facillitated introduction of the ketenedithioacetal moiety in **130** by treatment with CS_2 and then 1,3-dibromopropane. Grignard addition of methallylmagnesium bromide followed by Lewis acid induced cyclisation and aromatisation gave the tetrahydronapthalene derivative **131**. Deprotection of the hydroxy group followed by tosylation and displacement with the anion derived from 3-methylbut-2-enyl sulfone provided the alkylation product **132** as a 1 : 1 mixture of diastereoisomers. Upon exposure to ethylaluminium dichloride the sulfone underwent cyclisation to afford a 10 : 1 mixture of diastereoisomers in favour of the desired material **133** (**Scheme 14**).



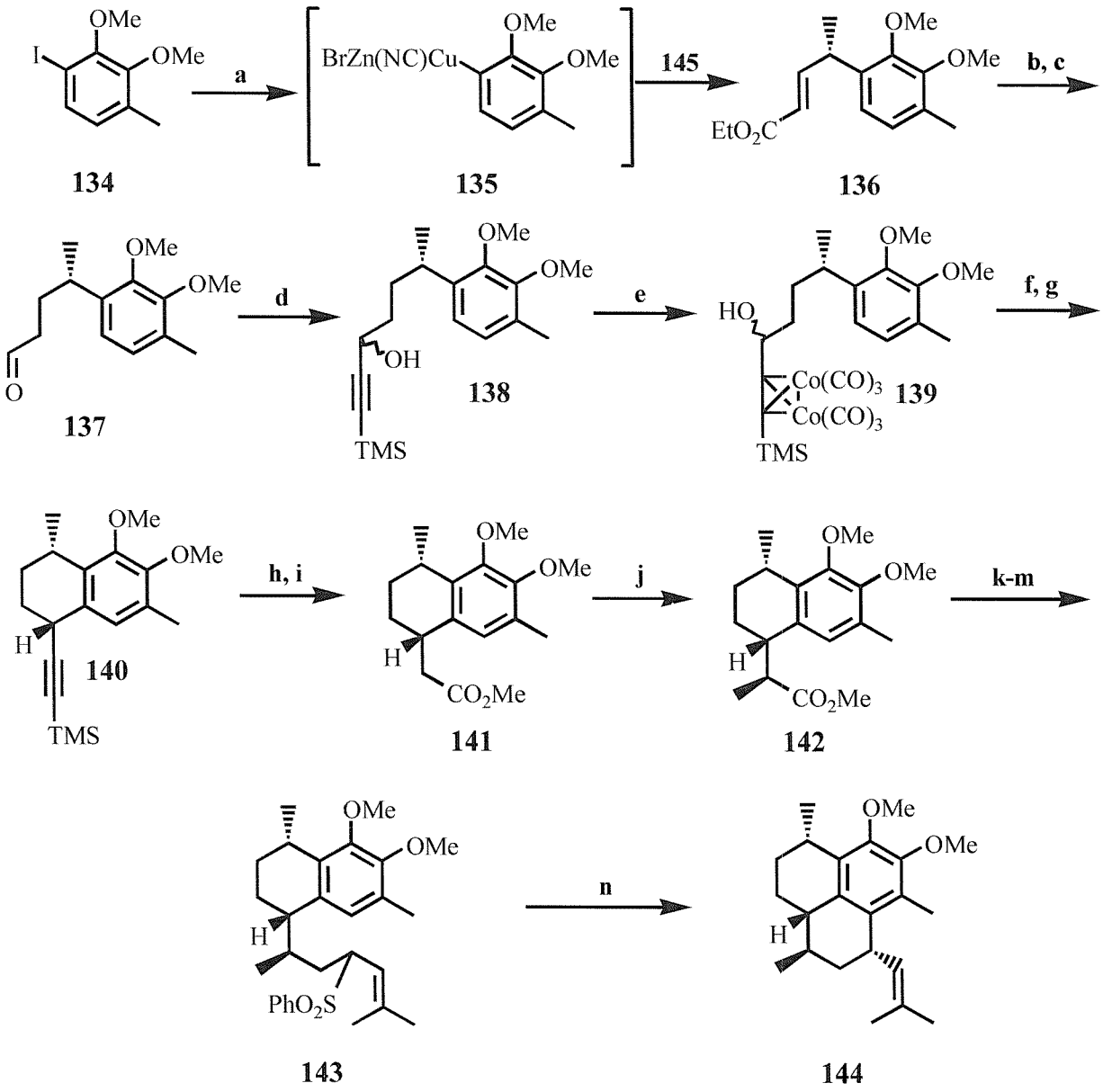
Reagents & Conditions: **a.** $VO(acac)_2$, *t*BuOOH, PhH. **b.** $NaBH_3CN$, $BF_3.OEt_2$. **c.** TBSCl, DMF, imidazole, **d.** Swern. **e.** LiHMDS, DMPU, THF then CS_2, $Br(CH_2)_3Br$. **f.** Methallyl-magnesium bromide. **g.** $BF_3.OEt_2$, MeOH-THF. **h.** TsCl, DMAP, NEt_3. **i.** $Me_2C{=}CHCH(Li)SO_2Ph$, THF. **j.** $EtAlCl_2$, THF.

Scheme 14

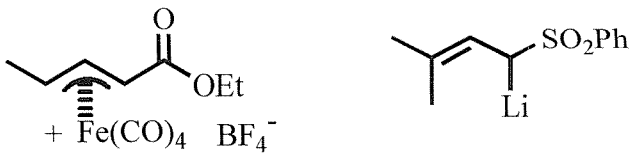
The Alternative Kocienski Approach[23]

Having explored routes to the pseudopterosin A-F aglycone Kocienski *et al.* turned their attention to the pseudopterosin G ring system and have reported a synthesis of the hexahydro-1*H*-phenalene system **144** which bears an enantiomeric relationship to that originally assigned as pseudopterosin G. The synthesis began with the iodo veratrole derivative **134** which on

lithiation and generation of the zinc cuprate reagent **135** underwent a highly regio- and enantio-facially selective addition to the enantiomericaly pure organo-iron complex **145** establishing the first stereogenic centre at C7. Reduction of the double bond followed by reduction of the ester gave the saturated aldehyde **137**. Addition of (trimethylsilyl)ethynylmagnesium bromide then gave the propargylic alcohols **138** as an inseparable mixture (1:1). The cobalt complex **139** was formed in the usual way and treatment of the complex with $BF_3.(OEt_2)$ induced cation formation and a highly diastereoselective cyclisation to give (after decomplexation) the tetrahydronapthalene **140**. Standard chemistry then afforded the methyl ester **141**. The third stereogenic centre was installed *via* a simple α-alkylation of the ester using LDA and iodomethane. The final ring of the aglycone dimethyl ether was installed by reduction of the ester, tosylation of the resulting alcohol, displacement of the tosylate with the anion **146** and treatment of the sulfone **143** with ethylaluminium dichloride. This sequence afforded tricycle **144** with a dr of 10 : 1 in favour of the desired diastereoisomer (**Scheme 15**). Kocienski noted that this material displayed several discrepancies with those data reported for the pseudopterosin G-J aglycone.



Reagents & Conditions: **a.** (i) *n*BuLi, THF-Et_2O. (ii) $ZnBr_2$, CuCN, LiCl. (iii) **145**. **b.** Mg, MeOH. **c.** DIBAL-H, DCM. **d.** TMS-C≡C-MgBr. **e.** $Co_2(CO)_8$, DCM. **f.** $BF_3.OEt_2$. **g.** $Fe(NO_3)_3.9H_2O$, MeOH. **h.** (i) $(C_6H_{11})_2BH$ (2 eq.), THF. (ii) NaOH, H_2O_2, MeOH. **i.** MeI, Tetramethylguanidine PhMe. **j.** LDA, THF then MeI. **k.** LAH, THF. **l.** TsCl, DMAP, NEt_3, DCM. **m.** **146**, THF. **n.** $EtAlCl_2$, DCM.

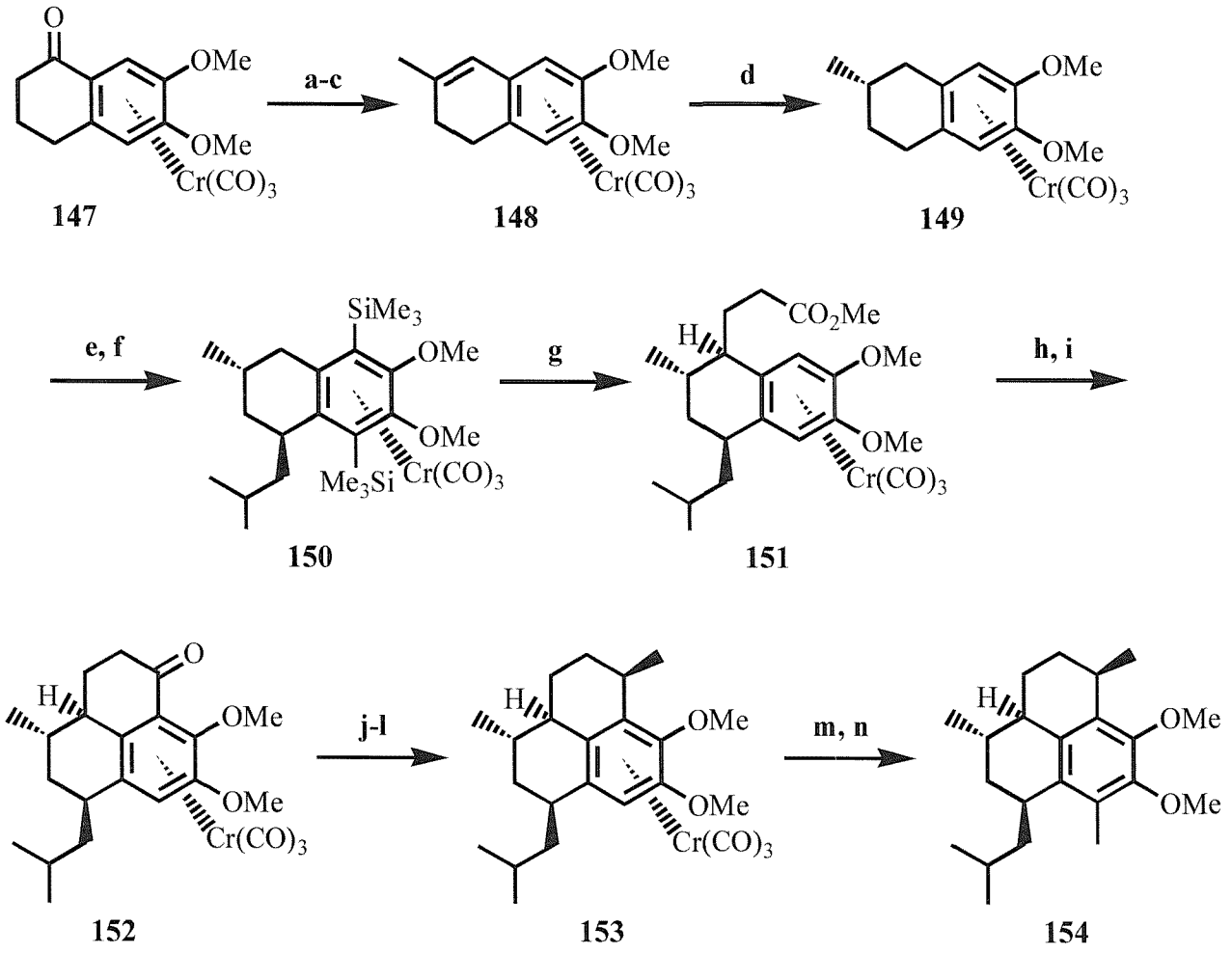


145 **146**

Scheme 15

The Schmalz Approach[24]

In 1994 Schmalz *et al.* disclosed a method to construct substituted hydrophenalenes based upon the reactivity of arene-$Cr(CO)_3$ complexes. The synthesis begins with the non racemic tetralone-$Cr(CO)_3$ derivative **147** obtained from racemic 6,7-dimethoxy-1-tetralone-$Cr(CO)_3$ by resolution. This enantiomericaly pure starting material is converted into the dihydronapthalene **148** by α-methylation, reduction and elimination. Rhodium catalysed hydrogenation (from the face opposite chromium) yields the endo complex **149** as a single diastereoisomer. Protection of the acidic aryl positions was achieved by conversion to a bis-silylated complex. Treatment with another equivalent of *n*BuLi then isobutyl iodide afforded the alkylated product **150** as a single regio- and diastereo- isomer. Functionalisation of the second benzylic position was achieved in a similar manner through lithiation of the benzylic centre followed by a Michael addition employing methyl-α-trimethylsilyl acrylate as the electrophile. Fluoride induced desilylation then gave ester **151**, which was hydrolysed and subjected to a Friedel Crafts acylation affording tricyclic ketone **152**. The benzylic methyl group was installed *via* boronate reduction of the carbonyl group, acetylation and treatment of the *exo*-alcohol with trimethylaluminium. Oxidative decomplexation of the metal then liberated the tricyclic material **154** related to the pseudopterosin G dimethyl ether (original assignment) (**Scheme 16**).



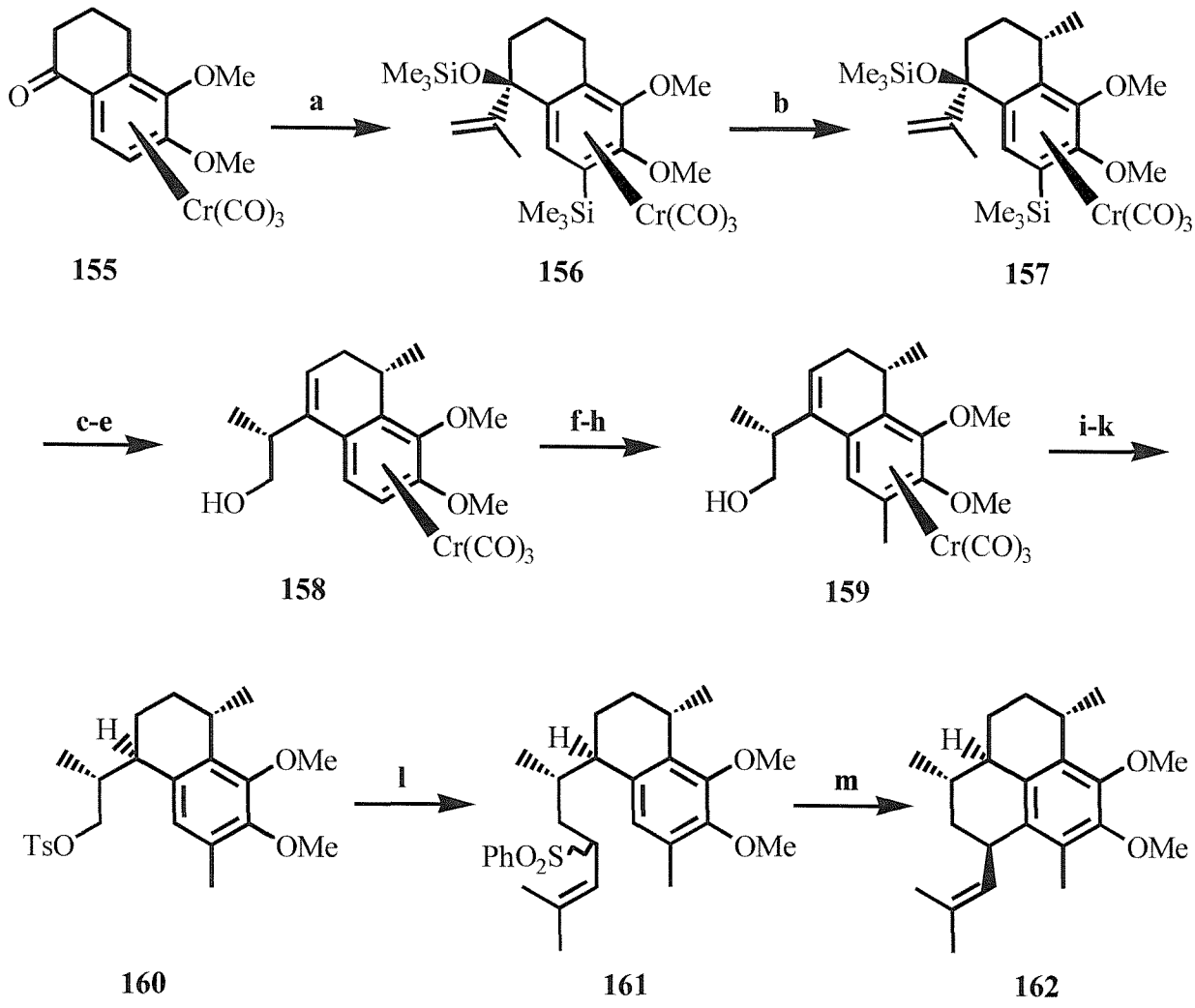
Reagents & Conditions: **a.** LiHMDS, THF, MeI, HMPA. **b.** $NaBH_4$, MeOH. **c.** TsOH, SiO_2, PhH. **d.** cat. Rh/Al_2O_3, H_2, 5 bar. **e.** LiTMP, TMSCl, THF. **f.** *n*BuLi, THF/HMPT then ICH_2CHMe_2. **g.** *n*BuLi, HMPT, $CH_2{=}C(SiMe_3)CO_2Me$, then aq. HCl, TBAF. **h.** NaOH, MeOH, H_2O. **i.** PPA. **j.** $NaBH_4$, MeOH. **k.** Ac_2O, py, cat. DMAP. **l.** Me_3Al, DCM. **m.** hν, air, Et_2O. **n.** *n*BuLi, TMEDA, hexane, then MeI.

Scheme 16

A Further Schmalz Approach[25]

Although Schmalz's original approach offered a diastereoselective synthesis of a tricycle related to pseudopterosin G **154** (original assignment), the synthesis failed to offer a method of installing the isobutenyl group. Three years after the publication of their original paper, Schmalz *et al.* reported a synthesis of the pseudopterosin A-F aglycone dimethyl ether and

seco-pseudopterosin aglycone dimethyl ether, again utilising an enantiomerically pure tetralone-$Cr(CO)_3$ complex **155** (**Scheme 15**).



Reagents & Conditions: a. Isopropenyllithium (3.5 eq.), THF then TMSCl. **b.** *n*BuLi, THF, MeI. **c.** $BH_3.SMe_2$, THF then NaOH, H_2O_2. **d.** TBAF, THF. **e.** TsOH, SiO_2, PhH. **f.** *t*$BuMe_2SiCl$, imidazole. **g.** *n*BuLi, THF then MeI. **h.** TBAF, THF. **i.** SmI_2 (4.5 eq), H_2O (2 eq.), THF/HMPA. **j.** Et_2O, hν, air. **k.** TsCl, NEt_3, DMAP. **l.** phenylprenylsulphone, *n*BuLi, THF. **m.** $EtAlCl_2$, DCM.

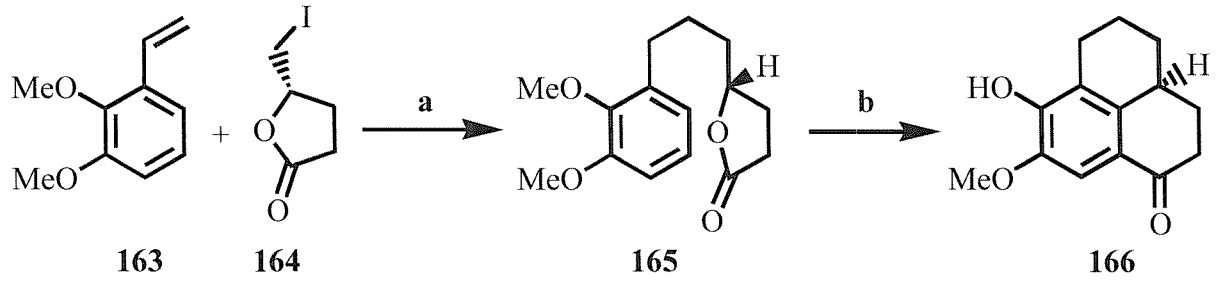
Scheme 15

A series of standard synthetic transformations performed upon the metal complex afforded the tosylate **160** which was displaced by the anion derived from phenylprenyl sulfone to give **161** as a 1 : 1 mixture of diastereoisomers. Exposure of sulfone **161** to ethylaluminium dichloride (developed by Kocienski *et al.*[22]) gave the pseudopterosin A aglycone dimethyl ether **162**.

The Harrowven Approach[26]

In 1994 Harrowven *et al.* published the results of their preliminary studies employing a sequential Friedel Crafts alkylation-acylation protocol which may be applied to the synthesis of pseudopterosin.

The analogue **165** was prepared by union of the iodolactone **164** with styrene **163** under standard tin mediated radical coupling conditions. Exposure of the lactone **165** to titanium tetrachloride then effected a sequential Friedel Crafts alkylation-acylation reaction and in addition also unmasked the *para* phenolic moiety giving **166**. This observation is particularly noteworthy given the importance of differentiation between the phenolic positions when attaching the respective glycosidal residues. The initial alkylation reaction was also observed to proceed, at least in part, with inversion of configuration about the lactone centre (**Scheme 16**).



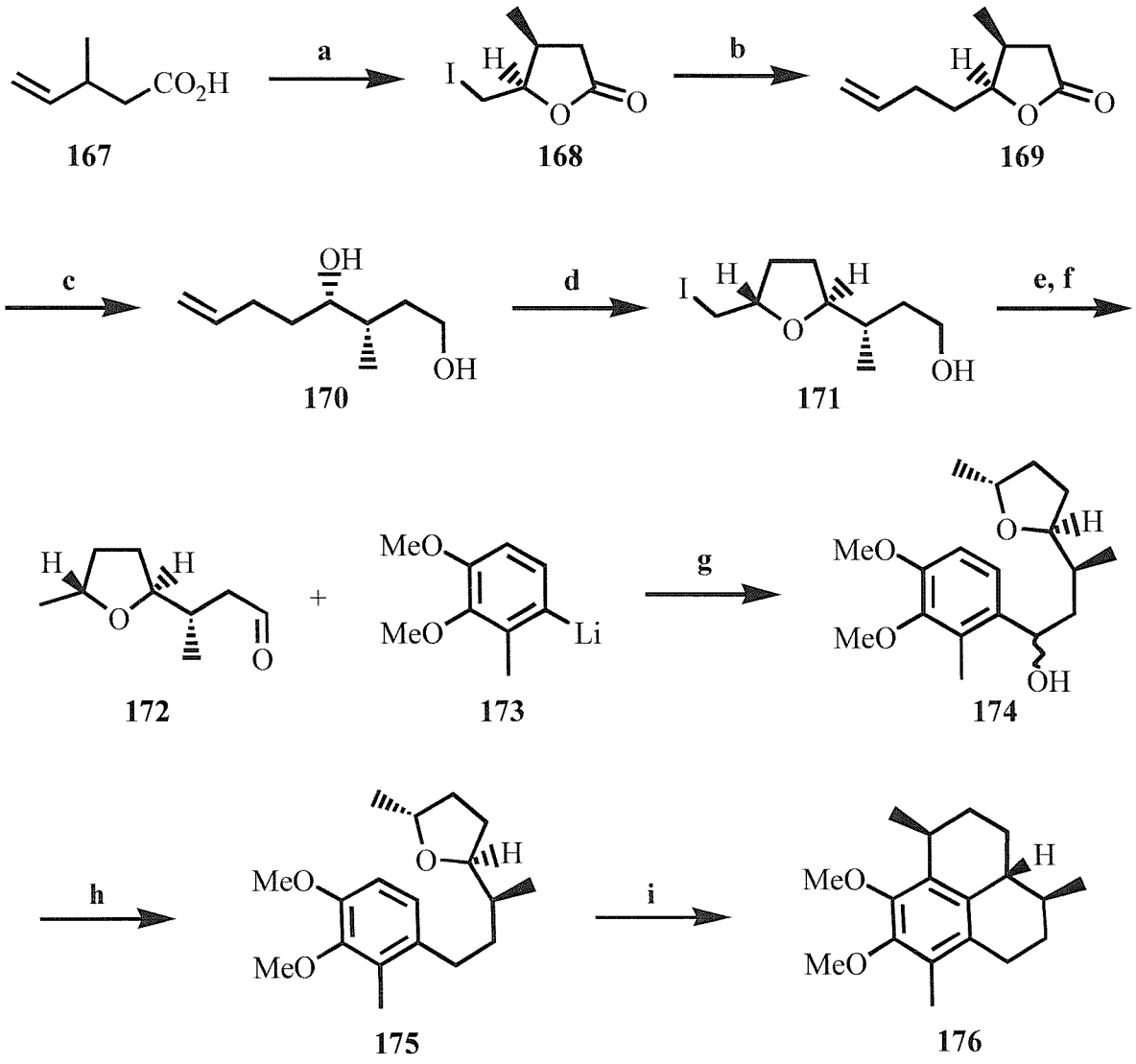
163 **164** **165** **166**

Reagents & Conditions: a. Bu_3SnH, AIBN, PhH, reflux. **b.** $TiCl_4$, DCM, reflux

Scheme 16

More recently, Harrowven and Sibley have described a new approach to the pseudopterosin framework in which a sequential annulation of an arene with a tetrahydrofuran features as the key step. Beginning with the known carboxylic acid **167**, kinetic lactonisation gave

iodolactone **168** as a separable 6 : 1 mixture of diastereoisomers. Tin mediated alkylation, reduction and thermodynamic iodoetherification then gave the tetrahydrofuran **171**. Reduction of the halide and Swern oxidation then afforded the aldehyde **172** which was coupled with the aryllithium **173** to give the benzylic alcohols **174** as a 1 : 1 mixture of diastereoisomers. Removal of the alcohol by hydrogenolysis then gave the tetrahydrofuran precursor **175**. Sequential cyclisation to the hexahydrophenalenone **176** was then induced by exposure of the material to $BF_3.OEt_2$ (**Scheme 17**).

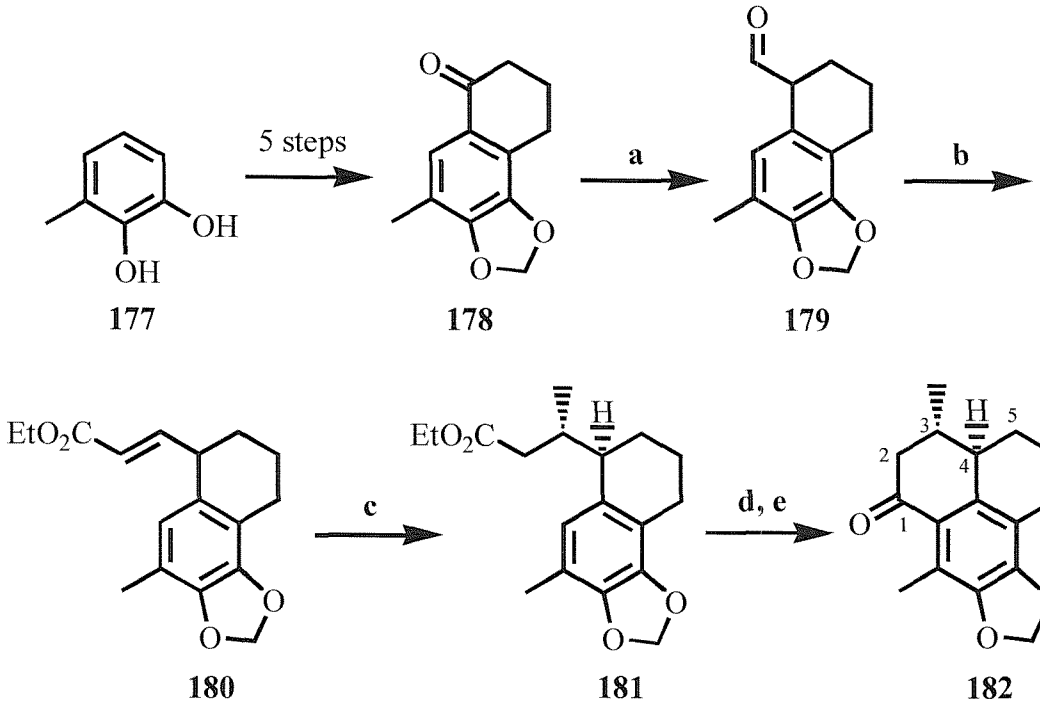


Reagents & Conditions: a. I_2, MeCN. **b.** Allyltributyltin, AIBN, THF. **c.** DIBAL-H, THF. **d.** I_2, MeCN. **e.** Bu_3SnH, AIBN, PhMe. **f.** $(COCl)_2$, DMSO, DCM, NEt_3. **g. 173**, THF. **h.** H_2, Pd/C, EtOH. **i.** $BF_3.OEt_2$, DCM, reflux.

Scheme 17

The Csaky and Plumet Approach[27]

The most recent approach to the hexahydro-1*H*-phenalene ring framework of the pseudopterosins has been described by Csaky and Plumet. Starting from commercially available 3-methylcatechol **177** a series of standard transformations yielded the tetralone **178**. Treatment with $Me_2S{=}CH_2$ gave the aldehyde **179** which was converted to the unsaturated ester **180** *via* a Wadsworth-Emmons reaction. Exposure of **180** to Me_2CuLi in the presence of TMSCl gave **181** as a single diastereoisomer. Finally hydrolysis of **181** followed by treatment with oxalyl chloride yielded the tricyclic precursor to pseudopterosin **182** (**Scheme 18**).



Reagents & Conditions: a. $Me_2S{=}CH_2$, NaH, DMSO. **b.** $(EtO)_2P(O)CH_2CO_2Et$, KO*t*Bu, THF. **c.** Me_2CuLi, TMSCl, THF. **d.** KOH, EtOH. **e.** $(COCl)_2$, PhMe.

Scheme 18

Despite being one of the most rapid entries to the phenalene ring system, this approach fails to introduce the methyl appendage at C7.

Chapter 2

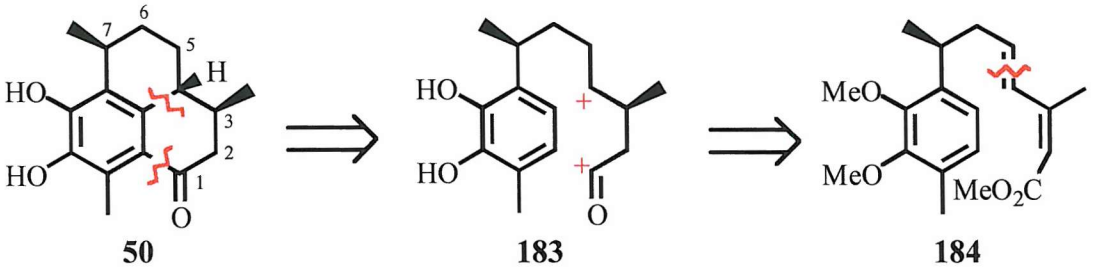
Our Approach to Pseudopterosin:

A Sequential Aromatic Alkylation Strategy

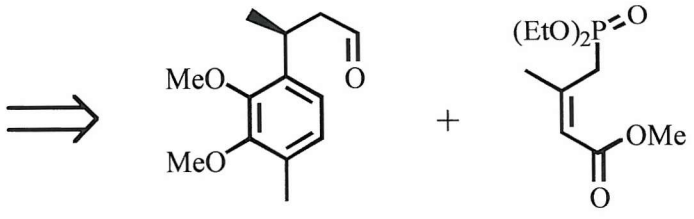
Synthetic Studies

Retrosynthesis

At the outset of this programme, eleven approaches to the pseudopterosins had been described in the literature.[13-27] These had largely relied on the elaboration of an aromatic ring onto an existing carbon framework in which most of the stereogenic centres had already been established. Of these, the syntheses of Corey and Carpino attracted our attention since they utilised the tricyclic ketone **50**.[14] This molecule appeared ideally suited for construction utilising a sequential Friedel-Crafts alkylation-acylation strategy *via* the synthon **183**. By employing diene **184** in the Friedel-Crafts alkylation-acylation sequence, we hoped to be able to control the relative stereochemistry at the C4 centre in the first cyclisation reaction and ultimately to control the relative stereochemistry at C3 centre *via* hydrogenation. We envisaged that this diene would result from a simple Wadsworth-Emmons olefination reaction of aldehyde **185** with phosphonate ester **186**. The synthesis of these two compounds is therefore crucial to the success of this programme.



50 **183** **184**



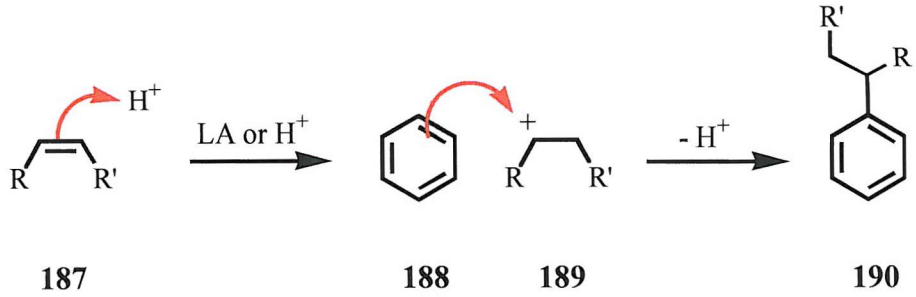
185 **186**

Friedel-Crafts Reactions Utilising an Olefin as the Electrophillic Counterpart

In 1892 Charles Friedel and James Mason Crafts published their first observations of the action of aluminium chloride in organic reactions, work which led to numerous synthetic methods bearing their names. Since then the scope and utility of the reaction has grown significantly and most noteworthy by the realisation that the reactions are catalysed by a range of acids and by no means limited to anhydrous aluminium chloride as the catalyst.[28] Olefins are especially good alkylating agents when employed in the Friedel-Crafts alkylation reaction and since the first demonstration of their applicability in the reaction they have been used so routinely that many authors fail to reference this particular synthetic method!

Mechanism

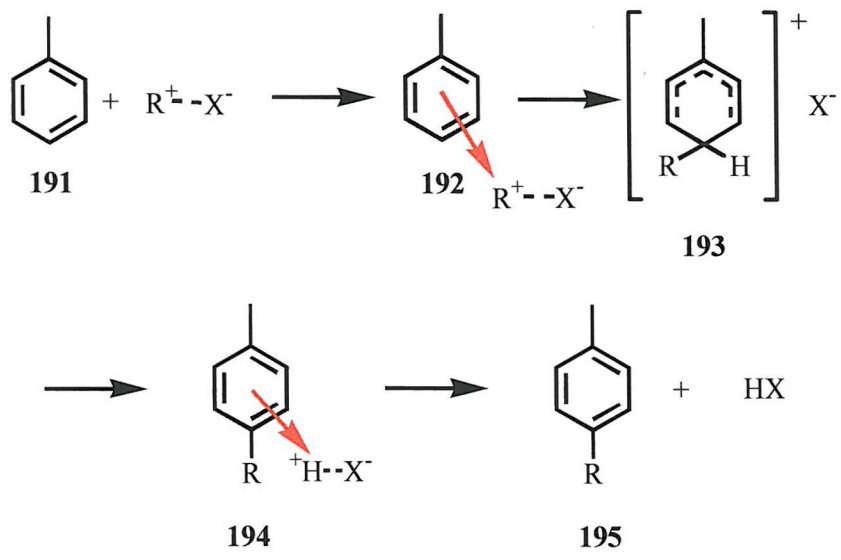
Friedel-Crafts alkylation processes usually refer to the cationic nuclear alkylation of an aromatic ring. When an olefin is utilised as the electrophillic reagent a carbocation is often an intermediate (which may form an ion pair with a counter ion), especially if the alkene generates a tertiary cation on protonation (**Scheme 19**). In other cases (particularly when the electrophillic reagent is an alcohol, halide or ether) the reaction may proceed *via* coordination of the catalyst to the olefin, resulting in a polarised bond that then reacts with the aromatic ring.



187 **188** **189** **190**

Scheme 19

Interaction of the catalyst-olefin complex with the aromatic ring is the second step in the alkylation sequence. It has been suggested by Nelson and Brown that in aromatic alkylation the electrophillic reagent interacts with the π electrons forming a complex that then undergoes a rearrangement to a σ complex.[29] Furthermore, Olah and Kuhn suggested that the incoming group attacks the centre of highest electron density forming a localised π complex which then undergoes rearrangement (**Scheme 20**).[30]



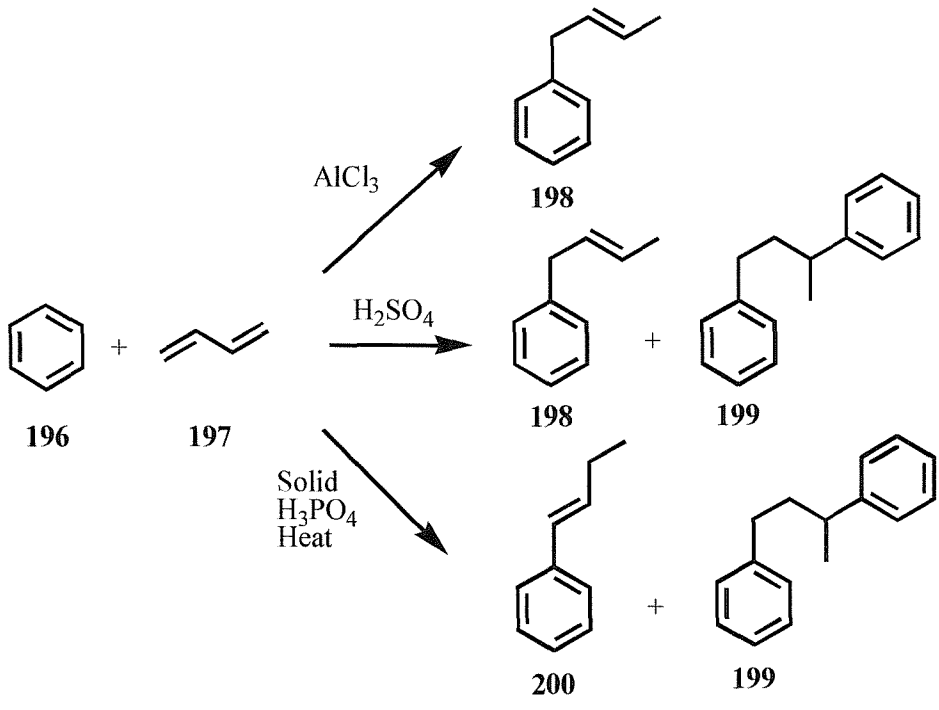
Scheme 20

Olah and Kuhn present strong evidence for this mechanism.[31] They suggest that π complex **192** collapses to a σ complex **193** with substituents directing the electrophile to the *ortho*, *meta*, or *para* positions. The ratio of these regioisomers is the result of the initial attack, the nature of the incoming group, the choice of catalyst and the directing effect of the arene substituents.

There have been many examples in the literature concerning the reaction of alkenes with arenes. In particular, with reference to our retrosynthesis, we were interested in the Friedel-Crafts alkylation with the diene **184**.

Friedel-Crafts Reactions with Dienes

Once again the reaction of substituted arenes with diene systems has been extensively explored in the literature.[28] In most cases the main products of alkylation result from formal 1,4 addition of the aromatic to the diene system. Proell *et al.* first demonstrated the reaction of butadiene with benzene, toluene, *p*-xylene, napthalene, and phenol using low molecular weight alkanesulphonic acids or aluminium trichloride as the catalyst.[32] In all cases the major products of the reaction were the corresponding 1-aryl-2-butenes, or products of further alkylation (**Scheme 20**).

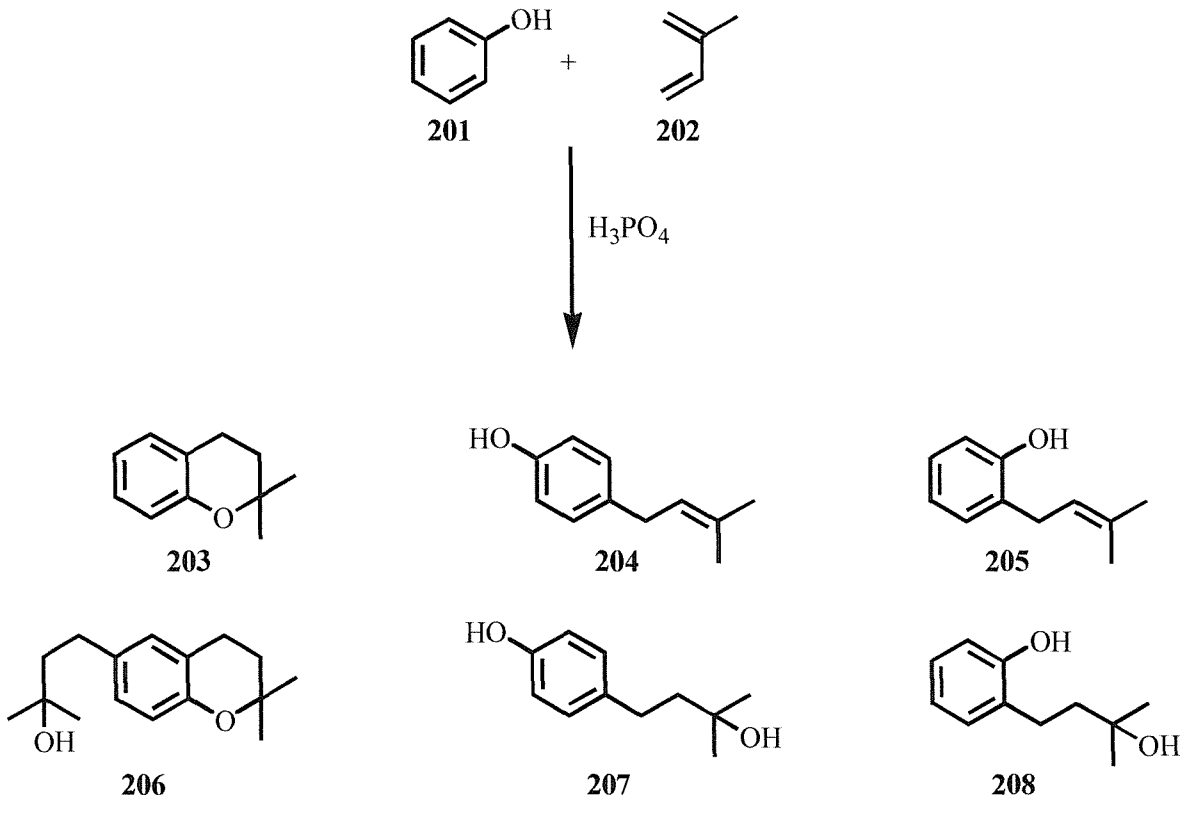


Scheme 21

This observation has been confirmed by Moeller *et al.* who used phosphoric acid as the catalyst in the butenylation of benzene, toluene and xylene.[33] Ipatieff, Pines and Schadd used stronger acids (sulphuric acid and hydrogen fluoride) and in addition to the usual 1,4 addition they also identified 1,3-diphenyl butane **199**.[34] Ipatieff *et al.* also used the extremely harsh

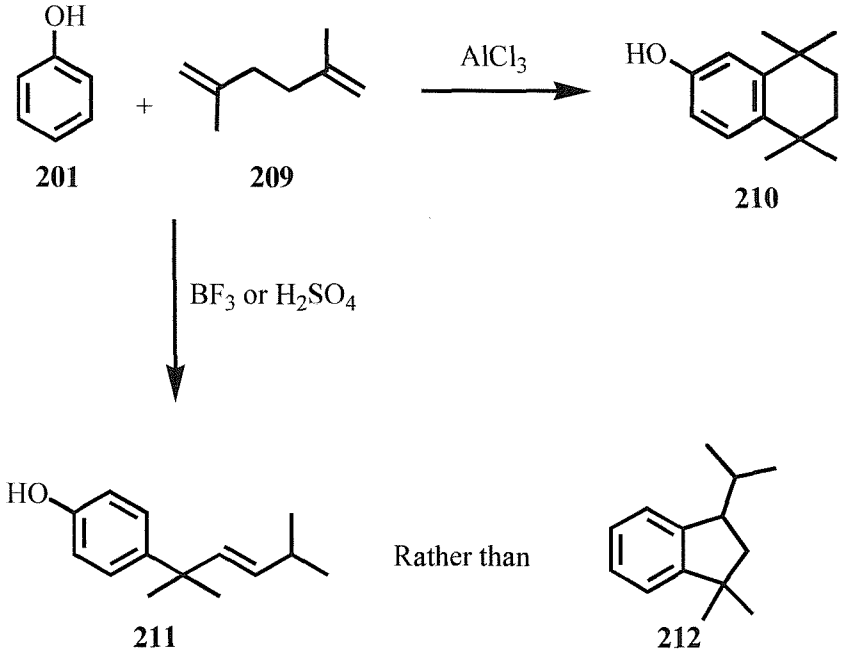
conditions of phosphoric acid at 27 atm. and 216 °C.[34] In this case double bond isomerisation occurs to give the conjugated product **200**.

When more activated aromatic systems, particularly phenols and aromatic ethers, are employed in the reaction with dienes a number of products are possible. The structure of the diene, the nature of substituents on the aromatic ring and the reaction conditions all influence the course of the reaction. Bader obtained six products **203-208** when phenol was mixed with isoprene in the presence of phosphoric acid.[35] In addition to the normal products of 1,4-addition to the diene, two tertiary alcohols and two chromans were formed (**Scheme 22**).



Scheme 22

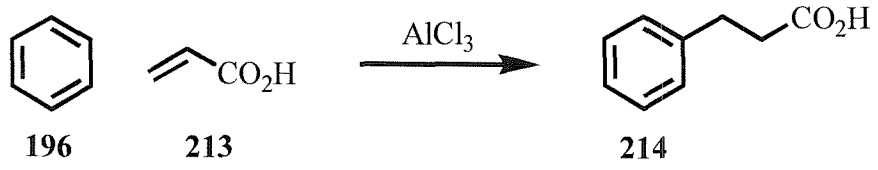
Of more interest to us is a study by Brunson and Kroeger of the reaction of 2,5-dimethyl-1,5-hexadiene **209** with various aromatics including phenol.[36] In that case the cyclialkylated product **210** formed on exposure to aluminium chloride. When the same reactants were mixed with sulphuric acid or boron trifluoride dietherate the acyclic material **211** was obtained (**Scheme 23**), though Brunson incorrectly assumed this was indane **212**, its identity was later confirmed by Jones and Schick.[37]



Scheme 23

Reaction of Aromatics with Unsaturated Esters and Carboxylic Acids

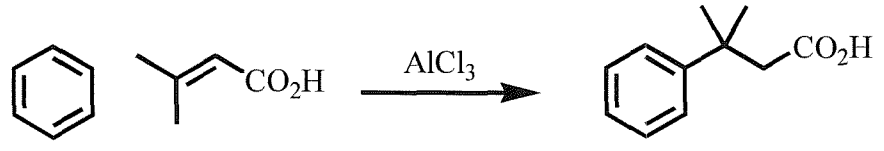
Eijkman first reported the addition of benzene and toluene to α,β-unsaturated acids.[38] The reaction of the former with acrylic acid yielded 3-phenylpropionic acid. The product arises from the 1,4 addition of the aromatic to the unsaturated acid (**Scheme 24**).



196 **213** **214**

Scheme 24

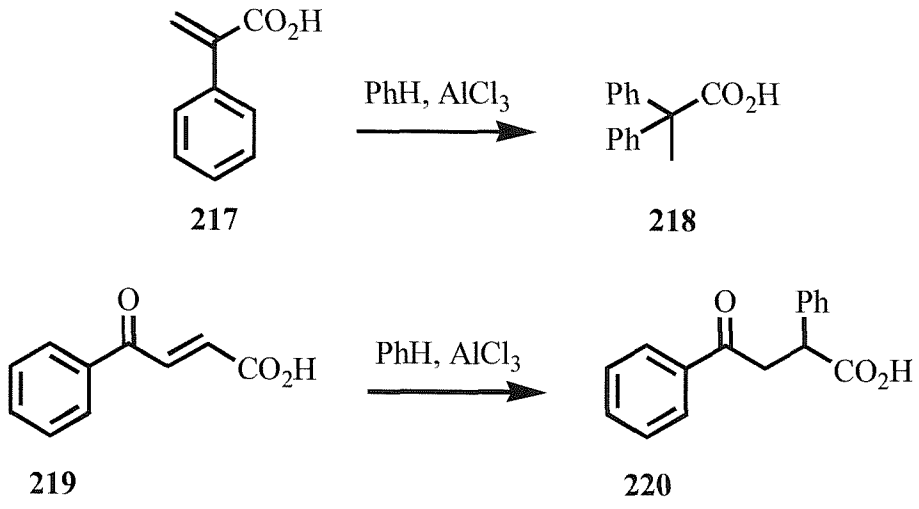
Eijkman also showed that hindered systems such as 3,3-dimethylacrylic acid **215** react in a similar manner (**Scheme 25**).



196 **215** **216**

Scheme 25

In general, β-addition to unsaturated carboxylates is common although α-addition may occur when the double bond polarity is altered sufficiently by some structural feature. Examples include α-phenylacrylic acid **217** and the dicarbonyl **219** (**Scheme 26**).[38]



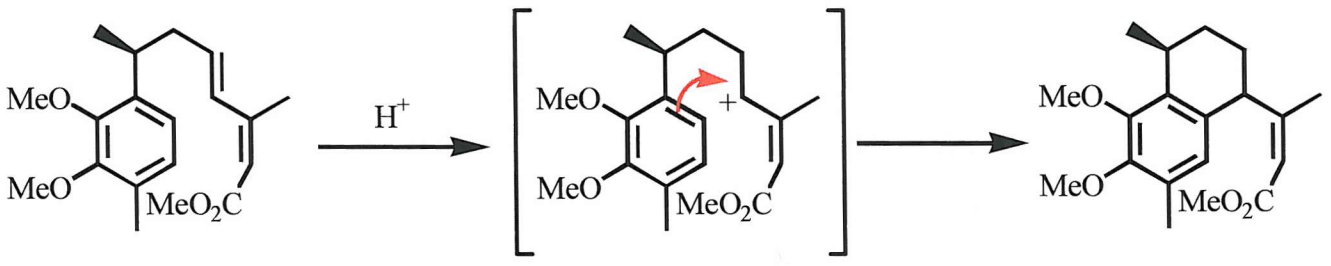
Scheme 26

In the latter example the electron withdrawing effect of the ketone far outweighs that of the acid, resulting in α-addition with respect to the acid.

Choice of Catalyst

Unreactive aromatics such as benzene require relatively strong Friedel-Crafts catalysts to achieve good yields of alkenylated aromatics. With the more reactive phenols and anisoles, milder catalysts are often employed since more forcing conditions tend to lead to polymerisation, ether cleavage or chroman formation. An example of this is provided by Bader who demonstrated that the reaction between butadiene and phenol was unsuccessful in the presence of aluminium chloride, concentrated sulphuric acid and phosphoric acid due to the formation of polymeric ethers and resinous material.[39] However, when exposed to borontrifluoride, aluminium chloride alcoholate or titanium tetrachloride, high yields of the alkenylated phenol were obtained.

In conclusion, we were hopeful that diene **184** in the presence of a suitable protic or Lewis acid would generate the stabilised carbocation **221**. A Friedel-Crafts cyclisation to bicyclic material **222** would then provide a key intermediate for the synthesis of pseudopterosin (**Scheme 27**). We were also hopeful that the cyclisation would proceed with some degree of diastereoselectivity.



184 **221** **222**

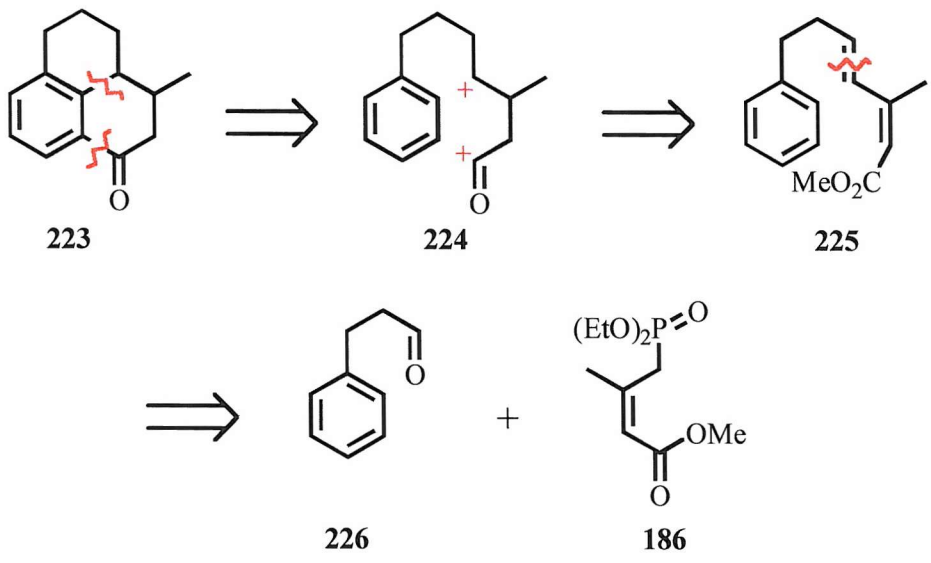
Scheme 27

Chapter 3

The Model Studies

The First Model Studies.

The aim of this programme is the synthesis of one of the pseudopterosins. We chose to begin our quest to this goal by examining a simplified system (**223**) in order to test our new cyclisation strategy (**Scheme 28**).

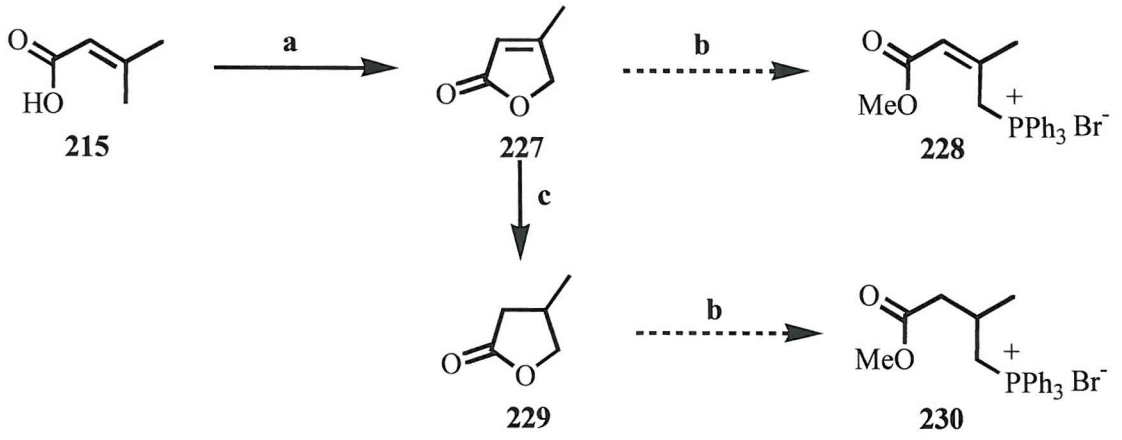


223 **224** **225**

226 **186**

Scheme 28

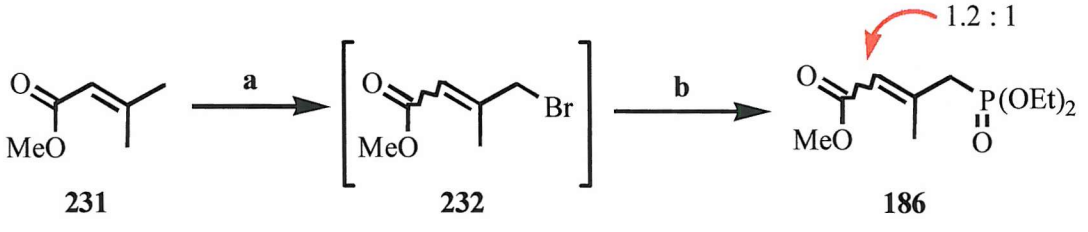
Given that 3-phenylpropionaldehyde (dihydrocinnamaldehyde) **226** is readily available, we turned our attention to the synthesis of the Wittig or Wadsworth-Emmons reagent **186**. Our first attempt involved persulfate oxidation of 3,3-dimethylacrylic acid **215** to give furanone **227**. Treatment with triphenylphosphine in methanolic HBr as described by Schmid *et al.* would then give the Wittig reagent **228** with the desired *(Z)*-geometry about the double bond.[40] Unfortunately this reaction proved troublesome since the furanone **227** was stable to the reaction conditions. Removal of the double bond by hydrogenation was readily achieved to give the γ-lactone **229**. Unfortunately this material also failed to provide Wittig reagent **230** (**Scheme 29**).



Reagents & Conditions: a. $K_2S_2O_8$, $MeCN/H_2O$, $AgNO_3$, $CuSO_4$. **b.** HBr, MeOH, PPh_3. **c.** H_2, Pd/C.

Scheme 29

We next sought to prepare the Wittig reagent **228** by allylic bromination of methyl 3,3-dimethyl acrylate and subsequent displacement of the halide with triphenylphosphine. Consultation of the literature however revealed that Wittig reagents of this type are particularly hygroscopic and decompose rapidly on standing in air.[41] The phosphonate ester (Wadsworth-Emmons reagent) **186** was therefore targeted. Bromination of **231** with *N*-bromosuccinimide and subsequent treatment of the bromide with triethyl phosphite yielded phosphonate ester **186** as an inseparable 1.2 : 1 mixture of *trans* : *cis* isomers (**Scheme 30**).[42]

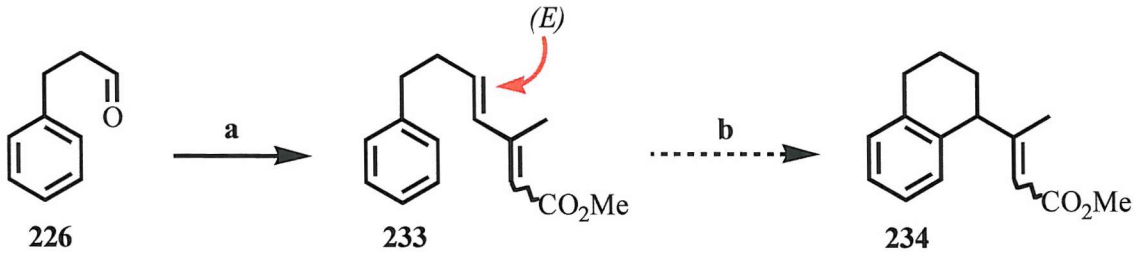


Reagents & Conditions: a. NBS, AIBN, $CHCl_3$, reflux. **b.** $P(OEt)_3$, 120°C.

Scheme 30

We were now in a position to couple the model aldehyde **226** and the Wadsworth-Emmons reagent **186**, and to investigate cyclisation of the resulting diene with Lewis and protic acids.

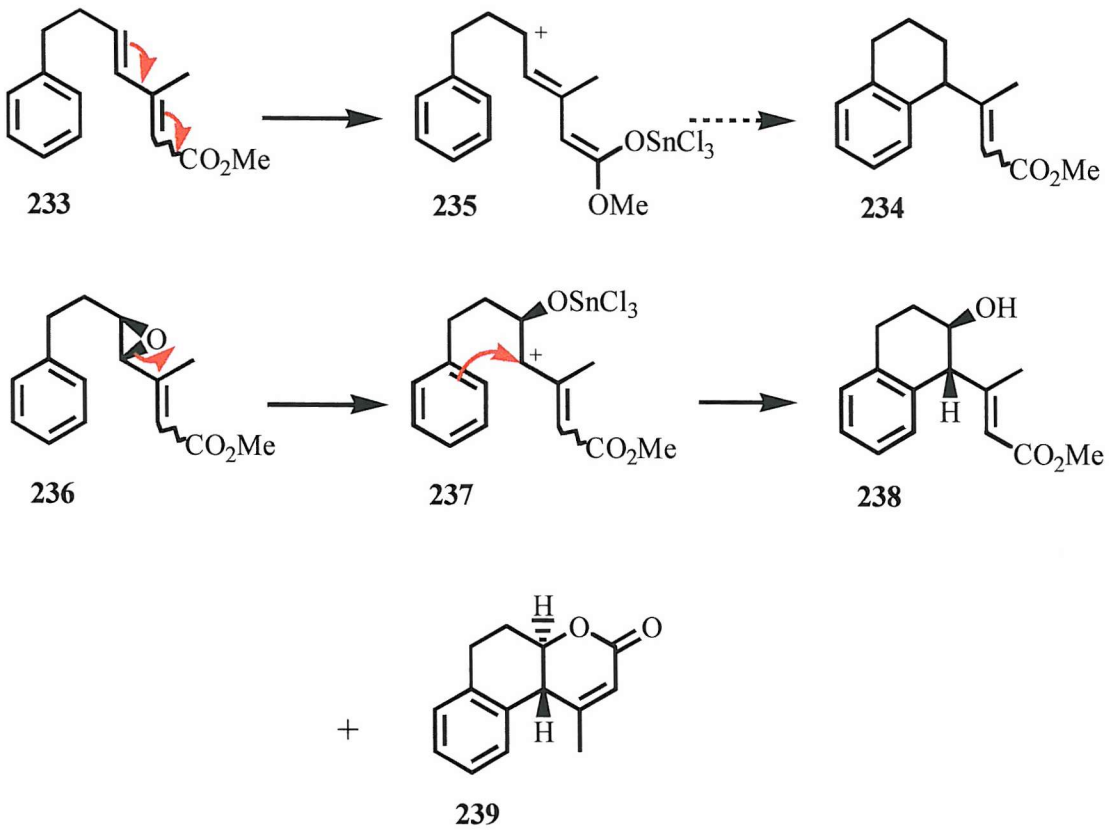
Coupling of the two reagents under standard Wadsworth-Emmons conditions resulted in an excellent yield of the desired diene **233**. Disappointingly however, exposure of this material to various Lewis acids ($TiCl_4$, $ZnCl_2$, $SnCl_4$, $BF_3.OEt_2$) and protic acids (H_2SO_4, HBr, PPA), failed to yield any of the desired bicyclic product **234**, the products of the reaction being either recovered diene **233** or products of decomposition (**Scheme 31**). A method to activate the disubstituted alkene was therefore sought.



Reagents & Conditions: a. 186, *n*BuLi, THF, 90%. **b.** H^+ or LA.

Scheme 31

Thus, peracid oxidation of the more electron rich double bond of **233** furnished a 1 : 1 diastereomeric mixture of epoxides **236**. Exposure to $SnCl_4$ gave the bicyclic alcohol **238** and the tricyclic material **239** in an overall 86% combined yield. Epoxidation presumably facilitates the Friedel-Crafts reaction not only by the introduction of bond strain but also by reversing the natural polarity of the double bond as depicted in **Scheme 32**.



Scheme 32

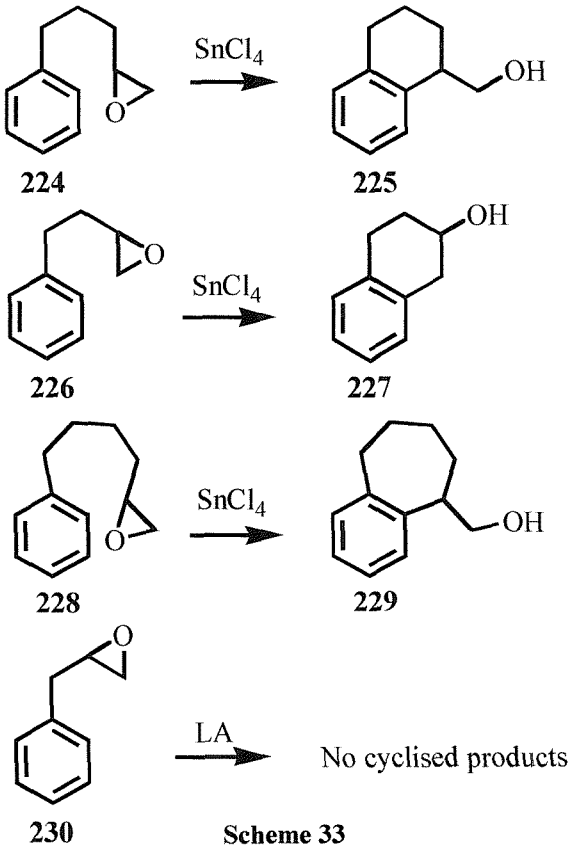
Friedel-Crafts Reactions with Epoxides

Although disappointed with the initial failure of our approach we were encouraged by the success of the epoxide cyclisation. We were keen to incorporate this reaction into our existing strategy and turned to the literature to explore the synthetic utility and applicability of this particular reaction to our approach.

The intramolecular alkylation of an aromatic ring utilising an epoxide as the electrophillic counterpart has until recently received little attention since it was first demonstrated in 1964 by Davidson and Norman.[43] However, in the last 20 years this is a reaction that has increasingly been exploited as a valuable method of constructing 6-7 membered rings fused to aromatic systems.[44] In addition to this, epoxides have an added dimension over other

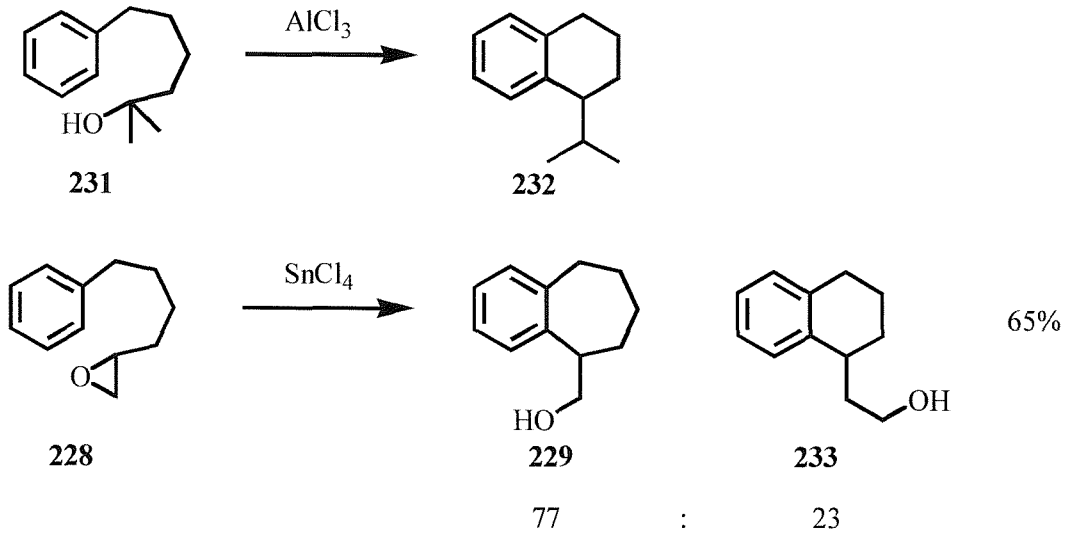
functional groups in that they can ring-open in either of two directions. The products resulting from the cyclialkylation reactions also contain a hydroxyl function two carbons removed from the aromatic nucleus. In 1983 Taylor *et al.* published a study of intramolecular arene alkylations with epoxides focusing in particular on their use for tetralin synthesis.[45]

Taylor showed that epoxides could be cyclised to give tetrahydronapthalenes in good yield by a number of different Lewis acids. Furthermore, seven membered ring cyclisations were found to be relatively easy, providing dilute reaction conditions were employed to minimise polymerisation, while five membered ring closures were least facile (**Scheme 33**). As expected cyclisation to a secondary centre was favoured over cyclisation to a primary epoxide position, while tertiary epoxides tended to undergo rearrangement rather than cyclisation.



Scheme 33

The observation that seven membered rings are relatively easy to form is in marked contrast to the comparable cyclisation with alcohols (**Scheme 34**). These favour formation of a six membered ring even when the alcohol is tethered to the arene with a five carbon chain, and cyclisation forms a tertiary centre rather than a quaternary centre.[45] It should be noted that exposure of the epoxide **228** to $SnCl_4$ gives two alkylation products **229** and **233**.[45]



Scheme 34

Mechanism

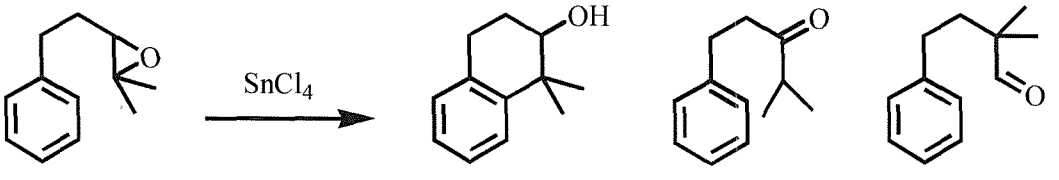
For the cyclisation of epoxides with primary and secondary centres, cyclisation occurs *via* simultaneous bond formation to the arene and bond scission of the epoxide (which may be considered as a borderline case of the S_N2 reaction). As discrete carbocations are not involved, cyclisations to form seven membered rings become facile compared to 1,2 hydrogen shifts or proton loss. The observation that cyclisation to a secondary epoxide centre is favoured over addition to a primary centre (which is not consistent with other S_N2 reactions) suggests that although weakly bound, the transition state complex of arene-epoxide-Lewis acid still contains carbocation character which is greatest at the secondary centre[46] (**Figure 4**).

234 Favoured

235 Less Favoured

Figure 4

In the case of cyclisation to tertiary epoxide centres it is likely that a discrete carbocation is formed as rearrangement competes with Friedel-Crafts cyclisation reactions. The reaction between tin tetrachloride and epoxide **236** provides a typical example[46, 47] (**Scheme 35**).

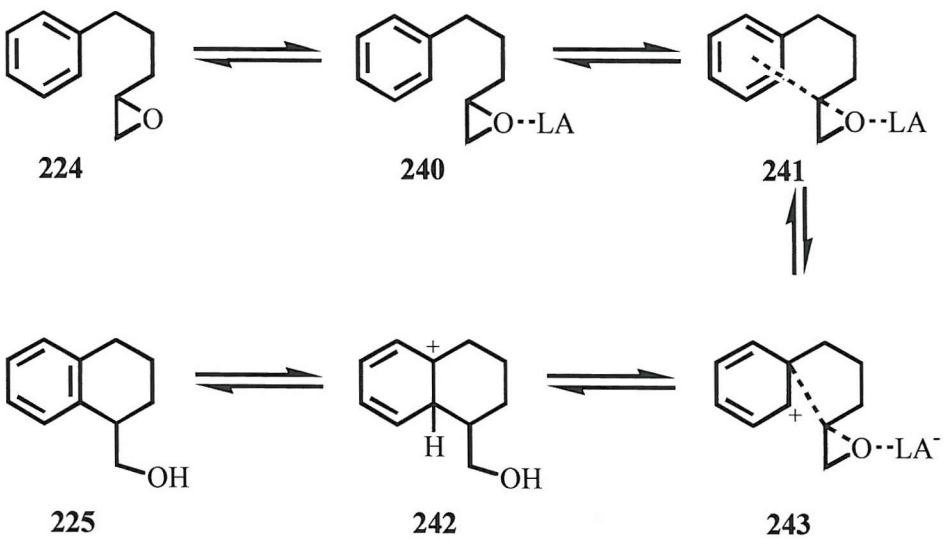


236 → **237** : **238** : **239**

29 : 29 : 42

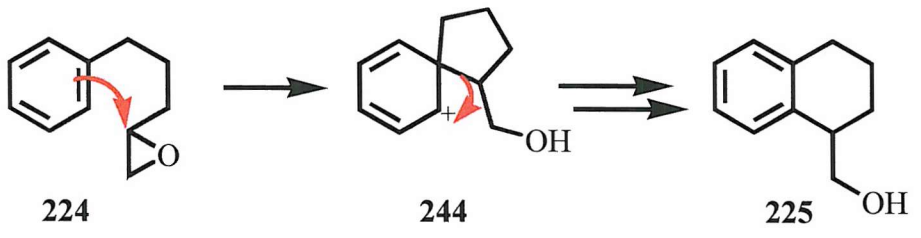
Scheme 35

Two mechanisms have been proposed for arene alkylations with epoxides. The first step is directly analogous to the Friedel-Crafts alkylation reaction (**Scheme 36**).[46]



Scheme 36

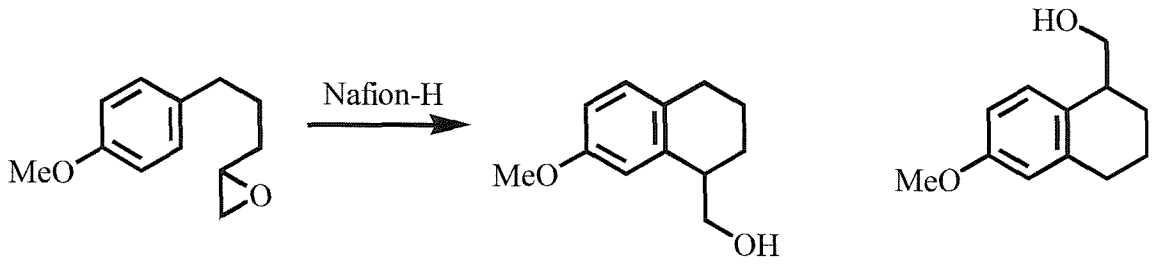
However, while cyclisation may result from direct attack of the electrophillic carbon atom at the *ortho* position (the so called Ar_2-6 mechanism) addition to the *ipso* position may also occur eg **224**. Rearrangement of the intermediate spiro compound **244** would then provide tetralin **225** after proton loss (**Scheme 37**).[46]



Scheme 37

Labelling experiments indicate that the reaction proceeds mainly *via* direct *ortho* attack, though the *ipso* pathway also occurs to some extent and is dependent upon the aromatic substitution pattern of the arene. Elings *et al.* in their investigation on solid acid catalysed

cyclialkylation reactions have concluded that the *ipso* pathway is negligible in their chosen system since only the rearrangement product arising from *ortho* attack is observed (**Scheme 38**).[48, 49]

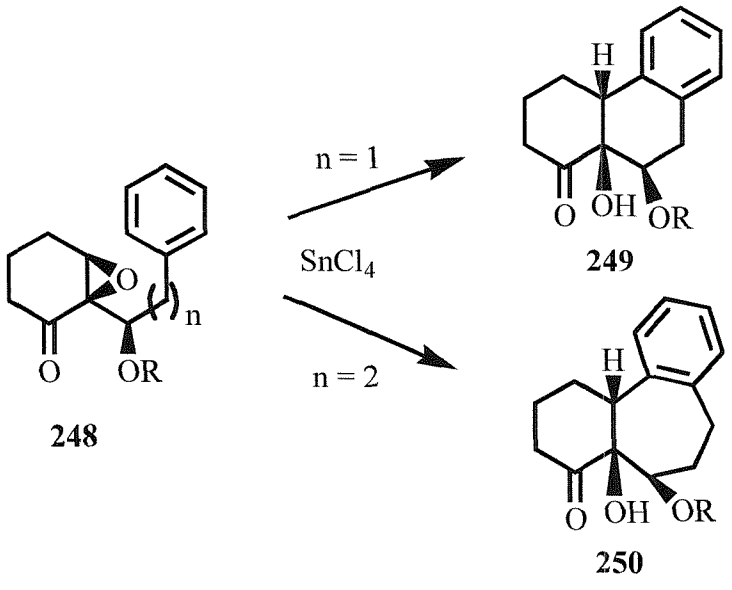


245 **246** **247**

100 : 0

Scheme 38

Despite the thorough investigation that this reaction has received in the last two decades, synthetic applications have been scarce. A notable exception to this is the synthesis of tricyclic keto diol compounds **249** and **250**, important intermediates in the synthesis of the more complex polyhydroxylated natural products gnididin, ingerol and grayarotoxin.[50] This application also demonstrates that, in S_N2 fashion, the reaction proceeds with inversion of configuration at the site of Friedel-Crafts attack (**Scheme 39**).



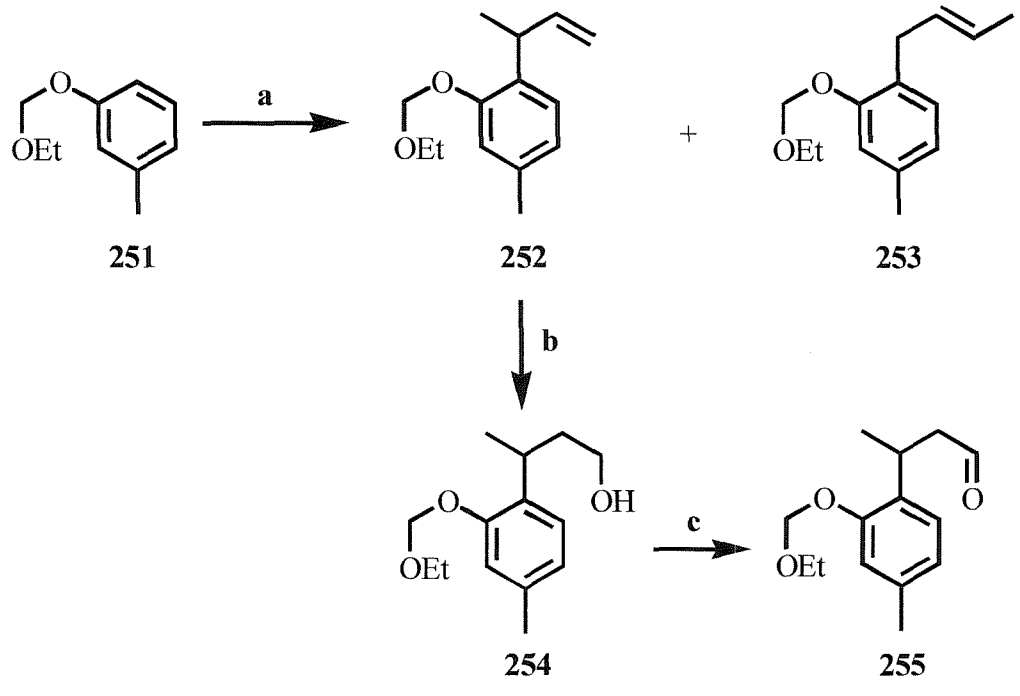
248 **249** **250**

Scheme 39

In conclusion, the use of an epoxide as the electrophillic counterpart in a Friedel-Crafts cyclialkylation reactions has potential application in our synthesis of pseudopterosin. A number of properties attract us to this method of constructing the first ring of pseudopterosin. Firstly, six membered ring cyclisations are favoured over five membered ring cyclisations. The aromatic ring in our system is highly activated potentially facilitating the reaction. Finally, as demonstrated above, due to the S_N2 character of the reaction mechanism, the reaction is stereospecific and rearrangement products are rare when a discrete carbocation is not formed.

The Effect of Aromatic Substitution

Encouraged by our model studies, we now wished to investigate the effect of aromatic substituents on the course of the reaction moving closer to the true aromatic nucleus of pseudopterosin. Our chosen starting material was ethoxymethyl protected *m*-cresol due to the ease of arene lithiation *ortho* to the protecting group.[51] The second aromatic hydroxy group could then be introduced at a later stage in the synthesis. In the first instance, we intended to synthesise the aldehyde **255** *via* lithiation of **251** and a transition metal (copper, palladium, zinc or nickel) mediated S_N2' addition to crotyl bromide or acetate.[52] Hydroboration and oxidation would then give alcohol **254**, a precursor of aldehyde **255** (**Scheme 40**).



Reagents & Conditions: a. (i)*t*BuLi, pentane. (ii) crotyl bromide / acetate, metal mediator, THF. **b.** (i) $BH_3.SMe_2$. (ii) NaOH, H_2O_2. **c.** Swern or Dess-Martin.

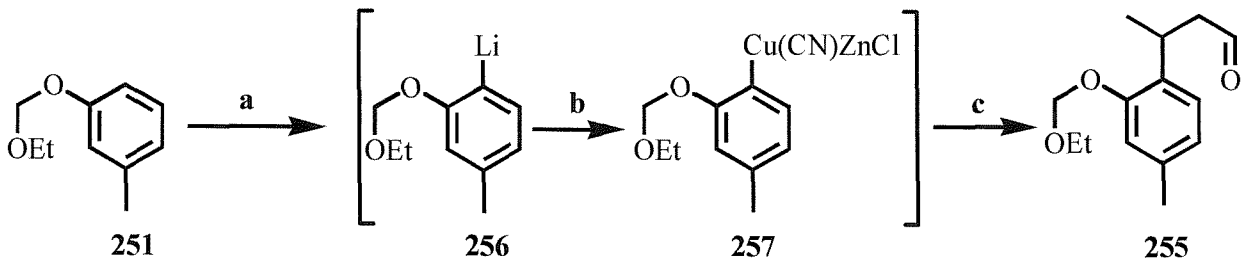
Scheme 40

Unfortunately, the S_N2' alkylation proved troublesome. Several reactions were undertaken and the results are summarised in the following table.

		Ratio of Products		
Electrophile	**Metal Mediator**	**252**	**253**	**Yield, %**
Crotyl Bromide	$CuI.P(OEt)_3$	1	1.8	80
``	$CuI.P(OEt)_3$ / $ZnCl_2$	1	6	83
``	$CuI.P(OEt)_3$ / $BF_3.OEt_2$	-	-	0
``	$PdCl_2$, PPh_3	1	15	88
``	$ZnCl_2$	-	-	0
Crotyl Acetate	$NiCl_2$, PPh_3	-	-	0

It is clear from these results that S_N2' displacement reactions with crotyl bromides and acetates are at best unpredictable, and that the precise ratio of products is likely to depend on a subtle balance between the nucleophilicity of the organometallic species and a combination of steric and electronic effects.

The key aldehyde **255** was therefore synthesised by a method developed in the Knochel laboratories.[53] Thus, *ortho* lithiation of **251** using *t*BuLi was followed by the addition of copper(I) cyanide, zinc chloride, lithium chloride and HMPA, to generate the mixed organometallic reagent **257**. Addition of crotonaldehyde and trimethylsilyl chloride to the reaction medium then furnished aldehyde **255**, albeit in a disappointing 36% yield after optimisation (the remainder being recovered starting material). (**Scheme 41**).

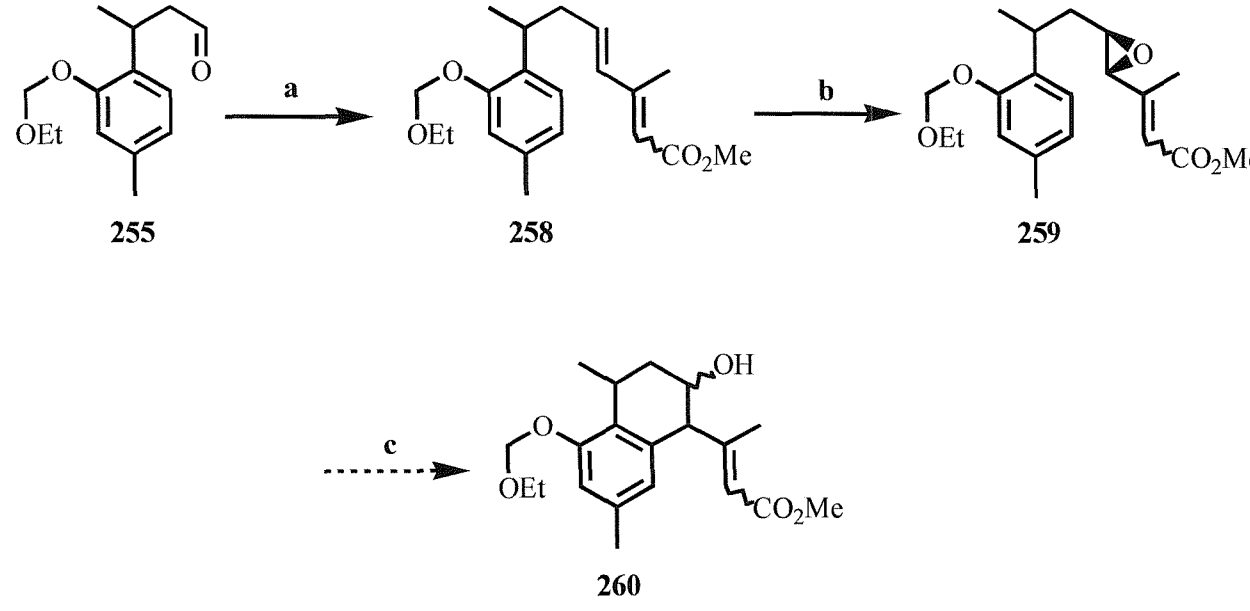


251 **256** **257** **255**

Reagents & Conditions: a. *t*BuLi, THF. **b.** CuCN, LiCl, $ZnCl_2$, HMPA. **c.** crotonaldehyde, Me_3SiCl, 36%.

Scheme 41

Attempts were made to improve the yield of this reaction using ultrasonic irradiation, a change of solvent and through the addition of Lewis acids. All of these proved unsuccessful. Nonetheless, with the desired aldehyde **255** and the Wadsworth-Emmons reagent **186** in hand we were in a position to proceed. Coupling these materials provided diene **258** as a 1 : 1 mixture of geometric isomers. Peracid oxidation then gave epoxides **259**. Unfortunately exposure of these to Lewis or protic acids did not lead to cyclisation, providing only recovered starting material or products of decomposition (**Scheme 42**).



255 **258** **259**

260

Reagents & Conditions: a. 186, *n*BuLi, THF, 58%. **b.** *m*CPBA, DCM. **c.** H^+ or LA.

Scheme 42

This apparent discrepancy between our model systems can be attributed to electronic effects. The aromatic oxygen substituent in **258** has the effect of biasing Friedel-Crafts alkylation reactions in favour of *ortho-* and *para-* alkylation. The HOMO of the aromatic ring in **258** resembles that of anisole (the oxygen atom being a more powerful donor than alkyl groups), whereas our earlier model system approximates that of toluene (**Figure 5**).[54]

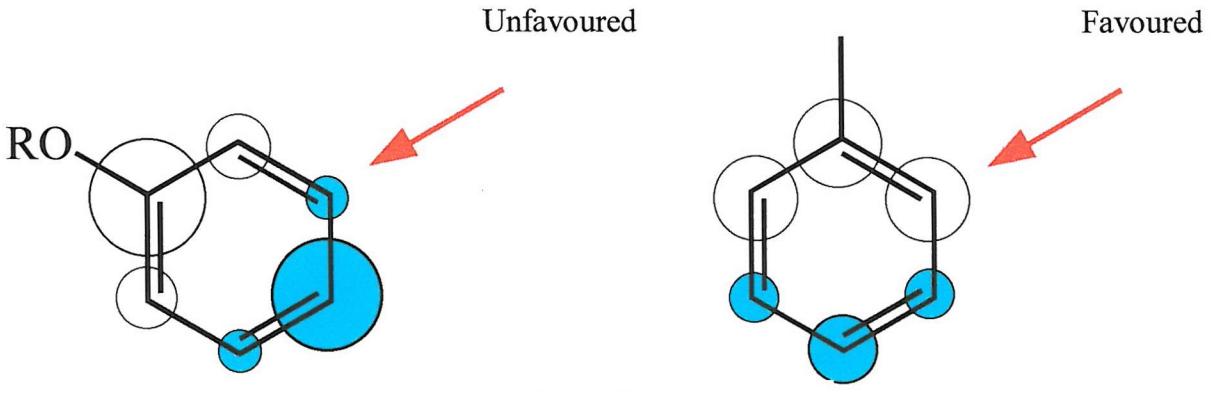
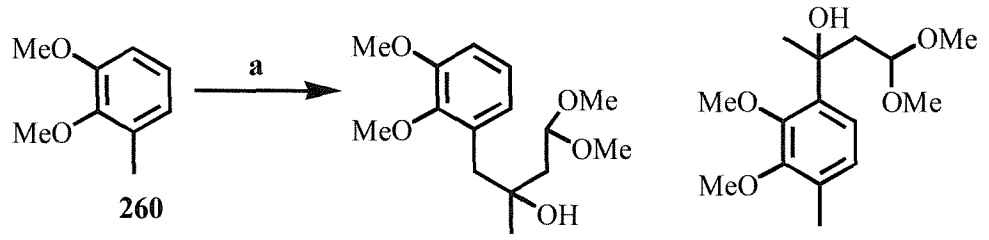


Figure 5

In light of these observations it was decided to attempt cyclisation with a more activated aromatic ring. Ideally *ortho*-lithiation of 3-methylveratrole, followed by transmetallation to the mixed copper zinc reagent analogous to **257** would facilitate Michael addition to crotonaldehyde giving the desired aldehyde. In practice this reaction proved troublesome. Though *ortho*-lithiation of 3-methylveratrole has been described by a number of groups,[55] this reaction has always yielded predominantly products derived from deprotonation of the methyl group. Thus, lithiation of **260** led to a 5 : 1 mixture of **261** and **262** after addition of acetylacetaldehyde dimethyl acetal (**Scheme 43**).



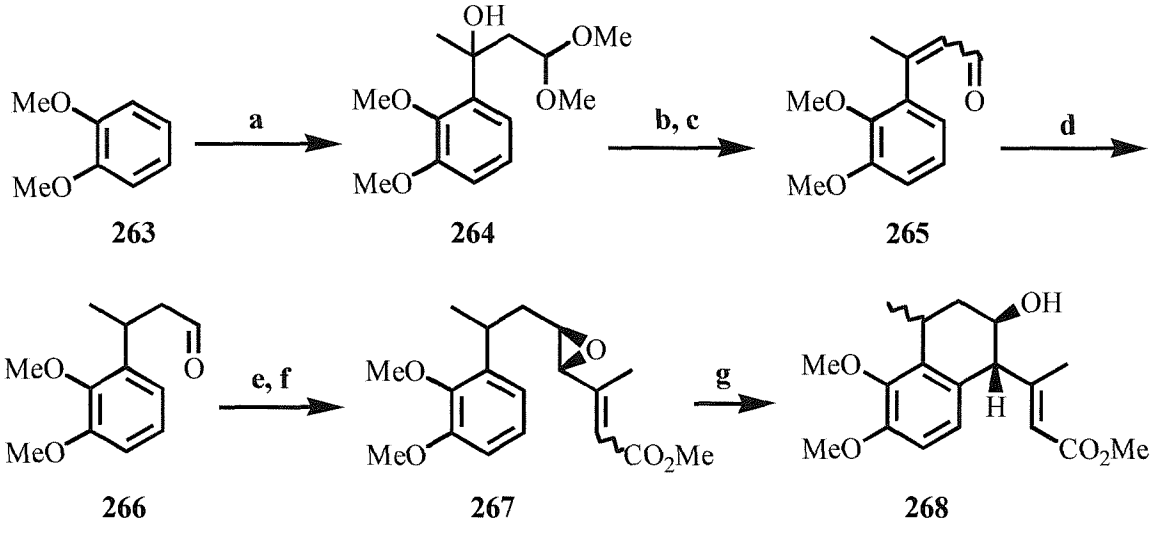
260 **261** **262**

5 : 1

Reagents & Conditions: a. *n*BuLi, TMEDA, Et_2O, $(MeO)_2CHCH_2COCH_3$

Scheme 43

To overcome this problem veratrole was chosen as the starting material with a view to introduce the aromatic methyl group at a later stage in the synthesis. We also modified our synthesis to avoid use of the highly toxic copper(I) cyanide and the potent carcinogen HMPA. The new route is described in **Scheme 44**.



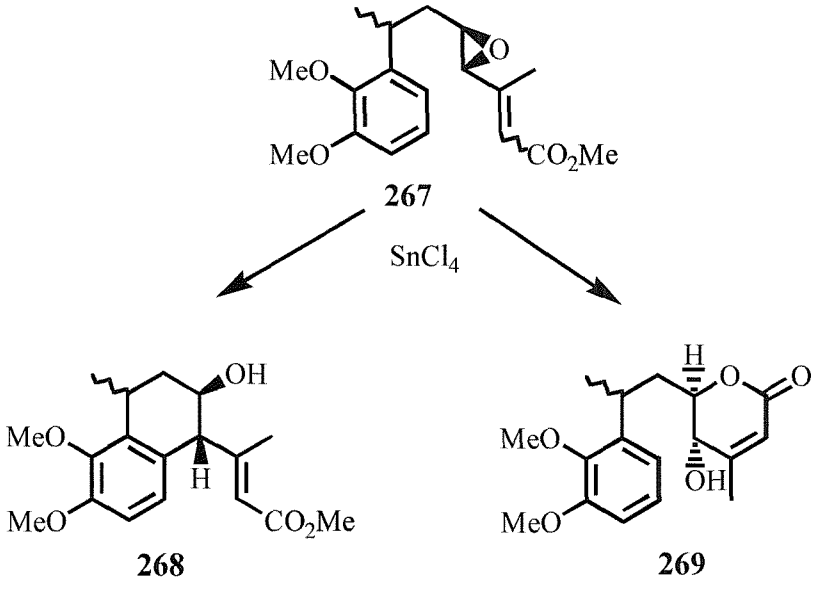
263 **264** **265**

266 **267** **268**

Reagents & Conditions: a. *t*BuLi, THF, $CH_3COCH_2CH(OCH_3)_2$, 29%. **b.** aq. HCl, Acetone. **c.** PPTS, PhMe 91%. **d.** H_2, Pd/C, cat. HCl 64%. **e. 186**, KO*t*Bu, 88%. **f.** *m*CPBA, 69%. **g.** $SnCl_4$, 35%.

Scheme 44

When **267** was exposed to tin(IV) chloride two pairs of diastereomeric products were formed, the products of Friedel-Crafts cyclisation **268** and the lactones **269**. It is interesting to note that the *(Z)*-alkenes of **267** provided lactones **269** while the *(E)*-alkenes gave the alcohols **268** (**Scheme 45**).



Scheme 45

Chapter 4

Extending the Approach

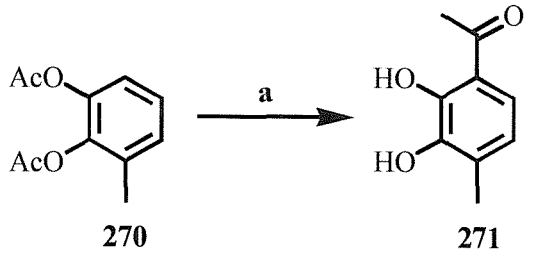
Extending the Approach

Though we had succeeded in effecting the first cyclisation, this approach was less than ideal and required some revision. A number of problems needed to be addressed. Firstly, the synthesis of the advanced precursor **267** is long and low yielding (particularly the first step and the key cyclisation reaction). Secondly, the epoxidation and subsequent annulation steps are unselective resulting in complex mixtures of diastereoisomers after cyclisation. Finally, the absence of the aromatic methyl group and the presence of a residual hydroxy group were undesirable.

Our attention now focused on other synthetic routes that would easily provide large quantities of material and allow the cyclisation step to be investigated more thoroughly. We also hoped to investigate methods of preparing the 3,6-disubstituted veratrole derivatives which contained an aromatic ring appropriately functionalised with respect to pseudopterosin. A number of possibilities were explored and are outlined in the following sections.

The Fries Rearrangement

Following the procedure of Cullinane and Edwards,[56] treatment of 3-methylcatechol diacetate with fused aluminium chloride resulted in an 18% yield of the desired *ortho*-acetophenone **271** with none of the corresponding *para* product being observed (**Scheme 46**). It is interesting to note that this reaction is extremely sensitive to variations in temperature. The desired product is only obtained if a finely ground mixture of dry aluminium chloride and the diacetate **270** are rapidly heated to 120°C, maintained at this temperature for 5 minutes, rapidly raised to 165°C over 5 minutes, then maintained at this temperature for a further 20 minutes. The use of an oversized reaction vessel is also essential to maximise the rate of heat transfer from the heat source to the reaction mixture.

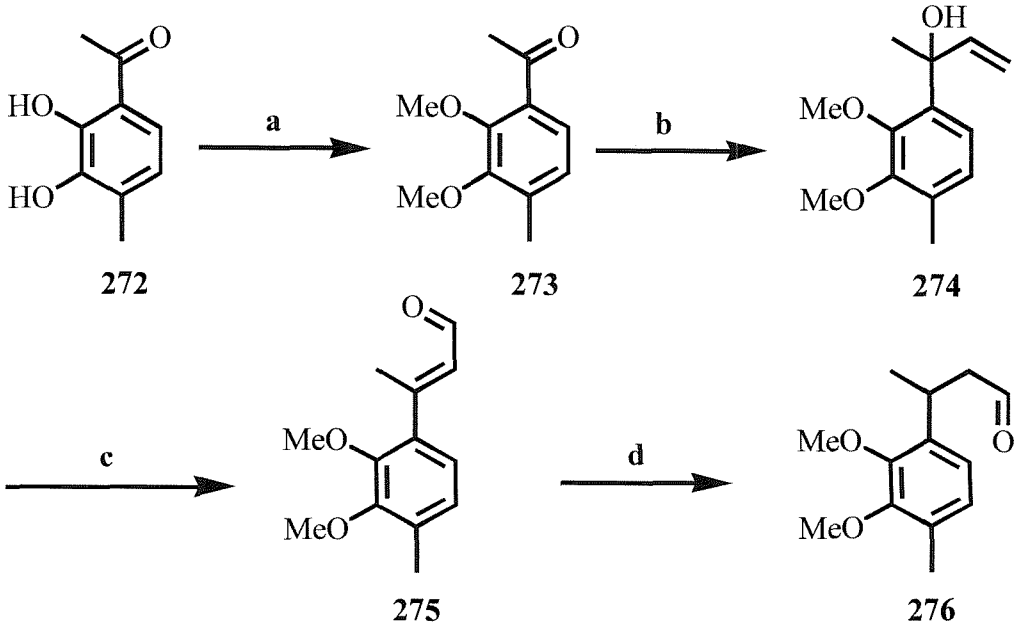


270 **271**

Reagents & Conditions: a. $AlCl_3$, 120°C-165°C, 18%.

Scheme 46

Methylation of **271** followed by Grignard addition of vinylmagnesium chloride yielded the tertiary alcohol **274** in excellent yield. Treatment of **274** with pyridinium chlorochromate (PCC) then induced oxidation with allylic rearrangement to give the aldehyde **275** as predominantly the *(E)* geometric isomer. This was hydrogenated under acidic conditions to give the saturated aldehyde **276** (**Scheme 47**).



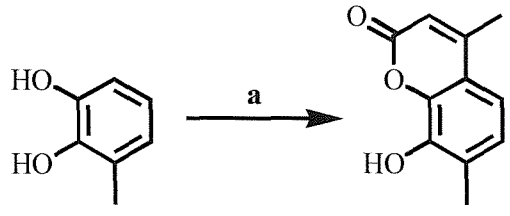
272 **273** **274** **275** **276**

Reagents & Conditions: a. KOH, MeI, DMSO, 96%. **b.** CH_2=CHMgCl, THF, 99%. **c.** PCC, DCM, 56%. **d.** H_2 Pd/C, MeOH, cat. HCl.

Scheme 47

The Pechmann Condensation Reaction

First described by Pechmann *et al.* in 1883, this reaction involves the condensation of acetoacetate derivatives with phenols in the presence of a suitable dehydrating reagent to yield substituted coumarins.[57] In our case, 3-methylcatechol was coupled with ethyl acetoacetate in concentrated sulfuric acid (acting both as solvent and dehydrating agent), to yield substituted coumarin **277** in 23% yield (**Scheme 48**).



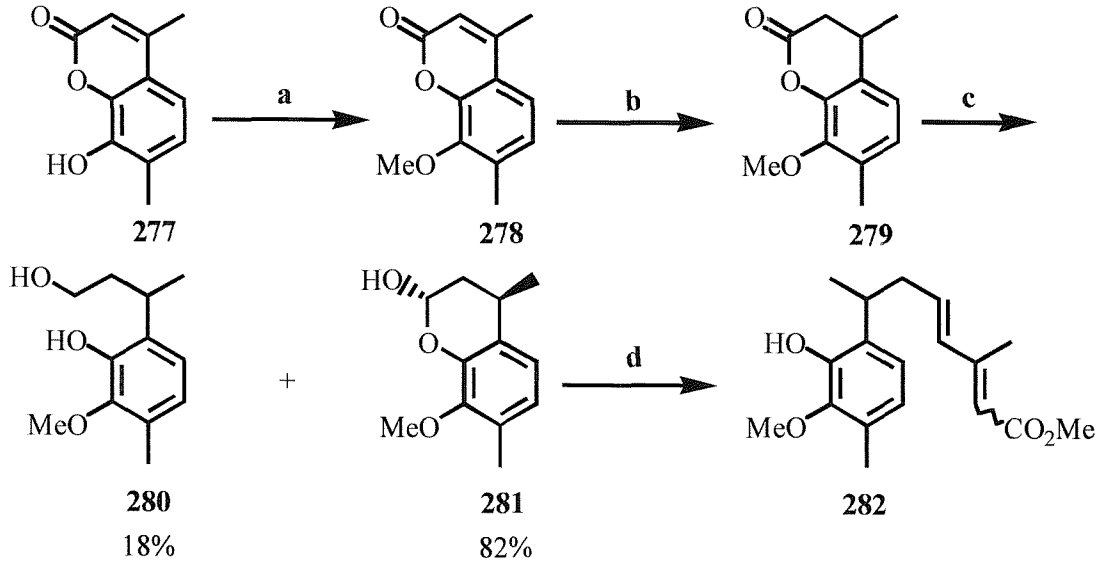
141 **277**

Reagents & Conditions: a. EAA, cH_2SO_4, 23%

Scheme 48

Attempts were made to improve the yield of this reaction by employing a number of methods described in the literature,[58] however these proved unsuccessful. Nonetheless, the reaction does allow access to multigram quantities of coumarin **277** from cheap and readily available starting materials. In addition, this approach provides a method of distinguishing between the two phenolic moieties, which may be important later in the synthesis when a sugar residue must be attached to the catechol. The aromatic ring of this molecule also contains the desired substitution pattern for the pseudopterosin skeleton, and the alkene geometry is fixed, potentially allowing the control of the absolute stereochemistry at the C7 centre through a catalytic asymmetric hydrogenation reaction[59] (a procedure which is well documented in the literature). The asymmetric hydrogenation of a related coumarin has also recently been described by McGuire *et al.*[60] We therefore chose to modify our approach to incorporate the coumarin **277**.

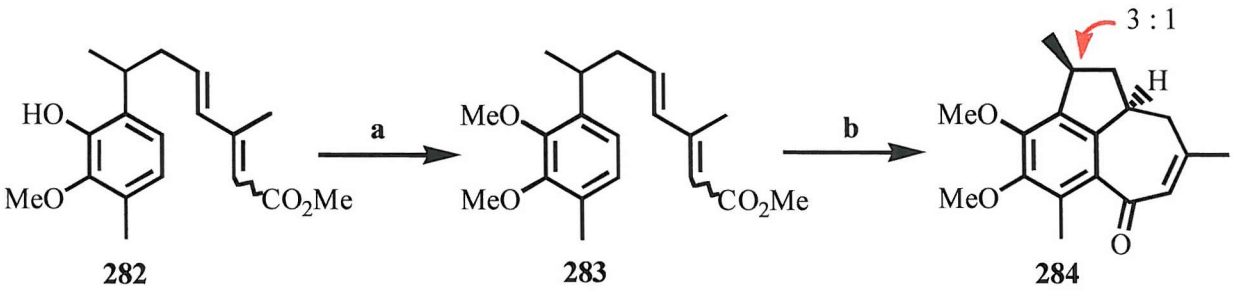
The New Approach



Reagents & Conditions: a. K_2CO_3, MeI, $(CH_3)_2CO$, reflux, 94%. **b.** H_2, Pd/C, EtOAc, 99%. **c.** DIBAL-H, THF, -78°C, 100%. **d. 186**, KO*t*Bu, THF, 59%.

Scheme 49

Incorporation of the coumarin **277** proved to be relatively straightforward. Protection of the remaining phenol as its methyl ether followed by hydrogenation of the double bond gave chromanone **279**. Slow addition of diisobutylaluminium hydride at low temperature then provides an 82 : 18 mixture of the lactol **281** and diol **280** in quantitative yield. Lactol **281** could then be coupled with the Wadsworth-Emmons reagent **186** to give **282** as a 3 : 2 mixture of *(Z)* and *(E)* isomers. Protection of the phenols **282** as their methyl ethers **283** then allowed us to examine the intramolecular Friedel-Crafts alkylation reaction. Though no reaction was observed when **283** was treated with methanesulfonic acid at 0°C in DCM, heating a mixture of these materials in the absence of solvent at 90°C for 20 minutes gave tricycle **284** as a 3 : 1 mixture of diastereoisomers and in 21% yield (**Scheme 50**).

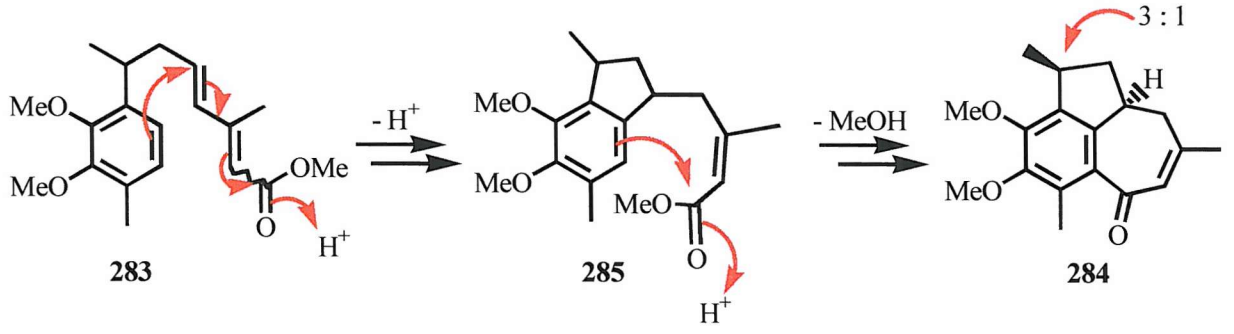


282 **283** **284**

Reagents & Conditions: a. K_2CO_3, MeI, $(CH_3)_2CO$, reflux, 94%. **b.** CH_3SO_3H, 90°C, 21%.

Scheme 50

That cyclisation initially leads to a five membered ring suggests that the reaction proceeds *via* protonation of the carbonyl group followed by a 1,6-addition to the conjugated alkene. The *(Z)*-alkene in **283** then helps to promote the second ring closure reaction (**Scheme 51**) while the *(E)*-alkene, akin to **285** is lost as undesired products.



283 **285** **284**

Scheme 51

Although disappointed by this observation, the reaction mechanism follows the course expected on electronic grounds.

Chapter 5

A Modified Approach to Pseudopterosin

Our Modified Approach to Pseudopterosin

Clearly we wished to control the cyclisation reactions and bias them to favour formation of a six membered ring. Our first thought on this matter was to include a functional group X that would stabilise a carbocation at the γ position relative to the carbonyl group. A Friedel-Crafts reaction would then give tetrahydronapthalene **289** (**Figure 6**).

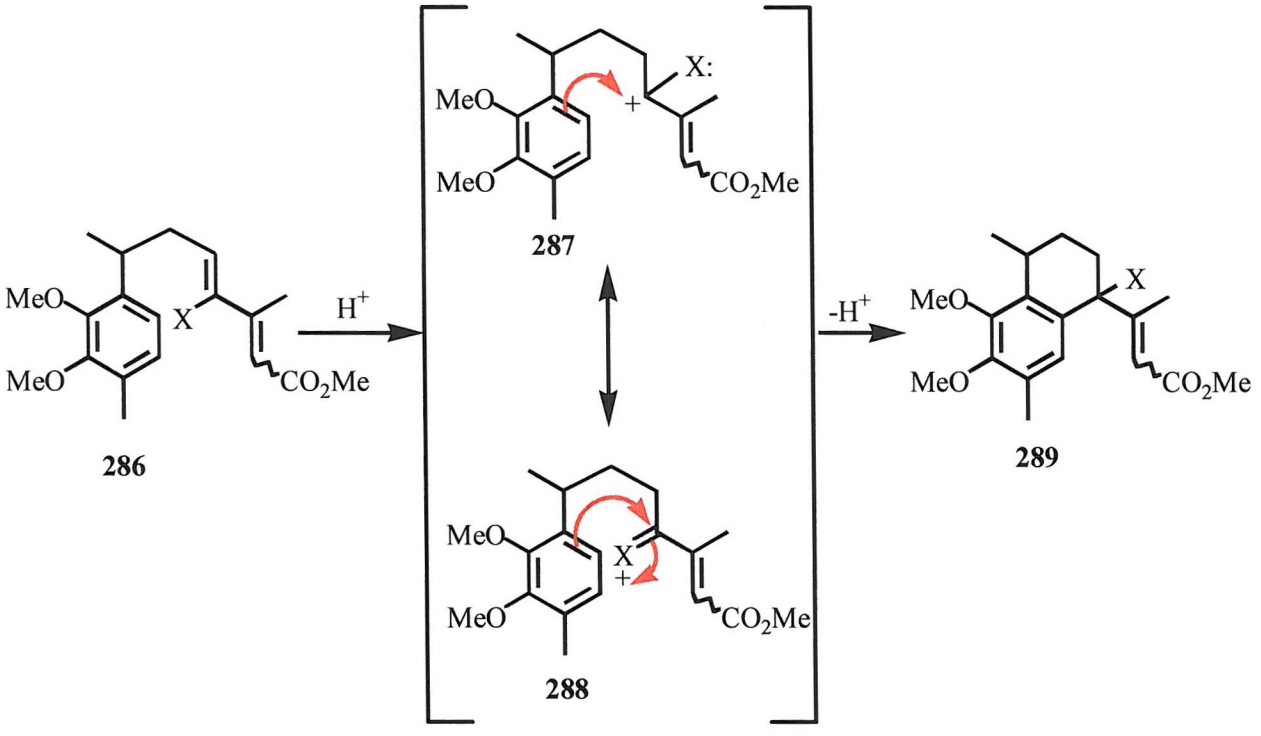
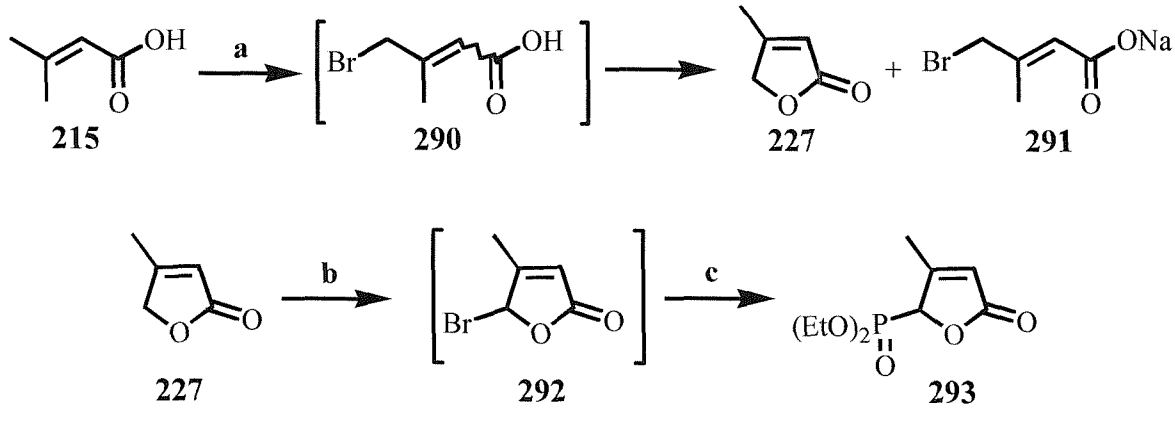


Figure 6. Proposed strategy for achieving cyclisation to a tetralin

The ideal candidates for the stabilising group X are oxygen and nitrogen, as these have lone pairs available to stabilise the intermediate carbocation. Our earlier work had shown that furanone **227** could be prepared easily *via* allylic bromination and this seemed ideal for the construction of a Wadsworth-Emmons reagent containing an oxygen atom at the allylic position. Indeed bromination of the furanone followed by displacement with triethylphosphite yielded phosphonate **293 (Scheme 52)**.[61]



Reagents & Conditions: a. (i) NBS, AIBN, CCl_4, Reflux. (ii) aq. $NaHCO_3$. **b.** NBS, AIBN, CCl_4, Reflux. **c.** $P(OEt)_3$.

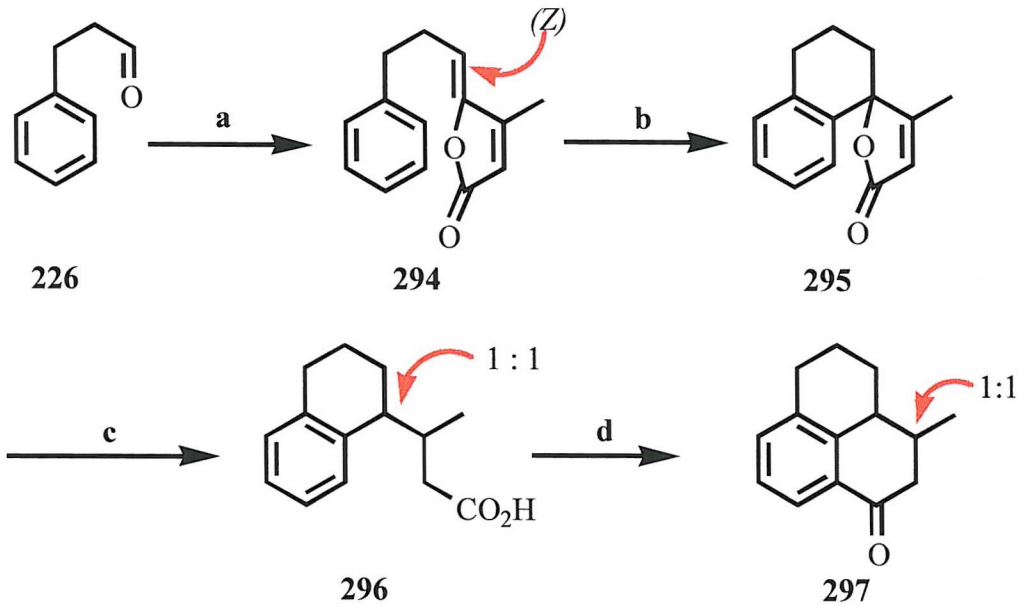
Scheme 52

We were now in a position to investigate the reaction of this novel Wadsworth-Emmons reagent with aldehydes and to explore possible cyclisation reactions.

The Second Model

We first examined the coupling of **293** with the model aldehyde 3-phenylpropionaldehyde **226**. We were delighted to observe that the olefination proceeded smoothly to give **294** as a single geometric isomer. Furthermore exposure of **294** to methanesulfonic acid resulted in a 91% yield of the spirofuranone **295**. Hydrogenation of the double bond in **295** additionally

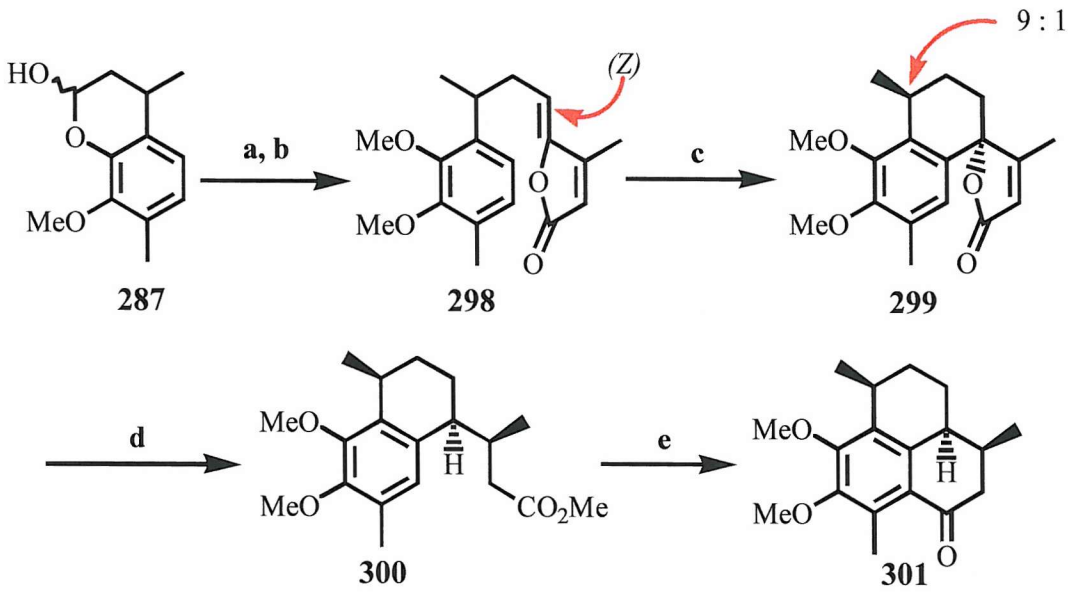
effected simultaneous hydrogenolysis of the benzyl ether to yield the acid **296** as a 1 : 1 mixture of diastereoisomers. Treatment of **296** with methanesulfonic acid then gave phenalenone **297** in excellent yield (**Scheme 53**).



Reagents & Conditions: a. 293, KO*t*Bu, THF, 88%. **b.** CH_3SO_3H, 90°C, 91%. **c.** H_2, Pd/C, EtOAc, 100%. **d.** CH_3SO_3H, 90°C, 90%.

Scheme 53

This new approach was now applied to the real system. Wadsworth-Emmons coupling of **293** and lactol **287** gave **298** after protection of the intermediate phenol as its methyl ether. Exposure of this compound to triflic acid at 78°C then underwent cyclisation to give the spirofuranone **299** as a 9 : 1 mixture of diastereoisomers (**Scheme 54**) which could be separated by crystalisation. Notably triflic acid was used in this case rather than methanesulfonic acid as the latter required higher reaction temperatures which lead to product decomposition. Even with triflic acid the reaction requires careful control of temperature, decomposition being observed above 80°C, while at 60°C no reaction was observed.



Reagents & Conditions: a. 293, KO*t*Bu, THF, 88%. **b.** K_2CO_3, MeI, $(CH_3)_2CO$, reflux, 87%. **c.** TfOH, 91%. **d.** H_2, Pd/C, MeOH, cat. HCl, 94%. **e.** TfOH, 90%.

Scheme 54

Hydrogenation of **299** under neutral conditions failed to effect hydrogenolysis of the benzyl ether. Under acidic conditions however, using methanol as the solvent, gave ester **300**. Unfortunately the reaction appeared to proceed with retention of configuration at the C4 centre. This result was particularly disappointing since literature precedent indicated that hydrogenolysis reactions proceed with inversion of configuration in most cases.[62] Treatment of **300** with triflic acid again induced cyclisation to give tricycle **301**, the identity of which was confirmed by X-ray crystallography.

The Origin of Diastereoselectivity

The cyclisation of enol ether **298** to spirofuranone **299** proceeds with excellent diastereoselectivity and we presume that this is controlled by the C7 methyl group. Thus, cyclisation favours transition state **302** over **303** where the incoming furanone and the C7 methyl groups are above and below the plane of the arene respectively (**Figure 7**).

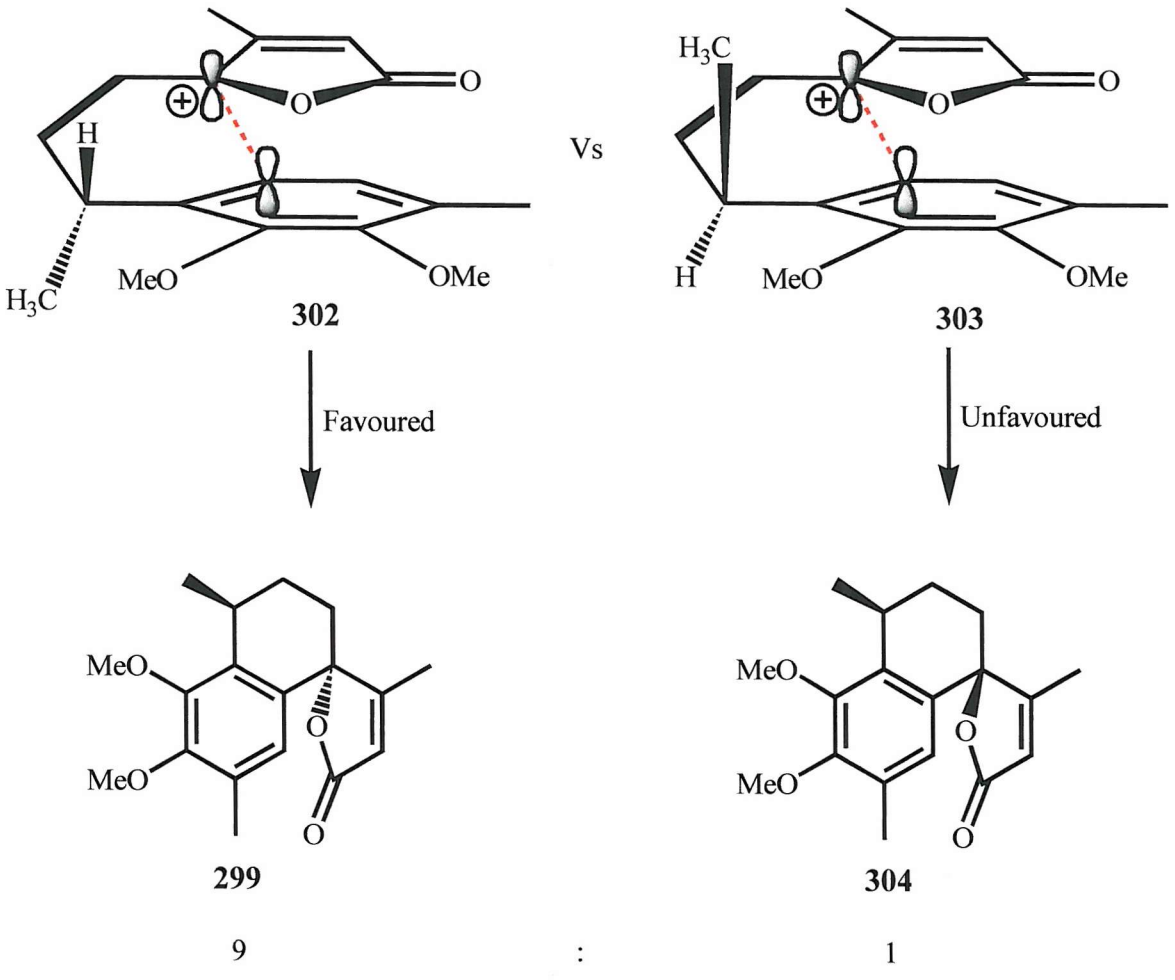
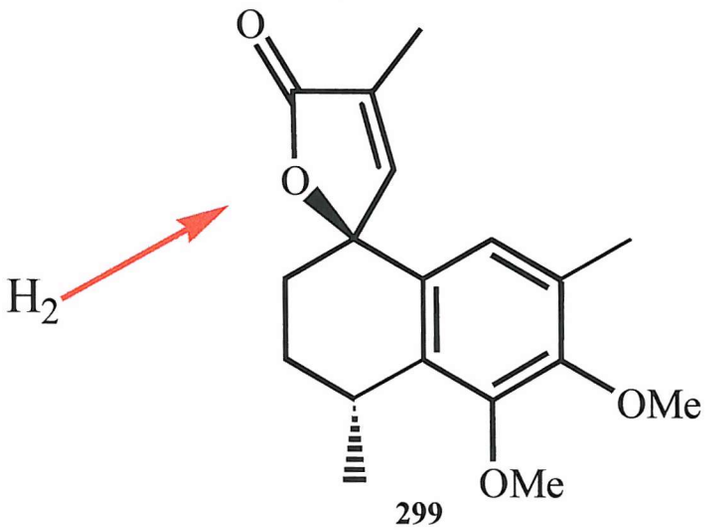


Figure 7

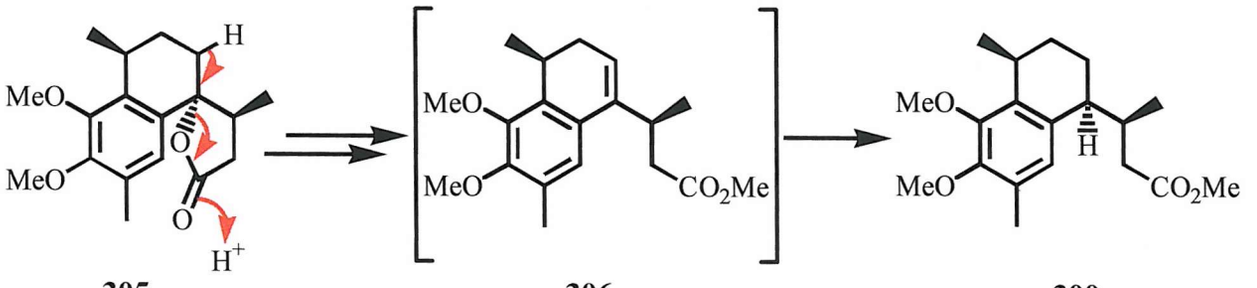
The hydrogenation also proceeds with excellent diastereoselectivity. The origin of this selectivity is explained in **Figures 8** and **10**. The two faces of the alkene in furanone **299** are significantly different in terms of their steric encumbrance. Hydrogenation therefore occurs exclusively from the least hindered face as shown below (**Figure 8**).



299

Figure 8

As the benzylic hydrogenolysis proceeded with retention of configuration at the benzylic centre, the reaction cannot proceed *via* a palladium stabilised benzylic cation. Instead, it appears that an elimination occurs under the acidic reaction conditions. Hydrogenation of the intermediate styrene **306** is then directed to the least hindered face, once again directed by the axial methyl group at C7 (**Scheme 55**, **Figure 10**).



305 **306** **300**

Scheme 55

This hypothesis is supported by the fact that if the hydrogenation reaction is repeated in the absence of acid the spirolactone **305** is isolated in quantitative yield. The structure and stereochemistry of spirolactone **305** and the tricycle **301** was confirmed by X-ray

crystallography which clearly showed the methyl group at C7 occupying an axial orientation in both cases (**Figure 9**).

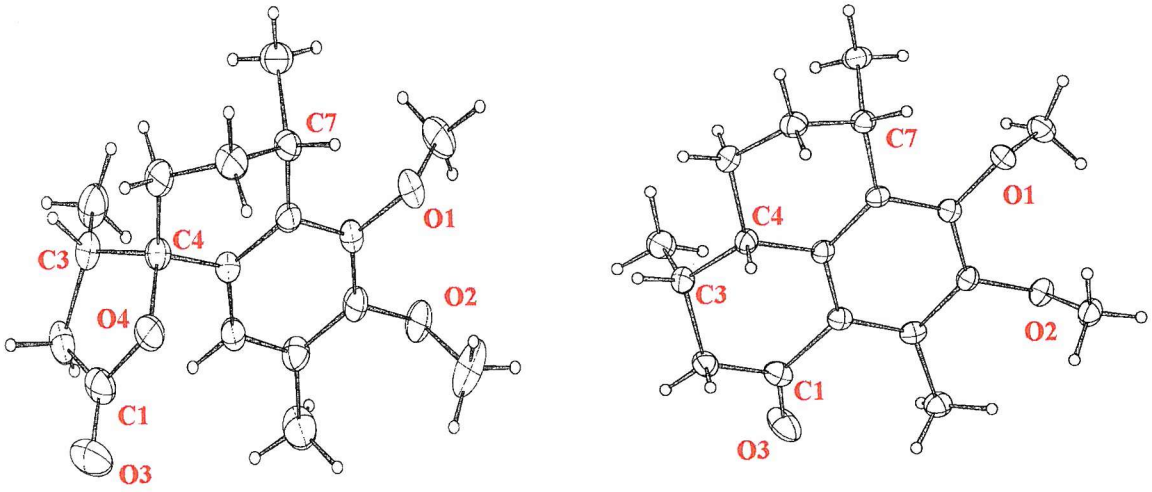


Figure 9 X-Ray crystal structure of spirolactone **305** and tricycle **301** with the stereogenic centres labelled according to pseudopterosin nomenclature.

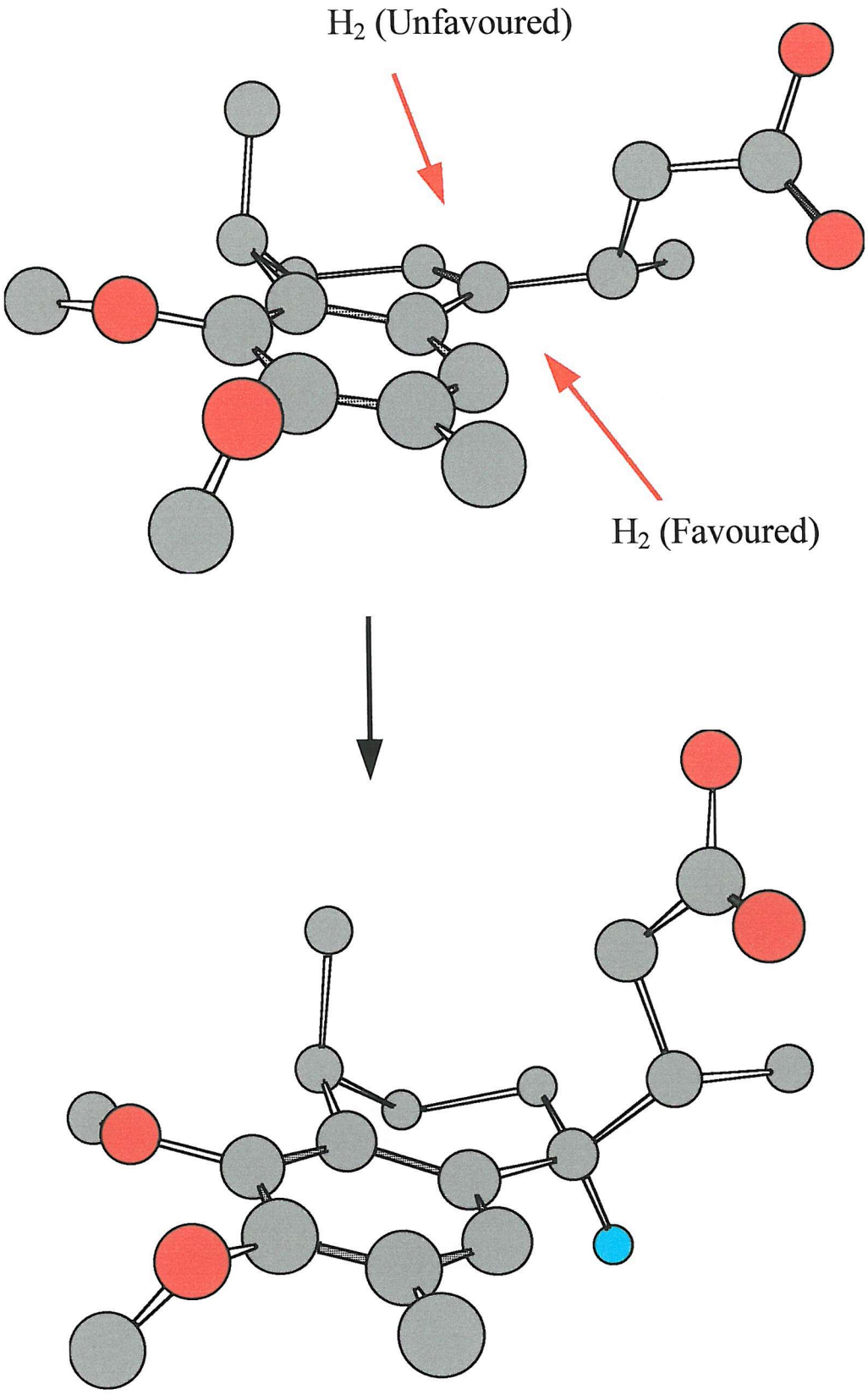


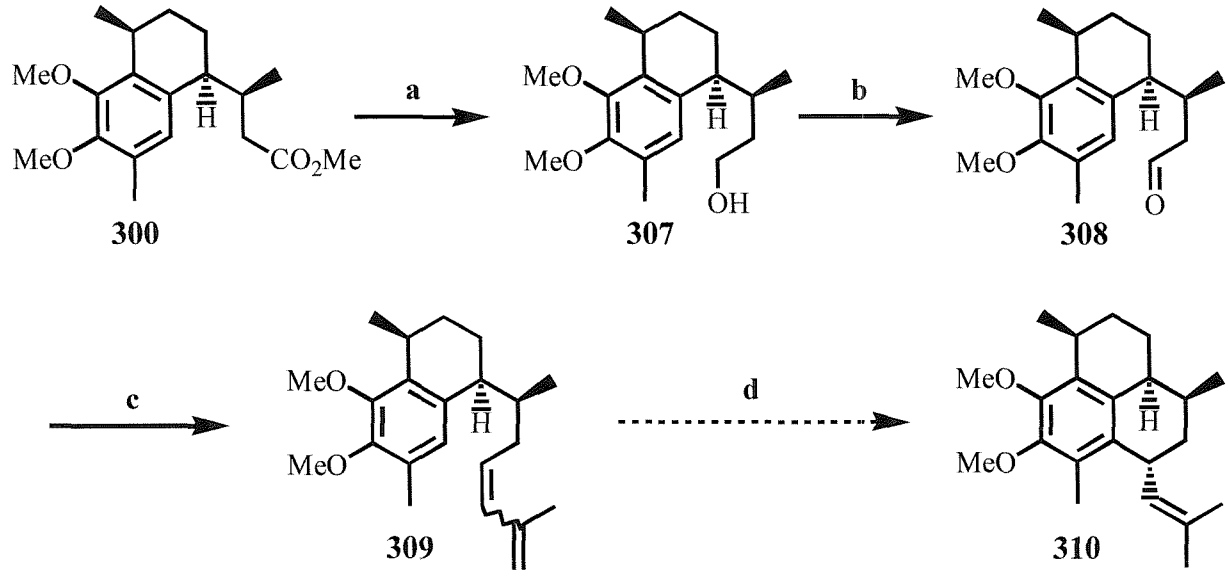
Figure 10 Explanation of diastereoselectivity in the hydrogenolysis reaction

Chapter 6

Towards a Synthesis of C4-epi-Pseudopterosin & Studies Towards a Natural Epimer

Towards A Full Total Synthesis of C4-epi-Pseudopterosin

Having developed a route to tricycle **301** our attention now focussed on establishing an endgame strategy for the synthesis of C4-*epi*-pseudopterosin aglycone **310**. We hoped that the methodology developed would, in due course, also be applicable to the total synthesis of a natural epimer.



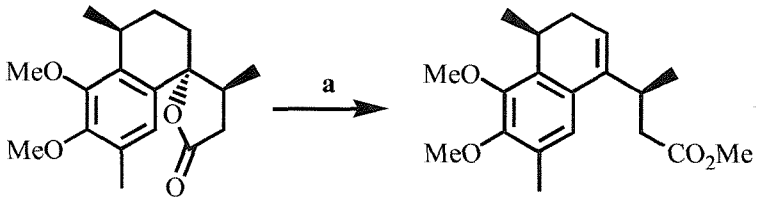
Reagents & Conditions: a. $LiBH_4$, Et_2O. **b.** Dess-Martin periodinane. **c.** KO*t*Bu, THF. **d.** CF_3SO_3H.

Scheme 56

Reduction of the methyl ester **300** followed by Dess-Martin oxidation of the resulting alcohol **307** gave aldehyde **308**. A Wittig olefination with methallyl phosphorane next furnished diene **309** as a 1 : 3 mixture of *trans* and *cis* isomers. Alas, exposure of this mixture to triflic acid in the absence of solvent led to decomposition of the reaction products.

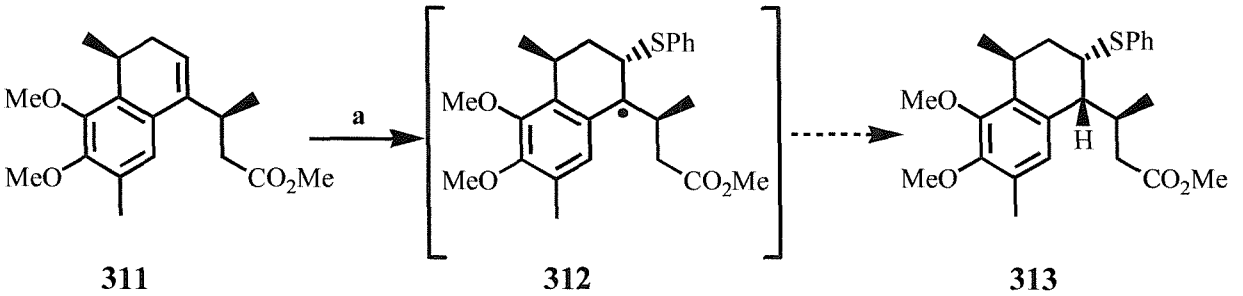
Having established this route (**Scheme 56**), our efforts were again focused on methods to control the stereochemistry at the C4 centre so as to prepare the ground for a synthesis of the

pseudopterosin A-F aglycone. Our first approach to this was to induce elimination of the spirolactone **305** to the styrene **311** (**Scheme 57**). Addition of a bulky thiyl radical to the olefin ought then to proceed with good stereocontrol leading to the intermediate **312**.[63] Delivery of a hydrogen atom to the least hindered face would then provide **313** with the correct configuration at C3, C4 and C7. Disappointingly, we were unable to effect the addition of a thiyl radical to the double bond, possibly due to the high steric demands imposed by this particular system (**Scheme 57**).



305 **311**

Reagents & Conditions: a. MeOH, cat. HCl, 99%

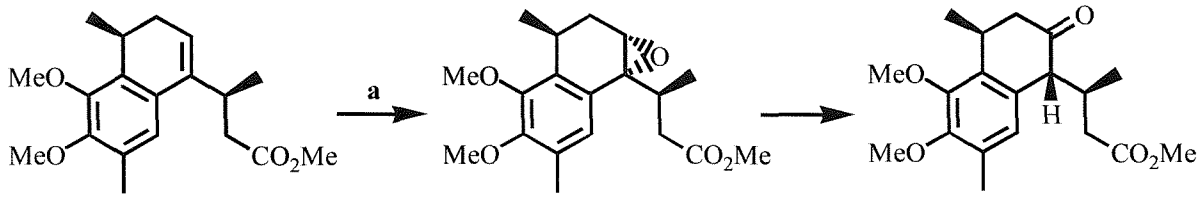


311 **312** **313**

Reagents & Conditions: a. PhSH, AIBN, PhMe, 110°C.

Scheme 57

Our next thought was to induce a 1,2-hydride shift *via* epoxidation of the double bond. Epoxidation would again be expected to proceed to the least hindered face. Exposure to a suitable Lewis or protic acid would give rise to the ketone **315** (**Scheme 58**).

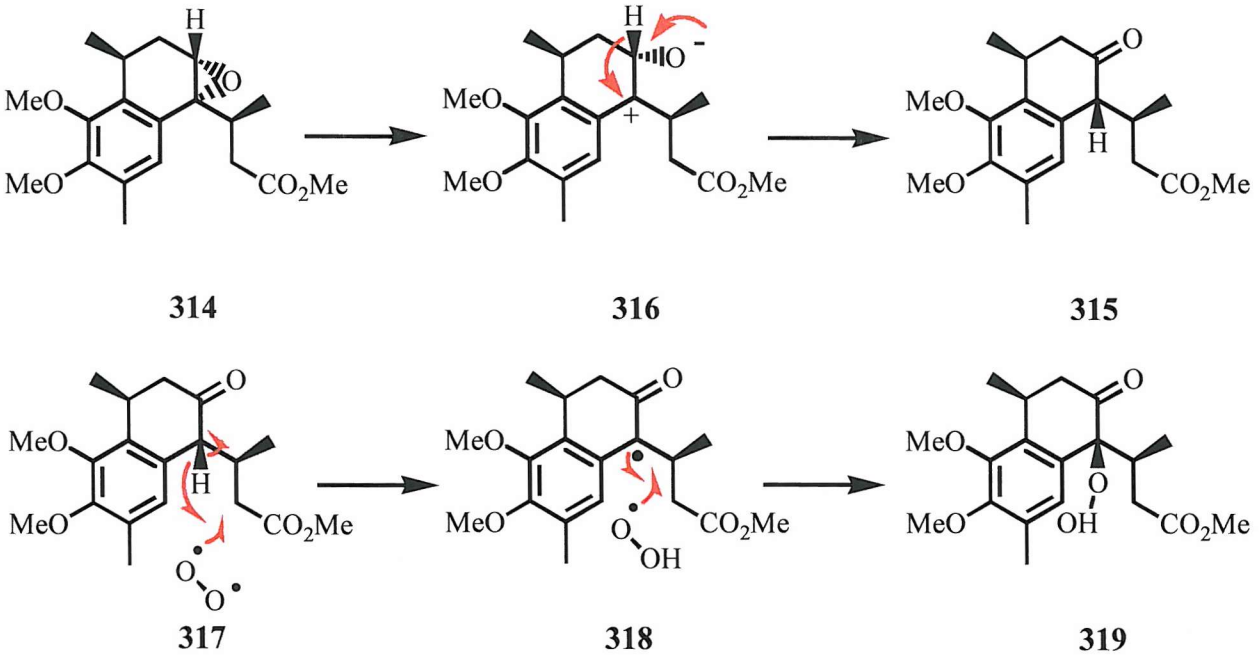


314 **314** **315**

Reagents & Conditions: a. *m*CPBA, DCM.

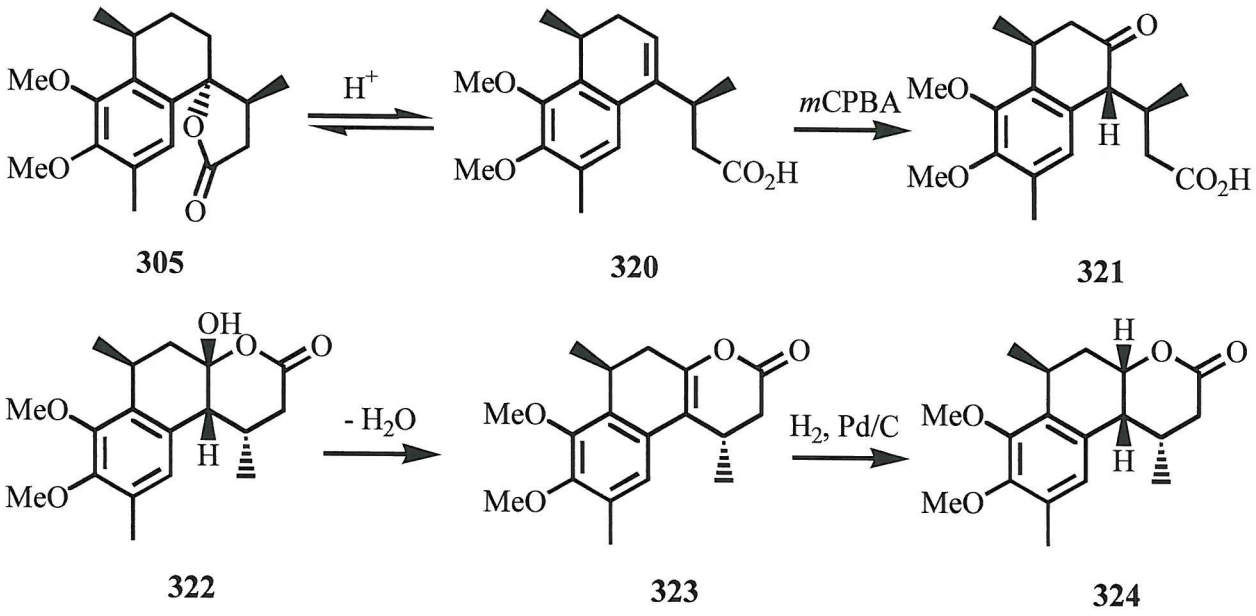
Scheme 58

Surprisingly, other work within the group[64] demonstrated that the ketone **315** could not be isolated. Instead peroxide **319** was given as a single diastereoisomer (confirmed by X-ray crystallography). We postulate that the desired hydride shift occurred to give the ketone **315**, which is oxidised by molecular oxygen to yield the peroxide **319** (**Scheme 59**).



Scheme 59

Since the highly activated benzylic position in **315** appeared highly susceptible to aerial oxidation we chose to examine a system where the carbonyl group would be reduced before it came into contact with atmospheric oxygen. We postulated that treatment of the carboxylic acid **320** with *m*CPBA would first give **321** but that this would spontaneously form hemiacetal **322**. Dehydration of the intermediate hemiacetal would then afford the enol ether **323** (**Scheme 60**), which on reduction of the double bond would give the desired lactone **324**. We were delighted to observe that on exposure of **305** to *m*CPBA in the presence of a catalytic quantity of methanesulphonic acid followed by hydrogenation, the tricyclic lactone **324** was isolated, the structure and relative stereochemistry being confirmed by X-ray crystallography (**Figure 12**).



305 320 321

322 323 324

Scheme 60

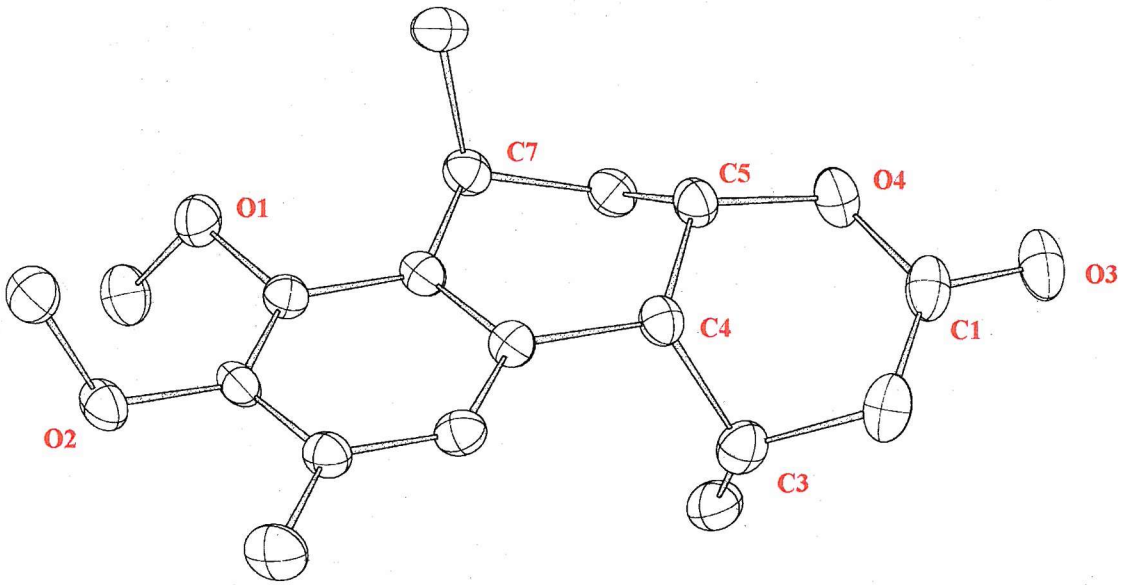
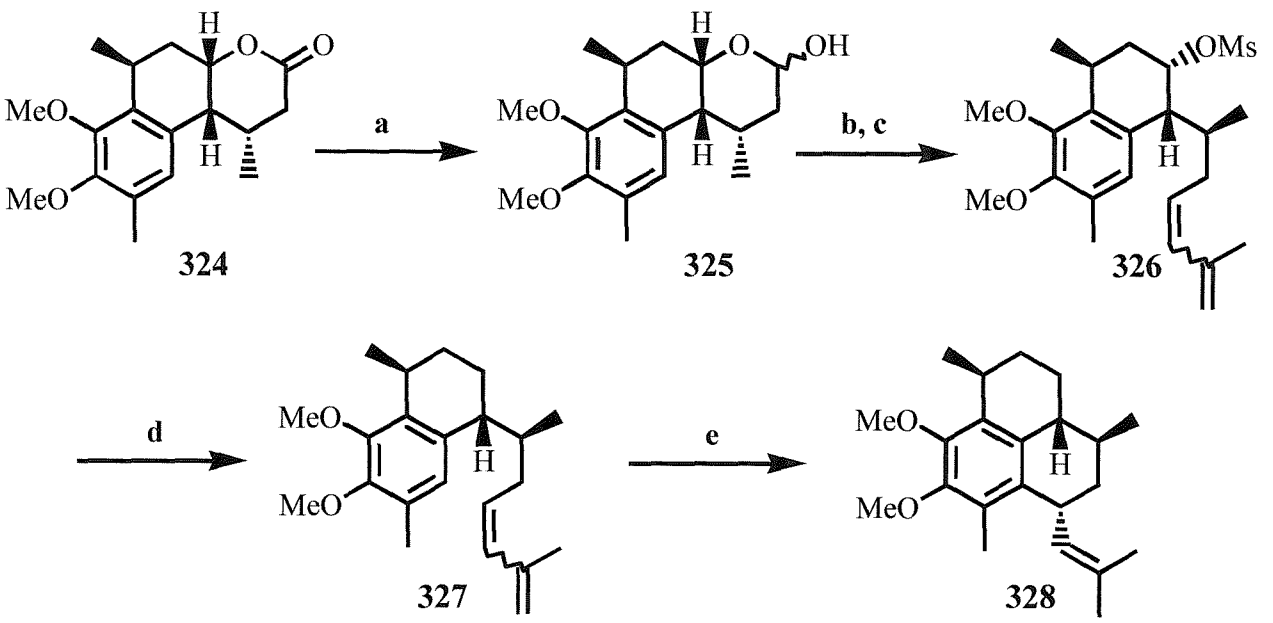


Figure 12 X-Ray crystal structure of **324** with the stereogenic centres labelled according to pseudopterosin nomenclature.

Future Directions

Now that we have established the desired stereochemistry at the C4 centre we may now propose a synthetic strategy to complete the synthesis of the pseudopterosin aglycone and the *seco*-pseudopterosin skeleton. We propose that DIBAL-H reduction of the lactone **324** will give the lactol **325** which may be coupled to the Wittig reagent methallyl triphenylphosphorane as described previously. Mesylation of the unmasked alcohol to give **326** followed by nucleophillic hydride displacement with lithium aluminium hydride will then furnish the cyclisation precursor **327**. On exposure to acid, we are hopeful that **327** will cyclise to give the pseudopterosin A dimethyl ether **328**. Our proposed strategy is described in **Scheme 61**.



Reagents & Conditions: a. DIBAL-H, THF. **b.** Methallyl triphenylphosphorane. **c.** MsCl, NEt_3, DCM. **d.** $LiAlH_4$, THF. **e.** MsOH.

Scheme 61

Chapter 7

Experimental

Experimental: General

All reactions requiring anhydrous conditions were conducted in dried apparatus under a nitrogen or argon atmosphere. Dry solvents were prepared by standard methods and commercial reagents were purified by distillation or recrystallisation where necessary. All reaction mixtures were magnetically stirred unless otherwise stated.

Organic solutions were concentrated at aspirator pressure using a Büchi-type rotary evaporator. All reactions were monitored by thin layer chromatography with Macherey-Nagel polygram Sil G/UV_{254} pre-coated aluminium sheets, thickness 0.25 mm. Compounds were visualised with UV, I_2, phosphomolybdic acid (PMA), potassium permanganate solution, or DNP in sulfuric acid. Column chromatography was performed on sorbsil C60 40 / 60H silica gel packed and run under low pressure. Petrol refers to petroleum ether bp. 40-60°C and ether refers to diethyl ether.

Melting points were determined on a Griffin instrument and are uncorrected. All samples were recrystallised prior to combustion analysis or melting point determination. Boiling points are only reported when distillation was not deleterious.

UV spectra were recorded on a Pye unicam (PU8800) UV/Vis spectrometer using methanol as the solvent. Maxima are reported as λ_{max} (nm) followed in parenthesis by the extinction coefficient, ε ($dm^3mol^{-1}cm^{-1}$).

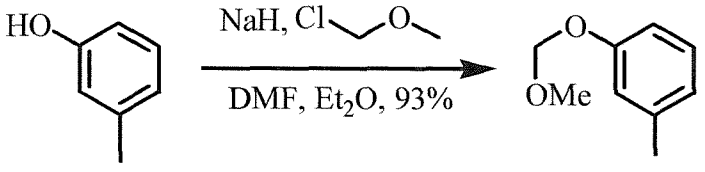
Infra red spectra were recorded on a Perkin Elmer 1600 series spectrometer using sodium chloride cells or a Nicolet spectrometer as thin films or chloroform solutions. Peaks are reported as ν_{max} (cm^{-1}) followed by a description using the following abbreviations: vs = very strong, s = strong, m = medium, w = weak, and br = broad.

^{1}H NMR spectra were recorded in Fourier transform mode on either a Bruker AC300 (300 MHz) or a Bruker AM400 (400 MHz) spectrometer as stated. Chemical shifts are reported in ppm relative to residual $CHCl_3$ (δ_H 7.27 ppm). Multiplicities are recorded as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, obsc. = obscured, app. = apparent and br. = broad. A signal marked with an asterisk (*), denotes a tentative assignment.

^{13}C NMR spectra were recorded on either a Bruker AC300 (75 MHz) or a Bruker AM400 (100 MHz) spectrometer as stated. Chemical shifts are recorded in ppm relative to the central $CDCl_3$ signal (δ_C 77.15 ppm). Multiplicities refer to signals predicted to be observed in an off resonance spectrum as determined by DEPT 45°, 90° and 135° experiments. A signal marked with an asterix (*), denotes a tentative assignment.

Mass spectra were run on a variety of instruments using the atmospheric pressure chemical ionisation (APCI), chemical ionisation (CI) or electron impact (EI) techniques. Values are recorded in atomic mass units (amu) and quoted relative to the base peak (100%).

1-Methoxymethoxy-3-methyl benzene.



$C_7H_8O = 108.14$ $C_9H_{12}O_2 = 152.19$

Sodium hydride, (5.54 g, 0.14 mmol, 60% dispersion in mineral oil) was washed with dry pentane (3 x 50 mL) and the residue was suspended in ether (40 mL) and dimethylformamide (10 mL). The grey suspension was cooled to 0°C and *m*-cresol (4.84 mL, 0.046 mol) added dropwise and stirred for 30 minutes until gas evolution had ceased. Chloromethyl methyl ether (3.5 mL, 0.046 mol) was then added and the mixture allowed to stir at room temperature for 3 hours. Excess sodium hydride was destroyed by the careful addition of water (30 mL). The organic phase was washed with water (3 x 50 mL), brine (2 x 50 mL), separated and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude residue subjected to flash column chromatography (5% ether / petroleum ether 40-60°C). Appropriate fractions were combined and solvent removed *in vacuo* to yield the product as a clear oil (6.49 g, 43 mmol, 93%). All data in agreement with literature values.[65]

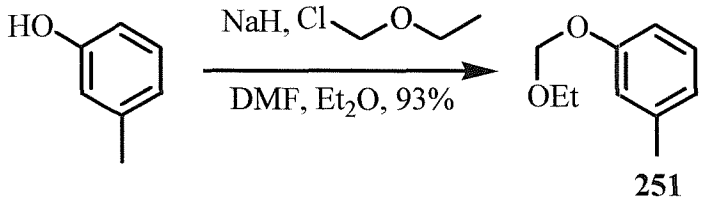
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.23 (1H, t, J = 8.0 Hz, Ar**H**), 6.90 (1H, s, Ar**H**), 6.87 (1H, d, J = 8.0 Hz, Ar**H**), 6.85 (1H, d, J = 8.2 Hz, Ar**H**), 5.20 (2H, s, OCH_2OMe), 3.52 (3H, s, CH_3O), 2.39 (3H, s, $ArCH_3$).

^{13}C NMR δ_C (75 MHz $CDCl_3$) 157.4 (s, **C**(Ar)), 139.7 (s, **C**(Ar)), 129.4 (d, **C**H (Ar)), 122.9 (d, **C**H (Ar)), 117.1 (d, **C**H (Ar)), 113.4 (d, **C**H (Ar)), 94.5 (t, $CH_3O\mathbf{C}H_2O$), 56.1 (q, $O\mathbf{C}H_3$), 21.7 (q, $Ar\mathbf{C}H_3$).

FT-IR (Thin film) 3037 m, 2977 s, 1603 s, 1491 s, 1458 s, 1391 m, 1311 m, 1252 s, 1152 s, 1107 s, 1031 s, 988 s, 909 w, 847 m cm^{-1}.

UV λ_{max} (ε_{max}) 279 (1105), 272 (1132), 231 (760) nm.

***1-Ethoxymethoxy-3-methyl benzene* (251).**



251

$C_7H_8O = 108.14$ $C_{10}H_{14}O_2 = 166.22$

Sodium hydride (13.2 g, 0.28 mol, 2.5 eq.) was washed with dry pentane (3 x 50 mL) and the residue was suspended in ether (100 mL) and dimethylformamide (50 mL). The grey suspension was cooled to 0°C and *m*-cresol (12.0 g, 0.11 mol) added dropwise and stirred for 30 minutes until gas evolution had ceased. Chloromethyl ethyl ether (10.4 g, 0.11 mol) was then added and the mixture allowed to stir at room temperature for 3 hours. Excess sodium hydride was destroyed by the careful addition of water (50 mL). The organic phase was washed with water (3 x 50 mL), brine (2 x 50 mL), separated and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude residue subjected to flash column chromatography (5% ether / petroleum ether 40-60°C). Appropriate fractions were combined and solvent removed *in vacuo* to yield the product as a clear oil (17.9 g, 0.11 mol, 98%). All data in agreement with literature values.[65]

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.21 (1H, t, J = 8.0 Hz, Ar**H**), 6.90 (1H, s, Ar**H**), 6.87 (1H, d, J = 8.0 Hz, Ar**H**), 6.85 (1H, d, J = 8.0 Hz, Ar**H**), 5.23 (2H, s, EtOC**H$_2$**O), 3.78 (2H, q, J = 7.5 Hz, $CH_3C\mathbf{H_2}O$), 2.40 (3H, s, Ar**CH$_3$**), 1.25 (3H, t, J = 7.5 Hz, **CH$_3$**CH_2O).

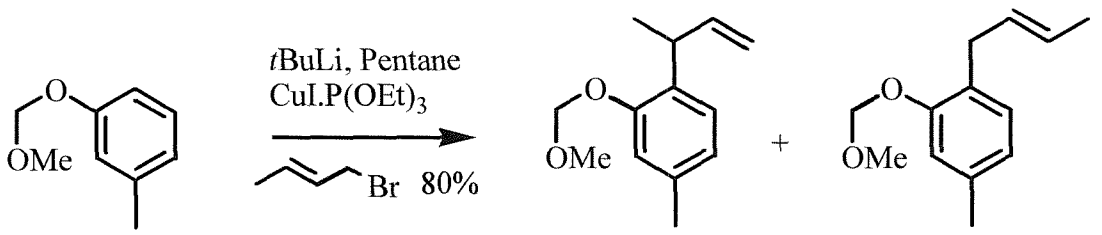
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 157.6 (s, **C**(Ar)), 139.7 (s, **C**(Ar)), 129.4 (d, **C**H (Ar)), 122.7 (d, **C**H (Ar)), 117.1 (d, **C**H (Ar)), 113.3 (d, **C**(Ar)), 93.3 (t, OCH_2O), 64.3 (t, CH_3CH_2O), 21.7 (q, ArCH_3), 15.3 (q, CH_3CH_2O).

FT-IR (Thin film) 3037 s, 2977 s, 1603 s, 1491 s, 1458 m, 1391 m, 1311 m, 1252 s, 1152 s, 1107 s, 1031 s, 988 s, 909 w, 847 w cm^{-1}.

LRMS (APCI +ve) 165 ($[M-H]^+$ 34%) 149 (100%).

UV λ_{max} (ε_{max}) 278 (1142), 271 (1155), 231 (730) nm.

3-(2-Methoxymethoxy-4-methylphenyl)but-1-ene* (252) & *1-(2-methoxymethoxy-4-methylphenyl)but-2-ene* (253). *(general procedure)



251 $C_9H_{12}O_2 = 152.19$

252 $C_{13}H_{17}O_2 = 205.27$ Minor

253 $C_{13}H_{17}O_2 = 205.27$ Major

1-Methoxymethoxy-3-methylbenzene (0.50 g, 3.3 mmol) was dissolved in pentane (10mL), cooled to –78°C and *tert*-butyllithium (1.7M solution in pentane, 3.0 mL, 4.0 mmol) was added with stirring. After 10 minutes the cooling bath was removed and the solution was allowed to warm to room temperature, forming a white precipitate. Stirring was ceased and the anion precipitate was allowed to settle for 5 hours. The supernatant pentane was decanted and the precipitate was dissolved in dry THF (15 mL). The solution was cooled to -78°C and copper(I) iodide triethylphosphite complex (or other additives) (1.41g, 3.95 mmol) was added. The resulting dark brown suspension was stirred for 30 minutes at room temperature, then cooled to -78°C and crotyl bromide (0.33 mL, 3.3 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with dichloromethane (50 mL), washed with ammonia solution (5 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$) and filtered. Solvent was removed from the filtrate *in vacuo* and the crude residue was subjected to flash column chromatography (5% ether / petroleum

ether 40-60°C) to yield the product as an inseparable mixture of S_N2 and S_N2' alkylated products, 0.54 g, 80% (ratio of S_N2 : S_N2' alkylated products 1.8 : 1).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Major isomer:** 7.07 (1H, d, J = 7.5 Hz, Ar**H**), 6.93 (1H, s, Ar**H**), 6.81 (1H, d, J = 7.5 Hz, Ar**H**), 5.55-5.29 (2H, m, CH_2CH=CH), 5.10 (2H, s, OCH_2O), 3.53 (3H, s, OCH_3), 3.34 (2H, br. d, J = 6.3 Hz, $ArCH_2CH$=), 2.23 (3H, s, $ArCH_3$), 1.70 (3H, dd, J = 6.3, 1.1 Hz, CH_3CH=). **Minor isomer:** 7.07 (1H, t, J = 7.4 Hz, Ar**H**), 6.91 (1H, s, Ar**H**), 6.80 (1H, t, J = 7.9 Hz, Ar**H**), 6.01 (1H, ddd, J = 16.9, 10.3, 6.1 Hz, CH_2=CH), 5.11 (2H, s, OCH_2O), 5.01-4.91 (2H, m, CH=CH_2), 3.81 (1H, br. quintet, J = 6.6 Hz, $ArCHCH_3$), 3.51 (3H, s, OCH_3), 2.23 (3H, s, $ArCH_3$), 1.34 (3H, d, J = 7.0 Hz, CH_3CH).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) **Major isomer:** 154.9 (s, **C**(Ar)), 137.1 (s, **C**(Ar)), 129.9 (d, **C**H (Ar)), 127.3 (s, **C**(Ar)), 125.9 (d, **C**H (Ar)), 122.6 (d, **C**H (Ar)), 115.0 (d, **C**H=CH)*, 114.9 (d, CH=**C**H)*, 94.5 (t, OCH_2O), 56.2 (q, OCH_3), 33.0 (t, $ArCH_2CH$=), 21.5 (q, $ArCH_3$), 18.1 (q, =$CHCH_3$). **Minor isomer:** 154.4 (s, **C**(Ar)), 143.1 (d, **C**H (Ar)), 131.7 (s, **C**(Ar)), 127.5 (d, **C**H (Ar)), 122.9 (s, **C**(Ar)), 122.7 (d, **C**H (Ar)), 117.1 (d, $CHCH$=CH_2), 112.8 (t, CH=CH_2), 94.6 (t, OCH_2O), 56.2 (q, OCH_3), 35.6 (d, $ArCHCH_3$), 21.5 (q, $ArCH_3$), 19.7 (q, $CHCH_3$).

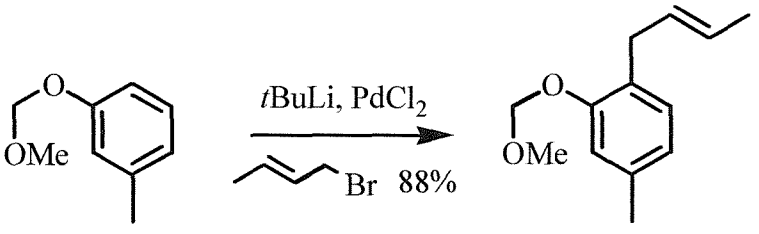
FT-IR (Thin film) 2918 s, 1614 m, 1582 m, 1507 s, 1451 m, 1396 w, 1253 s, 1210 w, 1153 s, 1124 s, 1078 s, 1017 s, 968 w, 924 m, cm^{-1}.

LRMS (APCI +ve) 206 (M^+, 5%), 205 ($[M-H]^+$ 32%), 175 ($[M-OMe]^+$ 100%).

HRMS (EI) M^+, $C_{13}H_{18}O_2$ Requires 206.1307. Found 206.1311.

UV λ_{max} (ε_{max}) 271 (937), 221 (3920) nm.

***1-(2-Methoxymethoxy-4-methylphenyl)but-2-ene* (253).**

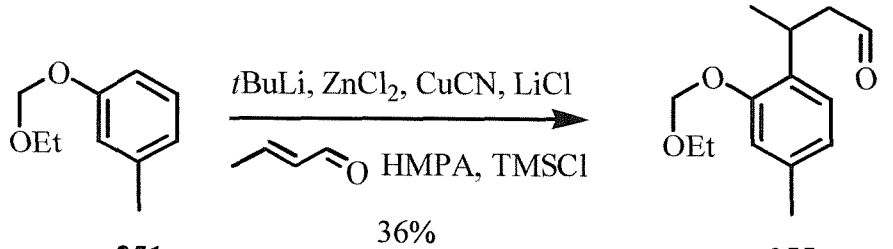


251 **253**

$C_9H_{12}O_2 = 152.19$ $C_{13}H_{17}O_2 = 205.27$

1-Methoxymethoxy-3-methylbenzene (0.51 g, 3.3 mmol) was dissolved in pentane (10mL), cooled to –78°C and *tert*-butyllithium (1.7M solution in pentane, 3.0 mL, 4.0 mmol) was added with stirring. After 10 minutes the cooling bath was removed and the solution was allowed to warm to room temperature, forming a white precipitate. Stirring was ceased and the anion precipitate was allowed to settle for 5 hours. The supernatant pentane was decanted and the anion precipitate suspended in ether (20 mL). Palladium(II) chloride (30 mg, 0.17 mmol) was then added and the suspension was cooled to -78°C. Crotyl bromide (0.33 mL, 3.3 mmol), was added dropwise with stirring and the reaction allowed to warm to room temperature and stirred for 15 minutes. Water (100 mL) was added and the reaction extracted into ether (3 x 30 mL). The organic fractions were combined, washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude residue was subjected to flash column chromatography (5% ether / petroleum ether 40-60°C) to yield the product (contaminated with ca. 7% of the S_N2' alkylated product) as a pale yellow oil, (584 mg, 88%). Spectral data as reported previously.

***3-(2-(Methoxyethoxy)-4-methylphenyl) butanal* (255).**



251 $C_{10}H_{14}O_2 = 166.22$

255 $C_{14}H_{20}O_3 = 236.31$

1-Ethoxymethoxy-3-methylbenzene (0.51 g, 3.1 mmol) was dissolved in dry pentane (10 mL) and cooled to –78°C. *tert*Butyllithium (1.7 M solution in pentane, 3.0 mL, 4.0 mmol) was added dropwise. The cooling bath was then removed and the solution allowed to warm to RT, forming a white precipitate. Stirring was then ceased and the anion precipitate allowed to settle for 5 hours. The supernatant pentane was decanted and the precipitate was dissolved in THF (15 mL) and cooled to 0°C. Zinc chloride (0.43 g, 3.2 mmol) was rapidly added and the yellow solution turned colourless. The solution was stirred for 30 minutes and then copper(I) cyanide (0.32 g, 3.3 mmol) and lithium chloride (0.16 g, 3.3 mmol) were added and the resulting green solution stirred for 30 minutes, after which time crotonaldehyde (0.44 mL, 4.9 mmol), trimethylsilylchloride (0.62 mL, 4.9 mmol) and HMPA (1.0 mL) were added and the solution stirred for 3 hours while warming to room temperature. The reaction was diluted with dichloromethane (50 mL), washed with saturated ammonium chloride solution (50 mL), 2M ammonia solution (5 x 50 mL), and brine (2 x 50 mL). The organic phase was separated, dried ($MgSO_4$) and filtered. The solvent was removed from the filtrate *in vacuo* and the crude residue was subjected to flash column chromatography (5% ether / petroleum ether 40-60°C) to yield firstly the product

as a pale yellow oil (264 mg, 1.1 mmol, 36%), and then recovered starting material (233 mg, 1.4 mmol, 45%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.64 (1H, t, J = 2.2 Hz, C**H**O), 6.99 (1H, d, J = 9.0 Hz, Ar**H**), 6.87 (1H, s, Ar**H**), 6.70 (1H, d, J = 9.0 Hz, Ar**H**), 5.16 (2H, s, EtOC**H$_2$**O), 3.64 (2H, q, J = 8.5 Hz, $CH_3C\mathbf{H_2}O$), 3.63 (1H, app sextet, J = 7.0 Hz, ArC**H**CH_3), 2.60 (1H, ddd, J = 17.7, 9.9, 2.2 Hz, C**H**HCHO), 2.49 (1H, ddd, J = 17.7, 9.9, 2.2 Hz, CH**H**CHO), 2.24 (3H, s, ArC**H$_3$**), 1.22 (3H, d, J = 8.9 Hz, ArCHC**H$_3$**), 1.17 (3H, t, J = 8.5 Hz, C**H$_3$**CH_2O).

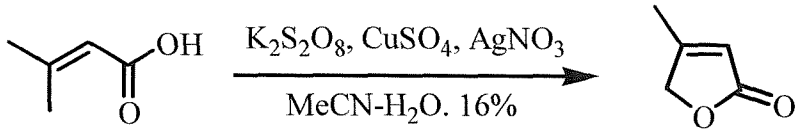
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 202.8 (d, **C**=O), 154.6 (s, **C**(Ar)), 137.6 (s, **C**(Ar)), 130.9 (s, **C**(Ar)), 126.9 (d, **C**H (Ar)), 122.6 (d, **C**H (Ar)), 115.0 (d, **C**H (Ar)), 93.3 (t, O**C**H_2O), 64.6 (t, $CH_3\mathbf{C}H_2O$), 50.9 (t, **C**H_2CHO), 27.7 (q, Ar**C**H_3), 21.4 (d, Ar**C**HCH_3), 20.8 (q, **C**H_3CH_2), 15.3 (q, **C**H_3CH_2O).

FT-IR (Thin film) 2959 s, 2825 s, 2722 m, 1724 s, 1613 m, 1579 m, 1507 s, 1452 s, 1398 m, 1350 w, 1292 w, 1252 s, 1209 m, 1154 s, 1133 s, 1077 s, 1014 s, 925 s, 856 w, 813 s, cm^{-1}.

LRMS (APCI +ve) 191 ($[M\text{-}OEt]^+$, 25%), 161 ($[M\text{-}EtOCH_2O]^+$, 100%).

UV λ_{max} (ε_{max}) 280 (1420), 274 (1460), 232 (1180) nm.

***3-Methyl-2-(5H)furanone* (227).**



215 **227**

$C_5H_8O_2 = 100.12$ $C_5H_6O_2 = 98.10$

To a solution of the acid (1.0 g, 10 mmol), in acetonitrile-water (100 mL, 50/50) was added silver nitrate (0.68 g, 4 mmol), and copper sulfate (0.68 g, 4 mmol). The resulting blue suspension was heated to 80°C and potassium persulfate (2.7 g, 10 mmol) was added portionwise over a period of 3 hours. The reaction was then refluxed for a further 8 hours, after which time the mixture was allowed to cool, diluted with water (100 mL) and extracted into ether (3 x 100 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and solvent removed *in vacuo*. The crude residue was subjected to flash column chromatography (50% ether / petroleum ether 40-60°C) to yield the furanone product as a yellow oil (157 mg, 1.6 mmol, 16 %). Data in agreement with literature values.[66]

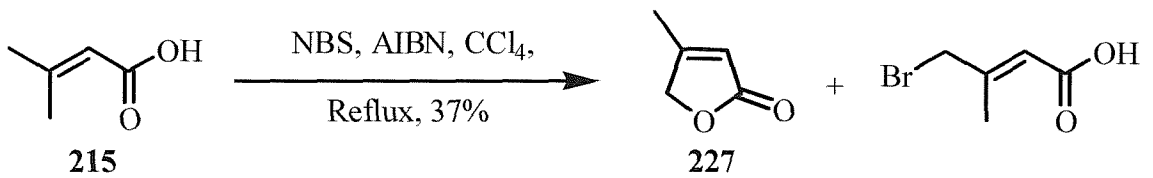
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 5.85 (1H, s, =C**H**), 4.73 (2H, s, CH_2O), 2.13 (3H, s, CH_3)

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 174.4 (s, **C**=O), 166.3 (s, CH_3C=CH), 116.5 (d, =**C**H), 74.1 (t, CH_2O), 14.3 (q, CH_3).

FT-IR (Thin film) 2954 m, 1778 s, 1643 s, 1443 m, 1378 m, 1308 m, 1179 m, 1143 s, 1038 m, 1014 m, 991 m, 944 m, 891 m, 837 m.

UV λ_{max} (ε_{max}) 271 (334), 228 (1020) nm.

***Alternative procedure for the preparation of 3-methyl-2-(5H)furanone* (227).**

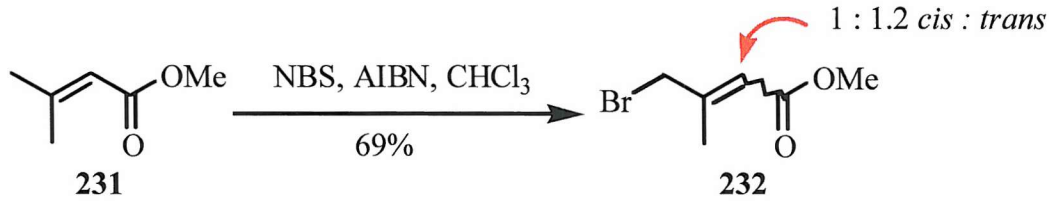


215 **227**

$C_5H_8O_2 = 100.12$ $C_5H_6O_2 = 98.10$ $C_5H_7O_2Br = 179.16$

3,3-Dimethylacrylic acid (25 g, 0.25 mol) was dissolved in carbon tetrachloride (300 mL), and *N*-bromosuccinimide (44.5 g, 0.25 mol) was added. The suspension was heated to reflux and AIBN (500 mg, 3.0 mmol) was added in a single portion. The mixture was refluxed for 1h after which time the reaction was allowed to cool and the solution washed with saturated sodium bicarbonate solution (3 x 150 mL). The organic fraction was separated, dried ($MgSO_4$) filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromtography (50-100% ether / petroleum ether 40-60°C) to yield the product furanone as a yellow oil (9.0 g, 93 mmol, 37%).

***Methyl (EZ)-3-bromomethylbut-2-enoate* (232).**



231 **232**

$C_6H_{10}O_2 = 114.14$ $C_6H_9O_2Br = 193.04$

To a solution of methyl 3,3-dimethylacrylate (2.0 g, 18 mmol), in chloroform (30 mL), was added *N*-bromosuccinimide (3.6 g, 20 mmol), and AIBN (50 mg, 0.3 mmol). The pale yellow solution was heated to reflux for 3 hours during which time the colour changed to red then colourless. The solution was allowed to cool to RT forming a white precipitate which was filtered off. The filtrate was concentrated *in vacuo* and the resulting red oil subjected to flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the brominated product as an inseparable 1 : 1.2 mixture of *cis* and *trans* isomers (2.4 g, 12.5 mmol, 69%). Data in agreement with literature values.[67]

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Trans* isomer:** 5.90 (1H, s, C=C**H**CO_2Me), 3.88 (2H, s, C**H$_2$**Br), 3.62 (3H, s, CO_2C**H$_3$**), 2.21 (3H, s, C**H$_3$**). ***Cis* isomer:** 5.73 (1H, s, C=C**H**CO_2Me), 3.75 (2H, s, C**H$_2$**Br), 3.61 (3H, s, CO_2C**H$_3$**), 2.00 (3H, s, C**H$_3$**).

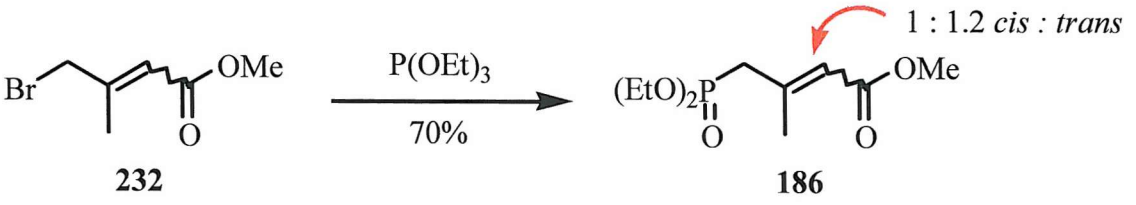
^{13}C NMR δ_C (75 MHz, $CDCl_3$) ***Trans* isomer:** 153.1 (s, **C**=O), 121.4 (s, **C**=CHCO_2Me), 119.0 (d, C=**C**HCO_2Me), 51.5 (q, CO_2**C**H$_3$), 38.3 (t, **C**H$_2$Br), 17.4 (q, **C**H$_3$CH=). ***Cis* isomer:** 153.1 (s, **C**=O), 121.4 (s,

C=CHCO$_2$Me), 119.1 (d, C=**C**HCO$_2$Me), 51.5 (q, CO$_2$**C**H$_3$), 29.7 (t, **C**H$_2$Br), 23.6 (q, **C**H$_3$CH=).

FT-IR (Thin film) 2966 w, 2945 w, 1718 s, 1646 w, 1435 m, 1359 m, 1250 m, 1231 s, 1217 m, 1157 s, 1039 w, 858 w, 742 w cm^{-1}.

LRMS (APCI +ve) 193 (M^+, 7%), 124, 100%.

***Methyl (EZ)-3-methyl-4-diethylphosphonobut-2-enoate* (186).**



232 **186**

$C_6H_9O_2Br = 193.04$ $C_{10}H_{19}PO_5 = 250.26$

A 1 : 1.2 mixture of *cis*- and *trans*-methyl 3-bromomethyl-but-2-enoate (7.6 g, 39.0 mmol) and triethyl phosphite (1.7 g, 10.3 mmol) were mixed and heated to 120°C for 16 hours to yield an inseparable 1 : 1.2 mixture of the *cis* and *trans* phosphonate product as a yellow oil (contaminated with *ca.* 10% triethyl phosphite) (6.8 g, 27.0mmol, 70%). Data in agreement with literature values.[68]

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Cis* isomer:** 5.79 (1H, br. d, J_{PH} = 7.0 Hz, C=C**H**CO_2Me), 4.07 (4H, m, 2 x $CH_3CH_2OP(O)$), 3.66 (3H, s, CO_2CH_3), 3.45 (2H, d, J_{PH} = 25.3 Hz, $CH_2PO(OEt)_2$), 2.03 (3H, br, s, CH_3C=CH), 1.38-1.25 (6H, m, 2 x CH_3CH_2O). ***Trans* isomer:** 5.76 (1H, br, d, J_{PH} = 5.9 Hz, C=C**H**CO_2Me), 4.07 (4H, m, 2 x $CH_3CH_2OP(O)$), 3.66 (3H, s, CO_2CH_3), 2.67 (2H, d, J_{PH} = 25.3 Hz, $CH_2PO(OEt)_2$), 2.29 (3H, br, s, CH_3C=CH), 1.38-1.25 (6H, m, 2 x CH_3CH_2O).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 166.5 (s, 2 x C=O), 150.1 (s, CH_3C=CH), 149.9 (s, CH_3C=CH), 119.6 (d, C=CH, J_{PC} = 11.3 Hz), 118.6 (d, C=CH, J_{PC} = 11.3 Hz), 61.4 (t, 2 x OCH_2CH_3), 51.1 (q, 2 x CO_2CH_3), 37.6 (t, J_{PC} = 135.6 Hz,

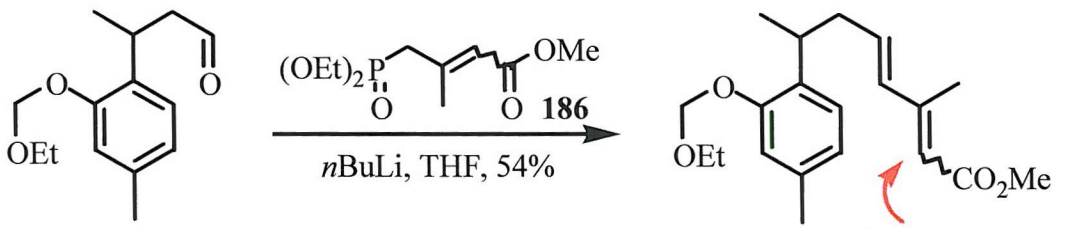
$(EtO)_2P(O)\mathbf{C}H_2$), 30.4 (t, J_{PC} = 134.5 Hz, $(EtO)_2P(O)\mathbf{C}H_2$), 26.3 (q, $\mathbf{C}H_3C{=}CH$), 20.2 (q, $\mathbf{C}H_3C{=}CH$), 16.4 (q, 2 x $\mathbf{C}H_3CH_2O$).

FT-IR (Thin film) 2986 s, 1716 s, 1651 s, 1439 m, 1393 m, 1360 m, 1228 s, 1164 s, 1024 s, 974 s, 881 w, 840 w, 796 w, cm^{-1}.

LRMS (APCI +ve) 251 ($[M+H]^+$, 15%), 219 ($[M-OEt]^+$, 100%).

UV λ_{max} (ε_{max}) 222 (3080).

***Methyl (2EZ, 4E)-3-methyl-7-(2-ethoxymethoxy-4-methylphenyl)oct-2, 4-dienoate* (258).**



255

$C_{14}H_{20}O_3 = 236.31$

258

$C_{20}H_{28}O_4 = 332.44$

The phosphonate **186** (600 mg, 2.4 mmol), was dissolved in dry THF (20 mL), cooled to –78°C and *n*-butyllithium (1.7 mL, 2.4 mmol) was added. The resulting yellow solution was stirred for 30 minutes, a THF solution of the aldehyde (280 mg, 1.2 mmol) was added and the solution allowed to warm to RT. After 2 hours, saturated ammonium chloride solution (20 mL) was added and the reaction extracted into ether (3 x 50 mL). The organic fractions were combined, dried, filtered and solvent removed *in vacuo* to yield the crude residue as a yellow oil. Purification by flash column chromatography (10% ether / petroleum ether 40-60°C) gave a 1 : 1.2 mixture of *cis* and *trans* isomers (214 mg, 0.64 mmol, 54%) as a colourless oil.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Cis* isomer:** 7.58 (1H, d, J = 15.8 Hz, $CHCH_2CH{=}C\mathbf{H}$), 7.07 (1H, d, J = 7.5 Hz, Ar**H**), 6.93 (1H, s, Ar**H**), 6.80 (1H, d, J = 7.5 Hz, Ar**H**), 6.10 (1H, m, $CH_2C\mathbf{H}{=}CH$), 5.70 (1H, s, $=C\mathbf{H}CO_2Me$), 5.22 (2H, s, $OC\mathbf{H_2}O$), 3.73 (2H, q, J = 7.4 Hz, $CH_3C\mathbf{H_2}O$), 3.69 (3H, s, $CO_2C\mathbf{H_3}$), 3.29 (1H, app. sextet, J = 7.5 Hz, $ArC\mathbf{H}CH_3$), 2.70-

2.35 (2H, m, $CHCH_2CH$=), 2.33 (3H, s, $ArCH_3$), 2.24 (3H, s, MeO_2CCH=CCH_3), 1.31-1.22 (6H, m, CH_3CH_2O, $ArCHCH_3$). ***Trans* isomer:** 7.07 (1H, d, J = 7.5 Hz, Ar**H**), 6.93 (1H, s, Ar**H**), 6.80 (1H, d, J = 7.5 Hz, Ar**H**), 6.04-5.93 (2H, m, $CHCH_2CH$=CH), 5.59 (1H, s, =$CHCO_2Me$), 5.21 (2H, s, OCH_2O), 3.74 (2H, q, J = 7.4 Hz, CH_3CH_2O), 3.69 (3H, s, CO_2CH_3), 3.29 (1H, app. sextet, J = 7.5 Hz, $ArCHCH_3$), 2.70-2.35 (2H, m, $CHCH_2CH$=), 2.33 (3H, s, $ArCH_3$), 1.95 2.24 (3H, s, MeO_2CCH=CCH_3), 1.31-1.22 (6H, m, CH_3CH_2O, $ArCHCH_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 167.8 (s, **C**=O), 166.9 (s, **C**=O), 154.8 (s, **C**=$CHCO_2CH_3$), 153.1 (s, **C**=$CHCO_2CH_3$), 151.7 (s, 2 x **C**(Ar)), 138.2 (d, 2 x CH_2CH=CH)*, 137.0 (s, **C**(Ar)), 136.9 (s, **C**(Ar)), 136.5 (d, CH_2CH=**C**H)*, 134.8 (d, CH_2CH=**C**H)*, 132.5 (s **C**(Ar)), 132.3 (s, **C**(Ar)), 128.9 (d, 2 x **C**H (Ar)), 126.8 (d, **C**H (Ar)), 126.7 (d, **C**H (Ar)), 122.5 (d,**C**H (Ar)), 117.4 (d, **C**H (Ar)), 115.4 (d, **C**H=CO_2CH_3), 115.0 (d, **C**H=CO_2CH_3), 93.4 (t, 2 x OCH_2O), 64.4 (t, 2 x CH_3CH_2O), 51.1 (q, 2 x CO_2CH_3), 41.0 (t, $CHCH_2CH$=), 40.8 (t, $CHCH_2CH$=), 32.4 (d, CH_3CHAr), 32.1 (d, CH_3CHAr), 21.5 (q, =CCH_3)*, 21.3 (q, =CCH_3)*, 20.5 (q, 2 x $ArCH_3$)*, 15.3 (q, 2 x $CHCH_3$), 14.0 (q, 2 x OCH_2CH_3).

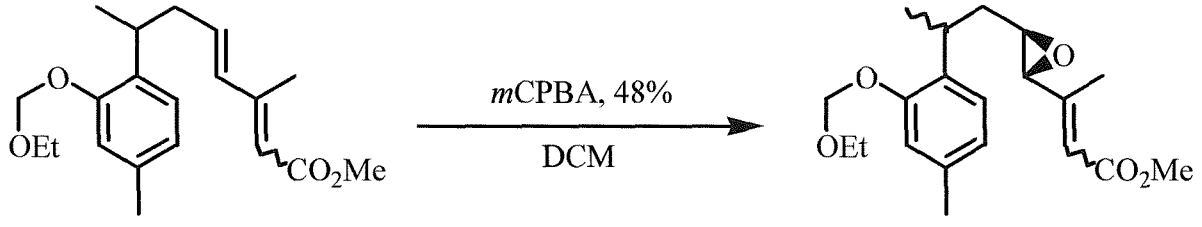
FT-IR (Thin film) 2974 s, 1716 s, 1636 w, 1612 m, 1579 w, 1506 m, 1434 m, 1391 w, 1356 w, 1243 s, 1758 s, 1102 m, 1079 m, 1014 s, 922 w, 860 w, cm^{-1}.

LRMS (APCI +ve) 333.4 ($[M+H]^+$, 7%), 287.3 ($[M-OEt]^+$, 100%).

HRMS (EI) M^+, $C_{20}H_{28}O_4$ Requires 332.19876. Found 332.19808.

UV λ_{max} (ε_{max}) 265 (25178), 202 (22106) nm.

Methyl rel-(2EZ, 4R, 5R, 7RS)-4, 5-epoxy-3-methyl-7-(2-ethoxymethoxy-4-methylphenyl)oct-2-enoate.



258 **259**

$C_{20}H_{28}O_4 = 332.44$ $C_{20}H_{28}O_5 = 348.44$

To a solution of the diene (100 mg, 0.3 mmol) in dichloromethane (20 mL) at 0°C was added dried *m*CPBA (208 mg, 0.6 mmol). The clear solution was stirred at 0°C for 3 hours then warmed to RT, washed with saturated sodium thiosulphate solution (2 x 30 mL) and water (3 x 20 mL). The organic fraction was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% ether / petroleum ether 40-60°C) to yield an inseparable 1 : 1 mixture of diasteriomers and a 1 : 1 mixture of geometric isomers (48 mg, 0.14 mmol, 48%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.08 (1H, m, 4 x Ar**H**), 6.94 (1H, br s, 4 x Ar**H**), 6.80 (1H, br d, J = 7.4 Hz, 4 x Ar**H**), 5.87 (1H, s, 2 x =C**H**CO_2Me), 5.84 (1H, s, =C**H**CO_2Me), 5.65 (1H, s, =C**H**CO_2Me), 5.27-5.20 (2H, m, 4 x O**CH$_2$**O), 3.81-3.67 (5H, m, 4 x CO_2**CH$_3$**, CH_3**CH$_2$**O), 3.48-3.32 (1H, m, 4 x ArC**H**CH_3), 2.85-2.63 (1H, m, 4 x CHC**H**-O), 2.32 (3H, s, 4 x Ar**CH$_3$**), 2.17-1.92 (1H, m, 4 x CH_2**CH**-O), 2.03 (3H, d, J = 1.1 Hz, **CH$_3$**C=CHCO_2CH_3), 1.84 (3H, d, J = 1.1 Hz, **CH$_3$**C=CHCO_2CH_3), 1.83-

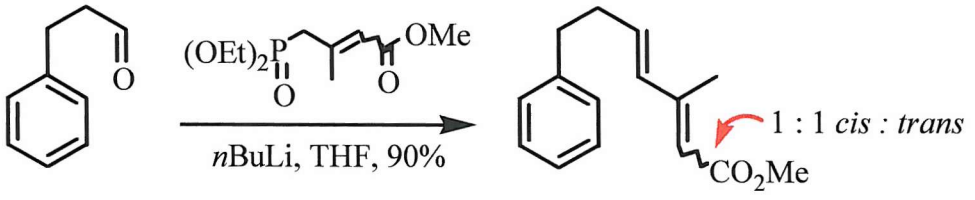
1.70 (2H, m, 4 x CH_3CHCH_2), 1.69 (3H, d, J = 1.1 Hz, $CH_3C{=}CHCO_2CH_3$), 1.66 (3H, d, J = 1.1 Hz, $CH_3C{=}CHCO_2CH_3$), 1.35-1.15 (6H, m, 4 x CH_3CH_2O, CH_3CHAr).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 166.8 (s, 2 x C=O), 166.5 (s, 2 x C=O), 156.2 (s, 2 x $C{=}CHCO_2CH_3$), 156.0 (s, 2 x $C{=}CHCO_2CH_3$), 154.8 (s, 2 x C(Ar)), 154.8 (s, C(Ar)), 154.7 (s, C(Ar)), 137.3 (s, 2 x C(Ar)), 137.3 (s, C(Ar)), 137.0 (s, C(Ar)), 132.3 (s, C(Ar)), 132.0 (s, C(Ar)), 131.8 (s, C(Ar)), 131.4 (s, C(Ar)), 126.9 (d, 2 x CH (Ar)), 126.8 (d, 2 x CH (Ar)), 126.6 (d, 2 x CH (Ar)), 122.7 (d, 2 x CH (Ar)), 122.6 (d, 2 x CH (Ar)), 119.3 (d, CH (Ar)), 115.7 (d, CH (Ar))*, 115.3 (d, $=CHCO_2CH_3$)*, 115.2 (d, $=CHCO_2CH_3$)*, 115.1 (d, $=CHCO_2CH_3$)*, 115.0 (d, $=CHCO_2CH_3$)*, 93.3 (t, 4 x OCH_2O), 64.4 (t, 2 x CH_3CH_2O), 64.4 (t, 2 x CH_3CH_2O), 61.1 (d, CH-O), 61.0 (d, CH-O), 59.5 (d, CH-O), 59.2 (d, CH-O), 57.4 (d, CH-O), 57.3 (d, CH-O), 57.0 (d, CH-O), 56.6 (d, CH-O), 51.3 (q, CO_2CH_3), 51.3 (q, CO_2CH_3), 51.2 (q, CO_2CH_3), 51.1 (q, CO_2CH_3), 40.3 (t, $CHCH_2CH$-O), 40.0 (t, $CHCH_2CH$-O), 39.7 (t, $CHCH_2CH$-O), 39.4 (t, $CHCH_2CH$-O), 31.1 (d, CH_3CHAr), 30.5 (d, CH_3CHAr), 30.1 (d, CH_3CHAr), 29.8 (d, CH_3CHAr), 21.5 (q, 2 x $ArCH_3$), 21.4 (q, 2 x $ArCH_3$), 20.8 (q, $=CCH_3$)*, 20.7 (q, $=CCH_3$)*, 18.6 (q, 2 x $=CCH_3$)*, 15.3 (q, 4 x OCH_2CH_3)*, 14.3 (q, 2 x $CHCH_3$), 13.9 (q, 2 x $CHCH_3$).

FT-IR (Thin film) 2949 s, 1716 s, 1657 m, 1603 w, 1497 w, 1436 m, 1379 w, 1359 w, 1317 w, 1254 m, 1222 s, 1157 s, 1041 m, 866 m, 749 m, 700 m, cm^{-1}.

UV $\lambda_{max}(\varepsilon_{max})$ 257 (1380), 224 (12600) nm.

***Methyl-2-(EZ,4E)-3-methyl-(7-phenyl)-hept-2,4-dienoate* (233).**



226 **233**

$C_9H_{10}O = 134.18$ $C_{15}H_{18}O_2 = 230.31$

To a precooled (-78°C) solution of the phosphonate ester (840 mg, 3.4 mmol) in THF (25 mL) was added *n*-butyllithium (2.2 mL, 3.5 mmol, 1.6M solution in hexane) and the resulting orange solution allowed to warm to RT and stirred for 30 mins. The solution was re-cooled to –78°C and 3-phenylpropionaldehyde (188 mg, 1.4 mmol) was added as a solution in THF (5 mL) and the solution allowed to warm slowly to RT and stirred for 1h. Water (20 mL) was added and the reaction extracted into ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the pure diene as a pale yellow oil as an inseperable 1 : 1 mixture of *cis* and *trans* isomers (290 mg, 1.3 mmol, 90%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Cis* isomer:** 7.58 (1H, d, J = 15.8 Hz, CH_2CH_2CH=C**H**), 7.23-7.06 (5H, m, 5 x Ar**H**), 6.05 (1H, m, CH_2C**H**=CH), 5.61 (1H, s, =C**H**CO_2Me), 3.63 (3H, s, CO_2C**H$_3$**), 2.78 (2H, app. t, J = 7.7 Hz, ArC**H$_2$**), 2.45 (2H, m, $ArCH_2$C**H$_2$**), 2.19 (3H, s, C=CC**H$_3$**). ***Trans* isomer:** 7.23-7.06 (5H, m, 5 x Ar**H**), 6.18-6.05 (2H, m, CH_2CH_2C**H**=C**H**),

5.55 (1H, s, =C**H**CO_2Me), 3.63 (3H, s, $CO_2C\mathbf{H_3}$), 2.80 (2H, app. t, J = 7.7 Hz, Ar$\mathbf{CH_2}$), 2.45 (2H, m, $ArCH_2\mathbf{CH_2}$), 1.90 (3H, s, C=C$\mathbf{CH_3}$).

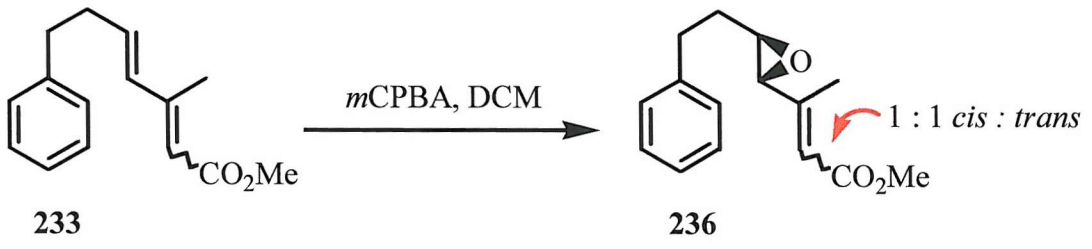
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 167.8 (s, **C**=O), 167.0 (s, **C**=O), 152.9 (s, **C**=$CHCO_2CH_3$), 151.6 (s, **C**=$CHCO_2CH_3$), 141.7 (s, **C**(Ar)), 141.5 (s, **C**(Ar)), 138.3 (d, 2 x CH_2**C**H=CH), 136.5 (d, 2 x CH_2CH=**C**H), 134.3 (d, 2 x **C**H (Ar)), 128.6 (d, 2 x **C**H (Ar)), 128.2 (d, 2 x **C**H (Ar)), 126.2 (d, 2 x **C**H (Ar)), 126.1 (d, 2 x **C**H (Ar)), 117.7 (d, =**C**HCO_2CH_3), 115.8 (d, =**C**HCO_2CH_3), 51.2 (q, 2 x OCH_3), 35.6 (t, ArCH_2), 35.6 (t, ArCH_2), 35.3 (t, $ArCH_2CH_2$), 35.0 (t, $ArCH_2CH_2$), 21.3 (q, C=CCH_3), 14.0 (q, C=CCH_3).

FT-IR (Thin film) 3026 m, 2947 s, 1715 s, 1637 s, 1611 s, 1496 m, 1453 m, 1434 m, 1380 w, 1357 w, 1241 s, 1157 s, 1041 m, 967 m, 920 w, 872 w, 749 s, 700 s cm^{-1}.

LRMS (APCI +ve) 247 ($[M+NH_4]^+$, 63%), 231 ($[M+H]^+$, 96%), 123 (100%).

UV λ_{max} (ε_{max}) 261 (3469), 212 (5714) nm.

***Methyl (rel-2EZ,4S,5S)-4,5-epoxy-3-methyl-7-phenylhept-2-enoate* (236).**



233 **236**

$C_{15}H_{18}O_2 = 230.31$ $C_{15}H_{18}O_3 = 246.30$

To a solution of the diene (150 mg, 0.65 mmol) in DCM (20 mL) at 0°C was added dried *m*CPBA (225 mg, 1.3 mmol) and the solution stirred for 9h. The solution was washed with saturated sodium thiosulfate solution (2 x 20 mL), water (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude product was subjected to flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the epoxides as a 1 : 1.2 mixture of (*E*) and (*Z*) isomers (109 mg, 0.44 mmol, 68%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Cis* isomer:** 7.35-7.09 (5H, m, Ar**H**), 5.90 (1H, s, =C**H**CO_2Me), 3.76 (3H, s, O**CH$_3$**), 2.99-2.71 (4H, m, 2 x C**H**-O, ArC**H$_2$**), 2.12-1.89 (2H, m, ArCH$_2$C**H$_2$**), 2.00 (3H, s, C**H$_3$**C=CO_2Me). ***Trans* isomer:** 7.35-7.09 (5H, m, Ar**H**), 5.87 (1H, s, =C**H**CO_2Me), 3.74 (3H, s, O**CH$_3$**), 2.99-2.71 (4H, m, 2 x C**H**-O, ArC**H$_2$**), 2.12-1.89 (2H, m, ArCH$_2$C**H$_2$**), 2.00 (3H, s, C**H$_3$**C=CO_2Me).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 166.9 (s, **C**=O), 166.5 (s, **C**=O), 156.0 (s, **C**=CHCO$_2$CH$_3$), 154.4 (s, **C**=CHCO$_2$CH$_3$), 141.3 (s, **C**(Ar)), 140.9 (s, **C**(Ar)), 128.7 (d, 2 x **C**H (Ar)), 128.6 (d, 2 x **C**H (Ar)), 128.6 (d, 2 x **C**H

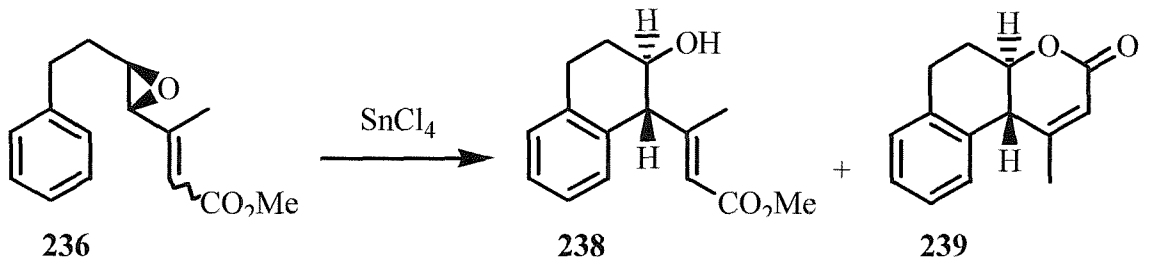
(Ar)), 126.4 (d, 2 x CH (Ar)), 126.2 (d, 2 x CH (Ar)), 119.3 (d, =CHCO$_2$CH$_3$), 115.9 (d, =CHCO$_2$CH$_3$), 60.9 (q, OCH$_3$), 59.6 (q, OCH$_3$), 57.8 (d, =CCH-O), 57.0 (d, =CCH-O), 51.4 (d, CH$_2$CH-O), 51.3 (d, CH$_2$CH-O), 34.0 (t, ArCH$_2$), 33.9 (t, ArCH$_2$), 32.2 (t, 2 x ArCH$_2$CH$_2$), 18.7 (q, =CCH$_3$), 14.2 (q, =CCH$_3$).

FT-IR (Thin film) 2986 w, 2942 w, 2863 w, 1716 s, 1636 w, 1501 w, 1453 w, 1433 m, 1377 w, 1255 w, 1221 s, 1154 s, 1044 w, 870 m, 746 m, cm^{-1}.

LRMS (CI) 246 (M^+, 1%), 230 ([(M+H)-CH$_3$]$^+$, 10%), 91 (100%).

UV $\lambda_{max}(\varepsilon_{max})$ 231 (8450) nm.

***Methyl (rel-1'S,2E,2'R)-3-(2'-hydroxy-1',2',3',4'-tetrahydronapth-1-yl)-3-methyl-2-propenoate* (238) & *(rel-4aS,10aR)-4-methyl-4a,9,10,10a-tetrahydrobenzo[f]chromen-2-one* (239).**



236 **238** **239**

$C_{15}H_{18}O_3 = 246.30$ $C_{15}H_{18}O_3 = 246.30$ $C_{14}H_{14}O_2 = 214.27$

A solution of the epoxide (85 mg, 0.35 mmol) in dichloromethane (10 mL) was cooled to 0°C and tin(IV) tetrachloride (0.4 mL, 0.35 mmol) was added. The resulting yellow solution was stirred for 2h, after which time water (10 mL) was added and the reaction extracted into dichloromethane (3 x 10 mL). Organic fractions were combined, dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude residue subjected to flash column chromatography (10% ether / petroleum ether 40-60°C) to yield firstly the bicyclic alcohol as a pale yellow oil (41 mg, 0.17 mmol, 48%) then the tricyclic product as a clear oil (29 mg, 0.13 mmol, 38%).

Data for Methyl (*rel*-1'S,2*E*,2'*R*)-3-(2'-hydroxy-1',2',3',4'-tetrahydronapth-1-yl)-3-methyl-2-propenoate.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.14 (3H, m, Ar**H**), 6.94 (1H, br. d, J = 8.0 Hz, Ar**H**), 5.85 (1H, s, =C**H**CO_2CH_3), 3.90 (1H, app. dt, J = 7.9, 3.5 Hz, C**H**OH), 3.63 (3H, s, $CO_2C\mathbf{H_3}$), 3.42 (1H, d, J = 7.9 Hz, ArC**H**), 2.88-2.80 (2H, m,

ArC**H**$_2$), 2.20-2.05 (1H, m, ArCH$_2$C**H**H), 2.01 (1H, br. s, O**H**), 1.95 (3H, s, C**H**$_3$C=CH), 1.79-1.64 (1H, m, ArCH$_2$CH**H**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 166.8 (s, **C**=O), 159.2 (s, **C**=CHCO$_2$CH$_3$), 136.4 (s, **C**(Ar)), 134.7 (s, **C**(Ar)), 129.0 (d, **C**H (Ar)), 126.9 (d, **C**H (Ar)), 126.5 (d, **C**H (Ar)), 121.5 (d, **C**H (Ar)), 121.1 (d, C=**C**HCO$_2$CH$_3$), 69.3 (d, **C**HOH), 60.0 (q, CO$_2$**C**H$_3$), 51.2 (d, Ar**C**H), 30.4 (t, Ar**C**H$_2$), 28.1 (t, ArCH$_2$**C**H$_2$), 16.3 (q, **C**H$_3$C=).

FT-IR (Thin film) 3436 s, 2946 s, 1718 s, 1643 s, 1578 w, 1491 w, 1436 m, 1386 w, 1362 w, 1281 w, 1226 s, 1156 s, 1112 w, 1051 s, 960 w, 911 w, 858 w, 747 w cm^{-1}.

LRMS (APCI +ve) 247 ([M+H]$^+$, 45%), 229 ([M-OH]$^+$, 100%), 228 ([M-H$_2$O]$^+$, 70%), 215 ([M-OMe]$^+$, 43%).

HRMS (CI) [M+NH$_4$]$^+$, $C_{15}H_{22}NO_3$ Requires 264.1626, found 264.1591.

UV λ_{max} (ε_{max}) 273 (747), 248 (1460)nm.

Data for (*rel*-4a*S*,10a*R*)-4-methyl-4a,9,10,10a-tetrahydrobenzo[*f*]chromen-2-one.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.33-7.16 (4H, m, Ar**H**), 5.82 (1H, s, C=C**H**CO$_2$), 4.23 (1H, app. dt, J = 8.3, 3.0 Hz, CH$_2$C**H**OCO), 4.12 (1H, d, J = 8.3 Hz, ArC**H**), 2.96 (1H, ddd, J = 14.2, 9.7, 5.2 Hz, ArC**H**H), 2.77 (1H, ddd, J = 13.9, 8.9, 1.5 Hz, ArCH**H**), 2.22-1.95 (2H, m, ArCH$_2$C**H**$_2$), 2.04 (3H, s, =CC**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 174.5 (s, **C**=O), 163.8 (s, **C**=$CHCO_2$), 159.7 (s, **C**(Ar)), 141.1 (s, **C**(Ar)), 128.7 (d, 2 x **C**H (Ar)), 126.3 (d, 2 x **C**H (Ar)), 116.7 (d, =**C**HCO_2), 80.9 (d, Ar**C**H), 68.9 (d, CH_2**C**H-O), 34.0 (t, Ar**C**H_2), 31.0 (t, $ArCH_2$**C**H_2), 19.2 (q, =**C**CH_3).

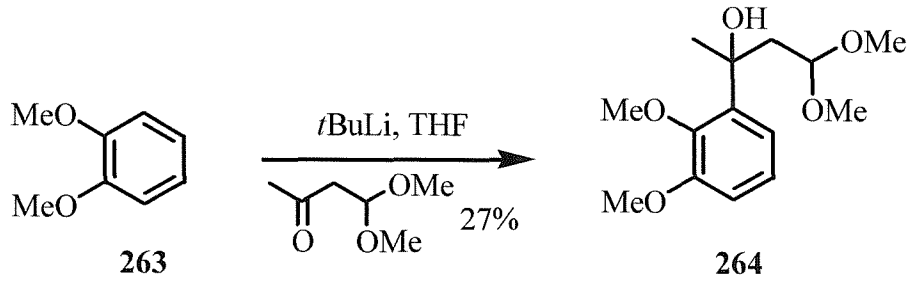
FT-IR (Thin film) 3388 w, 2910 w, 1693 s, 1640 w, 1489 w, 1457 w, 1440 w, 1377 w, 1250 s, 1042 s, 963 w, 867 w, 844 w, 750 m cm^{-1}.

LRMS (EI) 214 (M^+, 7%), 134 (38%), 91 (100%).

HRMS (EI) M^+, $C_{14}H_{14}O_2$ Requires 214.0994. Found 214.0996.

UV λ_{max} (ε_{max}) 212 (7180) nm.

***2-(2, 3-dimethoxyphenyl)-4, 4-dimethoxy-2-butanol* (264).**



$C_8H_{10}O_2 = 138.17$ $C_{14}H_{22}O_5 = 270.32$

Veratrole (10 g, 72 mmol), was dissolved in dry THF (100 mL) and the solution cooled to –78 °C. *t*-Butyllithium (51 mL, 72 mmol, 1.4 M solution in pentane) was added dropwise over 5 minutes and the resulting bright yellow solution allowed to warm to RT during which time a dense cream coloured precipitate formed. The reaction was cooled to –78 °C and acetylacetaldehyde dimethylacetal (9.5 g, 9.5 mL, 72 mmol) was added dropwise over 10 minutes and the reaction maintained at –78 °C for 3h. The reaction was quenched by the addition of saturated ammonium chloride solution (100 mL) and extracted into ether (3 x 100 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the filtrate concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (5-30% ether / petroleum ether 40-60 °C) to yield the product alcohol as a clear oil (5.2 g, 19 mmol, 27%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.24 (1H, d, J = 7.7 Hz, Ar**H**), 7.03 (1H, t, J = 7.7 Hz, Ar**H**), 6.88 (1H, d, J = 7.7 Hz, Ar**H**), 4.46 (1H, s, O**H**), 4.12 (1H, dd, J = 7.0, 2.6 Hz, C**H**$(OMe)_2$), 3.90 (3H, s, ArOC**H**$_3$) 3.87 (3H, s, ArOC**H**$_3$), 3.27 (3H, s, OC**H**$_3$), 3.21 (3H, s, OC**H**$_3$), 2.58 (1H, dd, J = 11.6, 2.6 Hz,

CHHCH(OMe)$_2$), 2.12 (1H, dd, J = 11.6, 7.0 Hz, CHHCH(OMe)$_2$), 1.55 (3H, s, CH_3).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 152.7 (s, C(Ar)), 145.7 (s, C(Ar)), 140.2 (s, C(Ar)), 123.3 (d, CH (Ar)), 118.9 (d, CH (Ar)), 111.7 (d, CH (Ar)), 103.7 (d, $CH(OCH_3)_2$), 72.6 (s, COH), 60.4 (q, OCH_3), 55.8 (q, OCH_3), 54.0 (q, OCH_3), 52.1 (q, OCH_3), 43.3 (t, $CH_2CH(OCH_3)_2$), 29.2 (q, CH_3).

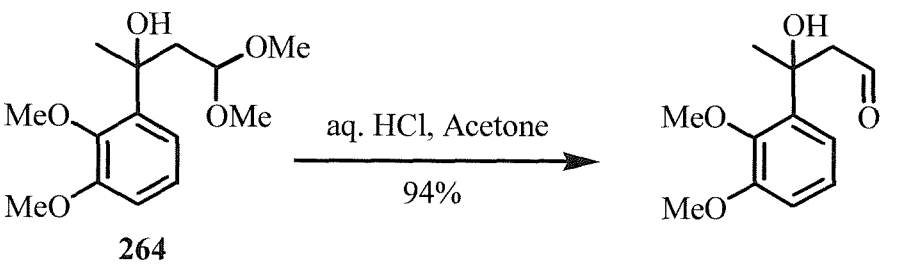
FT-IR (Thin film) 3492 s, 2936 s, 2833 m, 1580 m, 1473 s, 1426 m, 1391 m, 1362 m, 1299 m, 1266 s, 1224 m, 1192 m, 1120 s, 1083 s, 1057 s, 1005 s, 964 w, 926 w, 843 w, 827 w, 788 m, 749 m cm^{-1}.

LRMS (APCI +ve) 270 (M^+, 20%), 181 ([M-$CH_2CH(OMe)_2$]$^+$, 100%).

HRMS (EI) M^+, $C_{14}H_{22}O_5$ Requires 270.1467. Found 270.1458.

UV λ_{max} (ε_{max}) 273 (1770), 213 (6500), nm.

3-(2,3-Dimethoxyphenyl)-3-hydroxybutanal.



264

$C_{14}H_{22}O_5 = 270.32$ $C_{12}H_{16}O_4 = 224.25$

The acetal (1.0 g, 3.7 mmol), was dissolved in acetone (50 mL) and 2M aq. HCl (10 mL) was added. The solution was allowed to stand for 2h after which time water (100 mL) was added. The reaction was extracted into ether (3 x 100 mL) and the organic fractions combined, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude residue was subjected to flash column chromatography (20% ether / petroleum ether 40-60 °C) to yield the product aldehyde as a viscous yellow oil (0.78 g, 3.4 mmol, 94%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.71 (1H, t, J = 3.4 Hz, C**H**O), 7.07-6.86 (3H, m, Ar**H**), 4.48 (1H, br. s, O**H**), 3.96 (3H, s, ArOC**H**$_3$), 3.87 (3H, s, ArOC**H**$_3$), 3.19 (1H, dd, J = 15.4, 3.5 Hz, C**H**HCHO), 2.85 (1H, dd, J = 15.4, 3.4 Hz, CH**H**CHO), 1.65 (3H, s, C**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 203.1 (d, **C**HO), 152.8 (s, **C**(Ar)), 146.2 (s, **C**(Ar)), 138.6 (s, **C**(Ar)), 128.9 (d, **C**H (Ar)), 118.1 (d, **C**H (Ar)), 112.2 (d, **C**H (Ar)), 73.3 (s, **C**OH), 60.9 (q, O**C**H$_3$), 55.8 (q, O**C**H$_3$), 54.9 (t, **C**H$_2$CHO), 29.9 (q, **C**H$_3$).

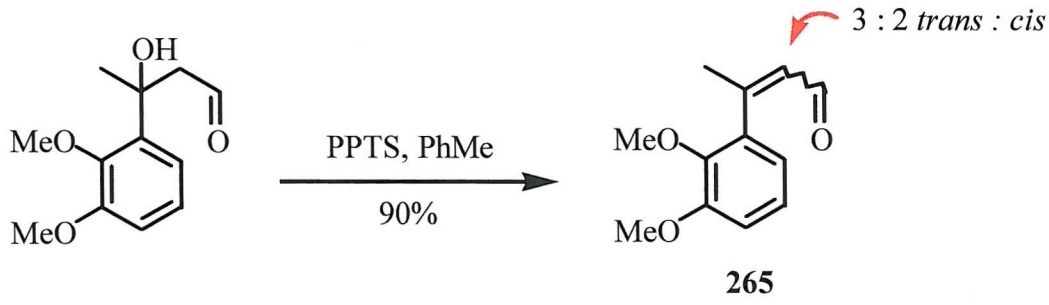
FT-IR (Thin film) 3476 s, 3080 w, 2938 s, 2836 m, 2741 w, 1720 s, 1581 s, 1474 s, 1427 s, 1367 m, 1300 s, 1267 s, 1225 m, 1148 w, 1088 m, 1053 s, 1002 s cm^{-1}.

LRMS (APCI +ve) 224 (M^+, 25%), 207 ($[M-OH]^+$, 50%), 181 ($[M-CH_2CHO]^+$, 100%).

HRMS (EI) M^+, $C_{12}H_{16}O_4$ Requires 224.1049. Found 224.1048.

UV λ_{max} (ε_{max}) 271 (1900), 212 (8250) nm.

***(EZ)-3-(2,3-Dimethoxyphenyl)-2-butenal* (265).**



265

$C_{12}H_{16}O_4 = 224.25$ $C_{12}H_{14}O_3 = 206.24$

The hydroxy aldehyde (0.5 g, 2.2 mmol) was dissolved in toluene (65 mL) and PPTS (100 mg) was added. The solution was refluxed under a soxhlet apparatus filled with 3Å molecular sieves for 2h after which time the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (10-20% ether / petroleum ether 40-60 °C) to yield the unsaturated aldehyde as an inseparable 3 : 2 mixture of *trans* : *cis* isomers (0.41 g, 1.9 mmol, 90%). Data recorded on mixture.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Major isomer:** 10.18 (1H, d, J = 9.4 Hz, C**H**O), 7.08-6.65 (3H, m, Ar**H**), 6.11 (1H, d, J = 9.4 Hz, C=C**H**CHO), 3.90 (3H, s, OC**H$_3$**), 3.83 (3H, s, OC**H$_3$**), 2.56 (3H, s, C**H$_3$**). **Minor isomer:** 9.40 (1H, d, J = 8.5 Hz, C**H**O), 7.08-6.65 (3H, m, Ar**H**), 6.15 (1H, d, J = 8.5 Hz, C=C**H**CHO), 3.89 (3H, s, OC**H$_3$**), 3.78 (3H, s, OC**H$_3$**), 2.29 (3H, s, =CC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) **Major isomer:** 191.3 (d, **C**HO), 158.9 (s, **C**=CHCHO), 152.9 (s, **C**(Ar)), 137.1 (s, **C**(Ar)), 136.1 (s, **C**(Ar)), 129.9 (d, **C**H (Ar)), 124.2 (d, **C**H (Ar)), 120.9 (d, **C**H (Ar)), 113.1 (d, =**C**HCHO), 61.1 (q, O**C**H_3), 55.9 (q, O**C**H_3), 18.4 (q, =**C**CH_3). **Minor isomer:** 193.3 (d, **C**HO), 160.2 (s, **C**=CHCHO), 152.9 (s, **C**(Ar)), 137.1 (s, **C**(Ar)), 129.8 (d, **C**H (Ar)), 124.0 (d, **C**H (Ar)), 121.6 (d, **C**H (Ar)), 120.9 (s, **C**(Ar)), 112.9 (d, =**C**HCHO), 60.9 (q, O**C**H_3), 55.8 (q, O**C**H_3), 26.2 (q, =**C**CH_3).

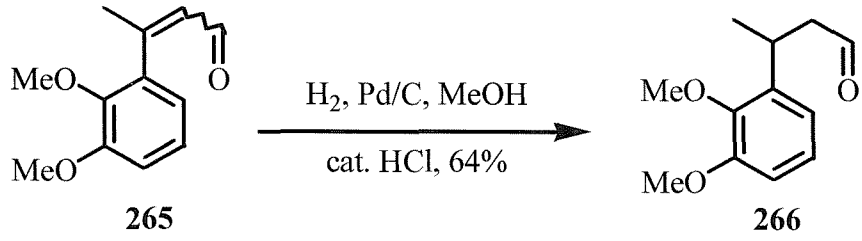
FT-IR (Thin film) 2936 m, 2837 m, 1672 s, 1576 m, 1473 s, 1425 m, 1389 w, 1323 w, 1266 s, 1230 m, 1171 w, 1151 w, 1103 m, 1047 m, 1004 m cm^{-1}.

LRMS (APCI +ve) 248 ($[M+MeCN]^+$, 15%), 207 ($[M+H]^+$, 100%).

HRMS (CI) $[M+NH_4]^+$, $C_{12}H_{18}NO_3$ Requires 224.1287. Found 224.1289.

UV λ_{max} (ε_{max}) 271 (6620), 222 (13500), 204 (13900) nm.

***3-(2,3-Dimethoxyphenyl)butanal* (266).**



265 **266**

$C_{12}H_{14}O_3 = 206.24$ $C_{12}H_{16}O_3 = 208.26$

To a solution of the aldehyde (230 mg, 1.1 mmol) in methanol (20 mL) was added 5% palladium on charcoal (50 mg) and the reaction vessel purged with hydrogen. The black suspension was stirred vigorously under a positive hydrogen pressure for 1h and then filtered through celite. The filtrate was concentrated *in vacuo* and the residue was re-dissolved in acetone (20 mL) and 2M aq. HCl (5 mL) was added. The clear solution was stirred for 1h then water (50 mL) was added and the reaction extracted into ether (3 x 50 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was subjected to flash column chromatography (10-20% ether / petroleum ether 40-60 °C) to yield the saturated aldehyde as a clear oil (227 mg, 1.09 mmol, 64%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.70 (1H, t, J = 2.5 Hz, C**H**O), 7.05 (1H, t, J = 8.5 Hz, Ar**H**), 6.81 (2H, app. d, J = 8.0 Hz, 2 x Ar**H**), 3.88 (6H, s, 2 x OC**H$_3$**), 3.79 (1H, app. sextet, J = 7.0 Hz, ArC**H**), 2.76 (1H, ddd, J = 15.3, 7.0, 2.5 Hz, C**H**H), 2.63 (1H, ddd, J = 15.3, 7.0, 2.5 Hz, CH**H**), 1.30 (3H, d, J = 7.0 Hz, CHC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 202.4 (d, **C**HO), 152.9 (s, **C**(Ar)), 146.5 (s, **C**(Ar)), 139.1 (s, **C**(Ar)), 124.4 (d, **C**H (Ar)), 118.8 (d, **C**H (Ar)), 110.6 (d, **C**H (Ar)), 60.9 (q, O**C**H_3), 55.8 (q, O**C**H_3), 51.2 (t, **C**H_2CHO), 27.6 (d, Ar**C**H), 21.6 (q, **C**H_3).

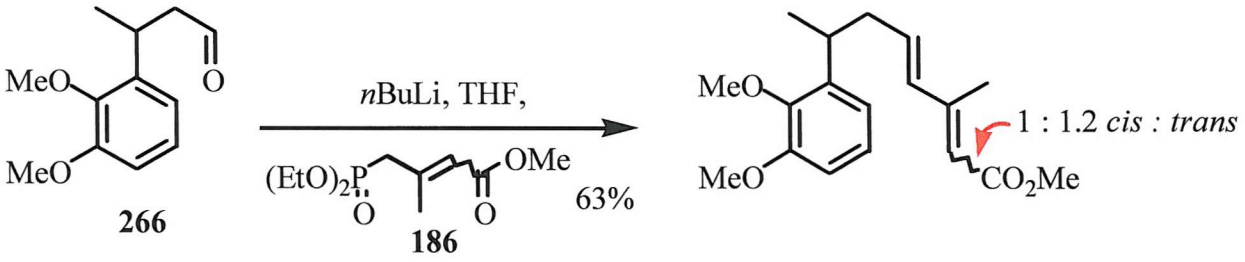
FT-IR (Thin film) 2963 m, 2834 w, 2723 w, 1723 s, 1676 w, 1582 m, 1477 s, 1430 m, 1356 w, 1297 w, 1266 s, 1220 m, 1169 w, 1061 m, 1006 m, cm^{-1}.

LRMS (APCI +ve) 209 ($[M+H]^+$, 5%), 208 (M^+, 35%), 191 ($[M-OH]^+$, 100%).

HRMS (EI) M^+, $C_{12}H_{16}O_3$ Requires 208.1099. Found 208.1098.

UV λ_{max} (ε_{max}) 220 (9930) nm.

Methyl (2EZ,4E)-7-(2,3-dimethoxyphenyl)-3-methyl-2,4-octadienoate.



$C_{12}H_{16}O_3 = 208.26$ $C_{18}H_{24}O_4 = 304.38$

To a solution of the phosphonate (833 mg, 3.8 mmol) in THF (20 mL) at –78 °C was added *n*-Butyllithium (2.88 mL, 3.8 mmol, 1.32 M solution in hexanes), and the resulting brown solution allowed to stir for 30 mins. The aldehyde (400 mg, 1.9 mmol) was then added and the solution allowed to warm to RT and stirred for 16 h. Water (20 mL) was added and the reaction extracted into ether (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (5-20% ether / petroleum ether 40-60 °C) to yield the diene product as a pale yellow oil and a 1.2 : 1 mixture of *trans* and *cis* geometric isomers (362 mg, 1.2 mmol, 63%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Cis* isomer:** 7.58 (1H, d, J = 15.4 Hz, CH_2CH=C**H**), 7.06 (1H, t, J = 7.7 Hz, Ar**H**), 6.83 (1H, d, J = 7.7 Hz, Ar**H**), 6.79 (1H, d, J = 7.7 Hz, Ar**H**), 6.07 (1H, m, CH_2C**H**=CH), 5.68 (1H, s, =C**H**CO_2CH_3), 3.87 (3H, s, ArOC**H$_3$**), 3.84 (3H, s, ArOC**H$_3$**), 3.70 (3H, s, CO_2C**H$_3$**), 3.35 (1H, app. sextet, J = 7.2 Hz, ArC**H**), 2.60-2.35 (2H, m, C**H$_2$**CH=CH), 2.23 (3H, s, C**H$_3$**CH=CH), 1.23 (3H, d, J = 7.2 Hz, CHC**H$_3$**). ***Trans* isomer:** 7.06

(1H, t, J = 7.7 Hz, Ar**H**), 6.83 (1H, d, J = 7.7 Hz, Ar**H**), 6.79 (1H, d, J = 7.7 Hz, Ar**H**), 6.07 (2H, m, CH_2**C**H=**C**H, 5.59 (1H, s, =**C**HCO$_2$CH$_3$), 3.87 (3H, s, ArOC**H$_3$**), 3.84 (3H, s, ArOC**H$_3$**), 3.70 (3H, s, CO$_2$C**H$_3$**), 3.35 (1H, app. sextet, J = 7.2 Hz, ArC**H**CH$_3$), 2.60-2.35 (2H, m, C**H$_2$**CH=CH), 1.95 (3H, s, C**H$_3$**CH=CH) 1.23 (3H, d, J = 7.2 Hz, CHC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 167.8 (s, **C**=O), 166.9 (s, **C**=O), 153.0 (s, **C**=CHCO$_2$CH$_3$), 152.8 (s, **C**=CHCO$_2$CH$_3$), 151.6 (s, 2 x **C**(Ar)), 146.6 (s, 2 x **C**(Ar)), 140.6 (s, **C**(Ar)), 140.3 (s, **C**(Ar)), 137.9 (d, 2 x CH_2**C**H=CH)*, 136.1 (d, CH_2CH=**C**H)*, 135.0 (d, CH_2CH=**C**H)*, 129.0 (d, **C**H (Ar)), 124.2 (d, **C**H (Ar)), 118.9 (d, **C**H (Ar)), 118.8 (d, **C**H (Ar)), 117.5 (d, =**C**HCO$_2$CH$_3$), 115.6 (d, =**C**HCO$_2$CH$_3$), 110.1 (d, **C**H (Ar)), 110.0 (d, **C**H (Ar)), 61.0 (q, 2 x O**C**H$_3$), 55.8 (q, 2 x O**C**H$_3$), 51.1 (q, 2 x CO$_2$**C**H$_3$), 41.5 (t, **C**H$_2$CH=CH), 41.2 (t, **C**H$_2$CH=CH), 32.4 (d, 2 x Ar**C**H(CH$_3$)), 21.4 (q, =C**C**H$_3$), 21.3 (q, =C**C**H$_3$), 14.0 (q, 2 x CH**C**H$_3$).

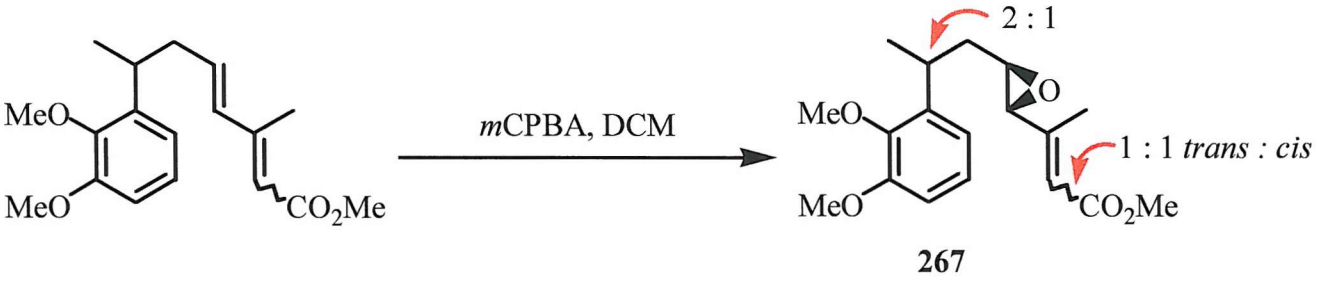
FT-IR (Thin film) 2958 s, 2834 w, 1714 s, 1636 m, 1609 m, 1583 w, 1477 s, 1431 s, 1378 w, 1358 w, 1294 m, 1274 s, 1242 s, 1220 m, 1158 s, 1066 m, 1009 m, 979 w, 921 w, 854 w, 787 w, 747 m cm^{-1}.

LRMS (APCI +ve) 368 ([M+Na+MeCN]$^+$, 25%), 322 ([M+NH$_4$]$^+$, 100%), 305 ([M+H]$^+$, 57%), 304 (M$^+$, 27%), 273 ([M-OMe]$^+$, 28%).

HRMS (CI) M$^+$, $C_{18}H_{24}O_4$ Requires 304.1675. Found 304.1681.

UV λ_{max} (ε_{max}) 263 (28600), 200 (22300) nm.

***Methyl rel-(2EZ,4S,5S,7RS)-4,5 epoxy-7-(2, 3-dimethoxyphenyl)-3-methyl-2 4-octadienoate* (267).**

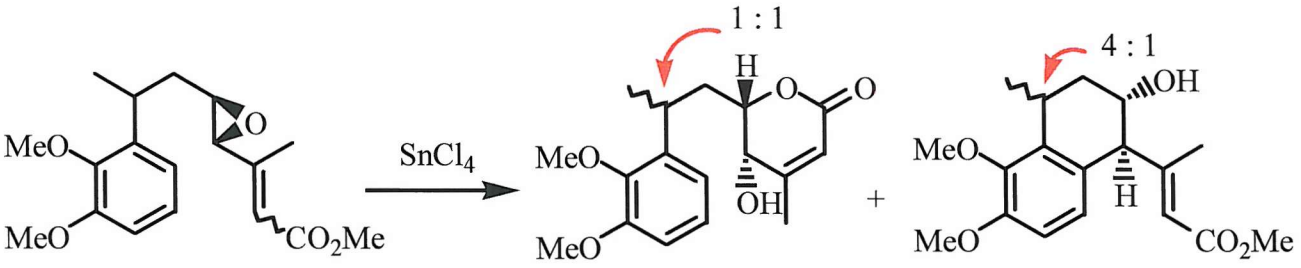


267

$C_{18}H_{24}O_4 = 304.38$ $C_{18}H_{24}O_5 = 320.38$

To a solution of the diene (100 mg, 0.3 mmol) in dichloromethane (20 mL) at $0^{O}C$ was added dried *m*CPBA (208 mg, 0.6 mmol). The clear solution was stirred at $0^{O}C$ for 3 hours then warmed to RT, washed with saturated sodium thiosulfate solution (2 x 30 mL) and water (3 x 20 mL). The organic fraction was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% ether / petroleum ether 40-60°C) to yield an inseparable 2 : 1 mixture of diastereoisomers and a 1 : 1 mixture of geometric isomers (48 mg, 0.14 mmol, 48%). Product unstable to chromatography and used crude in following reactions.

***rel-(2'RS,5S,6S)-6-(2'-(2',3'-dimethoxyphenyl)propyl)-)-5-hydroxy-4-methyl-5,6-dihydro-2H-pyran-2-one* (269) & *methyl (rel-1'R,2E,2'S,4RS)-3-(2'-hydroxy-5',6'-dimethoxy-4-methyl-1,2,3,4-tetrahydronapthyl-but-2-enoate* (268).**



267 $C_{18}H_{24}O_5 = 320.38$

269 $C_{17}H_{22}O_5 = 306.36$

268 $C_{18}H_{24}O_5 = 320.38$

To a cooled (0°C) solution of the epoxide (100 mg, 0.31 mmol) in DCM (30 mL) was added tin(IV) chloride and the resulting yellow solution was allowed to stir at 0°C for 2h. The reaction was washed with water (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude products were purified by flash column chromatography (20-50% ether / petroleum ether 40-60°C) to yield firstly the bicyclic lactones as a clear oil as a 1 : 1 mixture of diastereoisomers (32 mg, 0.11 mmol, 36%) and then the bicyclic alcohols as a pale yellow oil and a 4 : 1 mixture of diastereoisomers (21 mg, 0.07 mmol, 21%).

Data for the bicyclic alcohols methyl (*rel*-1'*R*,2*E*,2'*S*,4*RS*)-3-(2'-hydroxy-5',6'-dimethoxy-4-methyl-1,2,3,4-tetrahydronapthyl-but-2-enoate.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Major isomer:** 6.78 (1H, d, J = 8.5 Hz, Ar**H**), 6.67 (1H, d, J = 8.5 Hz, Ar**H**), 5.90 (1H, s, =C**H**CO_2Me), 3.92 (1H, obsc. m,

CHOH), 3.91 (6H, s, 2 x OCH_3), 3.76 (3H, s, OCH_3), 3.45 (1H, d, J = 8.6 Hz, ArCHCHOH), 3.29 (1H, app. sextet, J = 7.4 Hz, $ArCHCH_2$), 2.37 (1H, ddd, J = 13.1, 7.5, 3.9 Hz, CHHCHOH), 2.05 (3H, s, $=CCH_3$), 1.69 (1H, br. s, OH), 1.54 (1H, obsc. m, CHHCHOH), 1.43 (3H, d, J = 6.9 Hz, $ArCHCH_3$). **Minor isomer:** 6.78 (1H, d, J = 8.5 Hz, ArH), 6.71 (1H, d, J = 8.5 Hz, ArH), 6.03 (1H, s, $=CHCO_2Me$), 3.92 (1H, obsc. m, CHOH), 3.91 (6H, s, 2 x OCH_3), 3.86 (3H, s, OCH_3), 3.45 (1H, d, J = 8.6 Hz, ArCHCHOH), 3.29 (1H, app. sextet, J = 7.4 Hz, $ArCHCH_2$), 2.37 (1H, ddd, J = 13.1, 7.5, 3.9 Hz, CHHCHOH), 2.05 (3H, s, $=CCH_3$), 1.69 (1H, br. s, OH), 1.54 (1H, obsc. m, CHHCHOH), 1.33 (3H, d, J = 7.0 Hz, $ArCHCH_3$).

^{13}C NMR δ_C (100 MHz, $CDCl_3$) **Major isomer:** 167.0 (s, C=O), 159.4 (s, $C=CHCO_2Me$), 151.9 (s, C(Ar)), 147.9 (s, C(Ar)), 135.7 (s, C(Ar)), 127.9 (s, C(Ar)), 124.0 (d, CH (Ar)), 121.4 (d, CH (Ar)), 111.1 (d, $=CHCO_2Me$), 68.9 (d, CHOH), 60.7 (q, OCH_3), 59.7 (q, OCH_3), 56.1 (q, OCH_3), 51.4 (d, ArCHC=), 40.0 (t, CH_2), 29.7 (d, $ArCHCH_3$), 23.7 (q, $=CCH_3$), 16.4 (q, $CHCH_3$). **Minor isomer:** Some peaks obscured by major isomer. 166.9 (s, C=O), 124.1 (d, CH (Ar)), 121.1 (d, CH (Ar)), 111.5 (d, $=CHCO_2Me$), 65.3 (d, CHOH), 60.9 (q, OCH_3), 60.7 (q, OCH_3), 38.0 (t, CH_2), 29.0 (d, $ArCHCH_3$), 22.8 (q, $=CCH_3$), 16.1 (q, $CHCH_3$).

FT-IR (Thin film) 3464 w, 2926 w, 1716 s, 1644 w, 1486 m, 1437 m, 1415 w, 1281 s, 1224 s, 1154 s, 1056 s, 1011 w, 808 w cm^{-1}.

LRMS (CI) 338 ($[M+NH_4]^+$, 81%), 320 (M^+, 12%), 303 ($[M-OH]^+$, 100%).

HRMS (EI) M^+, $C_{18}H_{24}O_5$ Requires 320.1624. Found 320.1640.

UV λ_{max} (ε_{max}) 277 (2060), 224 (10900) nm.

Data for (*rel*-2'*RS*,5*S*,6*S*)-6-(2'-(2',3'-dimethoxyphenyl)propyl)-)-5-hydroxy-4-methyl-5,6-dihydro-2*H*-pyran-2-one

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Diastereoisomer A:** 7.05 (1H, m, Ar**H**), 6.88-6.77 (2H, m, Ar**H**), 5.74 (1H, s, =C**H**CO_2-), 4.15 (1H, m, CH_2C**H**-O), 4.03 (1H, br. s, C**H**OH), 3.88 (3H, s, OC**H$_3$**), 3.85 (3H, s, OC**H$_3$**), 3.53 (1H, m, ArC**H**CH_3), 2.20 (1H, br. t, J = 12.8 Hz, CHC**H**HCH-O), 2.06-1.87 (1H, m, CHCH**H**CH-O), 1.97 (3H, s, =CC**H$_3$**), 1.29 (3H, d, J = 7.0 Hz, ArCHC**H$_3$**). **Diastereoisomer B:** 7.05 (1H, m, Ar**H**), 6.88-6.77 (2H, m, Ar**H**), 5.77 (1H, s, =C**H**CO_2-), 4.15 (1H, m, CH_2C**H**-O), 4.03 (1H, br. s, C**H**OH), 3.87 (3H, s, OC**H$_3$**), 3.84 (3H, s, OC**H$_3$**), 3.53 (1H, m, ArC**H**CH_3), 2.20 (1H, br. t, J = 12.8 Hz, CHC**H**HCH-O), 2.06-1.87 (1H, m, CHCH**H**CH-O), 2.03 (3H, s, =CC**H$_3$**), 1.33 (3H, d, J = 7.0 Hz, ArCHC**H$_3$**).

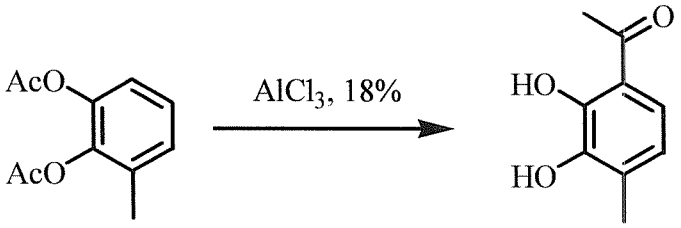
^{13}C NMR δ_C (100 MHz, $CDCl_3$) **Diastereoisomer A:** 163.7 (s, **C**=O), 159.2 (s, **C**=CHCO$_2$-), 153.4 (s, **C**(Ar)), 147.4 (s, **C**(Ar)), 139.5 (s, **C**(Ar)), 124.7 (d, **C**H (Ar)), 119.5 (d, **C**H (Ar)), 117.2 (d, =**C**HCO$_2$-), 110.7 (d, **C**H (Ar)), 80.8 (d, **C**HOH), 69.7 (d, CH_2**C**H-O), 61.4 (q, O**C**H$_3$), 56.1 (q, O**C**H$_3$), 40.5 (t, **C**H$_2$), 29.9 (d, Ar**C**HCH$_3$), 22.9 (q, =**C**CH$_3$), 19.4 (q, ArCH**C**H$_3$). **Diastereoisomer B:** 163.4 (s, **C**=O), 159.8 (s, **C**=CHCO$_2$-), 153.1 (s, **C**(Ar)), 146.4 (s, **C**(Ar)), 140.3 (s, **C**(Ar)), 125.1 (d, **C**H (Ar)), 119.0 (d,

CH (Ar)), 116.9 (d, =**C**HCO$_2$-), 110.7 (d, **C**H (Ar)), 80.6 (d, **C**HOH), 69.3 (d, CH$_2$**C**H-O), 61.4 (q, O**C**H$_3$), 56.1 (q, O**C**H$_3$), 41.0 (t, **C**H$_2$), 28.3 (d, Ar**C**HCH$_3$), 21.4 (q, =**C**CH$_3$), 19.6 (q, ArCH**C**H$_3$).

FT-IR (Thin Film) 3412 br. w, 2960 w, 2908 w, 1692 vs, 1581 w, 1477 s, 1431 m, 1379 w, 1297 m, 1265 vs, 1220 m, 1167 m, 1061 s, 1037 s, 1007 s, 978 w, 862 m, 847 w, 789 m, 749 m cm^{-1}.

UV λ_{max} (ε_{max}) 220 (2785), 206 (2876) nm.

***2,3-Dihydroxy-4-methylacetophenone* (271).**



270 **271**

$C_{11}H_{12}O_4 = 208.21$ $C_9H_{10}O_3 = 166.18$

Prepared as described by Cullinane and Edwards.[56] Thus, finely powdered 3-methylcatechol diacetate (25 g, 0.12 mol) and ground aluminium chloride (16.0 g, 0.12 mol) were mixed and heated to 90°C for 5 minutes. The temperature was then raised to 120°C and maintained at that temperature for 25 minutes. The resulting brown solid was allowed to cool and quenched by the addition of dilute HCl (200 mL) and extracted into DCM (3 x 200 mL). The solvent was removed *in vacuo* and the crude product purified by recrystallisation from petrol to yield the acetophenone as a white crystalline solid (3.6 g, 22 mol, 18%). Data in agreement with literature values.[69]

MP 65-67°C (petrol). Lit. 70°C (petrol).

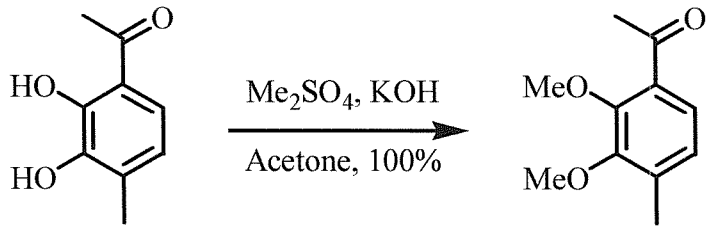
^{1}H NMR δ_H (300 MHz, $CDCl_3$) 12.50 (1H, s, ArO**H**), 7.19 (1H, d, J = 8.3 Hz, Ar**H**), 6.69 (1H, d, J = 8.3 Hz, Ar**H**), 5.80 (1H, s, ArO**H**), 2.61 (3H, s, ArCOC**H**$_3$), 2.31 (3H, s, ArC**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 204.7 (s, **C**=O), 149.1 (s, **C**(Ar)), 143.3 (s, **C**(Ar)), 131.5 (s, **C**(Ar)), 121.0 (d, **C**H (Ar)), 120.8 (d, **C**H (Ar)), 117.8 (s, **C**(Ar)), 26.6 (q, Ar**C**H_3), 16.3 (q, ArCO**C**H_3).

FT-IR ($CHCl_3$ solution) 3450 w, 2920 s, 1635 m, 1615 m, 1505 w, 1455 s, 1425 m, 1370 m, 1310 m, 1025 m, 790 w, 725 w, 655 m, cm^{-1}.

LRMS (CI) 166 (M^+, 60%), 151 ($[M\text{-}CH_3]^+$, 100%).

***2,3-Dimethoxy-4-methylacetophenone* (273).**



271 **273**

$C_9H_{10}O_3 = 166.18$ $C_{11}H_{14}O_3 = 194.23$

To a solution of 2,3-dihydroxy-4-methylacetophenone (0.5 g, 3.0 mmol) in acetone (30 mL), was added powdered potassium hydroxide (0.34 g, 6.0 mmol) and dimethylsulfate (0.57 mL, 0.76 g, 6.0 mmol) and the mixture stirred at ambient temperature for 4 h. Water (50 mL) was added and the reaction extracted with ether (3 x 50 mL). The combined organic extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was subjected to flash column chromatography (50 % ether / petroleum ether 40-60 °C) to yield the product as a yellow oil (0.62 g, 3.0 mmol, 100%). Data consistent with literature values.[70]

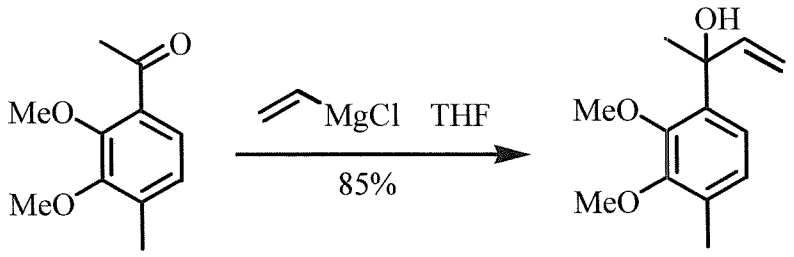
^{1}H NMR δ_H (300MHz, $CDCl_3$) 7.37 (1H, d, J = 8.0 Hz, Ar**H**), 6.98 (1H, d, J = 8.0 Hz, Ar**H**), 3.94 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.62 (3H, s, $ArCOCH_3$), 2.31 (3H, s, $ArCH_3$).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 199.4 (s, **C**=O), 153.1 (s, **C**(Ar)), 151.9 (s, **C**(Ar)), 137.9 (s, **C**(Ar)), 131.6 (s, **C**(Ar)), 125.9 (d, **C**H (Ar)), 124.5 (d, **C**H (Ar)), 61.2 (q, OCH_3), 60.2 (q, OCH_3), 31.2 (q, CH_3Ar), 16.3 (q, CH_3COAr).

FTIR (Thin film) 2937 m, 2857 w, 1678 s, 1601 s, 1566 w, 1462 s, 1403 s, 1357 s, 1272 s, 1228 w, 1192 w, 1173 w, 1123 s, 1055 s, 1017 s cm^{-1}.

LRMS (APCI +ve) 195 ($[M+H]^+$, 100%), 194 (M^+, 5%).

***3-Hydroxy-3-(2,3-dimethoxy-4-methylphenyl)-but-1-ene* (274).**



273 **274**

$C_{11}H_{14}O_3 = 194.23$ $C_{13}H_{18}O_3 = 222.28$

To a precooled solution (-78 °C) of 3,4-dimethoxy-5-methylacetophenone (0.4 g, 2.0 mmol) in THF (15 mL) was added vinylmagnesium chloride (2.0 mL, 3.4 mmol, 1.72 M in THF). The resulting pale yellow solution was allowed to warm to 0 °C and the solution stirred for 16 h. Saturated ammonium chloride solution (30 mL) was added and the reaction extracted into ether (3 x 50 mL). The combined organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (20% ether / petroleum ether 40-60 °C) to yield the alcohol as a yellow oil (351 mg, 1.69 mmol, 85%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 6.96 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.87 (1H, *J* = d, 8.1 Hz, Ar**H**), 6.17 (1H, dd, *J* = 17.2, 10.5 Hz, CH_2=C**H**), 5.17 (1H, dd, *J* = 17.3, 0.9 Hz, CH**H**=CH), 5.08 (1H, d, *J* = 10.6 Hz, C**H**H=CH), 4.67 (1H, br s, O**H**), 3.91 (3H, s, OC**H$_3$**), 3.78 (3H, s, OC**H$_3$**), 2.25 (3H, s, ArC**H$_3$**), 1.62 (3H, s, C**H$_3$**COH).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 151.6 (s, **C**(Ar)), 151.2 (s, **C**(Ar)), 146.7 (d, **C**H=CH_2), 137.3 (s, **C**(Ar)), 132.2 (s, **C**(Ar)), 125.4 (d, **C**H (Ar)), 121.3 (d, **C**H (Ar)),

111.4 (t, $\mathbf{C}H_2$=CH), 75.2 (s, **C**OH), 60.6 (q, O$\mathbf{C}H_3$), 59.8 (q, O$\mathbf{C}H_3$), 27.9 (q, Ar$\mathbf{C}H_3$), 15.8 ($\mathbf{C}H_3$COH).

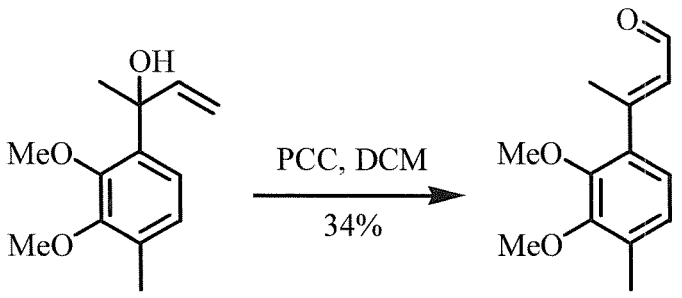
FT-IR (Thin film) 3504 m, 2980 m, 2937 m, 1602 w, 1461 s, 1404 s, 1356 m, 1273 s, 1225 m, 1183 w, 1112 m, 1051 s, 1018 s cm^{-1}.

LRMS (APCI +ve) 222 (M^+, 5%), 205 ($[M-OH]^+$, 100%), 195 ($[M-CH=CH_2]^+$, 24%).

HRMS (EI) M^+, $C_{13}H_{18}O_3$ Requires 222.1256. Found 222.1262.

UV λ_{max} (ε_{max}) 252 (1330), 216 (11300) nm.

(EZ)-3-(2 3-Dimethoxy-4-methylphenyl)-2-butenal.



274 **275**

$C_{13}H_{18}O_3 = 222.28$ $C_{13}H_{16}O_3 = 220.28$

To a solution of the allylic alcohol (1.2 g, 5.4 mmol) in dichloromethane (30 mL) was added pyridinium chlorochromate (3.5 g, 16.2 mmol) and the mixture allowed to stir for 16 h. The resulting black suspension was diluted with ether (50 mL) and the supernatant decanted and concentrated *in vacuo*. The crude black residue was subjected to flash column chromatography (10-20% ether / petroleum ether 40-60 °C) to yield firstly the aldehyde as a pale yellow oil and predominantly the *(E)* isomer (0.45 g, 2.1 mmol, 38%) then 2,3-dimethoxy-4-methylacetophenone as a yellow oil (0.36 g, 1.8 mmol, 34%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 10.17 (1H, d, J = 7.8 Hz, C**H**O), 6.93 (1H, d, J = 7.8 Hz, Ar**H**), 6.84 (1H, d, J = 7.8 Hz, Ar**H**), 6.14 (1H, d, J = 7.8 Hz, C**H**CHO), 3.85 (3H, s, OC**H$_3$**), 3.82 (3H, s, OC**H$_3$**), 2.55 (3H, s, CH=CC**H$_3$**), 2.29 (3H, s, ArC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 191.5 (d, **C**HO), 159.2 (s, **C**=CHCHO), 151.9 (s, **C**(Ar)), 150.3 (s, **C**(Ar)), 135.5 (s, **C**(Ar)), 134.0 (s, **C**(Ar)), 129.8 (d, **C**H

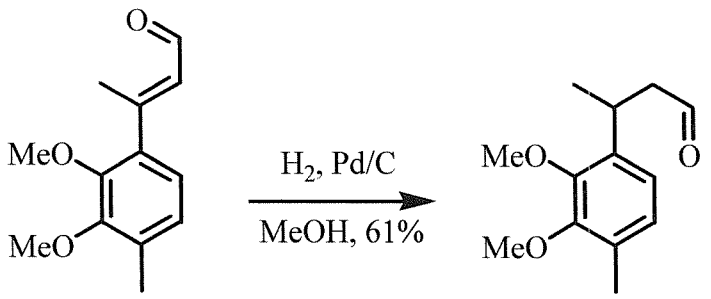
(Ar)), 126.0 (d, **C**H (Ar)), 123.2 (d, =**C**HCHO), 61.0 (q, O**C**H_3), 60.3 (q, O**C**H_3), 18.5 (q, Ar**C**H_3), 16.1 (q, CH=**C**CH_3).

FT-IR (Thin film) 2936 m, 2837 m, 1672 s, 1576 m, 1473 s, 1425 m, 1389 w, 1323 w, 1266 s, 1230 m, 1171 w, 1151 w, 1103 m, 1047 m, 1004 m cm^{-1}.

LRMS (EI) 220 (M^+, 4%), 189 ($[M\text{-}OMe]^+$, 100%), 174 ($[M\text{-}OMe\text{-}Me]^+$, 54%).

UV $\lambda_{max}(\varepsilon_{max})$ 271 (6620), 222 (13500), 204 (13900) nm.

***3-(2,3-Dimethoxy-4-methylphenyl)-butanal* (276).**



275 **276**

$C_{13}H_{16}O_3 = 220.27$ $C_{13}H_{18}O_3 = 222.28$

The unsaturated aldehyde (0.4 g, 1.8 mmol) was dissolved in methanol (50 mL) and HCl (0.5 mL) and 5% palladium on charcoal (25 mg) were added. The resulting black suspension was stirred under a hydrogen atmnosphere (1 atm) for 16 h, after which time the catalyst was removed by filtration. The filtrate was diluted with DCM (70 mL) and washed with dilute HCl (2 M, 3 x 100 mL). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the product aldehyde as a clear oil (0.25 g, 1.1 mmol, 61%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.71 (1H, t, J = 2.2 Hz, C**H**O), 6.89 (1H, d, J = 7.9 Hz, Ar**H**), 6.83 (1H, d, J = 7.9 Hz, Ar**H**), 3.89 (3H, s, OC**H$_3$**), 3.82 (3H, s, OC**H$_3$**), 3.72 (1H, app. sextet, J = 7.1 Hz, ArC**H**), 2.72 (1H, ddd, J = 16.4, 6.8, 2.0 Hz, C**H**HCHO), 2.65 (1H, ddd, J = 16.4, 7.8, 2.4 Hz, CH**H**CHO), 2.24 (3H, s, ArC**H$_3$**), 1.29 (3H, d, J = 7.0 Hz, C**H$_3$**CHAr).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 202.3 (d, **C**HO), 151.5 (s, **C**(Ar)), 150.5 (s, **C**(Ar)), 136.9 (s, **C**(Ar)), 130.6 (s, **C**(Ar)), 125.8 (d, **C**H (Ar)), 121.5 (d, **C**H (Ar)), 60.6 (q, O**C**H_3), 59.9 (q, O**C**H_3), 51.3 (t, **C**H_2CHO), 27.6 (d, Ar**C**HCH_3), 21.6 (q, Ar**C**H_3), 15.7 (q, ArCH**C**H_3).

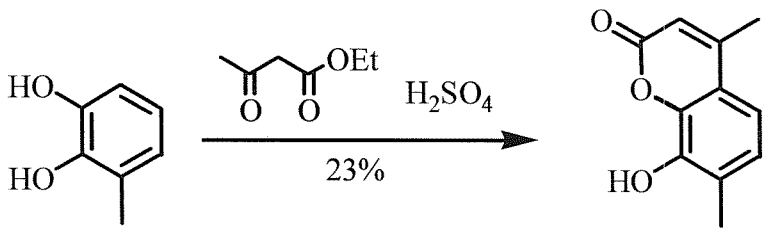
FT-IR (Thin film) 2963 w, 2928 w, 2827 w, 2714 w, 1724 s, 1491 w, 1462 s, 1409 s, 1333 w, 1277 s, 1223 m, 1175 w, 1122 w, 1068 s, 1023 s, 999 w, 900 w, 815 m, 788 w cm^{-1}.

LRMS (EI) 222 (M^+, 80%), 179 ([M-CH_2CHO]$^+$, 98%), 164 (100%), 152 ([M-CH_3CHCH_2CHO]$^+$, 60 %).

HRMS (EI) M^+, $C_{13}H_{18}O_3$ Requires 222.1256. Found 222.1255.

UV λ_{max} (ε_{max}) 263 (400), 216 (7020) nm.

***4,7-Dimethyl-8-hydroxycoumarin* (277).**



141 **277**

$C_7H_8O_2 = 124.14$ $C_{11}H_{10}O_3 = 190.20$

Prepared according to the procedure described by Pechmann *et al.*[57] Thus, to a cooled (0 °C) solution of 3-methylcatechol (30.0 g, 0.24 mol) in ethyl acetoacetate (65 mL) was added concentrated sulfuric acid (98 %, 270 mL) dropwise over a period of 2 h so that the temperature did not rise above 15 °C. The deep red solution was allowed to stir at 0 °C for a further two hours after which time the mixture was poured slowly onto ice (~400 g) and extracted into ether (5 x 300 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude solid was recrystalised from ethanol to yield the product as white needles (5.6 g, 29 mmol, 23%). Data in agreement with literature values.[71]

MP 200-202 °C (EtOH) lit. 204-206 °C (EtOH).

^{1}H NMR δ_H (300 MHz, DMSO) 7.17 (1H, d, J = 8.4 Hz, Ar**H**), 7.12 (1H, d, J = 8.4 Hz, Ar**H**), 6.35 (1H, s, C=C**H**), 2.39 (3H, s, CH=CC**H$_3$**), 2.27 (3H, s, ArC**H$_3$**).

^{13}C NMR δ_C (75 MHz, DMSO) 159.8 (s, **C**=O), 153.9 (s, **C**=CH), 142.3 (s, **C**(Ar)), 142.0 (s, **C**(Ar)), 129.0 (s, **C**(Ar)), 125.8 (d, **C**H (Ar)), 118.4 (s, **C**(Ar)),

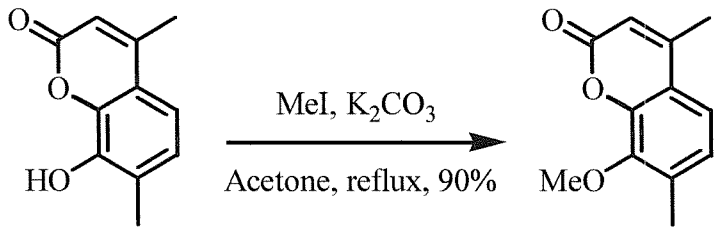
114.9 (d, C=CH), 113.1 (d, CH (Ar)), 18.3 (q, $ArCH_3$), 16.3 (q, $CH=CCH_3$).

FT-IR (Thin film) 3444 m, 2922 s, 2852 s, 1711 s, 1615 s, 1568 m, 1454 s, 1374 s, 1343 w, 1244 w, 1197 w, 153 w, 1136 m, 1050 m, 1012 w, 973 m cm^{-1}

LRMS (APCI +ve) 232 ($[MH+MeCN]^+$, 25%), 191 ($[M+H]^+$, 100%), 190 (M^+, 7%).

UV $\lambda_{max}(\varepsilon_{max})$ 296 (10700), 251 (9510), 204 (17500) nm.

***4,7-Dimethyl-8-methoxycoumarin* (278).**



277 **278**

$C_{11}H_{10}O_3 = 190.20$ $C_{12}H_{12}O_3 = 204.22$

To a solution of the coumarin (5.2 g, 27 mmol) in acetone (150 mL) was added potassium carbonate (18.9 g, 136 mmol) and methyl iodide (8.4 mL, 19.3 g, 136 mmol) and the mixture heated at reflux for 8 h. The reaction was concentrated *in vacuo*, water (150 mL) was added and the mixture extracted into ether (3 x 150 mL). The organic fractions were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The resulting pale yellow solid was recrystallised from petrol / chloroform to yield the methylated product as white needles (4.9 g, 24 mmol, 90%). Data in agreement with literature values.[71]

MP 142-145 °C (petrol-chloroform) lit. 134 °C (EtOH).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 7.23 (1H, d, J = 8.2 Hz, Ar**H**), 7.09 (1H, d, J = 8.2 Hz, Ar**H**), 6.22 (1H, s, C=C**H**), 3.96 (3H, s, OC**H$_3$**), 2.42 (3H, s, C=CC**H$_3$**), 2.37 (3H, s, ArC**H$_3$**).

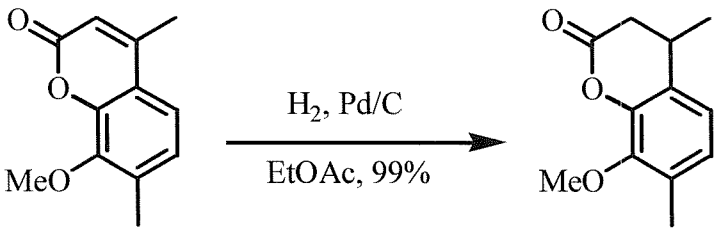
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 160.6 (s, **C**=O), 153.0 (s, **C**=CH), 147.0 (s, **C**(Ar)), 145.7 (s, **C**(Ar)), 135.6 (s, **C**(Ar)), 126.1 (d, **C**H (Ar)), 119.5 (s, **C**(Ar)), 119.0 (d, **C**H (Ar)), 114.1 (d, C=**C**H), 61.2 (q, O**C**H$_3$), 19.0 (q, Ar**C**H$_3$), 16.4 (q, C=C**C**H$_3$).

FT-IR (Thin film) 2822 s, 2852 s, 1727 s, 1609 w, 1561 w, 1456 s, 1474 m, 1268 w, 1240 w, 1178 w, 1142 w, 1065 w, 1011 w cm^{-1}.

LRMS (APCI +ve) 246 ($[MH+MeCN]^+$, 85%), 205 ($[M+H]^+$, 100%), 204 (M^+, 48%).

UV λ_{max} (ε_{max}) 288 (12000), 243 (5250), 211 (15700) nm.

***8-Methoxy-4,7-dimethylchroman-2-one* (279).**



278 **279**

$C_{12}H_{12}O_3 = 204.22$ $C_{12}H_{14}O_3 = 206.24$

The coumarin (4.5 g, 22 mmol) was dissolved in ethyl acetate (50 mL) and 5% palladium on charcoal (75 mg) was added. The resulting black suspension was stirred vigorously in a hydrogen atmosphere (1 atm.) for 16 h after which time the mixture was filtered through celite and the filtrate concentrated *in vacuo* to yield the product chromanone as a clear oil (4.5 g, 21 mmol, 99%). Data in agreement with literature values.[71]

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.87 (1H, d, J = 7.7 Hz, Ar**H**), 6.78 (1H, d, J = 7.9 Hz, Ar**H**), 3.82 (3H, s, OCH_3), 3.09 (1H, app. sextet, J = 7.0 Hz, CH_2CHCH_3), 2.76 (1H, dd, J = 15.6, 5.3 Hz, $CHHCO_2$-), 2.48 (1H, dd, J = 15.6, 7.2 Hz, $CHHCO_2$-), 2.27 (3H, s, $ArCH_3$), 1.33 (3H, d, J = 7.0 Hz, $CHCH_3$).

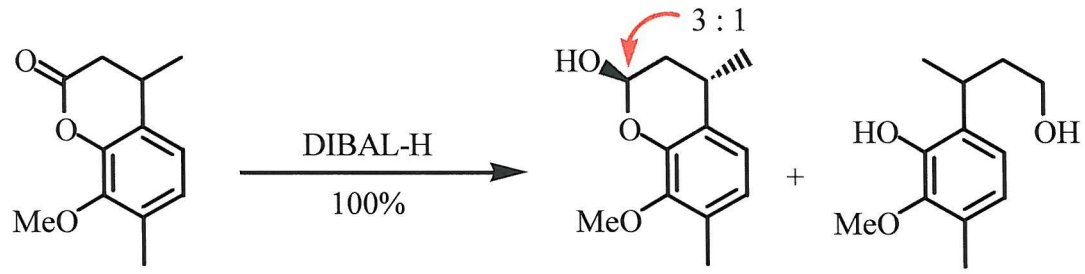
^{13}C NMR δ_C (75 MHz, $CDCl_3$) 168.1 (s, **C**=O), 146.1 (s, **C**(Ar)), 144.5 (s, **C**(Ar)), 131.4 (s, **C**(Ar)), 127.1 (s, **C**(Ar)), 126.2 (d, **C**H (Ar)), 120.8 (d, **C**H (Ar)), 61.1 (q, OCH_3), 37.0 (t, CH_2CO_2-), 29.7 (d, $ArCHCH_3$), 20.1 (q, $ArCH_3$), 15.9 (q, $CHCH_3$).

FT-IR (Thin film) 3516 m, 2961 m, 2931 m, 2873 w, 1771 s, 1618 w, 1581 w, 1497 m, 1455 s, 1418 s, 1344 m, 1323 w, 1270 s, 1244 m, 1151 s, 1109 s, 1060 s, 1037 s, 1005 m, 948 m, 814 m cm^{-1}.

LRMS (APCI +ve) 248 ($[MH+MeCN]^+$, 100%), 206 (M^+, 80%).

UV λ_{max} (ε_{max}) 208 (16700).

***8-Methoxy-4,7-dimethylchroman-2-ol* (281) & *3-(2-hydroxy-3-methoxy-4-methylphenyl)-butan-1-ol* (280).**



279 **281** **280**

$C_{12}H_{14}O_3 = 206.24$ $C_{12}H_{16}O_3 = 208.25$ $C_{12}H_{18}O_3 = 210.27$

To a precooled (-78 °C) solution of the lactone (4.0 g, 19 mmol) in THF (150 mL) was added di-isobutylaluminium hydride (23 mL, 23 mmol, 1.0 M solution in hexane) and the resulting clear solution stirred at –78 °C for 3 h. Water (5 mL) was added dropwise and the solution allowed to warm to RT. Magnesium sulfate (ca. 15 g) was added and the suspension stirred vigorously for 30 mins. The suspension was filtered and the filtrate concentrated *in vacuo* to yield firstly the lactol as a clear oil as a 1 : 3 mixture of *cis* and *trans* diastereoisomers (3.2 g, 15 mmol, 82%) then the alcohol as a white solid (0.6 g, 4.0 mmol, 18%).

Data for 8-Methoxy-4,7-dimethylchroman-2-ol.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Major isomer**: 6.83 (1H, d, J = 8.1 Hz, Ar**H**), 6.72 (1H, d, J = 8.1 Hz, Ar**H**), 5.72 (1H, br. t, J = 2.9 Hz, OC**H**O), 4.09 (1H, br. s, O**H**), 3.71 (3H, s, OC**H$_3$**), 3.15 (1H, app. dq, J = 16.9, 6.6 Hz, CH_2C**H**CH_3), 2.25 (3H, s, ArC**H$_3$**), 2.14-2.00 (1H, m, OCHC**H**H), 1.79-

1.64 (1H, m, OCHCH**H**), 1.24 (3H, d, J = 7.0 Hz, CHC**H**$_3$). **Minor isomer**: 6.78 (1H, d, J = 8.1 Hz, Ar**H**), 6.72 (1H, d, J = 8.1 Hz, Ar**H**), 5.57 (1H, br. dd, J = 8.1, 2.6 Hz, OC**H**O), 4.19 (1H, br. s, O**H**), 3.73 (3H, s, OC**H**$_3$), 2.94 (1H, app. dq, J = 16.6, 6.6 Hz, CH$_2$C**H**CH$_3$), 2.25 (3H, s, ArC**H**$_3$), 2.14-2.00 (1H, m, OC**H**HCH), 1.79-1.64 (1H, m, OCH**H**CH), 1.29 (3H, d, J = 7.0 Hz, CHC**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 146.5 (s, 2 x **C**(Ar)), 144.7 (s, 2 x **C**(Ar)), 130.0 (s, **C**(Ar)), 129.8 (s, **C**(Ar)), 126.7 (s, **C**(Ar)), 126.5 (s, **C**(Ar)), 122.4 (d, 2 x **C**H (Ar)), 122.1 (d, **C**H (Ar)), 121.9 (d, **C**H (Ar)), 94.6 (d, O**C**HO), 91.6 (d, O**C**HO), 60.4 (q, O**C**H$_3$), 60.3 (q, O**C**H$_3$), 37.5 (t, CH**C**H$_2$CH$_3$), 35.6 (t, CH**C**H$_2$CH$_3$), 28.3 (d, CH$_2$**C**HCH$_3$), 24.2 (d, CH$_2$**C**HCH$_3$), 21.1 (q, Ar**C**H$_3$), 20.6 (q, Ar**C**H$_3$), 15.8 (q, 2 x CH**C**H$_3$).

FT-IR (Thin film) 3419 s, 2959 s, 2929 s, 1615 w, 1574 w, 1494 m, 1453 s, 1419 s, 1265 s, 1211 s, 1150 m, 1125 m, 1089 s, 1017 s, 978 s, 939 w, 909 m, 875 w cm^{-1}.

LRMS (APCI +ve) 249 ([M+MeCN]$^+$, 9%), 208 (M$^+$, 100%), 191 ([M-OH]$^+$, 47%).

HRMS (EI) M$^+$, $C_{12}H_{16}O_3$ Requires 208.1094. Found 208.1098.

UV λ_{max} (ε_{max}) 274 (960), 219 (4760) nm.

Data for 3-(2-hydroxy-3-methoxy-4-methylphenyl)butan-1-ol

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.85 (1H, d, J = 7.9 Hz, Ar**H**), 6.70 (1H, d, J = 8.1 Hz, Ar**H**), 6.34 (1H, br. s, ArO**H**), 3.58 (1H, app. sextet, J = 6.9 Hz, ArC**H**CH_2), 3.48-3.28 (2H, m, C**H**$_2$OH), 2.47 (1H, br. s, O**H**), 2.29 (3H, s, ArC**H**$_3$), 1.94 (1H, app. ddt, J = 13.8, 8.6, 5.5 Hz, C**H**HCH$_2$OH), 1.64 (1H, app. ddt, J = 13.8, 9.9, 4.4 Hz, CH**H**CH$_2$OH), 1.29 (3H, d, J = 6.9 Hz, CHC**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 146.4 (s, **C**(Ar)), 145.1 (s, **C**(Ar)), 130.4 (s, **C**(Ar)), 128.0 (s, **C**(Ar)), 122.3 (d, **C**H (Ar)), 122.0 (d, **C**H (Ar)), 61.0 (t, **C**H$_2$OH), 60.6 (q, O**C**H$_3$), 40.8 (t, **C**H$_2$CH$_2$OH), 27.9 (d, Ar**C**H), 20.9 (q, Ar**C**H$_3$), 15.7 (q, CH**C**H$_3$).

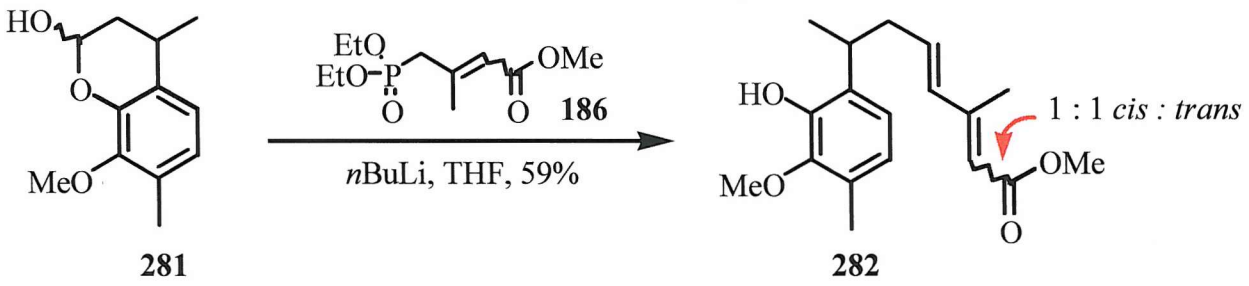
FT-IR ($CHCl_3$ solution) 3452 w, 3066 br. w, 2970 w, 2934 w, 1739 w, 1620 w, 1505 w, 1455 m, 1418 s, 1273 s, 1226 s, 1057 vs, 1015 s, 958 m, 891 w, 851 w, 800 m cm^{-1}.

LRMS (EI) 210 (M^+, 50%), 192 ([M-H_2O]$^+$, 25%), 165 ([M-CH_2CH_2OH], 100%]).

CHN $C_{12}H_{18}O_3$ Requires C: 68.55, H: 8.63, O: 22.83%. Found C: 68.59, H: 8.57%.

UV λ_{max} (ε_{max}) 273 (1870), 222 (3630) nm.

Methyl(2EZ, 4E)-7-(2-hydroxy, 3-methoxy-4-methylphenyl)-3-methyl-2, 4-octadienoate (282).



281

$C_{12}H_{16}O_3 = 208.25$

282

$C_{18}H_{24}O_4 = 304.38$

To a cooled (0°C) solution of the phosphonate (360 mg, 1.4 mmol) in THF (40 mL) was added *n*-butyllithium (1.8 mL, 1.4 mmol, 0.75 M in hexane) and the resulting orange solution was stirred at 0°C for 20 mins. The lactol (100 mg, 0.48 mmol) was then added dropwise as a solution in THF (5 mL) and the reaction allowed to stir for 2h. Water (40 mL) was added and the reaction extracted into ether (3 x 50 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude residue was subjected to flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the product diene as a pale yellow oil and a 1 : 1 mixture of *cis* and *trans* geometric isomers (86 mg, 0.28 mmol, 59%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) ***Cis* isomer:** 7.57 (1H, d, J = 15.8 Hz, CH_2CH=C**H**), 6.83 (1H, d, J = 7.9 Hz, Ar**H**), 6.66 (1H, d, J = 7.9 Hz, Ar**H**), 6.12 (1H, obsc. m, CH_2C**H**=CH), 5.82 (1H, br. s, O**H**), 5.59 (1H, s, =C**H**CO_2CH_3), 3.81 (3H, s, OC**H$_3$**), 3.24 (1H, app. sextet, J = 7.1 Hz, ArC**H**CH_3), 2.33-2.16 (2H, m, C**H$_2$**CH=CH), 2.30 (3H, s, ArC**H$_3$**), 1.96 (3H, s, =CC**H$_3$**), 1.24 (3H, d, J = 7.2 Hz, ArCHC**H$_3$**). ***Trans* isomer:** 7.57 (1H, d, J = 15.8 Hz,

$CH_2CH=CH$), 6.83 (1H, d, J = 7.9 Hz, Ar**H**), 6.66 (1H, d, J = 7.9 Hz, Ar**H**), 6.12 (2H, m, $CH_2CH=CH$), 5.82 (1H, br. s, O**H**), 5.67 (1H, s, $=CHCO_2CH_3$), 3.70 (3H, s, OCH_3), 3.24 (1H, app. sextet, J = 7.1 Hz, $ArCHCH_3$), 2.33-2.16 (2H, m, $CH_2CH=CH$), 2.30 (3H, s, $ArCH_3$), 2.23 (3H, s, $=CCH_3$), 1.24 (3H, d, J = 7.2 Hz, $ArCHCH_3$).

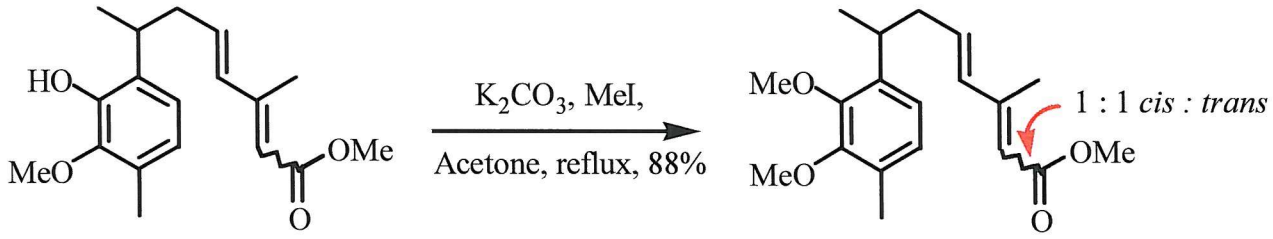
^{13}C NMR δ_C (75MHz, $CDCl_3$) 166.9 (s, **C**=O), 167.8 (s, **C**=O), 153.1 (s, **C**$=CHCO_2CH_3$), 151.7 (s, **C**$=CHCO_2CH_3$), 146.3 (s, **C**(Ar)), 145.2 (s, **C**(Ar)), 138.1 (d, 2 x CH_2**C**H=CH)*, 136.4 (d, $CH_2CH=$**C**H)*, 134.8 (d, $CH_2CH=$**C**H)*, 130.9 (s, **C**(Ar)), 130.7 (s, **C**(Ar)), 129.7 (s, **C**(Ar)), 129.4 (s, **C**(Ar)), 128.8 (d, **C**H (Ar)), 128.0 (s, **C**(Ar)), 127.8 (s, **C**(Ar)), 122.3 (d, **C**H (Ar)), 121.8 (d, **C**H (Ar)), 121.7 (d, **C**H (Ar)), 117.3 (d, $=$**C**HCO_2CH_3), 115.4 (d, $=$**C**HCO_2CH_3), 60.7 (q, OCH_3), 60.1 (q, OCH_3), 52.0 (q, OCH_3), 51.0 (q, OCH_3), 40.7 (t, CH_2), 40.6 (t, CH_2), 32.7 (d, Ar**C**HCH_3), 32.7 (d, Ar**C**HCH_3), 21.3 (q, ArCH_3), 20.1 (q, $=CCH_3$), 20.1 (q, ArCH_3), 15.9 (q, $=CCH_3$), 15.8 (q, $ArCHCH_3$) 14.0 (q, $ArCHCH_3$).

FT-IR (Thin Film) 3421 br. w, 2956 w, 2914 w, 1714 m, 1633 w, 1603 w, 1452 m, 1419 m, 1269 w, 1245 m, 1225 m, 1157 s, 1019 m, 801 w cm^{-1}.

LRMS (APCI +ve) 314 ($[M\text{-}OMe+MeCN]^+$, 32%), 305 ($[M+H]^+$, 74%), 273 ($[M\text{-}OMe]^+$, 100%).

HRMS (EI) M^+, $C_{18}H_{24}O_4$ Requires 304.1675. Found 304.1678.

***Methyl (2EZ,4E)-7-(2,3-dimethoxy-4-methylphenyl)-3-methylocta-2,4-dienoate* (283).**



282

$C_{18}H_{24}O_4 = 304.38$

283

$C_{19}H_{26}O_4 = 318.41$

To a solution of the phenol (80 mg, 0.26 mmol) in acetone (30 mL) was added potassium carbonate (72 mg, 0.52 mmol) and methyl iodide (140 mg, 0.06 mL, 1.0 mmol). The mixture was heated to reflux for 8h then water (30 mL) was added and the reaction extracted into ether (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the methylated product as a clear oil and a 1 : 1 mixture of *cis* and *trans* geometric isomers (73 mg, 0.23 mmol, 88%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) ***Cis* isomer:** 7.50 (1H, d, J = 15.8 Hz, CH_2CH=C**H**), 6.78 (2H, m, Ar**H**), 6.00 (1H, obsc. m, CH_2C**H**=CH), 5.33 (1H, br. s, =C**H**CO_2CH_3), 3.77 (3H, s, OC**H$_3$**), 3.75 (3H, s, OC**H$_3$**), 3.61 (3H, s, OC**H$_3$**), 3.19 (1H, app. sextet, J = 7.0 Hz, ArC**H**CH_3), 2.49-2.25 (2H, m, C**H$_2$**CH=CH), 2.18 (3H, s, ArC**H$_3$**), 1.89 (3H, s, =CC**H$_3$**), 1.16 (3H, d, J = 7.0 Hz, ArCHC**H$_3$**). ***Trans* isomer:** 6.78 (2H, m, Ar**H**), 6.00 (2H, obsc. m, CH_2C**H**=C**H**), 5.60 (1H, br. s, =C**H**CO_2CH_3), 3.77 (3H, s, OC**H$_3$**), 3.75

(3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.19 (1H, app. sextet, J = 7.0 Hz, $ArCHCH_3$), 2.49-2.25 (2H, m, $CH_2CH=CH$), 2.18 (3H, s, $ArCH_3$), 2.15 (3H, s, $=CCH_3$), 1.16 (3H, d, J = 7.0 Hz, $ArCHCH_3$).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 167.8 (s, C=O), 166.9 (s, C=O), 153.0 (s, 2 x C(Ar)), 151.6 (s, $C=CHCO_2CH_3$), 151.4 (s, $C=CHCO_2CH_3$), 150.7 (s, 2 x C(Ar)), 138.5 (s, C(Ar)), 138.2 (s, C(Ar)), 138.0 (d, CH (Ar)), 136.2 (d, CH (Ar)), 134.9 (d, CH (Ar)), 130.0 (s, C(Ar)), 129.9 (s, C(Ar)), 128.9 (d, CH (Ar)), 125.8 (d, 2 x $CH_2CH=CH$), 121.6 (d, $CH_2CH=CH$), 121.5 (d, $CH_2CH=CH$), 117.4 (d, $=CHCO_2CH_3$), 115.5 (d, $=CHCO_2CH_3$), 60.8 (q, 2 x OCH_3), 60.0 (q, 2 x OCH_3), 51.1 (q, 2 x CO_2CH_3), 41.7 (t, CH_2), 41.5 (t, CH_2), 32.4 (d, $ArCHCH_3$), 32.3 (d, $ArCHCH_3$), 21.3 (q, 2 x $ArCH_3$)*, 15.8 (q, 2 x $=CCH_3$)*, 14.0 (q, 2 x $CHCH_3$).

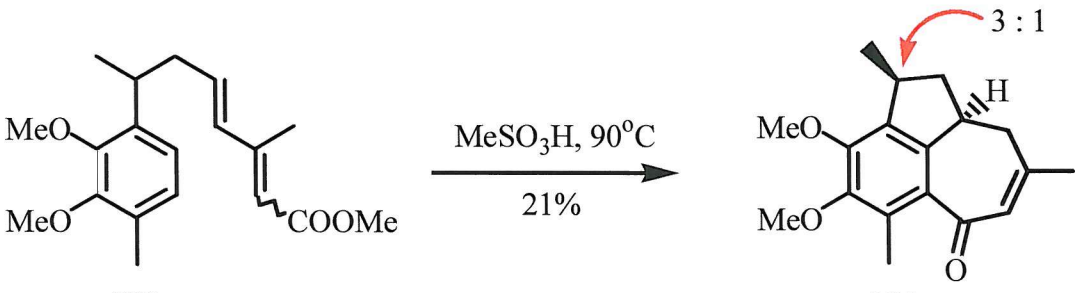
FT-IR (Thin Film) 2553 w, 1715 m, 1635 w, 1611 w, 1489 w, 1460 m, 1408 w, 1277 m, 1240 m, 1156 vs, 1068 m, 1025 m, 968 w, 913 w, 859 w, 812 w cm^{-1}.

LRMS (EI) 318 (M^+, 100%).

HRMS (EI) M^+, $C_{19}H_{26}O_4$ Requires 318.1831. Found 318.1828.

UV λ_{max} (ε_{max}) 265 (26100), 206 (21000) nm.

***(rel-2S,9aS)-3,4-dimethoxy-2,5,8-trimethyl-2,6,9,9a-tetrahydro-1H-benzo[cd]azulen-6-one* (284).**



283 $C_{19}H_{26}O_4 = 318.41$

284 $C_{18}H_{22}O_3 = 286.36$

To the ester (120 mg, 0.38 mmol) at 0°C was added methanesulfonic acid (36 mg, 0.40 mmol) and the mixture allowed to warm to RT then slowly warmed to 90°C over 1 h. The mixture was held at this temperature for 10 mins then allowed to cool. The residue was purified by flash column chromatography (20-50% ether / petroleum ether 40-60°C) to yield the enone as a yellow oil and inseperable 3 : 1 mixture of diastereoisomers (22 mg, 0.08 mmol, 21%)

^{1}H NMR δ_H (300MHz, $CDCl_3$) **Major diastereoisomer:** 6.16 (1H, s, COC**H**=C), 3.96 (3H, s, OC**H$_3$**), 3.78 (3H, s, OC**H$_3$**), 3.69 (1H, app. quintet J = 7.1 Hz, CH_2C**H**CH_2), 3.50 (1H, m, CH_3C**H**), 2.37 (2H, m, C**H$_2$**C=), 2.32 (3H, s, ArC**H$_3$**), 2.05-1.88 (2H, m, CH_3CHC**H$_2$**), 1.96 (3H, s, =CC**H$_3$**), 1.21 (3H, d, J = 7.1 Hz, C**H$_3$**CH). **Minor diastereoisomer:** 6.16 (1H, s, COC**H**=C), 3.96 (3H, s, OC**H$_3$**), 3.78 (3H, s, OC**H$_3$**), 3.69 (1H, app. quintet J = 7.1 Hz, CH_2C**H**CH_2), 3.37 (1H, sextet, J = 7.3 Hz, CH_3C**H**), 2.32 (3H, s, ArC**H$_3$**),

2.05-1.88 (2H, m, CH_3CHCH_2), 1.95 (3H, s, $=CCH_3$), 1.39 (3H, d, J = 7.1Hz, CH_3CH).

These assignments were confirmed by ^1H-^1H and ^1H-^{13}C correlation experiments.

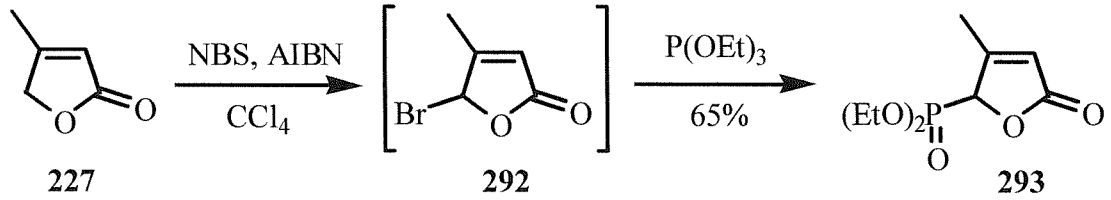
^{13}C NMR δ_C (75MHz, $CDCl_3$) 193.5 (s, 2 x C=O), 173.8 (s, 2 x C=CHCO), 154.6 (s, 2 x C(Ar)), 151.6 (s, C(Ar)), 151.9 (s, C(Ar)), 150.9 (s, 2 x C(Ar)), 141.6 (s, 2 x C(Ar)), 137.8 (s, 2 x C(Ar)), 132.9 (s, C(Ar)), 132.0(s, C(Ar)), 130.7 (d, 2 x C=CHCO), 60.4 (q, OCH_3), 60.3 (q, OCH_3), 60.2 (q, 2 x OCH_3), 43.2 (t, $CH_2C=$), 42.8 (d, CHC=CHCO), 42.4 (d, CHC=CHCO), 41.9 (t, $CH_2C=$), 40.8 (t, $CHCH_2CH$), 40.6 (t, $CHCH_2CH$), 37.5 (d, CH_3CH), 36.9 (d, CH_3CH), 27.6 (q, $CH_3C=$), 27.4 (q, $CH_3C=$), 22.5 (q, $ArCH_3$), 21.6 (q, $ArCH_3$), 13.6 (q, CH_3CH), 13.4 (q, CH_3CH).

FT-IR (Thin Film) 2936 w, 2834 w, 1670 vs, 1577m, 1472 s, 1425 m, 1387 w, 1323 w, 1265 s, 1230 m, 1152 m, 1103 s, 1047 m, 1004 s, 884 w, 789 m, 749 s cm^{-1}.

LRMS (APCI +ve) 328 ($[MH+MeCN]^+$, 10%), 287 ($[M+H]^+$, 100%)

UV λ_{max} (ε_{max}) 210 (14700) 254 (6460) nm.

***Diethyl 3-methyl-5-oxo-2,5-dihydro-2-furanyl-phosphonate* (293).**



227 **292** **293**

$C_5H_6O_2 = 98.10$ $C_5H_5O_2Br = 177.00$ $C_9H_{15}PO_5 = 234.21$

To a solution of the furanone (1.1 g, 11 mmol) in carbon tetrachloride (30 mL) was added *N*-bromosuccinimide (2.0 g, 11 mmol) and the mixture heated to reflux. AIBN (50 mg) was added and the yellow solution was maintained at reflux for 30 mins. The reaction was concentrated *in vacuo* and excess succinimide was removed by the addition of ether (30 ml) and filtration. The filtrate was concentrated *in vacuo* and the resulting yellow oil was dissolved in triethyl phosphite (1.8 g, 11 mmol) and the mixture heated to 150 °C for 30 minutes. The crude product was purified by flash column chromatography (10-30 % methanol / ether) to yield the pure phosphonate as a clear oil (1.7 g, 7.2 mmol, 65 %).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 5.96 (1H, br. s, C=C**H**), 5.10 (1H, d, J_{PH} = 15.4 Hz, PC**H**O), 4.19 (4H, dq, J = 15.4, 7.5 Hz, 2 x O**CH$_2$**), 2.27 (3H, s, **CH$_3$**C=CH), 1.31 (6H, dt, J = 15.4, 7.5 Hz, 2 x OCH$_2$**CH$_3$**).

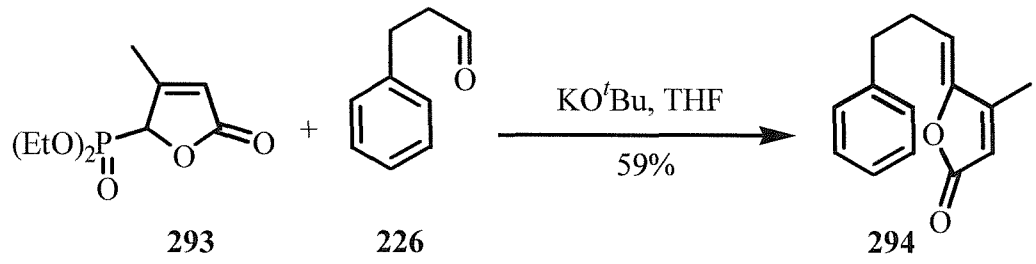
^{13}C NMR δ_C (75MHz, $CDCl_3$) 172.6 (s, **C**=O), 164.5 (s, J_{PC} = 4.4 Hz, **C**=CH), 117.8 (d, J_{PC} = 7.0 Hz, C=**C**HCO), 79.2 (d, J_{PC} = 162.3 Hz, **P**CHO), 64.0 (t, J_{PC} = 7.1 Hz, 2 x PO**CH$_2$**), 16.4 (q, J_{PC} = 5.4 Hz, **CH$_3$**C=CH), 15.1 (q, 2 x **CH$_3$**CH$_2$OP).

FT-IR (Thin film) 3442 br. w, 2973 w, 1786 m, 1755 m, 1637 w, 1441 w, 1390 w, 1279 w, 1251 m, 1163 w, 1138 w, 1019 vs, 978 m, 889 m, 786 w cm^{-1}.

LRMS (CI) 252 ($[M+NH_4]^+$, 100%), 235 ($[M+H]^+$, 100%).

HRMS (EI) M^+, $C_9H_{15}PO_5$ Requires 234.0657. Found 234.0654.

***4-Methyl-5-((Z)-3-phenylpropylidene)-2,5-dihydro-2-furanone* (294).**



293 **226** **294**

$C_9H_{15}PO_5 = 234.21$ $C_9H_{10}O = 134.18$ $C_{14}H_{14}O_2 = 214.26$

To a solution of the phosphonate (1.1 g, 4.7 mmol) in THF (20 mL) was added potassium *tert*-butoxide (0.54 g, 4.8 mmol) and the resulting red solution stirred at 0° C for 30 mins. A solution of 3-phenylpropionaldehyde (250 mg, 1.8 mmol) in THF (5 mL) was added *via* syringe and the resulting orange solution allowed to stir for 1h. Water (50 mL) was added and the reaction extracted into ether (3 x 50 mL), dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude red oil was subjected to flash column chromatography (20-30% ether / petroleum ether 40-60°C) to yield the pure product as a pale yellow oil and a single geometric isomer (240 mg, 1.1 mmol, 59%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 7.33-7.15 (5H, m, Ar**H**), 5.91 (1H, br. s, C=C**H**), 5.32 (1H, t, J = 7.2 Hz, CH_2C**H**=C), 2.84-2.69 (4H, m, Ar**C**$\mathbf{H_2}$**C**$\mathbf{H_2}$), 2.10 (3H, s, **C**$\mathbf{H_3}$).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 169.6 (s, **C**=O), 154.7 (s, **C**=CHCO), 151.1 (s, =**C**-O), 140.9 (s, **C**(Ar)), 128.6 (d, 2 x **C**H (Ar)), 128.5 (d, 2 x **C**H (Ar)), 126.3 (d, **C**H (Ar)), 116.3 (d, C=**C**HCO), 111.8 (d, **C**H=C-O), 35.2 (t, **C**H_2), 27.8 (t, **C**H_2), 11.8 (s, **C**H_3).

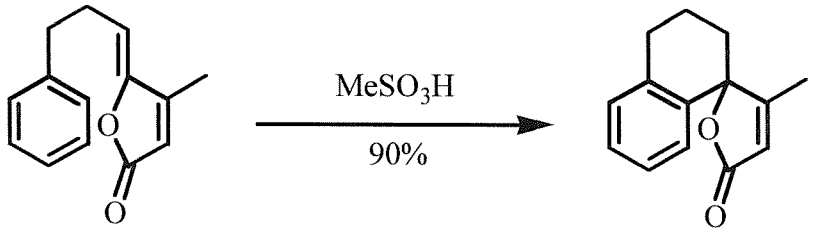
FT-IR (Thin Film) 2938 w, 1765 s, 1676 w, 1604 w, 1492 w, 1457 w, 1341 w, 1226 w, 1166 w, 1086 w, 1030 w, 990 w, 923 m, 847 m cm^{-1}.

LRMS (CI) 214 (M^+, 22%), 91 (100%).

HRMS (EI) M^+, $C_{14}H_{14}O_2$ Requires 214.0994. Found 214.1001.

UV λ_{max} (ε_{max}) 277 (3070), 204 (2290) nm.

***14-Methylspiro[1,2,3,4-tetrahydronapthalene-1,5'-5H-furan]-12-one* (295).**



294 **295**

$C_{14}H_{14}O_2 = 214.26$ $C_{14}H_{14}O_2 = 214.26$

The furanone (150 mg, 0.7 mmol) and methanesulfonic acid (100 mg, 0.1 mmol) were mixed under a nitrogen atmosphere and heated to 90°C for 10 mins. The resulting brown oil was subjected to flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the cyclised product as a yellow oil (135 mg, 0.6 mmol, 90%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 7.30-7.13 (3H, m, Ar**H**), 6.97 (1H, d, J = 7.8 Hz, Ar**H**) 6.01 (1H, s, C=C**H**CO), 3.00-2.74 (2H, m, Ar**C**$\mathbf{H_2}$$CH_2$), 2.22-1.93 (4H, m, $ArCH_2$**C**$\mathbf{H_2}$**C**$\mathbf{H_2}$), 1.91 (3H, s, **C**$\mathbf{H_3}$C=CH).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 172.4 (s, **C**=O), 172.0 (s, **C**=CHCO), 138.5 (s, **C**(Ar)), 131.1 (s, **C**(Ar)), 129.7 (d, **C**H (Ar)), 129.0 (d, **C**H (Ar)), 126.7 (d, **C**H (Ar)), 126.6 (d, **C**H (Ar)), 117.7 (d, C=**C**HCO), 88.4 (s, Ar**C**), 33.7 (t, Ar**C**H_2), 29.4 (t, $ArCH_2CH_2$**C**H_2), 19.4 (t, $ArCH_2$**C**H_2), 13.8 (q, **C**H_3C=CH).

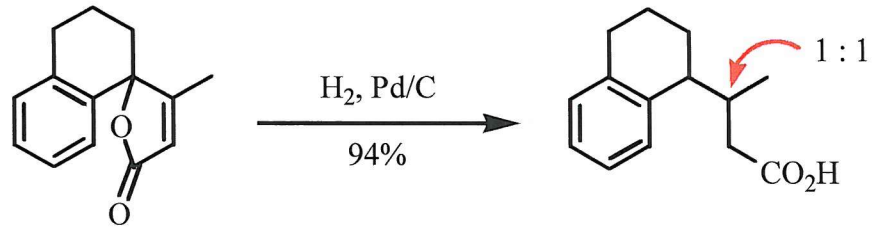
FT-IR (Thin Film) 2938 w, 1747 s, 1644 w, 1497 w, 1433 w, 1277 w, 1232 m, 1066 w, 940 s, 847 w cm^{-1}.

LRMS (CI) 232 ($[M+NH_4]^+$, 100%), 215 ($[M+H]^+$, 92%).

HRMS (CI) M^+, $C_{14}H_{14}O_2$ Requires 214.0994. Found 214.0997.

UV λ_{max} (ε_{max}) 263 (15300), 206 (8980) nm.

***3-(1,2,3,4-Tetrahydro-1-napthalenyl)-butanoic acid* (296).**



295 **296**

$C_{14}H_{14}O_2 = 214.26$ $C_{14}H_{18}O_2 = 218.29$

To a solution of the furanone (100 mg, 0.47 mmol) in ethyl acetate (10 mL) was added 5% palladium on charcoal (10 mg) and the black suspension stirred vigorously in a hydrogen atmosphere for 2h. The mixture was filtered through celite and the filtrate concentrated *in vacuo* to yield the carboxylic acid as a yellow oil and 1 : 1 mixture of diastereoisomers (96 mg, 0.44 mmol, 94%). Data recorded on mixture.

^{1}H NMR δ_H (300MHz, $CDCl_3$) **Diastereoisomer A:** 7.25-6.97 (4H, m, Ar**H**), 2.88-2.78 (1H, m, ArC**H**CH_2), 2.77-1.10 (9H, m, $CH_2CH_2CH_2CH(Ar)CHCH_2$), 1.05 (3H, d, J = 7.3 Hz, CH_3). **Diastereoisomer B:** 7.25-6.97 (4H, m, Ar**H**), 2.78-2.56 (1H, m, ArC**H**CH_2), 2.77-1.10 (9H, m, $CH_2CH_2CH_2CH(Ar)CHCH_2$), 0.72 (3H, d, J = 7.3 Hz, CH_3).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 180.5 (s, **C**=O), 180.1 (s, **C**=O), 139.1 (s, **C**(Ar)), 138.8 (s, **C**(Ar)), 138.6 (s, **C**(Ar)), 138.5 (s, **C**(Ar)), 129.3 (d, **C**H (Ar)), 129.2 (d, **C**H (Ar)), 128.1 (d, **C**H (Ar)), 127.8 (d, **C**H (Ar)), 126.1 (d, **C**H (Ar)), 125.9 (d, 2 x **C**H (Ar)), 125.7 (d, **C**H (Ar)), 42.7 (d, Ar**C**HCH$_2$), 41.5 (d, Ar**C**HCH$_2$), 40.1 (t, Ar**C**H$_2$), 36.6 (t, Ar**C**H$_2$), 34.1 (d, CH$_3$**C**H), 33.9 (d, CH$_3$**C**H), 30.3, (t, **C**H$_2$CO$_2$H), 30.1 (t, **C**H$_2$CO$_2$H), 24.0 (t, Ar**C**H$_2$CH$_2$),

23.4 (t, Ar**C**H_2CH_2), 22.1 (t, $ArCH_2CH_2$**C**H_2), 21.7 (t, $ArCH_2CH_2$**C**H_2), 18.6 (q, CH**C**H_3), 15.1 (q, CH**C**H_3).

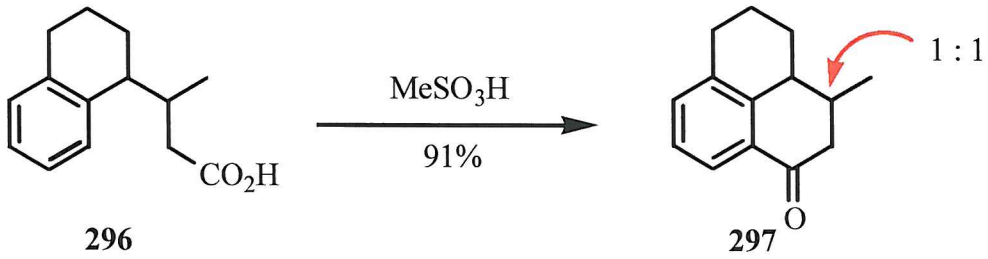
FT-IR (Thin Film) 2928 m, 2874 w, 1700 s, 1489 w, 1450 w, 1403 w, 1239 w, 1216 w, 938 w, 767 m cm^{-1}.

LRMS (CI) 218 (M^+, 10%), 158 ($[M-CH_2CO_2H]^+$, 22%), 131 ($[M-CH_3CHCH_2CO_2H]$, 100%).

HRMS (EI) M^+, $C_{14}H_{18}O_2$ Requires 218.1307. Found 218.1306.

UV λ_{max} (ε_{max}) 263 (305), 218 (3530) nm.

***3-Methyl-2,3,3,4,5,6-hexahydro-1H-1-phenalenone* (297).**



296

$C_{14}H_{18}O_2 = 218.29$

297

$C_{14}H_{16}O = 200.28$

The acid (50 mg, 0.22 mmol), and methanesulfonic acid (30 mg, 0.3 mmol) were mixed under a nitrogen atmosphere and heated to 90°C for 10 mins. The resulting brown oil was subjected to flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the cyclised product as a yellow oil, and inseparable 1 : 1 mixture of diastereoisomers (40 mg, 0.20 mmol, 91%). Data recorded on mixture.

^{1}H NMR δ_H (300MHz, $CDCl_3$) **Diastereoisomer A:** 7.84 (1H, t, J = 7.4 Hz, Ar**H**), 7.31-7.19 (2H, m, Ar**H**), 3.17-1.15 (10H, m, **$CH_2CH_2CH_2CHCHCH_2$**), 1.19 (3H, d, J = 7.3 Hz, **CH_3**). **Diastereoisomer B:** 7.84 (1H, t, J = 7.4 Hz, Ar**H**), 7.31-7.19 (2H, m, Ar**H**), 3.17-1.15 (10H, m, **$CH_2CH_2CH_2CHCHCH_2$**), 0.86 (3H, d, J = 7.3 Hz, **CH_3**).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 198.7 (s, 2 x **C**=O), 143.3 (s, **C**(Ar)), 140.4 (s, **C**(Ar)), 137.8 (s, **C**(Ar)), 136.9 (s, **C**(Ar)), 134.8 (d, **C**H (Ar)), 134.6 (d, **C**H (Ar)), 132.0 (s, 2 x **C**(Ar)), 126.2 (d, **C**H (Ar)), 126.1 (d, **C**H (Ar)), 125.1 (d, **C**H (Ar)), 124.6 (d, **C**H (Ar)), 48.1 (d, CH_2**C**H(Ar)), 47.8 (d, CH_2**C**H(Ar)), 43.3 (d, CH_3**C**HCH_2CO), 40.6 (d, CH_3**C**HCH_2CO), 36.4 (t, 2 x **C**H_2CO), 29.4 (t,

$ArCH_2$), 29.3 (t, $ArCH_2$), 27.9 (t, CH_2), 27.3 (t, CH_2), 23.0 (t, CH_2), 22.6 (t, CH_2), 19.4 (q, CH_3), 13.5 (q, CH_3).

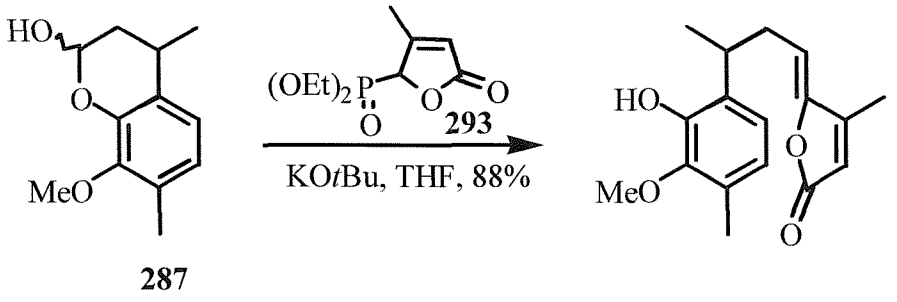
FT-IR (Thin film) 2919 m, 1738 m, 1716 s, 1683 s, 1613 w, 1455 m, 1408 w, 1349 w, 1281 m, 1237 m, 1156 s, 1071 w, 1026 m, 969 w, 917 w cm^{-1}.

LRMS (EI) 200 (M^+, 50%), 185 ($[M-CH_3]^+$, 12%), 158 (100%).

HRMS (EI) M^+, $C_{14}H_{16}O$ Requires 200.1201. Found 200.1194.

UV λ_{max} (ε_{max}) 297 (933), 259 (4270), 216 (6070) nm.

5-(Z)-3-(2-Hydroxy-3-methoxy-4-methylphenyl)butylidene)-4-methyl-2,5-dihydro-2-furanone.



287

$C_{12}H_{16}O_3$ = 208.25 $C_{17}H_{20}O_4$ = 288.34

To a solution of the phosphonate (3.5 g, 15.0 mmol) in THF (50 mL) was added potassium *tert* butoxide (1.7 g, 15.0 mmol) and the red solution allowed to stir for 30 mins. The lactol (1.2 g, 6.0 mmol) in THF (10 mL) was then added dropwise and the solution stirred at RT for 1h. Water (50 mL) was added and the reaction mixture extracted into ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30-50% ether / petroleum ether 40-60°C) to yield the desired product as a pale yellow oil (0.89 g, 3.1 mmol, 51%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 6.87 (1H, d, J = 7.8 Hz, Ar**H**), 6.66 (1H, d, J = 7.8 Hz, Ar**H**), 5.89 (1H, s, C=C**H**CO), 5.82 (1H, s, ArO**H**), 5.27 (1H, t, J = 7.4 Hz, CH_2CH=), 3.80 (3H, s, OCH_3), 3.30 (1H, app. sextet, J = 6.6 Hz, CH_2(Ar)C**H**CH_3), 2.72 (2H, t, J = 6.8 Hz, CHC**H**$_2$CH=), 2.29 (3H, s, ArCH_3), 2.10 (3H, s, C=CCH_3), 1.29 (3H, d, J = 7.4 Hz, CHCH_3).

^{13}C NMR δ_c (75 MHz, $CDCl_3$) 169.8 (s, **C**=O), 154.7 (s, **C**=CHCO), 151.2 (s, CH=**C**-O), 146.4 (s, **C**(Ar)), 145.2 (s, **C**(Ar)), 130.0 (s, **C**(Ar)), 128.1 (s, **C**(Ar)), 122.2 (d, **C**H (Ar)), 121.9 (d, **C**H (Ar)), 116.0 (d, C=**C**HCO), 112.1 (d, **C**H=C-O), 60.7 (q, O**C**H_3), 33.3 (t, **C**H_2), 32.7 (d, CH_3**C**HCH_2), 20.4 (q, Ar**C**H_3), 15.8 (q, =**C**CH_3), 11.9 (q, CH**C**H_3).

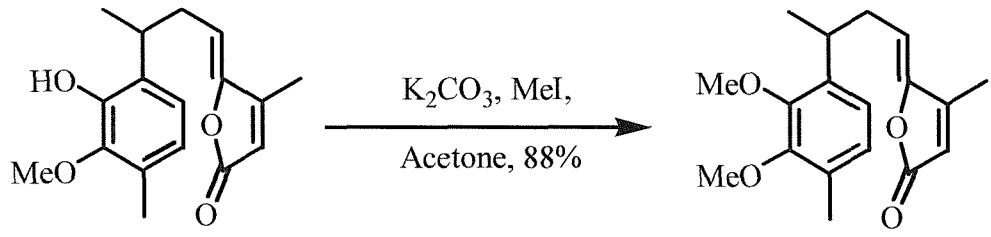
FT-IR (Thin Film) 3428 w, 2959 w, 1748 s, 1673 w, 1607 w, 1502 w, 1459 m, 1419 m, 1345 w, 1270 m, 1222 m, 1170 m, 1044 m, 1016 m, 941 m, 838 m, 755 s cm^{-1}.

LRMS (CI) 289 ($[M+H]^+$, 100%).

HRMS (EI) M^+, $C_{17}H_{20}O_4$ Requires 288.1362. Found 288.1371.

UV λ_{max} (ε_{max}) 275 (5330), 203 (10400) nm.

5-((Z)-3-(2,3-Dimethoxy-4-methylphenyl)-butylidene)-4-methyl-2, 5-dihydro-2-furanone (298).



298

$C_{17}H_{20}O_4 = 288.34$ $C_{18}H_{22}O_4 = 302.37$

To a solution of the phenol (0.89 g, 3.1 mmol) in acetone (30 mL) was added potassium carbonate (2.2 g, 16 mmol) and methyl iodide (2.3 g, 16 mmol) and the mixture heated at reflux for 16 h. Water (50 mL) was added and the reaction extracted into ether (3 x 50 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% ether / petroleum ether 40-60°C) to yield the methylated product as a clear oil (0.82 g, 2.7 mmol, 88%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 6.80 (2H, app. s, Ar**H**), 5.82 (1H, s, C=C**H**CO), 5.18 (1H, t, J = 6.9 Hz, CH_2CH=), 3.78 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.24 (1H, app. sextet, J = 7.5 Hz, ArC**H**), 2.67-2.45 (2H, m, $CHCH_2C$=), 2.17 (3H, s, $ArCH_3$), 2.00 (3H, s, $=CCH_3$), 1.19 (3H, d, J = 7.4 Hz, CH_3CH).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 169.7 (s, **C**=O), 154.6 (s, **C**=CHCO), 151.4 (s, O**C**=$CHCH_2$), 151.3 (s, **C**(Ar)), 150.7 (s, **C**(Ar)), 137.6 (s, **C**(Ar)), 130.3 (s, **C**(Ar)), 125.9 (d, **C**H (Ar)), 121.5 (d, **C**H (Ar)), 116.2 (d, =**C**HCO), 111.9 (d, **C**H=C-O), 60.8 (q, OCH_3), 60.6 (q, OCH_3), 34.1 (t, $CHCH_2CH$=), 32.3 (d, CH_3CHCH_2), 21.6 (q, $ArCH_3$), 15.8 (q, $=CCH_3$), 11.9 (q, $CHCH_3$).

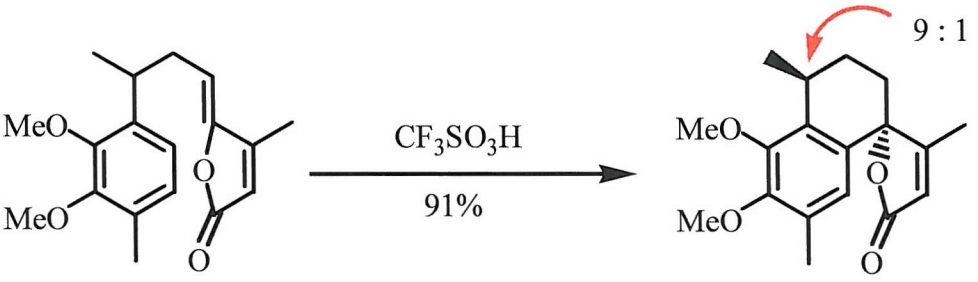
FT-IR (Thin Film) 2960 w, 1769 s, 1607 w, 1461 m, 1408 m, 1346 m, 1277 m, 1220 m, 1169 w, 1067 m, 1025 s, 914 w cm^{-1}.

LRMS (CI) 303 ($[M+H]^+$, 45%), 179 (100%).

HRMS (EI) M^+, $C_{18}H_{22}O_4$ Requires 302.1518. Found 302.1513.

UV λ_{max} (ε_{max}) 274 (9660), 203 (32600) nm.

***(rel-1'S,4S)-4-(1',6'-Dimethyl-7'8'-dimethoxy-1',2',3',4'-tetrahydronapth-4'-yl)-4-hydroxy-3-methyl-2-butenoic acid γ-lactone* (299).**



298

$C_{18}H_{22}O_4 = 302.37$

299

$C_{18}H_{22}O_4 = 302.37$

The furanone (500 mg, 1.7 mmol) and triflic acid (270 mg, 1.8 mmol) were mixed under nitrogen and the resulting brown oil was heated to 78°C for 10 mins. The crude product was subjected to flash column chromatography (30% ether / petroleum ether 40-60°C) to yield the cyclised product as a yellow oil and 9 : 1 mixture of diastereoisomers(454 mg, 1.7 mmol, 91%).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 6.51 (1H, s, Ar**H**), 6.01 (1H, s, C=C**H**), 3.90 (3H, s, OC**H$_3$**), 3.83 (3H, s, OC**H$_3$**), 3.32 (1H, br. m, CH_3C**H**CH_2), 2.44-2.21 (2H, m, C**H$_2$**), 2.19 (3H, s, ArC**H$_3$**), 1.98 (3H, s, C**H$_3$**C=CH), 1.77-1.64 (2H, m, C**H$_2$**), 1.25 (3H, d, J = 7.3 Hz CHC**H$_3$**).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 172.6 (s, **C**=O), 171.9 (s, **C**=CHCO), 152.2 (s, **C**(Ar)) 150.8 (s, **C**(Ar)), 136.3 (s, **C**(Ar)), 131.0 (s, **C**(Ar)), 125.8 (s, **C**(Ar)), 123.6 (d, **C**H (Ar)), 118.1 (d, C=**C**HCO), 88.7 (s, CH_2**C**(Ar)O), 60.5 (q, O**C**H_3),

59.8 (q, OCH_3), 28.4 (t, CH_2), 27.0 (d, CH_3CH), 26.2 (t, CH_2), 20.8 (q, $ArCH_3$), 16.0 (q, $CH_3C=CH$), 13.9 (q, CH_3CH).

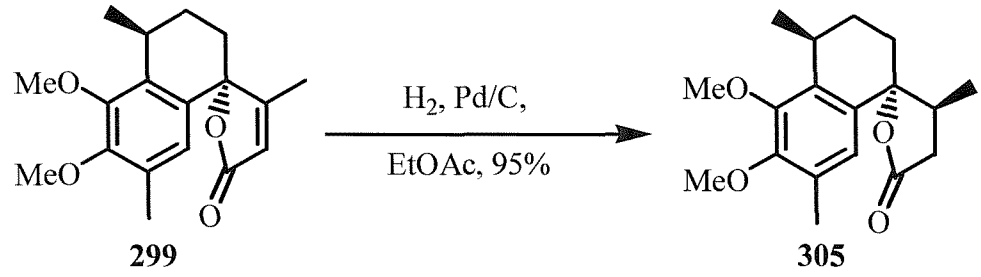
FT-IR (Thin Film) 2932 w, 1747 s, 1642 w, 1485 w, 1404 w, 1323 m, 1307 m, 1237 w, 1180 w, 1083 w, 1067 s, 1019 s, 953 w, 937 s, 844 w cm^{-1}.

LRMS (CI) 303 ($[M+H]^+$, 51%), 179 (100%).

HRMS (EI) M^+, $C_{18}H_{22}O_4$ Requires 302.1518. Found 302.1512.

UV λ_{max} (ε_{max}) 212 (19600) nm.

***(rel-1'S,3S,4S)-4-(1',6'-Dimethyl-7'8'-dimethoxy-1',2',3',4'-tetrahydronapth-4'-yl)-4-hydroxy-3-methyl-2-butanoic acid γ-lactone* (305).**



299 **305**

$C_{18}H_{22}O_4 = 302.37$ $C_{18}H_{24}O_4 = 304.38$

The furanone (100 mg, 0.33 mmol) was dissolved in ethyl acetate (10 mL) and 5% palladium on charcoal (20 mg) was added and the solution stirred vigorously in a hydrogen atmosphere (1atm) for 2h. The reaction was filtered through celite and the filtrate concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (20-40% ether / petroleum ether 40-60°C) to yield the product as a pale yellow oil (95 mg, 0.31 mmol, 95%) and as a 9 : 1 mixture of diastereoisomers. Trituration with pentane followed by recrystalisation from chloroform/hexane afforded the product as colourless prisms and as a single diastereoisomer.

MP 73-75°C (petrol / chloroform).

^{1}H NMR δ_H (300MHz, $CDCl_3$) 6.76 (1H, s, Ar**H**), 3.88 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.19 (1H, app. sextet, J = 6.9 Hz, ArC**H**), 2.93 (1H, dd, J = 16.1, 8.0 Hz, C**H**HC=O), 2.76-2.53 (2H, m, CH**H**C=O, C**H**CH_2C=O), 2.24 (3H, s, ArCH_3), 2.19-1.94 (4H, m, CH_2CH_2), 1.25 (3H, d, J = 8.1 Hz, $COCH_2CHCH_3$), 0.92 (3H, d, J = 7.1 Hz, CH_3CH(Ar)).

^{13}C NMR δ_c (75MHz, $CDCl_3$) 176.4 (s, **C**=O), 151.1 (s, **C**(Ar)), 151.0 (s, **C**(Ar)), 135.2 (s, **C**(Ar)), 130.8 (s, **C**(Ar)), 129.8 (s, **C**(Ar)), 123.8 (d, **C**H (Ar)), 88.4 (s, **C**-O(Ar)), 60.2 (q, O**C**H_3), 59.8 (q, O**C**H_3), 39.9 (d, CH_3**C**HCH_2), 37.9 (t, CH**C**H_2CH_2), 34.9 (t, $CHCH_2$**C**H_2), 27.4 (d, CH_3**C**HCH_2CO), 27.2 (t, **C**H_2CO), 22.0 (q, Ar**C**H_3), 17.5 (q, ArCH**C**H_3), 16.1 (q, CH_2CHCH_3).

These assignments were confirmed by ^{1}H-^{1}H and ^{1}H-^{13}C correlation experiments

FT-IR 2968 w, 2941 m, 1759 s, 1481 w, 1442 w, 1403 w, 1356 w, 1325 m, 1239 m, 1235 m, 1122 w, 1062 m, 1016 w, 992 w, 922 m, 855 w cm^{-1}.

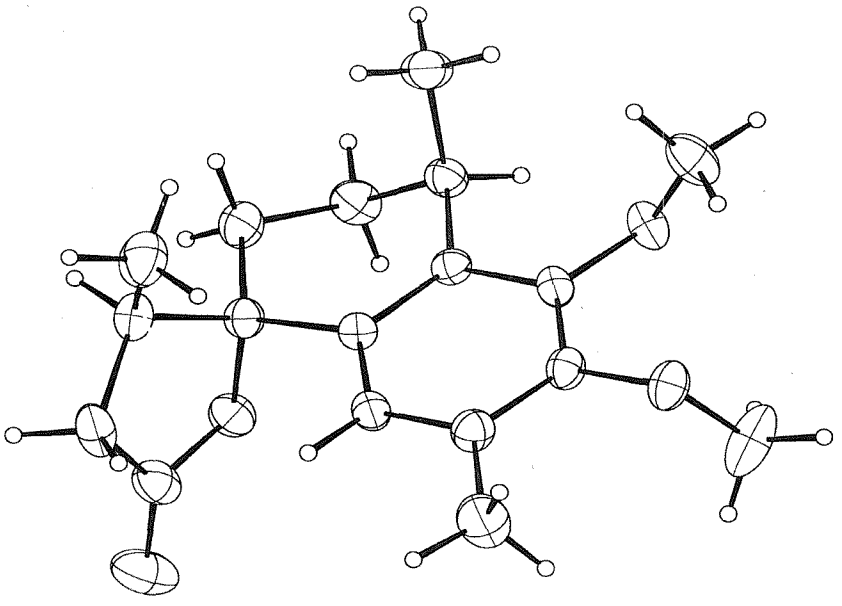
LRMS (CI) 305 ($[M+H]^+$, 100%), 247 (15%).

HRMS (EI) M^+, $C_{18}H_{24}O_4$ Requires 304.1675. Found 304.1661.

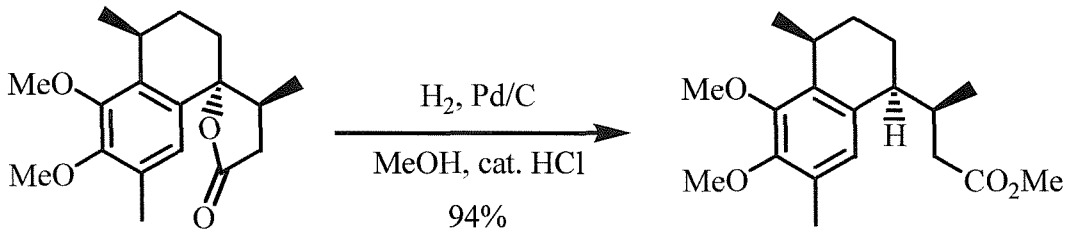
CHN $C_{18}H_{24}O_4$ Requires C : 71.03, H : 7.95, O : 21.02%. Found C : 70.94, H : 8.35%.

UV λ_{max} (ε_{max}) 212 (2980) nm.

Structure and relative stereochemistry was confirmed by X-ray crystallography.



***Methyl 3-(rel-1'S,3S,4'S)-5',6'-dimethoxy-4',7'-dimethyl-1',2',3',4'-tetrahydro-1'-napthalenyl)-butanoate* (300).**



305 $C_{18}H_{24}O_4 = 304.38$

300 $C_{19}H_{28}O_4 = 320.43$

To a solution of the lactone (250 mg, 0.82 mmol) in methanol (20 mL) was added palladium on charcoal (50 mg) and dilute hydrochloric acid (1M, 0.1 mL) and the solution was stirred vigorously in a hydrogen atmosphere (1 atm.) for 16 h. After this time the mixture was filtered through celite and the filtrate reduced *in vacuo*. The crude residue was subjected to flash column chromatography (30% ether / petroleum ether) to yield the pure ester as a colourless oil (247 mg, 0.77 mmol, 94%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.89 (1H, s, Ar**H**), 3.87 (3H, s, O**CH$_3$**), 3.80 (3H, s, O**CH$_3$**), 3.61 (3H, s, O**CH$_3$**), 3.13 (1H, m, ArC**H**), 2.86-2.75 (2H, m, ArC**H**, C**H**CH$_2$COOMe), 2.21 (3H, s, ArC**H$_3$**), 2.14 (1H, dd, J = 15.0, 3.1 Hz, C**H**HCOOMe), 2.01 (1H, dd, J = 15.1, 10.4 Hz, CH**H**COOMe), 1.78-1.42 (4H, m, C**H$_2$**C**H$_2$**), 1.19 (3H, d, J = 7.0 Hz, CHC**H$_3$**), 1.10 (3H, d, J = 6.5 Hz, CHC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 174.4 (s, **C**=O), 150.5 (s, **C**(Ar)), 149.0 (s, **C**(Ar)), 135.6 (s, **C**(Ar)), 134.0 (s, **C**(Ar)), 129.5 (s, **C**(Ar)), 124.2 (d, **C**H (Ar)),

60.4 (q, O**C**H_3), 59.8 (q, O**C**H_3), 51.5 (q, O**C**H_3), 42.5 (d, Ar**C**H), 35.9 (t, **C**H_2COOMe), 33.3 (d, Ar**C**H), 29.2 (t, **C**H_2), 27.2 (d, **C**HCH_2CO_2Me), 21.7 (q, Ar**C**H_3), 18.4 (q, **C**H_3), 17.8 (t, **C**H_2), 16.1 (q, **C**H_2).

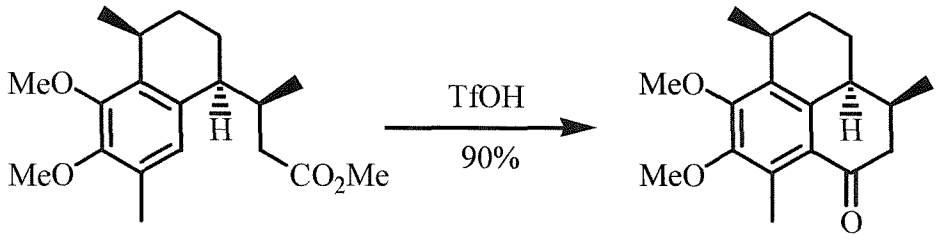
FT-IR (Thin Film) 2926 m, 2867 w, 1737 s, 1485 m, 1437 m, 1405 m, 1325 m, 1309 m, 1238 m, 1172 s, 1073 s, 1031 m, 1016 m, 911 w cm^{-1}.

LRMS (CI) 320 (M^+, 12%), 289 ([M-OMe]$^+$, 13%), 219 ([M-$CH_3CHCH_2CO_2Me$]$^+$, 100%).

HRMS (EI) M^+, $C_{19}H_{28}O_4$ Requires 320.1988. Found 320.1989.

UV λ_{max} (ε_{max}) 265 (320), 216 (5190) nm.

***(rel-3S,3aS,6S)-7,8-Dimethoxy-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydro-1H-1-phenalenone* (301).**



300 $C_{19}H_{28}O_4 = 320.43$

301 $C_{18}H_{24}O_3 = 288.38$

The methyl ester (55 mg, 0.17 mmol) and trifluoromethanesulfonic acid (45 mg, 0.3 mmol) were mixed then heated to 80°C for 25 mins. The crude brown mixture was purified by flash column chromatography (25 % ether / petroleum ether) to yield the cyclised product as colourless needles (44 mg, 0.15 mmol, 90%).

MP 92-94°C (Methanol-water).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 3.97 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.20 (1H, br. s, ArC**H**), 2.99 (1H, br. s, ArC**H**), 2.77 (1H, dd, J = 17.0, 5.2 Hz, C**H**HCO), 2.54 (1H, dd, J = 17.0, 2.1 Hz, CH**H**CO), 2.51 (3H, s, ArCH_3), 2.30 (1H, br. s, CHC**H**CH_3), 1.90-1.56 (4H, m, CH_2CH_2), 1.19 (3H, d, J = 7.0 Hz, CHC**H**$_3$), 0.83 (3H, d, J = 7.0 Hz, CHC**H**$_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 199.7 (s, **C**=O), 154.9 (s, **C**(Ar)), 149.9 (s, **C**(Ar)), 137.8 (s, **C**(Ar)), 134.3 (s, **C**(Ar)), 133.9 (s, **C**(Ar)), 127.7 (s, **C**(Ar)), 60.6 (q, OCH_3), 60.1 (q, OCH_3), 49.6 (t, $COCH_2$), 41.4 (d, Ar**C**H), 33.3 (d,

Ar**C**H), 29.6 (t, **C**H_2), 27.4 (d, CH**C**HCH_3), 22.7 (q, Ar**C**H_3), 22.6 (t, **C**H_2), 14.1 (q, CH**C**H_3), 13.8 (q, CH**C**H_3).

FT-IR ($CHCl_3$ solution) 2954 w, 2930 m, 1671 s, 1560 m, 1449 s, 1401 m, 1353 m, 1308 s, 1278 w, 1254 w, 1158 w, 1069 s, 1055 s, 1021 m, 935 w cm^{-1}.

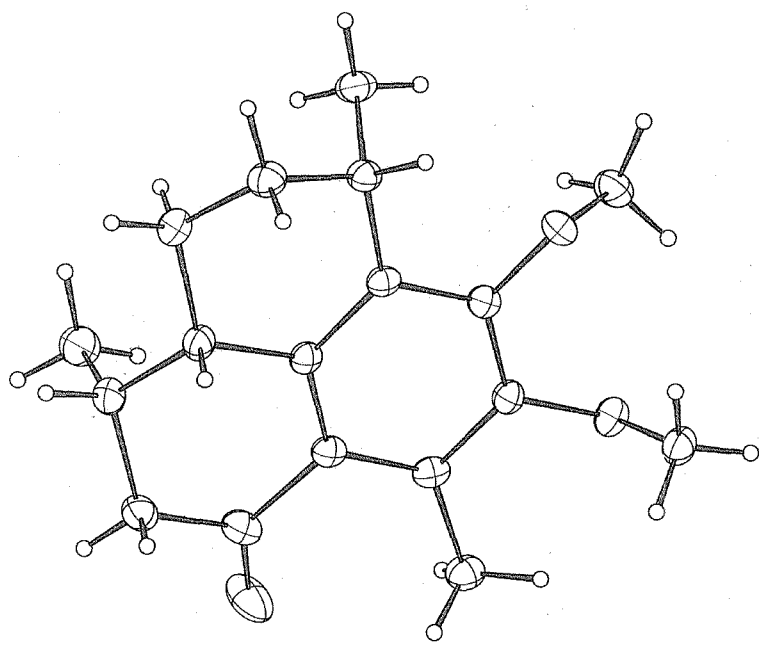
LRMS (CI +ve) 289 ($[M+H]^+$, 100%), 273 ($[M-CH_3]^+$, 22%).

HRMS (CI) $[M+H]^+$, $C_{18}H_{25}O_3$ Requires 289.1804. Found 289.1802.

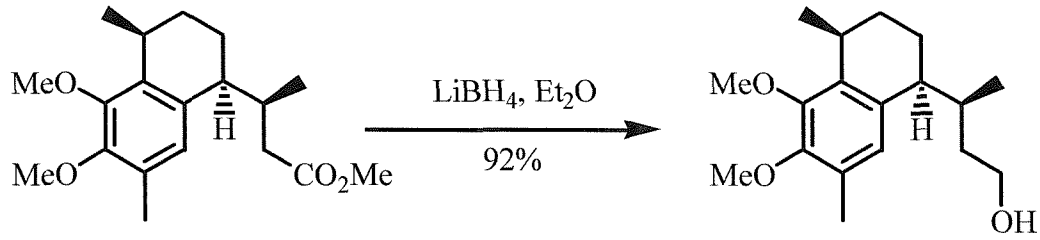
CHN $C_{18}H_{25}O_3$ Requires C: 74.97, H: 8.39, O: 16.64. Found C: 74.97, H: 8.67%.

UV λ_{max} (ε_{max}) 273 (5180), 212 (17300) nm.

Structure and relative stereochemistry was confirmed by X-ray crystallography.



(rel-1'S,3S,4'S)-5',6'-dimethoxy-4,7-dimethyl-1,2,3,4,-tetrahydronapthalenyl) butan-1-ol (307).



300 $C_{19}H_{28}O_4 = 320.43$

307 $C_{18}H_{28}O_3 = 288.38$

To a cooled (0°C) solution of the ester (210 mg, 0.65 mmol) in dry ether (15 mL) was added $LiBH_4$ (1.0 mL, 2.0 mmol, 2.0 M solution in THF). After18 h, water (10 mL) was added and the reaction extracted into ether (3 x 15 mL). The organic fractions were combined, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (40% ether / petroleum ether) to yield the product alcohol as a clear oil (174 mg, 0.60 mmol, 92%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 6.84 (1H, s, Ar**H**), 3.89 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.64 (1H, ddd, J = 10.4, 8.2, 5.0 Hz, C**H**HOH), 3.53 (1H, app. dt, J = 10.4, 7.4 Hz, CH**H**OH), 3.15 (1H, br. m, ArC**H**), 2.74 (1H, br. m, ArC**H**), 2.35 (1H, m, CHC**H**CH_3), 2.22 (3H, s, ArCH_3), 1.78-1.26 (7H, m, CH_2CH_2, CH_2CH_2OH), 1.20 (3H, d, J = 7.0 Hz, CHCH_3), 1.09 (3H, d, J = 6.9 Hz, CHCH_3).

^{13}C NMR δ_C (75MHz, $CDCl_3$) 150.5 (s, **C**(Ar)), 148.8 (s, **C**(Ar)), 135.6 (s, **C**(Ar)), 135.0 (s, **C**(Ar)), 129.2 (s, **C**(Ar)), 124.1 (d, **C**H (Ar)), 62.1 (t, $\mathbf{C}H_2OH$), 60.4 (q, $O\mathbf{C}H_3$), 59.9 (q, $O\mathbf{C}H_3$), 43.2 (d, $CH_3\mathbf{C}HCH_2$), 34.2 (t, $\mathbf{C}H_2$), 32.7 (d, $Ar\mathbf{C}HCHCH_3$), 29.2 (t, $\mathbf{C}H_2$), 27.2 (d, $Ar\mathbf{C}HCH_2$), 21.6 (q, $Ar\mathbf{C}H_3$), 18.4 (q, $CH\mathbf{C}H_3$), 17.6 (t, $\mathbf{C}H_2$), 16.0 (q, $CH\mathbf{C}H_3$).

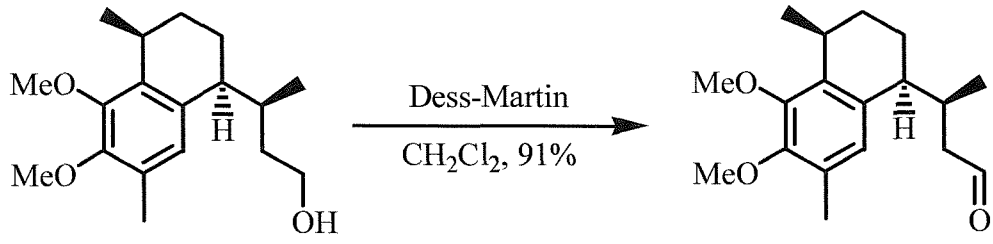
FT-IR (Thin Film) 3390 w, 2952 w, 2934 m, 2865 w, 1477 m, 1446 m, 1403 m, 1377 w, 1316 m, 1229 m, 1073 s, 1034 m, 1008 m, 913 w, 756 s cm^{-1}.

LRMS (EI) 292 (M^+, 9%), 219 ($[M\text{-}CH_3CHCH_2CH_2OH]^+$, 100%).

HRMS (EI) M^+, $C_{18}H_{28}O_3$ Requires 292.2038. Found 292.2033.

UV λ_{max} (ε_{max}) 265 (292), 208 (4270) nm.

***(rel-1'S,3S,4'S)-3-(5',6'-Dimethoxy-4',7'-dimethyl-1',2',3',4'-tetrahydronapthalenyl)-butanal* (308).**



307 **308**

$C_{18}H_{28}O_3 = 288.38$ $C_{18}H_{26}O_3 = 290.40$

To a cooled (0°C) solution of the alcohol (150 mg, 0.52 mmol) in dichloromethane (10 mL) was added Dess-Martin periodinane (318 mg, 0.78 mmol, 1.5 eq.) and the resulting suspension stirred for 2 h. Water (10 mL) was added and the organic phase separated, washed with saturated sodium bicarbonate solution (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (20% ether / petroleum ether) to yield the pure aldehyde as a pale yellow oil (135 mg, 0.47 mmol, 91%).

^{1}H NMR δ_H (300 MHz, $CDCl_3$) 9.66 (1H, s, C**H**O), 6.83 (1H, s, Ar**H**), 3.89 (3H, s, O**CH$_3$**), 3.81 (3H, s, O**CH$_3$**), 3.15 (1H, br. m, ArC**H**), 2.95-2.79 (2H, m, ArC**H**, C**H**CH$_2$CHO), 2.21 (3H, s, ArC**H$_3$**), 2.23-2.12 (2H, m, C**H$_2$**CHO), 1.80-1.45 (4H, m, C**H$_2$CH$_2$**), 1.20 (3H, d, J = 7.0 Hz, CHC**H$_3$**), 1.11 (3H, d, J = 7.0 Hz, ArCHC**H$_3$**).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) 203.2 (d, **C**HO), 150.6 (s, **C**(Ar)), 149.1 (s, **C**(Ar)), 135.8 (s, **C**(Ar)), 133.9 (s, **C**(Ar)), 129.7 (s, **C**(Ar)), 124.0 (d, **C**H (Ar)),

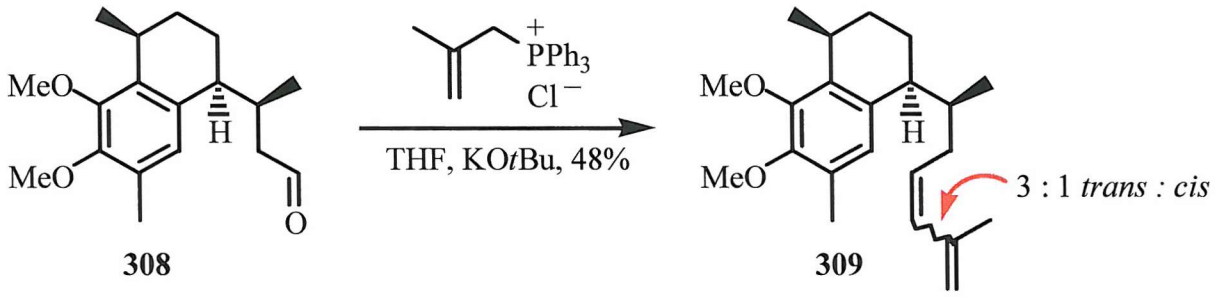
60.4 (q, O**C**H_3), 59.9 (q, O**C**H_3), 45.8 (t, **C**H_2CHO), 42.3 (d, CH_2**C**HAr), 31.2 (d, CH_3**C**HAr), 29.1 (t, CH**C**H_2CH_2), 27.2 (d, **C**HCH_2CHO), 21.6 (q, Ar**C**H_3), 18.7 (q, ArCHC**H**$_3$), 17.8 (t, $CHCH_2$**C**H_2), 16.0 (q, CH**C**H_3).

FT-IR (Thin Film) 2960 m, 2921 m, 2865 w, 2713 w, 1724 s, 1477 m, 1451 w, 1411 m, 1368 w, 1234 m, 1074 s, 1030 m, 1017 m, 913 w cm^{-1}.

LRMS (CI +ve) 305 (32%), 291 ($[M+H]^+$, 100%), 273 ($[M-OH]^+$, 62%), 219 (68%).

UV λ_{max} (ε_{max}) 269 (290), 216 (3370) nm.

***(rel-1S,3'E,4S,6'S)-1-(2'-Methylhepta-1',3'-dien-6'-yl)-5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronapthalene* (309).**



308 **309**

$C_{18}H_{26}O_3 = 290.40$ $C_{22}H_{32}O_2 = 328.49$

The Wittig reagent[72] (5.0 eq. 780 mg, 2.2 mmol) was suspended in THF (15 mL) and potassium *tert*-butoxide (247 mg, 2.2 mmol) was added in a single portion. The resulting orange solution was allowed to stir at RT for 15 mins then the aldehyde (128 mg, 0.44 mmol) was added as a solution in THF (5 mL). The solution was stirred for 30 mins then water (20 mL) was added and the reaction extracted into ether (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (10% ether / petroleum ether 40-60°C) to yield the diene as an inseperable 1 : 3 mixture of *cis* and *trans* isomers (69 mg, 0.21 mmol 48%). Data recorded on mixture.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) ***Trans* isomer:** 6.78 (1H, s, ArH), 5.97 (1H, d, J = 16.3 Hz, CH=CHC=CH_2), 5.44 (1H, app. dt, J = 16.3, 7.4 Hz, CH=CHC=CH_2), 4.73 (2H, br. s, =CH_2), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.06 (1H, br. m, ArCHCH_3), 2.69 (1H, br. m, ArCHCH_2), 2.20 (1H,

br. m, CH_2CHCH_3), 2.14 (3H, s, $ArCH_3$), 1.98-1.46 (6H, m, 3 x CH_2), 1.69 (3H, s, $=CCH_3$), 1.11 (3H, d, J = 6.9 Hz, CH_2CHCH_3), 0.98 (3H, d, J = 7.1 Hz, $ArCHCH_3$). ***Cis* isomer:** 6.75 (1H, s, ArH), 5.74 (1H, d, J = 11.1 Hz, $CH=CHC=CH_2$), 5.29 (1H, m, $CH=CHC=CH_2$), 4.73 (2H, br. s, $=CH_2$), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.06 (1H, br. m, $ArCHCH_3$), 2.69 (1H, br. m, $ArCHCH_2$), 2.20 (1H, br. m, CH_2CHCH_3), 2.13 (3H, s, $ArCH_3$), 1.98-1.46 (6H, m, 3 x CH_2), 1.69 (3H, s, $=CCH_3$), 1.11 (3H, d, J = 6.9 Hz, CH_2CHCH_3), 0.98 (3H, d, J = 7.1 Hz, $ArCHCH_3$).

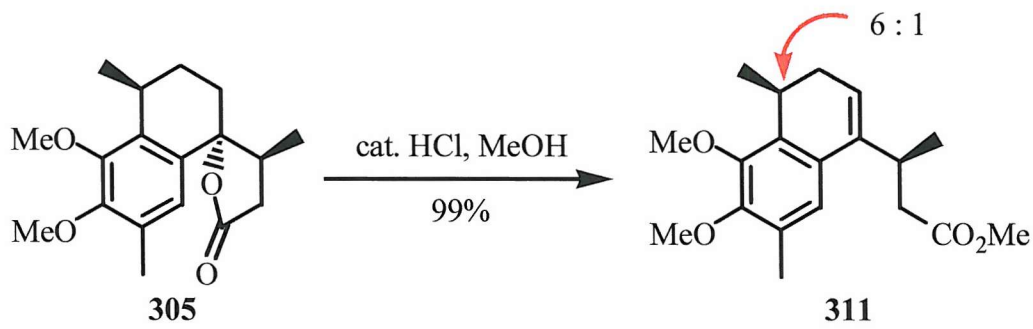
^{13}C NMR δ_C (75 MHz, $CDCl_3$) ***Trans* isomer:** 150.5 (s, C(Ar)), 148.8 (s, C(Ar)), 142.4 (s, C(Ar)), 137.4 (s, $CH_3C=CH_2$), 135.4 (s, C(Ar)), 133.8 (s, C(Ar)), 131.4 (t, $=CH_2$), 128.7 (d, CH=), 124.4 (d, CH (Ar)), 114.1 (d, =CH), 60.4 (q, OCH_3), 59.9 (q, OCH_3), 43.0 (t, $=CHCH_2$), 37.9 (d, $ArCHCH_3$), 37.0 (d, CH_2CHAr), 34.7 (t, CH_2), 29.3 (t, CH_2), 27.3 (d, CH_2CHCH_3), 21.7 (q, $ArCH_3$), 18.3 (q, $=CCH_3$), 17.9 (q, $CHCH_3$), 16.1 (q, $CHCH_3$). ***Cis* isomer:** 150.5 (s, C(Ar)), 148.8 (s, C(Ar)), 142.4 (s, C(Ar)), 137.4 (s, $CH_3C=CH_2$), 135.2 (s, C(Ar)), 133.7 (s, C(Ar)), 131.6 (t, $=CH_2$), 128.7 (d, CH=), 124.6 (d, CH (Ar)), 115.3 (d, =CH), 60.4 (q, OCH_3), 59.9 (q, OCH_3), 43.0 (t, $=CHCH_2$), 37.9 (d, $ArCHCH_3$), 37.0 (d, CH_2CHAr), 30.5 (t, CH_2), 29.9 (t, CH_2), 23.5 (d, CH_2CHCH_3), 22.6 (q, $ArCH_3$), 18.8 (q, $=CCH_3$), 18.3 (q, $CHCH_3$), 16.1 (q, $CHCH_3$).

FT-IR (Thin Film) 3052 w, 2958 m, 2923 m, 2869 w, 1480 m, 1434 s, 1403 m, 1372 w, 1317 m, 1072 s, 1027 m, 1016 m, 959 m, 920 m, 881 m cm^{-1}.

HRMS (EI) M^+, $C_{22}H_{32}O_2$ Requires 328.2402. Found 328.2399.

UV λ_{max} (ε_{max}) 259 (730), 212 (3430) nm.

***Methyl (rel-3S,4'S)-3-(5',6'-dimethoxy-4',7'-dimethyl-3',4'-dihydronapthalenyl)-butanoate* (311).**



305 **311**

$C_{18}H_{24}O_4 = 304.38$ $C_{19}H_{26}O_4 = 318.41$

The spirolactone (120 mg, 0.39 mmol) was dissolved in methanol (20 mL) and dilute HCl (0.5 mL) was added. The solution was allowed to stir at RT for 16h then concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography (25% ether / petroleum ether 40-60°C) yielded the title compound as a clear oil (123 mg, 0.39 mmol, 99%) and inseparable 6:1 mixture of diastereoisomers.

^{1}H NMR δ_H (300 MHz, $CDCl_3$) **Major diastereoisomer:** 6.94 (1H, s, Ar**H**), 5.70 (1H, br. d, J = 5.0 Hz, C**H**=), 3.89 (3H, s, OC**H$_3$**), 3.84 (3H, s, OC**H$_3$**), 3.66 (3H, s, OC**H$_3$**), 3.28 (2H, m, ArC**H**CH$_3$, C**H**CH$_2$CO$_2$CH$_3$), 2.64 (1H, dd, J = 15.3, 5.1 Hz, C**H**HCO$_2$CH$_3$), 2.42 (1H, dd, J = 15.3, 6.7 Hz, CH**H**CO$_2$CH$_3$), 2.36-2.11 (2H, m, C**H$_2$**CH=), 2.28 (3H, s, ArC**H$_3$**), 1.25 (3H, d, J = 6.9 Hz, CHC**H$_3$**), 1.01 (3H, d, J = 7.0 Hz, CHC**H$_3$**). **Minor diastereoisomer:** 7.00 (1H, s, Ar**H**), 5.63 (1H, br. d, J = 5.0 Hz, C**H**=), 3.89 (3H, s, OC**H$_3$**), 3.84 (3H, s, OC**H$_3$**), 3.69 (3H, s, OC**H$_3$**), 3.28 (2H, m, ArC**H**CH$_3$,

$CHCH_2CO_2CH_3$), 2.64 (1H, dd, J = 15.3, 5.1 Hz, $CHHCO_2CH_3$), 2.42 (1H, dd, J = 15.3, 6.7 Hz, $CHHCO_2CH_3$), 2.36-2.11 (2H, m, CH_2CH=), 2.28 (3H, s, $ArCH_3$), 1.14 (3H, d, J = 6.9 Hz, $CHCH_3$), 1.04 (3H, d, J = 7.0 Hz, $CHCH_3$).

^{13}C NMR δ_C (75 MHz, $CDCl_3$) **Major diastereoisomer:** 173.5 (s, C=O), 150.4 (s, C(Ar)), 149.7 (s, C(Ar)), 138.9 (s, C(Ar)), 133.8 (s, C(Ar)), 129.3 (s, C(Ar)), 129.2 (s, CH=C), 120.4 (d, CH (Ar)), 119.6 (d, CH=C), 60.8 (q, OCH_3), 60.0 (q, OCH_3), 51.6 (q, CO_2CH_3), 41.6 (t, $CH_2CO_2CH_3$), 30.6 (d, $ArCHCH_3$), 30.2 (t, CH_2CH=), 25.1 (q, CH_2CHCH_3), 19.7 (q, $ArCH_3$), 19.6 (q, $ArCHCH_3$), 16.1 (q, $CHCH_3$). **Minor diastereoisomer:** Some peaks obscured by major diastereoisomer. 118.7 (d, CH=C), 40.7 (t, $CH_2CO_2CH_3$), 30.8 (d, $ArCHCH_3$), 30.1 (t, CH_2CH=), 21.0 (q, $ArCH_3$), 19.8 (q, $ArCHCH_3$).

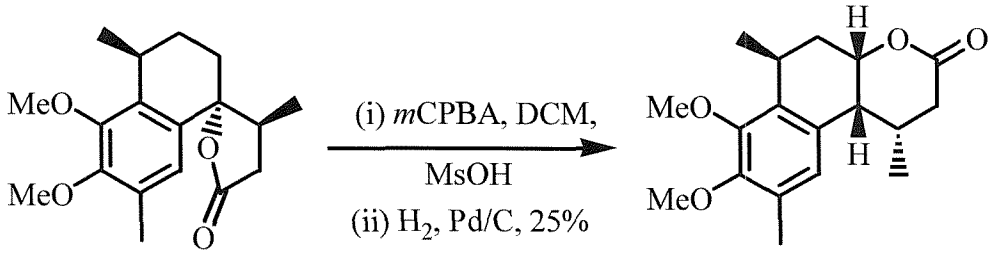
FT-IR (Thin film) 2960 m, 2922 m, 1737 s, 1479 m, 1450 m, 1405 m, 1340 m, 1224 w, 1192 m, 1159 m, 1078 s, 1067 m, 1054 m, 1022 s, 963 w, 921 w, 871 m cm^{-1}.

LRMS (EI) 318 (M^+, 4%), 217 ($[M\text{-}CH_3CHCH_2CO_2CH_3]^+$, 100%).

HRMS (EI) M^+, $C_{19}H_{26}O_4$ Requires 318.1831. Found 318.1828.

UV λ_{max} (ε_{max}) 267 (6470), 218 (14900) nm.

***(rel-1S,4aS,6R,10bR)-7,8,-Dimethoxy-1,6,9-trimethyl-1,2,4a,5,6,10b-hexahydrobenzo[f]-2-chromenone* (324).**



305 **324**

$C_{18}H_{24}O_4 = 304.38$ $C_{18}H_{24}O_4 = 304.38$

The spirolactone (36 mg, 0.12 mmol) was dissolved in DCM (20 mL) and methanesulfonic acid (10 mg) was added. The solution was purged with nitrogen under ultrasonic irradiation for 15 mins. *m*CPBA (35 mg, 0.20 mmol) was added as a solution in DCM (5 mL) and the solution allowed to stir at RT for 6 h. The solution was rapidly washed with sodium thiosulfate solution (2 x 30 mL) and the organic fraction dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in methanol (20 mL) and 5% palladium on charcoal (20 mg) was added. The black suspension was stirred under a hydrogen atmosphere (1 atm.) for 1 h then filtered through celite and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (20-40% ether / petroleum ether 40-60°C) to yield the title product as colourless prisms (9 mg, 0.030 mmol, 25%).

MP 104-106°C (petrol).

^{1}H NMR δ_H (400 MHz, $CDCl_3$) 6.77 (1H, s, Ar**H**), 5.09 (1H, ddd, J = 13.2, 8.3, 5.1 Hz, CH_2**C**H-OC=O), 3.92 (3H, s, OC**H**$_3$), 3.83 (3H, s, OC**H**$_3$), 3.37 (2H, m,

ArC**H**CH$_3$, ArC**H**CHCH$_3$), 2.77 (1H, dd, J = 16.9, 5.4 Hz, C**H**HCO$_2$-), 2.63 (1H, dd, J = 16.9, 2.4 Hz, CH**H**CO$_2$-), 2.58 (1H, obsc. m, ArCHC**H**CH$_3$), 2.23 (3H, s, ArC**H$_3$**), 2.13 (1H, ddd, J = 12.8, 5.1, 2.2 Hz, ArCHC**H**H), 2.03 (1H, app. dt, J = 12.8, 5.6 Hz, ArCHCH**H**), 1.22 (3H, d, J = 7.1 Hz, CHC**H$_3$**), 0.86 (3H, d, J = 7.3 Hz, CHC**H$_3$**).

These assignments were confirmed by ^{1}H-^{1}H and ^{1}H-^{13}C correlation experiments.

^{13}C NMR δ_C (100 MHz, $CDCl_3$) 169.3 (s, **C**=O), 149.1 (s, **C**(Ar)), 148.6 (s, **C**(Ar)), 132.6 (s, **C**(Ar)), 129.7 (s, **C**(Ar)), 129.1 (s, **C**(Ar)), 124.0 (d, **C**H (Ar)), 75.4 (d, **C**H-OC=O), 59.4 (q, O**C**H$_3$), 58.7 (q, O**C**H$_3$), 37.7 (d, Ar**C**H), 37.3 (t, **C**H$_2$CO$_2$-), 34.1 (t, CH$_3$CH**C**H$_2$), 31.5 (d, Ar**C**H), 26.8 (d, **C**HCH$_2$CO$_2$-), 20.8 (q, Ar**C**H$_3$), 15.4 (q, **C**H$_3$), 14.9 (q, **C**H$_3$).

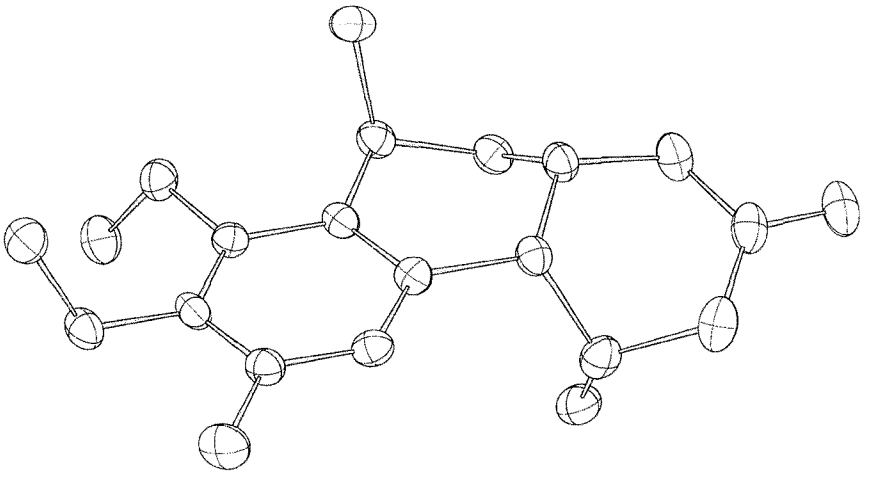
FT-IR (Thin Film) 2955 w, 2925 w, 2870 w, 1735 s, 1483 m, 1459 w, 1407 w, 1388 w, 1324 m, 1234 m, 1078 m, 1057 s, 1027 m, 1003 w, cm^{-1}.

LRMS (EI) 304 (M^+, 63%), 289 ([M-Me]$^+$, 9%), 217 (100%), 203 (68%).

HRMS (ES) [M+H]$^+$ $C_{18}H_{25}O_4$ Requires 305.1753. Found 305.1754.

UV λ_{max} (ε_{max}) 207 (5140) nm.

Structure and relative stereochemistry was confirmed by X-ray crystallography.



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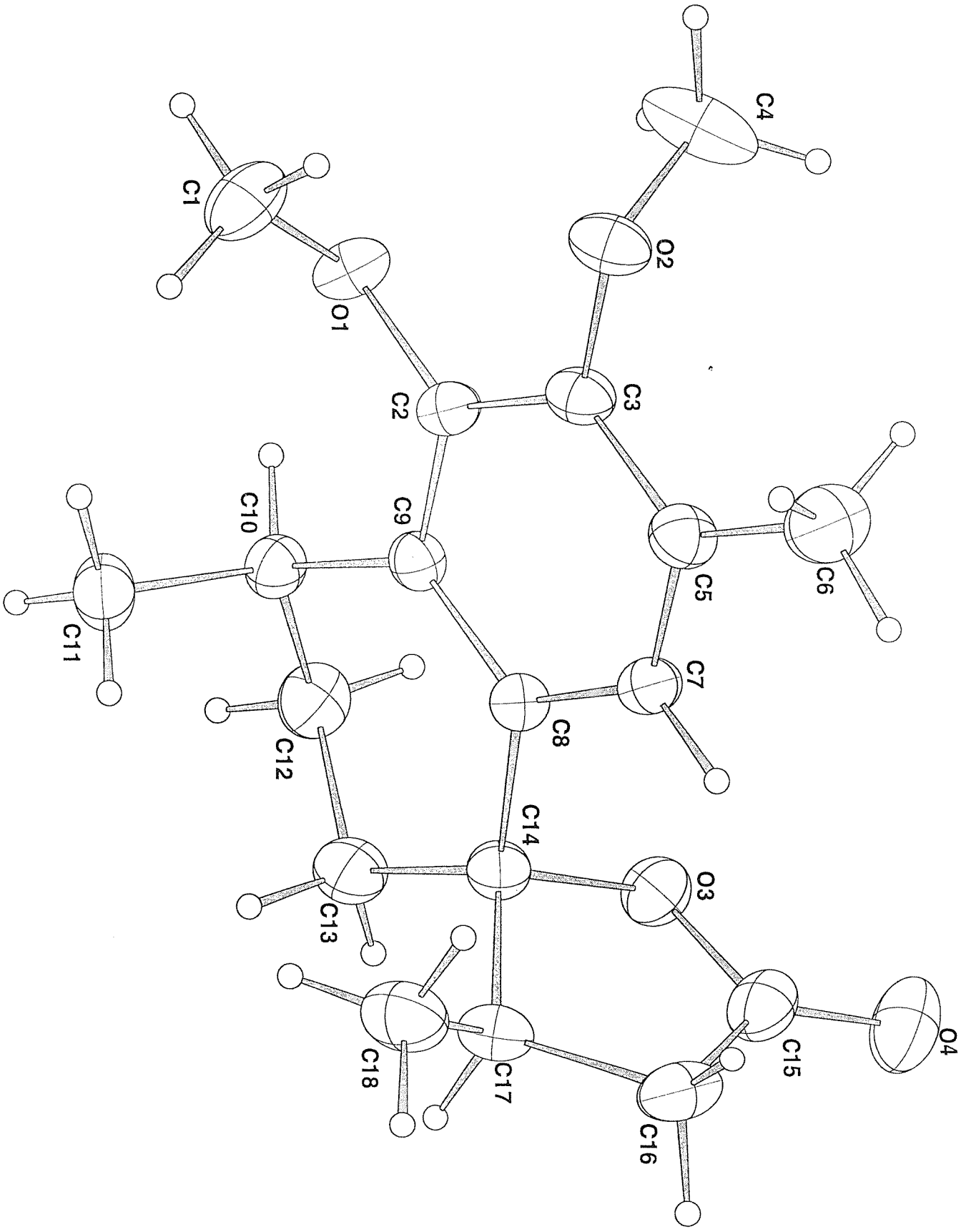
Appendix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O4
C16

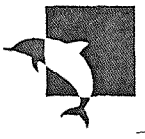

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Table 1. Crystal data and structure refinement.

Identification code	**99sot065**	
Empirical formula	$C_{18}H_{24}O_4$	
Formula weight	304.37	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 13.820(3) Å	$\alpha = 90°$
	b = 9.7038(19) Å	$\beta = 90°$
	c = 24.273(5) Å	$\gamma = 90°$
Volume	3255.2(11) Å^3	
Z	8	
Density (calculated)	1.242 Mg / m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	1312	
Crystal	Block; Colourless	
Crystal size	0.3 × 0.2 × 0.1 mm^3	
θ range for data collection	2.70 – 24.96°	
Index ranges	$-16 \le h \le 16$, $-11 \le k \le 11$, $-28 \le l \le 28$	
Reflections collected	14365	
Independent reflections	2840 [R_{int} = 0.0676]	
Completeness to θ = 24.96°	99.6 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.993 and 0.935	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2840 / 0 / 204	
Goodness-of-fit on F^2	0.947	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0516, $wR2$ = 0.1342	
R indices (all data)	$R1$ = 0.0891, $wR2$ = 0.1561	
Largest diff. peak and hole	0.159 and –0.174 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω 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**: *SHELXS97* (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.*
O1	1627(1)	2578(1)	6401(1)	49(1)	1
O2	1936(1)	1981(2)	5289(1)	52(1)	1
O3	5574(1)	1226(1)	6747(1)	50(1)	1
O4	6761(2)	70(2)	6340(1)	78(1)	1
C1	1043(2)	3683(3)	6190(1)	68(1)	1
C2	2554(1)	2495(2)	6193(1)	37(1)	1
C3	2712(2)	2155(2)	5645(1)	41(1)	1
C4	1487(2)	672(3)	5338(1)	90(1)	1
C5	3646(2)	2022(2)	5441(1)	45(1)	1
C6	3825(2)	1665(3)	4847(1)	72(1)	1
C7	4405(2)	2210(2)	5804(1)	43(1)	1
C8	4272(2)	2523(2)	6361(1)	37(1)	1
C9	3325(2)	2662(2)	6562(1)	36(1)	1
C10	3113(2)	2977(2)	7159(1)	42(1)	1
C11	2916(2)	4522(2)	7239(1)	55(1)	1
C12	3933(2)	2450(2)	7524(1)	52(1)	1
C13	4896(2)	3003(2)	7332(1)	55(1)	1
C14	5148(2)	2624(2)	6741(1)	42(1)	1
C15	6373(2)	1162(3)	6428(1)	54(1)	1
C16	6659(2)	2562(2)	6229(1)	58(1)	1
C17	5997(2)	3537(2)	6537(1)	50(1)	1
C18	5708(2)	4847(2)	6234(1)	67(1)	1

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

O1–C2	1.379(3)
O1–C1	1.437(3)
O2–C3	1.388(2)
O2–C4	1.418(3)
O3–C15	1.348(3)
O3–C14	1.480(2)
O4–C15	1.208(3)
C2–C3	1.387(3)
C2–C9	1.402(3)
C3–C5	1.388(3)
C5–C7	1.381(3)
C5–C6	1.504(3)
C7–C8	1.400(3)
C8–C9	1.403(3)
C8–C14	1.524(3)
C9–C10	1.509(3)
C10–C12	1.526(3)
C10–C11	1.536(3)
C12–C13	1.508(3)
C13–C14	1.522(3)
C14–C17	1.552(3)
C15–C16	1.496(3)
C16–C17	1.513(3)
C17–C18	1.522(3)
C2–O1–C1	115.76(17)
C3–O2–C4	113.33(17)
C15–O3–C14	111.21(17)
O1–C2–C3	120.77(19)
O1–C2–C9	117.73(19)
C3–C2–C9	121.34(19)
C2–C3–O2	120.22(19)
C2–C3–C5	120.74(19)
O2–C3–C5	119.0(2)
C7–C5–C3	117.8(2)
C7–C5–C6	121.1(2)
C3–C5–C6	121.1(2)
C5–C7–C8	123.0(2)
C7–C8–C9	118.67(19)
C7–C8–C14	119.58(19)
C9–C8–C14	121.67(19)
C2–C9–C8	118.39(19)
C2–C9–C10	119.34(19)
C8–C9–C10	122.26(18)
C9–C10–C12	110.21(18)
C9–C10–C11	110.64(17)
C12–C10–C11	112.67(18)
C13–C12–C10	110.90(19)
C12–C13–C14	114.02(19)
O3–C14–C13	107.61(17)
O3–C14–C8	105.29(15)
C13–C14–C8	113.79(18)
O3–C14–C17	103.01(16)
C13–C14–C17	109.63(18)
C8–C14–C17	116.46(18)
O4–C15–O3	120.4(2)
O4–C15–C16	128.5(2)
O3–C15–C16	111.17(19)
C15–C16–C17	104.3(2)

C16–C17–C18	116.2(2)
C16–C17–C14	104.96(18)
C18–C17–C14	115.58(19)

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}
O1	33(1)	57(1)	57(1)	11(1)	2(1)	4(1)
O2	48(1)	58(1)	49(1)	6(1)	−17(1)	−10(1)
O3	47(1)	48(1)	54(1)	4(1)	−5(1)	8(1)
O4	82(2)	80(1)	73(1)	−7(1)	0(1)	37(1)
C1	48(2)	77(2)	79(2)	7(1)	−5(1)	24(1)
C2	30(1)	38(1)	43(1)	5(1)	−1(1)	−1(1)
C3	38(1)	41(1)	44(1)	4(1)	−10(1)	−2(1)
C4	98(2)	86(2)	85(2)	11(2)	−38(2)	−45(2)
C5	45(1)	50(1)	39(1)	−1(1)	−3(1)	−3(1)
C6	60(2)	112(2)	43(2)	−13(2)	−1(1)	1(2)
C7	33(1)	51(1)	44(1)	−5(1)	1(1)	−1(1)
C8	34(1)	38(1)	40(1)	−2(1)	−1(1)	−1(1)
C9	38(1)	31(1)	40(1)	−1(1)	−1(1)	−1(1)
C10	40(1)	45(1)	39(1)	−2(1)	3(1)	2(1)
C11	60(2)	51(1)	53(2)	−11(1)	0(1)	7(1)
C12	56(2)	62(1)	38(1)	1(1)	−1(1)	6(1)
C13	48(2)	68(2)	47(2)	−8(1)	−11(1)	1(1)
C14	38(1)	45(1)	43(1)	−3(1)	−7(1)	2(1)
C15	45(2)	70(2)	47(2)	−6(1)	−8(1)	16(1)
C16	34(1)	78(2)	62(2)	3(1)	−1(1)	−4(1)
C17	39(1)	56(1)	55(2)	−2(1)	−8(1)	−8(1)
C18	60(2)	56(2)	84(2)	7(1)	−7(2)	−13(1)

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.*
H1A	1352	4548	6267	102	1
H1B	418	3662	6362	102	1
H1C	969	3577	5799	102	1
H4A	1901	−21	5183	135	1
H4B	881	681	5144	135	1
H4C	1374	471	5720	135	1
H6A	3493	825	4758	107	1
H6B	4506	1547	4787	107	1
H6C	3589	2396	4616	107	1
H7	5033	2126	5671	51	1
H10	2524	2477	7262	50	1
H11A	3457	5043	7104	82	1
H11B	2824	4712	7623	82	1
H11C	2345	4776	7038	82	1
H12A	3820	2735	7902	63	1
H12B	3945	1451	7514	63	1
H13A	5399	2654	7573	65	1
H13B	4890	3999	7366	65	1
H16A	6564	2642	5834	69	1
H16B	7332	2751	6313	69	1
H17	6351	3830	6866	60	1
H18A	6276	5377	6151	100	1
H18B	5282	5380	6462	100	1
H18C	5383	4609	5897	100	1

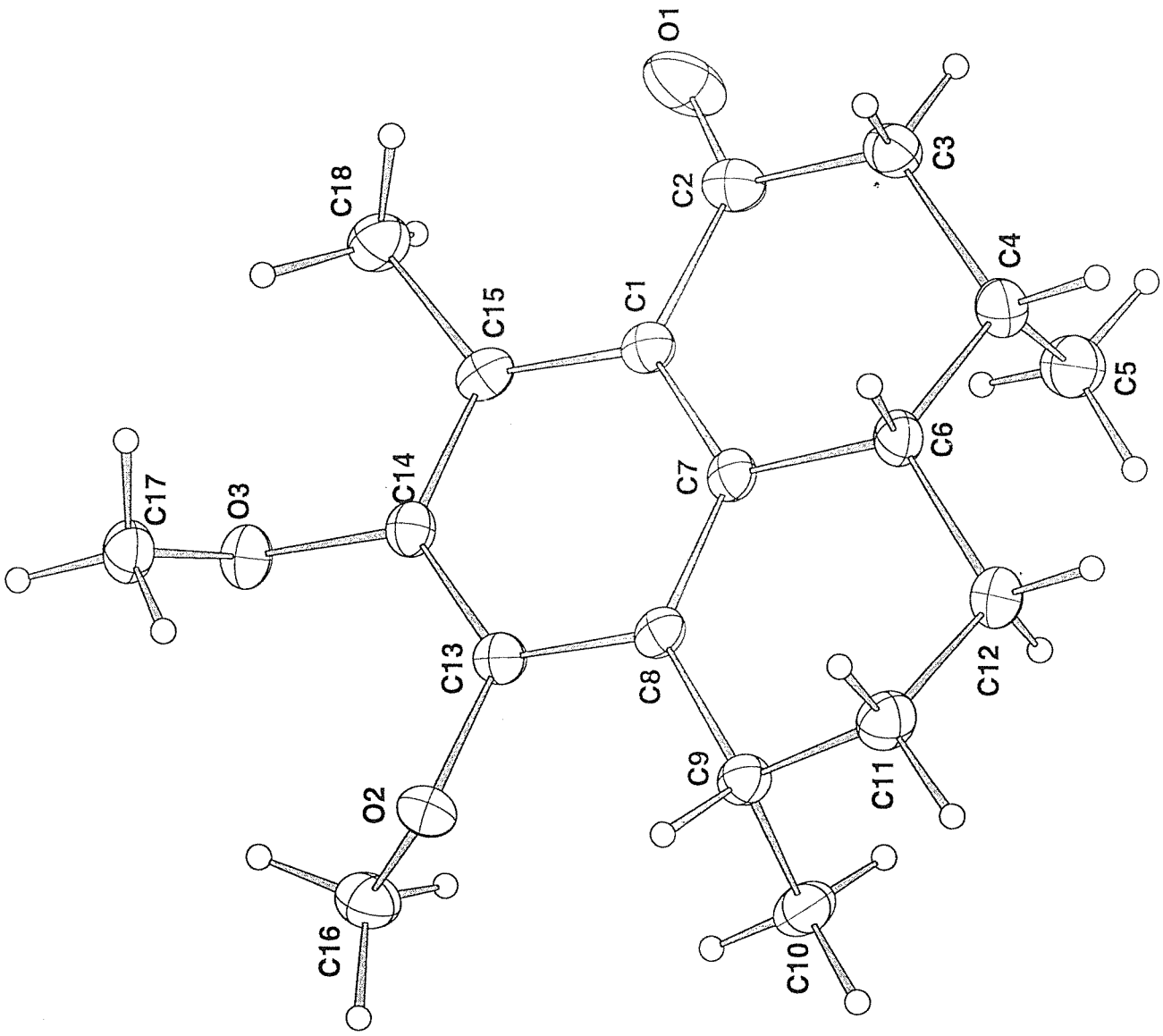
O1
C2
C3
C4
C5
C6
C7
C1
C15
C18
C14
O3
C17
C13
C8
C12
C9
C11
O2
C16
C10

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Table 1. Crystal data and structure refinement.

Identification code	**00sot003**	
Empirical formula	$C_{18}H_{24}O_3$	
Formula weight	288.37	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.957(2) Å	α = 90°
	b = 15.091(3) Å	β = 110.93(3)°
	c = 9.835(2) Å	γ = 90°
Volume	1519.0(5) Å^3	
Z	4	
Density (calculated)	1.261 Mg / m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	624	
Crystal	Needle; colourless	
Crystal size	0.4 × 0.075 × 0.075 mm^3	
θ range for data collection	2.40 – 27.53°	
Index ranges	$-13 \le h \le 14$, $-19 \le k \le 19$, $-12 \le l \le 12$	
Reflections collected	14826	
Independent reflections	3473 [R_{int} = 0.0716]	
Completeness to θ = 27.53°	99.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.952 and 0.806	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3473 / 0 / 204	
Goodness-of-fit on F^2	0.957	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0559, $wR2$ = 0.1371	
R indices (all data)	$R1$ = 0.1064, $wR2$ = 0.1623	
Largest diff. peak and hole	0.396 and –0.249 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω 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:** *SHELXS97* (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.*
O1	5516(2)	−1934(1)	8741(3)	59(1)	0.90
O1'	4957(17)	−1603(11)	8560(20)	51(6)	0.10
O2	8828(1)	1650(1)	9591(1)	32(1)	1
O3	7497(1)	765(1)	7009(1)	35(1)	1
C1	6588(2)	−565(1)	9634(2)	29(1)	1
C2	5844(2)	−1382(1)	9715(2)	37(1)	1
C3	5541(2)	−1538(1)	11074(2)	36(1)	1
C4	6661(2)	−1262(1)	12448(2)	36(1)	1
C5	7830(2)	−1866(1)	12727(2)	45(1)	1
C6	6935(2)	−283(1)	12310(2)	31(1)	1
C7	7198(2)	−64(1)	10926(2)	27(1)	1
C8	7978(2)	664(1)	10909(2)	26(1)	1
C9	8739(2)	1200(1)	12255(2)	31(1)	1
C10	10193(2)	963(1)	12774(2)	39(1)	1
C11	8172(2)	1077(1)	13454(2)	38(1)	1
C12	7958(2)	106(1)	13675(2)	37(1)	1
C13	8099(2)	908(1)	9589(2)	27(1)	1
C14	7427(2)	458(1)	8304(2)	28(1)	1
C15	6694(2)	−297(1)	8305(2)	29(1)	1
C16	9860(2)	1538(1)	9033(2)	41(1)	1
C17	6703(2)	1533(1)	6469(2)	37(1)	1
C18	6009(2)	−747(1)	6856(2)	37(1)	1

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

O1–O1'	0.761(15)
O1–C2	1.223(3)
O1'–C2	1.251(17)
O2–C13	1.375(2)
O2–C16	1.432(2)
O3–C14	1.383(2)
O3–C17	1.433(2)
C1–C15	1.412(2)
C1–C7	1.423(2)
C1–C2	1.496(3)
C2–C3	1.506(3)
C3–C4	1.523(3)
C4–C5	1.515(3)
C4–C6	1.523(3)
C6–C7	1.525(2)
C6–C12	1.526(3)
C7–C8	1.395(2)
C8–C13	1.401(2)
C8–C9	1.521(2)
C9–C11	1.528(3)
C9–C10	1.532(3)
C11–C12	1.511(3)
C13–C14	1.391(2)
C14–C15	1.394(2)
C15–C18	1.514(2)
O1'–O1–C2	74.1(14)
O1–O1'–C2	70.1(12)
C13–O2–C16	116.12(13)
C14–O3–C17	112.72(13)
C15–C1–C7	120.44(16)
C15–C1–C2	120.79(16)
C7–C1–C2	118.77(16)
O1–C2–O1'	35.8(8)
O1–C2–C1	122.26(19)
O1'–C2–C1	115.6(9)
O1–C2–C3	119.47(18)
O1'–C2–C3	114.9(11)
C1–C2–C3	118.24(16)
C2–C3–C4	112.40(15)
C5–C4–C6	114.78(16)
C5–C4–C3	110.93(17)
C6–C4–C3	107.93(14)
C4–C6–C7	113.31(15)
C4–C6–C12	113.65(15)
C7–C6–C12	112.82(15)
C8–C7–C1	120.11(16)
C8–C7–C6	119.56(15)
C1–C7–C6	120.22(15)
C7–C8–C13	118.63(15)
C7–C8–C9	123.75(15)
C13–C8–C9	117.59(15)
C8–C9–C11	111.10(15)
C8–C9–C10	110.33(15)
C11–C9–C10	112.07(15)
C12–C11–C9	110.81(15)
C11–C12–C6	110.46(15)
O2–C13–C14	121.17(15)
O2–C13–C8	117.38(15)

C14–C13–C8	121.27(15)
O3–C14–C13	119.18(15)
O3–C14–C15	119.73(15)
C13–C14–C15	121.09(15)
C14–C15–C1	118.19(15)
C14–C15–C18	117.28(16)
C1–C15–C18	124.46(16)

Symmetry transformations used to generate equivalent atoms:

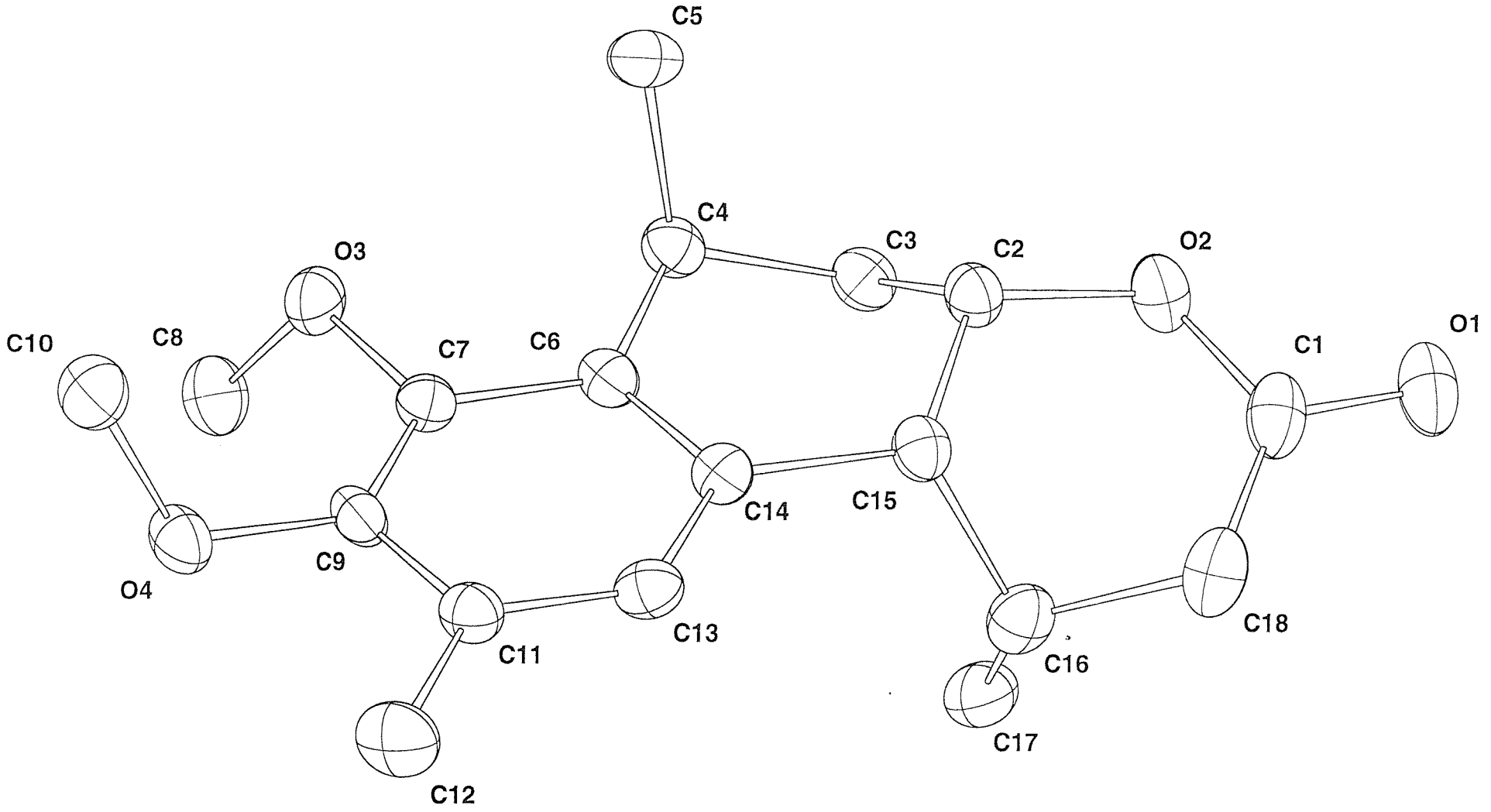
C5
C4
C3
C2
O2
O1
C1
O3
C8
C10
C7
C6
C14
C15
C9
O4
C13
C18
C11
C16
C17
C12

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Table 1. Crystal data and structure refinement.

Identification code	**00SOT088**
Empirical formula	$C_{18}H_{22}O_4$
Formula weight	302.36
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 9.7571(10) Å
	b = 16.4896(17) Å β = 92.514(5)°
	c = 10.3234(14) Å
Volume	1659.3(3) Å^3
Z	4
Density (calculated)	1.210 Mg / m^3
Absorption coefficient	0.085 mm^{-1}
$F(000)$	648
Crystal	Colourless needle
Crystal size	0.30 × 0.07 × 0.06 mm^3
θ range for data collection	3.16 – 23.25°
Index ranges	$-10 \le h \le 10, -18 \le k \le 18, -11 \le l \le 11$
Reflections collected	4735
Independent reflections	2239 [R_{int} = 0.1231]
Completeness to θ = 23.25°	94.1 %
Absorption correction	Empirical
Max. and min. transmission	0.9949 and 0.9751
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2239 / 0 / 200
Goodness-of-fit on F^2	1.041
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0835, $wR2$ = 0.2148
R indices (all data)	$R1$ = 0.1303, $wR2$ = 0.2476
Extinction coefficient	0.000(7)
Largest diff. peak and hole	0.346 and –0.335 e Å^{-3}

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω 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:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 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: All hydrogen atoms were placed in idealised positions and refined using a riding model.
C2 = S, C4 = S, C15 = R, C16 = S

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.*
C1	10839(5)	1080(2)	4950(6)	61(2)	1
C2	8410(4)	959(2)	4119(4)	48(1)	1
C3	7389(4)	1629(2)	4335(4)	48(1)	1
C4	6122(4)	1507(2)	3454(4)	46(1)	1
C5	5230(5)	806(2)	3919(5)	57(1)	1
C6	6499(4)	1382(2)	2078(4)	43(1)	1
C7	5492(4)	1480(2)	1064(5)	45(1)	1
C8	3749(5)	2491(3)	1041(5)	64(2)	1
C9	5759(5)	1342(2)	−213(4)	46(1)	1
C10	3666(5)	854(3)	−1196(5)	68(2)	1
C11	7055(5)	1101(2)	−549(4)	48(1)	1
C12	7350(6)	958(3)	−1943(5)	71(2)	1
C13	8037(5)	1008(2)	435(5)	49(1)	1
C14	7803(4)	1132(2)	1740(4)	44(1)	1
C15	8937(4)	954(2)	2762(4)	47(1)	1
C16	10233(4)	1483(3)	2620(5)	57(1)	1
C17	10019(5)	2396(3)	2805(5)	64(1)	1
C18	11294(5)	1143(3)	3607(6)	68(2)	1
O1	11615(4)	1066(2)	5903(4)	74(1)	1
O2	9501(3)	1017(2)	5150(3)	64(1)	1
O3	4173(3)	1693(2)	1428(3)	54(1)	1
O4	4742(3)	1448(2)	−1188(3)	57(1)	1

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

C1–O1	1.215(5)	C7–O3	1.402(5)
C1–O2	1.335(6)	C8–O3	1.430(5)
C1–C18	1.477(8)	C9–C11	1.384(7)
C2–O2	1.475(5)	C9–O4	1.393(5)
C2–C3	1.511(6)	C10–O4	1.436(5)
C2–C15	1.513(7)	C11–C13	1.375(6)
C3–C4	1.515(5)	C11–C12	1.498(7)
C4–C6	1.497(6)	C13–C14	1.392(6)
C4–C5	1.536(6)	C14–C15	1.523(5)
C6–C14	1.397(6)	C15–C16	1.549(6)
C6–C7	1.413(5)	C16–C18	1.527(6)
C7–C9	1.373(6)	C16–C17	1.532(6)
O1–C1–O2	116.9(6)	C11–C9–O4	119.0(4)
O1–C1–C18	124.0(5)	C13–C11–C9	117.5(4)
O2–C1–C18	119.1(4)	C13–C11–C12	122.3(5)
O2–C2–C3	107.8(3)	C9–C11–C12	120.2(4)
O2–C2–C15	113.8(4)	C11–C13–C14	124.1(4)
C3–C2–C15	113.2(3)	C13–C14–C6	118.4(4)
C2–C3–C4	109.9(3)	C13–C14–C15	119.8(4)
C6–C4–C3	111.1(4)	C6–C14–C15	121.8(4)
C6–C4–C5	111.1(3)	C2–C15–C14	112.0(4)
C3–C4–C5	111.8(3)	C2–C15–C16	113.4(3)
C14–C6–C7	117.4(4)	C14–C15–C16	113.4(4)
C14–C6–C4	122.8(4)	C18–C16–C17	111.7(4)
C7–C6–C4	119.7(4)	C18–C16–C15	105.2(4)
C9–C7–O3	120.9(4)	C17–C16–C15	115.2(4)
C9–C7–C6	122.5(4)	C1–C18–C16	115.4(4)
O3–C7–C6	116.5(4)	C1–O2–C2	125.0(4)
C7–C9–C11	120.1(4)	C7–O3–C8	114.4(3)
C7–C9–O4	120.9(4)	C9–O4–C10	114.6(3)

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}
C1	58(3)	41(2)	80(4)	−8(2)	−22(3)	9(2)
C2	50(3)	53(2)	40(3)	0(2)	−4(2)	−1(2)
C3	55(3)	47(2)	42(3)	−1(2)	2(2)	2(2)
C4	49(3)	44(2)	45(3)	3(2)	4(2)	4(2)
C5	60(3)	55(2)	58(3)	9(2)	15(2)	−3(2)
C6	53(3)	37(2)	38(3)	0(2)	−2(2)	−3(2)
C7	46(3)	40(2)	48(3)	5(2)	−1(2)	−3(2)
C8	63(3)	59(3)	67(4)	1(2)	−7(3)	14(2)
C9	59(3)	43(2)	36(3)	8(2)	−9(2)	−5(2)
C10	77(3)	59(3)	68(4)	0(2)	−16(3)	−19(2)
C11	56(3)	48(2)	40(3)	−1(2)	1(2)	−7(2)
C12	93(4)	78(3)	42(3)	−14(2)	6(3)	−15(3)
C13	51(3)	51(2)	47(3)	−5(2)	9(2)	−5(2)
C14	47(2)	41(2)	43(3)	−4(2)	1(2)	−1(2)
C15	50(3)	44(2)	45(3)	−2(2)	−5(2)	1(2)
C16	48(3)	68(3)	55(3)	−8(2)	9(2)	3(2)
C17	57(3)	59(3)	75(4)	8(2)	6(3)	−8(2)
C18	54(3)	74(3)	76(4)	−18(3)	−10(3)	11(2)
O1	81(2)	56(2)	82(3)	−3(2)	−39(2)	3(2)
O2	63(2)	75(2)	52(2)	4(2)	−14(2)	6(2)
O3	48(2)	53(2)	62(2)	5(1)	−2(2)	5(1)
O4	70(2)	50(2)	50(2)	6(1)	−16(2)	−12(1)

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	7923	433	4242	57	1
H3A	7810	2161	4150	58	1
H3B	7129	1627	5251	58	1
H4	5562	2014	3484	55	1
H5A	4996	903	4820	85	1
H5B	5739	295	3865	85	1
H5C	4387	773	3369	85	1
H8A	2819	2592	1325	95	1
H8B	3758	2536	95	95	1
H8C	4380	2890	1439	95	1
H10A	3000	969	−1910	103	1
H10B	3206	875	−371	103	1
H10C	4058	313	−1312	103	1
H12A	6520	1061	−2486	106	1
H12B	7641	395	−2056	106	1
H12C	8082	1324	−2197	106	1
H13	8932	848	210	59	1
H15	9233	383	2601	56	1
H16	10577	1394	1733	68	1
H17A	9332	2592	2159	95	1
H17B	10888	2680	2698	95	1
H17C	9699	2497	3677	95	1
H18A	11567	596	3316	82	1
H18B	12120	1492	3610	82	1