Synthetic Investigations into Alotane Derived Sesterterpenoid Marine Natural Products.

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Synthetic Investigations into Alotane Derived Sesterterpenoid Marine Natural Products

Harold John Shirley

Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy, at The University of London

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22nd May 2015

Dedicated To My Late Grandparents,

Margaret & Geoffrey Reeve

Acknowledgements

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During the course of this work, the association with other members of The School of Biological and Chemical Sciences has been most pleasurable. Past and present members of The Bray Research Group are thanked for their support and friendship.

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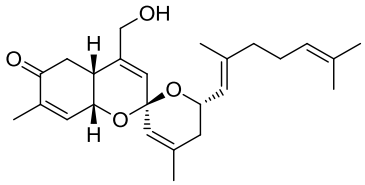
I am heartily indebted to my loving family and friends, who have offered their support in so many different ways over the last few years.

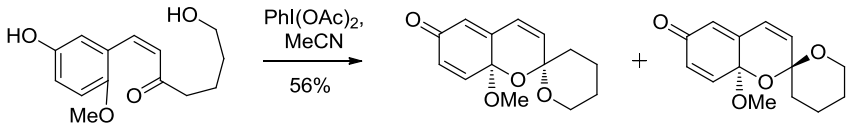
Abstract

Phorbaketal A (**I**) and phorone A (**II**) are members of a growing family of biologically active sesterterpenoid natural products, derived from marine sponges. These compounds possess potent biological activities and intriguing molecular architectures, which have inspired efforts towards their total synthesis.



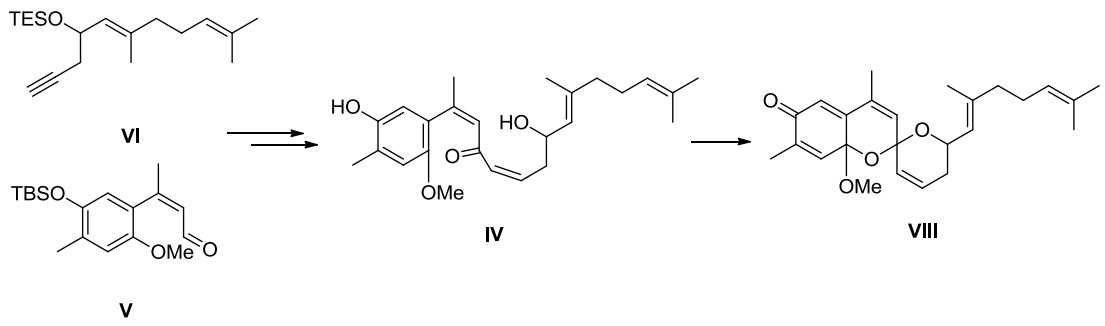
Phorbaketal A (**I**) Phorone A (**II**)

Early work in this thesis describes how new methodology is developed aimed at the synthesis of phorbaketal A (**I**). The synthesis and subsequent treatment of the model hydroxyphenol **III** with $PhI(OAc)_2$ led to the development of a new method for spiroketal synthesis *via* cascade oxidative dearomatisation.

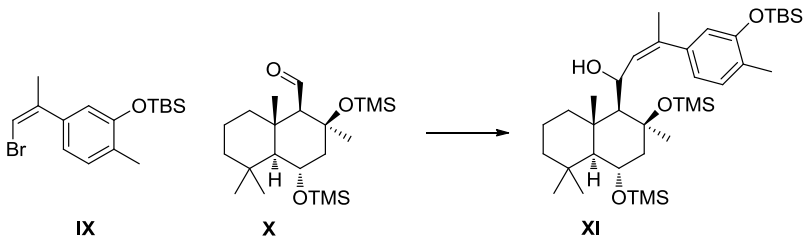


III

This new spiroketalisation method was then further elaborated for the total synthesis of phorbaketal A (**I**). This required the construction of the noralotane carbon skeleton **IV**, employing the union of the aryl aldehyde **V** and the propargylated geraniol **VI**. Treatment of the noralotane **IV** with $PhI(OAc)_2$ gave the spiroketal **VIII** as a complex mixture of labile diastereomers. This new method for spiroketalisation ultimately proved unsuitable for the total synthesis of these spiroketal natural products. Following this, attempts at expanding the substrate scope for this new oxidative dearomatisation method were explored for the formation of a range of saturated spiroketals.



The second part of this thesis describes efforts towards the total synthesis of the related sesterterpenoid natural product phorone A (**II**). Considerable synthetic effort led to synthesis of the novel (*Z*)-bromoalkene **IX** and the drimane aldehyde **X**, which were coupled to give the ansellane alcohol **XI**, in a total of 17 steps. This work represents the first ever synthesis of the ansellane skeleton. Efforts to oxidise and cyclise the alcohol **XI** were initiated; however difficulties with eliminative dehydration prevented its conversion to phorone A (**2**). The final work in this thesis describes alternate coupling methods aimed at circumventing these unforeseen issues.



Abbreviations

ATP	adenosine triphosphate
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bz	benzoyl
cAMP	cyclic adenosine monophosphate
COSY	correlation spectroscopy
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMP	Dess-Martin periodinane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EC_{50}	concentration giving 50% maximum effectiveness
Fod	tris[6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione]
HEK293	human embryonic kidney cells
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
K_a	acid dissociation constant
LDA	lithium diisopropylamide
LiDBB	lithium di-tertbutylbiphenyl
*m*CPBA	*meta*-chloroperoxybenzoic acid
mp	melting point

m/z	mass to charge ratio
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
ORTEP	oak ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PIDA	phenyliodine diacetate
PIFA	phenyliodine bis(trifluoroacetate)
PKA	protein kinase A
PMB	*para*-methoxybenzyl ether
PMP	*para*-methoxyphenol
PG	protecting group
p-TSA	*para*-toluenesulfonic acid
R_f	retention factor
Red-Al	reducing aluminium
rt	room temperature
TLC	thin layer chromatography
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilane
TCBC	2,4,6-trichlorobenzoyl chloride
TES	triethylsilane
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilane
TMEDA	tetramethylethylenediamine
TMS	trimethylsilane

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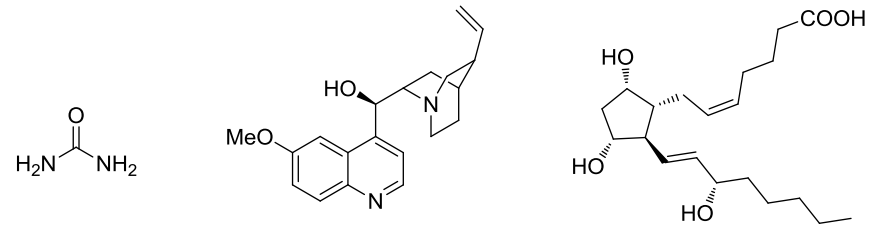
1. Introduction

1.1 Total Synthesis of Natural Products

The science and art of total synthesis continues to captivate and inspire scientists. Conceived in 1828 with F. Wöhler's synthesis of urea (**1**),[1] this Science saw rapid growth during the 20th century, with outstanding chemists such as Nobel laureates R. B. Woodward and E. J. Corey making ground-breaking contributions to the field (Figure 1).[2] Often inspired by the graceful way in which Nature constructs complex organic frameworks, this discipline acts to push forward the boundaries of synthetic organic chemistry.



Urea (**1**) (*Wöhler, 1828*)

Quinine (**2**) - Antimalarial (*Woodward, 1944*)

Prostaglandin $F_{2\alpha}$ (**3**) - Labour inducer (*Corey, 1969*)

Figure 1 - Total synthesis of urea (**1**)[1], quinine (**2**)[3] and prostaglandin $F_{2\alpha}$ (**3**)[4]

This ability to synthesise biologically active compounds has had a momentous impact upon medicine. The synthesis of natural products and their derivates plays a key role in drug discovery and development today. Success in achieving the total syntheses of biologically active compounds has particular advantages in offering a reliably large supply of a rare compound, allowing for detailed structure–activity relationship (SAR) studies and lead optimisations.[5]

1.2 Marine Natural Products

It is often remarked that we know more about the surface of the moon than we do the oceans on Earth. Since more than 70% of our planet is covered by oceans, marine organisms provide a considerably large and unexplored bioresource for drug discovery.[6] The sedentary lifestyle adopted by many marine organisms requires them to often produce highly toxic secondary metabolites as a means of defence against predators.[7] Such secondary metabolites and their derivatives have been used for the treatment of many diseases, most notably for the treatment of various cancers. Over the past decade several marine natural products and their derivates have been identified and approved or in clinical trials as anti-cancer drugs.[8]

An example is synthetic compound E7974 (**4**), a derivative of marine natural product hemiasterlin, which is now under phase I clinical trials as an anti-tumour drug candidate (Figure 2).[9] Upon the isolation of halichondrin B (**5**) from sponge *H. okadai*, this 32 chiral centre bearing natural product was found to have potent cytotoxicity against cancer cell lines.[10] However, clinical trials of **5** as an anti-cancer drug were abandoned due to issues in sponge supply.[11] If **5** had become a successful drug, multi-tonne quantities of the sponge would have been required annually, inevitably causing significant environmental disruption. However, after SAR studies, the more potent and chemically simplified synthetic compound eribulin mesylate (**6**) was designed, which is now a US FDA (Food and Drug Administration) approved drug for the treatment of breast cancer.[12]

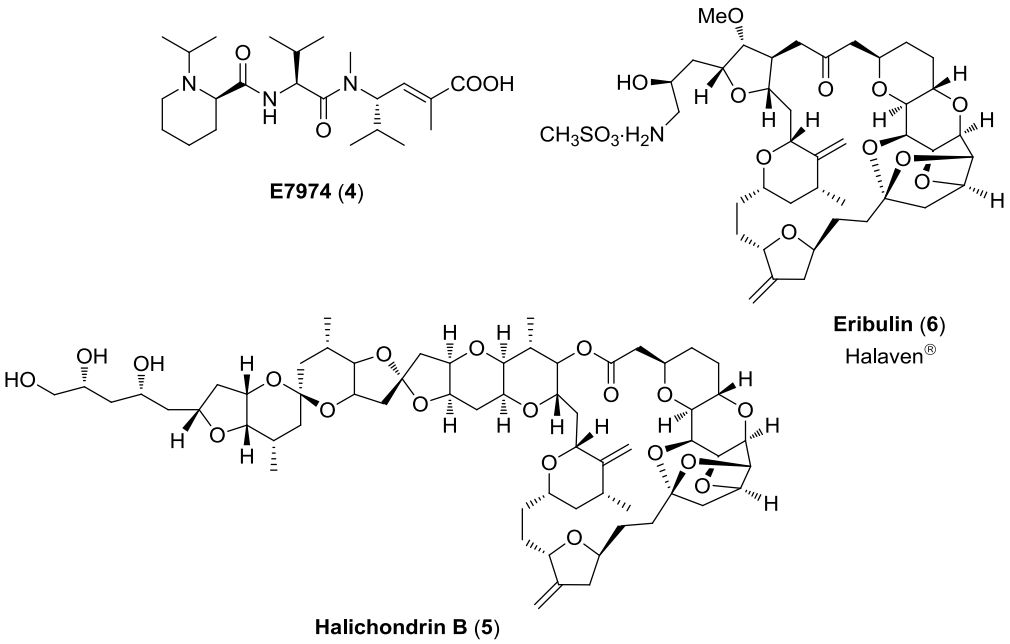


Figure 2 - E7974 (**4**); halichondrin B (**5**); eribulin (**6**) anti-cancer drug

1.3 Sesterterpenoids

Sestertepenoids are a class of terpenoid that have been isolated from various sources in nature including fungi, insects, plants and marine species.[13] They are constructed of five isoprenyl units, bearing C_{25} carbon skeletons (Table 1).

Table 1 - Nomenclature of terpenes

	Number of Isoprenyl Units
Hemiterpenes	1
Monoterpenes	2
Sesquiterpenes	3
Diterpenes	4
Sesterterpenes	***5***
Triterpenes	6
Tetraterpenes	8

Although the rarest class of terpenoid, consisting of only around 1000 known compounds,[14] the sesterterpenoid class of natural product exhibits diverse structures

with a range of biological properties.[15] The first ever identified sesterterpenoid was ophiobolin A (**7**), isolated in 1965 from the terrestrial fungus *Ophiobolus miyabeanus*, and later shown to exhibit nanomolar toxicity towards certain cancer cell lines.[16] Manoalide (**8**) is a potent analgesic and anti-inflammatory isolated initially from the marine sponge *Luffariella variabilis* in 1980.[17] The scalaranes are a relatively large family of biologically active sesterterpenoids; the recent isolation of several cytotoxic scalaranes including similan A (**9**), from the Thai marine sponge *Hyrtios gumminae* has been reported.[18]

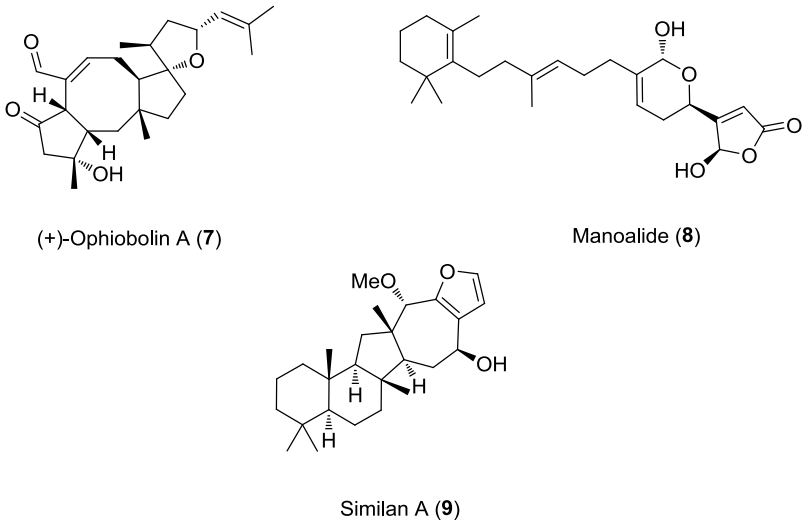


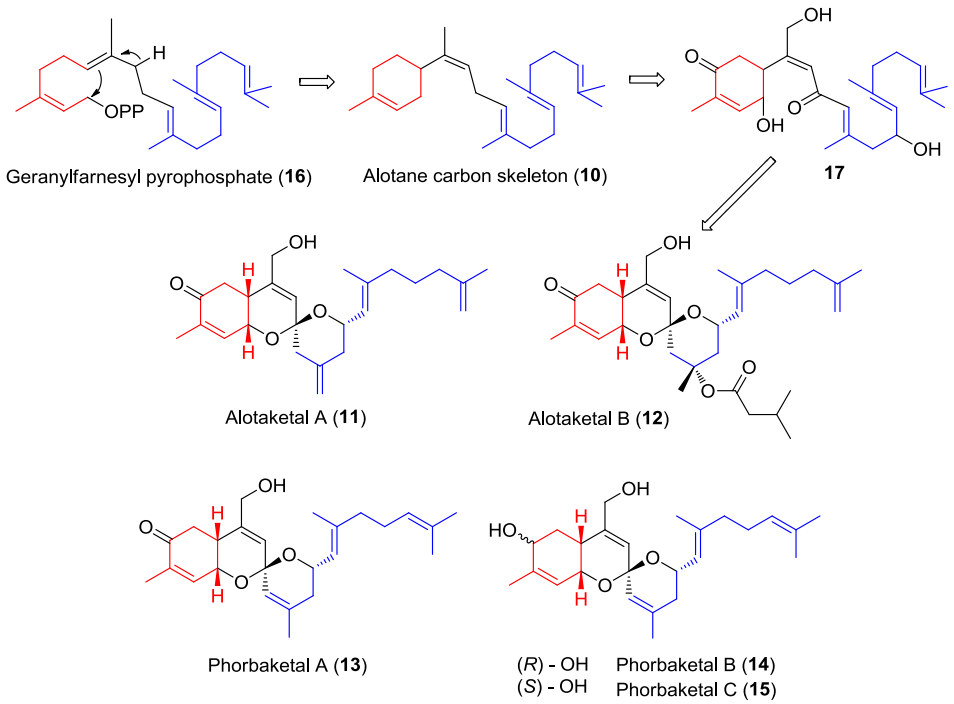
Figure 3 - Example sesterterpenoid natural products

With the vast number of possible arrangements of a C_{25} framework, sesterterpenoids have unsurprisingly presented many new carbon skeletons. A new biosynthetically related family of sesterterpenoids derived from marine sponges has emerged over recent years, exhibiting exciting structural diversity and biological properties.

1.4 Alotane Derived Natural Products

An ever-expanding family of biosynthetically related sesterterpenoid marine natural products possess a number of newly identified carbon skeletons. The first disovered of this family being the alotane carbon skeleton (**10**), in 2009 by Andersen *et al.*, with the isolation of the 6,6-spiroketal containing alotaketals A (**11**) and B (**12**) from the Papau New Guinean marine sponge *Hamigera sp.*[19] This was shortly followed by the reported isolation of the related phorbaketals A, B and C (**13**–**15**), from the Korean marine sponge *Phorbas sp.*, by Rho and co-workers (Scheme 1).[20]

The alotane carbon skeleton (**10**) is biosynthetically derived from partial cyclisation of geranyl farnesyl pyrophosphate (**16**), in the formation of a six-membered ring. It is proposed that processes to oxygenated intermediates *e.g.* **17**, are followed by spiroketalisation processes towards the alotaketal and phorbaketal frameworks.



Scheme 1 - Biosynthesis of the alotaketals A, B (**11**, **12**); phorbaketals A–C (**13**–**15**)

Skeletal rearrangements of the alotane carbon skeleton (**10**) give rise to a number of other recently discovered sesterterpenoid skeletons including the ansellane (**16**),[21] phorane (**17**),[22] phorbasane (**18**)[23] and isophorbasane (**19**) skeleton groups of natural product (Figure 4).

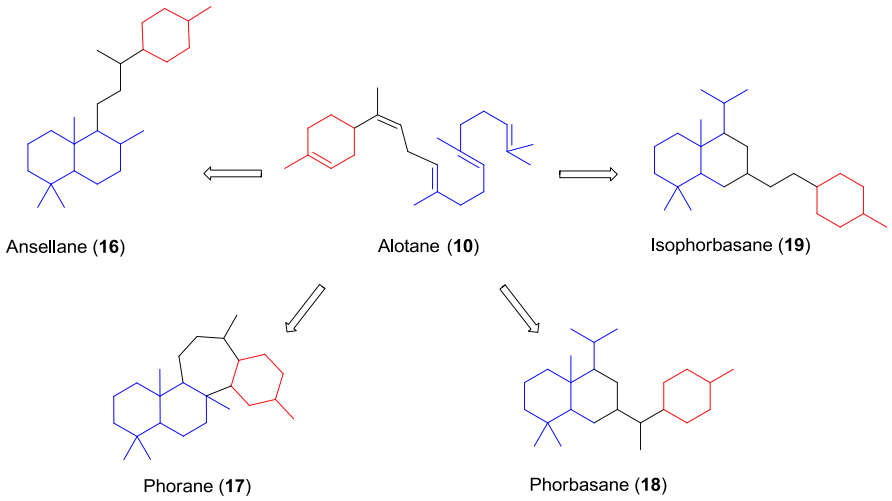


Figure 4 - Carbon skeletons deriving from the alotane carbon skeleton (**10**)

It is proposed that the *trans*-decalin systems possessed by the ansellane (**16**) and phorane skeletons (**17**) are formed *via* cyclisations of farnesyl tethers (Scheme 2). With the formation of the *trans*-decalin intermediates *e.g.* **20**, cyclisation processes may occur in the formation of various ansellane skeleton bearing natural products *e.g*. cyclisation steps to form ansellone A (**21**) or ansellone B (**22**).*

Alternatively, aromatisation of the cyclohexenone ring leads to aromatic ring intermediates *e.g.* **23**, which are prone to intramolecular electrophilic aromatic substitution processes *e.g.* in the formation of phorone A (**24**). Alternative

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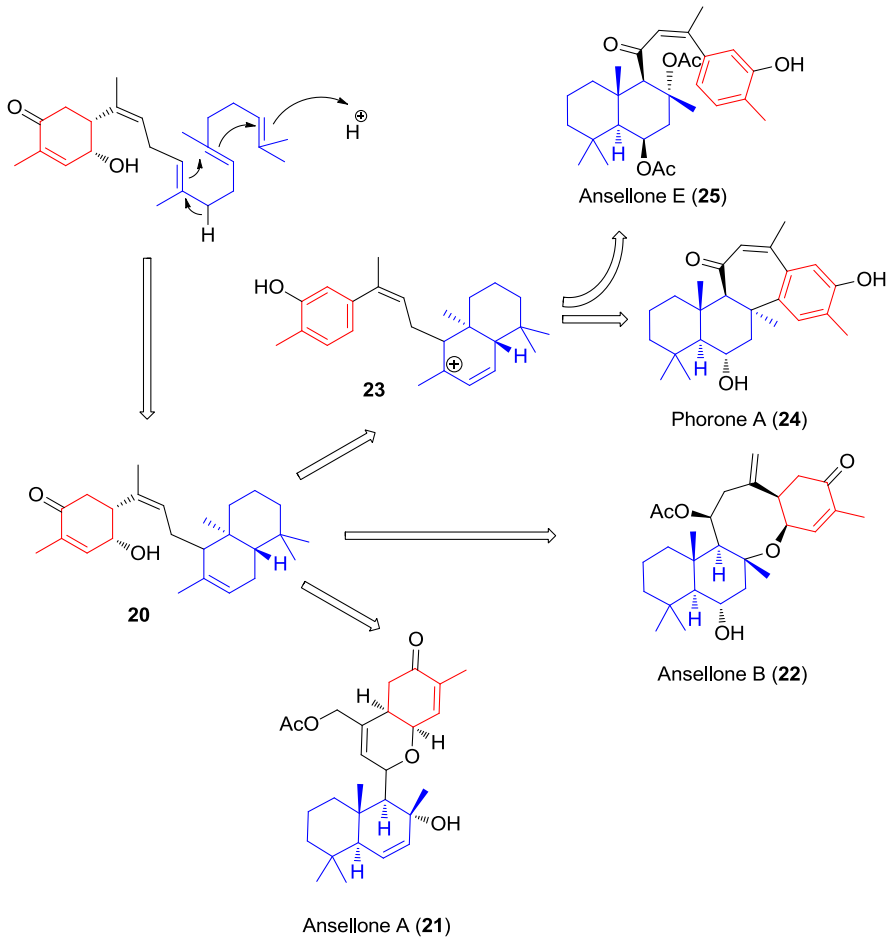
* There are mistakes in the lettering of ansellones (A−F) in the literature. The author has reassigned them in chronological order of discovery. Ansellones A−D were correctly assigned by J. Daoust in her PhD thesis, University of British Columbia, 2005. Ansellone E (previously ansellone B) in *Org. Lett*., 2012, **14**, 4486−4489; ansellone F (previously ansellone C) in *J. Nat. Prod.*, 2015, **78**, 218–224.

nucleophilic attack from an acetate ion may result in the formation of ansellone E (**25**).



Scheme 2 - proposed biosynthesis of various alotane derived sesterterpenoids

This alotane carbon skeleton derived family of sesterterpenoids have shown consistent expansion throughout the course of the work described in this thesis. They have emerged as a family of exciting biologically active metabolites, displaying a broad range of biological properties. Amongst this family, a large number of alotaketal and phorbaketal natural products have now been identified.

1.5 Alotaketals and Phorbaketals

As previously mentioned, the isolation of alotaketals A and B (**11**, **12**) from marine sponge *Hamigera sp.* was reported by Andersen and co-workers in 2009.[19] This

discovery was shortly followed by the reported isolation of the structurally similar phorbaketals A, B and C (**13**–**15**) by Rho and co-workers from the Korean marine sponge *Phorbas sp.*[20] It was found that these natural products displayed intruiging biological properties, which probably acted to spur on isolation of many other related natural products.

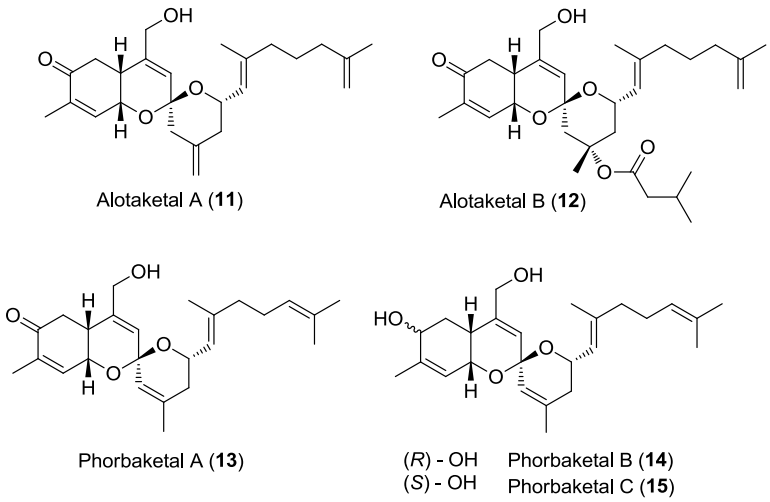


Figure 4 - Isolation of alotaketals (A and B) and phorbaketals (A−C)

In 2013, Wang *et al*. reported the isolation of phorbaketals D–K (**26**–**33**)[24] from the South Korean marine sponge *Monanchora sp.* (Figure 5). This was followed by the reported isolation of phorbaketals L–N (**34**–**36**)[25] from marine sponge *Phorbas sp*. in 2014. Additionally, alotaketal C (**37**) was isolated from the same marine sponge species in 2013.[24] Seemingly also derived from the alotane carbon skeleton, the related gombaspiroketals A–C (**38**-**40**)[26] should be noted, being isolated very recently from the sponge *Clathria gombawuiensi*.

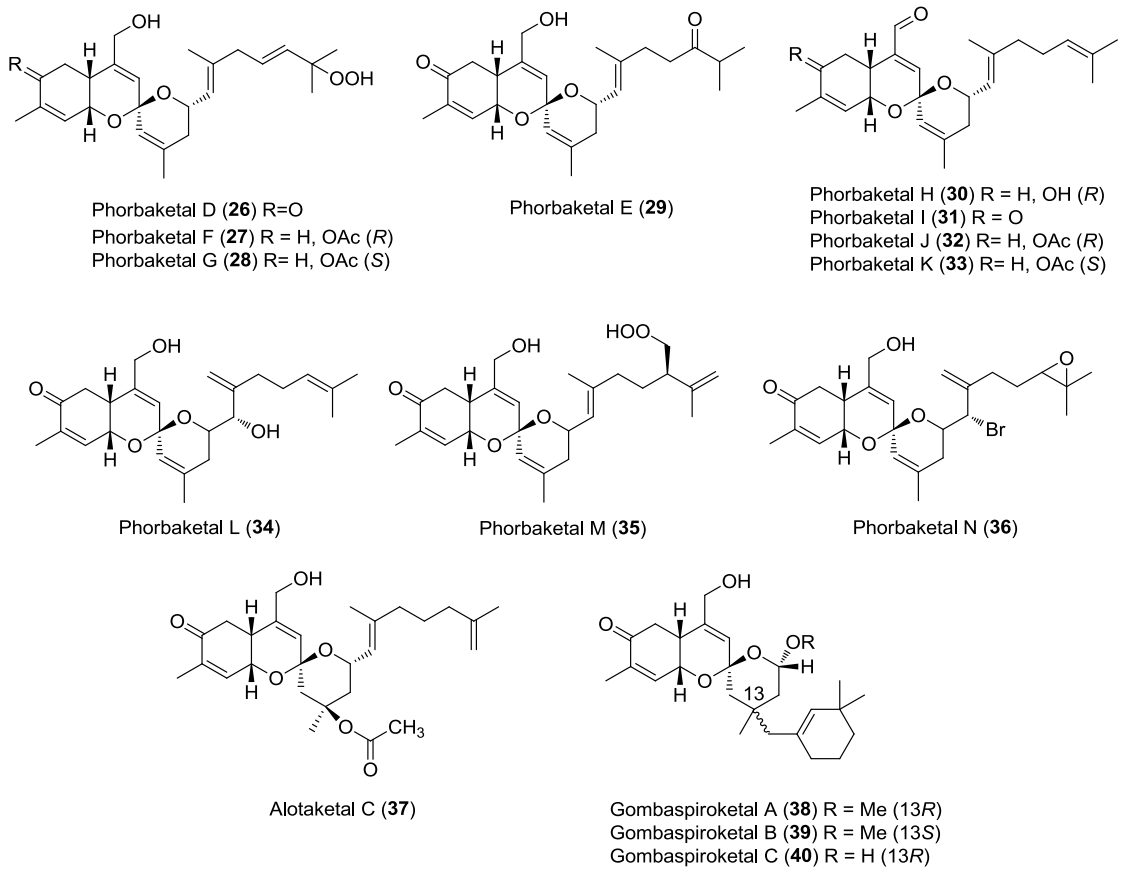


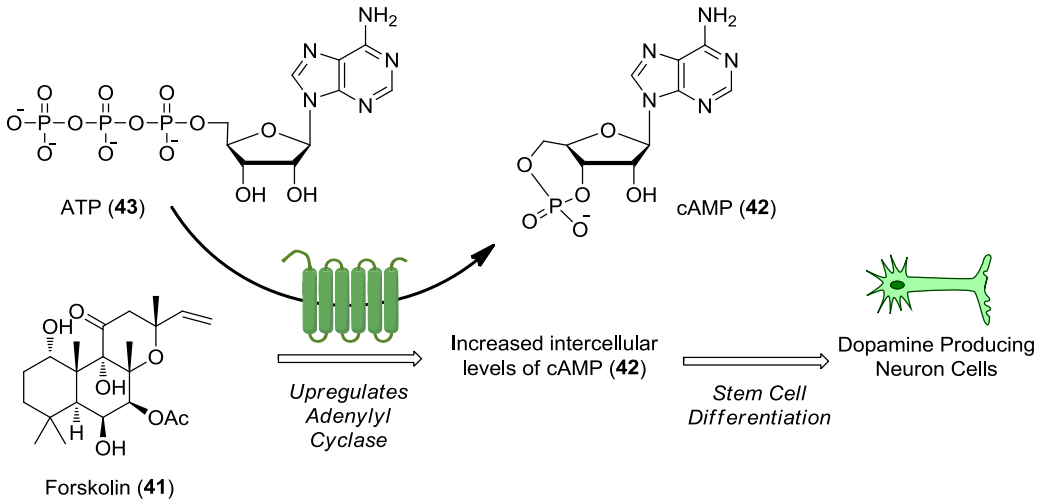
Figure 5 - Phorbaketals D–N (**26**–**36**); alotaketal C (**37**); gombaspiroketals A–C (**38**–**40**)

Some of these alotaketal and phorbaketal analogues have demonstrated intruiging biological properties. It seems that this ever-growing family of natural products provide an exciting opportunity for drug development investigations into the treatment of a range of diseases and also for use as important biological tools.

1.5.1 Biological Properties of Alotaketals and Phorbaketals

Currently the diterpenoid forskolin (**41**) is strongly relied upon as a biological tool to provide increased intercellular levels of cyclic adenosine monophosphate (cAMP) (**42**) by activation of adenylyl cyclase.[27] The enzyme adenylyl cyclase facilitates the conversion of adenosine triphosphate (ATP) (**43**) to cAMP (**42**) (Scheme 3). The formed cAMP can bind to cAMP dependent protein kinase (PKA) resulting in an

increased rate of the phosphorylation of certain proteins. These proteins are often important for cellular functions such as gene transcription or ion channels. Small molecules that can alter intercellular levels of cAMP thus have important effects within the cell, making them powerful biological tools.



Scheme 3 - Forskolin (**41**) for increased levels of cAMP (**42**)

As a result of its bioactivity, forskolin (**41**) is a commonly used biological tool for investigating the role of cAMP in cellular processes.[28] In particular, increased levels of cAMP are known to potentiate the differentiation of stem cells into dopamine producing neuron cells, and so forskolin (**41**) is an important tool in the development of potential neurodegenerative disease (*e.g.* Parkinson's disease) treatments.[29]

It has been found that alotaketals A and B (**11**, **12**) activate the cAMP pathway, with identified EC_{50} (the concentration giving 50% maximum effectiveness) values of 18 and 240 nM respectively.[19] Remarkably, it was found that alotaketal A (**11**) is in fact 170 times more potent than forskolin (EC_{50} 3 μM) for activation of the cAMP signalling pathway (Table 2). Hence, alotaketal A (**11**) has potential utility as an

attractive replacement to forskolin (**41**), which is expensive* due to its scarcity in nature and has greater structural complexity.

Table 2 - cAMP pathway activators

Substrate	EC_{50}
Forskolin	3 μM
Alotaketal A	8 nM
Alotaketal B	240 nM

The phorbaketals have also displayed various striking biological activities. It has been identified that phorbaketal A (**13**) acts to promote osteogenic differentiation in human mesenchymal stem cells, suggesting its potential use in drug discovery towards treatments for the progressive bone disease osteoporosis. Added to this, phorbaketal A (**13**) has also displayed inhibition of adipocyte differentiation and fatty acid synthesis in the liver, indicating its potential use in the drug discovery of obesity treatments.[30]

Phorbaketals H (**30**) and I (**31**) have been shown to exhibit weak cytotoxicity against renal cancer cell lines.[24] More strikingly, phorbaketal N (**36**) has displayed potent cytotoxicity against human pancreatic cancer cell lines. It has been proposed that phorbaketal N (**36**) could assist discovery of much needed drug leads for the treatment of pancreatic cancers.[25]

Due to these potentially very useful biological activities, there has been interest in the total synthesis of the alotaketal and phorbaketal natural products. Contemporaneously to the work described within this thesis, two total syntheses of

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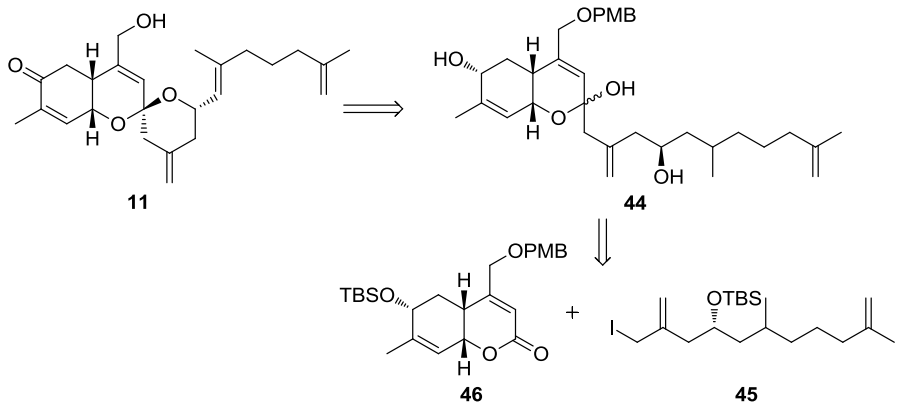
*sigmaaldrich.com - £14.50/mg 'Forskolin from *Coleus forskohlii*, ≥98%'

alotaketal A (**11**) and work towards the total synthesis of phorbaketal A (**13**), have been reported in the literature.

1.5.2 Contemporaneous Total Syntheses of Alotaketals and Phorbaketals

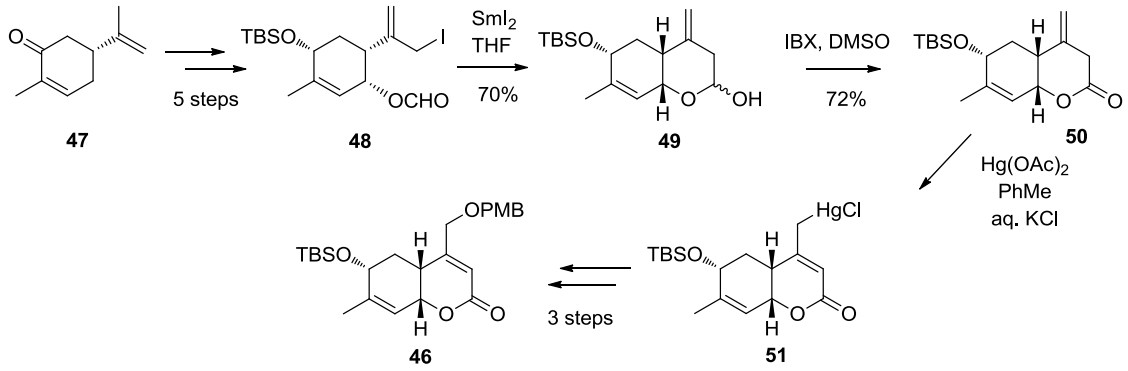
1.5.2.1 Total Synthesis of Alotaketal A by Yang *et al.*

The first total synthesis of alotaketal A (**11**) was reported by Yang *et al.* in 2012.[31] Their retrosynthetic analysis revealed a potential acid catalysed strategy for formation of the 6,6-spiroketal core, *via* a lactol fragment **44**. The synthesis of the lactol **44** was anticipated to proceed *via* the late-stage coupling of allyl iodide **45** and bicyclic lactone **46** (Scheme 4).



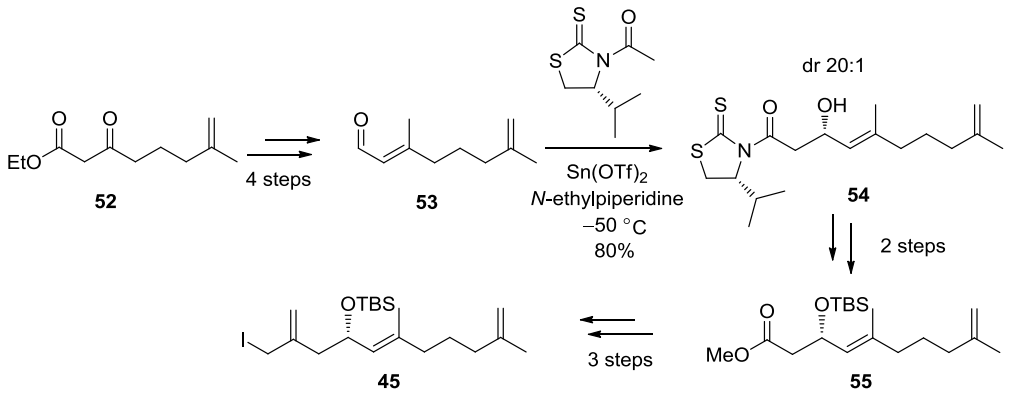
Scheme 4 - Retrosynthetic analysis of alotaketal A (**11**) by Yang *et al.*

The synthesis of bicyclic lactone **46** started from readily available (*R*)-(–)-carvone (**47**) (Scheme 5). A key step involved use of an unusual SmI_2-induced reductive allylation step from allyl iodide **48**, to give lactol **49**. After oxidation of the lactol **49** to the lactone **50** using 2-iodoxybenzoic acid (IBX), the employment of $Hg(OAc)_2$ assisted regioselective formation of allylmercury chloride species **51**. This species was then converted to the *para*-methoxybenzyl ether (PMB) protected alcohol **46** over three synthetic steps.



Scheme 5 - Synthesis of bicyclic lactone **46**

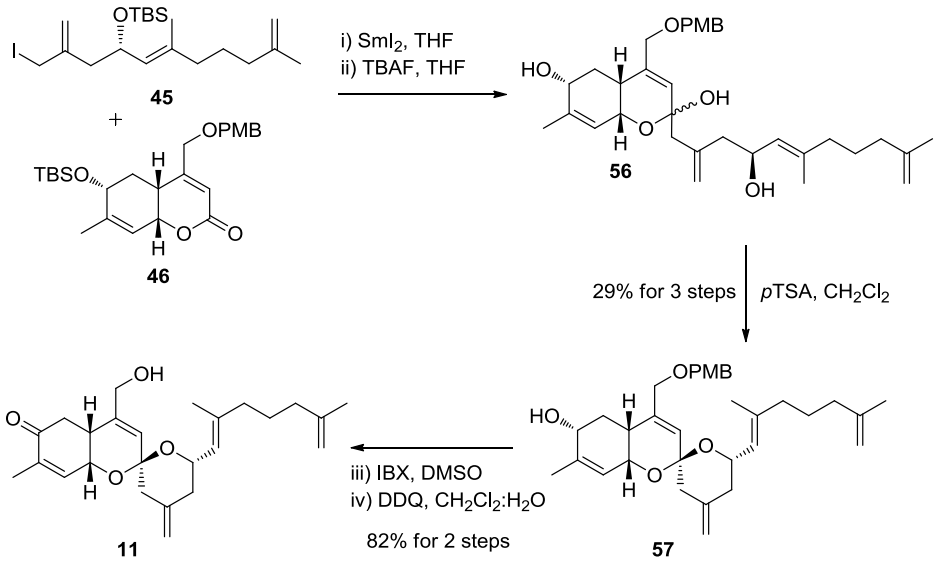
The synthesis of the allyl iodide **45** was achieved in ten steps from β-ketoester **52** (Scheme 6). A key step involved employing the Nagao aldol protocol for diastereoselective addition to aldehyde **53**, giving allylic alcohol **54** as the major diastereomeric product. After methanolysis and TBS protection to ester **55**, conversion to allyl iodide **45** was achieved over three subsequent steps.



Scheme 6 - Synthesis of allyl iodide **45**

Attempts of the generation of organolithium or organomagnesium species from allyl iodide **45**, to faciliate nucleophilic addition to the bicyclic lactone **46**, were unfruitful. Instead, Barbier conditions mediated by SmI_2 were found to assist the addition of allyl iodide **45** to lactone **46**, to give lactol **56** (Scheme 7). Subsequent desilylation using fluoride and acid catalysed spiroketalisation using *para*-

toluenesulfonic acid (*p*TSA) were performed without purification of the intermediates, giving the spiroketal **57** as a single diastereomer. The final steps to alotaketal A (**11**) involved oxidation of the allylic alcohol **57** to the ketone functionality using IBX and lastly removal of the PMB ether protecting group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 7).

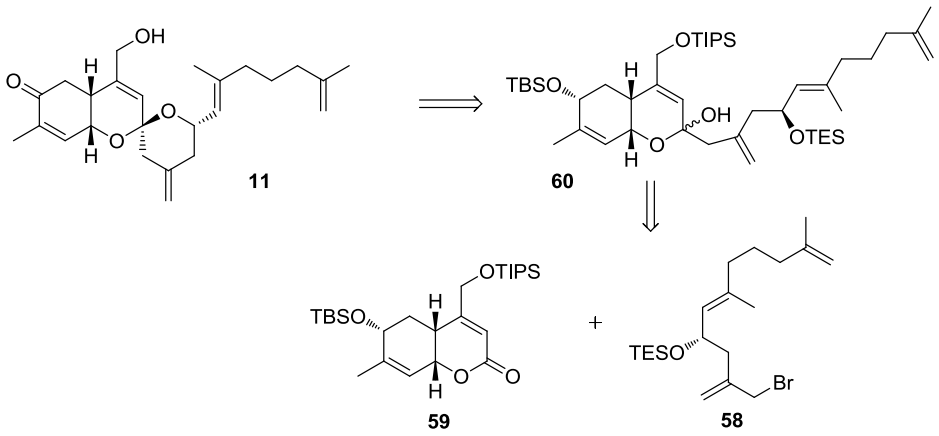


Scheme 7 - Final steps towards alotaketal A (**11**)

This pioneering total synthesis of alotaketal A (**11**) served to confirm the stereochemical assignments previously made by Andersen *et al.*[19]

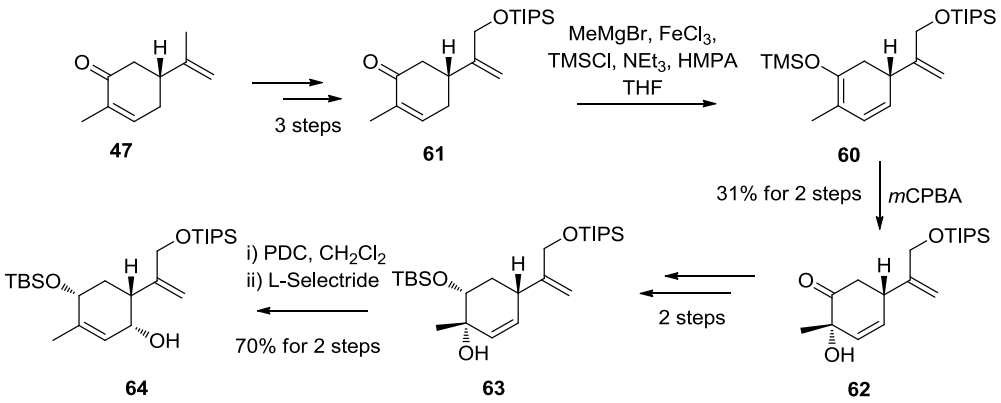
1.5.2.2 Total Synthesis of Alotaketal A by Dalby *et al.*

Only half a year later, a second total synthesis of alotaketal A (**11**) was reported by Dalby *et al.*[32] Overall, the strategy was similar to that of the pioneering work by Yang *et al*. In this strategy, addition of allyl bromide **58** to lactone **59** was planned for the formation of lactol **60**, with subsequent steps involving acid catalysed formation of the spiroketal core (Scheme 8).



Scheme 8 - Retrosynthetic analysis of alotaketal A

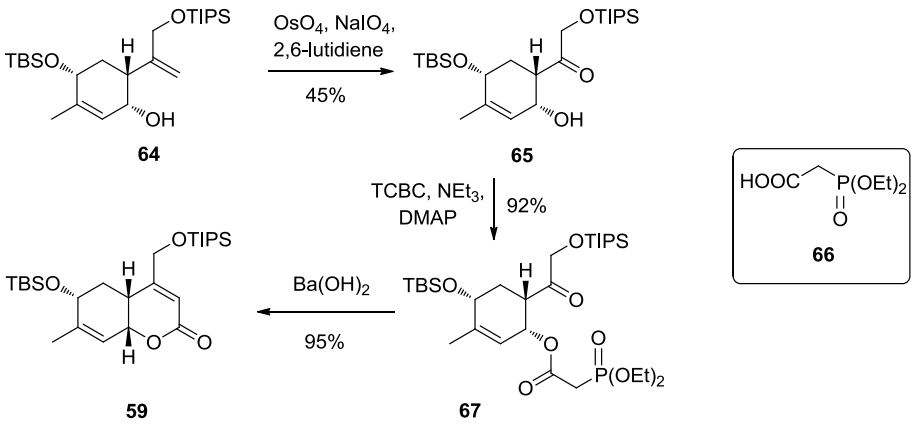
The synthesis of bicyclic lactone **59** started from (*R*)-carvone (**47**) (Scheme 9). Following base assisted formation of silyl dienyl ether **60** from ketone **61**, Rubottom oxidation using *m*CPBA allowed access to tertiary alcohol **62**. PDC mediated the allylic rearrangement of tertiary alcohol **63** for formation of an enone intermediate which was reduced using L-selectride to give alcohol **64**.



Scheme 9 - Towards bicyclic lactone **59**

The synthesis of the bicyclic lactone **59** from alcohol **64** was achieved *via* a Horner-Wadsworth-Emmons olefination strategy. Cleavage of the terminal alkene using Johnson-Lemieux conditions gave ketone **65** and subsequent Yamaguchi conditions with phosphonate **66** were used to assist the formation of β-keto-phosphonate **67**.

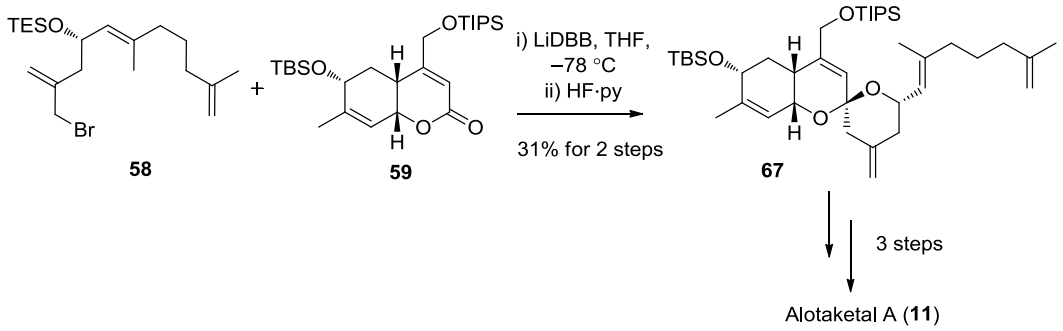
Subsequent deprotonation of the phosphonate **67** with barium hydroxide mediated intramolecular olefination to the bicyclic lactone **59**.



Scheme 10 - Synthesis of bicyclic lactone **59**

The synthesis of allyl bromide **58** started from readily available starting material geraniol. In brief, a similar Nagao aldol approach to that used by Yang *et al.* was used to install the secondary alcohol with dr 95:5, which was subsequently silylated to the TES protected allyl bromide **58** (Scheme 11).

In a similar observation to Yang *et al.*, difficulties in forming organolithium or organomagnesium species from allyl bromide **58** were encountered. However, it was found that using an excess of lithium di-*tert*-butylbiphenyl (LiDBB) facilitated the required nucleophilic addition to the lactone **59** (Scheme 11). Treatment of the addition product with HF·pyridine assisted selective removal of the triethylsilane (TES) ether protecting group, with concurrent acid catalysed spiroketalisation to give spiroketal **67**. Final steps to alotaketal A (**11**) involved removal of the remaining silyl ether protecting groups and the required oxidation level adjustments.

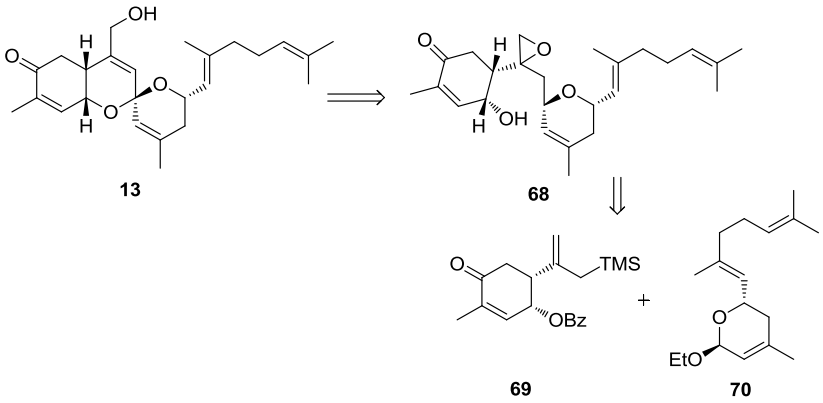


Scheme 11 - Total synthesis of alotaketal A (**11**) by Dalby *et al.*

This shorter synthesis of alotaketal A (**11**) employing readily available starting materials (*R*)-carvone and geraniol will likely be useful for the synthesis of alotaketal, phorbaketal or other non-natural analogues for SAR studies and biological evaluations.

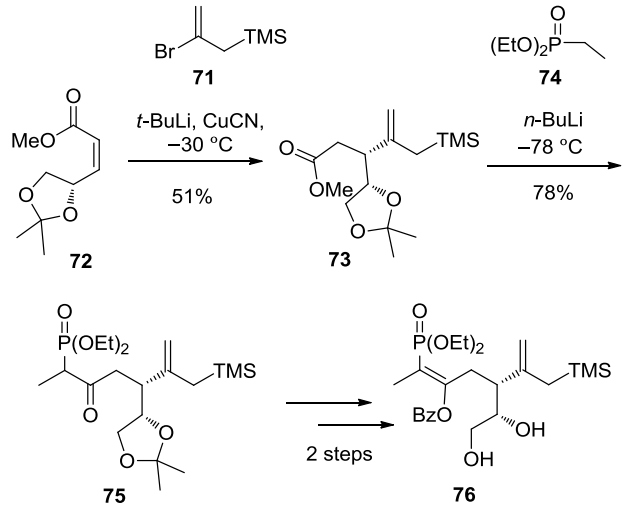
1.5.2.3 Efforts Towards Phorbaketal A by Brimble *et al.*

Efforts towards the total synthesis of phorbaketal A (**13**) were reported very recently, in February 2015, by the group of M. Brimble.[33] Upon unsuccesful attempts to reproduce the synthesis of silyl dienol ether **60**, as was reported by Yang and co-wokers, a synthetic strategy which deviated from the previously discussed (*R*)-carvone based syntheses of alotaketal A (**11**) was devised. Their retrosynthetic analysis led them to an oxidative cyclisation strategy for formation of the 6,6-spiroketal core from **68**, *via* the late-stage coupling of *mono*-cyclic fragments **69**, **70** (Scheme 12).



Scheme 12 - retrosynthesis of phorbaketal A (**13**) by Brimble *et al.*

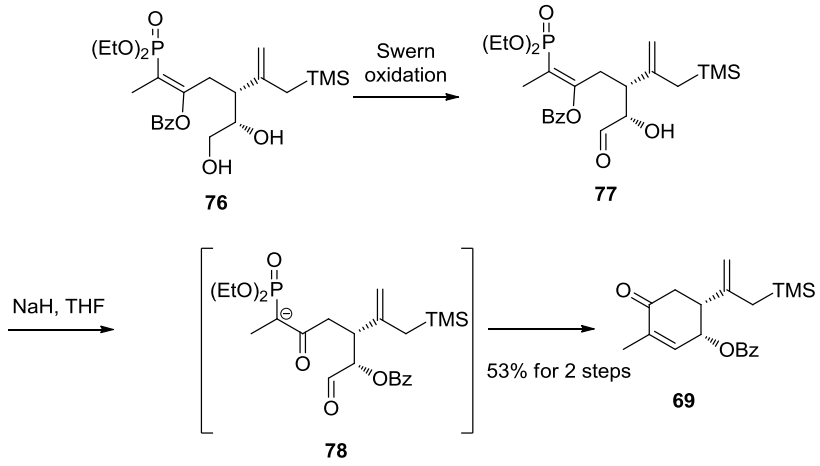
The synthesis of allyl silane fragment **69** was achieved *via* a Horner-Wadsworth-Emmons olefination strategy. Firstly, conjugate addition of allyl bromide **71** to (*Z*)-ester **72**, *via* an organocopper species, gave ester **73** (Scheme 13). Addition of deprotonated diethyl ethylphosphonate (from **74**) to the ester **73** assisted conversion to phosphonate **75**, which was subsequently converted to benzoyl enol ether **76**.



Scheme 13 - Synthesis of benzoyl enol ether **76**

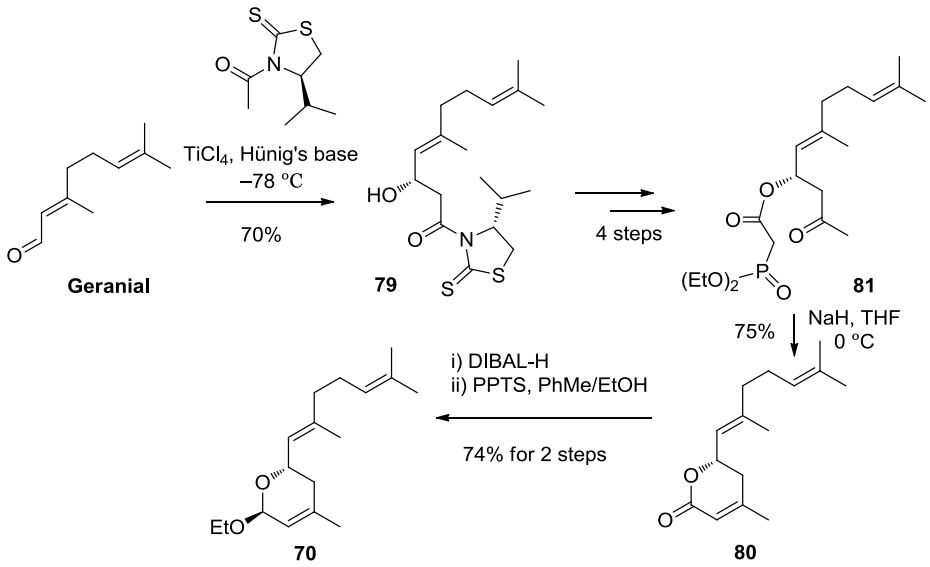
Final steps towards allyl silane **69** involved Swern oxidation, to give unstable aldehyde **77** (Scheme 14). In an elegant step, the treatment of aldehyde **77** with sodium hydride mediated alkoxide formation resulting in intramolecular transfer of

the benzoyl group, and thus generation of the phosphonate anion **78**, which then participated in an intramolecluar olefination process to give allyl silane **69**.



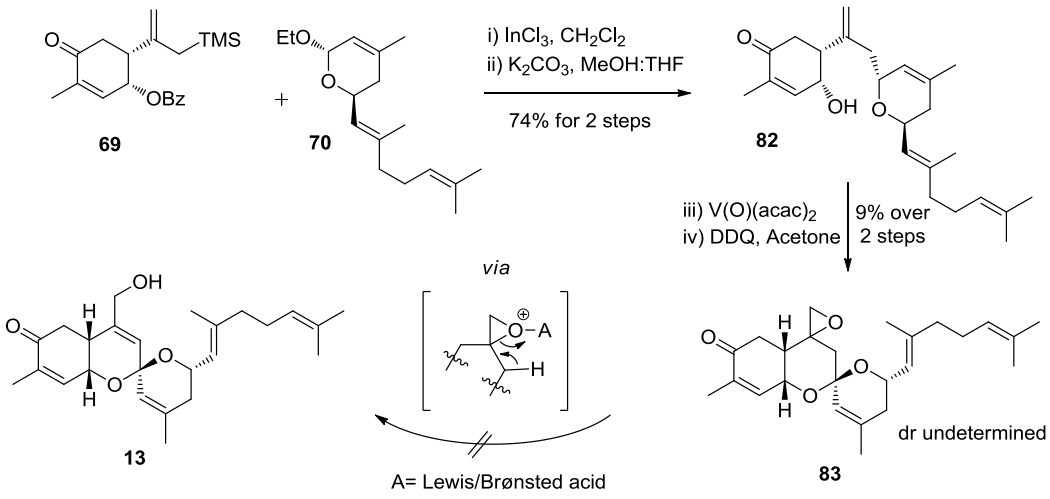
Scheme 14 - Synthesis of allyl silane **69**

The synthesis of acetal fragment **70** began with a Nagao-Fujita aldol reaction between the acetylated auxillary and geranial to give alcohol **79** (Scheme 15). A key step involved formation of lactone **80** *via* an intramolecular Horner-Wadsworth-Emmons olefination of phosphonate **81**. Subsequent conversion of the lactone **80** to the acetal **70** was achieved over reduction and acetalisation steps.



Scheme 15 - Formation of acetal fragment **70**

The coupling of allyl silane **69** with lactone **70** was achieved using $InCl_3$-promoted Hosomi-Sakurai conditions to give alcohol **82** (Scheme 16). Following removal of the benzoyl protecting group and epoxidation of the terminal alkene, the key oxidative cyclisation step using DDQ was successful for formation of the 6,6-spiroketal **83**. The anticipated final step to phorbaketal A (**13**) would involve conversion of the epoxide **83** to the required allylic alcohol motif. However after extensive screening, the required conditions for this transformation were not found, and the total synthesis of phorbaketal A (**13**) was not achieved.



Scheme 16 - Final steps towards phorbaketal A (**13**)

This synthesis of the phorbaketal core structure will undoubtedly assist future endeavours towards the synthesis of phorbaketal and alotaketal natural and non-natural analogues for biological testing and SAR studies.

1.6 Methods for the Formation of Spiroketals

1.6.1 The Anomeric Effect

The anomeric effect is a stereoelectronic effect which describes the preference for electronegative substituents adjacent to a heteroatom with an available lone pair of

electrons in a cyclohexane ring to adopt an axial conformation, instead of the normally encountered preference for subtituents to reside in the sterically favoured equatorial position. There have been many postulations on the origins of this effect.[34] Among these, n-σ^* hyperconjugation stabilisation is often regarded as the most significant.[35] The stabilising *exo* anomeric effect involves a donation of the exocyclic heteroatom lone pair to the σ^* orbital of the C–heteroatom bond within the ring. The stabilising *endo* anomeric effect involves the donation of the lone pair of the cyclic heteroatom to the σ^* orbital of the exocyclic C–heteroatom bond (Figure 6).

These effects have particular importance in heteroatom-substituted tetrahydropyran rings and thus play a crucial role in the stereochemical outcome of many spiroketal-forming reactions.

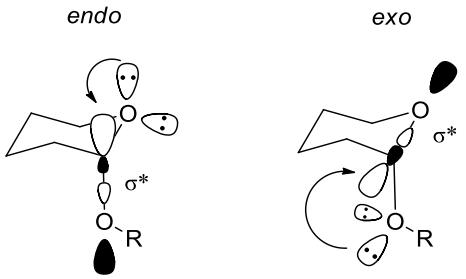
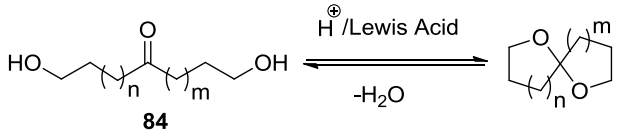


Figure 6 - *Exo* and *Endo* anomeric effects

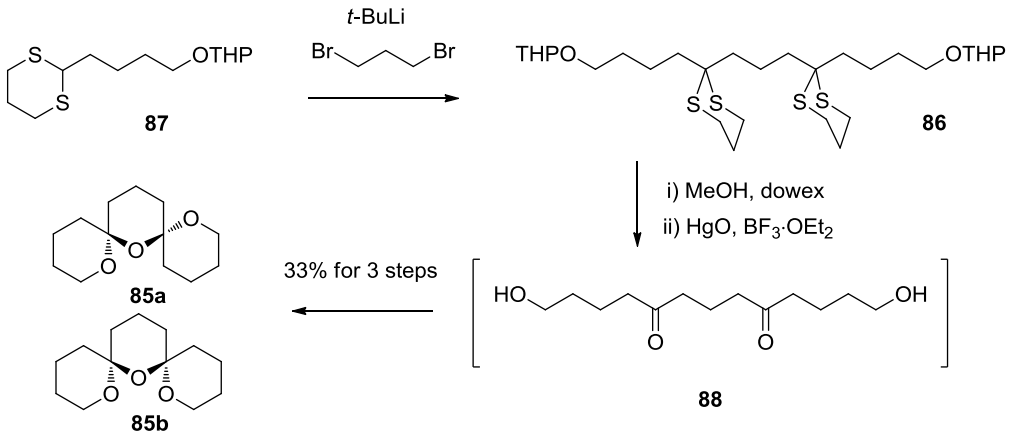
1.6.2 Acid catalysed spiroketalisation

Acid catalysed cyclisation of dihydroxy ketals *e.g.* **84** is probably the most prevalent method for spiroketal synthesis (Scheme 17). The reversible nature of this process allows exploitation of the stabilising anomeric effect. A voluminous number of strategies towards dihydroxy ketal derivates *e.g.* **84** have been devised.[36]



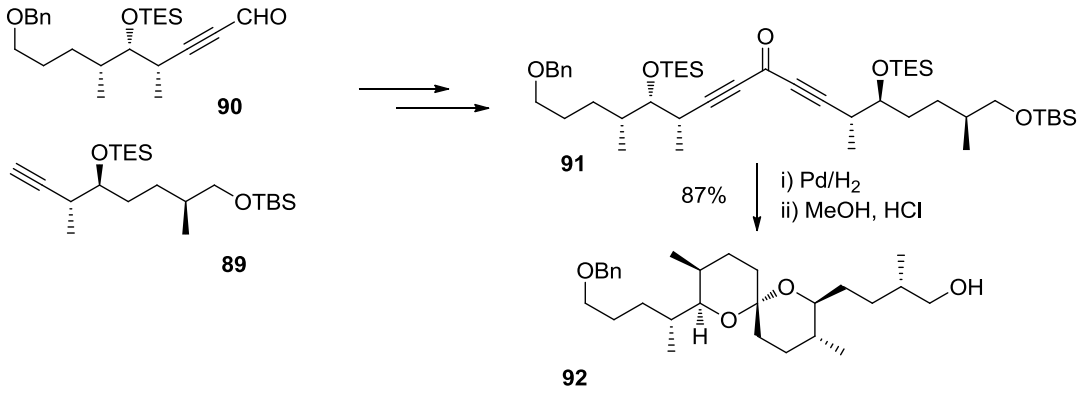
Scheme 17- Acid catalysed spiroketal formation from dihydroxy ketal derivates **84**

A common strategy for the formation of dihydroxy ketal derivates uses an umpolung approach involving ketones protected as 1,3-dithianes, as acyl anion equivalents. An example of this was reported by Stepanian *et al.* towards the synthesis of the tricyclic spiroketals **85a** and **85b** (Scheme 18).[37] The construction of **86** was achieved from 1,3-dithiane **87**. Following the removal of all protecting groups, spiroketalisation *via* intermediate **88** was achieved using HgO and $BF_3 \cdot OEt_2$.



Scheme 18 - 1,3-Dithiane approach to tricyclic spiroketals **85a** and **85b**

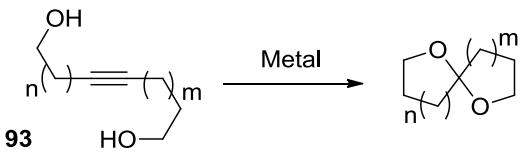
The nucleophilic addition of organometallics to aldehydes and lactones is commonly utilised for the formation of dihydroxy ketals. This strategy was employed by Marshall *et al.* towards the formal total synthesis of tautomycin. Nucleophilic addition of alkyne **89** to aldehyde **90** was followed by oxidation to ketone **91** (Scheme 19). Hydrogenation of the di-alkyne substrate **91** was followed by acid-catalysed spirocyclisation to give the 6,6-spiroketal **92**.[38]



Scheme 19 - Acetylide anion approach

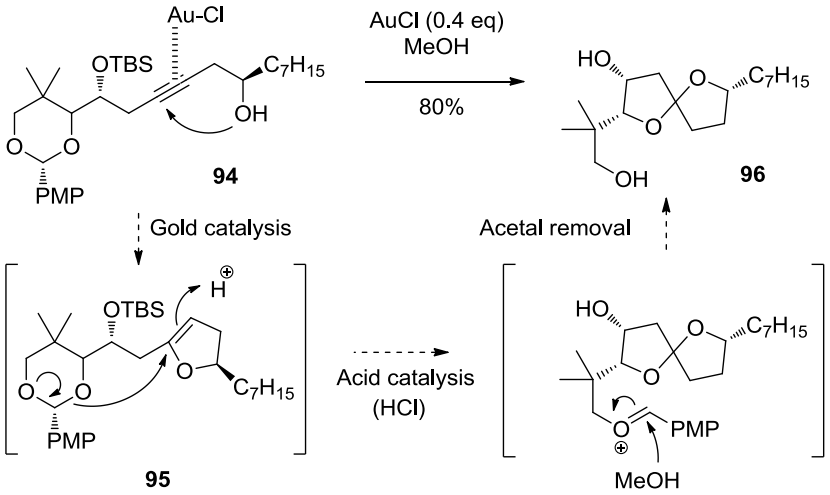
1.6.3 Other Methods for Spiroketal Formation

Cycloisomerisation is an emerging strategy for the synthesis of spiroketals that harnesses the alkyne π system activating properties of many transitions metals, and has been utilised in a number examples (Scheme 20). Examples of cycloisomerisation of alkynediols (*e.g.* **93**) have been reported using rhodium, iridium, palladium, gold and other complexes.[39]



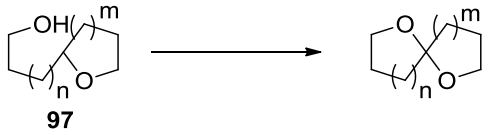
Scheme 20 - Cycloisomerisation approach

A recent study by Tlais *et al.* explores the ability of a number of late transition metal complexes to catalyse alkyne diol cycloisomerisation.[40] It was found that gold(I) chloride was most suited for the required transformation. The proposed mechanism involves gold catalyzed cyclisation of alkyne **94** to furanyl intermediate **95** which then leads to the formation of spiroketal **96.**



Scheme 21 - Gold(I)-catalysed spiroketalisation

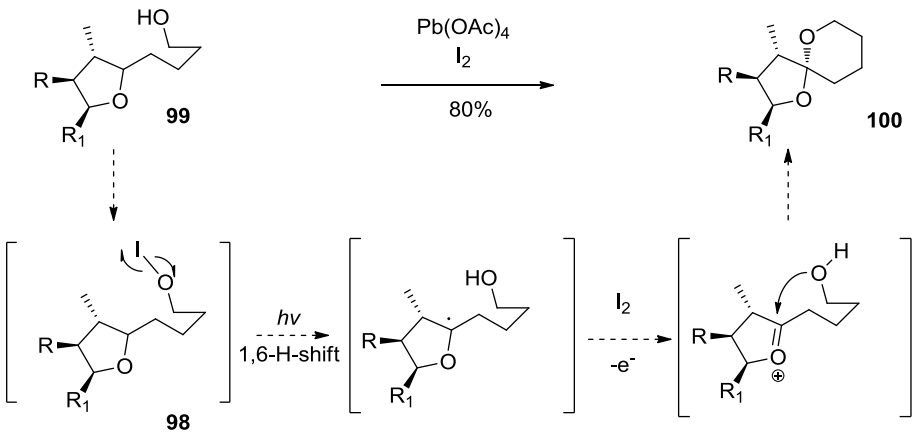
Oxidative radical cyclisation is a less common approach towards spiroketal formation (Scheme 22). This method was briefly introduced in previously discussed efforts towards phorbaketal A (**13**) by Brimble *et al*., using DDQ.[33] This method can be utilised during the synthesis of acid-sensitive compounds as a substitute for more traditional acid catalysed methods. The hydrogen abstraction *e.g.* from **97** can be driven by radical species, heat or light (Scheme 22).[41]



Scheme 22 - Intramolecular hydrogen abstraction

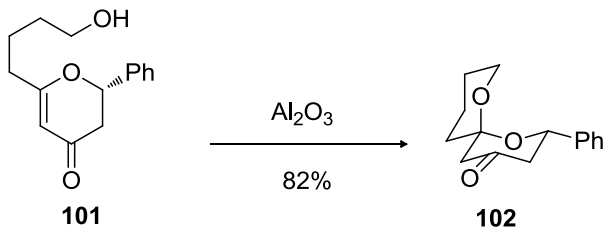
Much of the initial exploration of this method was pioneered by Suarez.[42] In his reported synthesis of a spiroketal containing steroid **100**, a 1,6-hydrogen shift process was postulated (Scheme 23). The initial step involves formation of an I–O bond **98** from alcohol **99**, which undergoes light- or heat-induced homolytic cleavage. A 1,6-hydrogen shift is proposed to be followed by carbocation formation upon oxidation

with I_2. In the final proposed step, nucleophilic attack of the hydroxyl group leads to formation of the spiroketal **100**.



Scheme 23 - 1,6-Hydrogen shift towards steroid **100**. R_1, R_2 = steroidal framework

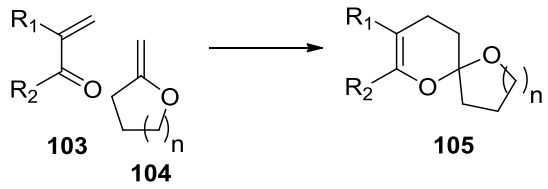
A number of strategies involving conjugate (Michael) addition have been devised. A common approach using α,β-unsaturated ketones was firstly demonstrated by Danishefsky *et al*., when treatment of cyclic enone **101** with neutral alumina mediated the conjugate addition of the hydroxyl group tether, in the diastereoselective formation of the 6,6-spiroketal **102** (Scheme 24).[43] The reversible nature of the conjugate addition step allows for excellent stereocontrol, allowing one to exploit anomeric effects.



Scheme 24 - Conjugate addition to α,β-unsaturated ketone **101**

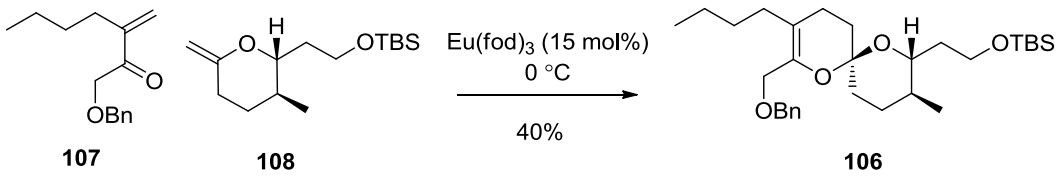
The formation of spiroketals can be achieved *via* a hetero-Diels-Alder (HDA) cycloaddition reaction between an α,β-unsaturated carbonyl compound (*e.g*. **103**) and

vinyl ethers (*e.g.* **104**). The formation of enol ethers *e.g.* **105** is advantageous since it allows for further modification of the ring system (Scheme 25).



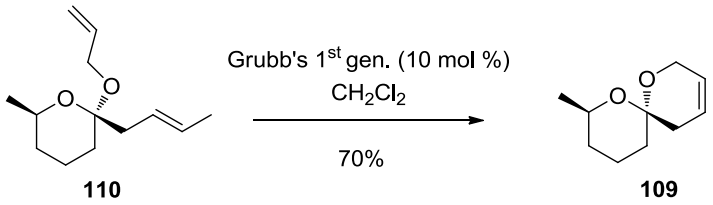
Scheme 25 - Example of Hetero-Diels-Alder approach

It is well-documented that the spiroketal core of the natural product (–)-reveromycin A undergoes thermodynamically driven acid-catalysed isomerisation, in the alleviation of steric interactions between alkyl side chains - be it at the loss of the stabilising anomeric effect. To overcome this problem, Sous *et al.* employed a hetero-Diels-Alder approach for the formation of the spiroketal core **106** (Scheme 26).[44] This kinetically controlled reaction between α,β-unsaturated ketone **107** and vinyl ether **108** was promoted by the Lewis acid $Eu(fod)_3$ (fod = tris[6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione]) and afforded spiroketal **106** as a single diastereomer.



Scheme 26 - HDA towards the total synthesis of (−)-reveromycin A

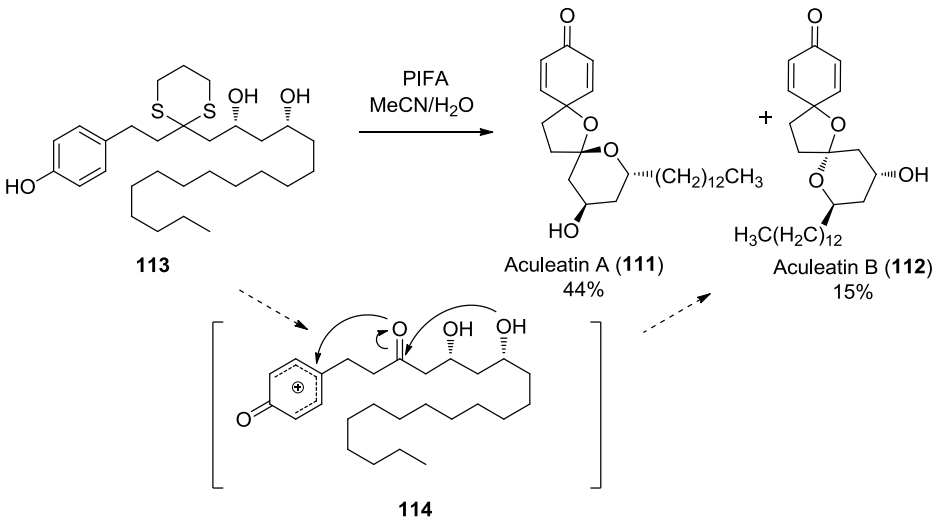
The ring-closing metathesis of alkenes for the synthesis of spiroketals is an approach which was pioneered by Ghosh *et al*. in 2004, with the synthesis of spiroketal **109**. In this example, Grubbs 1st generation catalyst was employed for the ring closing metathesis of acetal **110** (Scheme 27).[45]



Scheme 27 - Ring Closing Metathesis approach by Ghosh *et al.*

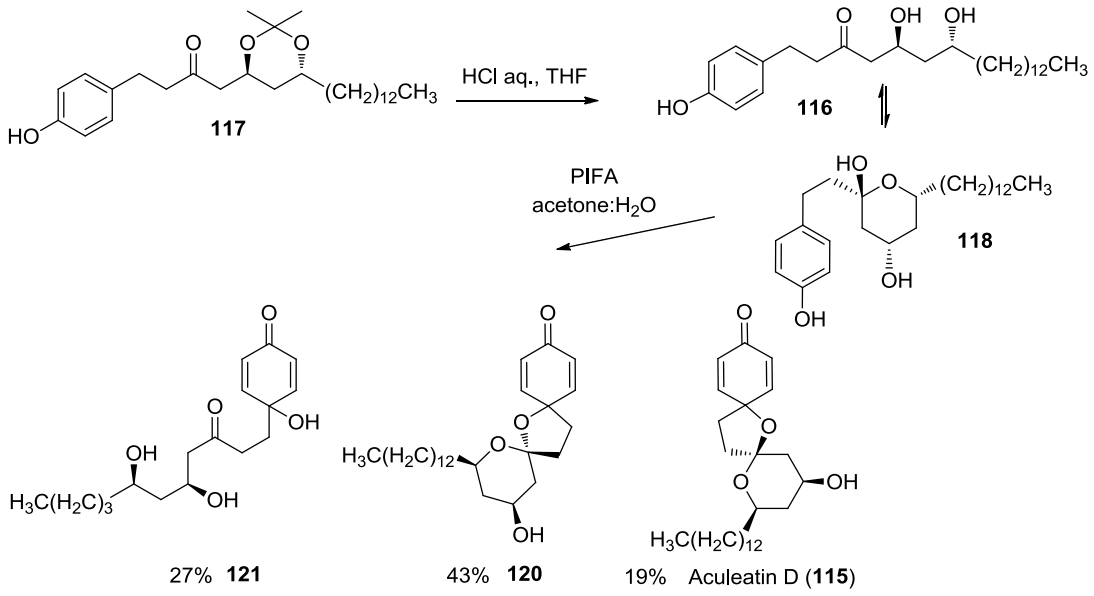
1.6.4 Cascade Oxidative Dearomatisation for Spiroketal Formation

Very relevant to the work presented within this thesis is the cascade oxidative dearomatisation strategy for the formation of spiroketals. Such a pathway was first demonstrated by Wong in the total synthesis of aculeatins A (**111**) and B (**112**), which are anti-malarial natural products.[46] Treatment of dithiane phenol **113** with the $PhI(OCOCF_3)_2$ (PIFA) as oxidant resulted firstly in removal of the dithiane protecting group and then concomitant oxidation of the phenol, resulting in spiroketalisation to give the spiroketal epimers, aculeatins A (**111**) and B (**112**) (Scheme 28). A possible mechanism for spiroketalisation would involve the formation of phenoxenium intermediate **114**, which is prone to nucleophilic attack from the tethered hydroxyketone chain.



Scheme 28 - Synthesis of aculeatins A (**111**) and B (**112**)

This strategy was also adopted by Baldwin *et al.* for the total synthesis of aculeatin D (**115**) (Scheme 29).[47] Hydrolysis of the acetonide protected 1,3-diol **117** in aq. HCl resulted in an equilibriating mixture of lactol **118** and ketone **116**. Treatment of this mixture with $PhI(OCOCF_3)_2$ (PIFA) resulted in spiroketalisation to give a varying ratio of products, dependant upon the choice of solvents. A 9:1 mixture of $Me_2C{=}O{:}H_2O$ gave a 19:43:27 ratio of percentage yields for aculeatin D (**115**), aculeatin D epimer (**120**) and ketone **121**.



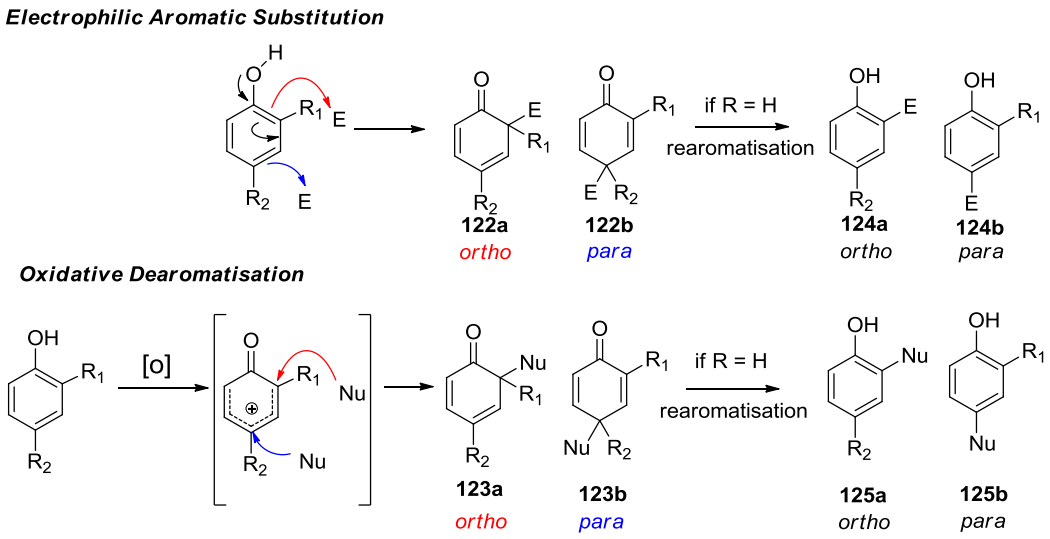
Scheme 29 - Formation of aculeatin D (**115**)

These syntheses of some aculeatin natural products demonstrate an elegant cascading method for the formation of the spiroketal cores. This cascading oxidative dearomative strategy facilitates a rapid increase in molecular complexity, with the formation of a chiral centre and two C−O bonds in one single step. There are significant opportunities for the development of new methods for spiroketalisation by exploiting similar oxidative dearomatisation techniques.

1.7 Oxidative Dearomatisation of Phenols

Electrophilic aromatic substitution reactions, *e.g* Friedel-Crafts treactions,[48] exploit the nucleophilicity of the aromatic π-system, typically involving reactions with strongly electrophilic species. However, two-electon oxidative dearomatisation of phenols enables an umpolung reactivity, whereby the phenol ring becomes electrophilic and prone to intra- and intermolecular nucleophilic attack (Scheme 30).[49]

Dearomatised phenol substrates *e.g.* **122a/b** and **123a/b** are useful synthetic entities and can be used in a range of transformations: including Diels-Alder and conjugate (Michael) addition reactions. Alternatively, with the substitution occurring on a carbon atom on which a hydrogen atom is attached, thermodynamically driven rearomatisation back to an aromatised system *e.g.* to **124a/b** and **125a/b** can occur.

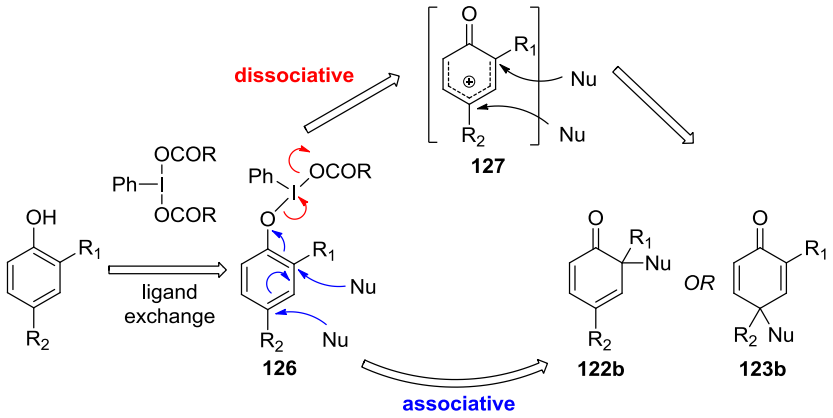


Scheme 30 - Reactivity of phenols

Heavy metal oxidants *e.g.* thallium(III), lead(IV) and bismuth(V) have traditionally been used to mediate the two-electron oxidation of phenols.[49] However, in recent years, these extremely toxic heavy metal oxidants have largely been substituted for

the non-toxic, bench-stable and inexpensive hypervalent iodine(III) reagents. In particular, the commercially available reagents $PhI(OAc)_2$ (PIDA) and $PhI(OCOCF_3)_2$ (PIFA) have been shown to be especially versatile oxidants in phenol oxidative dearomatisation reactions.

There is not a universally accepted pathway for the two-electron oxidation of phenols using iodine(III) reagents, and differing mechanisms have been proposed with varying conditions and phenol substrates. The phenyl-λ^3-iodanyl group (**126**, Scheme 31) has remarkable nucleofugality, with quantitative analysis by solvolysis experiments for the $Ph(BF_4)I$ unit revealing *one million times better* leaving group ability than the triflate group![50] This super-nucleofugality has been argued in favour of a dissociative mechanism, which would lead to phenoxenium intermediates *e.g* **127**, being highly susceptible to inter- or intramolecular nucleophilic attack.[51] An associative mechanism has also been proposed, whereby the departure of the phenyl-λ^3-iodanyl group and nucleophilic attack occur in a concerted mechanism (Scheme 31).[52] Other proposed mechanisms for iodine(III) species phenol oxidation include ligand-coupling processes[53] and radical pathways[54]. The mechanisms for two-electron phenol oxidation with iodine(III) species are not yet fully understood and are still subject to much discussion and debate in the literature.

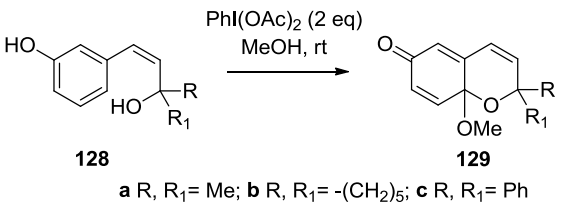


Scheme 31 - Dissocative and associative mechanisms of phenol oxidations

Nevertheless, regardless of the exact mechanism for oxidation, coordination of a phenol to form phenyl-λ^3-iodanyl intermediates *e.g.* **126** makes the respective ring highly susceptibile to inter- and intramolecular nucleophilic attack. As has already been alluded to, this versatile umpolung strategy has been employed for use in a range of synthetic transformations, including: C–O, C–C and C–N bond forming reactions.[49]

1.8 Oxidative Dearomatisations by Pelter et al.

Pelter *et al*. have described the oxidative dearomatisation of phenols with nucleophilic attack from exogenous methanol and intramolecular *ortho*-cyclisation of tethered alcohols to give dearomatised acetalised products. For example, treatment of phenols **128a−c** with $PhI(OAc)_2$ in MeOH resulted in the formation of dearomatised substrates **129a−c** (Scheme 32).[55]

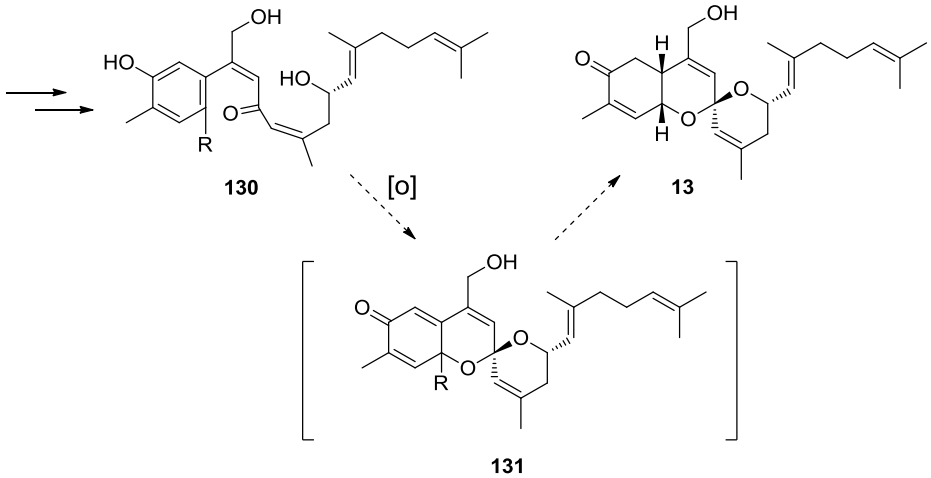


Scheme 32 - Oxidative *ortho*-dearomatisations acetalisations reported by Pelter *et al.*

1.9 Initial Aims of Work

The initial aims of the work presented within this thesis were the development of a new method for spiroketalisation *via* cascade oxidative dearomatisation for use in the total synthesis of the alotaketal and phorbaketal natural products.

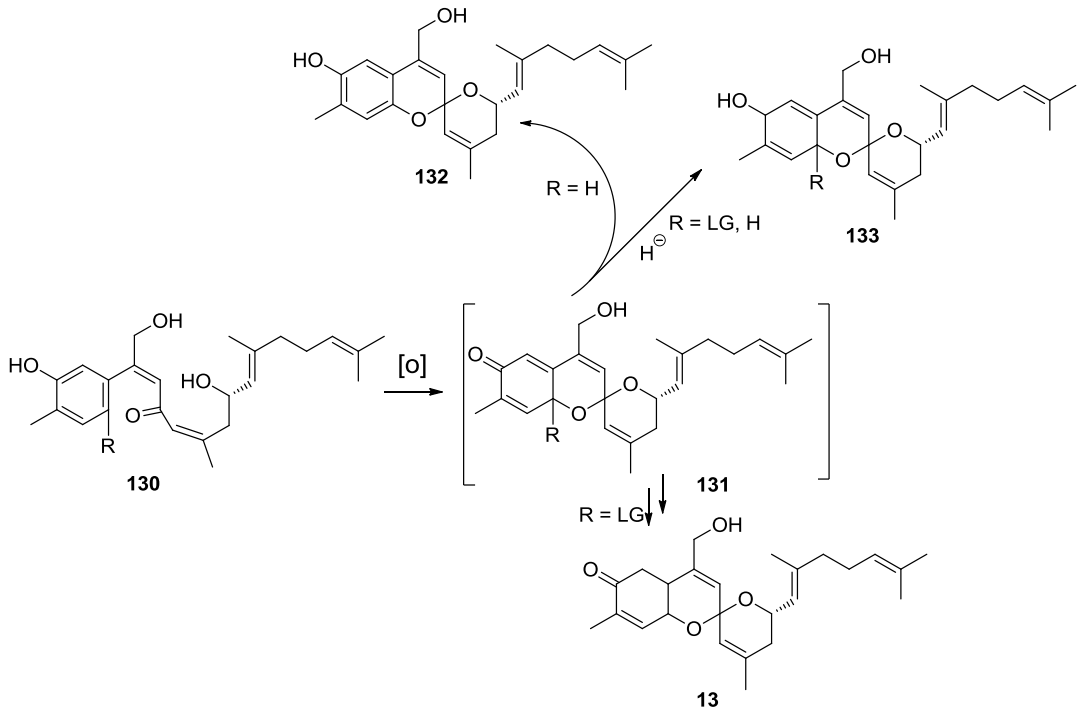
Treatment of a hydroxyphenol substrate *e.g.* **130** with a suitable oxidant was envisaged to mediate a cascade oxidative dearomatisation process and lead to the formation of the 6,6-spiroketal core and cyclohexadienone moiety *e.g*. **131** in a single synthetic step (Scheme 33). The previously discussed cascade oxidative dearomatisation strategies employed for the synthesis of the aculeatin natural products involved *ipso*-cyclisation of a tethered hydroxyketone chain onto an oxidised ring to form a 5,6-spiroketal (Scheme 28). However, this newly envisaged strategy required an unexplored *ortho*-cyclisation of a hydroxyketone chain (comparable to Pelter, Scheme 32), for the formation of a 6,6-spiroketal. Phorbaketal A (**13**) was selected as the first natural product to demonstrate the envisaged strategy (Scheme 33).



Scheme 33 - Cascade oxidative dearomatisation for the synthesis of phorbaketal A (**13**) R = H or leaving group (LG)

The employment of a suitable reducible leaving group (R = LG) would give direct access to the cyclohexadienone substrates *e.g.* **131**. It was thought that a suitable leaving group could then be removed in reduction steps from **131** towards the cyclohexenone moiety possessed by the target natural product.

Rearomatisation of intermediate **131** was expected for when R = H, to give aromatic substrates *e.g.* **132** (Scheme 34). Immediate reduction of ketone intermediate **131** to alcohol **133** could circumvent rearomatisation when R = H, and subsequent adjustments could give access to the desired cyclohexenone moiety possessed by the alotaketals and phorbaketals. However this strategy was less favoured, chiefly since it was thought that the lifetime of the intermediate **131** would likely be too short for trapping with a hydride before aromatisation would occur.



Scheme 34 - Envisaged strategy towards phorbaketal A (**13**)

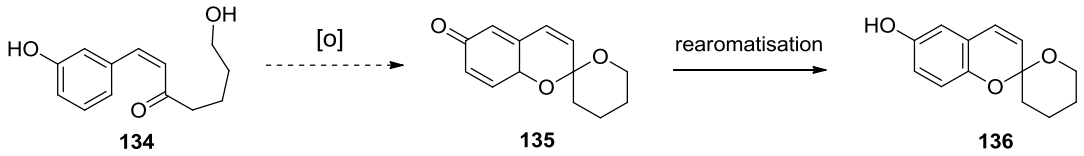
Initial work involved an investigation into the newly proposed method for spiroketalisation by cascade oxidative dearomatisation using a model system.

2. Results and Discussion I

2.1 Development of Spiroketalisation by Cascade Oxidative Dearomatisation

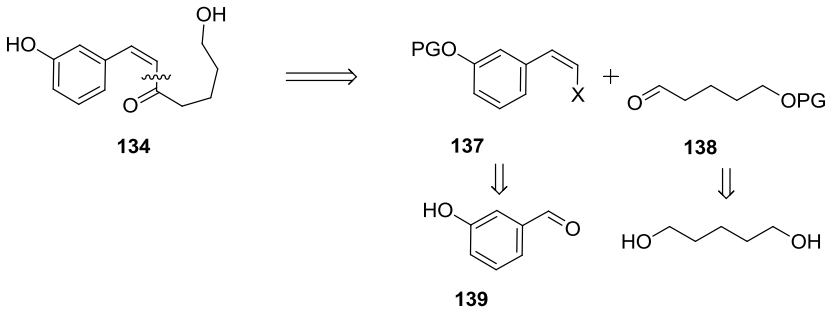
2.1.1 Initial Model Studies

An investigation into the effect of treating hydroxyphenol model substrate **134** with an oxidant would give insight into whether *ortho*-spiroketalisation in such a system was possible. The stability of the proposed cyclohexadienone spiroketal product **135** was unknown, although thermodynamically driven rearomatisation to phenol **136** was expected (Scheme 35). Nevertheless, the aim of this initial model study was to prove that formation of the 6,6-spiroketal core was achievable *via* the envisaged cascade oxidative dearomatisation pathway.



Scheme 35 - Proposed spiroketalisation *via* cascade oxidative dearomatisation

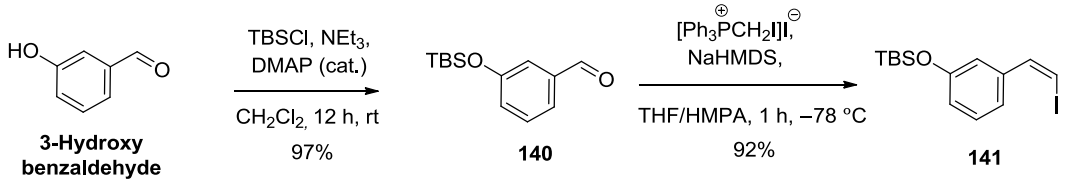
Retrosynthetic analysis of model substrate hydroxyphenol **134** revealed the possibility of a key addition of a haloalkene fragment **137** to aldehyde **138**, *via* a halogen-metal exchange/trapping process (Scheme 36). The synthesis of haloalkene **137** was envisaged to proceed *via* a (*Z*)-selective Wittig halo-olefination of the aryl aldehyde **139**. The synthesis of alkyl aldehyde **138** was expected to proceed *via* *mono*-hydroxyl protection of 1,5-pentanediol, followed by oxidation *via* various oxidation method options, to give aldehyde **138**.



Scheme 36 - Retrosynthetic analysis of hydroxyphenol **134**

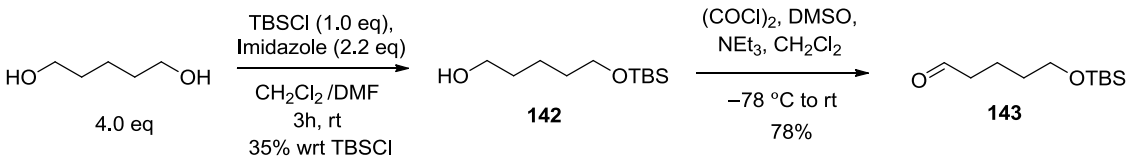
It was decided to protect the phenol **139** as a *tert*-butyldimethylsilyl (TBS) ether since this silyl protecting group has well-established stability in a range of reaction conditions as well as its frequently reported ease of removal by a myriad of methods. Accordingly, treatment of 3-hydroxybenzaldehyde with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of NEt_3 and 4-dimethylaminopyridine (DMAP) mediated protection of the phenol, to give aryl aldehyde **140** (Scheme 37).[56]

The aldehyde **140** was subjected to Wittig olefination using (iodomethyl)triphenyl phosphonium iodide, which was deprotonated with sodium hexamethyldisilazane (NaHMDS), to give the novel (*Z*)-iodoalkene **141** (Scheme 37). Analysis of the ^{1}H NMR spectrum revealed the (*Z*)-alkenyl proton signals had a coupling constant of $^3J_{cis}$ = 8.7 Hz. This value exactly matched those for the (*Z*)-alkene protons reported in the literature for the analogue (*Z*)-iodo-2-phenylethene.[57] The (*E*)-alkene minor product was not observed by analysis of the ^{1}H NMR spectrum of the crude reaction mixture after protic work-up.



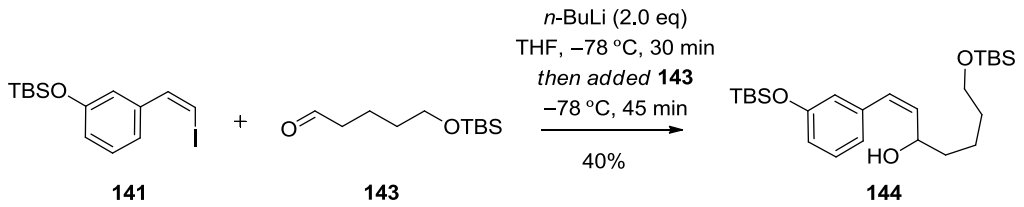
Scheme 37 - TBS protection and Wittig olefination to (*Z*)-iodoalkene **141**

Following previously reported procedures, the *mono*-silyl ether protection of 1,5-pentanediol was achieved by treatment with TBSCl in the presence of imidazole, to give the *mono*-alcohol **142**.[58] As before, the TBS protecting group was chosen due to its known stability under the forecasted reaction conditions and its ease of removal when required. Moreover, the use of a TBS ether protecting group alongside TBS group protected (*Z*)-iodoalkene **141** opened up the possibility for a late-stage global deprotection strategy. The primary alcohol **142** was then oxidised to the aldehyde **143** by Swern oxidation (Scheme 38).[59]



Scheme 38 - TBS ether *mono*-protection and Swern oxidation to aldehyde **143**

The iodine-lithium exchange of (*Z*)-iodoalkene **141** was mediated using *n*-BuLi for *in situ* formation of the desired organolithium species, which was added to aldehyde **143** to give (*Z*)-alcohol **144** after protic work-up (Scheme 39). The low 40% yield may have been due to enolisation of the aldehyde **143** under the basic conditions.

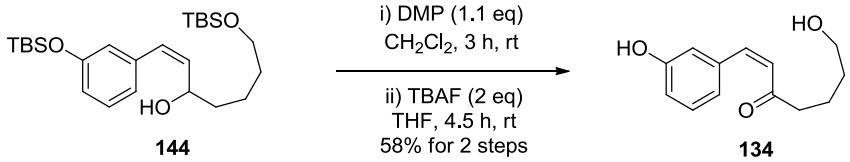


Scheme 39 - Addition of (*Z*)-iodoalkene **141** to aldehyde **143**

Oxidation of the (*Z*)-allylic alcohol **144** to a (*Z*)-enone intermediate was achieved using the Dess-Martin periodinane (DMP) (Scheme 40).[60] At this point, a concern was the possible isomerisation of the (*Z*)-enone moiety to the thermodynamically

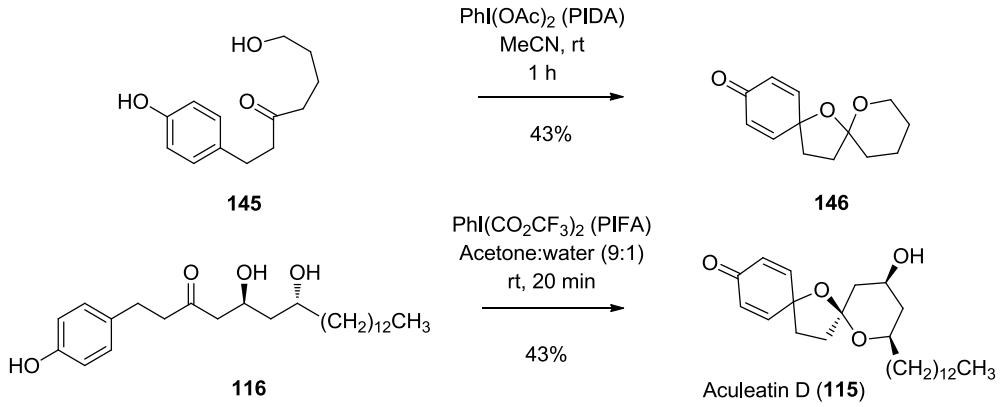
more stable (*E*)-enone system by either photolytic or thermal pathways. For this reason, the substrate was stored in the dark at 4 °C and used within 2–3 days. Under such conditions, no degradation was detected by TLC or ^{1}H NMR spectroscopy.

Following this, the concurrent removal of both silyl ether protecting groups was conveniently achieved using TBAF as a source of fluoride (2 eq.) to give (*Z*)-hydroxyphenol **134** (Scheme 40). Retention of the crucial (*Z*)-alkene stereochemistry was confirmed by comparison of the 12.8 Hz alkenyl *J* coupling constant with analogous (*Z*)-enone moieties in the literature, which typically range from 12.5–13.0 Hz.[61] In contrast, (*E*)-enone moieties have alkenyl *J* coupling constants ranging from 16.0–16.5 Hz.[62] Upon storage, the degradation of **134** to a complex mixture was observed, however this was prevented by storing under an atmosphere of argon in the dark at 4 °C and using the unstable substrate within 2–3 days.



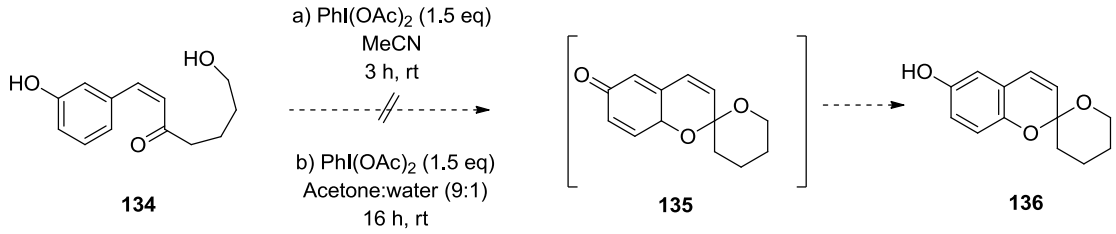
Scheme 40 - DMP oxidation and TBAF deprotection to (*Z*)-hydroxyphenol **134**

Upon the successful synthesis of (*Z*)-hydroxyphenol **134**, an investigation into the proposed method for spiroketalisation *via* cascade oxidative dearomatisation was initiated. Firstly, conditions for similar cascades reported by Baldwin *et al*. (Scheme 41) were implemented.[47]



Scheme 41 - Oxidative *ipso*-dearomative cyclisations reported by Baldwin *et al.*

Following conditions reported by Baldwin, attempts at spiroketalisation using $PhI(OAc)_2$ in MeCN and then Me_2CO:H_2O (9:1) were unfruitful (Scheme 42). Under these conditions analysis by TLC and ^1H NMR revealed a mixture of unidentifiable by-products and the desired spiroketal product **136** was not observed.

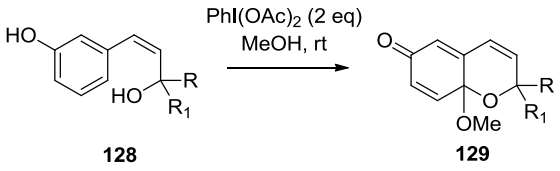


Scheme 42 - Attempted oxidative cyclisation of hydroxyphenol **134**

One concern with this reaction was that upon rearomatisation of the spiroketal intermediate **135**, the newly regenerated phenol **136** could react further with $PhI(OAc)_2$ leading to a variety of unknown by-products. An additional concern was the nucleophilic competition of water versus the desired cyclisation of the tethered alcohol. The nucleophilic attack of water at various stages in the cyclisation could result in a range of poly-oxygenated by-products.

2.1.2 Model studies using MeOH as exogenous nucleophile

As previously mentioned, Pelter *et al*. have demonstrated the treatment of phenols **128a−c** with $PhI(OAc)_2$ in MeOH in the formation of dearomatised substrates **129a−c** (Scheme 43).[55]

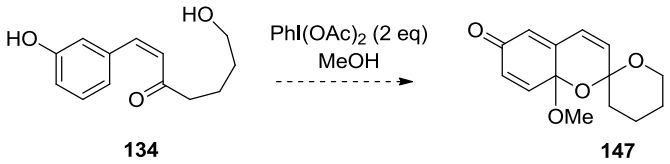


128 **129**

a R, R_1= Me; **b** R, R_1= -$(CH_2)_5$; **c** R, R_1= Ph

Scheme 43 - Oxidative *ortho*-dearomatisations acetalisation reported by Pelter *et al.*

In a similar fashion to Pelter *et al*., it was decided to investigate using MeOH as an exogenous nucleophile towards the formation of the desired spiroketal core **147**.



134 **147**

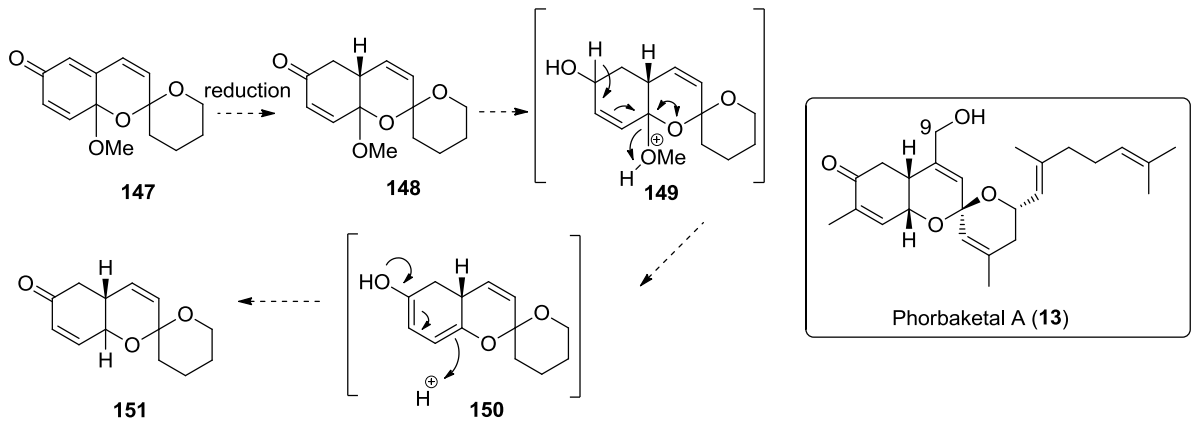
Scheme 44 - Proposed route for spiroketalisation using MeOH an exogenous Nu

It was of interest to explore the use of this strategy since it could give direct access to cyclohexadienone spiroketal structures. With interest in the future utilisation of this method for the total synthesis of phorbaketal A, a route was devised for the replacement of the undesired methoxy substituent with the required hydrogen atom (Scheme 45).

The devised route firstly involved removal of the undesired alkene in the cyclohexadienone motif **147**. In this model system, this was believed to be unfeasible, since di-substiuted alkenes are normally reduced more rapidly than tri-

substitiuted alkenes. However, in the phorbaketal A system both alkenes are trisubstitued and it was believed the primary alcohol at C9 (see Scheme 45) could steer chemoselective reduction of the desired alkene. For example, Wilkinson's catalyst is known to assist very selective hydrogenation of conjugated alkenes in the presence of other alkenes. Additionally, Wilkinson's catalyst is known to coordinate hydroxyl groups allowing very selective hydrogenation of allylic or homoallylic alkenes.[63] Other alkene reduction methods could involve various metal hydrides (*e.g.* copper hydrides), also taking advantage of the hydroxyl group to coordinate to the metal.

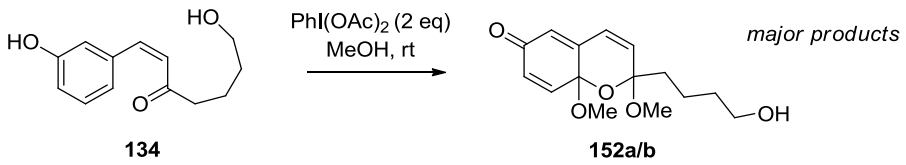
In this model system, reduction of the ketone **148** to alcohol **149** was then proposed to potentially result in elimination of the undesired methoxy substituent to give enol **150**. This enol intermediate **150** could then tautomerise to cyclohexenone **151** to install the desired hydrogen atom. One concern with this strategy was the ejection of the spiroketal ether rather than the desired methoxy group.



Scheme 45 - Route to phorbaketal A model **151** from methoxy substrate **147**

To investigate this incorporation of methanol, an initial reaction involved treatment of hydroxyphenol **134** with $PhI(OAc)_2$ (2 eq) using MeOH as solvent. The reaction

was periodically monitored by TLC over 4 h which indicated consumption of the starting material. After this time ^{1}H NMR analysis revealed a number of signals corresponding to methoxy group protons (*i.e.* incorporation of MeOH). The major products were partially isolated* by flash column chromatography and after analysis of the ^{1}H NMR spectrum were deduced to be dearomatised substrates **152a** and **152b**. Starting from 30 mg of starting material **124**, these compounds were isolated in small quantities (≈1 mg), and a second attempt at purification led to their total loss through degradation on silica gel. Consequently, thorough characterisation was not possible.



Scheme 46 - Oxidative cyclisation of hydroxyphenol **134**

The ^{1}H NMR spectra of **152a** and **152b** were indicative of two partially separated diastereomers. The major singlet resonances at 3.08–3.45 ppm were believed to correspond to methoxy group protons. A comparison of key proton resonances with dearomatised substrate **153**, previously synthesised by Pelter[55], revealed very similar chemical shifts and *J* coupling constants (Table 2).

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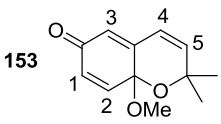
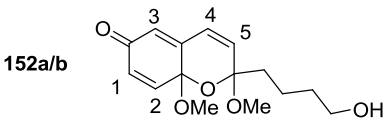
* Eluted from the column as partially separated mixtures with variable amounts of each diastereomer.

Table 2 - Dearomatised substrates **152a/b** comparison to literature compound **153**





	153 (ppm, Hz)	**152a**	**152b**
H-1	6.18 (dd, *J*= 10.2, 2.0)	6.30 (dd, *J*= 10.3, 2.0)	6.26 (dd, *J*= 10.3, 2.0)
H-2	6.25 (d, *J*=10.2)	6.61 (d, *J*= 10.3)	6.50 (d, *J*= 10.3)
H-3	5.93 (d, *J*= 2.0)	6.10 (d, *J*= 2.0)	6.05 (d, *J*= 2.0)
H-4	6.10 (d, *J*= 10.2)	6.00 (d, *J*= 10.3)	6.10 (d, *J*= 10.3)
H-5	6.65 (d, *J*= 10.2)	6.73 (d, *J*= 10.3)	6.76 (d, *J*= 10.3)
OMe	3.12 (s)	3.16 (s), 3.08 (s)	3.45 (s), 3.23 (s)

To help visualise the similarities of the chemical shift values of these compounds a $\Delta\partial$ bar chart* was devised. Note similar and typically small $\Delta\partial$ values for H-1 to H-5.

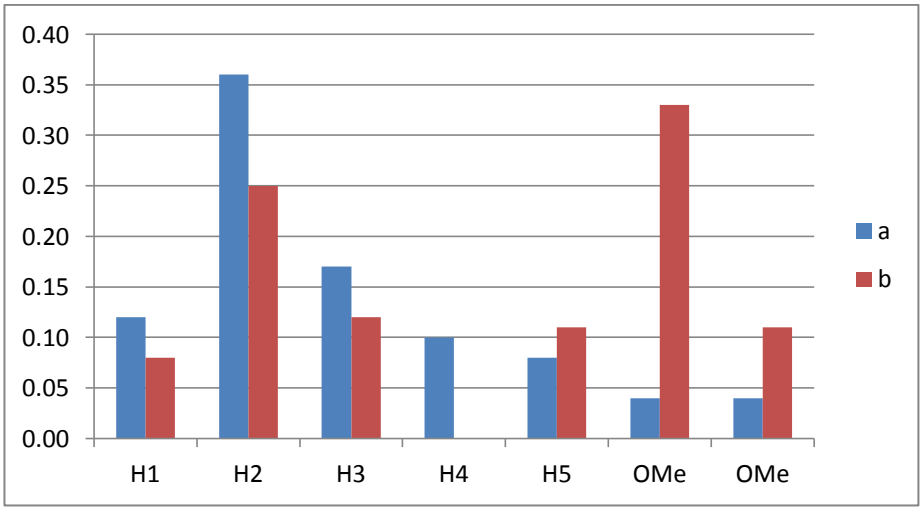


Chart 1 - * $\Delta\partial$ values comparing substrates **152a** and **152b** to compound **153**

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* $\Delta\partial = \left| \partial_{\mathbf{152}} - \partial_{\mathbf{153}} \right|$

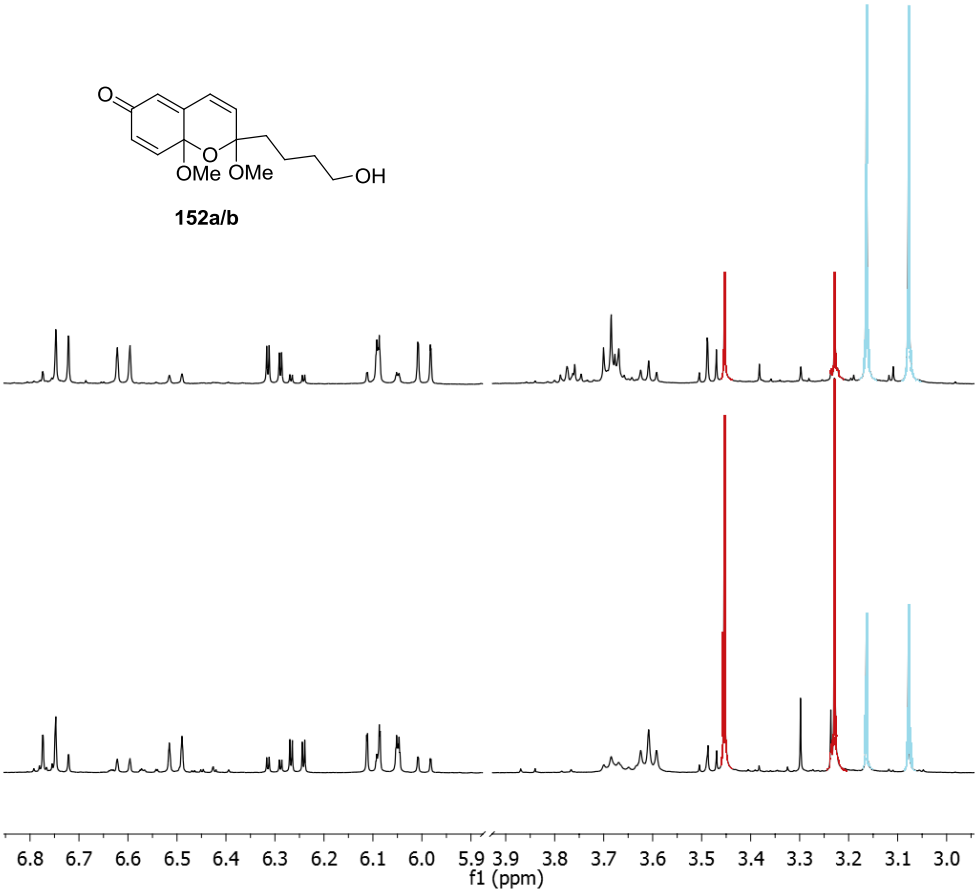
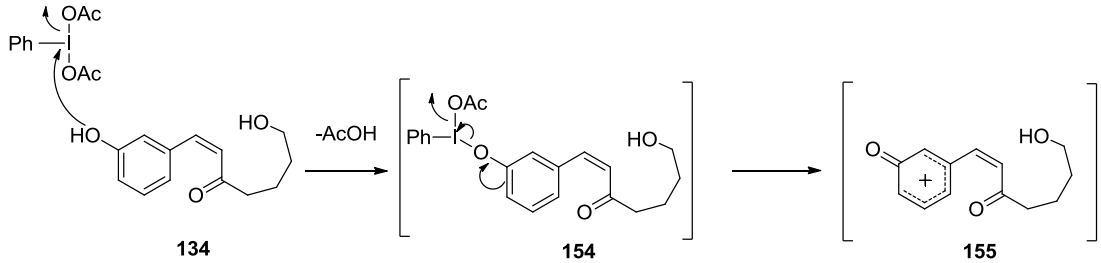


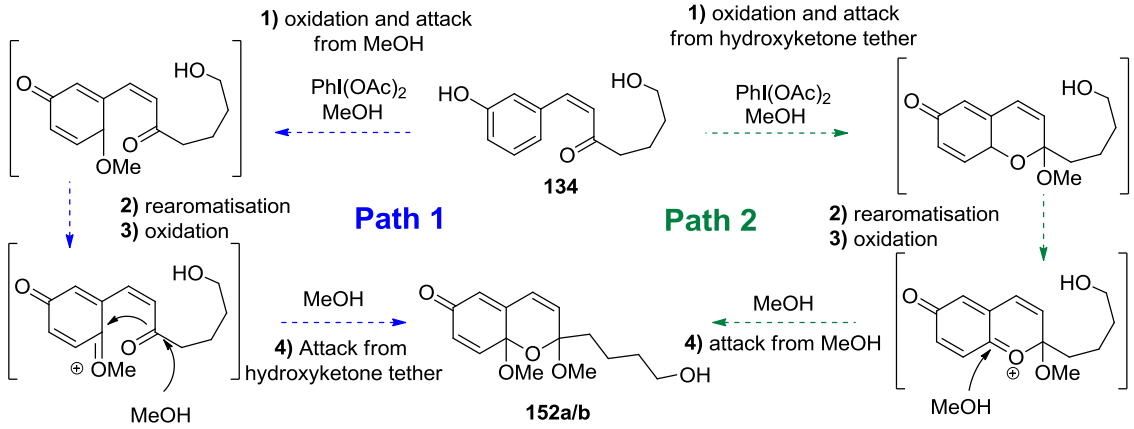
Figure 7 – ^{1}H NMR for proposed dearomatised substrates **152a/b**

The exact mechanism for the formation of these dearomatised substrates **152a/b** is not known. The initial step must involve a ligand exchange, with the nucleophilic attack of the phenol **134** onto the iodine(III) centre, to form the phenyl-λ^3-iodanyl intermediate **154** (Scheme 47). As previously discussed, the oxidation process mediated by $PhI(OAc)_2$ (and other hypervalent iodine oxidants) is known to occur *via* different mechanisms depending on a variety of factors, and it is unclear which mechanism is at play in this reaction. As an example, a dissociative mechanism has been depicted in Scheme **47**, with the formation of phenoxenium intermediate **155**.



Scheme 47 - Dissociative mechanism for oxidation of phenol **134** by $PhI(OAc)_2$

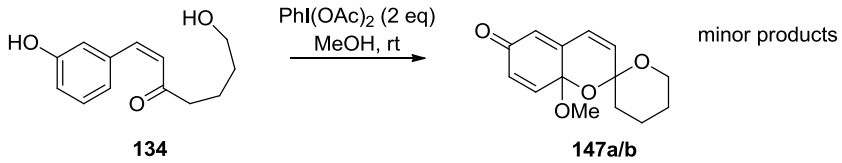
Regardless of the mechanism of oxidation, the ring becomes prone to nucleophilic attack upon formation of a phenyl-λ^3-iodanyl intermediate **154**. It is unknown by which order each nucleophile participates in this reaction. A possible path (path 1) involves the initial attack of MeOH onto the oxidised ring. This is followed by thermodynamically driven rearomatisation and then the new phenol is oxidised by a second equivalent of $PhI(OAc)_2$. The final step involves nucleophilic attack from the hydroxyketone tether. Cyclisation of the tether could occur in a concerted fashion, as is depicted in Scheme **48**. Other possible mechanisms for the attack of the hydroxyketone tether involve the formation of oxocarbenium intermediates or lactol formation. A second path with the reversed order of addition of each nucleophile is also possible (path 2).



Scheme 48 - Mechanism for formation of dearomatised substrates **152a/b**

The apparent observation of these elusive compounds encouragingly revealed that $PhI(OAc)_2$ was a suitable oxidant for the oxidation of the phenol ring, which was in turn susceptible to the desired site of nucleophilic attack. Cyclisation of the ketone tether was believed to have occurred, albeit only partially in the desired fashion.

A final minor product present was isolated by flash column chromatography (<1 mg). The ^{1}H NMR spectrum revealed intriguing dearomatised structures seemingly as a mixture of two diastereomers, each bearing only one methoxy substituent. After careful analysis of the ^{1}H NMR spectrum these dearomatised structures were assigned as spiroketals **147a** and **147b**.

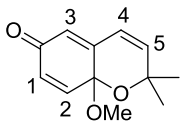


Scheme 49 - Formation of spiroketals **147a** and **147b**

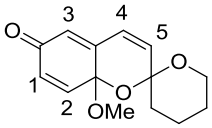
Again, comparison of the key ^{1}H NMR resonances with dearomatised literature compound **153** revealed protons in a magnetically similar environment.[55] In particular, the proton resonance corresponding to key hydrogen atom H-5 had a notably different chemical shift, being close to the proposed spiroketal core (Table 3). To help visualise the similarities of the chemical shift values of these compounds **147a** and **147b** a $\Delta\partial$ bar chart was devised (Chart 2). The protons were notably more deshielded (resonated lower field) than in substrate **153**, and this was speculated to be due to the neighbouring electron withdrawing spiroketal core. Each purported diastereomer had remarkably similar and patterned $\Delta\partial$ values for all protons H1-H5.

Table 3 - Dearomatised substrates **147a/b** comparison to literature compound **153**

153



147a/b



	153 (ppm, Hz)	**147a**	**147b**
H-1	6.18 (dd, *J*= 10.2, 2.0)	6.25 (dd, *J*= 10.3, 2.0)	6.29 (d, *J*= 10.3, 2.0)
H-2	6.25 (d, *J*=10.2)	6.38 (d, *J*= 10.3)	6.44 (d, *J*= 10.3)
H-3	5.93 (d, *J*= 2.0)	6.02 (d, *J*= 2.0)	6.05-6.07 (m)
H-4	6.10 (d, *J*= 10.2)	6.07 (d, *J*= 10.3)	6.05-6.07 (m)
H-5	6.65 (d, *J*= 10.2)	6.85 (d, *J*= 10.3)	6.78 (d, *J*= 10.3)
OMe	3.12 (s)	3.28 (s)	3.18 (s)

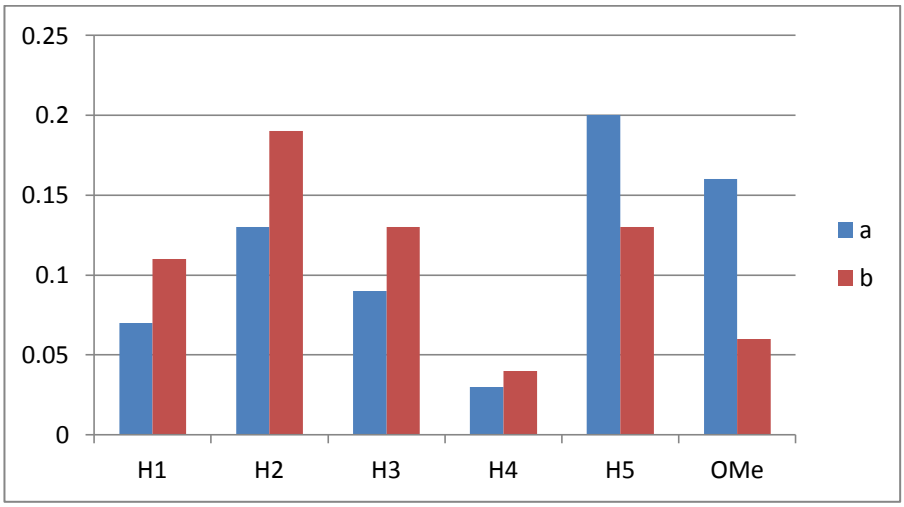


Chart 2 - $\Delta\partial$ values* for comparison of substrates **147a/b** resonances to **153**

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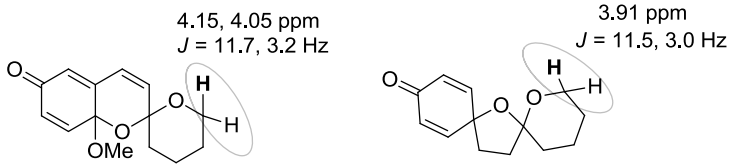
* $\Delta\partial = \left| \partial_{147} - \partial_{153} \right|$

Furthermore to this analysis, the OCH_2 protons of the alkyl tether which resonated as a triplet (J = 7.1 Hz) in the starting material **134** had become diastereotopic, with mutual coupling to one another. One OCH proton resonated as an apparent triplet of doublets (for each diastereomer, major at 4.15 and minor at 4.05 ppm), with coupling constants J = 11.7, 3.2 Hz. For the related spiroketal substrate **146** synthesised by Baldwin, the analogous OCH proton resonated as a triplet of doublets at 3.91 ppm with J = 11.5, 3.0 Hz, which they assigned as the axial conformer.[47] With this careful analysis the author was confident that the hydroxy group had indeed cyclised.



Scheme 50 - Spiroketals **147a/b** versus Baldwin reported spiroketal **146**

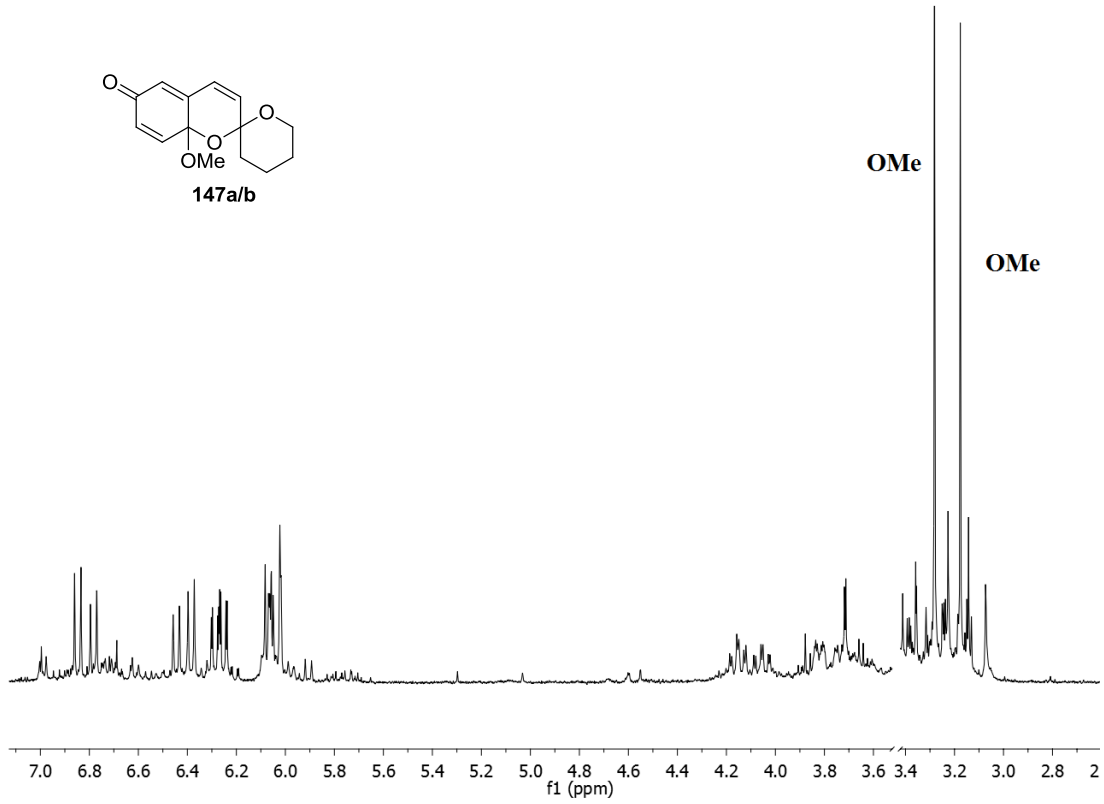
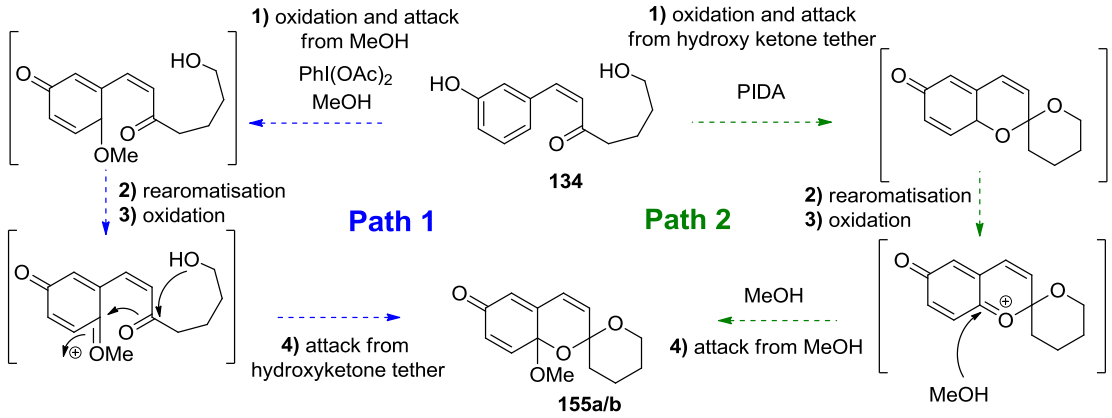


Figure 8 - ^{1}H NMR of proposed spiroketal diastereomers **147a** and **147b**

With the small quantity of the presumed spiroketals **147a** and **147b** obtained it was not possible to perform thorough analysis of these substrates and a further attempt at isolation led to complete loss due to degradation on silica gel. Although the author was confident that the spiroketal diastereomers **147a** and **147b** had been isolated, making this bold claim at the time would have been unwise solely from careful analysis of ^{1}H NMR data. This result will be revisited in a later section within this thesis.

A mechanism for the formation of these spiroketals was theorised. As before, regardless of the mechanism of oxidation, the ring becomes prone to nucleophilic attack upon formation of the phenyl-λ^{3}-iodanyl intermediate. It is unclear in which order each nucleophile participates. The first possible path involves the direct

addition of MeOH to the ring (path 1). This is followed by thermodynamically driven rearomatisation and then the newly regenerated phenol is oxidised by a second equivalent of $PhI(OAc)_2$. The final step involves nucleophilic attack from the hydroxy ketone tether. This could occur in a concerted fashion as is shown in Scheme **51**. Other possible mechanisms for the attack of the tether involve the formation of an oxocarbenium intermediate or lactol formation. A second path (path 2) is also possible, with the reversed order of addition of the respective nucleophiles.

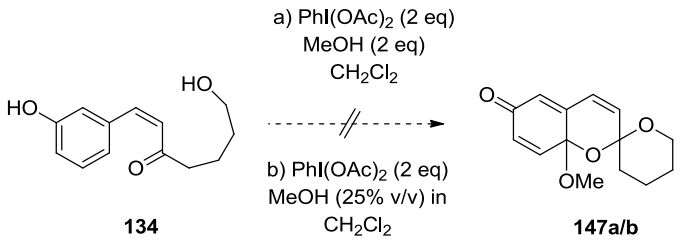


Scheme 51 - Mechanism for formation of spiroketals **147a** and **147b**

In this investigation, the presence of the major dearomatised products **147a/b** indicated that MeOH, being in excess, was competing with the desired intramolecular cyclisation of the hydroxyketone tether. For this reason it was decided to investigate the effect of lowering the molar equivalents of MeOH in the reaction so as to increase the probability of intramolecular hydroxyl cyclisation over intermolecular nucleophilic attack from MeOH.

The reaction was repeated using only two equivalents of MeOH in CH_2Cl_2, and secondly a 25% MeOH solution in CH_2Cl_2. Both of these attempts were

unsuccessful, with ^{1}H NMR analysis of the crude mixtures after evaporation of solvents indicating a large mixture of unidentifiable degradation products.



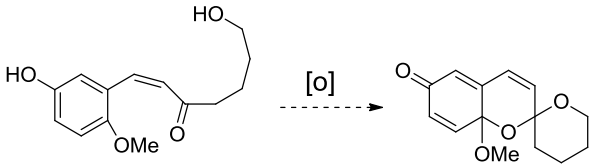
Scheme 52 - Attempted spiroketalisation using $PhI(OAc)_2$/MeOH

The apparent isolation of dearomatised compounds **147a/b** was encouraging since their presence suggested that oxidation by $PhI(OAc)_2$ was occurring and that cyclisation of the ketone tether was occurring; albeit only partially in the desired fashion. The suspected isolation of spiroketal diastereomers **147a/b** was especially encouraging and served as proof-of-concept.

From this initial model study, the author suspected that the presence of exogenous MeOH was hindering formation of the desired spiroketal core by nucleophilic competition. In light of evidence suggestive of the formation of the spiroketal core, work was continued towards further exploring this newly devised method for spiroketalisation. It was decided to eliminate the need for an exogenous nucleophile for the synthesis of the desired cyclohexadienone spiroketal structures.

2.1.3 Further Model Studies

After the preliminary investigations, a second model system was envisaged, incorporating a methoxy substituent *ortho* to the tethered hydroxyl ketone chain. This revised system would eliminate the need for an exogenous nucleophile, and the previously encountered rearomatisation pathways to give direct access to the desired cyclohexadienone spiroketal structures. The pre-incorporation of a methoxy substituent was believed to be a better strategy towards the total synthesis of phorbaketal A. The previously encountered problems with nucleophilic competition and undesired by-products would be incredibly detrimental during a future late-stage cyclisation step towards the total synthesis of phorbaketal A. Whereas, the pre-incorporation of a methoxy substituent was envisaged to give direct access to the desired cyclohexadienone spiroketal moieties **147** as the major reaction products. To this end, a synthesis of methoxy bearing model substrate **156** was devised, with which the oxidative cyclisation step could again be investigated.

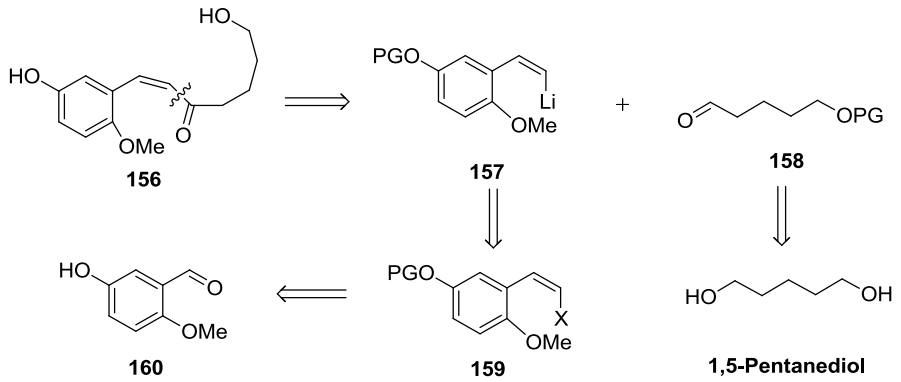


156 **147**

Scheme 53 - Second model system **156** for spiroketal formation

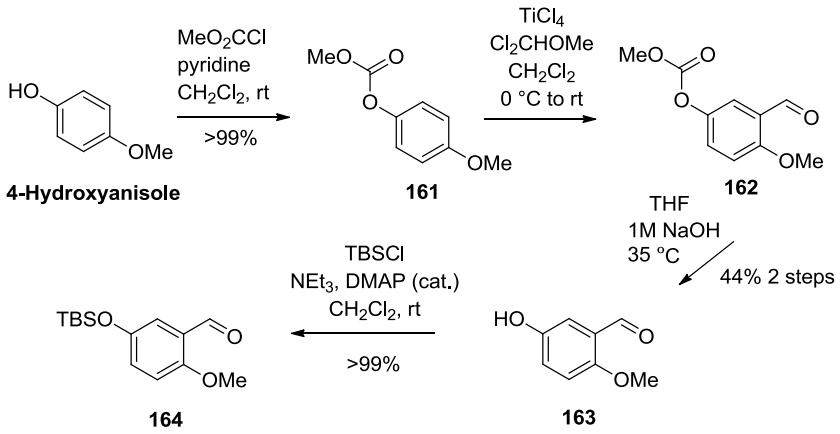
Retrosynthetic analysis of hydroxyphenol **156** was conducted in a similar fashion to the previous model substrate **134**. Retrosynthetic cleavage of a central C–C bond revealed synthons corresponding to an organolithium fragment **157** and aldehyde fragment **158** (Scheme 54). The formation of the organolithium **157** could be generated by *in situ* halogen-lithium exchange from haloalkene fragment **159** using

n-BuLi. The desired (*Z*)-haloalkene **159** could be synthesised *via* a (*Z*)-selective halo-Wittig olefination method from aryl aldehyde fragment **160**.



Scheme 54 - Retrosynthetic analysis of hydroxyphenol **156**

Initial synthetic efforts were focused towards the synthesis of (*Z*)-haloalkene fragment **159**, firstly involving the synthesis of aryl aldehyde fragment **160**. Using a reported procedure, conversion of 4-hydroxyanisole to methyl carbonate ester **161** was achieved by treatment with methyl chloroformate in the presence of pyridine (Scheme 55). [64] Following this, Rieche formylation of carbonate **161** using $TiCl_4$ and Cl_2CHOMe gave aryl aldehyde **162**.[64] The carbonate group is far less activating than the methoxy group, and hence formylation occurs regioselectively *ortho* to the methoxy group.. Hydrolysis of the carbonate functional group was achieved by warming in 1M NaOH. Upon the synthesis of phenol **163** it was decided to protect the phenol using a TBS ether group due to its effective employment in the previous model study synthesis. This protection was achieved by treating the phenol **163** with TBSCl, in the presence of NEt_3 and a catalytic amount of DMAP to give novel aryl aldehyde **164**.



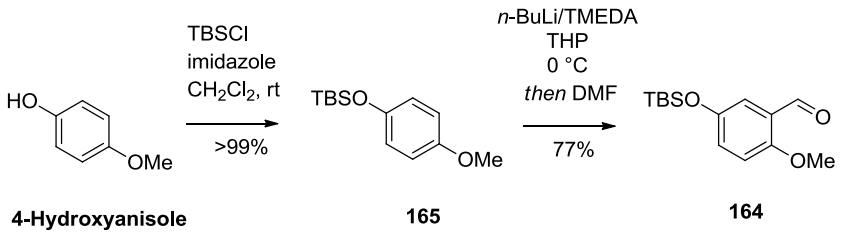
Scheme 55 - Synthesis of aryl aldehyde **164**

Unfortunately, in the author's hands the described Rieche formylation of carbonate **161** proved to be unreliable and further attempts revealed an unexplainable mixture of aldehyde resonances in the ^{1}H NMR spectrum of the crude reaction mixture after protic work-up. Consequently, a more reliable method for the formation of aryl aldehyde **164** was required.

It was proposed that protection of 4-hydroxy anisole, with a bulky silyl ether group, may provide a significant steric barrier and electron donating ability to inhibit lithiation *ortho* to the protected phenol, and consequently promote lithiation regioselectively *ortho* to the less sterically demanding and less electron donating methoxy group. Subsequent quenching of the organolithium species with dimethylformamide (DMF) was proposed to give direct access to aryl aldehyde **164** after protic work-up. There is precedence in the literature for the *ortho*-lithiation and formylation of anisole analogues,[65] however the effect of a silyl ether attached to an anisole ring upon the regioselectivity of lithiation was unknown.

To investigate this proposal, 4-hydroxyanisole was protected as the bulky TBS silyl ether by treatment with TBSCl in the presence of imidazole (Scheme 56).[66]

Accordingly, the anisole **165** was subjected to *ortho*-lithiation using *n*-BuLi/TMEDA at 0 °C in THP* and subsequent quenching of the organolithium with DMF and protic work-up afforded aryl aldehyde **164** in 77% yield.[67] Analysis of the ^{1}H NMR spectrum after protic work-up indicated completely regioselective formylation *ortho* to the methoxy group. The author was content with having enhanced the previous unreliable four step (53% yielding) synthesis to a two step (77% yielding) synthesis of the novel aryl aldehyde **164**. This was convenient as it allowed the synthesis of aryl aldehyde **164** within one working day. The potentially unstable aryl aldehyde **164** could then be used immediately after purification.



Scheme 56 - Novel synthesis of aryl aldehyde **164**

The synthesis of the aryl aldehyde **164** allowed investigations into the subsequent *Z*-selective Wittig olefination step to ensue. The first conditions employed for the Wittig olefination used (iodomethyl)triphenylphosphonium iodide which was deprotonated with NaHMDS. Analysis of the crude ^{1}H NMR spectrum after protic work-up revealed conversion to the (*Z*)-iodoalkene **166**, with the expected iodoalkenyl proton resonances at 6.86 and 7.03 ppm, with mutual coupling constant of $^{3}J_{cis}$ = 8.9 Hz. This *J* coupling constant was consistent with the previously synthesised (*Z*)-iodoalkene **166** and the aforementioned analogous structures in the literature.[57] Unfortunately, the (*Z*)-alkene **166** could not be isolated using flash

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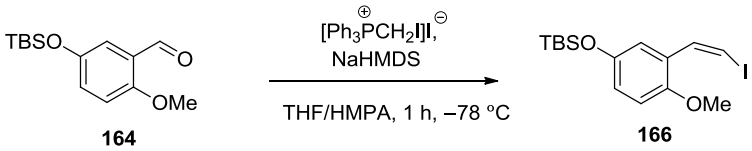
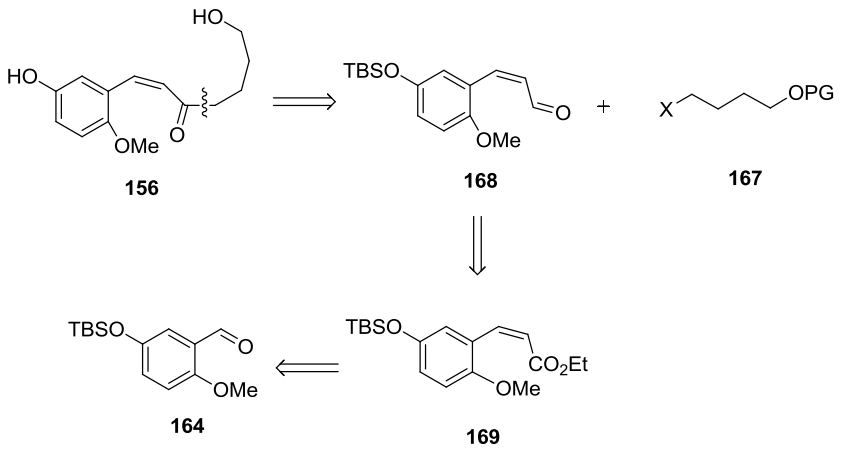
* The solvent tetrahydropyran (THP) was selected because *n*-BuLi is known to deprotonate THF near room temperature.

column chromatography on silica gel. Furthermore, storage of the crude product in a fumehood overnight revealed substantial degradation to a mixture of unidentifiable products. This glaring instability issue discouraged the use of similar haloalkene entities during the synthesis of model substrate **156**.



Scheme 56 - Wittig olefination of aryl aldehyde **164**

A second retrosynthetic analysis of hydroxyphenol **156** was conducted (Scheme 57). This revealed an alternative possible synthetic path involving the addition of halogenated alkyl fragment **167** to (*Z*)-aldehyde fragment **168** using a halogen-metal exchange/trapping method (Scheme 57). It was anticipated that the formation of the (*Z*)-ester **169** could be achieved *via* a (*Z*)-selective Horner-Wadsworth-Emmons olefination method from aryl aldehyde **164**.

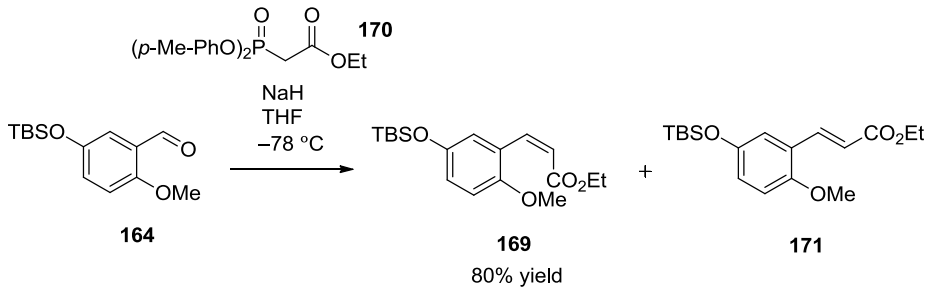


Scheme 57 - Alternative retrosynthetic analysis of hydroxyphenol **156**

To this end, initial efforts in the newly devised synthetic plan were towards the synthesis of (*Z*)-aldehyde fragment **168**. The Ando-modified (*Z*)-selective Horner-

Wadsworth-Emmons procedure was envisaged for the formation of (*Z*)-alkene ester **169**. This would be followed by oxidation level adjustments of the ester functional group to the desired aldehyde functional group. The Ando-protocol allowed the synthesis of the required phosphonate using reagents which were readily available in the laboratory. The synthesis of the Ando-modified phosphonate **170** was achieved in two steps using a reported procedure.[68]

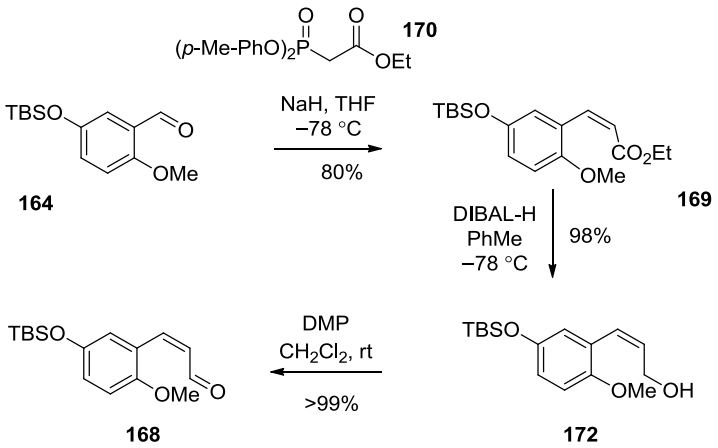
An olefination reaction between phosphonate **170** and aryl aldehyde **164** was attempted under various conditions reported by Ando.[69] Optimal conditions for this reaction employed NaH as the base, at a temperature of –78 °C. After protic work-up ^{1}H NMR analysis revealed conversion to two alkene compounds. Analysis of the alkenyl protons revealed *Z*:*E* isomers in a 6.1:1.0 ratio. Conveniently, separation of the isomers was achieved by careful flash column chromatography and led to the isolation of the desired (*Z*)-alkene **169** in 80% yield. The geometry of each alkene stereoisomer was confirmed by comparison of the alkenyl proton coupling constants (**169** $^{3}J_{Z}$ = 12.4 Hz *versus* **171** $^{3}J_{E}$ = 16.1 Hz).



Scheme 58 - Ando-olefination of aryl aldehyde **164** to (Z)-ester **169**

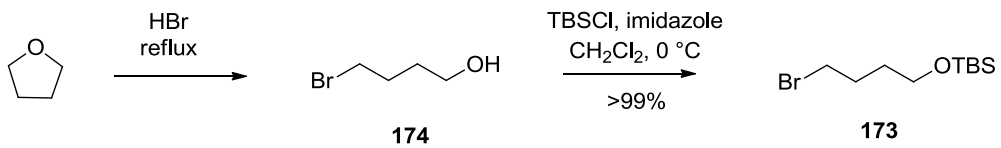
Following the formation of (*Z*)-ester **169**, procedures for adjusting the oxidation levelof the ester group to the desired (*Z*)-aldehyde **168** was probed. Treatment of the (*Z*)-ester **169** with diisobutylaluminium-hydride (DIBAL-H) at –78 °C unfortunately

did not facilitate direct reduction to the (*Z*)-aldehyde **168**, instead over-reduction to the (*Z*)-alcohol **172** occured. This over-reduction is in fact a well-reported phenomenon for DIBAL-H reduction of α,β-unsaturated esters.[70] Nevertheless, reduction of the (*Z*)-ester **169** using DIBAL-H (2.1 eq.) gave smooth conversion to the (*Z*)-allylic alcohol **172**. Subsequently, the (*Z*)-allylic alcohol **172** was then oxidised to the desired (*Z*)-aldehyde **168** using Dess-Martin periodinane.[60]



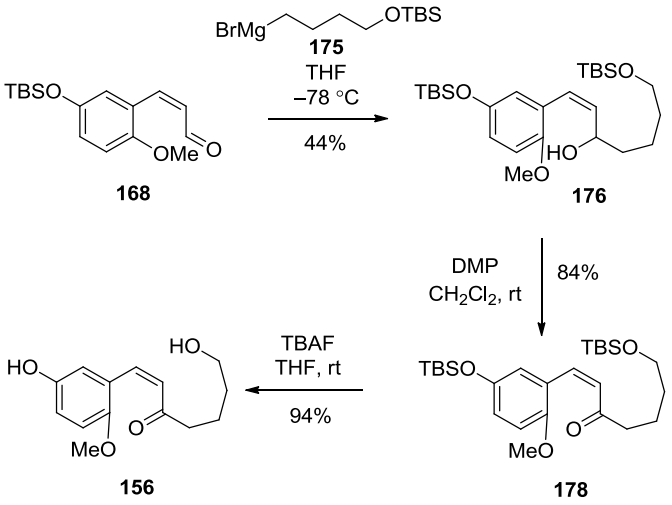
Scheme 59 - Synthesis of aldehyde **168**

The previously described retrosynthetic analysis indicated that addition of an alkyl halide fragment **167** to aldehyde **168** could give access to the required carbon framework. For the synthesis of alkyl halide fragment **167**, efforts were focused towards the synthesis of alkyl bromide **173** using a reported procedure. Treatment of tetrahydrofuran (THF) with aq. hydrobromic acid gave bromo alcohol **174**.[71] The bromo alcohol **174** was then protected as a silyl ether by treatment with TBSCl in the presence of imidazole, to give the alkyl bromide **173** (Scheme 60).[72]



Scheme 60 - Synthesis of alkyl bromide **173**

The formation of a Grignard species from alkyl bromide **173** and its subsequent addition to the aldehyde **168** was planned (Scheme 61). The required Grignard reagent was generated *in situ* by heating alkyl bromide **173** over magnesium turnings and a crystal of iodine in THF. The Grignard species **175** was added to the (*Z*)-aldehyde **168** at –78 °C to give (*Z*)-alcohol **176** in 44% yield. This low yield was due to competing reduction of the (*Z*)-aldehyde **168**[*] by the α,β-saturated Grignard reagent **175**, to return (*Z*)-alcohol **172**, as has been described for similar Grignard reagents in the literature.[73] Following this, oxidation of the (*Z*)-alcohol **176** with Dess-Martin periodinane[60] assisted the conversion to (*Z*)-enone **178**. Finally, fluoride mediated the concurrent removal of both silyl ether protecting groups, to give hydroxyphenol **156**. Retention of the crucial (*Z*)-alkene stereochemistry was confirmed by comparison of the 12.7 Hz alkenyl proton *J* coupling constant with similar (*Z*)-enone moieties in the literature, ranging from 12.5–13.0 Hz.[61]



Scheme 61 - Synthesis of hydroxyphenol **156**

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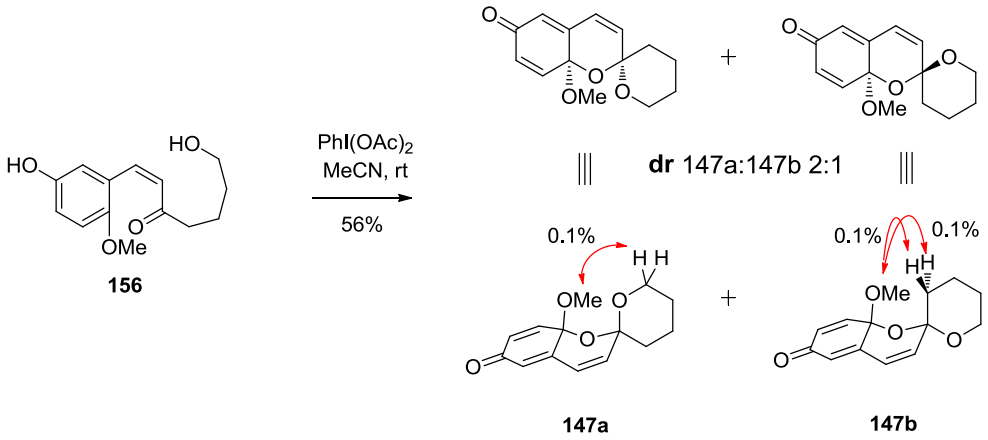
[*] Reduction occurs through a 6-membered transition state, whereby the Grignard reagent acts as a hydride source.

2.1.3.1 Spiroketalisation *via* Model System

Upon the succesful formation of hydroxyphenol **156** the key cascade oxidative dearomatisation strategy for spiroketal formation was examined. Gratifyingly, under the conditions reported by Baldwin,[47] oxidation of hydroxyphenol **156** with $PhI(OAc)_2$ in MeCN gave two spiroketal products **147a/b** in a 2:1 ratio as judged by ^1H NMR integrations, directly after evaporation of the solvent. The products were isolated by flash column chromatography and assigned as spiroketal diastereomers major **147a** and minor **147b**, in a 56% combined yield.



Scheme 62 - Synthesis of spiroketals **147a** and **147b**

The stereochemistry of each diastereomer was revealed through nOe difference experiments. For major spiroketal diastereomer **147a**, saturation of the OCH_3 resonance in the ^1H NMR spectrum revealed a 0.1% nOe enhancement to one O–CH proton on the pyran ring (Figure 9). For the minor spiroketal diastereomer **147b**, saturation of the OCH_3 resonance revealed a 0.1% nOe enhancement to alkyl C–CH_2 protons of the pyran ring (Figure 10). As expected, both of these very small nOe signals were entirely exclusive for each isolated diastereomer. The very small nOe percentage enhancement values observed are probably as a result of a large distance between these protons (since nOe intensity is proportional to $1/r^6$).

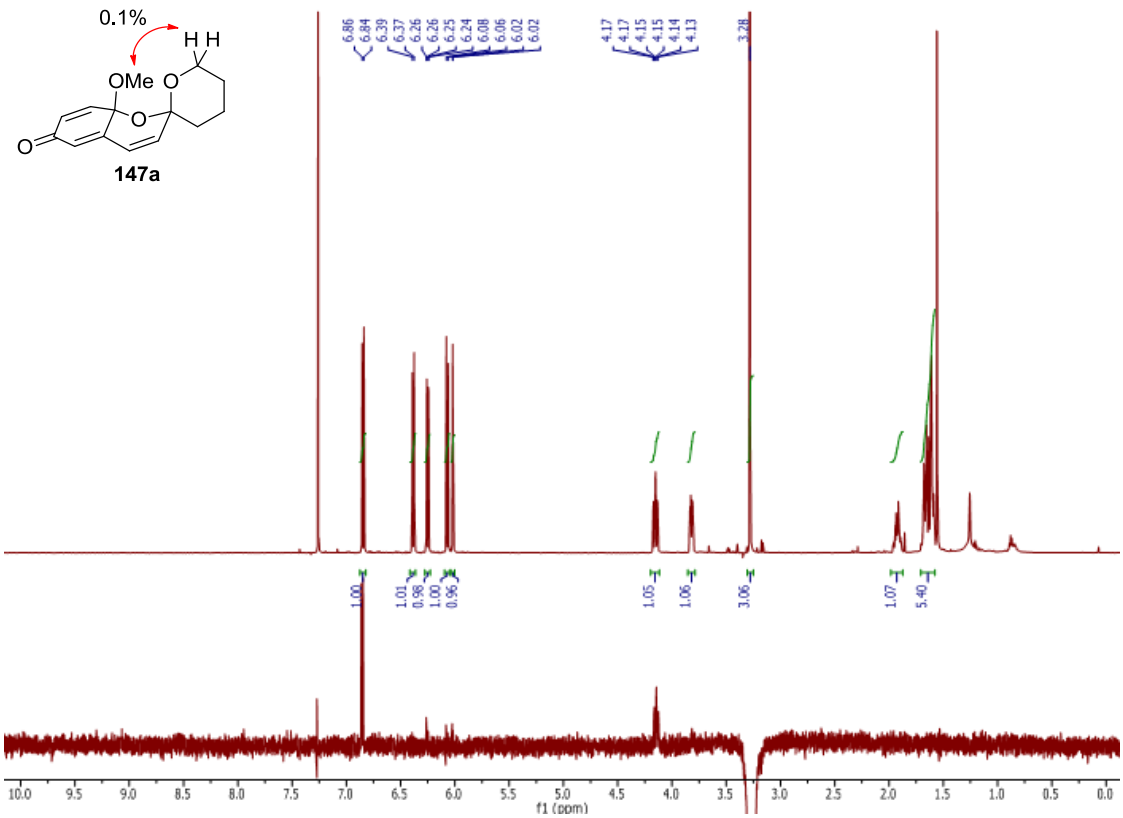


Figure 9 - NOESY difference experiment for major spiroketal **147a**

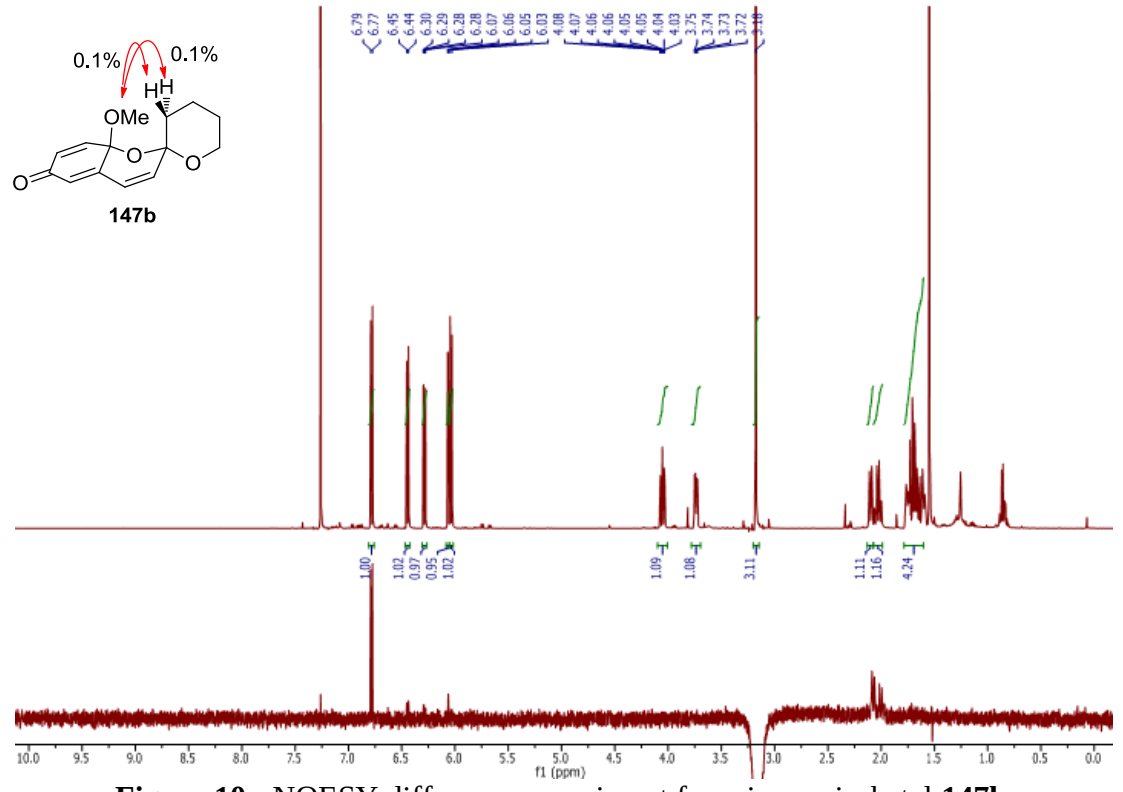
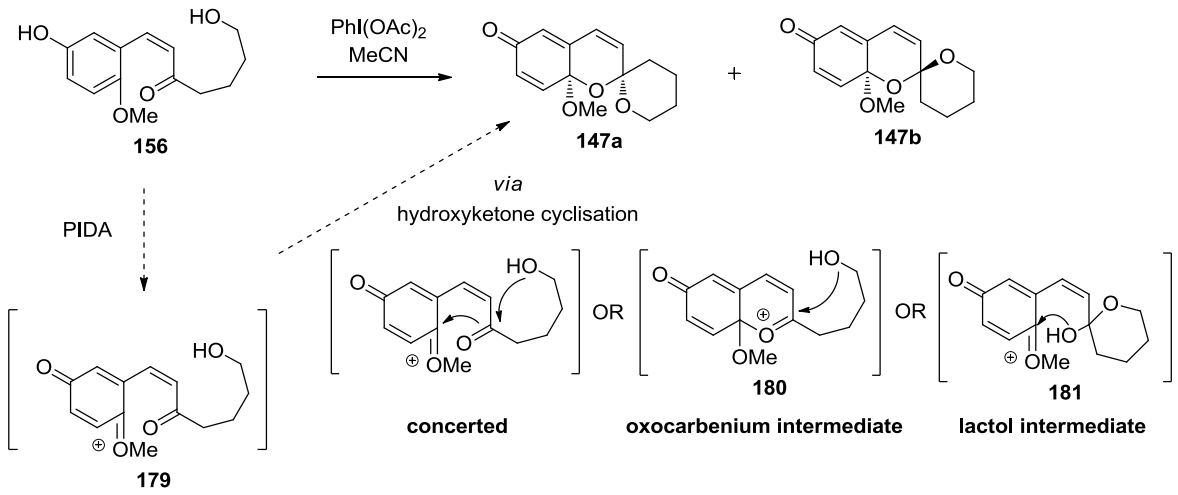


Figure 10 - NOESY difference experiment for minor spiroketal **147b**

The spirocentre carbon atom resonated in the ^{13}C NMR spectrum at 95.3 (**147a**) and 96.3 ppm (**147b**), within the characteristic chemical shift region for a spiroketal centre.

A precise mechanism for this novel spiroketalisation has not been determined. But it can be postulated that the initial step must involve, as in previous examples, nucleophilic attack of the phenol onto the iodine(III) centre to form a phenyl-λ^3-iodanyl intermediate. Regardless of the exact mechanism for two-electron oxidation, the phenol ring becomes prone to nucleophilic attack from the hydroxyketone tether. As an example, a dissociative mechanism with the formation of oxocarbenium intermediate **179** is depicted in Scheme 63.

The order of events for the cyclisation of the hydroxyl ketone tether is also not known. Possible mechanisms include: a concerted cyclisation onto the ring, the formation of an oxocarbenium intermediate **180** which then suffers attack from the hydroxyl group or the formation of a lactol **181** which attacks the ring (Scheme 63).



Scheme 63 - Possible mechanisms for spiroketals **147a** and **147b** formation

2.1.4 Conclusion

With the successful demonstration of the newly developed method for spiroketalisation the author was intrigued to revisit data obtained from the initial model study. The ^{1}H NMR spectra of each newly isolated spiroketal was compared to the ^{1}H NMR spectrum of the mixture of proposed spiroketals **147a** and **147b** obtained *via* the initial model system (Figure 11). Gratifyingly, it was found that spiroketals **147a** and **147b** had indeed been formed in the initial model system, albeit as impure minor products.

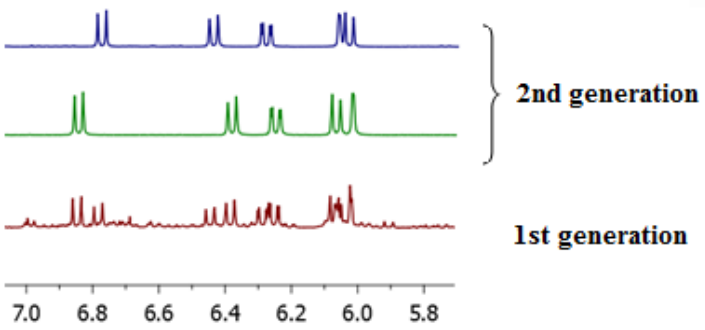
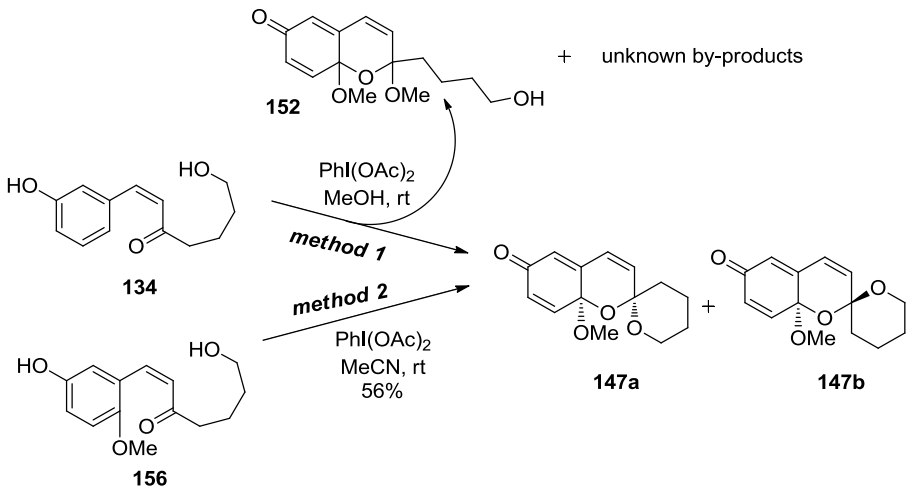


Figure 11 - ^{1}H NMR spectra **147a** and **147b** formation from methods 1 and 2

The work presented so far describes the demonstration of two related strategies for a new method of spiroketalisation *via* cascade oxidative *ortho*-dearomatisation. The 1st generation method involves the use of exogenous MeOH which is incorporated in the final dearomatised spiroketals **147a** and **147b**, previously described as minor products. The 2nd generation method involves the pre-incorporation of a methoxy substituent *ortho* to the tethered chain to give spiroketals **147a** and **147b** as the major reaction products in overall 56% yield.



Scheme 64 - Summary of developed spiroketalisation methods 1 and 2

Upon confirmed formation of the desired spiroketals **147a** and **147b**, it was decided to investigate whether this newly developed method could be applied to the total synthesis of phorbaketal A. An investigation into the substrate scope of this new methodology was also of interest. Both of these synthetic ventures will be discussed in the following sections.

2.2 Towards phorbaketal A

An investigation into the use of the newly developed method for the installation of the cyclohexenone and spiroketal moieties possessed by phorbaketal A was initiated. A challenge towards the synthesis of phorbaketal A would be installation of the stereocentre and geranyl chain at C16 (Figure 12). The effect of this stereocentre on the diastereoselectivity during the spiroketalisation step was unknown. Moreover, the installation of trisubstituted (*Z*)-alkene moieties at C8–C10 and C12–C13 would pose major synthetic challenges.

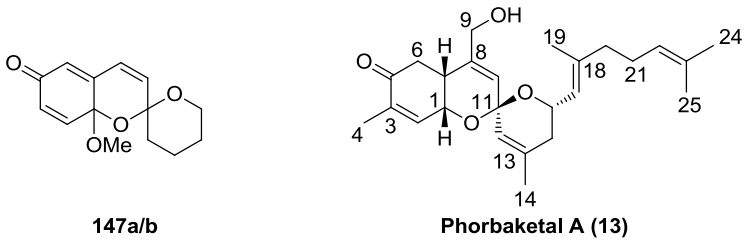
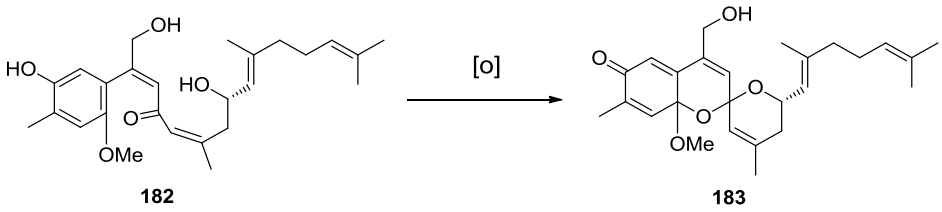


Figure 12 - Spiroketals **147a/b** compared to phorbaketal A (**13**)

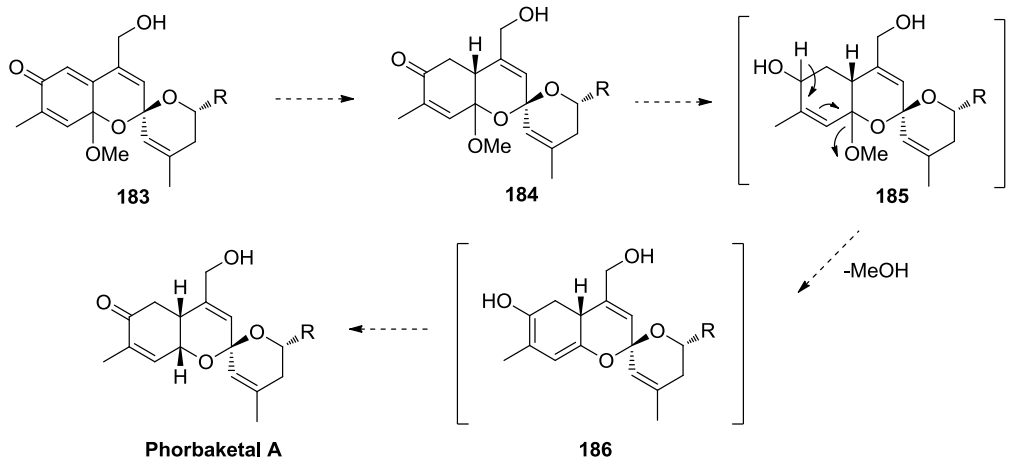
Treatment of hydroxyphenol **182** with an oxidant *e.g.* ($PhI(OAc)_2$) was proposed to effect a cascade oxidative dearomatisation to give cyclohexadienone spiroketal substrates **183** (Scheme 65). The removal of the methoxy group, as previously discussed, would require some challenging reduction steps towards the cyclohexenone moiety possessed by phorbaketal A.



Scheme 65 - Cascade oxidative dearomatisation to phorbaketal A precursor **183**

It was anticipated that upon formation of spiroketal substrate **183**, chemoselective removal of the undesired C6-C7 trisubstituted alkene could later be achieved using the primary alcohol as a directing group. As has been previously discussed, Wilkinson's catalyst can assist selective hydrogenation of conjugated alkenes. Additionally, Wilkinson's catalyst is known to coordinate hydroxyl groups allowing selective hydrogenation of allylic or homoallylic alkenes.[74] Other reduction method options could involve metal hydrides, also taking advantage of coordination of the hydroxyl group with the metal to steer chemoselective reduction of the C6-C7 trisubstituted enone. Following this, reduction of the ketone **184** to alcohol **185** could

result in elimination of the undesired methoxy substituent to (after tautomerisation of **186**) ultimately give the desired cyclohexenone moiety possessed by phorbaketal A **187** (Scheme 66).



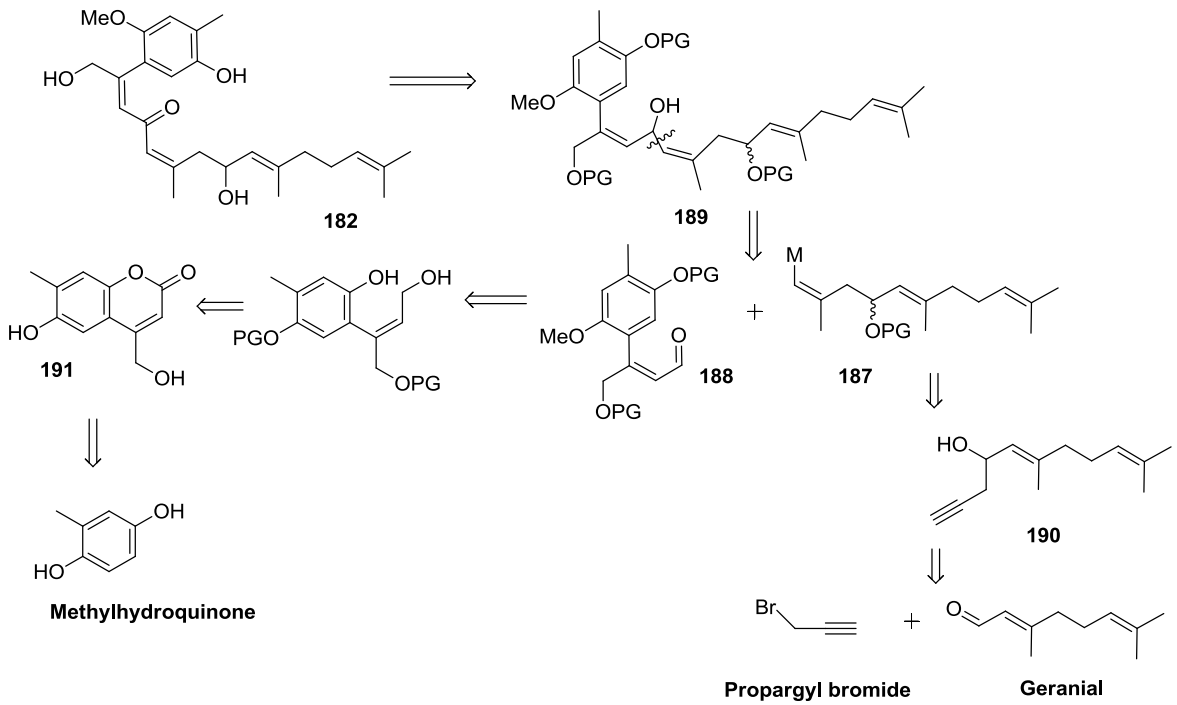
Scheme 66 - Anticipated reduction steps towards phorbaketal A; R = geranyl

A synthesis of hydroxyphenol **182** was planned, with which the key cascade oxidative dearomatisation pathway and subsequent steps could be probed.

2.1.1 Synthesis of Hydroxyphenol 182

Retrosynthetic analysis of hydroxyphenol **182** revealed a possible addition of (Z)-organometallic fragment **187** to (*Z*)-aldehyde **188** to give an alcohol **189**, which would complete a synthesis of the alotane carbon skeleton (Scheme 67). The synthesis of (*Z*)-organometallic fragment **187** was envisaged to proceed from a (*Z*)-vinyl iodide formed *via* an *anti*-carbometallation step *via* alkyne **190**. Examples of *anti*-carbometallation of homopropargyl alcohols in the literature include those proceeding *via*: carbotitanation,[75] carbomagnesiation[76] and (more recently) Negishi-type Zr-catalysed carboalumination[77] processes. The synthesis of alkyne **190** was projected to proceed using a known procedure for the addition of propargyl bromide into geranial. The (*Z*)-aldehyde fragment **188** was envisaged to originate from

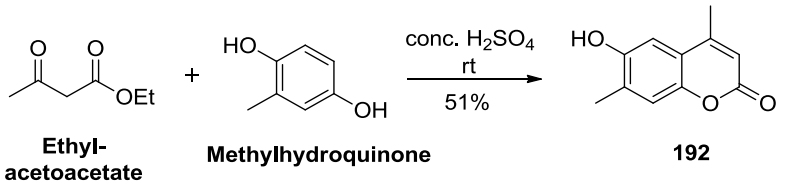
coumarin fragment **191**, which would allow convenient access to the otherwise synthetically challenging trisubstituted (*Z*)-alkene moiety. The synthesis of the coumarin fragment would proceed *via* a reported Pechmann condensation procedure from methyl hydroquinone. In order to concentrate on investigating the key steps of the synthesis, it was decided early on that initial investigations would employ a racemic mixture of the alkyne fragment **190**.



Scheme 67 - Retrosynthetic analysis of hydroxyphenol **182**

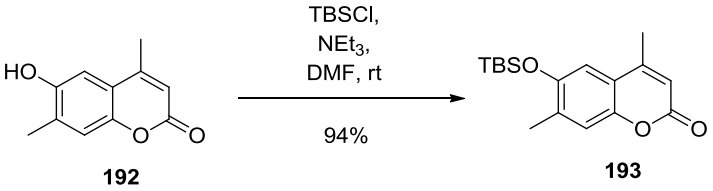
Initial synthetic efforts were focused towards the synthesis of aldehyde fragment **188**. The synthesis of coumarin **192** was achieved using a reported Pechmann condensation procedure from commercially available reagents methylhydroquinone and ethylacetoacetate, using concentrated H_2SO_4 as solvent (Scheme 68).[78] This convenient reaction gave clean conversion to the coumarin **192**, which was used directly after work-up and the removal of water. This step established the

synthetically challenging trisubstituted (*Z*)-alkene (C8−10), whilst also incorporating the two additional methyl groups (C4 and C9) present in phorbaketal A.



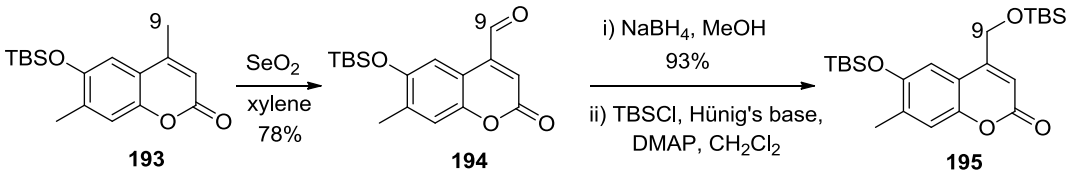
Scheme 68 - Pechmann condensation for synthesis of coumarin **192**

The sparingly soluble coumarin **192** had its phenol group protected as a silyl ether by treatment with TBSCl and NEt_3 in DMF, to give the readily soluble and highly crystalline coumarin **193** (Scheme 69a).



Scheme 69a - TBS protection of coumarin **192**

At this point the author wishes to mention work which was completed in collaboration with an MSci student, Christopher Arul. This work demonstrated the installation of the desired C9-hydroxyl group, *via* a regioselective allylic oxidation route from coumarin **193**.[79] Treatment of **193** with SeO_2 mediated conversion to aldehyde **194**. Following this, $NaBH_4$ reduction of the aldehyde **194** and protection of the newly formed primary alcohol as its TBS silyl ether gave access to coumarin **195** (Scheme 69b).



Scheme 69b - Synthesis of C9-oxy coumarin **195**

These results were encouraging, however initial efforts were focused upon establishing the more key synthetic steps of the synthesis, using the easily accesible coumarin **193**. Reduction of the lactone moiety within coumarin **193** to the desired (*Z*)-allylic alcohol **196** proved to be challenging (Scheme 70). Treatment of the coumarin **193** with a range of reducing agents: $LiAlH_4$, $LiBH_4$, $NaBH_4$ and DIBAL-H all resulted in low yields (0 – 30%) along with varying amounts of suspected 1,4-reduction. However, reduction using $LiAlH_4$ and BnCl for the *in situ* formation of AlH_3[80] was optimal; giving (*Z*)-allylic alcohol **196** in 61% yield. Chemoselective methylation of the phenol in the presence of the primary alcohol was achieved under basic conditions with Cs_2CO_3 and MeI. Subsequent allylic alcohol oxidation was achieved using MnO_2 to give (*Z*)-aldehyde **197**.

To ascertain the stereochemistry of the potentially isomerisable (*Z*)-enone motif, nOe experiments were conducted. The alkenyl proton was irradiated in a nOe difference experiment, leading to a 0.96% enhancement of the neighbouring methyl group resonance, confirming the desired (*Z*)-alkene stereochemistry had been retained. Following this, gradual crystallisation of the (*Z*)-aldehyde **197** over a few days allowed for further confirmation of the (*Z*)-alkene stereochemistry by X-ray crystallographic analysis (Figure 13).

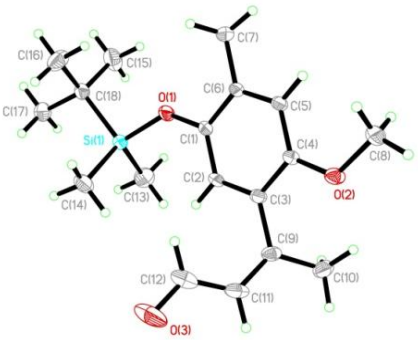
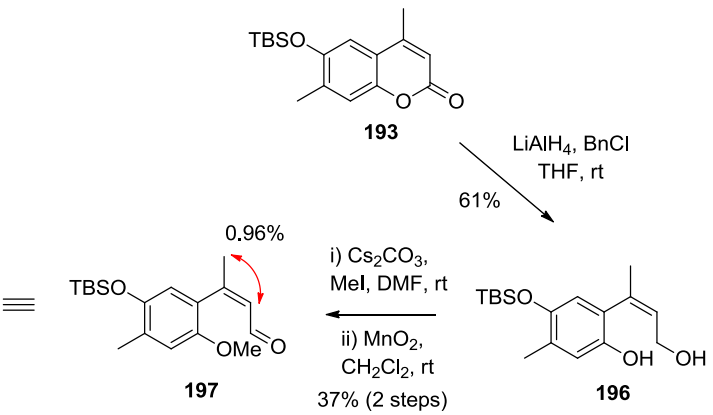
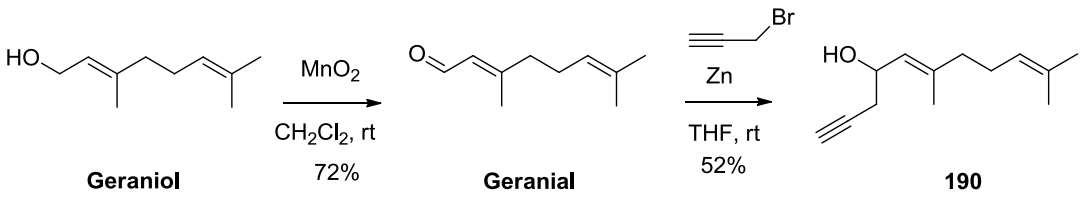


Figure 13 - ORTEP of **197**



Scheme 70 - Synthesis of (*Z*)-aldehyde **197**

With the formation of (*Z*)-aldehyde **197**, synthetic efforts were focused towards the synthesis of alkyne **190**. Oxidation of inexpensive and commercially available geraniol to geranial was achieved using MnO_2 (Scheme 71). Following this, a zinc-mediated Reformatsky addition* of propargyl bromide to geranial facilitated formation of alkyne **190**.[81] Although this method did not allow enantioselective formation of the chiral centre required at the C16 position of phorbaketal A (see Figure 12, Page 66), it was decided to investigate the key steps towards phorbaketal A using this racemic mixture, before enantioselective alternatives could be investigated. Such future enantioselective step options were anticipated to include asymmetric reduction of a ketone or lipase deacetylation processes.



Scheme 71 - Reformatsky addition for alkyne **190**

With the formation of alkyne **190**, attempts at a Negishi *anti*-carboalumination were conducted. Treatment of alkyne **190** with trimethyl aluminium and zirconium dichloride was followed by refluxing for three days in order to achieve (*E*)- to (*Z*)-alkene isomerisation to intermediate **198**. This was followed by quenching of the reaction mixture with iodine. Unfortunately, analysis of the ^{1}H NMR spectrum after protic work-up revealed a completely unidentifiable mixture of degradation products, with no characteristic alkenyl resonances.

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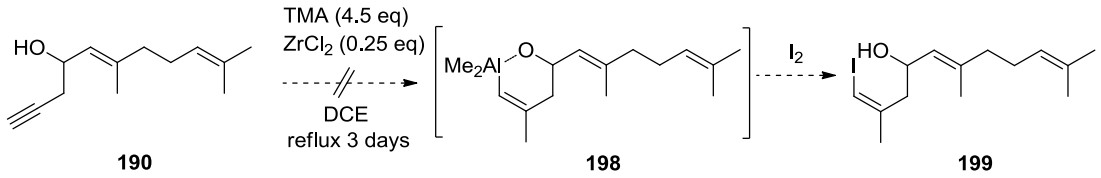
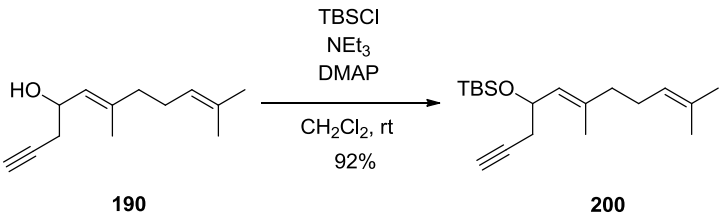
* Very violent reaction! Caution needed.



Scheme 72 - Attempted Negishi *anti*-carboalumination of alkyne **190**

Although time invested in the development of this carboalumination step could lead us to the desired alkene fragment **199**, at this stage it was decided to focus on achieving the more adventurous novel key steps later in the sequence towards the synthesis of phorbaketal A.

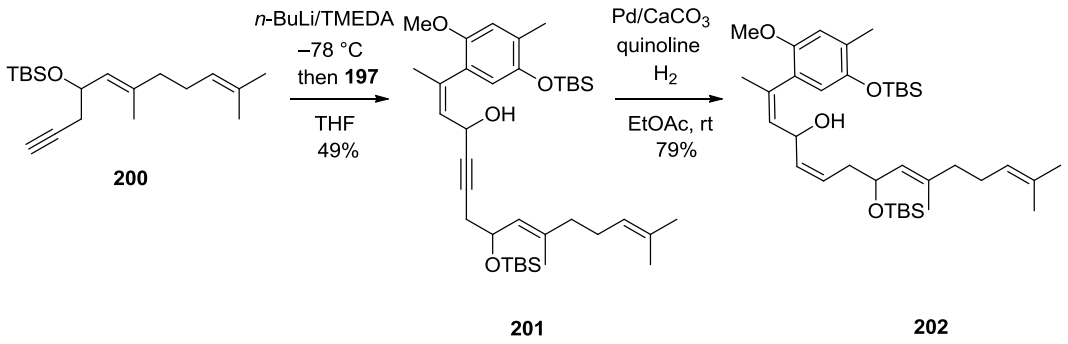
It was envisaged that *in situ* formation of a lithium acetylide species formed by deprotonation of the terminal alkyne proton of an alkyne **190** analogue would allow nucleophilic addition to aldehyde **197**. To investigate this, alkyne **190** was firstly silyl protected using TBSCl in the presence of NEt_3, to give alkyne **200**.



Scheme 73 - Synthesis of O-TBS protected alkyne **200**

Treatment of alkyne **200** with *n*-BuLi mediated *in situ* formation of lithium acetylide species, which was quenched by the addition of (*Z*)-aldehyde **197** to give (*Z*)-propargyl alcohol **201** upon protic work-up (Scheme 74). The noralotane skeleton bearing alcohol **201** was isolated as a mixture of two diastereomers which co-eluted by flash column chromatography. Being a mixture of diastereomers, unambiguous assignment of every carbon atom in analysis of the ^{13}C NMR spectrum was

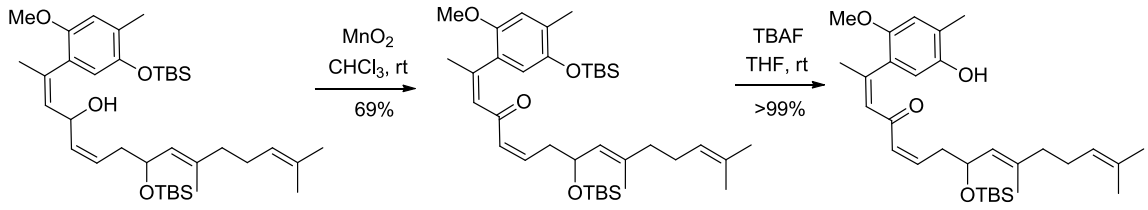
unattainable until elimination of the newly formed chiral centre in a later step. Following this, treatment of propargyl alcohol **201** with Lindlar catalyst under one atmosphere of hydrogen facilitated smooth hydrogenation of the alkyne moiety to the desired (*Z*),(*Z*)-alkene **202**.



Scheme 74 - Synthesis of (*Z*),(*Z*)-alkene **202**

Upon isolation of (*Z*),(*Z*)-alkene **202**, oxidation of the allylic alcohol moiety using MnO_2 was achieved, to give (*Z*),(*Z*)-enone **203** (Scheme 75). With formation of the π conjugated enone system possible degradation through (*Z*)- to (*E*)-alkene isomerisations was feared. With this in mind, the (*Z*),(*Z*)-enone **203** was stored in a −30 °C freezer under argon, and thankfully no isomerisation was observed by ^{1}H NMR analysis during storage. With the removal of one stereocentre and hence the substrate no longer being a mixture of two diastereomers, analysis of (*Z*),(*Z*)-enone **203** by ^{13}C NMR pleasingly became more simplistic.

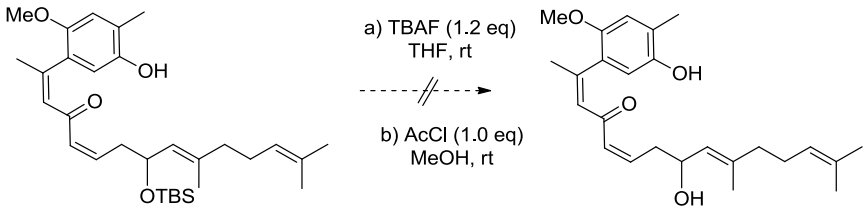
For the concurrent removal of both silyl groups, (*Z*),(*Z*)-enone **203** was treated with TBAF (2.5 eq) and the reaction was monitored by TLC. After 2 h, TLC analysis revealed conversion to a more polar (slower eluting) compound as expected upon the deprotection of the polar hydroxyl groups. However, after protic work-up ^{1}H NMR analysis revealed removal of the phenolic TBS group only to give **204**.



202 **203** **204**

Scheme 75 - Synthesis of (*Z*),(*Z*)-enone **203** and silyl deprotection to **204**

The phenol **204** was again treated with TBAF (1.2 eq), and following of the reaction by TLC over 5 h revealed consumption of the starting material. However upon protic work-up the ^{1}H NMR spectrum revealed degradation to a complex mixture. Removal of the stubborn secondary TBS group was then attempted under acidic conditions with MeOH and AcCl (1.0 eq) (for the formation of dry HCl). However in similar fashion the ^{1}H NMR spectrum revealed degradation to a complex mixture. Potential degradation pathways of the highly unsaturated substrates, in basic or acidic conditions, could include migration of double bonds, isomerisation of double bonds and sigmatropic rearrangements or intramolecular hetero Diels–Alder reactions.



204 **205**

Scheme 76 - Attempted deprotection of secondary alcohol **204**

Being unable to remove the seemingly stubborn secondary TBS group and the need to synthesise greater quantities of alkyne **190**, it was decided to employ a more labile silyl protecting group on the secondary hydroxyl group.

The relative stability of common silyl protecting groups to acid and base hydrolysis has been studied.[82] In acidic media the relative resistance is: trimethylsilane (TMS) (1) < triethylsilane (TES) (64) < TBS (20,000) < triisopropylsilane (TIPS) (700,000). In basic media the relative resistance is: TMS (1) < TES (10-100) < TBS (20,000) < TIPS (100,000). Each group with added steric bulk displays a very large increase in resistance to hydrolysis (Figure 14). Of the common silyl groups, the TES group is the next most labile after the TBS group.

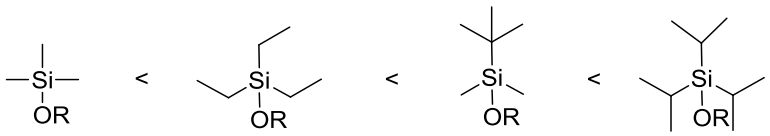
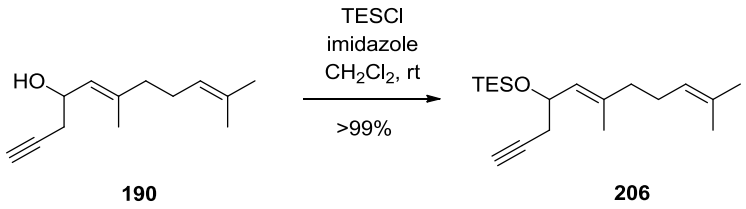


Figure 14 - Relative stability of silyl protecting groups

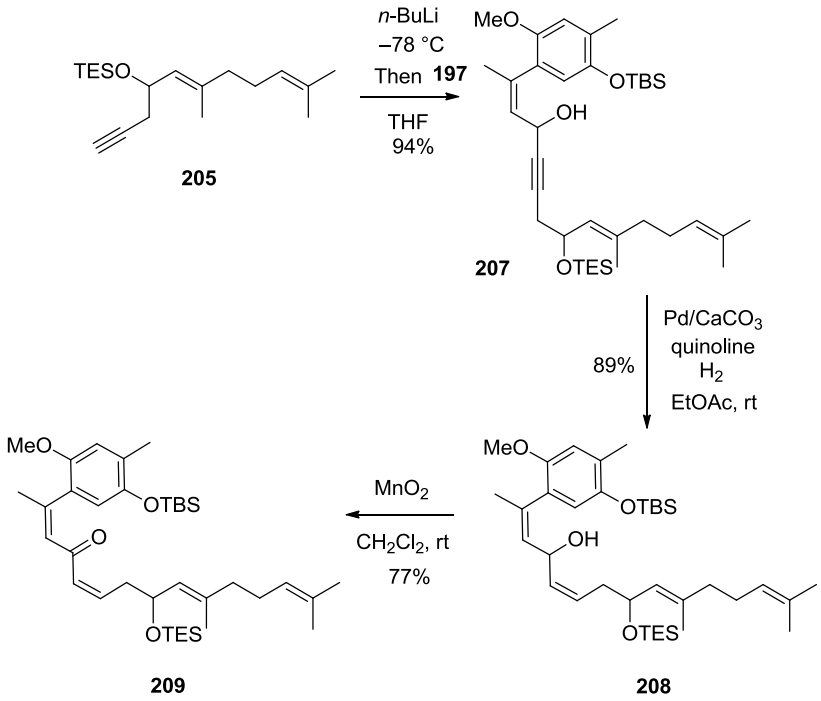
Thus, it was decided to repeat the same steps of the synthesis, substituting the TBS ether protecting group of alkyne **200** with the much more labile TES ether protecting group. This strategy was initiated by the treatment of alkyne **190** with TESCl in the presence of imidazole, to give smooth conversion to the TES group bearing **206** (Scheme 77).



Scheme 77 - Synthesis of TES protected alkyne **206**

The synthesis of ketone **209**, bearing a TES protected secondary alcohol, was achieved in three synthetic steps analogous to those previously discussed (and with

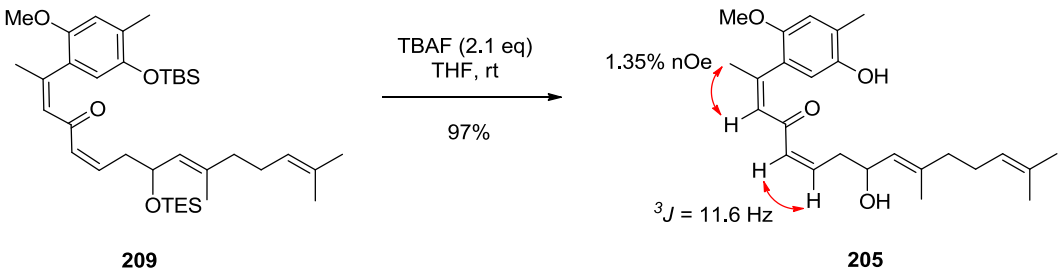
better yields) (Scheme 78). To the author's delight, removal of the more labile TES group was not encountered during these steps.



Scheme 78 - Synthesis of (*Z*),(*Z*)-enone **209**

Upon the successful synthesis of the (*Z*),(*Z*)-enone **209**, a method for the removal of both silyl protecting groups was again investigated. Concurrent removal of both silyl protecting groups was achieved using TBAF as a source of fluoride, to give hydroxyphenol **205** in a 97% yield (Scheme 79). Unfortunately, storage of the hydroxyphenol **205** over a few days led to degradation to an unidentifiable mixture of compounds, as determined by ^{1}H NMR analysis. To avoid this degradation of the unstable substrate (after eleven synthetic steps), after work-up, the purified hydroxyphenol **205** was stored under argon in a freezer at −80 °C and used within 2−3 days.

At this stage, confirmation of both crucial (*Z*)-alkene geometries was required. The C12–C13 alkenyl protons co-resonated as a multiplet in the ^{1}H NMR spectrum at 400 MHz. However by running the ^{1}H NMR experiment at 600 MHz the expected coupling constant of J = 11.6 Hz could be extrapolated from the more resolved multiplet, to confirm the (*Z*)-alkene geometry. Added to this, a NOESY experiment revealed a nOe between the C12–C13 alkenyl protons. Conformation of the C8-C10 (*Z*)-alkene *via* a nOe difference experiment involved irradiation of the C10 alkenyl proton, resulting in a 1.35% nOe enhancement of the adjacent alkenyl methyl group.



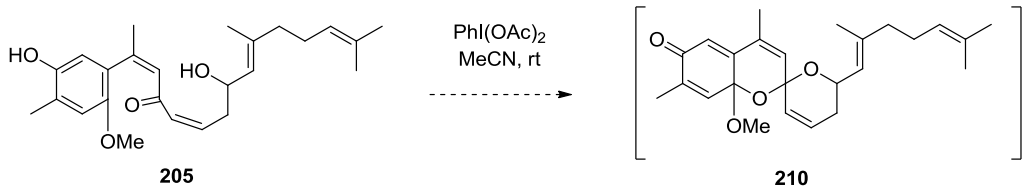
209 **205**

Scheme 79 - Synthesis of (*Z*),(*Z*)-hydroxyphenol **205**

2.2.2 Spiroketalisation of (*Z*),(*Z*)-Hydroxyphenol 205

Upon the succesful synthesis of (*Z*),(*Z*)-hydroxyphenol **205**, bearing the noralotane carbon skeleton, investigations into the key cascade oxidative dearomatisation step ensued. Treatment of hydroxyphenol **205** with $PhI(OAc)_2$ in MeCN (Scheme 80) was followed by TLC analysis, and upon consumption of starting material the solvent was removed *in vacuo*. Analysis of the crude mixture by ^{1}H NMR spectroscopy indicated a complex mixture of unidentifiable products from which no information about the fate of the starting material was obtained. By repeating this reaction in MeCN-d_3 and monitoring by ^{1}H NMR, the the build up of the expected acetic acid

by-product of $PhI(OAc)_2$ at 1.96 ppm was observed, but also unexpectedly revealing the build-up of MeOH, observed as a singlet resonating at 3.28 ppm (Figure 15).*



Scheme 80 - Attempted synthesis of spiroketal **210**

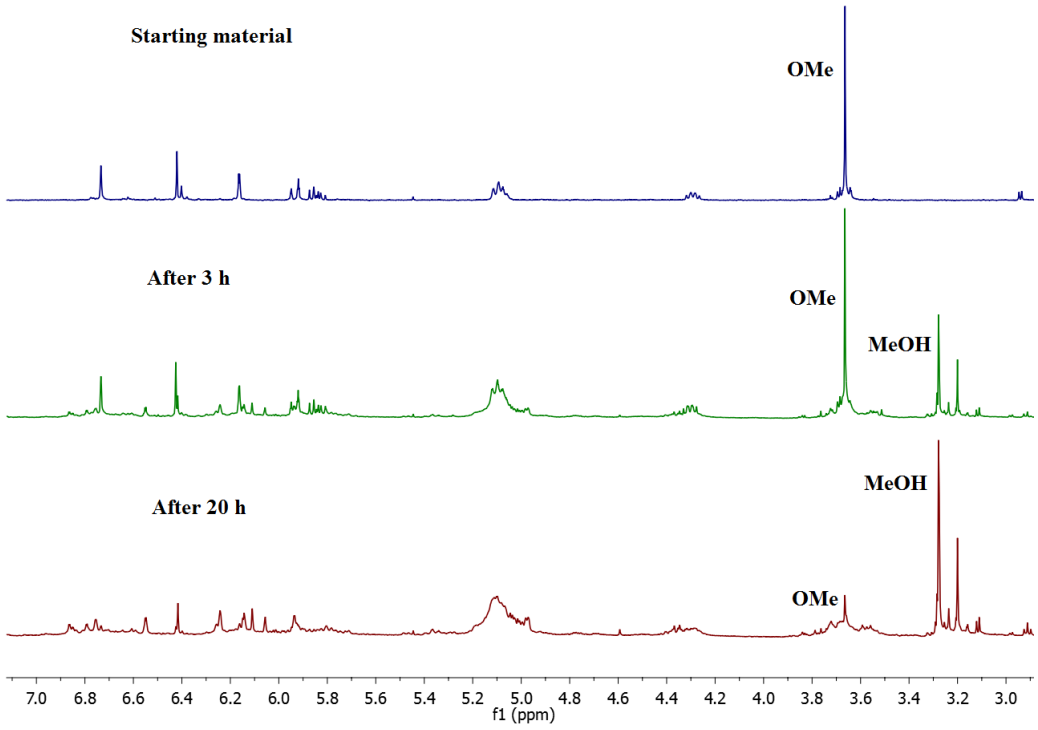


Figure 15 - ^{1}H NMR observed elimination of MeOH from spiroketal **210**

The apparent build up of MeOH over time indicated elimination of the methoxy substituent, presumably *via* protonation by acetic acid, to give intermediate **211** and subsequent elimination to form an oxocarbenium intermediate **212** (Scheme 81). The fate of this oxocarbenium intermediate **212** could then be envisaged in a number of

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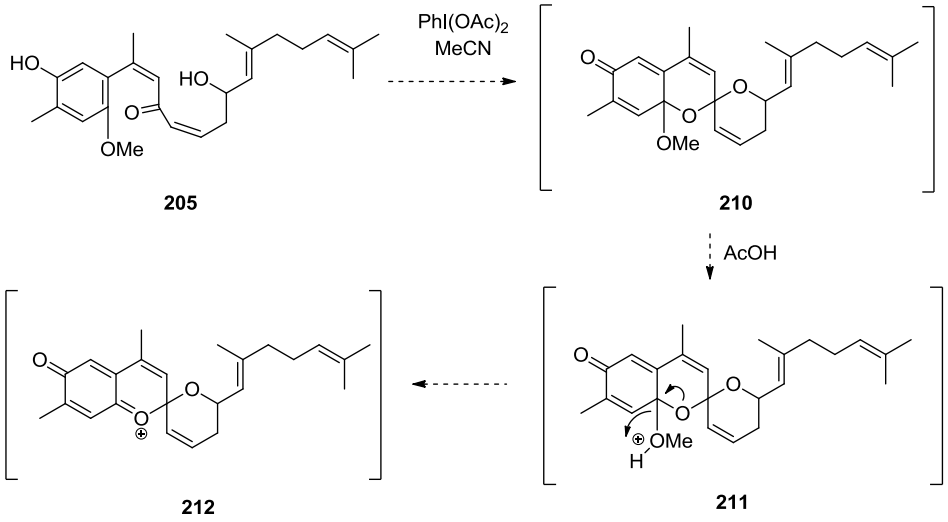
* Reported resonance of MeOH in CD_3CN in *J. Org. Chem*, 1997, **62**, 7512−7515.

degradation steps including nucleophilic attack from adventitious water to give oxygenated by-products.



Scheme 81 - Acetic acid degradation of proposed spiroketal **210**

In an aim overcome this alarming sensitivity to weakly acidic conditions, the reaction was repeated in the presence of pyridine (2.5 eq). This base was chosen to buffer the reaction because it is very weak (pK_a conjugate acid = 5.3); conforming with very mild reaction conditions. Moreover, deuterated pyridine was available, allowing ^1H NMR monitoring to be conducted in a straightforward manor.

Initially hydroxyphenol **205** was treated with $PhI(OAc)_2$ in the presence of d_5-pyridine (2.6 eq) in d_3-MeCN. Following the reaction by TLC analysis revealed the consumption of starting material **205** over 20 min. Before work-up crude ^1H NMR analysis revealed the presence of four well-defined singlets in the methoxy region (2.8–3.4 ppm). After this, the reaction was diluted with diethyl ether, and the organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated. The organic residue was then dissolved in $CDCl_3$ for NMR analysis. Analysis of the ^1H NMR revealed a complex mixture of products, although there was a clear presence of

four well defined singlets at 3.39, 3.33, 3.24 and 3.18 ppm. It was presumed that these four singlets may have corresponded to the four methoxy signals of the four expected diastereomeric spiroketal products.

Isolation of these sensitive compounds for thorough characterisation proved *extremely* challenging. Simple removal of the volatiles *in vacuo* after reaction gave degradation and was deemed unsuitable since it involved concentrating the acid-sensitive compounds with pyridinium acetate. Thus, typically the reaction mixture was placed directly onto the solid phase of a column. Attempts of purification using acidic silica, neutral silica, florisil, basic alumina, grade II basic alumina and preparative TLC on silica were unfruitful and gave complete compound degradation. Isolation of two of the apparent 'major diastereomers' was achieved using grade III basic alumina, however in a very low yield. A 56% yield of a mixture of four apparent diastereomers was eventually achieved using grade IV basic alumina, however the purity of the sample as judged by NMR analysis was poor.

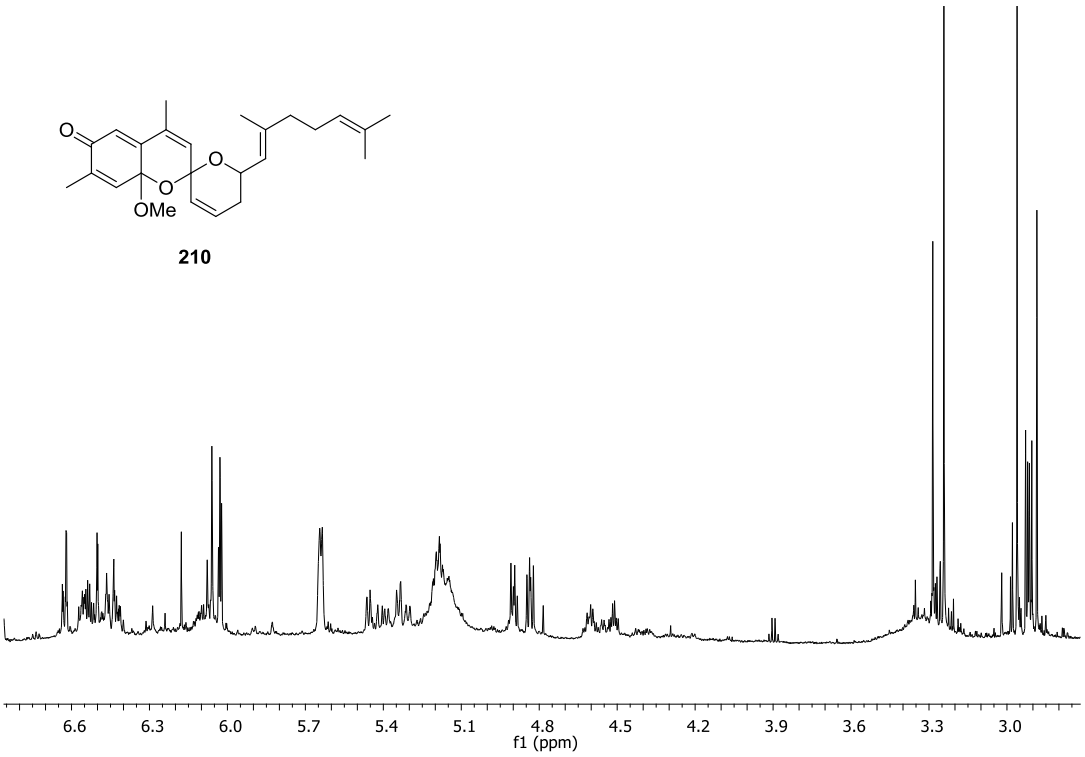
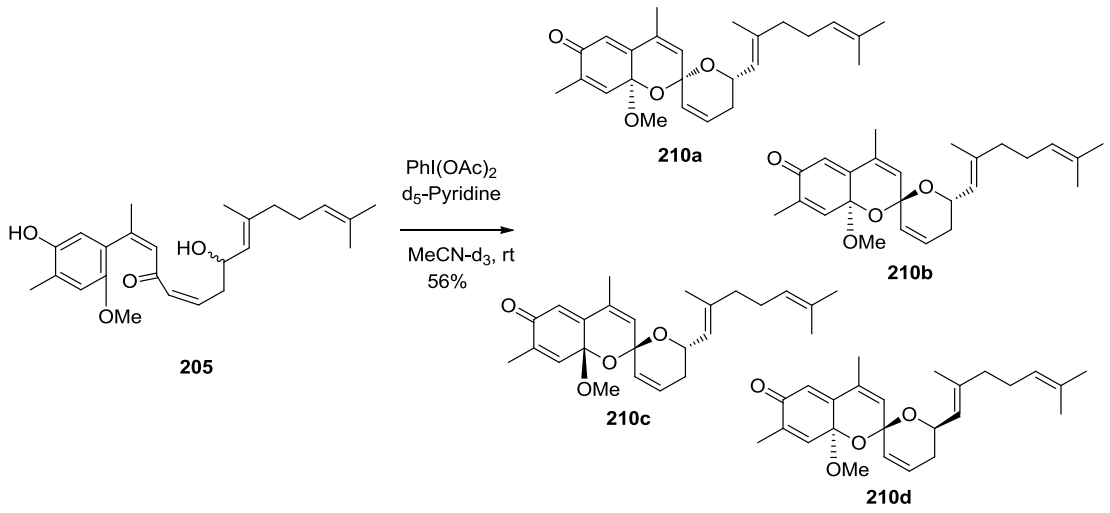


Figure 16 - Proposed spiroketals (**210a-d**) purified on grade IV basic alumina (600 MHz, C_6D_6)



Scheme 82 - Proposed formation of spiroketal diastereomers **210a-d**

Being an impure mixture of four diastereomers in an already complex system made thorough and conclusive chemical analysis unattainable. The ^{1}H NMR for the

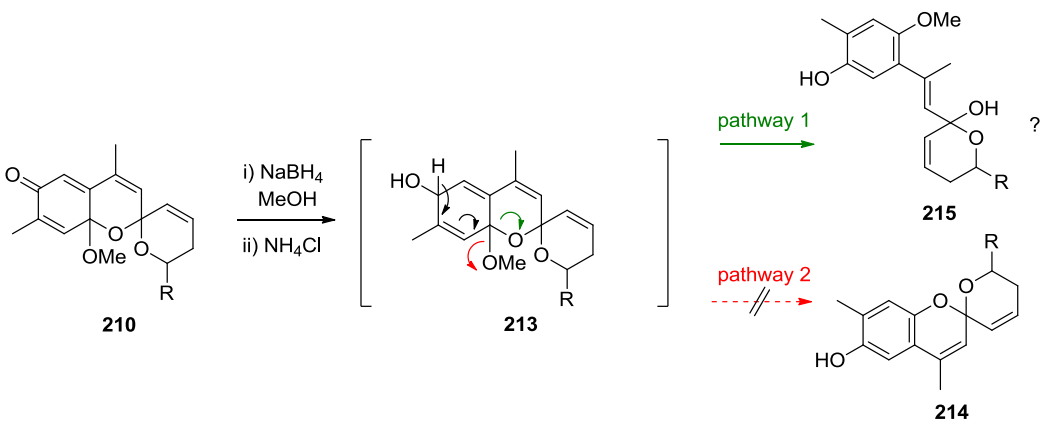
mixture was highly characteristic of a mixture of four diastereomers (figure 16). Key protons could be assigned through a COSY experiment.

Encouragingly, HRMS analysis of the mixture revealed the expected *m/z* ion peak for the desired spiroketals. The ^{13}C NMR spectrum revealed the presence of 6 signals around 186 ppm which were believed to correspond to the C=O carbon atom of the dearomatised spiroketal diastereomers, and some unidentified by-products. Moreover, the ^{13}C NMR spectrum revealed the presence of 6 signals around 92 ppm, which is a characteristic shift region for a spiroketal centre. However, upon observation of the ^{13}C NMR spectrum the compounds had shown further considerable degradation, and so this could not be assigned fully. It should be noted that although their formation seems apparent, their structures were *not conclusively determined*. Attempts of establishing the stereochemistry of each diastereomer by NOESY and nOe difference experiments with irradiation of various protons of each diastereomer in the mixture were unsuccessful.

With the aim to overcome these problems in substrate isolation it was decided to attempt reduction of the ketone moiety of **210** to alcohol **213**, which was then envisaged to aromatise *via* elimination of the methoxy substituent to give the presumed-to-be more stable phenolic spiroketals **214** (Scheme 83, pathway 2). Also, it was thought that removal of one chiral centre, and the resolution of the mixture into two diastereomers, may simplify isolation and characterisation. Although this transformation would not direct the synthesis towards the cyclohexenenone moiety possessed by phorbaketal A, it was believed that the removal of the labile methoxy substituent would allow proper isolation and characterisation of the spiroketals. Additionally, if rearomatisation with ejection of the methoxy group could be

demonstrated, this would suggest that elimination of the methoxy group *via* the previously described route (Scheme 83) may also be possible.

To investigate this, the mixture of four diastereomeric ketones (**210a-d**), purified using grade IV basic alumina, was treated with $NaBH_4$. After protic work-up analysis of the ^1H NMR spectrum revealed a mixture of products which were clearly bearing methoxy substituents, with several resonances ranging from 3.74–3.77 ppm. The chemical shift of the major methoxy signal strongly indicated it was an anisole derivative, and did in fact *exactly* match the chemical shift of the anisole moiety possessed by precursor dihydroxy ketone **205**, at 3.74 ppm. This analysis indicated aromatisation and ejection of the ether of the spiroketal core had occured rather than the desired ejection of MeO (Scheme 83, pathway 2 to give **215**). The structure of the products could not be fully determined. The presence of the methoxy substituent in the ^1H NMR spectrum clearly indicated that ejection of the methoxy substituent had not occurred. Further to this, HRMS analysis revealed the presence of the expected ion for phenol **215**. These data were sufficient evidence for the author to abandon this approach towards obtaining more stable substrates.



Scheme 83 - Reduction of ketone **210** and subsequent rearomatisation. R= geranyl

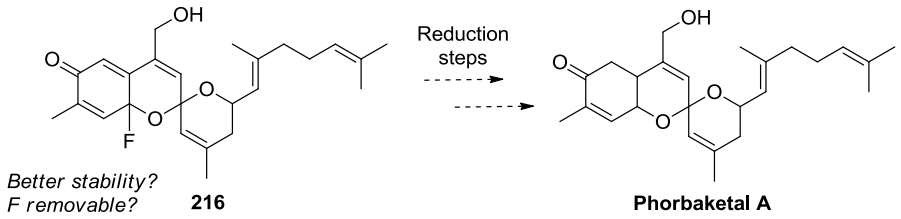
The instability of the dearomatised spiroketal substrates **210** was very discouraging in the efforts towards the total synthesis of phorbaketal A. As previously discussed, the future steps towards the total synthesis of phorbaketal A (or close analogue) would involve the chemoselective removal of the undesired enone, reduction of the ketone moiety and ejection of the methoxy substituent. The investigation into rearomatisation pathways *via* reduction of the ketone **210** revealed a fatal set-back; that ejection of the spiroketal ether seemed to be the favoured aromatisation pathway. This suggested that elimination of the methoxy group *via* the previously described route (Scheme 83) towards phorbaketal A would likely be unachievable. With these results in mind, coupled with the reduced novelty in any synthesis due to the reported syntheses of alotaketal A by Yang and Dalby, it was decided to discontinue this approach towards the total synthesis of phorbaketal A.

2.2.3 Fluorine Incorporation Studies

Some time was spent investigating the use of fluorine in substitution for the methoxy substituent used in the previous investigations. Fluorine is not easily protonated, but was potentially a leaving group in place of a methoxy substituent in the envisaged strategy towards phorbaketal A. For example, fluorine has been shown to be a plausible leaving group, as a consequence of its unparalleled electronegativity, during rearomatisation processes *e.g.* S_NAr mechanisms *via* Meisenheimer complex intermediates.[83]

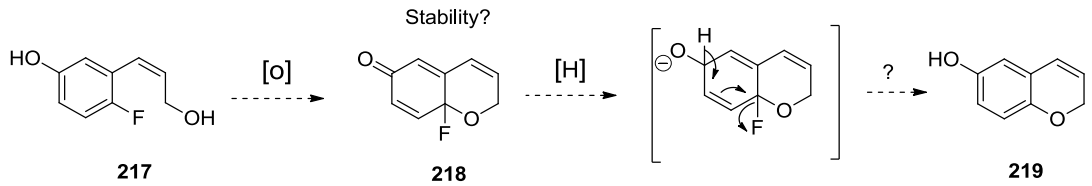
In this work, it was thought that fluorine could serve as a superior leaving group relative to the required spiroketal ether during rearomatisation and/or elimination processes. Being non-protonatable, it was hypothesised that fluorine spiroketal analogues *e.g.* **216** may demonstrate better stability, allowing better isolation and

characterisation of spiroketal products analogous to **210a-d**. Since ^{19}F possesses spin (I = ½) and is NMR active, this could allow observation of nOes between ^{19}F and the ring systems, potentially allowing structural assignment of the spiroketal diastereomers.



Scheme 84 - Proposed fluorine substituted spiroketals **216** towards phorbaketal A

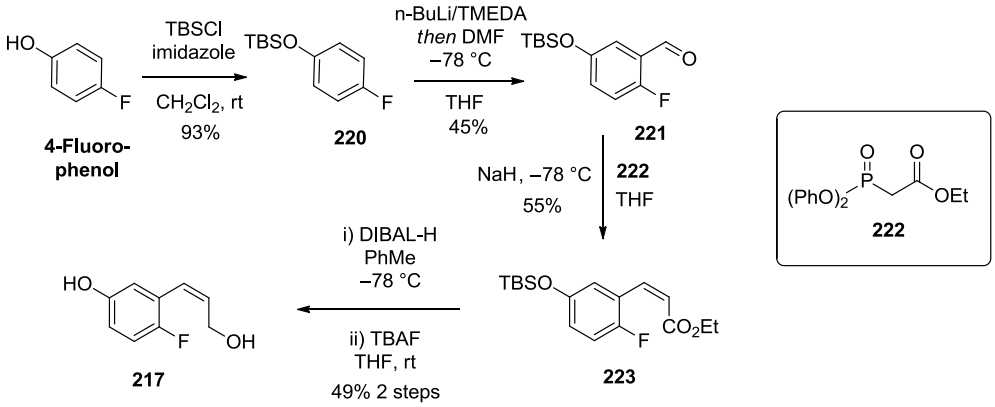
To investigate this, synthesis of the model substrate **217** was envisaged. Treatment of hydroxyphenol **217** with an oxidant would potentially assist cyclisation *via* oxidative dearomatisation to give highly novel cyclised substrate **218** (Scheme 85). The observed stability of the cyclised substrate **218** would then allow judgement as to whether a similar fluorine system could be employed towards the total synthesis of phorbaketal A. Also, treatment of the ketone **218** with a hydride source could then reveal whether ejection of fluorine or oxygen was favoured during aromatisation.



Scheme 85 - Proposed Synthesis of chromene **219**

The synthesis of hydroxyphenol **217** was achieved in five steps. Firstly, the TBS protection of 4-fluorophenol was achieved by treatment with TBSCl in the presence of imidazole (Scheme 86). Treatment of the protected phenol **220** with *n*-BuLi/TMEDA mediated *ortho*-lithiation (respective to fluorine), and upon quenching

with DMF and protic work-up, gave aryl aldehyde **221**.[84] An Ando-modified Horner-Wadsworth-Emmons olefination of aldehyde **221** using phosphonate **222,** gave novel ester **223** in a 1:10 *E:Z* ratio. The (*Z*)-alkene stereochemistry of the major (Z)-alkene product was confirmed by analysis of the *J* coupling constant value of the alkenyl protons, $^{3}J_{cis}$ = 12.5 Hz. Following this, DIBAL-H mediated reduction of the (*Z*)-ester **223** to the alcohol functionality. Finally, removal of the silyl ether protecting group was achieved using TBAF as a source of fluoride, to give hydroxyphenol **217**.



Scheme 86 - Synthesis of hydroxyphenol **217**

Hydroxyphenol **217** was treated with $PhI(OAc)_2$ in $CDCl_3$ and the reaction was periodically monitored *in situ* by ^{1}H NMR spectroscopy (Scheme 87). Dearomatisation with intramolecular cyclisation of the hydroxyl group was suspected due to the seperation of the previously co-resonant O-CH_2 protons into *J*-coupled diastereotopic OCH_a and OCH_b protons at 4.42 and 4.30 ppm on the newly formed ring. In general, the chemical shift of the previously aromatic protons were shifted upfield, as expected upon the destruction of the aromatic system and corresponding ring current.

However, with monitoring over 5 h, the dearomatised substrate **218** showed gradual degradation to an unidentifiable mixture.

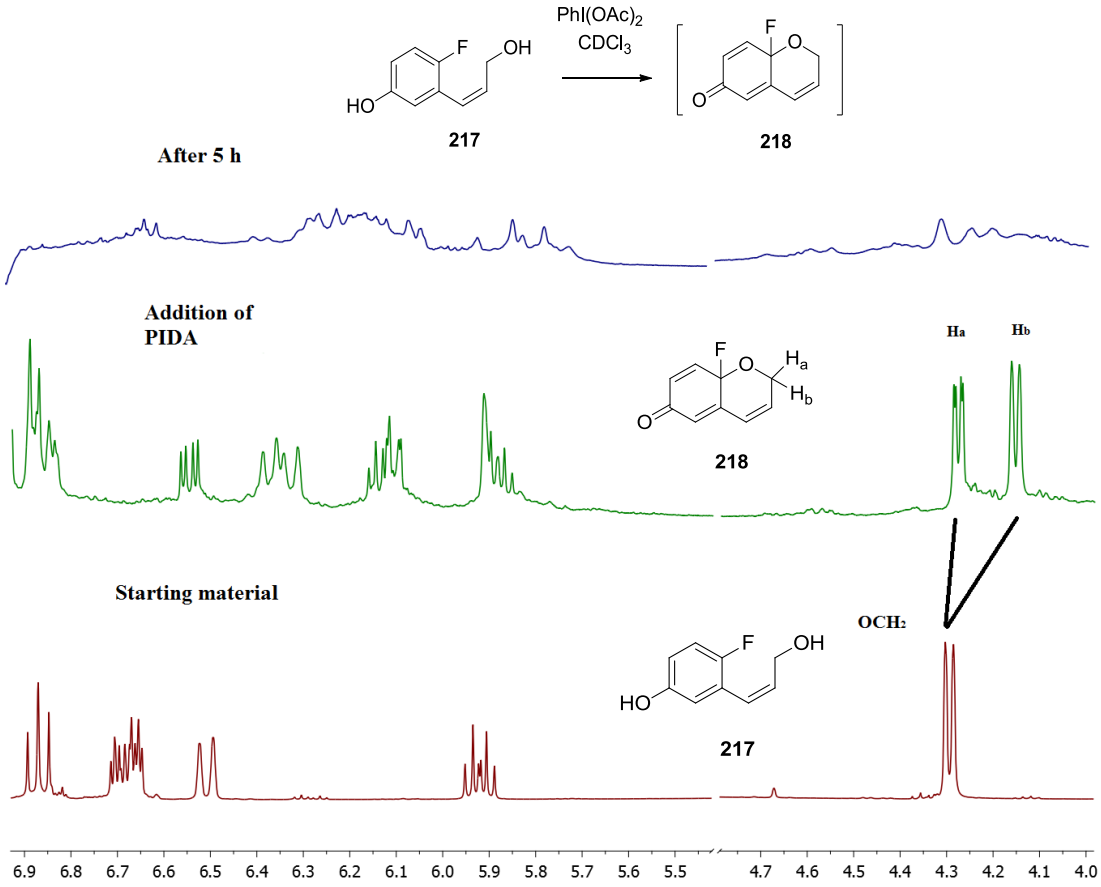


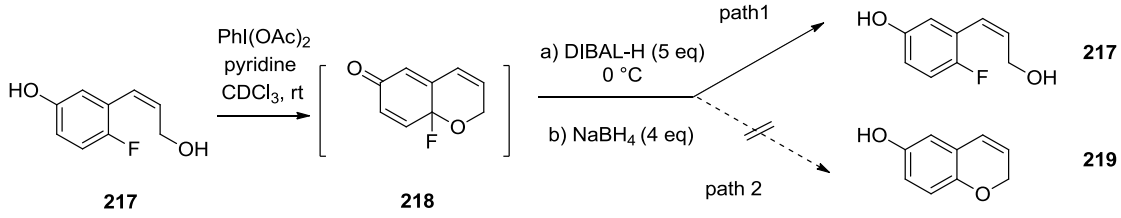
Figure 17 - ^{1}H NMR observed degradation of proposed cyclised substrate **218**

Having observed complete degradation of the proposed dearomatised substrate **218** under the mild reaction conditions, an investigation into the effect of rapid treatment of the unstable intermediate **218** with a hydride source was initiated. This investigation would potentially reveal whether rearomatisation with the elimination of fluoride was possible.

Firstly, treatment of hydroxyphenol **217** with $PhI(OAc)_2$ was buffered with pyridine (Scheme 87), and the consumption of the starting was observed by ^{1}H NMR analysis of an aliquot of the reaction mixture. After this time, an excess of DIBAL-H (5 eq.)

was added immediately at 0 °C. Upon protic work-up after 1 h, analysis of the crude ^{1}H NMR spectrum revealed the predominant presence of hydroxyphenol **217** starting material and a mixture of unidentified products. No evidence for the formation of chromene **219**, for which ^{1}H NMR spectrum data had been previously reported in the literature, was obtained.[85] In similar fashion, the dearomatised substrate **218** was also treated with an excess of $NaBH_4$ (4 eq.) at 0 °C. After protic work-up analysis of the ^{1}H NMR suggested the presence of hydroxyphenol **217**, and a mixture of degradation products, with no proton resonances matching those reported for chromene **219** in the literature.

Seemingly under these conditions, rearomatisation with elimination of the oxygen atom was the preferred pathway (Scheme 87, path 1). Due to this, and also the observed instability issues for dearomatised substrate **218**, this short investigation into the use of fluorine as a substituent during oxidative dearomatisation came to an end.



Scheme 87 - Attempted synthesis of chromene **219**

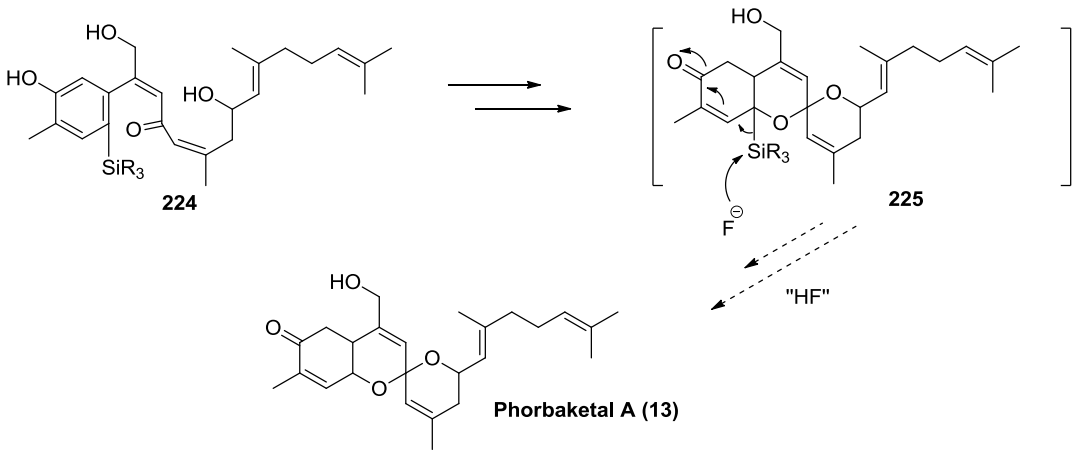
2.2.4 Conclusion and Future Work

The glaring instability issues encountered from synthesis of the proposed methoxy-bearing dearomatised substrates **210** and fluorine-bearing dearomatised substrates **218** were extremely discouraging for the use of this strategy towards the total synthesis of phorbaketal A. Subsequent investigations into rearomatisation pathways

via reduction of the ketone **210** revealed a fatal set-back *i.e.* ejection of the methoxy substituent was the favoured pathway during aromatisation. The rearomatisation pathway explored from fluorine-bearing dearomatised substrates **218** suggested the preferred elimination of oxygen over fluorine.

Therefore it was decided to discontinue investigations into the use of the newly developed method for spiroketalisation by cascade oxidative dearomatisation towards the total synthesis of phorbaketal A.

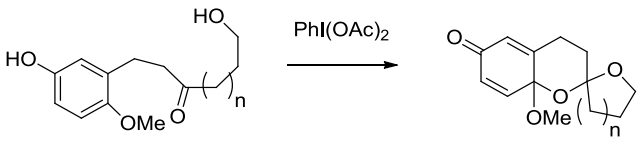
The author believes that some future investigations could involve the effect of using different substituents *ortho* to the tethered chain, in substitution for the investigated methoxy or fluorine substituents. One substituent worth investigating could be a silyl group. This could provide a better stability of the respective dearomatised substrates *e.g.* **225**, and treatment of the dearomatised product with a fluoride source could allow for an alternative pathway to phorbaketal A (Scheme 88).



Scheme 88 - Silyl strategy for phorbaketal A (**13**)

2.3 Methodology Scope Exploration

With the partially successful showcasing of the new method for spiroketalisation, efforts towards the expansion of this method into a more general method for spiroketalisation were conducted. The author set out to investigate whether the (*Z*)-alkene present in the initial model system was an essential motif and thus to probe whether saturated spiroketal rings could be synthesised. The formation of model substrates **226** and **227** for the formation of 6,6- and 6,5-spiroketals **228** and **229** respectively was envisaged (Scheme 89).

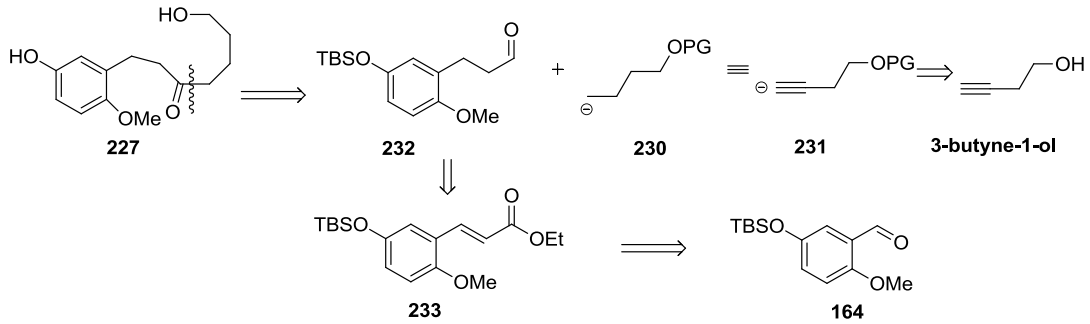


226/227 **228/229**

Scheme 89 - Proposed synthesis of spiroketals **228** and **229**; n =1, 2 respectively

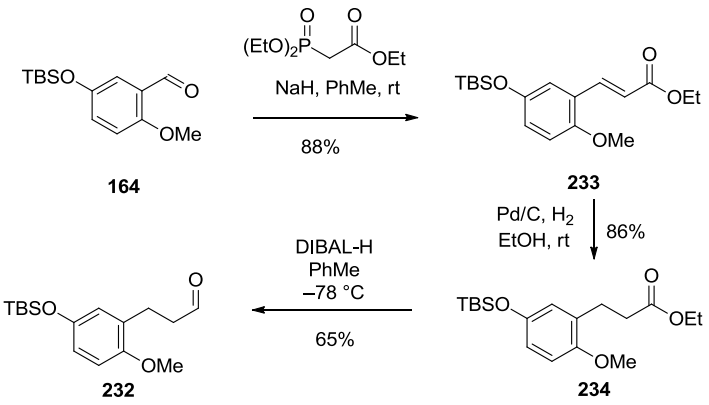
2.3.1 Synthesis of Hydroxyphenol 227

Retrosynthetic analysis of hydroxyphenol **227** (n=2) was carried out in similar fashion to previous model substrates (Scheme 90). Retrosynthetic cleavage of a central C–C bond revealed a nucleophilic synthon **230** which corresponded to an acetylide fragment **231**, and electrophilic aldehyde fragment **231**. In the forward synthetic plan it was envisaged that the alkyne moiety would be fully hydrogenated to the desired saturated alkyl chain. Formation of the aldehyde fragment **232** was anticipated *via* Horner-Wadsworth-Emmons olefination of the previously synthesised aryl aldehyde **164**, with subsequent oxidation level transformations.



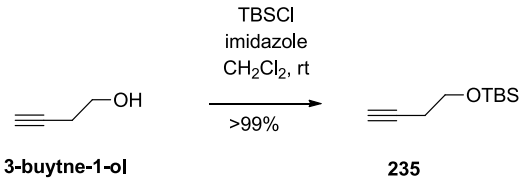
Scheme 90 - Retrosynthetic analysis of hydroxyphenol **227**

Following this retrosynthetic pathway, the synthesis of hydroxy phenol **227** was achieved in ten synthetic steps. The aryl aldehyde substrate **164** was synthesised in the same novel steps as previously described. Firstly, Horner-Wadsworth-Emmons olefination of aldehyde **164**, using triethyl phosphonoacetate, gave access to (*E*)-ester **233** (Scheme 91). Upon isolation of the novel (*E*)-ester **233**, hydrogenation of the alkene moiety over Pd/C gave smooth conversion to the ester **234**. Following this, the ester **234** was directly reduced to the aldehyde **232** using DIBAL-H at –78 °C.



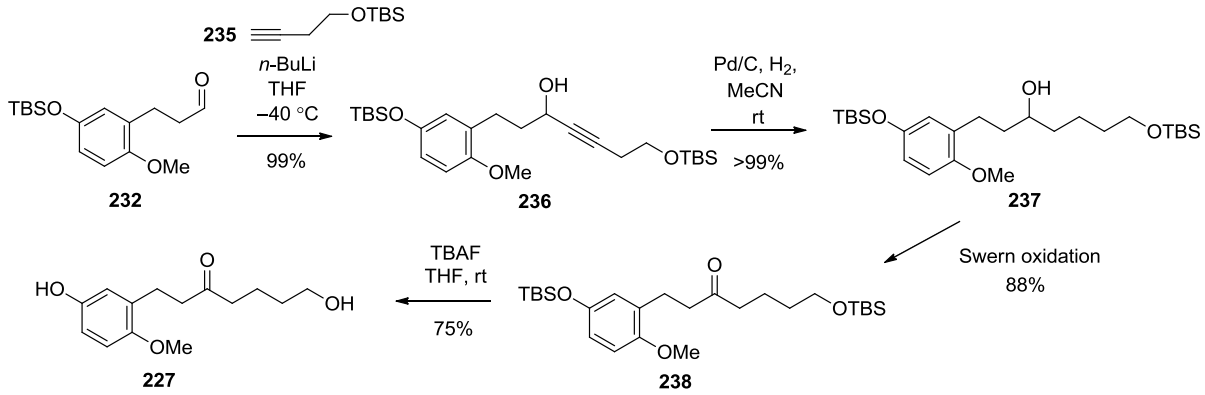
Scheme 91 - Synthesis of aldehyde **232**

Silyl protection of 3-butyne-1-ol was achieved *via* a known procedure using TBSCl and imidazole, to give alkyne **235** in quantitative yield (Scheme 92).[86]



Scheme 92 - Synthesis of alkyne **235**

Treatment of alkyne **235** with *n*-BuLi mediated the *in situ* formation of the lithium acetylide anion, to which aldehyde **232** was added, giving alcohol **236** after protic work-up (Scheme 93). Following this, the alkyne **236** was hydrogenated over Pd/C in MeCN to give alcohol **237**. The secondary alcohol **237** was oxidised using a Swern oxidation to give the ketone **238**. Finally, the concurrent removal of both TBS groups was achieved using TBAF to give hydroxyphenol **227**.



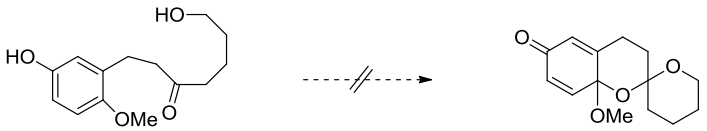
Scheme 93 - Synthesis of hydroxyphenol **227**

2.3.2 Attempted Spiroketalisation of Hydroxyphenol 227

Upon the synthesis of hydroxyphenol **227** spiroketalisation *via* cascade oxidative dearomatisation was examined. Treatment of hydroxyphenol **227** with $PhI(OAc)_2$ resulted in the consumption of starting material as indicated by TLC. Removal of the volatiles *in vacuo* and observation of the crude reaction mixture by ^1H NMR spectroscopy indicated a complex mixture of unidentifiable products, with no

indication of the expected cyclisation products. This reaction was repeated with an excess of pyridine to buffer the acetic acid by-product and monitoring by ^{1}H NMR spectroscopy again indicated a complex mixture with no signs of the expected cyclisation products. TLC analysis of these reactions only gave material on the baseline (apart from iodobenzene on the solvent front), even in neat EtOAc. Treatment of hydroxyphenol **227** with phenyliodine *bis*(trifluoroacetate) (PIFA) gave an unexpected deep blue/green solution, with the ^{1}H NMR spectrum after evaporation of the solvent revealing a complex mixture of unidentified products.

Table 4 - Conditions for attempted spiroketalisation of **227**



227 **229**

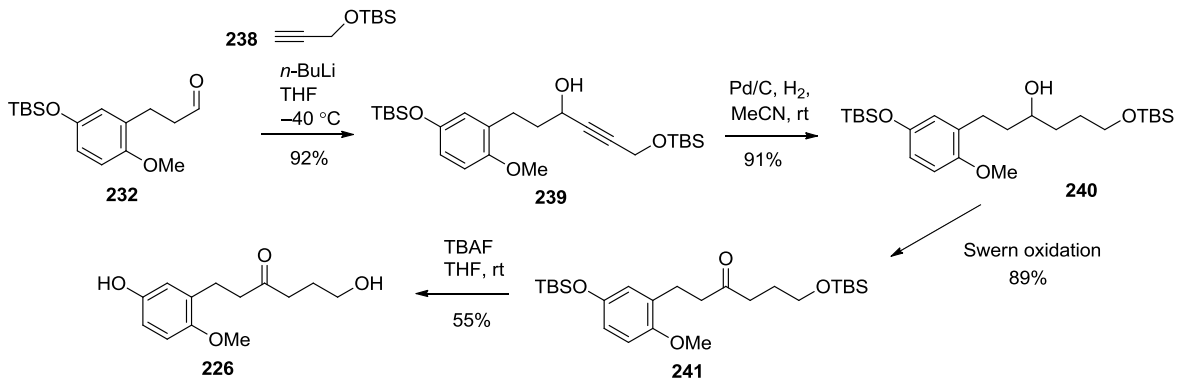
Conditions	Conversion (%)
$PhI(OAc)_2$ (1.7 eq.), MeCN, 1h	0
$PhI(OAc)_2$ (1.5 eq.), pyridine (3.0 eq.), MeCN, 16 h	0
PIFA (2.1 eq.), pyridine (2.7 eq.), MeCN,1 h	0

The fate of the starting material in these attempts could not be determined. It was suggested that the dearomatised products may be prone to rapid degradation *via* facile elimination of the methoxy substituent or other unknown processes. Alternatively, it was proposed that the acetic acid by-product of the oxidants may participate in nucleophilic competition with the desired intramolecular cyclisation.

Contemporaneously to the synthesis of hydroxyphenol **227**, the synthesis of analogous hydroxyphenol **226**, for an investigation into the synthesis of analogous 6,5- spiroketal **228**, was conducted.

2.3.3 Synthesis of Hydroxyphenol 226

The synthesis of analogous hydroxyphenol **226** was achieved using the same synthetic strategy as for hydroxyphenol **226** (Scheme 94). The silyl protection of propargyl alcohol was achieved using the reported procedure with TBSCl and imidazole to give alkyne **238**.[87] The subsequent four steps analogous to those previously conducted were successful to give hydroxyphenol **226**.

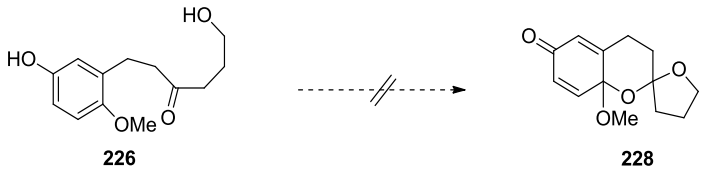


Scheme 94 - Synthesis of hydroxyphenol **226**

Attempts for the spiroketalisation of **226** were conducted in similar fashion to the previous substrate (Table 5).

2.3.4 Attempted Spiroketalisation of Hydroxyphenol 226

Table 5 - Attempts towards spiroketal **228**



226 **228**

Conditions	Conversion (%)
$PhI(OAc)_2$ (1.0 eq.), MeCN, 1 h	0
$PhI(OAc)_2$ (1.5 eq.), MeCN, 16 h	0
$PhI(OAc)_2$ (1.0 eq.), pyridine (1.8 eq.), MeCN, 16 h	0

In similar fashion as before, under the attempted conditions, evidence for the formation of the desired 6,5-spiroketal **228** was not observed, with apparent complete degradation to unidentifiable mixtures.

2.2.5 Conclusion

Seemingly, the presence of the (*Z*)-alkene moiety is imperative for the previously observed spiroketalisation by cascade oxidative dearomatisation to occur under the conditions tested. Alternatively, the (*Z*)-alkene may prevent degradation of the dearomatised products. Certainly, the (*Z*)-alkene forces the ketone into fairly close proximity to the aromatic ring, which may be essential for cyclisation to occur under the tested conditions.

In conclusion, it was found that saturated hydroxyl phenol substrates **226** and **227** do not allow the isolation of spiroketals **228** and **229** respectively, under similar conditions used for the previous synthesis of spiroketals **147a/b**. At this point in this work the author was discouraged towards further exploring the use of the demonstrated spiroketalisation by cascade oxidative dearomatisation method.

As previously discussed, the utilisation of this method for the total synthesis of phorbaketal A was proved unsuitable. At this point in this work, two total syntheses of alotaketal A had been reported[31,32] and so an investigation into alternative synthetic staregies towards the alotaketals and phorbaketals would have reduced novelty.

With an eagerness to further explore the synthesis of the discussed emerging family of sesterterpenoid secondary metabolites, and having gained aptitude for the synthesis of complex terpenoid structures, the author was drawn towards the intriguing sesterterpenoid natural product phorone A.

3. Results and Discussion II

3.1 Introduction to Phorones A and B

Phorone A (**24**) is a sesterterpenoid isolated by Wang *et al*. from the marine sponge *Phorbas* sp. in 2012.[22] Very recently in January 2015, the isolation of phorone B (**242**) was reported by Woo *et al.* from the marine sponge *Clathria gombawuiensis* (Figure 18). [22]

These natural products belong to a family of biosynthetically related sesterterpenoids, their structure deriving from the alotane skeleton also possessed by the phorbaketals and alotaketals. Phorones A and B (**24** and **242**) are the only known natural products possessing the 'phorane' carbon skeleton. Added to this, they both possess highly novel and intriguing *cis*-fused seven-membered rings. Phorone B was found to be moderately active towards some cancer cell lines.[22]

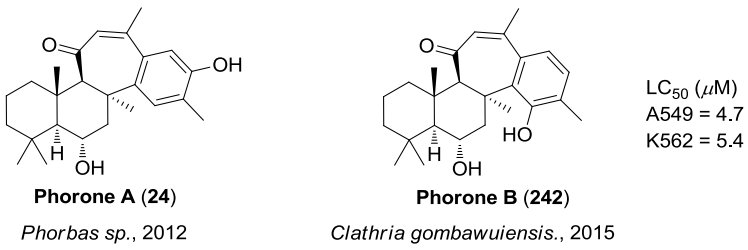
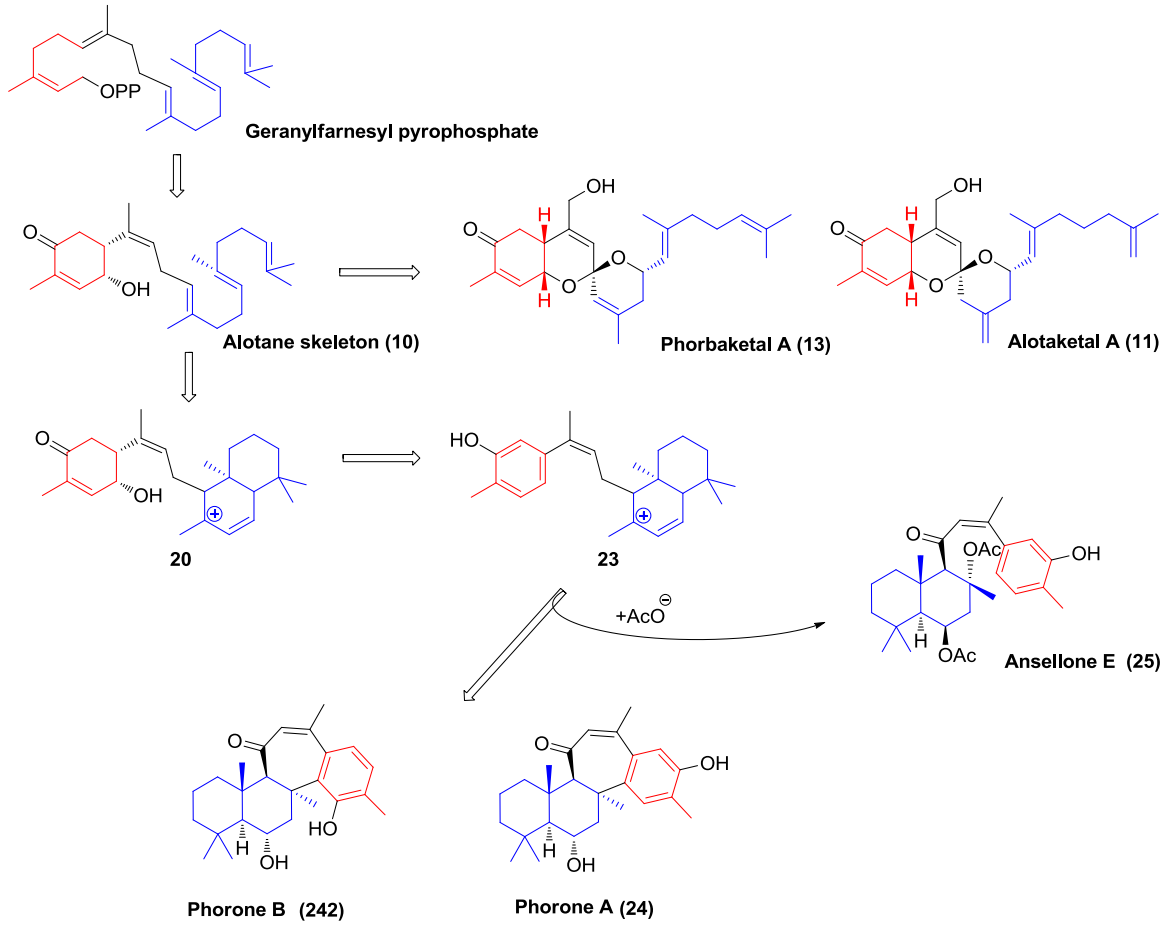


Figure 18 - Phorone A (**24**) and phorone B (**242**)

The proposed biosynthesis of these sesterterpenoids suggests a key electrophilic aromatic substitution process *via* a carbocation intermediate *e.g.* **23** (Scheme 95). This electrophilic aromatic substitution can occur with *para*- or *ortho*-regioselectivity to the phenol, to give phorone A or phorone B respectively. The formation of phorone B *via* this process requires greater steric demand, forming four neighbouring substituents on the aromatic ring. It is proposed that phorone A is the major product and phorone B the minor product in this biosynthetic process.

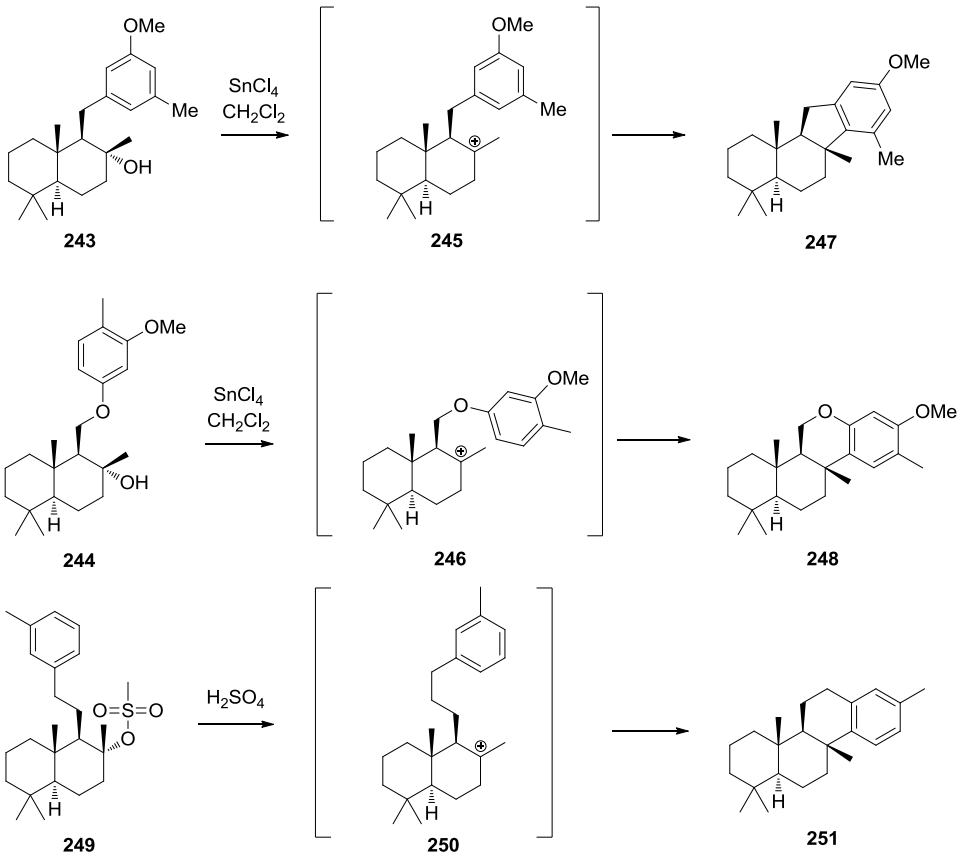
Alternative trapping of the carbocation intermediate **23** with an acetate anion, and subsequent oxidation processeses, are proposed to proceed to the related sesterterpenoid natural product ansellone E (**25**).



Scheme 95 - Proposed biosynthesis of phorone A (**24**) and phorone B (**242**)

Examples of carbocation intermediates similar to **23** and subsequent electrophilic aromatic substitution processes are revealed in the synthesis of some analogous substrates in the literature (Scheme 96).[88] For example, treatment of alcohols **243** and **244** with Lewis acid ($SnCl_4$) promotes formation of the carbocation intermediates (**245** and **246** respectively) which are prone to nucleophilic attack from aromatic systems to form *trans*-fused five- and six-membered rings **247** and **248** respectively. Alternatively, as demonstrated by Corey *et al.*,[89] a mesylate leaving group (**249**)

allows formation of the carbocation intermediate **250** upon treatment with H_2SO_4, resulting in subsequent formation of *trans*-fused six-membered ring **251**. Presumably these examples result in the formation of *trans*-fused rings due to the steric demand provided by the substituted decalin system, in particular the axial methyl groups.



Scheme 96 - Analogous examples of electrophilic aromatic substitution

In light of this precendence, the *cis*-fused stereochemistry of the seven-membered ring possessed by phorone A and B was somewhat unexpected. It was thought that the (*Z*)-alkene moiety possessed by phorone A, or the increased size of the ring, may someway favour formation of the *cis*-fused ring. It is proposed that cyclisation results in steric clashing with the neighbouring axial methyl groups, which may promote formation of the *trans*-fused ring (Figure 19). The author suggests that the oxygen lone pair of the secondary alcohol may coordinate to the carbocation and block attack

of the aromatic moiety from the lower face, to disfavour formation of the *trans*-fused ring. It is plausible that a *trans*-fused phorone A natural product does exist, but has not yet been isolated.

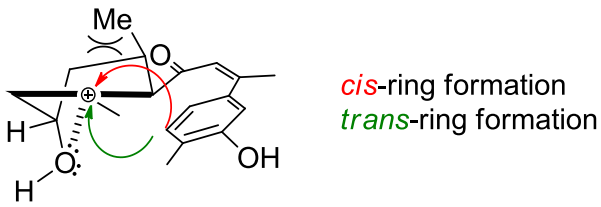


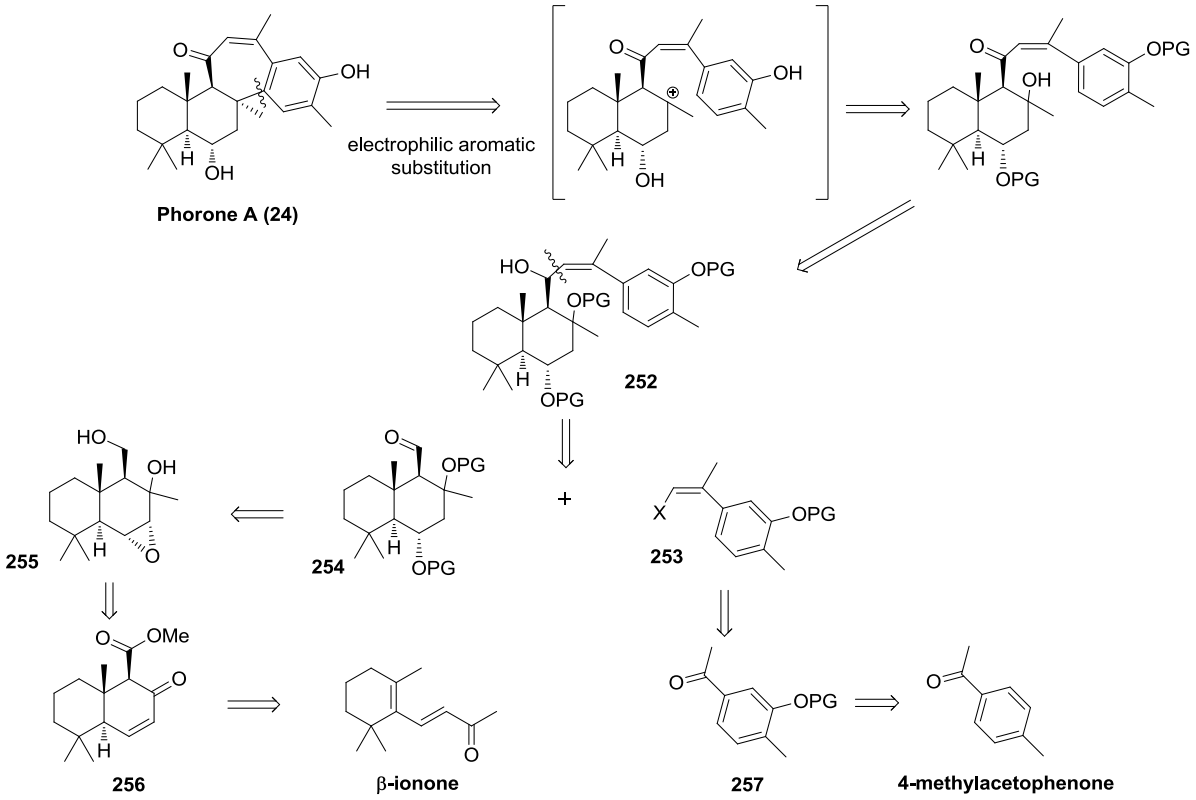
Figure 19 - Proposed model for *cis*- or *trans*-ring formation towards phorone A

3.2 Retrosynthetic Analysis of Phorones A and B

The planned total synthesis of phorone A discussed herein is believed to be partially biomimetic since it involves formation of carbocation intermediate **23**, or an analogue, for the formation of the *cis*-fused seven-membered ring *via* electrophilic aromatic substitution. After the recent isolation of phorone B, it was anticipated that the key electrophilic aromatic substitution step would give a mixture of phorones A and B.

Retrosynthetic analysis of phorone A (**24**) involved initial retrosynthetic cleavage of the C–C bond directly linking the aromatic system to the decalin system (Scheme 97). In the biosynthesis of phorones A and B the electrophilic synthon could equate to a hydroxyl, acetyl (refer to ansellone E) or protonatable alkene group. The synthesis of ansellane alcohol **252** was envisaged to proceed with the addition of a (*Z*)-haloalkene fragment **253** to aldehyde fragment **254** *via* a halogen-metal exchange method, and thus relied upon similar chemistry to that experienced in the previous phorbaketal A project (results & discussion I). The synthesis of aldehyde fragment **254** was planned over several steps from epoxide **255**, *via* regioselective reductive

opening of the epoxide moiety, for installation of the required secondary alcohol. The synthesis of epoxide **255** was anticipated to proceed over several steps from known ester **256**. The synthesis of (*Z*)-haloalkene fragment **253** was anticipated to proceed *via* an olefination method from acetophenone **257**.



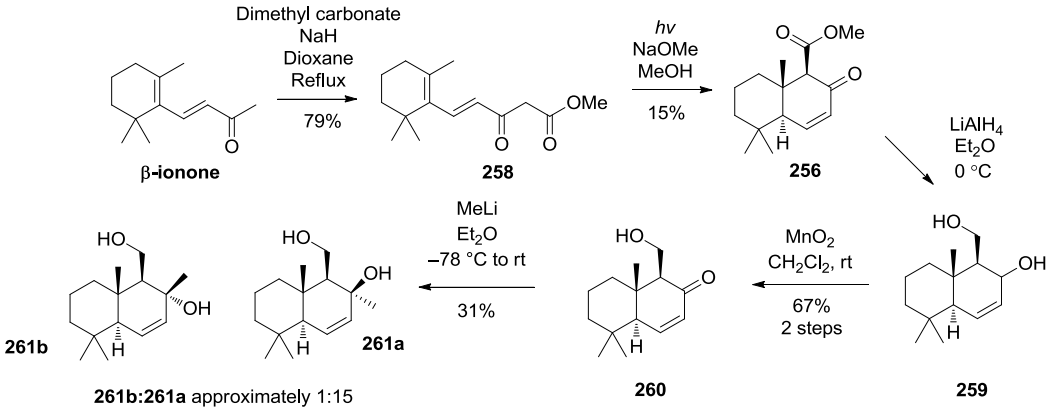
Scheme 97 - Retrosynthetic analysis of phorone A (**24**)

3.3 Synthesis and Reactivity of Aldehyde Fragment 254 Analogues

This work was initiated with synthetic efforts towards aldehyde fragment **254**. Using a reported procedure, the synthesis of ester **258** was achieved by the treatment of β-ionone with dimethyl carbonate and sodium hydride in refluxing dioxane (Scheme 98).[90] Photochemically-induced cyclisation of the ester **258** to the *trans*-decalin ester **256** was achieved using the procedure reported by White *et al.*, by irradiation of the ester **258**, in the presence of NaOMe, with a 400 W mercury lamp photochemical

reactor* over 24 h.[91] Typically, photochemical reactions were run on 10 g batches, with 4 × 10 g reactions giving around 2–3 g of ester **256**. Albeit highly inefficient and labour intensive, this synthetic step facilitated a rapid increase in molecular complexity, with the formation of three required chiral centres. Moreover, β-ionone is inexpensive† and the ester **258** could be synthesised in up to 60 g quantities in one day.

Following previously reported procedures, treatment of the ester **256** with $LiAlH_4$ facilitated global reduction of the ester and ketone functionalities to give diol **259**. Selective oxidation of the allylic alcohol **259** was achieved using MnO_2 to give ketone **260**. Subsequent to this, the ketone **260** was then treated with MeLi to give diol **261a** as the major diastereomeric product, with formation of the drimane carbon skeleton.[92] For all steps described henceforth, the formed diasteteromers were used as a mixture. Confirmation of each diastereomers stereochemistry were made during the characterisation of later synthesised substrates (*vide infra*).



Scheme 98 - Synthesis of diol **261**

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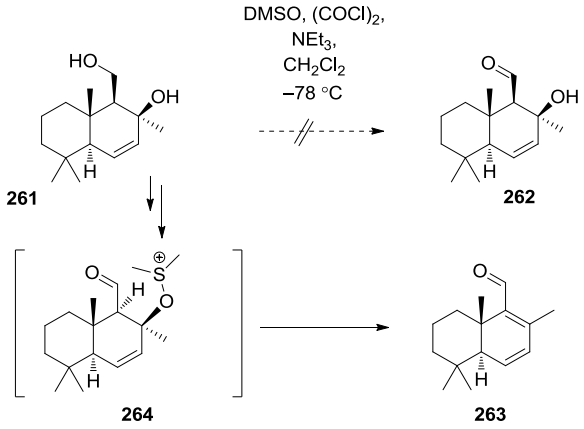
* Medium pressure 400 W mercury lamp, with an immersion well.

† 100 g for £16.50 from sigmaaldrich.com

A key future step would involve addition of (Z)-alkene fragment **253** to aldehyde **254** analogues, synthesised by oxidation of the primary alcohol possessed by diol **261**. Thus, methods for the oxidation of primary alcohol **261** to the aldehyde functional group were probed.

Initially Swern oxidation was attempted for the synthesis of aldehyde **262** from diol **261**. Analysis of the reaction mixture by ^{1}H and ^{13}C NMR indicated that elimination of the tertiary alcohol had occurred to give dienal **263**. The main new aldehyde signal resonated as a singlet at 10.06 ppm. It was proposed that this elimination may occur *via* alkoxysulfonium ion intermediate **264**, mediating elimination of the oxygen atom with the neighbouring *anti*-conformed hydrogen atom. Alternatively, HCl generated by oxalyl chloride* could facilitate the elimination by protonation of the tertiary alcohol. Nevertheless, this result was a positive indication that the tertiary alcohol could readily eliminate under particular conditions, as was required for a later step in the projected synthesis of phorone A.



Scheme 99 - Degradation of diol **261** during Swern oxidation

Undeterred by this result, it was subsequently found that utilisation of Dess-Martin periodinane mediated selective oxidation of the primary alcohol **261** to the aldehyde

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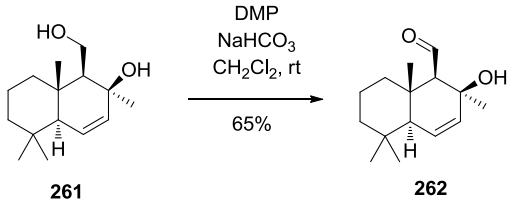
* DMSO was not purified before use and had undetermined H_2O content.

262 (Scheme 100) without any problems. The reaction was buffered with sodium bicarbonate as it was feared the AcOH by-product of the oxidant could facilitate the previously encountered elimination of the tertiary alcohol.

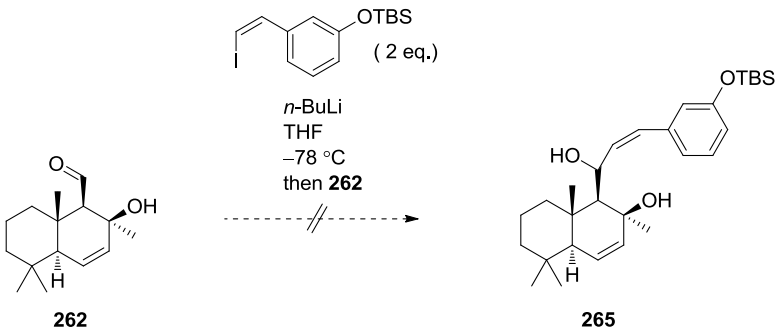


261 **262**

Scheme 100 - Synthesis of aldehyde **262**

Upon the synthesis of aldehyde **262** it was decided to test whether addition of the (*Z*)-iodoalkene **141**, *via* the organolithium species generated in previous work, could be achieved. The (*Z*)-iodoalkene **141** would model the addition of the synthetically more challenging (*Z*)-haloalkene fragement **253,** which would later be required.

Treatment of (*Z*)-Iodoalkene **141** with *n*-BuLi was followed by the addition of aldehyde **262** (Scheme 101). After protic work-up analysis of the crude ^{1}H NMR revealed that no resonating signal corresponding to a newly formed carbinol proton could be found and new aldehyde signals resonated between 9.7–10.1 ppm. The major new aldehyde signal resonated as a singlet, indicative of a similar elimination of the tertiary alcohol as was previously observed.



262 **265**

Scheme 101- Attempted addition to aldehyde **262**

To circumvent the issues involving elimination of the tertiary alcohol, it was decided to investigate the use of hydroxyl protecting groups. As aldehyde **262** was also susceptible to degradation upon storage, it was hoped that protection of the tertiary alcohol would additionally prevent or slow this degradation.

It was decided to install a TMS ether protecting group on the tertiary hydroxyl group. This would involve protection of both hydroxyl groups possessed by diol **261** and subsequent selective removal of the primary TMS ether. This selectivity was thought to be achievable since primary TMS ethers are vastly more labile than tertiary TMS ethers. Although TMS ethers are typically very labile protecting groups, it was proposed that their employment may be suitable in the sterically crowded environment provided by the *trans*-decaline system.

Firstly, diol **261** was treated with TMSCl in the presence of imidazole and DMAP to give di-TMS ether protected substrate **266**. For selective removal of the primary TMS ether, the substrate **266** was firstly dissolved in MeOH:petrol (9:1)* and then oven-dried K_2CO_3 was added. This assisted methanolysis of the primary TMS ether over 4 h to give alcohol **267**. The TMS protected tertiary alcohol remained intact using these mild conditions. The isolated primary alcohol **267** was then oxidised to

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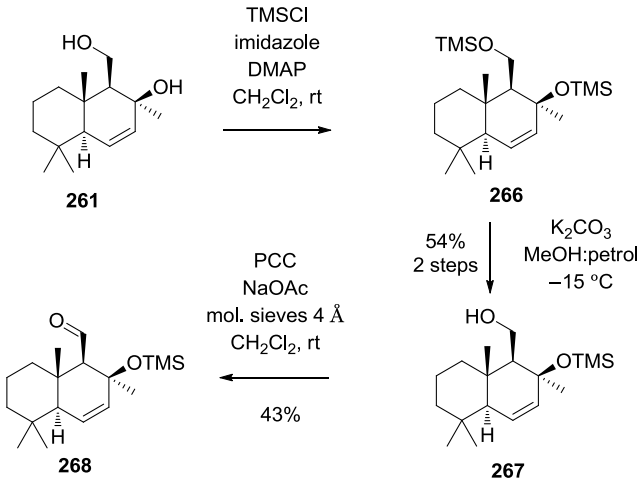
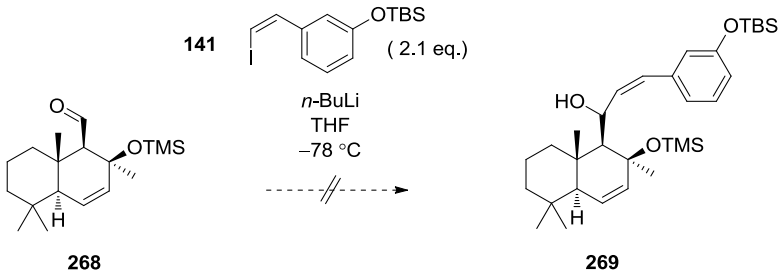
* Petrol was required to solubilise the apolar substrate **266** in MeOH

aldehye **268** using pyridinium chlorochromate (PCC), buffered with NaOAc (Scheme 102).



Scheme 102 - Synthesis of aldehyde **268**

Upon the successful synthesis of tertiary alcohol protected aldehyde **268**, the addition of (*Z*)-iodoalkene **141** was again investigated. Similarly to previous examples, (*Z*)-iodoalkene **141** was treated with *n*-BuLi at –78 °C, followed by the addition of aldehyde **268**. After protic work-up analysis of the crude ^{1}H NMR spectrum revealed several new aldehyde resonances between 9.5–9.8 ppm and no signal corresponding to a newly formed carbinol proton could be found.

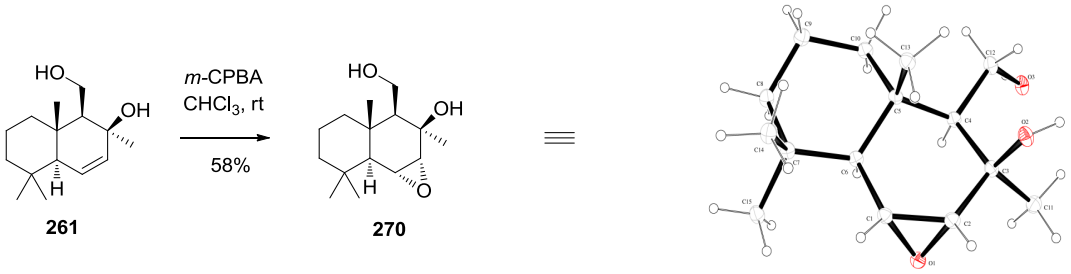


Scheme 103 - Attempted addition of (Z)-iodoalkene **141** to aldehyde **268**

Following these results, it was decided to investigate installation of the secondary alcohol possessed by phorone A. It was thought that removal of the alkene may

dissuade elimination and the other degradation pathways encountered thus far. As was previously discussed in the retrosynthetic analysis, the alkene moiety possessed by the decalin system could allow installation of an epoxide which could be reductively ring-opened for installation of the required secondary alcohol possessed by phorone A. At the time it was unknown whether epoxidation would occur with *anti*- or *syn*-diastereofacial selectivity relative to the axial tertiary alcohol.

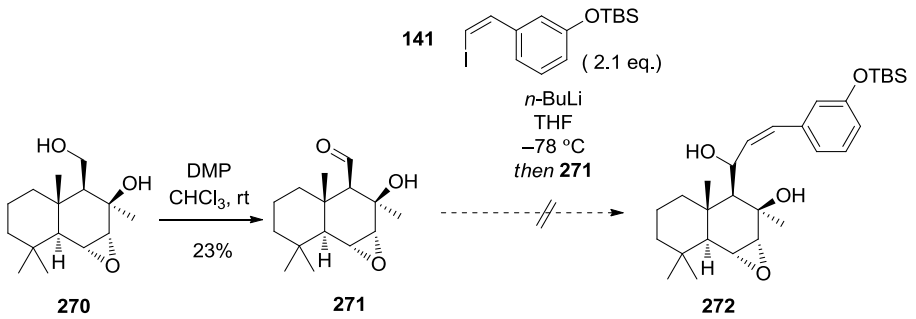
To investigate this, diol **261** was treated with the alkene epoxidising agent *m*-CPBA. Gratifyingly, it was found that *m*-CPBA facilitated epoxidation with *anti*-diastereofacial selectivity to give epoxide **270** (Scheme 104). To the author's delight, the required stereochemistry of the epoxide **270** was confirmed by X-ray crystallographic analysis (Figure 20). The observed *anti*-diastereofacial selectivity may be due to unfavourable steric interactions between the approaching peracid and the two axial methyl groups of the decalin system, favouring approach from the opposite face. This unfavourable steric demand must outweigh the favourable effect of hydrogen bonding between the axial tertiary alcohol and the peracid, as is normally observed in cyclic allylic alcohol systems to give *syn*-diastereofacial selectivity for epoxidation.[93]



Scheme 104 - Synthesis of epoxide **270**; **Figure 20 -** ORTEP of epoxide **270**

Upon the installation of the epoxide, it was decided to investigate the addition of (*Z*)-iodoalkene to an aldehyde analogue. The primary alcohol **270** was oxidised to the

aldehyde **271** using DMP, in a low, albeit unoptimised 23% yield. Addition of the (*Z*)-iodoalkene **141** *via* the organolithium species formed *in situ*, proved unsuccessful. Analysis of the ^{1}H NMR spectrum after protic work-up did not reveal any of the desired carbinol proton signals. Added to this, several new aldehyde signals resonated between 9.7–10.0 ppm.

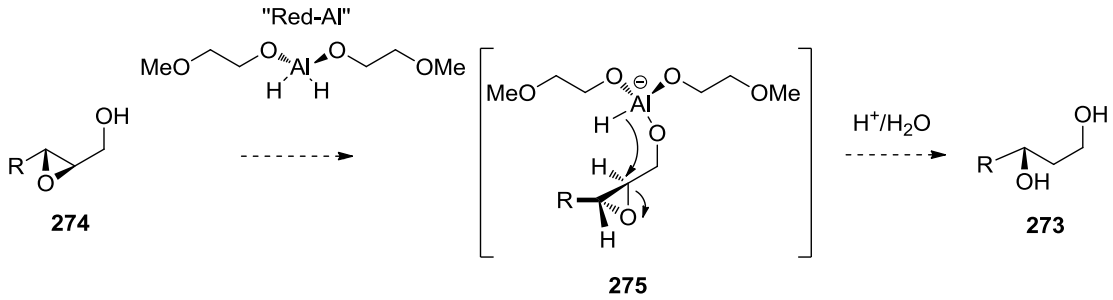


Scheme 105 - Synthesis of aldehyde **271** and attempted addition of **141**

The author was undeterred by the failure to add (*Z*)-iodoalkene **141** to a range of analogous aldehydes, and it was decided to focus towards synthesising structures closer resembling phorone A, in the hope that 'natural analogues' may demonstrate better stability and reactivity. To this end, it was decided to explore the ring-opening of epoxide **270** in order to install the desired secondary alcohol possessed by phorone A.

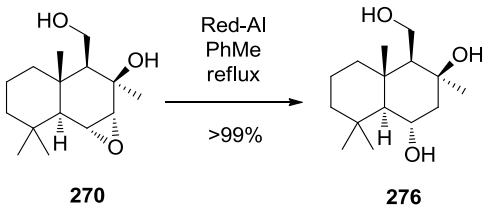
For the reductive ring opening of epoxide **270**, regioselective attack of the hydride to form a 1,3-diol species *e.g.* **273** was required (Scheme 106). Red-Al is a commonly utilised reagent for the highly selective synthesis of 1,3-diols by regioselective reductive ring-opening of 2,3-epoxy alcohols *e.g.* **274**. The initial addition of Red-Al to such 2,3-epoxy alcohols results in the coordination of aluminium to the alcohol, releasing hydrogen gas, to give trialkoxy aluminate intermediate **275**. This is followed by an intramolecular transfer of a hydride from aluminium, resulting in the

selective formation of 1,3-diols *e.g*. **273**. Attack to form the 1,2-diol does not usually occur because the approach path of the hydride to form this species cannot be collinear to the C–O bond which must be broken. Other reducing agents, such as DIBAL-H, do not allow this selectivity of ring opening, and usually give large amounts of 1,2-diol product.



Scheme 106 - 2,3-Epoxy alcohols reductive ring opening using Red-Al

To investigate this pathway, 2,3-epoxy alcohol **270** was treated with an excess of Red-Al at room temp. Monitoring of the reaction by TLC analysis revealed no reaction had occurred over 4 h. Eventually it was found that heating the reaction to 110 °C over 16 h allowed for regioselective ring-opening of the epoxide to give 1,3-diol **276** (Scheme 107). The newly formed alkoxy proton resonated as a clear triplet of doublets in the ^{1}H NMR spectrum. Comparison of the alkoxy resonance with that reported for phorone A revealed a very close match: for phorone A [4.3 ppm, td, J = 10.8, 3.1 Hz], for **276 [**4.1 ppm, td, J = 11.0, 4.0 Hz]. Further confirmation of the stereo- and regiochemistry was obtained by X-ray crystallographic analysis of a subsequently synthesised substrate (*vide infra*).

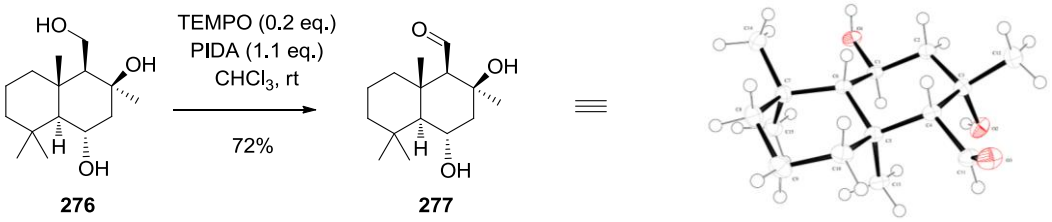


270 **276**

Scheme 107 - Reductive ring opening of 2,3-epoxy alcohol **270** using Red-Al

Having triumphed in the stereo- and regioselective installation of the penultimate chiral centre possessed by phorone A (**24**), efforts were focused towards the oxidation of the primary alcohol **276** to an aldehyde, with which subsequent addition steps or protecting group strategies could be explored.

Chemoselective oxidation of the primary alcohol to the aldehyde functionality, in the presence of the secondary and tertiary alcohols was required. Frequently used reagents for the selective oxidation of primary alcohols to aldehydes employ catalytic amounts of TEMPO with a co-oxidant.[94] It was found that treatment of triol **276** with TEMPO (0.2 eq.) and co-oxidant $PhI(OAc)_2$ (1.1 eq.) resulted in smooth conversion to aldehyde **277,** with no apparent oxidation of the secondary or tertiary alcohols (Scheme 108). Upon the isolation of large crystals of the aldehyde **277**, the stereo- and regiochemistry of the secondary alcohol and aldehyde moieties were confirmed through X-ray crystallographic analysis (Figure 21). Upon storage of the aldehyde **277** in a fridge, no epimerisation of the aldehyde group was observed.



276 **277**

Scheme 108 - Formation of aldehyde **277**; **Figure 21** - ORTEP image **277***

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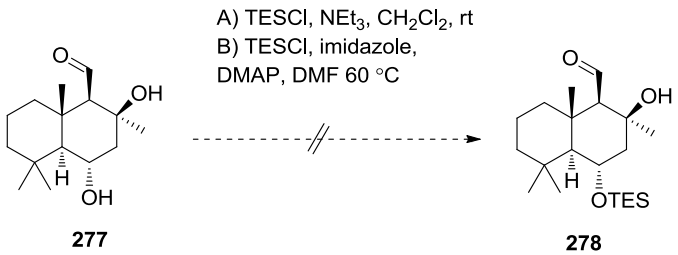
* Mirror image of **277** to that depicted in Scheme 108

Addition of a highly basic organometallic species to the di-hydroxy group bearing aldehyde **277** seemed unfeasible since a large excess of the organometallic species would be required to generate a potentially unstable di-alkoxide species. Thus, protecting group strategies for the protection of the hydroxyl group(s) possessed by aldehyde **277** were investigated.

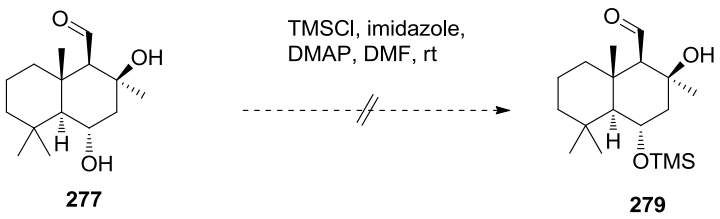
It was proposed that triethylsilane (TES) protection would be most suitable for protection of the secondary alcohol **277**. As previously discussed, this silyl group is commonly used for the protection of secondary alcohols due to its 'mid-range susceptibility to hydrolysis' relative to other common silyl protecting groups and can normally be removed with fluoride sources or other mild protocols. Aldehyde **277** was treated with TESCl, triethylamine and DMAP (cat.). Remarkably, after 16 h the starting material remained unreacted. A second attempt involved treatment of aldehyde **277** with TESCl, imidazole and DMAP (cat.) in DMF, with heating to 60 °C. Following the reaction by TLC analysis over 72 h again revealed only starting material. It was proposed that the hydroxyl groups were very poorly nucleophilic, perhaps due to the steric demand of the substituted decalin system.



Scheme 109 - Attempted TES protection of secondary alcohol **277**

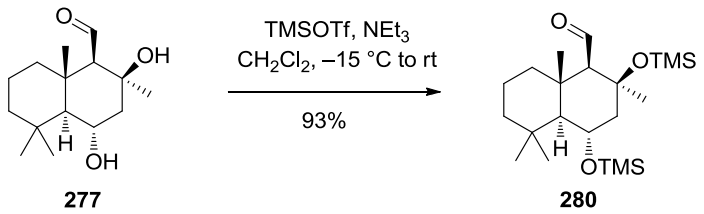
With the hypothesis that the secondary alcohol was in a very sterically crowded environment, it was proposed that the smaller and typically very labile TMS

protecting group may prove robust enough for utilisation in the projected synthetic steps. Surprisingly, treatment of aldehyde **277** with TMSCl, imidazole and DMAP (cat.) gave no reaction over 24 h.



Scheme 110 - Attempted TMS protection of secondary alcohol **277**

It became evident that for protection of the alcohol(s), a stronger silylating agent (*i.e*. stronger electrophile) than silyl chlorides would be required. Indeed, treatment of aldehyde **277** with the potent silylating agent TMSOTf (2 eq) facilitated swift protection of the secondary *and* tertiary alcohols (Scheme 111).



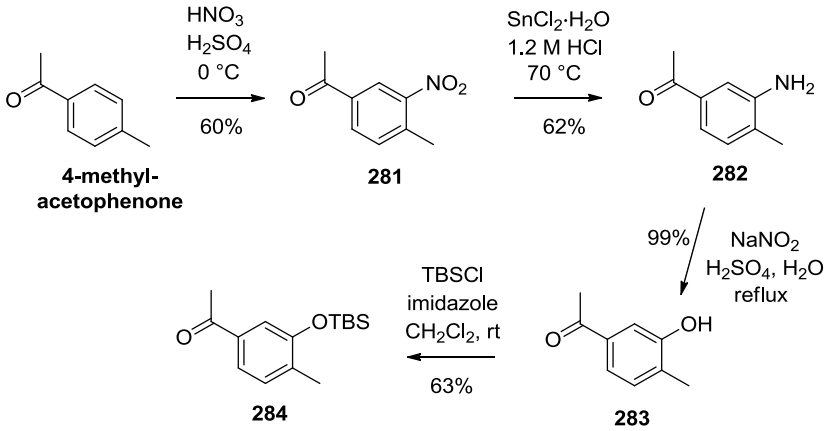
Scheme 111 - TMS protection of secondary and tertiary alcohols to **280**

Contemporaneously to the investigations leading to the synthesis of aldehyde **280**, work was also focused on the synthesis of (*Z*)-haloalkene fragment **253**. This will now be discussed, and work towards its addition to aldehyde **280** will be discussed in due course.

3.4 Synthesis of (*Z*)-Haloalkene Fragment 253

Initial work towards the synthesis of (*Z*)-haloalkene fragment **253** involved the synthesis of phenolic acetophenone fragment **257** *via* some previously reported procedures.[95] Firstly, commercially available 4-methyl-acetophenone was subjected to nitration using HNO_3 and H_2SO_4, to give 3-nitro-4-methyl-acetophenone (**281**) as the sole product. Reduction of the nitro group to amine **282** was initially achieved *via* hydrogenation over Pd/C. Unfortunately, this convenient procedure was not scalable; on a scale >3 g the same conditions gave a range of unidentified products. Alternatively, reduction of the nitro group to aniline **282** was achieved using stannous chloride dihydrate in 1.2 M HCl, although frustratingly giving abundant amounts of insoluble and toxic tin by-products during work-up.

With the formation of aniline **282**, the synthesis of phenol **283** was achieved *via* a diazotisation step using sodium nitrite, with the *in situ* substitution of the diazonium ion by water*. The phenol **283** was then protected as its TBS silyl ether by treatment with TBSCl in the presence of imidazole, to give the novel acetophenone **284**.



Scheme 112 - Synthesis of acetophenone **284**

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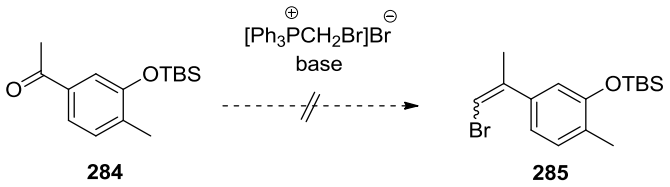
* Take care - potentially explosive diazonium salt!

For the synthesis of the (*Z*)-haloalkene fragment **253** from acetophenone **284** utilisation of a Wittig olefination method was planned. Initial investigations using bromo-methyl triphenylphosphonium for the formation of (*Z*)-bromoalkene **285** were conducted (Table 6). The Wittig salt was deprotonated with NaHMDS, and then acetophenone **284** was added. After monitoring over 16 h, ^{1}H NMR analysis after protic work-up revealed some trace alkene region signals, but predominantly unreacted starting material. Subsequently, the salt was treated with potassium *t*-butoxide, which was again followed by addition of acetophenone **284**. After 16 h analysis of the reaction mixture indicated, in similar fashion, that no/residual alkene formation had occurred. Also, using potassium *t*-butoxide and heating to 100 °C for 16 h, ^{1}H NMR spectroscopy analysis of the crude mixture gave the same result. In a final attempt, sodium hydride was employed as the base, and after heating at 50 °C for 16 h ^{1}H NMR analysis of the crude mixture revealed no olefination had occured. It should be noted that examples for the formation of haloalkenes from acetophenone analogues *via* halogenated Wittig reagents are scarcely found in the literature. An alternative olefination method was sought.

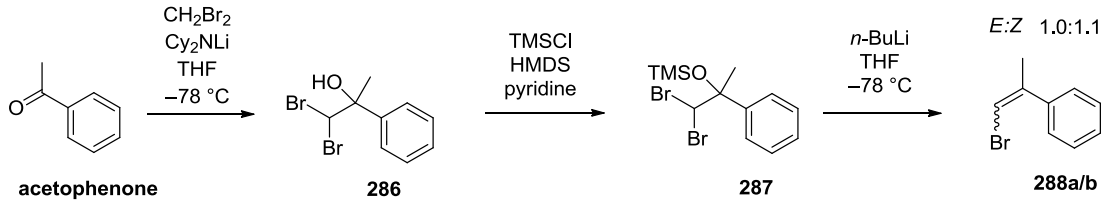
Table 6 - Conditions for attempted Wittig olefination of acetophenone **284**



284 **285**

Conditions	Yield (%)
t-BuOK, THF, –78 °C to r.t, 16 h	0
t-BuOK, PhMe, 100 °C, 16 h	0
NaHMDS, THF, 16 h	0
NaH, THF, 50 °C, 16 h	0

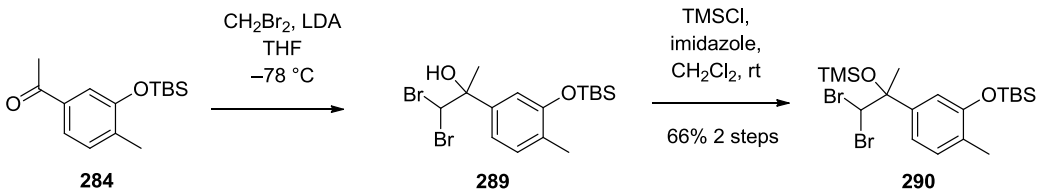
Of the few known methods for such a transformation, trisubstituted bromoalkene formation from acetophenone has been reported by Barluenga *et al*.[96] This method involved addition of dibromomethane deprotonated with $LiNCy_2$ to acetophenone to form the tertiary alcohol **286** (Scheme 113). Subsequent to this addition, trimethylsilylation of **287** with HMDS was followed by treatment with *n*-BuLi, to give *mono*-halogenated olefins **288** in 1.0:1.1 *E:Z* ratio. An investigation was initiated into the employment of this largely unexploited olefination method for the synthesis of (*Z*)-haloalkene fragment **253**.



acetophenone **286** **287** **288a/b**

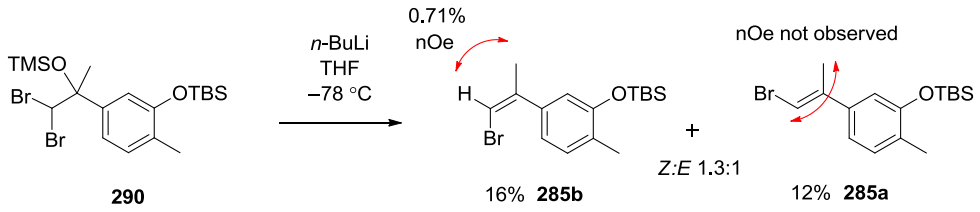
Scheme 113 - Barluenga synthesis of bromoalkenes **288a/b**

Slightly modified conditions, reported by Ando *et al.*, were employed towards the synthesis of (*Z*)-bromoalkene **285**, using more readily available bases: lithium diisopropylamine (LDA) in the initial addition step and imidazole as the base during the trimethylsilylation step.[97] Treatment of acetophenone **284** with dibromomethane which had been deprotonated by LDA facilitated smooth conversion to tertiary alcohol **289**. Subsequently, the alcohol **289** was protected as the trimethylsilyl ether by treatment with TMSCl in the presence of imidazole, to give dibromo species **290** (Scheme 114).



Scheme 114 - Synthesis of dibromo species **290**

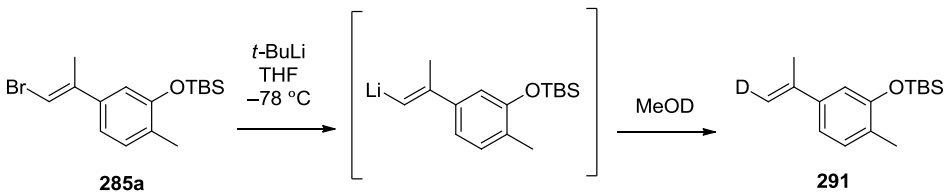
Finally, treatment of the dibromo species **290** with *n*-BuLi gave access to the novel (*E*)- and (*Z*)-alkenes **285a** and **285b** respectively (Scheme 115). The author was delighted that the exceptionally apolar stereoisomers were fully separable by careful flash column chromatography, eluted in pure *n*-hexane. The stereochemistry of each alkene isomer was determined by NOESY experiments. Irradiation of the alkenyl proton of the second eluting isomer revealed a 0.71% nOe enhancement at the neighbouring alkenyl methyl group resonance. The first eluting isomer did not reveal an nOe enhancement at the alkenyl methyl group resonance. The second eluting stereoisomer was assigned as (*E*)-bromo alkene **285a**, and the first eluting stereoisomer as (Z)-bromoalkene **285b**.



Scheme 115 - Synthesis of (*Z*)-alkene **285b** and (*E*)-alkene **285a**

Analysis of the ^{1}H NMR spectrum directly after protic work-up indicated a *Z:E* ratio of 1.3:1, demonstrating that a slightly (*Z*)-alkene selective olefination had been achieved.

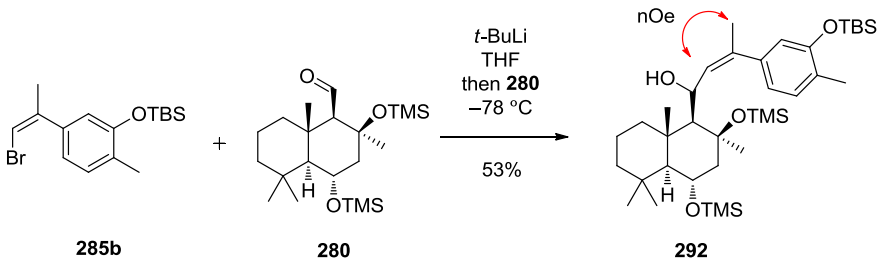
With the succesful formation of novel bromoalkenes **285a/b**, it was decided to probe methods for bromine-lithium exchange of the alkenyl bromine atom and *in situ* trapping with an electrophile. The lithiating ability of the bromoalkenes was initially investigated *via* deuteration experiments. The treatment of (*E*)-bromoalkene **285a** with *t*-BuLi at –78 °C generated a bright-yellow solution. This was followed by the addition of deuterated methanol (Scheme 116). After protic work-up, analysis of the ^{1}H NMR spectrum revealed remarkably clean conversion to deuterated alkene **291**. As expected, no isomerisation of the (*E*)-alkene had occurred, which would otherwise presumably result in a mixture of isomers upon protic work-up. The incorporation of deuterium was further confirmed through ^{13}C NMR spectroscopy and HRMS. Upon this result, work was focused upon trapping the analogous (*Z*)-organolithium species with the previously synthesised aldehyde **280**.



Scheme 116 - Lithiation/deuteration of (*E*)-alkene **285a**

3.5 Synthesis of Ansellane Alcohol 292

Having demonstrated the ability to lithiate (*E*)-alkene **285a** using *t*-BuLi, it was decided to investigate the lithiation of (*Z*)-bromoalkene **285b** and subsequent nucleophilic addition to aldehyde **280.** Treatment of (*Z*)-bromoalkene **285b** with *t*-BuLi mediated *in situ* bromine-lithium exchange, giving a bright-yellow solution, which was followed by the addition of aldehyde **280** (Scheme 117). Delightfully, analysis of the ^{1}H NMR after protic work-up revealed a new carbinol proton resonance, suggestive of succesful addition of the organolithium species to the aldehyde functional group. Indeed, ansellane alcohol **292** was isolated by flash column chromatography. As was predicted, the TMS ether protecting groups were robust enough to withstand the harsh reaction conditions.



285b **280** **292**

Scheme 117 - Synthesis of ansellane alcohol **292**

From analysis of the ^{13}C NMR spectrum, ansellane alcohol **292** was seemingly isolated as a single diastereomer. The stereochemistry of the newly formed chiral centre was not determined since it would be destroyed in a subsequent step. A 2D NOESY experiment revealed an nOe between the alkenyl proton and the alkenyl methyl group, confirming the expected retention of the crucial (*Z*)-alkene stereochemistry.

This synthesis of ansellane alcohol **292** is the first reported synthesis of the ansellane carbon skeleton possessed by ansellones A−D (**293**–**296**), ansellone E (**25**), ansellone

F (**297**) and related natural product phorbadione (**298**) (Figure 22). The work presented so far has established the important stereoselective installation of the secondary alcohol possessed by phorones A (**24**) and B (**242**), and also ansellones B (**294**) and D (**295**), *via* a reductive epoxide ring-opening strategy. Added to these advancements, a strategy towards the installation of the challenging trisubstituted (*Z*)-alkene motif possessed by phorone A (**24**), B (**242**) and ansellone E (**25**) has been devised.

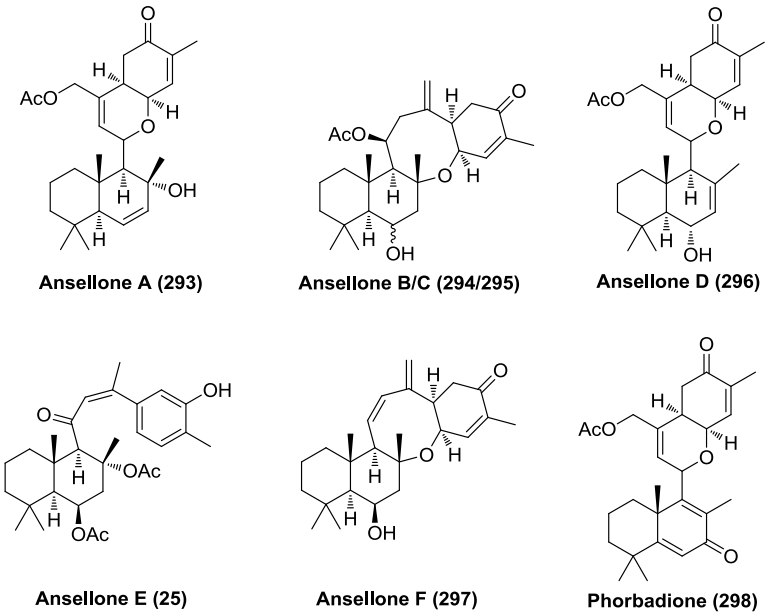
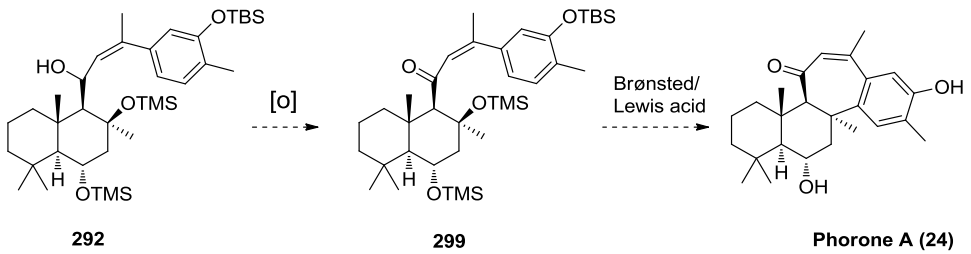


Figure 22 - Ansellane skeleton possessing natural products

Upon the satisfying construction of the entire ansellane carbon skeleton (**16**) and with the installation of all-but-one chiral centre, work was solely focused on achieving the first total synthesis of phorone A (**24**).

The end game required oxidation of the allylic alcohol **292** to enone **299**, removal of silyl protecting groups and treatment of the tertiary alcohol species with Lewis or Brønsted acid to affect the final electrophilic aromatic substitution step. It was anticipated that global silyl group removal and electrophilic aromatic substitution

may well occur concurrently, under suitably acidic conditions, potentially making phorone A only two synthetic steps from reach!



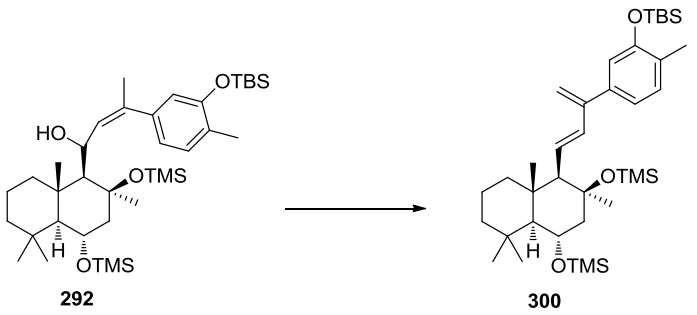
292 299 Phorone A (24)

Scheme 118 - Anticipated steps to phorone A (**24**)

3.6 End Game

3.6.1 Attempts to oxidise ansellane alcohol 292

Upon the first synthesis of ansellane alcohol **292**, storage at room temperature over several days unfortunately showed total degradation to a mixture of products. One major constituent upon degradation was isolated by flash column chromatography and was revealed as ansellane diene **300** after thorough spectroscopic analysis (Scheme 119). The ^{1}H NMR spectrum suggested the formation of a new (*E*)-alkene, with each alkenyl proton having a mutual coupling constant of $^{3}J_{E}$ = 15.8 Hz. The ^{13}C NMR spectrum showed no resonance which could be attributed to the carbinol carbon atom, and revealed the formation of two additional alkenyl carbon atoms. The newly formed terminal alkenyl carbon atom resonated in a negative phase in a DEPT-135 experiment. Moreover, HRMS revealed the *m/z* ion peak expected for ansellane diene **300**.



Scheme 119 - Degradation of ansellane alcohol **292** to ansellane diene **300**

Seemingly, this unforeseen transformation occurred spontaneously, although the author does speculate whether the degradation was as a result of potential residual silica gel after column chromatography* or other residual reagents in the apparently clean storage flask. It was proposed that ansellane alcohol **292**, bearing the (*Z*)-alkene moiety, was under high steric demand around the newly formed alcohol. Thus, it was proposed that elimination of the secondary alcohol to give ansellane diene **300** acts to mitigate this disfavourable steric crowding in a thermodynamically favoured process. The formation of the further extended π bonded system possessed by **300** is possibly also a thermodynamically favouring factor. Nevertheless, storage of the ansellane alcohol **292** in a −30 °C freezer and using within several days prevented this set-back from occurring again.

The labile nature of this transformation has shed some light on potential biosynthetic pathways of the ansellone natural products. Upon the recent reported isolation of ansellone F (**297**) in January 2015, it was remarkable to see that this natural product shared a similar 1,3-diene system to ansellane diene **300**. The author speculates that ansellone F may acquire this 1,3-diene system in a similar deoxygenating elimination process, from proposed intermediate **301** (Scheme 120, Route 2). This elimination

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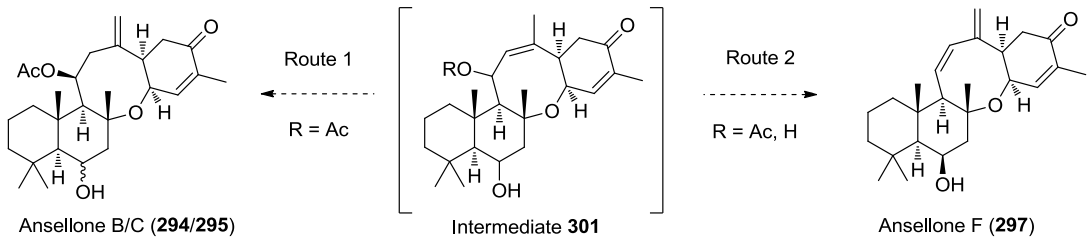
* Residual silica gel can occasionally pass through sintered disc of columns.

process may relieve ring strain caused by the trisubstituted (*Z*)-alkene motif residing in the 8-membered ring of the proposed intermediate **301.** Alongside this, it is suggested that the terminal alkene possessed by ansellone B/C (**294**/**295**) is aquired by an alkene migration step from the same intermediate **301**, perhaps to relieve the ring strain of the 8-membered ring (Route 1).

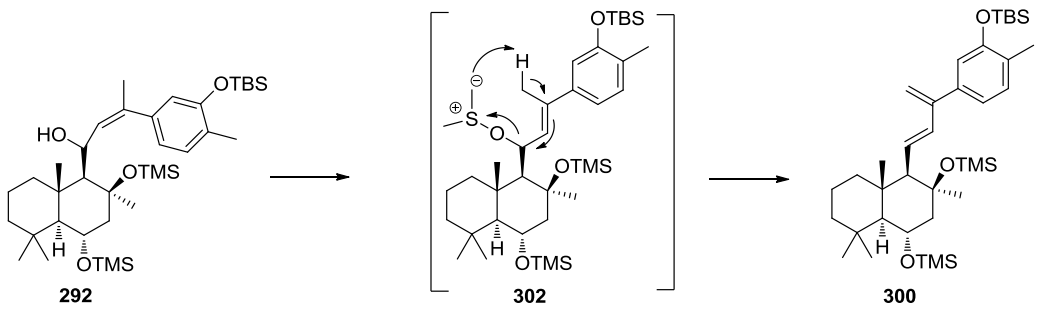
Phorones A (**24**) and B (**242**) can presumably endure the ring strain caused by the trisubstituted (*Z*)-alkene motif since the strain is lower in the 7-membered ring and additionally isomerisation of the alkene would result in the loss of the stabilising conjugated π bond system.



Scheme 120 - Proposed biosynthetic route to ansellone B/C (**294**/**295**) and F (**297**).

As was mentioned, following successful formation of ansellane alcohol **292** over 17 synthetic steps, an investigation into the oxidation of the allylic alcohol to the enone **299** was initiated (Table 7). Initially, treatment of ansellane alcohol **292** with MnO_2 demonstrated a complete lack of reactivity. Treatment at room temperature and at 60 °C both revealed the presence of starting material only. Remarkably, treatment of ansellane alcohol **292** with freshly prepared DMP also showed no apparent oxidation, even when a large excess of the oxidant was added. A Swern oxidation procedure proved to give complete degradation of the alcohol **292** to a mixture of degradation compounds, including ansellane alkene **300**. It was proposed that this

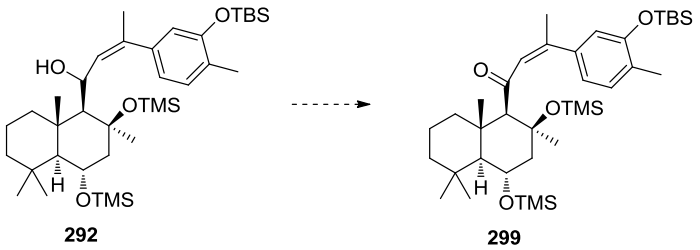
elimination may occur *via* alkoxysulfonium ion intermediate **302**, mediating elimination of the oxygen atom.



Scheme 121 - Degradation of ansellane alcohol **292** to **300** during Swern oxidation

Treatment with $PhI(OAc)_2$/TEMPO over 16 h also gave no reaction, recovering starting material only. The final attempt of treatment with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) gave only starting material over 4 days.

Table 7 - Conditions for attempted oxidation of ansellane alcohol **292**

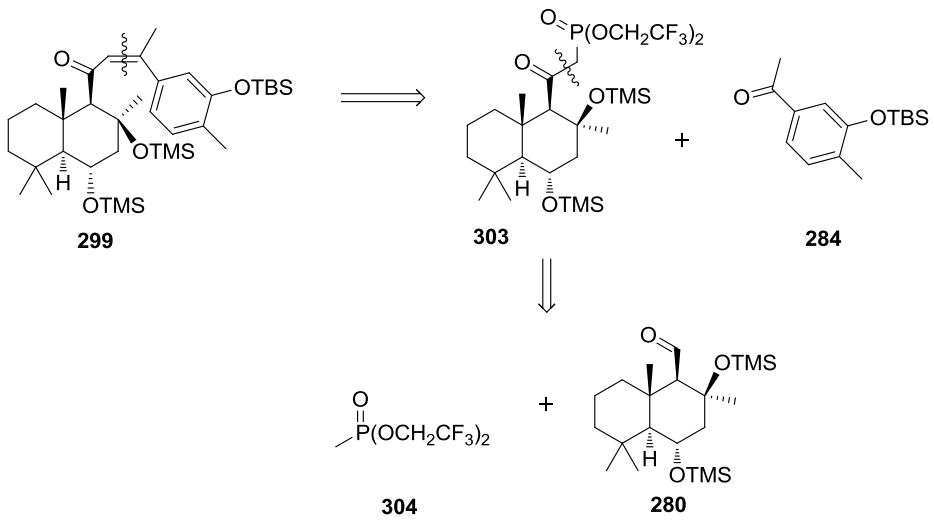


Conditions	Conversion (%)
MnO_2, CH_2Cl_2, room temp, 16 h	0
MnO_2, $CHCl_3$, 60 °C, 16 h	0
DMP, $NaHCO_3$, $CHCl_3$, 16 h	0
$(COCl)_2$, DMSO, NEt_3, CH_2Cl_2-78 °C	degradation
PIDA, TEMPO, CH_2Cl_2, 16 h	0
IBX, DMSO, 4 days	0

Frustratingly, despite being so close to phorone A, this route was abandoned at this point due to the astonishing inability to oxidise the allylic alcohol of **292** and the observed deoxygenative elimination process assisting degradation, observed using conventional methods for oxidation. Added to this, a lack of material at this late-stage made oxidation method probing very challenging. An alternative pathway was sought, which would preferably avoid the use of such sensitive and elusive allylic alcohol intermediates.

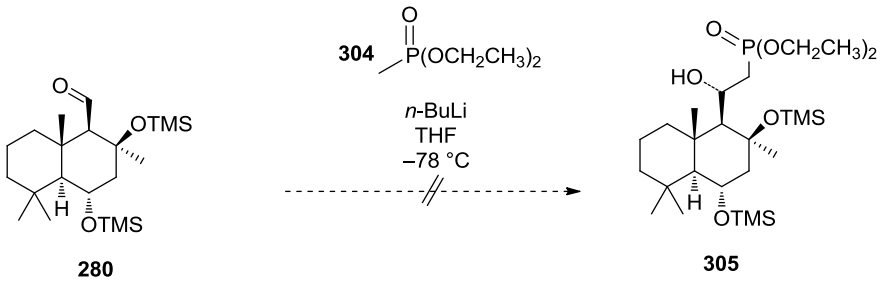
3.6.2 Still-Gennari Olefination Approach to Phorone A

An alternative synthetic plan to phorone A was devised. Retrosynthetic analysis of phorone A revealed that disconnection of the alkene could allow a Horner-Wadsworth-Emmons strategy for installation of the alkene (Scheme 122). With the use of Still-Gennari phosphonate **303**, a (*Z*)-selective olefination reaction with acetophenone **284** would give direct access to ansellane ketone **299**. Formation of the desired β-ketophosphonate **303** could be achieved *via* the deprotonation and subsequent addition of commercially available bis(2,2,2-trifluoroethyl) methylphosphonate (**304**) with subsequent oxidation level alteration.



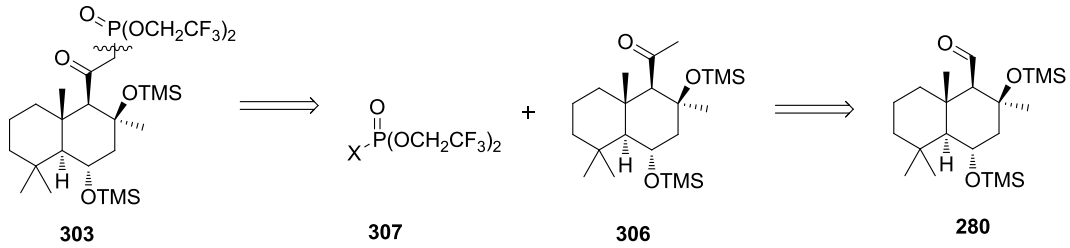
Scheme 122 - Retrosynthetic analysis of ansellane ketone **299**

To investigate this strategy to phosphonate **303**, the aldehyde **280** was added to a solution of phosphonate **304**, which had been deprotonated using *n*-BuLi. After protic work-up, none of desired product could be identified by ^{1}H NMR analysis, and the aldehyde starting material **280** seemed to remain unreacted.



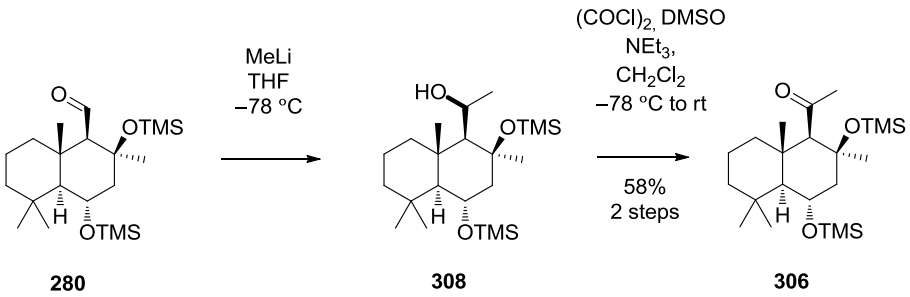
Scheme 123 - Attempted phosphonate **305** formation

With time constraints coming near the end of the PhD, efforts were not invested in the development of suitable reaction conditions for this strategy towards phosphonate **303**. Instead, an alternative retrosynthetic cleavage of β-ketophosphonate **303** revealed another possible synthetic strategy (Scheme 124). Nucleophilic addition of ketone fragment **306**, *via* its enolate, to halophosphonate fragment **307** could allow direct access to the desired phosphonate **303**. The ketone **306** would be synthesised from aldehyde **280** using a methyl-organometallic reagent, followed by oxidation level correction.



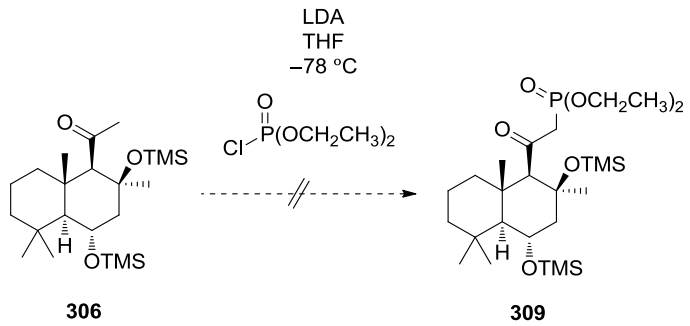
Scheme 124 - Alternative retrosynthetic analysis of phosphonate **303**

Firstly, treatment of aldehyde **280** with MeLi assisted conversion to alcohol **308**. Following this, Swern oxidation provided the smooth conversion to the ketone **306**.



Scheme 125 - Synthesis of ketone **306**

In order to investigate the future synthesis of Still-Gennari phosphonate fragment **303**, it was decided to initally attempt the formation of phosphonate **309** using the comparatively inexpensive reagent, diethyl chlorophosphate. Ketone **306** was enolised *in situ* using LDA, followed by the addition of diethyl chlorophosphate. Unfortunately, none of the desired product was observed by NMR analysis of the reaction mixture after protic work-up. In particular, the characteristic α CH_2 protons expected around 2–3 ppm for the desired β-ketophosphonate **309** were not observed.

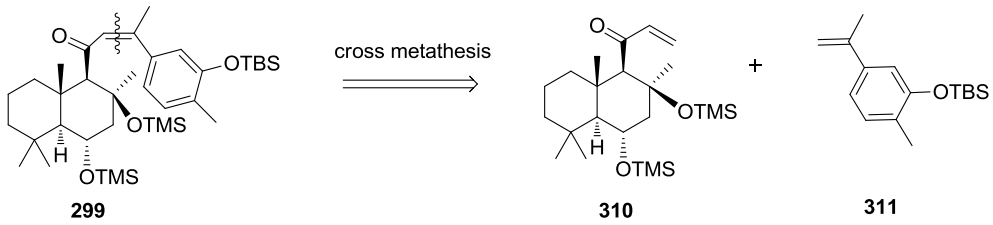


Scheme 126 - Attempted synthesis of phosphonate **309**

Efforts towards the utilisation of a Still-Gennari phosphonate for the total synthesis of phorone A were unfruitful. The author believed that installation of the phosphonate **309** would require significant time for development and since only a short amount of time was available for further laboratory work, efforts were focused on an alternative strategy.

3.6.3 Cross Metathesis Strategy for Phorone A

An alternative retrosynthetic analysis of phorone A (**24**) revealed that by cleavage of the C=C alkenyl bond possessed by ansellane ketone fragment **299**, a cross metathesis strategy could potentially be used. A cross metathesis reaction between enone fragement **310** and styrenyl fragment **311** could give direct access to the desired enone system possessed by phorone A (**24**).



Scheme 127 - Retrosynthesis of ansellane ketone **299**

A major concern using this planned strategy was the *E:Z* selectivity using conventional Grubbs catalysts, which normally highly favour formation of *E*-alkenes. However, it was thought that (*E*)- to (*Z*)-alkene isomerisation could be possible under suitable acidic conditions, which were likely to be used in the final step for electrophilic aromatic substitution for the formation of the phorane skeletone. Added to this, (*Z*)-alkene selective Grubbs catalysts have now been reported in the literature,[98] with some being commercially available.* Therefore, an investigation into the utility of a cross metathesis strategy towards phorone A was initiated.

Synthesis of the ketone **310** was achieved in two steps from previously prepared aldehyde **280**. Firstly, addition of vinyl magnesium bromide to aldehyde **280** mediated unoptimised conversion to alcohol apparently as a single diastereomer **312**, which was then oxidised to ketone **310** using MnO_2.

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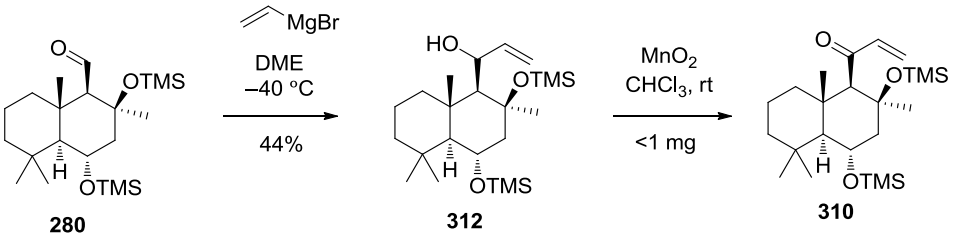
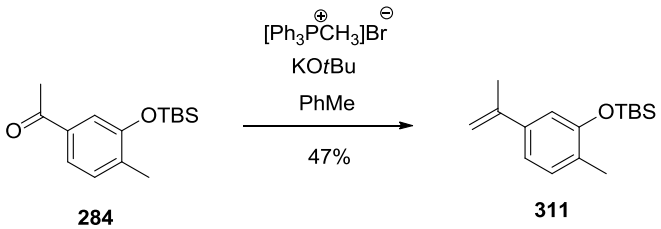
* Visit sigmaladrich.com for a selection of Grubbs catalysts



Scheme 128 - Synthesis of enone **310**

The synthesis of styrenyl fragment **311** was achieved *via* a Wittig olefination reaction. Treatment of acetophenone **284** with methyltriphenylphosphonium bromide and potassium *t*-butoxide facilitated smooth conversion to the novel styrene **311**, in an unoptimised 47% yield.

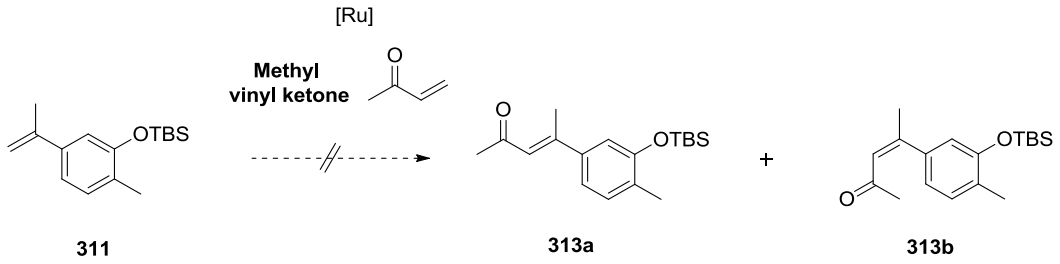


Scheme 129 - Synthesis of styrene **311**

Since only small quantities (<1 mg) of the enone **310** had been synthesised at the time, and with time set against the author towards the end the PhD, it was required to model the envisaged cross metathesis pathway using a more available enone substrate. Methyl vinyl ketone was readily available in the laboratory and a good model substrate enone for cross metathesis with the styrene **311**.

Using methyl vinyl ketone, firstly Grubbs 2nd generation catalyst (1 mol %) was employed. After 16 h and evaporation of the solvent, analysis by ^{1}H NMR spectroscopy revealed starting materials only. Using the same catalyst at 80 °C over 16 h also gave starting materials only. In a final attempt, Hoveyda-Grubbs catalyst (5

mol %) was employed at 80 °C over 16 hours. Again, analysis of the crude mixture by ^{1}H NMR spectroscopy revealed starting materials only.



Scheme 130 - Cross metathesis of styrene **311** and methyl vinyl ketone

Table 8 - Conditions for attempted cross metathesis of styrene **311** and methyl vinyl ketone

Catalyst	Conditions	Conversion (%)
Grubbs' 2nd gen.	0.01 eq, CH_2Cl_2, rt, 16 h	0
Grubbs' 2nd gen.	0.01 eq, PhMe, 80 °C, 16 h	0
Hoveyda-Grubbs' 2nd gen.	0.05 eq, PhMe, 80 °C, 16 h	0

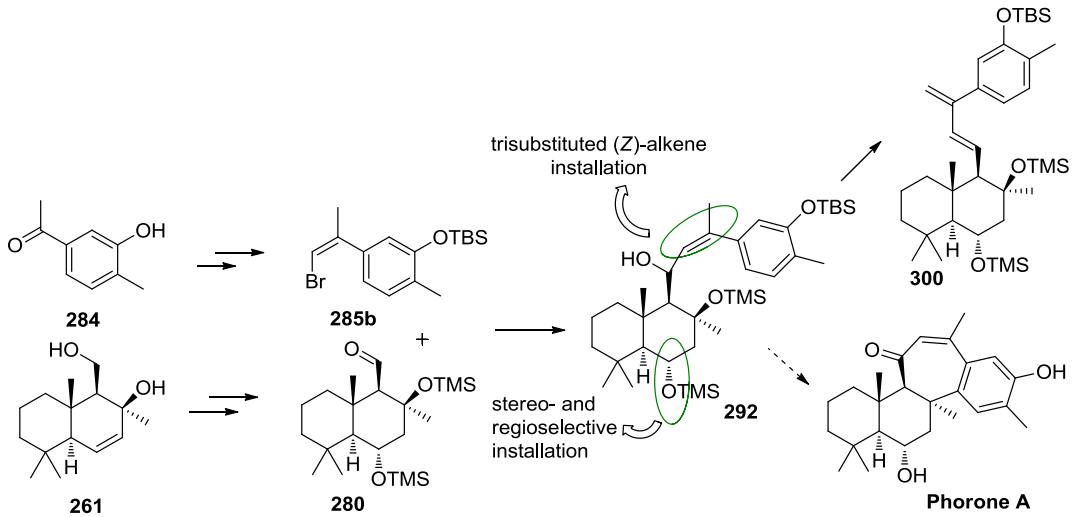
Cross metathesis of these substrates using commonly available Grubbs catalysts was not achieved under the conditions employed. Due to time restrictions, efforts towards the development of a cross metathesis strategy for the total synthesis of phorone A (**24**) were halted at this point.

3.7 Conclusion and Future Work

The work presented in this chapter describes efforts towards the total synthesis of phorone A. An initial synthetic strategy gave access to ansellane alcohol **292**, which is the first ever synthesis of the ansellane carbon skeleton possessed by the natural

products ansellones A-D (**293**–**296**), ansellone E (**25**), ansellone F (**297**) and related natural product phorbadione (**298**).

During the initial synthetic work, a strategy was devised for the stereoselective installation of the secondary alcohol possessed by phorones A and B (**24** and **242**) and ansellones B and D (**294** and **296**), *via* stereoselective epoxide installation and reductive opening of the epoxide (Scheme 131). Added to these accomplishments, a strategy towards the installation of the challenging trisubstituted (*Z*)-alkene motif possessed by phorone A and B (**24**, **242**) and ansellone E (**25**) has been achieved. The labile degradation of ansellane alcohol **292** to ansellane diene **300** and the astonishing inability to oxidise the secondary alcohol gives heed to avoid such precarious intermediates in future synthetic plans towards phorone A (**24**) and the related natural products. These synthetic accomplishments leading to ansellane alcohol **292** will provide invaluable guidance for future total syntheses of related sesterterpenoid natural products, in which there will undoubtedly be great interest.

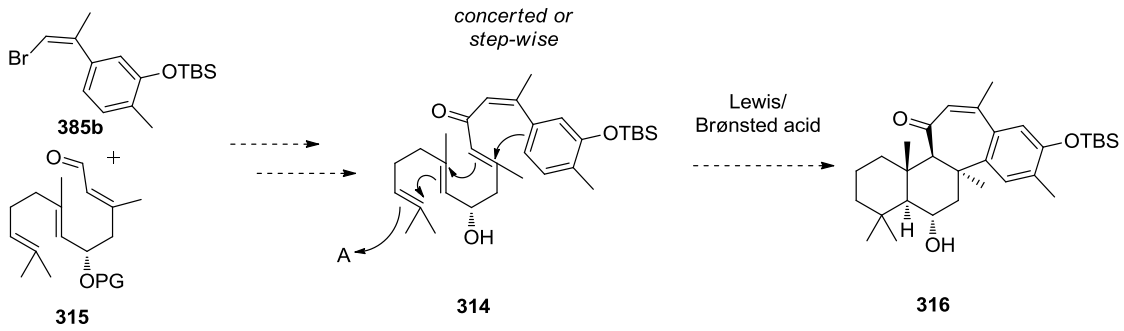


Scheme 131 - Summary of accomplishments to ansellane alcohol **292**

Following the set-back encountered by the inability to oxidise ansellane alcohol **292** to the desired enone functional group, alternative synthetic strategies avoiding such sensitive allylic alcohol moities towards phorone A (**24**) were investigated. An investigation into a Still-Genari olefination strategy firstly involved the successful formation of ketone **306**. However, attempts at the formation of Still-Gennari phosphonates required for this route were unfruitful. A final strategy investigated the potential for using a cross metathesis route for the formation of the (*Z*)-alkene motif. Preliminary model investigations exploring the cross metathesis of styrene **311** with methyl vinyl ketone using some of Grubbs catalysts were discouraging with no cross metathesis apparent.

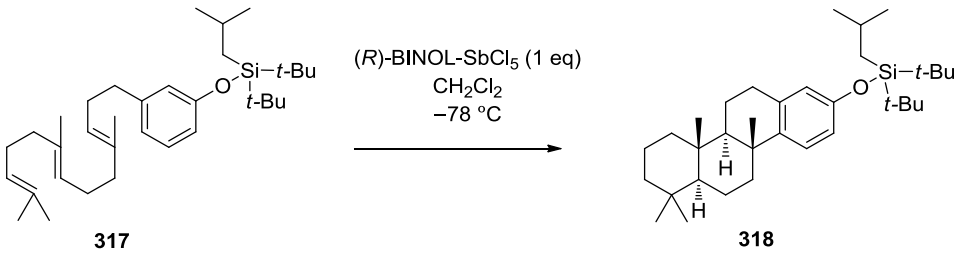
Future work may involve investing further development time in exploring the Still-Gennari and cross-metathesis propsed routes towards phorone A (**24**).

A polycyclisation strategy towards phorone A (**24**) has been hypothesised. Treatment of the polyolefin **314** with a Lewis- or Brønsted acid is envisaged to result in a completely or partially concerted cascade reaction with electrophilic aromatic substitution for the formation of the phorane carbon skeleton (Scheme 132). The Stork-Eschenmoser hypothesis states that during polyolefin cascades a '*trans* double bonds lead to *trans*-ring junctions' and that '*cis*-double bonds lead to *cis*-ring junctions'.[99] Thus (*E*,*E*,*E*)-farnesal derivative **315** would give the desired *trans*-decalin system **316** upon cyclisation. The synthesis of polyolefin **314** could be achieved *via* the addition of (*Z*)-bromoalkene **385b** to farnesal derivative **315,** as has similarly been demonstrated in this work.



Scheme 132 - Cascade pathway to phorone A (**24**), A = Lewis/Brønsted acid

This strategy is similar to a highly enantioselective cyclisation reaction recently demonstrated by the group of E. J. Corey.[100] Treatment of polyolefin **317** with the chiral Lewis acid catalyst, (*R*)-BINOL-$SbCl_5$, resulted in a polycyclisation to give tetracyclic product **318** with 86% ee (Scheme 133).



Scheme 133 - Corey polycyclisation to **318**

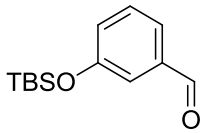
4. Experimental

4.1 General Experimental Details

Commercially available reagents were used as received without further purification. All reactions that required anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of argon. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Visualisation of TLC plates was performed by fluorescence quenching and potassium permanganate, anisaldehyde or vanillin type dips. Unless specifically stated flash chromatography procedures were performed using Kieselgel 60 (40–63 μm). Basic alumina solid phases were varied in Brockmann grade by adding distilled H_2O, shaking vigorously and leaving in sealed flask overnight: (Brockmann grade I - H_2O added 0 wt. %, Brockmann grade II - H_2O added 3 wt. %, Brockmann grade III - H_2O added 6 wt. %, Brockmann grade IV - H_2O added 10 wt. %). Petrol refers to the fraction of petroleum boiling from 40–60 °C. Brine refers to a saturated aqueous solution of sodium chloride. Infrared spectra were recorded directly on a Bruker Tensor 37 FTIR machine fitted with a PIKE MIRacle ATR accessory as either solids or neat oils. Infrared spectra are reported as follows: wavelength (cm^{-1}) and intensity of absorbance (s = strong, m = medium, w = weak, vw = very weak, br = broad). ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were typically recorded on Bruker AV400 machines at 400, 101, 162 and 376 MHz respectively. Chemical shifts (ppm) are reported relative to the residual protonated solvent resonance: $CDCl_3$ [δ_H 7.26, δ_C 77.2], C_6D_6 [δ_H 7.16, δ_C 128.1], DMSO-d_6 [δ_H 2.50, δ_C 39.5], acetone-d_6 [δ_H 2.05, δ_C 206.3], CD_4OD [δ_H 3.31, δ_C 49.0]. ^{1}H NMR data are reported as follows: chemical shift (δ), integration, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, qn= quintet and m = multiplet,), *J* coupling constant(s) (Hz), and assignment. ^{1}H NMR signals were assigned using chemical shift, scalar coupling patterns,

standard two dimensional NMR experiments. ^{13}C NMR signals were assigned using chemical shift, DEPT-135 experiments and standard two dimensional NMR experiments.

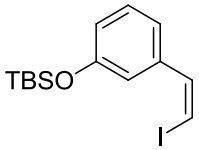
4.2 Experimental Procedures and Compound Characterisation



3-(*tert*-Butyldimethylsilyloxy)benzaldehyde 140

To a stirred solution of NEt_3 (1.90 mL, 13.5 mmol) and one crystal of DMAP in CH_2Cl_2 (500 mL) was added 3-Hydroxybenzaldehyde (1.10 g, 9.01 mmol) at 23 °C. To this was added TBSCl (2.04 g, 13.5 mmol), followed by continued stirring for 2 h. After this time water (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (SiO_2, 10% Et_2O in petrol) gave the title compound as yellow oil which slowly crystallised to orange needles on standing (2.06 g, 97%). Data are consistent with those previously reported in the literature.[56]

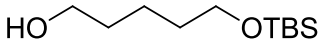
υ_{max}/cm^{-1} 1702s (C=O), 1583m, 1482m, 1387w, 1277s, 1144w; ^1H NMR (400 MHz, $CDCl_3$) δ 9.94 (1H, s, CHO), 7.45 (1H, td, J = 7.6 and 1.3 Hz, ArCH), 7.38 (1H, t, J = 7.6 Hz, ArCH), 7.31–7.33 (1H, m, ArCH), 7.12–7.09 (1H, m, ArCH), 0.97 (9H, s, $SiC(CH_3)_3$), 0.21 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.0 (CHO), 156.4 (ArCO), 138.0 (Ar*C*CHO), 130.1 (ArCH), 126.5 (ArCH), 123.5 (ArCH), 119.9 (ArCH), 25.6 ($SiC(CH_3)_3$), 18.2 (SiC), –4.2 ($Si(CH_3)_2$).



(*Z*)-(*tert*-Butyldimethylsilyloxy)(3-(2-iodovinyl)phenoxy)) 141

To a stirred suspension of iodomethylenetriphenylphosphorane (675 mg, 1.27 mmol) in THF (3 mL) was slowly added NaHMDS (0.53 mL, 2 M in THF, 1.06 mmol) at 23 °C. The solution was stirred for 10 min before the resultant orange-red solution was cooled to –78 ºC, followed by addition of HMPA (1.50 mL) and then a solution of 3-((*tert*-butyldimethylsilyl)oxy)benzaldehyde **140** (250 mg, 1.06 mmol) in THF (2 mL). After stirring at –78 ºC for 1 h, NH_4Cl (sat. aq., 2 mL) was added to the solution and after warming to room temp, the mixture was filtered over a short pad of Celite® which was then washed with *n*-hexane (10 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 90% Et_2O in *n*-hexane) to give the *title compound* as yellow oil (351 mg, 92%).

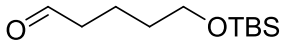
υ_{max}/cm^{-1} 2927w, 2856w, 1703w, 1595w, 1575w, 1471w, 1281s, 1250s; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06–6.99 (3H, m, 2 × ArCH, IHC=C*H*), 6.93 (1H, d, *J* = 7.7 Hz, ArCH), 6.61 (1H, dd, *J* = 8.0 and 1.6 Hz, ArCH), 6.33 (1H, d, *J* = 8.5 Hz, I*H*C=CH), 0.79 (9H, s, $SiC(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (ArCO), 138.6 (=CH), 138.1 (Ar_q), 129.4 (ArCH), 122.0 (ArCH), 120.4 (ArCH), 119.7 (ArCH), 79.2 (=CHI), 25.9 ($SiC(CH_3)_3$), 18.4 (SiC), -4.2 ($Si(CH_3)_3$); *m/z* calculated for $[C_{14}H_{22}OISi]^+$ 361.0479 found $[M + H]^+$ 361.0478.



5-(*tert*-Butyldimethylsilyloxy)pentan-1-ol 142[58]

To a stirred solution of 1,5-pentanediol (25.0 mL, 239 mmol) and imidazole (4.00 g, 58.8 mmol) in DMF (25 mL) was added a solution of TBSCl (4.00 g, 26.5 mmol) in CH_2Cl_2 (4 mL) dropwise over 1 h. The solution was then stirred for a further 2 h. After this time the solution was diluted with Et_2O (50 mL), the separated organic layer was washed with water (3 × 20 mL), brine (20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 1% Et_2O in petrol) to give the title compound as colourless oil (2.00 g, 35% wrt TBSCl). Data are consistent with those previously reported in the literature.[58]

υ_{max}/cm^{-1} 3335br (O–H), 2929w, 2857w, 1472w, 1360w, 1253w, 1096m,; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (4H, apt t, J= 6.5 Hz, 2 × OCH_2) 1.57–1.49 (4H, m, 2 × OCH_2CH_2), 1.40-1.33 (2H, m, $CH_2CH_2CH_2$), 0.85 (9H, s, $SiC(CH_3)_3$), 0.00 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 63.0 (2 × CO), 32.5 (CH_2–CH_2–OH), 26.0 (CH_2–CH_2–OSi), 25.6 ($SiC(CH_3)_3$), 22.0 (CH_2), 18.4 (SiC), –5.3 ($Si(CH_3)_2$).

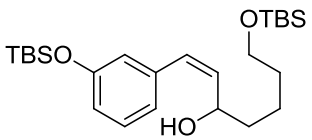


5-(*tert*-Butyldimethylsilyloxy)pentanal 143[59]

To a solution of oxalyl chloride (0.39 mL, 4.55 mmol) in CH_2Cl_2 (8 mL) cooled to –78 ºC was added dropwise a solution of DMSO (0.65 mL, 9.15 mmol) in CH_2Cl_2 (3 mL), followed by continued stirring for 20 min. Subsequently **142** (1.00 g, 4.59 mmol) was added slowly, followed by further stirring for 20 min. After this time

NEt_3 (3.20 mL, 23.0 mmol) was added dropwise and the solution was stirred for a further 15 min. After this time the reaction was then allowed to warm to room temp and stirring was continued for 45 min. Water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 10% Et_2O in petrol) to give the title compound as colourless oil (770 mg, 78%). Data are consistent with those previously reported in the literature.[59]

υ_{max}/cm^{-1} 1727s (C=O), 831m, 562m; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.7 Hz, CHO), 3.63 (2H, t, J = 6.3 Hz, H_2COTBS), 2.45 (2H, td, J = 7.5 and 1.7 Hz, CH_2CHO), 1.74–1.66 (2H, m, OHCCH$_2$CH_2), 1.59–1.51 (2H, m, CH_2CH$_2$OTBS), 0.89 (9H, s, SiC$(CH_3)_3$), 0.05 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7 (CHO), 62.7 (OCH_2), 43.8 (CH_2), 32.3 (CH_2), 26.1 (SiC$(CH_3)_3$), 18.8 (CH_2), 18.5 (SiC), –5.2 (Si$(CH_3)_2$).

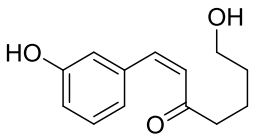


(*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-1-(3-((*tert*butyldimethylsilyl)oxy) phenyl)hept-1-en-3-ol 144

To a solution of (*Z*)-iodoalkene **141** (200 mg, 0.56 mmol) in THF (10 mL) cooled to –78 °C was added *n*-BuLi (0.25 mL, 2M in hexanes, 0.50 mmol) dropwise, following continued stirring for 30 min. After this time aldehyde **143** (134 mg, 0.62 mmol) in THF (2 mL) was added and the solution was stirred for a further 45 min. NH_4Cl (sat. aq.) (2 mL) was added dropwise at –78 °C. After warming to room temp, EtOAc (10

mL) was added and the separated organic layer was washed with brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 20% Et_2O in petrol) to give the *title compound* as pale yellow oil (101 mg, 40%).

υ_{max}/cm^{-1} 3442br (O–H), 2920m, 2884m, 1400s, 1412m, 1319m, 1250s, 1217s, 1099s, 1030m; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.19 (1H, t, *J* = 7.8 Hz, ArCH), 6.87 (1H, d, *J* = 7.8 Hz, ArCH), 6.79–6.73 (2H, m, 2 × ArCH), 6.48 (1H, d, *J* = 11.6 Hz, Ar–*H*C=CH), 5.64 (dd, *J* = 11.6 and 2.3 Hz, Ar–HC=C*H*), 4.61–4.55 (1H, m, *H*C–OH), 3.60 (2H, t, *J* = 6.4 Hz, *H*$_2$C–OTBS), 1.72–1.26 (6H, m, 3 × CH_2), 0.99 (9H, s, $SiC(CH_3)_3$) 0.89 (9H, s, $SiC(CH_3)_3$), 0.21 (6H, s, $Si(CH_3)_2$), 0.04 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (ArCO), 138.2 (ArCH), 134.8 (Ar_q), 131.0 (Ar*C*=C), 129.4 (=C), 122.0 (ArCH), 120.5 (ArCH), 119.2 (ArCH), 68.0 (C–OH), 63.2 (C–OSi), 37.5 (CH_2), 32.9 (CH_2), 26.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 21.9 (CH_2), 18.5 (SiC), 18.4 (SiC), –4.3 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$); *m/z* calculated for $[C_{25}H_{46}O_3Si_2Na]^+$ 473.2878 found $[M + Na]^+$ 473.2874.

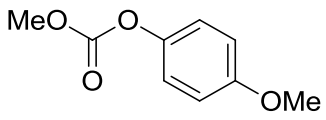


(*Z*)-7-Hydroxy-1-(3-hydroxyphenyl)hept-1-en-3-one 134

To a stirred solution of (*Z*)-alcohol **144** (260 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) was added freshly prepared Dess–Martin periodinane[60] (267 mg, 0.63 mmol) in one portion followed by continued stirring for 3 h. After this time, $NaHCO_3$ (sat. aq.) (10 mL) was added and the organic layer was separated, dried over Na_2SO_4 and filtered. Following evaporation of the solvent *in vacuo*, purification of the residue by flash

column chromatography (SiO_2; 10% Et_2O in petrol) gave a ketone which was used immediately in the next step. To a solution of the aforementioned ketone (228 mg, 0.51 mmol) in THF (1 mL) was added TBAF (1.02 mL, 1 M in THF, 1.02 mmol). The resultant yellow solution was stirred at 23 ° C for 4.5 h. After this time, water (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 60% Et_2O in petrol) to give *the title compound* as light yellow oil (46 mg, 58% for two steps). *The product displayed rapid degradation and was stored in the dark at 4 °C.*

ν_{max}/cm^{-1} 3350br (O–H), 2930w, 1739s (C=O), 1610m, 1578m, 1448, 1229s, 1217s, 1059m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, appt t, J = 7.8 Hz, ArCH), 7.09 (1H, s, ArCH), 6.94 (1H, d, J = 7.5 Hz, ArCH), 6.84 (1H, dd, J = 7.8 and 1.7 Hz, ArCH), 6.81 (1H, d, J = 12.8 Hz, Ar–C*H*=CH), 6.16 (1H, d, J = 12.8 Hz, Ar–CH=C*H*), 3.55 (2H, t, J = 6.3 Hz, CH_2C=O), 2.45 (2H, t, J = 7.0 Hz, CH_2OH), 1.75–1.66 (2H, m, CH_2CH$_2$C=O), 1.58–1.51 (2H, m, CH_2CH$_2$C–OH); *m*/*z* calculated for $[C_{13}H_{17}O_3]^+$ 221.1172 found. $[M + H]^+$ 221.1172.

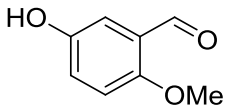


4-Methoxyphenyl methyl carbonate 161[64]

To a stirred solution of 4-hydroxyanisole (500 mg, 4.03 mmol) in pyridine (0.49 mL, 6.08 mmol) and THF (2 mL) cooled to 0 °C was added methyl chloroformate (0.62 mL, 8.00 mmol) dropwise *very cautiously* over 5 min. The solution was stirred at 0 ºC for 1 h then allowed to reach 23 °C and stirred for a further 1 h. After this time,

water (5 mL) was added and the seperated organic phase was repeatedly washed with copious amounts of $CuSO_4$ (sat. aq.), brine (7 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound as colourless oil (670 mg, quantitative yield) which was used without further purification. Data are consistent to those previously reported in the literature.[64]

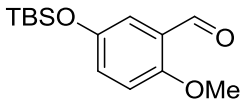
ν_{max}/cm^{-1} 2900w, 1750s (C=O), 1230m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.75 (4H, m, ArCH), 3.87 (3H, s, ArCOCH_3), 3.77 (3H, s, COOCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4 (ArCO), 154.7 (C=O), 144.8 (ArCO), 121.8 (2 × ArCH), 114.5 (2 × ArCH), 55.4 (2 × OCH_3).



5-(*tert*-Butyldimethylsilyloxy)-2-methoxybenzaldehyde 163[64]

To a stirred solution of **161** (1.22 g, 7.34 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C was added $TiCl_4$ (8.44 mL, 1 M, 8.44 mmol) was added followed by dichloromethoxymethane (1.58 mL, 17.30 mmol) and the solution was stirred at 23 °C for 1 h. After this time, water (10 mL) was added and the separated aqueous layer was extracted with Et_2O (3 × 20mL). The combined organic layers were separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude brown solid. The brown solid was dissolved in THF (28 mL) and to this was added NaOH (29 mL, 1 M aq. sol.,). The solution was heated at 35 ºC for 24 h. After this time HCl (1 M) was added until pH 7 was reached. The organic layer was extracted with EtOAc (2 × 20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the title compound as yellow needles (580 mg, 44% for 2 steps). Data are consistent with those previously reported in the literature.[64]

mp 108–110 ºC (lit 110–115 ºC)[64]. ν_{max}/cm^{-1} 3222br (O–H), 1656s (C=O), 1609w, 1440s, 1471s, 1440s, 1306s, 1221s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (1H, s, CHO), 7.36 (1H, d, J = 3.2 Hz, ArCH), 7.12 (1H, dd, J = 9.0 and 3.2 Hz, ArCH), 6.90 (1H, d, J = 9.0 Hz, ArCH), 3.88 (3H, s, OCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3 (C=O), 156.6 (ArCO), 149.9 (ArCO), 125.0 (Ar*C*CHO), 123.6 (ArCH), 113.7 (ArCH), 113.4 (ArCH), 56.2 (OCH_3).



5-(*tert*-Butyldimethylsilyloxy)-2-methoxybenzaldehyde 164

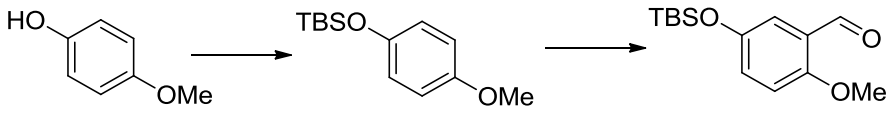
Preparation 1:

To a stirred solution of 5-(*tert*-butyldimethylsilyloxy)-2-methoxybenzaldehyde **163** (4.00 g, 26.3 mmol) in CH_2Cl_2 (50 mL) was added TBSCl (4.40 g, 29.2 mmol) and NEt_3 (4.10 mL, 29.4 mmol). After continued stirring for 16 h, water (20 mL) was added. The organic layer was separated, dried over $MgSO_4$ and filtered. After evaporation of the solvent *in vacuo* the crude residue was purified by flash column chromatography (SiO_2, 20% EtOAc in petrol) to give the *title compound* as yellow oil that slowly formed yellow needles (6.93 g, quantitative yield).

mp 30–31 °C; ν_{max}/cm^{-1} 2930w, 2858w, 1682s (C=O), 1491s, 1390m, 1261s, 1214s, 1156m, 1028m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (1H, s, CHO), 7.25 (1H, d, J = 3.1 Hz, ArCH), 7.02 (1H, dd, J = 8.9 and 3.1 Hz, ArCH), 6.84 (1H, d, J = 8.9 Hz, ArCH), 3.86 (3H, s, OCH_3), 0.95 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5 (C=O), 156.8 (ArCO), 149.4 (ArCO), 127.7 (ArCH), 125.3 (ArCH), 118.4 (Ar_q), 112.9 (ArCH), 56.1 (OCH_3), 25.7 ($SiC(CH_3)_3$),

18.1 (SiC), –4.5 ($Si(CH_3)_2$), *m*/*z* calculated for $[C_{14}H_{23}O_3Si]^+$ 267.1411 found. [M + H]$^+$ 267.1115.

Preparation 2:



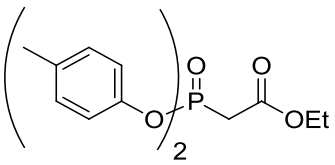
1-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzene 165

To a stirred solution of 4-methoxyphenol (4.00 g, 32.2 mmol) in CH_2Cl_2 (30 mL) was added TBSCl (5.30 g, 35.2 mmol) and imidazole (2.40 g, 35.2 mmol) at 23 °C. After stirring for 2 h, water (10 mL) was added and the separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purifiied by flash column chromatography (SiO_2, 10% Et_2O in petrol) to give the title compound as colourless oil (7.00 g, 92%). Data are consistent with those previously reported in the literature.[66]

ν_{max}/cm^{-1} 2951m, 2931m, 1510s, 1255m, 1235; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (4H, s, 4 × ArCH), 3.76 (3H, s, OCH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (ArCO), 149.5 (ArCO), 120.8 (2 × ArCH), 114.6 (2 × ArCH), 55.8 (OCH_3), 25.9 ($SiC(CH_3)_3$), 18.3 (SiC), –4.4 ($Si(CH_3)_2$).

To a stirred solution of 4-(methoxyphenoxy)-*tert*-butyldimethylsilane **165** (2.00 g, 8.38 mmol) and TMEDA (1.30 mL, 8.67 mmol) in anhydrous tetrahydropyran (10 mL) was slowly added *n*-BuLi (6.8 mL, 2.5 M in hexanes, 17.0 mmol) dropwise at 0 °C. The solution was allowed to warm to room temp and stirring was continued for a further 2 h. After this time, the solution was cooled to 0 °C before DMF (1.00 mL,

13.0 mmol) was slowly added dropwise. The reaction was allowed to warm to room temp over 2 h before being cooled to 0 °C and quenched by dropwise addition of water (5 mL). The reaction mixture was diluted with Et_2O (20 mL) before the separated organic phase was washed with water (5 × 10 mL), then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2, 20% EtOAc in petrol) to give the *title compound* as pale yellow oil which crystallised to pale yellow crystals upon standing (1.70 g, 77%). Data were in accord to the alternative preparation (page 143).



Ethyl (di-*p*-tolylphosphono)acetate 170

To triethyl phosphonoacetate (0.57 mL, 2.87 mmol) cooled to 0 °C was carefully added PCl_5* (1.50 g, 7.20 mmol). The mixture was then heated at 75 °C for 17 h. After this time, careful removal of the volatile by-products *in vacuo* was followed by dissolution of the dichlorophosphonate in PhMe (20 mL) and addition of NEt_3 (0.75 mL, 5.41 mmol) then *p*-cresol (454 mg, 4.20 mmol). After stirring for 17 h, water (20 mL) was added and the separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography to give the title compound as pale yellow oil (400 mg, 61% for 2 steps). Data are consistent with those previously reported in the literature.[69]

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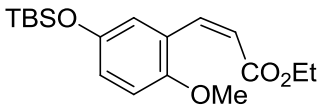
* PCl_5 is classified as **fatal** by inhalation!

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (8H, s, 8 × ArCH), 4.23 (2H, q, J = 7.1 Hz, OCH_2), 3.22 (2H, d, J = 21.5 Hz, CH_2), 2.31 (6H, s, 2 × $ArCH_3$), 1.28 (3H, t, J = 7.1 Hz, CH_3); ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.96.

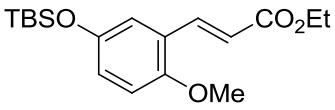


(*Z*)-Ethyl 3-(5-(*tert*-butyldimethylsilyloxy)-2-methoxyphenyl)acrylate 169

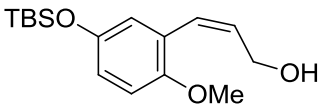
To a stirred solution of ethyl (di-*p*-tolylphosphono)acetate **170** (696 mg, 2.00 mmol) in THF (10 mL) was added NaH (48 mg, 2.00 mmol) portionwise at –78 °C. The solution was allowed to warm to 0 °C with continued stirring for 30 min. After this time the solution was cooled to –78 °C before the aldehyde **164** (350 mg, 1.31 mmol) was added portionwise. Stirring was continued at –78 °C for 2 h. The solution was allowed to warm to room temp before NH_4Cl (sat. aq., 5 mL) was added. The reaction mixture was diluted with Et_2O (20 mL) before the separated organic layers were washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a residue that was determined as an 85:15 mixture of *Z*:*E* isomers by ^{1}H NMR. Purification by flash column chromatography (SiO_2, 5% → 10% Et_2O in petrol) afforded the *Z*-isomer as pale yellow oil (348 mg, 80%).

ν_{max}/cm^{-1} 2930m, 2858m, 1721s (C=O), 1628w, 1577w, 1489s, 1464m, 1424m, 1282w, 1219s (C−O), 1163s, 1033s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, J = 12.4 Hz, C*H*=$CHCO_2$), 7.04 (1H, d, J = 2.8 Hz, ArCH), 6.77 (1H, dd, J = 8.9 and 2.8 Hz, ArCH), 6.72 (1H, d, J = 8.9 Hz, ArCH), 5.94 (1H, d, J = 12.4 Hz, CH=C*H*CO_2), 4.14 (2H, q, J = 7.2 Hz, OCH_2), 3.78 (3H, s, OCH_3), 1.21 (3H, t, J = 7.2 Hz, CH_2CH_3), 0.97 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C=O), 152.0 (ArCO), 148.7 (ArCO), 138.2 (*C*H=$CHCO_2$), 125.0

(Ar_q), 122.0 (ArCH), 121.3 (ArCH), 120.4 (ArCH), 111.3 (CH=*C*HCO$_2$), 60.2 (OCH_2), 56.1 (OCH_3), 25.9 (SiC(*C*H$_3$)$_3$), 18.3 (SiC), 14.2 (CH_3), –4.4 (Si(CH_3)$_2$); *m*/*z* calculated for $[C_{18}H_{29}O_4Si]^+$ 337.1830 found $[M + H]^+$ 337.1834.



Data for minor (*E*)-alkene **171:** ν_{max}/cm^{-1} 2931m, 2858m, 1708s (C=O), 1631s, 1575w, 1493m, 1464m, 1317m, 1278m, 1253s (C−O), 1160s, 1033s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 16.1 Hz, C*H*=CHCO$_2$Et), 6.98 (1H, d, *J* = 2.8 Hz, ArCH), 6.80 (1H, dd, *J* = 8.9 and 2.8 Hz, ArCH), 6.77 (1H, d, *J* = 8.9 Hz, ArCH), 6.45 (1H, d, *J* = 16.1 Hz, CH=C*H*CO$_2$Et), 4.26 (2H, q, *J* = 7.1 Hz, OC*H*$_2$), 3.83 (3H, s, OCH_3), 1.34 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 0.98 (9H, s, SiC(CH_3)$_3$), 0.18 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C=O), 153.3 (ArCO), 149.4 (ArCO), 139.9 (*C*H=CHCO$_2$), 124.2 (Ar_q), 122.8 (ArCH), 119.8 (ArCH), 119.0 (ArCH), 112.3 (CH=*C*HCO$_2$), 60.5 (OCH_2), 56.1 (OCH_3), 25.8 (SiC(*C*H$_3$)$_3$), 18.3 (SiC), 14.5 (Me), –4.3 (Si(CH_3)$_2$); *m*/*z* calculated for $[C_{18}H_{29}O_4Si]^+$ 337.1830 found $[M + H]^+$ 337.1834.

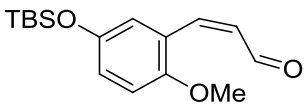


(*Z*)-3-(5-(*tert*-Butyldimethylsilyloxy)-2-methoxyphenyl)prop-2-en-1-ol 172

To a stirred solution of ester **169** (310 mg, 0.92 mmol) in PhMe (10 mL) was slowly added DIBAL-H (1.93 mL, 1.0 M in PhMe, 1.93 mmol) dropwise at –78 °C. After stirring for 2 h, MeOH (1 mL) was added slowly and the solution was allowed to warm to 23 °C over 1 h. A saturated solution of Rochelle salt (10 mL) was added and

the mixture was vigorously stirred for 30 min. The separated organic phase was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The organic phase was filtered through a short plug of silica gel before being evaporated *in vacuo* to give the *title compound* as pale yellow oil (268 mg, 98%).

ν_{max}/cm^{-1} 3349br (OH), 2954m, 2930m, 2857m, 2897m, 1489s, 1463m, 1417m, 1282m, 1216s (C−O), 1032m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76–6.70 (2H, m, 2 × ArCH), 6.65–6.58 (2H, m, ArCH and C*H*=CHCO), 5.90 (1H, dt, J = 11.8 and 6.6 Hz, CH=C*H*CO), 4.31 (2H, dd, J = 6.6 and 5.4 Hz, OCH_2), 3.78 (3H, s, OCH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.18 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7 (ArCO), 149.0 (ArCO), 131.2 (Ar–C=*C*), 126.8 (Ar–*C*=C), 126.2 (Ar_q), 121.9 (ArCH), 119.7 (ArCH), 111.6 (ArCH), 60.0 (OCH_2), 56.1 (OCH_3), 25.8 ($SiC(CH_3)_3$), 18.3 (SiC), –4.3 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{16}H_{25}O_3Si]^+$ 293.1567 found [M – 2H + H]$^+$ 293.1572.

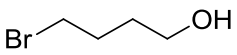


(*Z*)-3-(5-(*tert*-Butyldimethylsilyloxy)-2-methoxyphenyl)acrylaldehyde 168

To a stirred solution of alcohol **172** (212 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane[60] (305 mg, 0.72 mmol). The solution was stirred for 2 h after which time water (5 mL) was added. The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 10% Et_2O in petrol) to give the *title compound* as yellow oil (161 mg, quantitative yield).

ν_{max}/cm^{-1} 2955m, 2930m, 2857m, 1674s (conjugated C=O), 1576w, 1489s, 1419m, 1219s (C−O), 1030m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (1H, d, J = 8.1 Hz, C*H*O), 7.70 (1H, d, J = 11.5 Hz, C*H*=CHCO), 6.87 (1H, dd, J = 8.8 and 2.8 Hz, ArCH),

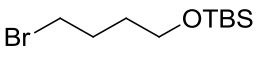
6.79–6.75 (2H, m, 2 × ArCH), 6.15 (1H, dd, *J* = 11.5 and 8.1 Hz, CH=C*H*CO), 3.82 (3H, s, OCH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (C=O), 152.2 (ArCO), 148.9 (ArCO), 144.7 (*C*H=CHCHO), 130.0 (CH=*C*HCHO), 123.9 (Ar_q), 123.5 (ArCH), 122.3 (ArCH), 111.7 (ArCH), 56.0 (OCH_3), 25.7 ($SiC(CH_3)_3$), 18.2 (SiC), –4.5 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{16}H_{25}O_3Si]^+$ 293.1567 found $[M + H]^+$ 293.1572.



4-Bromo-1-butanol 174

To stirred and refluxing THF (60 mL) was added HBr (27 mL, 48% in water, 0.24 mol) dropwise, followed by continued reflux for 2 h. After this time the reaction was cooled to 0 °C and neutralised with $NaHCO_3$ (sat. aq.) (judged as pH 7 by indicator paper). The organic layer was then separated and washed with water (60 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the title compound as yellow oil (12.3 g, 33%) which was used without further purification. Data are consistent with those previously reported in the literature.[71]

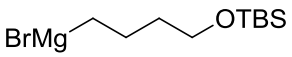
ν_{max}/cm^{-1} 3338w, 2917w, 1646w, 1433w, 1049m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (2H, t, *J* = 6.3 Hz, OCH_2), 3.45 (2H, t, *J* = 6.7 Hz, $BrCH_2$), 2.00–1.93 (2H, m, CH_2), 1.75–1.68 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 61.7 (OCH_2), 33.8 (CH_2), 31.1 (CH_2), 29.3 (CH_2).



4-Bromo-1-(*tert*-butyldimethylsilyloxy)butane 173

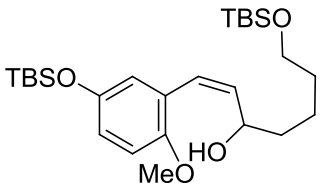
To a solution of 4-bromo-1-butanol **174** (500 mg, 3.3 mmol) in CH_2Cl_2 (30 mL) was added imidazole (445 mg, 6.5 mmol) and TBSCl (7.39 g, 4.9 mmol) at 0 °C. After stirring for 2 h at 0 °C, water (20 ml) was added. The organic layer was separated, dried over $MgSO_4$ and filtered. Purification of the residue by flash column chromatography (SiO_2; 10% Et_2O in petrol) gave the title compound as pale yellow oil (8.82 g, quantitative yield). Data are consistent with those previously reported in the literature.[72a]

ν_{max}/cm^{-1} 2990w, 2858w, 2361w, 1468m; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (2H, t, J = 6.1 Hz, OCH_2), 3.45 (2H, t, J = 6.8 Hz, $BrCH_2$), 1.98–1.90 (2H, m, CH_2), 1.69–1.62 (2H, m, CH_2), 0.89 (9H. s, $SiC(CH_3)_3$), 0.05 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.3 (OCH_2), 34.1 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 26.1 ($SiC(CH_3)_3$), 18.5 (SiC), –5.2 ($Si(CH_3)_2$).



(4-((*tert*-Butyldimethylsilyl)oxy)butyl)magnesium bromide 175

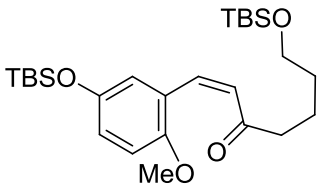
To a vigorously stirred suspension of magnesium turnings (0.48 g, 19.9 mmol) and a small pellet of I_2 in THF (15 mL) was added alkyl bromide **173** (1.33 g, 4.96 mmol) in THF (5 mL). After warming to reflux over 1 h and then allowing to cool to 23 °C, a cloudly grey mixture had formed. The Grignard **175** in THF, with an undetermined molarity, was used immediately in the next step (page 152).[72b]



(*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-1-(3-((*tert*butyldimethylsilyl)oxy)(6-methoxy)phenyl)hept-1-en-3-ol 176

To a stirred solution of aldehyde **168** (670 mg, 3.00 mmol) in THF (10 mL) at –78 °C was slowly added Grignard **175** (15 mL in THF prepared from 1.33 g of alkyl bromide, see page 149). The solution was stirred for 2 h, after which time NH_4Cl (sat. aq., 2 mL) was added. The reaction was allowed to warm to room temp before the mixture was diluted with Et_2O (20 mL). The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* before the residue was purified by flash column chromatography (SiO_2; 30% Et_2O in petrol) to give the *title compound* as pale yellow oil (484 mg, 44%).

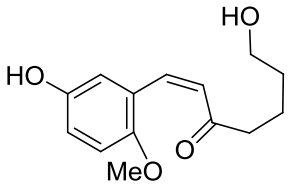
ν_{max}/cm^{-1} 3399br (O-H), 2929m, 2857m, 1490s, 1472m, 1419m, 1252s (C−O), 1216s, 1098s, 1035m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76–6.66 (3H, m, 3 × ArCH), 6.53 (1H, d, J = 11.5 Hz, *H*C=C), 5.68 (1H, dd, J = 11.5 and 9.4 Hz, C=C*H*), 4.43–4.34 (1H, m, OC*H*), 3.77 (3H, s, OCH_3), 3.58 (1H, t, J = 6.5 Hz, OCH_2), 1.89 (1H, brs, OH), 1.70–1.30 (6H, m, 3 × CH_2), 0.98 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6 (ArCO), 149.1 (ArCO), 135.1 (*C*H=CCO), 126.6 (Ar_q), 126.5 (CH=*C*CO), 121.9 (ArCH), 119.6 (ArCH), 111.8 (ArCH), 68.3 (OCH), 63.3 (OCH_2), 56.2 (OCH_3), 37.0 (CH_2), 33.0 (CH_2), 26.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.9 (CH_2), 18.5 (SiC), 18.3 (SiC), –4.3 ($Si(CH_3)_2$), –5.1 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{26}H_{48}O_4Si_2Na]^+$ 503.2983 found $[M + Na]^+$ 503.2976.



(*Z*)-7-((*tert*-butyldimethylsilyl)oxy)-1-(3-((*tert*butyldimethylsilyl)oxy)(6-methoxyphenyl)hept-1-en-3-one 178

To a stirred solution of (*Z*)-allylic alcohol **176** (476 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (2.50 g, 5.89 mmol). Stirring was continued for 24 h, after which time water (2 mL) was added. The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 15% Et_2O in petrol) to give the *title compound* as yellow oil (396 mg, 84%).

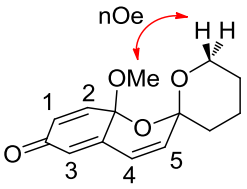
ν_{max}/cm^{-1} 2953m, 2929m, 2886w, 2857m, 1691m (C=O), 1595w, 1576w, 1489m, 1252m, 1218s, 1099m, 1032m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, d, J = 12.7 Hz, C*H*=CHCO), 6.90 (1H, d, J = 2.8 Hz, ArCH), 6.78 (1H, dd, J = 8.8 and 2.8 Hz, ArCH), 6.73 (1H, d, J = 8.8 Hz, ArCH), 6.14 (1H, d, J = 12.7 Hz, CH=C*H*CO), 3.78 (3H, s, OCH_3), 3.55 (2H, t, J = 6.4 Hz, OCH_2), 2.43 (2H, t, J = 7.4 Hz, O=CCH_2), 1.64–1.54 (2H, m, CH_2), 1.49–1.40 (2H, m, CH_2), 0.97 (9H, s, SiC$(CH_3)_3$) 0.87 (9H, s, SiC$(CH_3)_3$), 0.17 (6H, s, Si$(CH_3)_2$), 0.02 (6H, s, Si$(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5 (C=O), 151.8 (ArCO), 148.9 (ArCO), 134.9 (C*H*=CHCO), 129.2 (CH=*C*HCO), 125.4 (Ar_q), 122.0 (ArCH), 121.5 (ArCH), 111.5 (ArCH), 63.0 (OCH_2), 56.0 (OCH_3), 42.9 (O=C*C*H_2), 32.4 (OCH_2*C*H_2), 26.1 (SiC(*C*$H_3)_3$), 25.8 (SiC(*C*$H_3)_3$), 20.8 (O=CCH_2*C*H_2), 18.5 (SiC), 18.3 (SiC), –4.4 (Si$(CH_3)_2$), –5.2 (Si$(CH_3)_2$); *m*/*z* calculated for $[C_{26}H_{47}O_4Si_2]^+$ 479.3007 found $[M + H]^+$ 479.3002.



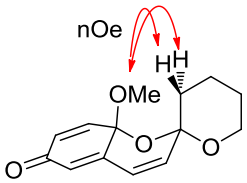
(*Z*)-7-Hydroxy-1-(3-hydroxy-6-methoxyphenyl)hept-1-en-3-one 156

To a stirred solution of (*Z*)-Enone **178** (300 mg, 0.627 mmol) in THF (5 mL) was added a solution of TBAF (1.38 mL, 1.0 M in THF, 1.38 mmol). The solution was stirred at room temp for 90 min, after which time NH_4Cl (sat. aq., 5 mL) was added. The reaction mixture was diluted with Et_2O (20 mL), before the separated organic phase was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* before the residue was purified by flash column chromatography (SiO_2; 100% EtOAc) to give the *title compound* as yellow oil (147 mg, 94%).

ν_{max}/cm^{-1} 3361br (OH), 2939m (C–H), 1679m (C=O), 1585w, 1496s, 1463s, 11281m, 11179m, 1222s, 1030m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, d, J = 12.7 Hz, C*H*=CHCO), 6.97 (1H, d, J = 3.0 Hz, ArCH), 6.84 (1H, dd, J = 8.8 and 3.0 Hz, ArCH), 6.77 (1H, J = 8.8 Hz, ArCH), 6.17 (1H, J = 12.7 Hz, CH=C*H*CO), 5.80 (brs, ArCOH), 3.80 (3H, s, OCH_3), 3.61 (2H, t, J = 6.0 Hz, OCH_2), 2.51 (2H, t, J = 7.0 Hz, O=CC*H*$_2$), 1.99 (1H, brs, CH_2OH), 1.74–1.65 (2H, m, CH_2), 1.57–1.49 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3 (C=O), 151.6 (ArCO), 149.3 (ArCO), 135.5 (*CH*=CHCO), 129.0 (CH=*C*HCO), 125.1 (ArCH), 123.9 (Ar_q), 117.7 (ArCH), 112.1 (ArCH), 62.4 (OCH_3), 56.2 (OCH_2), 42.1 (O=C*C*H$_2$), 31.9 (CH_2), 20.0 (CH_2); *m*/*z* calculated for $[C_{14}H_{19}O_4]^+$ 251.1278 found $[M + H]^+$ 251.1273.



147a



147b

8a-Methoxy-3',4',5',6'-tetrahydrospiro[chromene-2,2'-pyran]-6(8aH)-one 147a /147b

To a stirred solution of hydroxyphenol **156** (25 mg, 0.10 mmol) in MeCN (1 mL) was added $PhI(OAc)_2$ (48 mg, 0.15 mmol). The solution was stirred for 40 min, after which time the solvent was evaporated *in vacuo*. ^1H NMR analysis of the residue revealed that the spiroketal diastereomers had been produced in 1:2 ratio*. The residue was purified by flash column chromatography (SiO_2; 20% EtOAc in petrol) to give the *title compounds* as yellow oils (**147a** = 8 mg; **147b** = 6 mg; total yield 56%). The stereochemical assignment of each diastereomer was made through NOESY difference experiments.

Spiroketal **147a** (8 mg): ν_{max}/cm^{-1} 2940m, 1667s (C=O), 1619s, 1441w, 1381w, 1285m, 1200m, 1137s, 1090s, 1044s; ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, d, J = 10.2 Hz, =C2H), 6.39 (1H, d, J = 10.2 Hz, =C5H), 6.25 (1H, dd, J = 10.2 and 2.0 Hz, =C1H), 6.07 (1H, d, J =10.2 Hz, =C4H), 6.02 (1H, d, J = 2.0 Hz, =C3H), 4.15 (1H, td, J = 11.7 and 3.2 Hz, OCH_a), 3.85–3.79 (1H, m, OCH_b), 3.28 (3H, s, OCH_3), 1.91–1.65 (6H, m, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.0 (C=O), 146.8 (=C_q),

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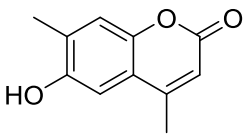
* As judged by comparison of each diastereomer's OCH_3 resonance in the ^1H NMR spectrum directly after the removal of solvent.

142.4 (=C), 137.1 (=C), 129.5 (=C), 123.3 (=C) 123.2 (=C), 95.3 ($OC_{spiro}O$), 90.8 (OCO), 62.3 (OCH_2), 51.5 (OCH_3), 36.4 (CH_2), 24.8 (CH_2), 18.3 (CH_2); *m*/*z* calculated for $[C_{26}H_{17}O_4]^+$ 249.1121 found $[M + H]^+$ 249.1120.

Spiroketal **147b** (6 mg): ν_{max}/cm^{-1} 2941m, 1662s (C=O), 1621s, 1440w, 1367w, 1290m, 1289m, 1229m, 1200m, 1141m, 1089m, 1066m; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, d, *J* = 10.2 Hz, =C2H), 6.45 (1H, d, *J* = 10.2 Hz, =C5H), 6.29 (1H, dd, *J* = 10.2 and 2.0 Hz, =C1H), 6.07 (1H, d, *J* = 2.0 Hz, =C3H), 6.04 (1H, d, *J* = 10.2 Hz, =C4H), 4.06 (1H, td, *J* = 11.7 and 3.1 Hz, OCH_a), 3.77–3.71 (1H, m, OCH_b), 3.18 (3H, s, OCH_3), 2.14–1.57 (6H, m, 3 × CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.9 (C=O), 146.2 (=C_q), 142.7 (=C), 137.2 (=C), 129.9 (=C), 124.4 (=C), 123.5 (=C), 96.3 ($OC_{spiro}O$), 92.6 (OCO), 62.4 (OCH_2), 51.1 (OCH_3), 35.6 (CH_2), 24.8 (CH_2), 18.7 (CH_2); *m*/*z* calculated for $[C_{26}H_{17}O_4]^+$ 249.1121 found $[M + H]^+$ 249.1121.

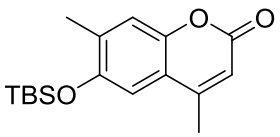
6-Hydroxy-4,7-dimethyl-2H-chromen-2-one 192



To a mixture of methyl hydroquininone (6.00 g, 48.3 mmol) and ethyl acetoacetate (3.36 mL, 25.8 mmol) was cautiously added conc. H_2SO_4 (20 mL). After stirring for 16 h, the mixture was poured onto ice-cold water (500 mL) and allowed to warm to room temp. The precipitate was collected by vacuum filtration and rinsed with copious amounts of water, followed by Et_2O (5 × 20 mL). The solid was then dried at 0.1 mbar for 16 h to give the title compound as a beige amorphous solid (2.52 g, 51%). For the purpose of melting point characterisation a small amount of

amorphous solid was purified by recrystallisation from EtOH to give brown needles. Data are consistent with those previously reported in the literature.[78]

mp 208–209 °C (lit. 207–208 °C)[78]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (1H, s, ArCH), 7.02 (1H, s, ArCH), 6.28 (1H, s, =CH), 2.35 (3H, s, CH_3), 2.22 (3H, s, CH_3);^{13}C NMR (101 MHz, DMSO-d_6) δ 160.2 (C=O), 152.7 (=C_q), 152.0 (ArCO), 146.2 (ArCO), 130.3 (Ar_q), 117.9 (ArCH), 117.8 (Ar_q), 113.4 (=CH), 108.3 (ArCH), 18.0 (CH_3), 16.2 (CH_3).

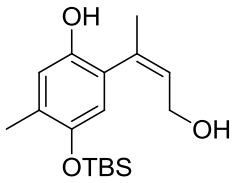


(*tert*-Butyldimethylsilyloxy)-4,7-dimethyl-2H-chromen-2-one 193

To a stirred solution of 6-hydroxy-4,7-dimethyl-2H-chromen-2-one **192** (1.00 g, 5.26 mmol) in DMF (40 mL) was added NEt_3 (0.80 mL, 5.77 mmol) and TBSCl (871 mg, 5.77 mmol). The solution was stirred at 23 °C for 17 h, after which time water (30 mL) was added. The separated organic layer was washed with water (4 × 20 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (SiO_2; 20% Et_2O in petrol) to give the *title compound* as colourless needles (1.50 g, 94%).

mp 92–94 °C; ν_{max}/cm^{-1} 2954w, 2930w, 2893w, 2858w, 1710s (C=O), 1557m, 1501m, 1414m, 1387m, 1281m, 1234m, 1165m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, s, ArCH), 6.90 (1H, s, ArCH), 6.22 (1H, s, =CH), 2.36 (3H, s, CH_3), 2.29 (3H, s, $ArCH_3$), 1.04 (9H, s, $SiC(CH_3)_3$), 0.24 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (C=O), 152.0 (=C_q), 150.6 (ArCO), 148.2 (ArCO), 134.9 (Ar_q), 119.0 (ArCH), 118.3 (Ar_q), 114.4 (=CH), 112.5 (ArCH), 25.9 ($SiC(CH_3)_3$), 18.7

(Ar*C*H_3), 18.4 (SiC), 17.5 (CH_3), –4.1 (Si(CH_3)$_2$); *m*/*z* calculated for [$C_{17}H_{25}O_3Si$]$^+$ 305.1567 found [M + H]$^+$ 305.1567.

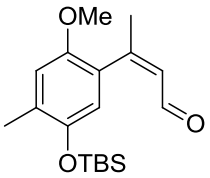


(*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-(4-hydroxybut-2-en-2-yl)-5-methylphenol 196

To a stirred suspension of $LiAlH_4$ (338 mg, 8.9 mmol) in THF (60 mL) was added BnCl (1.0 mL, 8.9 mmol) at 23 °C. After stirring for 35 min, 6-(*tert*-butyldimethylsilyloxy)-4,7-dimethyl-2H-chromen-2-one **193** (1.8 g, 5.9 mmol) in THF (40 mL) was added dropwise *via* a cannula over 5 min. After 15 min the solution was cooled to 0 °C and cautiously quenched by dropwise addition of NH_4Cl (sat. aq., 2 mL). After warming to room temp the mixture was filtered and the solids were rinsed with EtOAc (20 mL). The filtrate was washed with water (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude residue was purified by flash column chromatography (SiO_2; 25%→50% EtOAc in petrol) to give the *title compound* as pale yellow oil, which upon standing for two days formed pale yellow needles (1.10 g, 61%).

mp 72–75 °C; ν_{max}/cm^{-1} 3287br (O–H), 2956w, 2930w, 2858w, 1659w, 1498m, 1472m, 1255s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (1H, s, ArCH), 6.42 (1H, s, ArCH), 5.93–5.88 (1H, m, =CH), 5.43 (1H, s, ArCOH), 3.93 (2H, d, J = 7.3 Hz, OCH_2), 2.15 (3H, s, ArCH_3), 2.00 (3H, brs, CH_3), 1.00 (9H, s, SiC(CH_3)$_3$), 0.17 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6 (ArCO), 145.7 (ArCO), 137.1 (Ar–*C*=), 129.6 (Ar_q), 127.6 (=CH), 125.0 (Ar_q), 118.5 (ArCH), 118.4 (ArCH), 60.5

(OCH_2), 25.9 ($SiC(CH_3)_3$), 25.6 (CH_3C=), 18.4 (SiC), 16.9 ($ArCH_3$), –4.1 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{17}H_{28}O_3Si + NH_4Cl]^+$ 326.2146 found 326.2149.



(*Z*)-3-(5-((*tert*-Butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)but-2-enal 197

To a stirred solution of (*Z*)-allylic alcohol **196** (1.10 g, 3.57 mmol) and MeI (0.24 mL, 3.86 mmol) in DMF (30 mL) was added Cs_2CO_3 (1.60 g, 4.90 mmol). Stirring was continued for 17 h, with subsequent addition of water (101 mL) and Et_2O (100 mL). The separated organic layer was washed with water (4 × 20 mL), brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give *(Z)-anisole* as yellow oil which was used directly in the next step. A solution of *(Z)-anisole* (610 mg, 1.9 mmol) and activated MnO_2 (3.3 g, 38.0 mmol) in CH_2Cl_2 (20 mL) was stirred for 1 h at 23 °C. After this time, the solid was filtered off and the solid was rinsed with EtOAc (2 × 10 mL). The filtrate was dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and purification by flash column chromatography (SiO_2; 20% Et_2O in petrol) gave the *title compound* as yellow oil, which upon standing crystallised into pale yellow plates (410 mg, 37% over 2 steps).

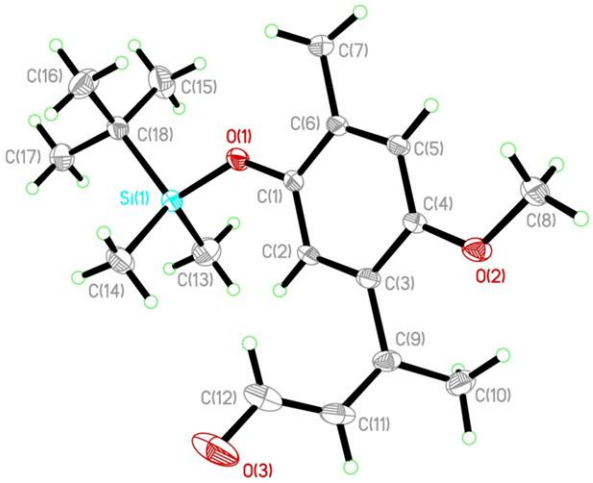
mp 40–43 °C; ν_{max}/cm^{-1} 2955w, 2931w, 2858w, 1677s (conjugated C=O), 1499s, 1464m, 1399s, 1254m, 1210s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (1H, d, J = 8.2 Hz, CHO), 6.72 (1H, s, ArCH), 6.53 (1H, s, ArCH), 6.08 (1H, dq, J = 8.2 and 1.4 Hz, =CH), 3.76 (3H, s, OCH_3), 2.23 (6H, s, 2 × CH_3), 1.00 (9H, s, $SiC(CH_3)_3$), 0.18 (6H, s, $(SiCH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8 (C=O), 160.4 (Ar–*C*=C),

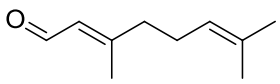
150.3 (ArCO), 147.3 (ArCO), 130.5 (Ar_q), 129.8 (C=*C*H), 125.3 (Ar_q), 120.4 (ArCH), 114.2 (ArCH), 56.1 (OCH_3), 26.1 (=C*C*H_3), 25.9 (SiC(*C*H_3)$_3$), 18.4 (SiC), 17.3 (Ar*C*H_3), –4.1 (Si(CH_3)$_2$); *m*/*z* calculated for $[C_{18}H_{29}O_3Si]^+$ 321.1880 found [M + H]$^+$ 321.1884.

X-Ray Crystallographic Data 197:

These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

CCDC 1043759 contains the supplementary crystallographic data for this compound.



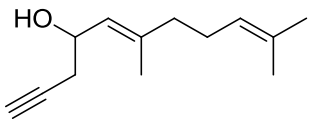


(*E*)-3,7-dimethylocta-2,6-dienal (geranial)

Activated MnO_2 (28.2 g, 0. 32 mol) was slowly added to a stirred solution of geraniol (5.00 g, 32.4 mmol) in CH_2Cl_2 (50 mL) with continued was stirring for 72 h.

After this time, the mixture was filtered and rinsed with CH_2Cl_2 (4 × 20 mL). The solvent was removed *in vacuo* to give the title compound pale yellow oil (4.20 g, 72%) which was used without further purification. Data are consistent with those previously reported in the literature.[81]

ν_{max}/cm^{-1} 2967w, 2916w, 2856w, 1671s (C=O), 1611m, 1441m, 1378m, 1193m, 1120m; ^1H NMR (400 MHz, $CDCl_3$) δ 9.99 (1H, d, J = 8.0 Hz, CHO), 5.90–5.86 (1H, m, =CH), 5.10–5.04 (1H, m, =CH), 2.26–2.18 (4H, m, 2 × CH_2), 2.16 (3H, d, J = 1.7 Hz, CH_3), 1.69 (3H, s, CH_3), 1.61 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4 (C=O), 163.8 (=C), 133.1 (=C), 127.6 (=C), 122.7 (=C), 40.8 (CH_2), 25.9 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 17.7 (CH_3).



6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol 190

To a stirred mixture of geranial (4.20 g, 28 mmol) and zinc dust (18 g) (activated by washing with dilute HCl) in THF (50 mL) was added propargyl bromide (8.8 mL, 84 mmol) at 0 °C. The solution was allowed to reach room temp and then NH_4Cl (aq. sat., 5 mL) was added (vigorous reaction!)[*]. The mixture was vigorously stirred for 3 h after which time more NH_4Cl (sat. aq., 40 mL) was added. The mixture was filtered and rinsed with Et_2O (50 mL). The filtrate was washed with water and the separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 5→50% Et_2O

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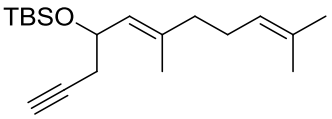
* Reaction prone to a rapid exothermic rate increase. Use excessively large RBF to prevent over-spill and a blast shield.

in petrol) to give the title compound as pleasant smelling pale yellow oil (2.80 g, 52%). Data are consistent with those previously reported in the literature.[81]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (1H, d, J = 8.5 Hz, =CH), 5.09 (1H, t, J = 6.5 Hz, =CH), 4.58–4.52 (1H, m, OCH), 2.43–2.40 (2H, m, CH_2), 2.15–1.99 (4H, m, 2 × CH_2), 1.83–1.80 (1H, m, C≡CH), 1.71 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.60 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (=C), 131.9 (=C), 125.8 (=C), 123.9 (=C), 81.0 (C≡*C*H), 70.5 (*C*≡CH), 66.9 (CO), 39.6 (*C*H_2C≡), 27.9 (CH_2), 26.5 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 16.9 (CH_3).

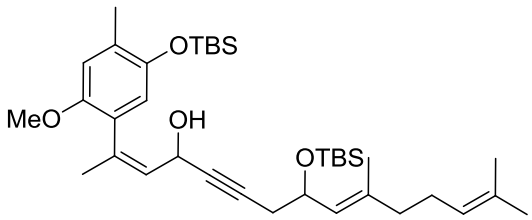


(*E*)-4-(*tert*-Butyldimethylsilyloxy)-6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol 200

To a stirred solution of (*E*)-6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol **190** (825 mg, 4.26 mmol) in CH_2Cl_2 (30 mL) was added TBSCl (707 mg, 4.69 mmol), NEt_3 (0.9 mL, 6.49 mmol) and DMAP (1 crystal) at 23 °C. After stirring for 17 h, water (10 mL) was added. The organic layer was separated, washed with water (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 2% EtOAc in petrol) to give the *title compound* as colourless oil (1.20 g, 92%).

ν_{max}/cm^{-1} 3314w (C≡CH), 2956m, 2929m, 2856m, 2737m, 2122vw (C≡C), 1671w (C=C), 1471w, 1378w, 1361w, 1070s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18–5.14 (1H, m, =CH), 5.12–5.07 (1H, m, =CH), 4.53 (1H, dt, J = 8.5 and 6.4 Hz, OCH), 2.39 (1H, ddd, J = 16.5, 6.6 and 2.6 Hz, ≡CCH_a), 2.27 (1H, ddd, J = 16.5, 6.3 and 2.6 Hz, ≡CCH_b), 2.13–1.98 (4H, m, 2 × CH_2), 1.92 (1H, t, J = 2.6 Hz, ≡CH), 1.67 (3H, s, CH_3), 1.66 (3H, s, CH_3), 1.60 (3H, s, CH_3), 0.88 (9H, s, SiC(CH_3)$_3$), 0.06 (3H, s,

$SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5 (=C), 131.7 (=C), 128.1 (=C), 124.2 (=C), 82.0 (C≡*C*H), 69.3(*C*≡CH), 68.6 (CO), 39.6 (CH_2C≡), 28.7 (CH_2), 26.4 (CH_2), 26.0 (SiC(CH_3)$_3$), 25.8 (CH_3), 18.4 (SiC), 17.8 (CH_3), 16.9 (CH_3), –4.2 (Si(CH_3)), –4.7 (Si(CH_3)); *m*/*z* calculated for $[C_{19}H_{35}OSi]^+$ 307.2452 found. [M + H]$^+$ 307.2446.

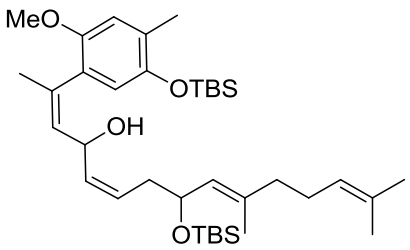


(2*Z*,9*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethylpentadeca-2,9,13-trien-5-yn-4-ol 201

To a stirred solution of (*E*)-4-(*tert*-butyldimethylsilyloxy)-6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol (240 mg, 0.78 mmol) and TMEDA (100 µL, 0.68 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexanes, 0.27 mL, 0.68 mmol) at –78 °C. The solution was allowed to warm to 20 °C with continued stirring for 1.5 h. After this time the solution was cooled to –78 °C and aldehyde **197** (167 mg, 0.52 mmol) in THF (5 mL) was added dropwise. After 15 min the solution was allowed to warm to 20 °C and was immediately poured onto an ice cold sol. NH_4Cl (sat. aq., 10 mL). The separated organic layer was washed with water (10 mL), dried over $NaSO_4$ and filtered. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 20% Et_2O in petrol) to give the *title compound* as yellow oil and a undetermined mixture of diastereomers (160 mg, 49%).

ν_{max}/cm^{-1} 3454br (O–H), 2955m, 2929m, 2856m, 1669m, 1573m, 1500m, 1463m, 1399m, 1373m, 1362m, 1307m, 1253m, 1209s, 1067m; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, s, ArCH), 6.50 (1H, s, ArCH), 5.65 (1H, dq, *J* = 9.4 and 1.4 Hz, =C*H*C–

OH), 5.13–5.06 (2H, m, 2 × =CH), 4.65–4.60 (1H, m, HOC*H*), 4.52–4.56 (1H, m, TBSO–C*H*), 3.73 (3H, s, OCH_3), 2.45–2.37 (1H, m, ≡C–CH_a), 2.30–2.23 (1H, m, ≡C–CH_b), 2.20 (3H, s, $ArCH_3$), 2.12–1.97 (7H, m, 2 × CH_2, CH_3), 1.67 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.01 (9H, s, $SiC(CH_3)_3$), 0.869 and 0.866 (9H, 2 × s, $SiC(CH_3)_3$), 0.19 (6H, s, $Si(CH_3)_2$), 0.052 and 0.047 (3H, 2 × s, $Si(CH_3)_2$), 0.029 and 0.026 (3H, 2 × s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 147.7, 137.2, 136.3, 131.8, 131.7, 128.9, 128.4, 127.5, 124.3, 120.1, 114.8, 83.3, 83.2, 81.5, 81.4, 69.02, 69.00, 60.8, 56.6, 39.8, 39.8, 29.3, 26.5, 26.1, 26.1, 26.0, 25.0, 18.5, 18.0, 17.3, 17.02, 17.0, –3.9, –4.0, –4.1, –4.1, –4.5*; *m*/*z* calculated for $[C_{37}H_{62}O_4Si_2 + NH_4]^+$ 644.4525 found 644.4513.



(2*Z*,5*Z*,9*E*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethylpentadeca-2,5,9,13-tetraen-4-ol 202

A solution of (*Z*)-propargyl alcohol **201** (160 mg, 0.26 mmol), Lindlar catalyst (60 mg) and quinoline (6 µL) in EtOAc (9 mL) was vigorously stirred under 1 atm of hydrogen at 23 °C. After 23 h additional Lindlar catalyst (150 mg) was added over 8 h with continued stirring. After this time the solution was filtered and rinsed with EtOAc (10 mL). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 10% Et_2O in petrol) to give the *title compound* as pale yellow oil and an undetermined mixture of diastereomers (126 mg, 78%).

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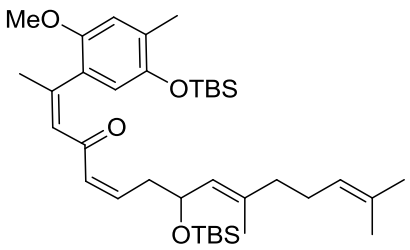
* Due to a mixture of two diastereomers the ^{13}C NMR spectrum could not be assigned.

ν_{max}/cm^{-1} 3459br (O–H), 2855w, 2929w, 2857w, 1500m, 1464m, 1398m, 1253m, 1208s, 1058m 1012m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, s, ArCH), 6.54–6.50 (1H, m, ArCH), 5.61–5.51 (2H, m, ArC=C*H*, HOC–C*H*=CH), 5.48–5.37 (1H, m, HOC–CH=C*H*), 5.09–5.02 (2H, m, 2 × =C*H*), 4.70–4.61 (1H, m, HO–C*H*), 4.30–4.21 (1H, m, TBSO–C*H*), 3.73 (3H, s, OCH_3), 2.36 (s, OH), 2.20 (3H, s, CH_3), 2.13–1.84 (9H, m, 3 × CH_2, CH_3), 1.66 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.51 (3H, m, CH_3), 1.01 (9H, s, $SiC(CH_3)_3$), 0.83 (9H, s, $SiC(CH_3)_3$), 0.18 (6H, m, $Si(CH_3)$), –0.03 (3H, 2 × s, $Si(CH_3)_2$), –0.04 (3H, 2 × s, $Si(CH_3)$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 150.1, 147.6, 147.6, 134.8, 134.8, 133.5, 133.1, 131.6, 129.8, 129.0, 128.9, 128.4, 128.3, 128.3, 128.2, 127.9, 124.2, 119.9, 119.8, 114.4, 69.7, 69.5, 66.4, 65.8, 56.3, 39.6, 39.6, 36.8, 36.7, 26.4, 26.4, 26.0, 26.0, 25.9, 25.8, 18.3, 17.8, 17.1, 16.5, –4.0, –4.1, –4.2, –4.3, –4.6, –4.7; *m*/*z* calculated for $[C_{37}H_{64}O_4Si_2]^+$ 628.4338 found $[C_{37}H_{64}O_4Si_2]^+$ 628.4341

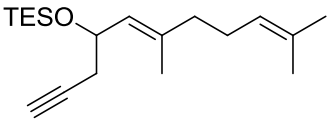


(2*Z*,5*Z*,9*E*)-8-((*tert*-butyldimethylsilyl)oxy)-2-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethylpentadeca-2,5,9,13-tetraen-4-one 203

To a stirred solution of (*Z*),(*Z*)-dienol **202** (84 mg, 0.13 mmol) in $CHCl_3$ (1 mL) was added activated MnO_2 (464 mg, 5.2 mmol) at 23 °C. After 25 h, the mixture was filtered over a 3 cm plug of silica and washed with Et_2O (10 mL). The solvent was removed *in vacuo* to give the *title compound* as yellow oil (56 mg, 69%).

ν_{max}/cm^{-1} 2956m, 2929m, 2857m, 1652m (C=O), 1609m (C=O), 1501m, 1464m, 1400m, 1374m, 1254m, 1211s, 1064m, 1021w, 1005m, 1064m, 1021m; ^{1}H NMR

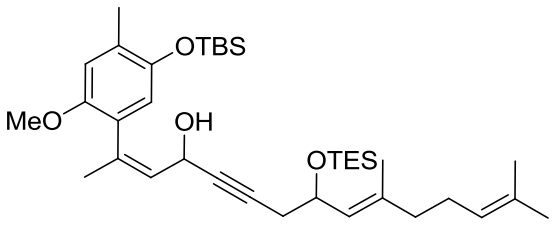
(400 MHz, $CDCl_3$) δ 6.66 (1H, s, ArCH), 6.43 (1H, s, ArCH), 6.15 (1H, s, Ar–C=CH), 5.91–5.81 (2H, m,O=C–C*H*=CH, O=C–CH=C*H*), 5.12–5.03 (2H, m, 2 × =CH), 4.38 (1H, dt, J = 8.4, 6.5 Hz, OCH), 3.72 (3H, s, OCH_3), 2.67–2.62 (2H, m, TBSO–C–CH_2), 2.20 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.09–2.02 (2H, m, CH_2), 1.97–1.93 (2H, m, CH_2), 1.65 (3H, s, CH_3), 1.59–1.55 (6H, m, 2 × CH_3), 0.99 (9H, s, $SiC(CH_3)_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.13 (6H, s, $Si(CH_3)_2$), –0.01 (3H, s, $Si(CH_3)$), –0.02 (3H, s, $Si(CH_3)$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7 (C=O), 149.9 (=C_q), 148.7 (ArCO), 147.4 (ArCO), 143.5 (=CH), 135.1 (Ar_q), 131.6 (Ar_q), 130.4 (=CH), 129.5 (=C_q), 129.0 (=CH), 128.0 (=CH), 128.0 (=C_q), 124.3 (=CH), 119.5 (ArCH), 114.1 (ArCH), 69.5 (OCH), 56.0 (OCH_3), 39.6 (CH_2), 38.6 (CH_2), 26.4 (CH_3), 26.2 (CH_2), 26.0 (CH_3), 25.9 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.33 (SiC), 18.29 (SiC), 17.8 (CH_3), 17.3 (CH_3), 16.6 (CH_3), –4.10 ($Si(CH_3)$), –4.13 ($Si(CH_3)$), –4.7 ($Si(CH_3)_2$).



(*E*)-4-(Triethylsilyloxy)-6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol 206

To a stirred solution of 6,10-dimethyl-undeca-5,9-dien-1-yn-4-ol (2.5 g, 13 mmol) in CH_2Cl_2 (20 mL) was added TESCl (2.3 mL, 14 mmol) and imidazole (2.1 g, 30 mmol). The solution was stirred for 17 h, after which time water (20 mL) was added. The organic layer was separated and washed with NH_4Cl (sat. aq., 10 mL), water (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue that was filtered over 3 cm plug of silica to give the *title compound* as colourless oil (3.99 g, quantitative yield).

ν_{max}/cm^{-1} 3314w (H−C≡C), 2955m, 2935m, 2913m, 2876m, 2122w (C≡C), 1671w, 1513m, 1378m, 1238m, 1070s, 1005s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21–5.16 (1H, m =CH), 5.12–5.07 (1H, m, =CH), 4.53 (1H, dt, J = 8.7 and 6.4 Hz, OCH), 2.41 (1H, ddd, J = 16.5, 6.2, 2.7 Hz, CH_a), 2.29 (1H, ddd, J = 16.5, 6.7 and 2.7 Hz, CH_b), 2.14–1.98 (4H, m, 2 × CH_2), 1.92 (1H, apparent t, J = 2.7 Hz, C≡CH), 1.68–1.66 (6H, m, 2 × CH_3), 1.61 (3H, s, CH_3), 0.95 (9H, s, J = 7.8 Hz, Si(CH_3)$_3$), 0.59 (6H, q, J = 7.8 Hz, Si(CH_2)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7 (=C), 131.7 (=C), 127.8 (=C), 124.2 (=C), 81.7 (HC≡), 69.5 (≡C), 68.2 (OC), 39.7 (CH_2), 28.8 (CH_2), 26.4 (CH_2), 25.8 (CH_3), 17.8 (CH_3), 17.0 (CH_3), 6.9 (Si(CH_2)$_3$(*C*H_3)$_3$), –5.0 (Si(*C*H_2)$_3$(CH_3)$_3$); *m*/*z* calculated for [$C_{19}H_{34}OSi$ + NH_4]$^+$ 324.2717 found [M + NH_4]$^+$ 324.2717.

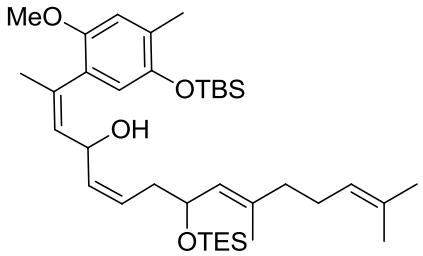


(2*Z*,9*E*)-8-((Triethylsilyl)oxy)-2-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethylpentadeca-2,9,13-trien-5-yn-4-ol 207

To a stirred solution of alkyne **206** (2.08 g, 6.78 mmol) in THF (20 mL) was added *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.75 mmol) at –78 °C. After stirring for 30 min, the solution was warmed to –45 °C with continued stirring for 30 min. After this time the solution was cooled to –78 °C followed by the slow addition of aldehyde **197** (1.67 g, 5.45 mmol) in THF (5 mL). After stirring for 10 min the solution was allowed to warm to 0 °C and was then quenched with NH_4Cl (sat. aq.). The organic layer was diluted with Et_2O (50 mL) and washed with water (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which

was purified by flash column chromatography (SiO_2; 10% Et_2O in petrol) to give the *title compound* as pale yellow oil and an unidentified mixture of diastereomers (3.13 g, 94%).

ν_{max}/cm^{-1} 3343br (O–H), 2954m, 2930m, 2877m, 2858m, 1750w, 1667w, 1500m, 1463m, 1399m, 1209s, 1058m, 1013m; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, s, ArCH), 6.50 (1H, s, ArCH), 5.65 (1H, d, J = 9.3 Hz, ArC=CH), 5.16–5.07 (2H, m, 2 × =CH), 4.62 (1H, m, HOC*H*), 4.49 (1H, dt, J = 8.6 and 6.7 Hz, TESOC*H*), 3.73 (3H, s, OCH_3), 2.47–2.40 (1H, m, ≡CCH_a), 2.33–2.26 (1H, m, ≡CCH_b), 2.20 (3H, s, CH_3), 2.10–1.96 (7H, m, 2 × CH_2, CH_3), 1.68–1.65 (6H, m, 2 × CH_3), 1.60 (3H, s, CH_3), 1.00 (9H, s, $SiC(CH_3)_3$), 0.94 (9H, t, J = 7.9 Hz, $Si(CH_2CH_3)_3$), 0.57 (6H, q, J = 7.9 Hz, $Si(CH_2CH_3)_3$), 0.19 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 147.6, 137.1, 136.5, 131.7, 128.7, 128.2, 128.0, 127.3, 124.2, 119.9, 119.9, 114.6, 82.9, 81.4, 81.3, 68.5, 60.7, 56.5, 39.7, 39.7, 29.2, 26.4, 26.4, 25.9, 25.8, 24.9, 18.4, 17.8, 17.2, 16.9, 16.9, 6.9, 5.0, –4.1, –4.1; *m*/*z* calculated for $[C_{37}H_{64}O_4Si_2]^+$ 628.4338 found $[M]^+$ 628.4328.

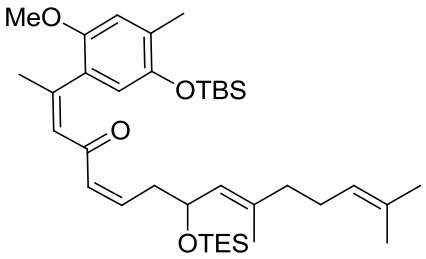


(2*Z*,5*Z*,9*E*)-2-(5-((*tert*-Butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethyl-8-((triethylsilyl)oxy)pentadeca-2,5,9,13-tetraen-4-ol 208

A solution of (*Z*)-propargyl alcohol **207** (3.13 g, 4.99 mmol), Lindlar catalyst (945 mg) and quinoline (0.30 mL) in EtOAc (15 mL) was stirred under 1 atm of hydrogen. After 72 h, the mixture was filtered and the solids were rinsed with EtOAc (4 × 10

mL). The solvent was removed *in vacuo* and puification of the residue by flash column chromatography (SiO_2; 10% Et_2O in petrol) gave the *title compounds* as pale yellow oil and an unidentified mixture of diastereomers (2.80 g, 89%).

ν_{max}/cm^{-1} 3444br (O–H), 2954m, 2930m, 2877m, 2858m, 1500m, 1463m, 1398m, 1398m, 1254m, 1208s, 1058m, 1011s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, s, ArCH), 6.56–6.50 (1H, m, ArCH), 5.64–5.56 (2H, m, 2 × =CH), 5.48–5.38 (1H, m, =CH), 5.11–5.05 (2H, m, 2 × =CH), 4.70–4.61 (1H, m, OCH), 4.33–4.22 (1H, m, OCH), 3.72 (3H, s, OCH_3), 2.20 (3H, s, CH_3), 2.08–1.92 (9H, m, 3 × CH_2, CH_3), 1.67 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.55–1.53 (3H, m, CH_3), 1.01 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, t, J = 7.9 Hz, $Si(CH_2C\mathit{H}_3)_3$), 0.51 (6H, q, J = 7.9 Hz, $Si(C\mathit{H}_2CH_3)_3$), 0.18 (6H, m, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 150.2, 147.6, 147.5, 135.1, 135.0, 134.0, 133.7, 131.6, 131.6, 129.8, 129.8, 128.8, 128.6, 128.4, 128.3, 128.2, 127.6, 124.2, 124.2, 119.9, 119.8, 114.4, 69.2, 69.0, 66.2, 65.5, 56.3, 39.6, 39.6, 36.9, 36.6, 26.4, 26.4, 25.9, 25.8, 25.8, 25.3, 25.2, 18.3, 17.8, 17.1, 16.6, 16.6, 6.9, 6.9, 4.9, 4.9, –4.0, –4.1, –4.1; *m*/*z* calculated $[C_{37}H_{62}O_4Si_2]$ 626.4181 found $[M]^+$ 626.4186.

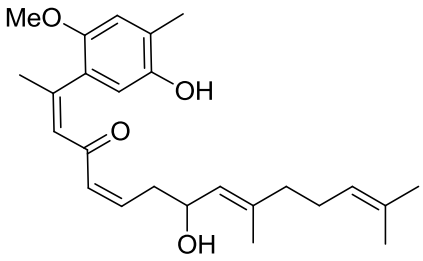


(2*Z*,5*Z*,9*E*)-2-(5-((*tert*-Butyldimethylsilyl)oxy)-2-methoxy-4-methylphenyl)-10,14-dimethyl-8-((triethylsilyl)oxy)pentadeca-2,5,9,13-tetraen-4-one 209

To a stirred solution of (*Z*),(*Z*)-dienol **208** (1.30 g, 2.07 mmol) in CH_2Cl_2 (10 mL) was added activated MnO_2 (1.8 g, 20.7 mmol) at room temp. Upon stirring for 48 h the flask was equipped with a reflux condenser and the reaction was warmed to 40

°C with the further addition of MnO_2 (2.3 g). After stirring for 17 h, the mixture was filtered under vacuum and the solid was rinsed with EtOAc (4 × 25 mL). The bright-yellow filtrate was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (SiO_2; 10% Et_2O in petrol) gave the *title compound* as yellow oil (1.0 g, 77%). The compound was stored under argon in the dark at –80 °C.

ν_{max}/cm^{-1} 2955m, 2931m, 2877m, 2858m, 1651m (C=O), 1609m (C=O), 1500m, 1463m, 1399m, 1374m, 1255m, 1210s, 1062m, 1210m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, s, ArCH), 6.43 (1H, m, ArCH), 6.15 (1H, q, J = 1.4 Hz, Ar–C=CH), 5.91–5.80 (2H, m, 2 × =CH), 5.12 (1H, dq, J = 8.6 and 1.3 Hz, =CH), 5.09–5.04 (1H, m, =CH), 4.39 (1H, dt, J = 7.8 and 6.8 Hz, OCH), 3.72 (3H, s, OCH_3), 2.72–2.58 (2H, m, CH_2), 2.20 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.08–2.02 (2H, m, CH_2), 1.98–1.92 (2H, m, CH_2), 1.65 (3H, s, CH_3), 1.58 (6H, s, 2 × CH_3), 0.99 (9H, s, $SiC(CH_3)_3$), 0.90 (9H, t, J = 7.9 Hz, $Si(CH_2C\mathit{H}_3)_3$), 0.53 (6H, q, J = 7.9 Hz, $Si(C\mathit{H}_2CH_3)_3$), 0.13 (6H, s, $Si(C\mathit{H}_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7 (C=O), 149.9 (ArC=C_q), 148.7 (ArCO), 147.4 (ArCO), 143.3 (=CH), 135.3 (Ar_q), 131.6 (Ar_q), 130.4 (=CH), 129.4 (=C_q), 128.9 (=CH), 128.1 (=C_q), 128.0 (=CH), 124.3 (=CH), 119.5 (ArCH), 114.1 (ArCH), 69.1 (OCH), 56.0 (OCH_3), 39.7 (CH_2), 38.6 (CH_2), 26.4 (CH_2), 26.2 (CH_3), 25.9 ($SiC(CH_3)_3$), 25.8 (CH_3), 18.3 (SiC), 17.8 (CH_3), 17.3 (CH_3), 16.7 (CH_3), 7.0 ($Si(CH_2\mathit{C}H_3)_3$), 5.1 ($Si(\mathit{C}H_2CH_3)_3$), –4.1 ($Si(CH_3)_2$); *m/z* calculated for [$C_{25}H_{62}O_4Si_2$] 626.4181 found [M]$^+$ 626.4174.

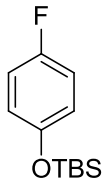


(2*Z*,5*Z*,9*E*)-8-Hydroxy-2-(5-hydroxy-2-methoxy-4-methylphenyl)-10,14-dimethylpentadeca-2,5,9,13-tetraen-4-one 205

To a stirred solution of (*Z*),(*Z*)-dienone **209** (1.00 g, 1.59 mmol) in THF (15 mL) was slowly added TBAF (1.60 mL, 1M in THF, 1.60 mmol) over 2 min at 0 °C. Subsequently, the solution was allowed to warm to 23 °C and after stirring for a further 15 min, the solution was poured onto CH_2Cl_2 (20 mL) and NH_4Cl (sat. aq., 10 mL) with vigorous stirring. The organic layer was separated, washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (SiO_2; 20% Et_2O in petrol) to give the *title compound* as thick orange oil (620 mg, 97%). The compound was left under high vacuum (*ca.* 0.1 mmHg) overnight under darkness and then stored under argon in a –80 °C freezer.

ν_{max}/cm^{-1} 3306br (O–H), 2965w, 2916w, 2855w, 1641m (conjugated C=O), 1621m (conjugated C=O), 1505m, 1454m, 1408s, 1202s, 1057m, 1016m, 1002m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, s, ArCH), 6.47 (1H, s, ArCH), 6.16 (1H, s, Ar–C=CH), 5.92–5.78 (3H, m, O=C–CH=C*H*, O=C–C*H*=CH, ArCOH), 5.21 (1H, d, *J* = 8.3 Hz, HOCC=C*H*), 5.09–5.03 (1H, m, CH_2C=C*H*), 4.49–4.42 (1H, m, HOC*H*), 3.74 (3H, s, OCH_3), 2.95 (OH), 2.80–2.71 (1H, m, HOC–CH_a), 2.55–2.47 (1H, m, HOC–CH_b), 2.25 (3H, s, CH_3), 2.18 (3H, s, CH_3), 2.10–1.95 (4H, m, 2 × CH_2), 1.66 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.59 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1 (C=O), 151.7 (=*C*–Me), 149.5 (ArCO), 147.8 (ArCO), 141.0 (=CH), 138.6

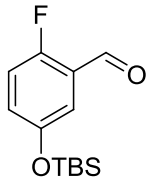
(Ar_q), 131.9 (Ar_q), 130.9 (=CH), 130.0 (=CH), 127.4 ($=C_q$), 127.2 (=CH), 125.8 ($=C_q$), 124.1 (=CH), 117.4 (ArCH), 114.2 (ArCH), 68.7 (OCH), 56.2 (OCH_3), 39.6 (CH_2) , 37.5 (CH_2), 26.5 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 17.8 (CH_3), 16.7 (CH_3), 16.4 (CH_3) ppm; *m*/*z* calculated for $[C_{25}H_{32}O_4]^+$ 397.2379 found $[M - H]^+$ 397.2376.



1-(*tert*-Butyldimethylsilyloxy)-4-fluorobenzene 220

To a stirred solution of 4-fluorophenol (4.21 g, 37.6 mmol) in CH_2Cl_2 (20 mL) was added imidazole (5.40 g, 79.3 mmol) and then TBSCl (6.20 g, 41.1 mmol). The solution was stirred for 16 h and then NH_4Cl (aq. sat.) (10 mL) was added with vigorous stirring. The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give pale yellow oil (7.97 g, 93%). The title compound was used without further purification. Data are consistent with those previously reported in the literature.[84]

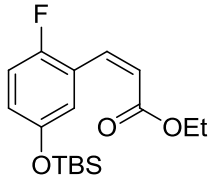
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94–6.88 (2H, m, 2 × ArCH), 6.80–6.74 (2H, m, 2 × ArCH), 0.99 (9H, s, ($SiC(CH_3)_3$)), 0.18 (6H, s, ($Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (d, J = 238.6 Hz, ArF), 156.6 (ArCO), 151.8 (d, J = 2.2 Hz, 2 × ArCH), 121.0 (d, J = 8.1 Hz, 2 × ArCH), 25.8 ($SiC(CH_3)_3$), 18.3 (SiC), –4.4 ($Si(CH_2)_2$); *m*/*z* calculated for $[C_{12}H_{19}FOSi + NH_4Cl]^+$ 186.0925 found $[M + NH_4Cl]^+$ 186.0922.



5-(*tert*-Butyldimethylsilyloxy)-2-fluoro-benzaldehyde 221

A attired solution of 1-(*tert*-butyldimethylsilyloxy)-4-fluorobenzene **220** (3.96 g, 17.5 mmol) and TMEDA (2.9 mL, 19.5 mmol) in THF (50 mL) was cooled to –78 °C and then *n*-BuLi (9.4 mL, 23.5 mmol) was added slowly. Upon stirring for 1 h DMF (2.2 mL, 28.8 mmol) was added, followed with continued stirring for 30 min. After this time the solution was allowed to warm to 23 °C and NH_4Cl (aq. sat., 10 mL) was added. The reaction was diluted with Et_2O (30 mL) and water (30 mL) was added. The separated organic phase was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography (SiO_2; petrol → 5% Et_2O in petrol) to give the title compound as slightly pale yellow oil (2.06 g, 45%). Data are consistent with those previously reported in the literature.[84]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, s, CHO), 7.27–7.25 (1H, m, ArCH), 7.06–7.03 (2H, m, 2 × ArCH), 0.98 (9H, s, $SiC(CH_3)_3$), 0.20 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.1 (d, J = 6.6 Hz, CHO), 157.4 (d, J = 252.4 Hz, ArF), 152.3 (d, J = 2.5 Hz, ArCO), 128.2 (d, J = 8.6 Hz, ArCH), 124.7 (d, J = 9.5 Hz, Ar) 118.1 (d, J = 2.1 Hz, ArCH), 117.4 (d, J = 22.1 Hz, ArCH) 25.7 ($SiC(CH_3)_3$), 18.3 (SiC), –4.4 ($Si(CH_3)_2$); ^{19}F NMR (376 MHz, $CDCl_3$) δ –131.81 to –131.86 (m, ArF).

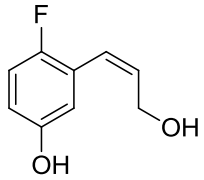


(*Z*)-Ethyl 3-(5-((*tert*-butyldimethylsilyl)oxy)-2-fluorophenyl)acrylate 223

To a stirred solution of ethyl (diphenylphosphono)acetate[69] (1.45 g, 4.37 mmol) in THF (50 mL) was added NaH (60% in mineral oil) (119 mg, 4.95 mmol) in three portions at 0 °C. After 20 min the solution was cooled to –78 °C and aldehyde **221** (740 mg, 2.91 mmol) in THF (10 mL) was added slowly (along the side of the RBF wall). Stirring was continued at –78 °C for 2 h before the solution was allowed to warm to 20 °C over 15 min followed with the addition of NH_4Cl (sat. aq.) (5 mL). The reaction mixture was diluted with Et_2O (50 mL) before the organic layer was washed with water (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a residue that contained a 9:19 mixture of *E*:*Z* isomers as judged by ^{1}H NMR spectroscopy *via* integration of alkenyl-proton signals. The isomers were separated by flash column chromatography (SiO_2; 2% Et_2O → 10% Et_2O in petrol) to give the *(Z)-isomer title compound* as pale yellow oil (550 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, dd, J = 3.0 and 3.2 Hz, ArCH), 6.93 (1H, d, J = 12.5 Hz, ArCH=C), 6.88 (1H, d, J = 9.1 Hz, ArCH), 6.75 (1H, ddd, J = 9.1, 4.1 and 3.2 Hz, ArCH), 6.04 (1H, d, J = 12.5 Hz, ArCH=C*H*), 4.16 (2H, q, J = 7.1 Hz, CH_2), 1.23 (3H, t, J = 7.1 Hz, CH_3), 0.98 (9H, s, $SiC(CH_3)_3$), 0.19 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.9 (C=O), 155.2 (d, J = 243.7 Hz, ArF), 151.1 (d, J = 2.57, ArCO), 134.9 (d, J = 3.36 Hz, ArCH), 123.7 (d, J = 14.8 Hz, Ar_q), 122.5 (d, J<1 Hz, =CH), 121.8 (d, J = 8.2 Hz, ArCH), 121.5 (d, J = 2.7 Hz, ArCH),

115.7 (d, J = 23.7 Hz, =CH), 60.5 (OCH_2), 25.8, 18.3, 14.2 (CH_3), –4.5; *m*/*z* calculated $[C_{17}H_{26}O_3SiF]^+$ 325.1630 found $[M + H]^+$ 325.1632.

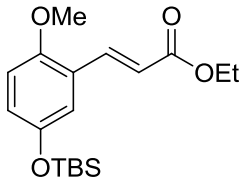


(*Z*)-4-Fluoro-3-(3-hydroxyprop-1-en-1-yl)phenol 217

To a stirred solution of (*Z*)-ester **223** (550 mg, 1.7 mmol) in PhMe (10 mL) was added DIBAL-H (3.6 mL, 3.6 mmol) at –78 °C. After stirring for 2 h, the solution was allowed to warm to 20 °C and NH_4Cl (5 mL) then a saturated solution of Rochelle salt (10 mL) was added and the mixture was vigorously stirred for 30 min. The separated organic phase was diluted with Et_2O (10 mL), washed with water (10 mL), dried over $MgSO_4$ and filtered. The organic phase was filtered through a 1 inch plug of Celite® before the solvent was evaporated *in vacuo* to give the alcohol colourless oil (410 mg, 89%) which was used directly. To a stirred solution of (*Z*)-allylic alcohol (220 mg, 0.78 mmol) in THF (5 mL) was added TBAF (0.86 mL, 0.86 mmol) at 0 °C. The solution was allowed to warm to 20 °C and after 1 h, was poured onto CH_2Cl_2 (10 mL) and ice cold NH_4Cl (10 mL, sat. aq.) with vigorous stirring. The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography (SiO_2; 100% petrol then 100% EtOAc) to give the *title compound* as thick orange oil (71 mg, 55%).

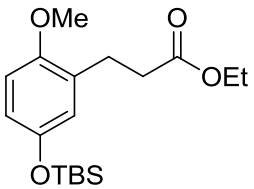
ν_{max}/cm^{-1} 3284br (O–H), 3021m, 2930m, 1588m, 1492s, 1454s, 1292m, 119s, 1014m; ^1H NMR (400 MHz, acetone-d_6) δ_H 6.97–6.91 (1H, m, ArCH), 6.77–6.72 (2H, m, 2 × ArCH), 6.46–6.42 (1H, m, ArCH=C), 5.95 (1H, dt, J = 11.8 and 6.3 Hz, ArCH=C*H*), 4.29 (2H, dd, J = 6.3 and 1.3 Hz, CH_2), 3.98 (1H, brs, CH_2OH), 3.07

(1H, brs, PhOH); ^{13}C NMR (101 MHz, Acetone-d_6) δ 154.7 (ArF, d, J = 237.0 Hz), 154.0 (ArCO, d, J = 2.2 Hz), 135.8 (s, =CH), 125.6 (d, J = 16.1 Hz, Ar_q), 122.4 (d, J = 3.7 Hz, =CH), 117.4 (d, J = 3.2 Hz, ArCH), 116.4 (d, J = 24.1 Hz, ArCH), 116.2 (d, J = 8.1 Hz, ArCH), 59.7 (s, OCH_2); *m*/*z* calculated for $[C_9H_9FO_2 + NH_4]^+$ found 186.0925 $[M + NH_4]^+$ 186.0922.



(*E*)-Ethyl-3-(5(*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)acrylate 233

To a stirred solution of triethyl phosphonoacetate (700 mg, 2.6 mmol) in PhMe (10 mL) was added NaH (127 mg, 5.3 mmol) portionwise over 2 min. After 30 min aldehyde **164** (700 mg, 5.3 mmol) in PhMe (5 mL) was added. After stirring for 1 h, the reaction was quenched by the addition of NH_4Cl (sat. aq., 5 mL). The seperated organic phase was washed with water (20 mL), separated, dried over $MgSO_4$ and filtered. The residue was purified by flash column chromatography (SiO_2; 20% Et_2O in petrol) to give the *title compound* as pale yellow oil (770 mg, 88%). Data were in accord with those obtained *via* Ando-olefination method (page 145).

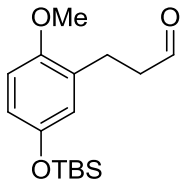


Ethyl 3-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)propanoate 234

A solution of (*E*)-ester **233** (770 mg, 2.3 mmol) and 10% Pd/C (100 mg) in EtOH (10 mL) was vigorously stirred under 1 atm of hydrogen for 4 h. After this time the solution was diluted with EtOAc (30 mL) and filtered. The solvent was removed *in*

vacuo and the residue was purified by flash column chromatography (SiO_2; 20% Et_2O in petrol) to give the *title compound* as pale yellow oil (670 mg, 86%).

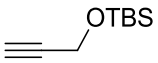
ν_{max}/cm^{-1} 2955w, 2930w, 2858w, 1735m (C=O), 1497s, 1444m, 1221s (C−O), 1180m, 1036s; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, J = 8.6 Hz, ArCH), 6.66–6.62 (2H, m, 2 × ArCH), 4.12 (2H, q, J = 7.1 Hz, CH_2), 3.76 (3H, s, $ArCOCH_3$), 2.88 (2H, t, J = 8.1 Hz, CH_2), 2.57 (2H, t, J = 8.1 Hz, CH_2), 1.24 (3H, t, J = 7.1 Hz, CH_3), 0.97 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C=O), 152.2 (ArCO), 149.1 (ArCO), 129.9 (Ar_q), 121.9 (ArCH), 118.0 (ArCH), 111.1 (ArCH), 60.4 (CH_2), 55.7 (OCH_3), 34.4 (CH_2), 26.1 (CH_2), 25.8 ($SiC(CH_3)_3$), 18.3 (SiC), 14.4 (CH_3), –4.4 ($Si(CH_3)_2$); *m/z* calculated for $[C_{18}H_{31}O_4Si]^+$ 339.1986 found $[M + H]^+$ 339.1989.



3-(5-((*tert*-Butyldimethylsilyl)oxy)-2-methoxyphenyl)propanal 232

To a stirred solution of ester **234** (5.46 g, 16 mmol) in PhMe (150 mL) cooled to –78 °C was very slowly added DIBAL-H (17.7 mL, 1 M in PhMe, 17.7 mmol) over 15 min. After continued stirring for 1 h, MeOH (5 mL), HCl (1 M, 5 mL) and Rochelle salt (sat. aq., 5 mL) were slowly added sequentially to the reaction. After allowing the solution to warm to 23 °C, the organic phase was washed with water (30 mL), separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and purification of the residue by flash column chromatography (SiO_2; 20% Et_2O in petrol) gave the *title compound* as pale yellow oil (3.60 g, 65%).

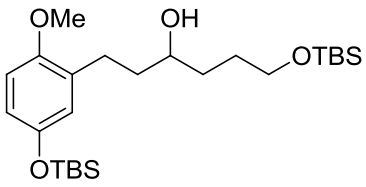
ν_{max}/cm^{-1} 2954m, 2930m, 2899m, 2857m, 2834m, 1830m (C=O), 1496s, 1285m, 1253m, 1219s, 1181m, 1035m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, t, J = 1.7 Hz, CHO), 6.70–6.63 (3H, m, 3 × ArCH), 3.76 (3H, s, OCH_3), 2.88 (2H, t, J = 7.5 Hz, CH_2), 2.69 (2H, td, J = 7.5 and 1.7 Hz, CH_2), 0.97 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4 (C=O), 152.0 (ArCO), 149.2 (ArCO), 129.6 (Ar_q), 121.9 (ArCH), 118.2 (ArCH), 111.1 (ArCH), 55.7 (OCH_3), 44.0 (CH_2), 25.8 ($SiC(CH_3)_3$), 23.6 (CH_2), 18.3 (SiC), –4.4 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{16}H_{27}O_3Si]^+$ 295.1724 found $[M + H]^+$ 295.1728.



1-(*tert*-Butyldimethylsiloxy)-3-propyne 238

To a stirred solution of propargyl alcohol (6.00 g, 0.107 mol) in CH_2Cl_2 (70 mL) was added imidazole (15.3 g, 0.225 mol) and TBSCl (17.8 g, 0.118 mol) at 20 °C. After stirring for 2 h, water (10 mL) was added. The separated organic layer was washed with water (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and purification of the residue by flash column chromatography (SiO_2; 5% Et_2O in petrol) gave the title compound as yellow liquid (12.7 g, 70%). Data are consistent with those previously reported in the literature.[87]

ν_{max}/cm^{-1} 3313m (HC≡C), 2956m, 2930m, 2899m, 2858m, 2121w (C≡C), 1499m, 1427m, 1254m, 1091s, 1004m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–4.31 (2H, brs, OCH_2), 2.39–2.37 (1H, brs, C≡CH), 0.91 (9H, s, $SiC(CH_3)_3$), 0.13 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.6 (C≡C), 73.0 (C≡C), 51.7 (CH_2), 25.9 (SiC), 18.4 ($SiC(CH_3)_3$), –5.1 ($Si(CH_3)_2$).

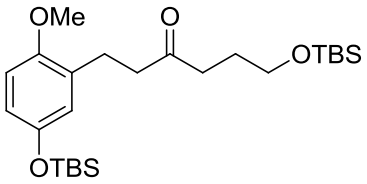


6-((*tert*-Butyldimethylsilyl)oxy)-1-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)hexan-3-ol 240

To a stirred solution of 1-(*tert*-butyldimethylsiloxy)-3-propyne (2.30 g, 13.5 mmol) in THF (50 mL) was added *n*-BuLi (4.1 mL, 2.5 M, 10.3 mmol) at –40 °C. After stirring for 40 min aldehyde **232** (2.00 g, 6.79 mmol) in THF (20 mL) was added. After continued stirring for 50 min at –40 °C, the reaction was quenched by the addition of NH_4Cl (sat. aq., 5 mL) and then allowed to warm to 20 °C. The separated organic phase was dried over $MgSO_4$ and filtered. After removal of the solvents *in vacuo* the residue was Purified by flash column chromatography (SiO_2; 5% Et_2O in petrol to 50% Et_2O in petrol) gave propargylic alcohol **236** as pale yellow oil (2.9 g, 92%). A solution of propargylic alcohol **236** (450 mg, 0.97 mmol) and 10% Pd/C (45 mg) in MeCN (2 mL) was vigorously stirred under 1 atm of hydrogen. After stirring for 19 h the hydrogen balloon was removed and $MgSO_4$ (approx. 500 mg) was added to the mixture which was then filtered and rinsed with Et_2O. The solvent was removed *in vacuo* to give the *title compound* as colourless oil (413 mg, 91%) which was used without further purification.

ν_{max}/cm^{-1} 3422br (O–H), 2953m, 2929m, 2897m, 2858m, 1496s, 1471m, 1464m, 1283m, 1253m, 1220m, 1096m, 1038m, 981m. ^1H NMR (400 MHz, $CDCl_3$) δ 6.70–6.61 (3H, m, 3 × ArH), 3.78 (3H, s, OCH_3), 3.64 (2H, t, J = 5.8 Hz, OCH_2), 3.57–3.51 (1H, m, OCH), 2.78 (1H, OH), 2.74–2.61 (2H, m, CH_2), 1.81–1.43 (6H, m, 3 ×

CH_2), 0.97 (9H, s, $SiC(CH_3)_3$)), 0.89 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$), 0.05 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (ArO), 149.4 (ArO), 131.7 (Ar), 122.0 (ArH), 117.6 (ArH), 111.3 (ArH), 63.7 (OCH_2), 56.1 (OCH_3), 38.0 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 26.3 (CH_2), 26.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.5 (SiC), 18.3 (SiC), –4.3 ($Si(CH_3)_2$), –5.2 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{25}H_{49}O_4Si_2]^+$ 469.3164 found $[M + H]^+$ 469.3159.

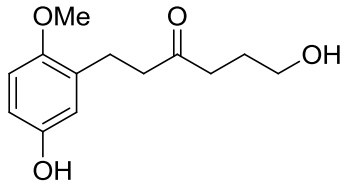


6-((*tert*-Butyldimethylsilyl)oxy)-1-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)hexan-3-one 241

Oxalyl chloride (0.61 mL, 7.11 mmol) was slowly added to a solution of DMSO (1.01 mL, 1.42 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After stirring for 10 min, alcohol **240** (1.10 g, 2.35 mmol) in CH_2Cl_2 (10 mL) was added. After continued stirring for 1 h, NEt_3 (3.20 mL, 23.1 mmol) was added and then the reaction was allowed to warm to 23 °C over 90 min. After this time water (5 mL) was added and the separated organic phase was washed with water (20 mL). The separated organic layer was dried over $MgSO_4$ and filtered to give a residue which was purified by flash column chromatography (SiO_2; petrol → 50% Et_2O in petrol) to give the *title compound* as yellow oil (860 mg, 89%).

ν_{max}/cm^{-1} 2954m, 2929m, 2896m, 2857m, 1715m (C=O), 1497s, 1464m, 1442m, 1284m, 1220s, 1095s, 1037m. ^1H NMR (400 MHz, $CDCl_3$) δ 6.69–6.61 (3H, m, 3 × ArH), 3.76 (3H, s, OCH_3), 3.60 (2H, t, J = 6.1 Hz, OCH_2), 2.81 (2H, t, J = 7.3 Hz, O=C–CH_2), 2.67 (2H, t, J = 7.2 Hz, O=C–CH_2), 2.47 (2H, t, J = 7.3 Hz, CH_2), 1.81–

174 (2H, m, CH_2), 0.97 (9H, s, $SiC(CH_3)_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C210.6 (C=O), 152.2 (ArO), 149.2 (ArO), 130.5 (Ar), 121.9 (ArH), 117.9 (ArH), 111.2 (ArH), 62.4 (OCH_2), 55.8 (OCH_3), 43.0 (CH_2), 39.3 (CH_2), 27.0 (CH_2), 26.1 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.2 (CH_2), 18.5 (SiC), 18.3 (SiC), –4.3 ($Si(CH_3)_2$), –5.2 ($Si(CH_3)_2$); *m*/*z* calculated for $[C_{25}H_{47}O_4Si_2]^+$ 467.3007 found $[M + H]^+$ 467.2998.

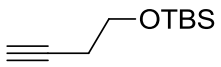


6-Hydroxy-1-(5-hydroxy-2-methoxyphenyl)hexan-3-one 226

To a solution of ketone **241** (860 mg, 1.84 mmol) in THF (50 mL) was added TBAF (3.86 mL, 1.0 M in THF, 3.86 mmol). After stirring for 2.5 h, the solution was poured into a beaker of NH_4Cl (aq. sat.) and CH_2Cl_2. After stirring for 5 min the organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; petrol → 100% EtOAc) to give the *title compound* as pale yellow oil (240 mg, 55%).

ν_{max}/cm^{-1} 3355 (O–H), 2936w, 2834w, 1701m (C=O), 1596w, 1500s, 1461m, 1436s, 1285m, 1217s, 1030s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70–6.61 (3H, m 3 × ArH), 6.18 (s, PhOH), 3.75 (3H, s, OCH_3), 3.61 (2H, t, J = 6.1 Hz, OCH_2), 2.82 (2H, t, J = 6.3 Hz, Ar–CH_2), 2.70 (2H, t, J = 7.2 Hz, CH_2), 2.52 (2H, t, J = 6.8 Hz, $ArCH_2$), 1.81 (2H, apparent qn, J = 6.4 Hz, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (C=O), 151.5 (ArO), 149.8 (ArO), 130.4 (Ar), 117.4 (Ar), 113.6 (Ar), 111.8

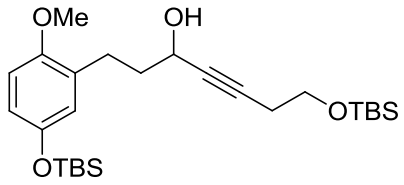
(Ar), 62.4 (OCH_3), 56.0 (OCH_2), 42.7 (CH_2), 40.0 (CH_2), 26.4 (CH_2), 25.2 (CH_2); *m*/*z* calculated for $[C_{13}H_{18}O_4 + Na]^+$ 261.1097 found $[M + Na]^+$ 261.1099.



1-(*tert*-Butyldimethylsilyloxy)-3-butyne 235

To a solution of 3-butyn-1-ol (1.12 g, 16.0 mmol) in CH_2Cl_2 (30 mL) was added TBSCl (2.71 g, 18.0 mmol) and imidazole (2.29 g, 33.6 mmol). After stirring for 16 h, water (10 mL) was added. The separated organic layer was dried over $MgSO_4$ and filtered. Purification of the residue by flash column chromatography (SiO_2; 5% Et_2O in petrol) gave the title compound as a colourless liquid. Data are in agreement with those previously reported in the literature.[86]

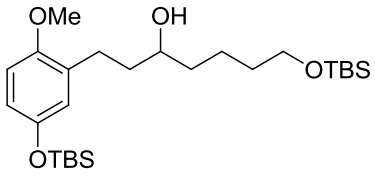
ν_{max}/cm^{-1} 3315w (HC≡C), 2955w 2930w, 2885w, 2858w, 2124w (C≡C), 1472w, 1464w, 1387w, 1362w, 1254m, 1103s. ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (2H, t, *J* = 7.2 Hz, OCH_2), 2.40 (2H, dt, *J* = 7.2 and 2.7 Hz, CH_2), 1.95 (1H, t, *J* = 2.7 Hz, ≡H), 0.90 (9H, s, $SiC(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 81.7 (C≡*C*), 69.4 (*C*≡C), 61.9 (OCH_2), 26.0 ($SiC(CH_3)_2$), 23.0 (CH_2), 18.5 (SiC), –5.2 ($SiC(CH_3)_2$).



7-((*tert*-Butyldimethylsilyl)oxy)-1-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)hept-4-yn-3-ol 236

To a stirred solution of alkyne **235** (1.45 g, 7.30 mmol) in THF (20 mL) was added *n*-BuLi (2.2 mL, 2.5 M in hexanes, 5.50 mmol) at –40 °C. After stirring for 1 h aldehyde **232** (1.08 g, 3.66 mmol) in THF (5 mL) was added. Upon continued stirring for 10 min the solution was warmed to 0 °C and after 5 min the reaction was quenched with the addition of NH_4Cl (sat. aq) (5 mL). The organic layer was washed with NH_4Cl (sat. aq, 5 mL), water, then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and purification by flash column chromatography (SiO_2; 5% Et_2O in petrol to Et_2O) gave the *title compound* as colourless oil (1.75 g, 99%).

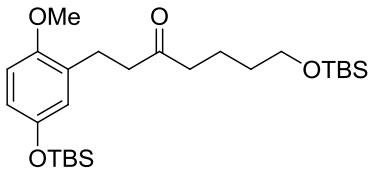
ν_{max}/cm^{-1} 3426br (O–H), 2954w, 2929w, 2857w, 2857w, 1496m, 1419w, 1283w, 1253s, 1104m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, J = 8.5 Hz, ArCH), 6.66–6.61 (2H, m, 2 × ArCH), 4.32–4.26 (1H, m, HO–C*H*), 3.77 (3H, s, OCH_3), 3.71 (2H, t, J = 7.3 Hz, OCH_2), 2.79–2.63 (2H, m, Ar–CH_2), 2.43 (2H, td, J = 7.2 and 2.0 Hz, ≡CCH_2), 2.08 (1H, m, OH), 2.02–1.85 (2H, m, CHCH_2), 0.97 (9H, s, $SiC(CH_3)_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 0.16 (6H, s, $Si(CH_3)_2$), 0.07 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (ArCO), 149.3 (ArCO), 130.7 (Ar_q), 122.1 (ArCH), 117.9 (ArCH), 111.3 (ArCH), 82.40 (C≡C) , 82.39 (C≡C), 62.1 (OCH_2, OCH_3), 56.0 (OCH), 38.3 (CH_2), 26.1 (CH_2), 26.0 ($SiC(CH_3)_3$) , 25.9 ($SiC(CH_3)_3$), 23.3 (CH_2), 18.5 (SiC), 18.3 (SiC), –4.3 ($SiC(CH_3)_2$), –5.1 ($SiC(CH_3)_2$); *m*/*z* calculated [$C_{26}H_{46}O_4Si_2$ + NH_4] 496.3273 found [M + NH_4] 496.3277.



7-((*tert*-Butyldimethylsilyl)oxy)-1-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)heptan-3-ol 237

A solution of alcohol **236** (1.61 g, 3.44 mmol) and 5% Pd/C (319 mg) in MeCN (7 mL) was vigorously stirred under 1 atm of hydrogen. After stirring for 20 h, the hydrogen balloon was removed and $MgSO_4$ (approx. 500 mg) was added to the mixture which was then filtered and rinsed with Et_2O (30 mL). The solvent was then removed *in vacuo* to give the *title compound* as colourless oil (1.61 g, quantitative yield), which was used without further purification.

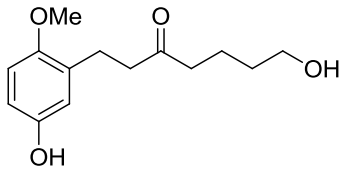
ν_{max}/cm^{-1} 3435br (O–H), 2952w, 2929w, 2857w, 1496m, 1389m, 1284m, 1219s, 1098m, 1038m, 1005m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, d, J = 8.4 Hz, ArCH), 6.65–6.61 (2H, m, 2 × ArCH), 3.78 (3H, s, OCH_3), 3.60 (2H, t, J = 6.4 Hz, OCH_2), 3.53–3.46 (1H, m, OCH), 2.83–2.59 (2H, m, $ArCH_2$), 2.09 (1H, d, J = 4.3 Hz, OH), 1.73–1.63 (2H, m, CH_2), 1.53–1.31 (6H, m, 3 × CH_2), 0.97 (9H, s, $SiC(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_2$), 0.16 ($Si(CH_3)_2$), 0.04 ($Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (ArCO), 149.5 (ArCO), 131.5 (Ar_q), 122.0 (ArCH), 117.7 (ArCH), 111.4 (ArCH), 70.8 (OCH), 63.4 (OCH_2), 56.1 (OCH_3), 38.1 (CH_2), 37.2 (CH_2), 33.0 (CH_2), 26.14 ($SiC(CH_3)_3$), 26.1 (CH_2), 25.9 ($SiC(CH_3)_3$), 22.2 (CH_2), 18.5 (SiC), 18.3 (SiC), –4.3 ($SiC(CH_3)_2$), –5.1 ($SiC(CH_3)_2$). *m/z* calculated $[C_{26}H_{51}O_4Si_2]^+$ 483.3320 found $[M + H]^+$ 483.3324.



7-((*tert*-Butyldimethylsilyl)oxy)-1-(5-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)heptan-3-one 238

Oxalyl chloride (0.86 mL, 10.0 mmol) was slowly added to a stirred solution of DMSO (1.40 mL, 0.020 mol) in CH_2Cl_2 (30 mL) at –78 °C. After stirring for 10 min alcohol **237** (1.60 g, 3.31 mmol) in CH_2Cl_2 (20 mL) was added. After continued stirring for 1 h, NEt_3 (4.6 mL, 0.03 mol) was added and then the cooling bath was removed with continued stirring at room temp for 1 h. After this time NH_4Cl (aq. sat., 5 mL) was added and the mixture was transferred to a separating funnel. The separated organic layer was dried over $MgSO_4$ and filtered to give a crude residue which was purified by flash column chromatography (SiO_2; 10% Et_2O in petrol) to give the *title compound* as yellow oil (1.40 g, 88%).

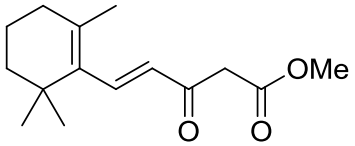
ν_{max}/cm^{-1} 2953w, 2929w, 2895w, 2857w, 1715m (C=O), 1497m, 1284m, 1221s, 1098m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, J = 9.5 Hz, ArCH), 6.64–6.61 (2H, m, 2 × ArCH), 3.76 (3H, s, OCH_3), 3.60 (2H, t, J = 6.3 Hz, OCH_2), 2.81 (2H, t, J = 7.7 Hz, $ArCH_2$), 2.65 (2H, t, J = 7.7 Hz, O=CCH_2), 2.41 (2H, t, J = 7.4 Hz, O=CCH_2), 1.66–1.58 (2H, m, CH_2), 1.53–1.46 (2H, m, CH_2), 0.97 ($SiC(CH_3)_2$), 0.89($SiC(CH_3)_2$), 0.16 ($Si(CH_3)_2$), 0.04 ($Si(CH_3)_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7 (C=O), 152.2 (ArCO), 149.2 (ArCO), 130.5 (Ar_q), 121.9 (ArCH), 117.9 (ArCH), 111.2 (ArCH), 63.0 (OCH_2), 55.8 (OCH_3), 42.9 (CH_2), 42.7 (CH_2), 32.5 (CH_2), 26.1($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 25.2 (CH_2), 20.5 (CH_2), 18.5 (SiC), 18.3 (SiC), –4.3 ($Si(CH_3)_2$), –5.2 ($Si(CH_3)_2$). *m*/*z* calculated $[C_{26}H_{49}O_4Si_2]^+$ 481.3164 found $[M + H]^+$ 481.3166.



7-Hydroxy-1-(5-hydroxy-2-methoxyphenyl)heptan-3-one 227

To a solution of ketone **238** (1.41 g, 2.93 mmol) in THF (30 mL) was added TBAF (6.10 mL, 1M in THF, 6.10 mmol). After stirring for 2.5 h NH_4Cl (aq. sat., 5 mL) was added. Subsequently Et_2O (30 mL) was added and the separated organic layer was washed with NH_4Cl (aq. sat., 20 mL). The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a residue which was purified by flash column chromatography (SiO_2; 10% EtOAc in petrol → EtOAc) to give the *title compound* as pale yellow thick oil (550 mg, 75%).

ν_{max}/cm^{-1} 3350br (O–H), 2942w, 2834w, 1699m (C=O), 1569w, 1500s, 1458m, 1438m, 1407w, 1365w, 1285s, 1031s. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68–6.61 (3H, m, 3 × ArCH), 3.72 (3H, s, OCH_3), 3.57 (3H, s, OCH_2), 3.06 (1H, s, ArCOH), 2.79 (2H, t, J = 7.3 Hz, CH_2), 2.66 (2H, t, J = 7.3 Hz, CH_2), 2.38 (2H, t, J = 7.0 Hz, OCH_2), 1.64–1.55 (2H, m, CH_2), 1.52–1.45 (2H, m, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5 (C=O), 151.3 (ArCO), 149.90 (ArCO), 130.29 (Ar_q), 117.39 (ArCH), 113.5 (ArCH), 111.8 (ArCH), 62.2 (OCH_3), 56.0 (OCH_2), 42.5 ($ArCH_2$ and O=CCH_2) 31.9 (O=CCH_2), 25.1 (CH_2), 19.8 (CH_2). *m*/*z* calculated for $[C_{14}H_{20}O_4 + NH_4]^+$ 270.1700 found $[M + NH_4]^+$ 270.1700.



Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-3-keto-4-pentenoate 258

Dimethyl carbonate (42.0 g, 0.43 mol) was added to a strongly stirred suspension of NaH (60% in mineral oil) (18.5 g, 0.46 mol) in dioxane (130 mL) at 23 °C. After heating to reflux, β-ionone (22.0 g, 0.11 mol) in dioxane (30 mL) was added over 4 h (using a syringe pump)*, following continued heating for 1.5 h. After this time the reaction was cooled to 0 °C, and neutralised by cautious addition of 4 M HCl (until pH 7 as judged by indicator paper) and then Et_2O (200 mL) was added. The organic layer was repeatedly washed with water, then brine (100 mL), separated, dried over $MgSO_4$ and filtered. The solvents were removed *in vacuo* to give the title compound as orange oil (23 g, 79%). Data are consistent with those previously reported in the literature.[90]

^{1}H NMR indicates equilibration of enol:ketone 3:7 with the alkenyl proton resonating at 4.97 ppm.

ν_{max}/cm^{-1} 2931w, 2866w, 1743m (C=O), 1715m (C=O), 1655m (C=O), 1590m, 1445w, 1398w, 1362w, 1236s, 1153s, 1020m. Characterisation for ketone in mixture: ^{1}H NMR (400 MHz, $CDCl_3$) 7.36 (1H, d, J = 16.0 Hz, =CH), 6.19 (1H, d, J =16.0 Hz, =CH), 3.73 (3H, s, CH_3), 3.62 (2H, s, CH_2), 2.09–2.01 (2H, m, CH_2), 1.76 (3H, s, CH_3), 1.64–1.43 (4H, m, 2 × CH_2), 1.06 (6H, s, 2 × CH_3); *m/z* calculated for $[C_{15}H_{23}O_3]^+$ 251.1642 found $[M + H]^+$ 251.1638.

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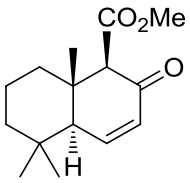
* Slow addition is crucial for succesful reaction.



Methyl 5,5,8a-trimethyl-2-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate 256

A solution of sodium methoxide (freshly prepared from 1.83 g sodium sticks and anhydrous MeOH) in anhydrous MeOH (50 mL), was added to a solution of ester **258** (13.0 g, 52.9 mmol) in anhydrous MeOH (100 mL). The solution was irradiated in an immersion well photochemical reactor using a high pressure 400 W Hg lamp under a stream of nitrogen with strong stirring for 20 h.* After this time NH_4Cl (aq. sat., 100 mL) was added. The solution was diluted with Et_2O (200 mL), washed with NH_4Cl (aq. sat., 20 mL), separated, dried over $MgSO_4$ and filtered. After removal of the solvents *in vacuo*, purification of the residue by flash column chromatography (SiO_2; 10% Et_2O → 50% Et_2O in petrol) gave the title compound as pale yellow needles (1.90 g, 15%). Data are consistent with those previously reported in the literature.[91]

mp 111–115 °C (lit[91] 111–113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, dd, J = 10.3 and 2.1 Hz, OC–CH=C*H*), 6.14 (1H, dd, J = 10.3 and 3.3 Hz, OC–C*H*=CH), 3.73 (3H, s, OCH_3), 3.26 (1H, s, MeO_2CCH), 2.19 (1H, apparent t, J = 2.7 Hz, CH=CH–C*H*), 1.57–1.09 (6H, m, 3 × CH_2), 1.06 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.80 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2 (O=C), 169.2 (O=C), 150.5 (=C), 130.2 (=C), 69.4 (H*C*–C=O), 56.3 (CH), 51.7 (OCH_3), 43.7 (C_q), 41.1 (CH_2), 37.9 (CH_2), 32.9 (C_q), 32.7 (CH_3), 22.6 (CH_3), 18.3 (CH_2), 14.0 (CH_3).

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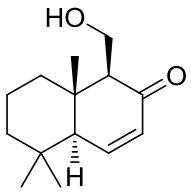
* Fire risk - *always* use a water flow cut-off switch!

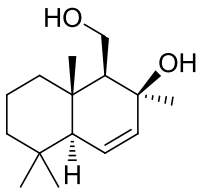


1-(Hydroxymethyl)-5,5,8a-trimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one 260

To a stirred solution of ester **256** (1.70 g, 6.79 mmol) in Et_2O (50 mL) was added $LiAlH_4$ (520 mg, 13.7 mmol) at 0 °C. After 2 h at 0 °C NH_4Cl (sat. aq., 10 mL) was added cautiously to the resultant green-solution with vigorous stirring. The separated organic layer was washed with water (30 mL), brine (30 mL), dried over $MgSO_4$ and filtered under vacuum. The solid was washed with Et_2O (5 × 20 mL). The filtrate was reduced *in vacuo* to give the title compound as orange needles which were used directly. To a stirred solution of the diol **259** (1.25 g, 5.57 mmol) in CH_2Cl_2 (20 mL) was added MnO_2 (5.80 g, 66.7 mmol), with continued stirred for 24 h or until completion by TLC. After this time the mixture was filtered under vaccum and rinsed repeatedly with EtOAc. The filtrate was then dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give the title compound as orange waxy oil (870 mg, 67% for two steps) which was used without further purification. Data are consistent with those previously reported in the literature.[92]

ν_{max}/cm^{-1} 3440br (O–H), 2926m, 2869m, 1662s (C=O), 1460w, 1385w, 1385m, 1367m, 1204m, 1033s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, dd, J = 10.2 and 2.1 Hz, =CH), 6.07 (1H, dd, J =10.2 and 3.3 Hz, =CH), 3.92 (1H, dd, J = 11.1 and 8.7 Hz, OCH_a), 3.67 (1H, m, OCH_b), 3.25 (1H, s, OH), 2.30 (1H, dd, J = 8.7 and 3.2 Hz, $HOCH_2CH$), 2.23 (1H, appt t, J = 2.7 Hz, CH=CHC*H*), 1.73–1.04 (6H, m, 3 × CH_2), 1.02 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.87 (3H, s, CH_3); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 204.0 (C=O), 151.5 (=C), 130.0 (=C), 64.0 (H*C*C=O), 58.6 (OCH_2), 56.3 (H*C*C=), 43.2 (C_q), 40.9 (CH_2), 37.6 (CH_2), 32.8 (C_q), 32.7 (CH_3), 22.5 (CH_3), 18.4 (CH_2), 14.9 (CH_3); *m/z* calculated for $[C_{14}H_{23}O_2]^+$ 223.1693 found $[M + H]^+$ 223.1692.

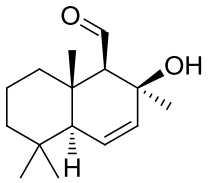


1-(Hydroxymethyl)-2,5,5,8a-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-ol 261

To a stirred solution of ketone **260** (2.05 g, 9.22 mmol) in Et_2O (20 mL) was added MeLi (29.0 mL, 1.6 M, 46.4 mmol) at –78 °C. After stirring for 6 h at –78 °C the reaction was allowed to warm to 23 °C and upon immediate cooling to –78 °C NH_4Cl (sat. aq.) (10 mL) was added. After allowing warming to 23 °C the separated organic layer was washed with water (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give an orange residue which was purified by flash column chromatography (SiO_2; 20% → 50% EtOAc in petrol) to give the title compound as a cream coloured solid (663 mg, 31%) and identified as a ≈15:1 mixture of diastereomers. Data were consistent with those previously reported in the literature.[92]

m.p. 120–122 °C; ν_{max}/cm^{-1} 3350br (O–H), 2924s, 2869s, 1453m, 1383m, 1384s, 1131s, 1080s, 1035s; NMR assignments for major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (1H, dd, J = 10.1, 2.1 Hz, =CH), 5.64 (1H, dd, J = 10.1 and 3.0 Hz, =CH), 4.05 (2H, d, J = 4.4 Hz, OCH_2), 2.51 (1H, brs, OH), 1.91–1.82 (1H, m, CH_a), 1.71–1.63 (1H, m, CH_b), 1.59 (1H, apparent t, J = 2.4 Hz, CH=CHC*H*), 1.54–

1.41 (2H, m, CH_2), 1.37 (3H, s, $OCCH_3$), 1.29 (1H, t, J = 4.4 Hz, OCH_2CH), 1.19–1.15 (2H, m, CH_2), 1.08 (3H, s, CH_3), 0.91 (3H, s, CH_3), 0.88 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5 (=C), 128.0 (=C), 72.1 (OC_q), 60.3 (OCH_2), 58.6 (OCH_2CH), 54.8 (=CCH), 41.2 (CH_2), 37.6 (CH_2), 36.8 (C_q), 32.9 (CH_3), 32.8 (Me_2C_q), 30.8 (CH_3), 22.0 (CH_3), 18.4 (CH_2), 15.8 (CH_3); *m/z* calculated [$C_{15}H_{26}O_2$ – H_2O + NH_4] 238.2165 found [M –H_2O + NH_4] 238.2163.

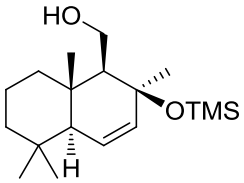


2-Hydroxy-2,5,5,8a-tetramethyl-1,2,4a,5,6,7,8,8a octahydronaphthalene-1-carbaldehyde 262

To a solution of alcohol **261** (80 mg, 0.34 mmol) in $CHCl_3$ (0.5 mL) was added $NaHCO_3$ (80 mg, 0.95 mmol) and Dess-Martin periodinane[60] (258 mg, 0.61 mmol). After stirring for 10 min, water (0.5 mL) and $CHCl_3$ (3 mL) were added. The organic layer was separated, dried over $MgSO_4$ and filtered. The title compound was purified by flash column chromatography (SiO_2; 20% EtOAc in petrol) to give the *title compound* as pale yellow oil (23 mg, 65%). *The compound showed degradation and was used immediately*.

^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (1H, d, J = 3.1 Hz, CHO), 5.76 (1H, dd, J = 10.2 and 1.6 Hz, C=CH-C_q), 5.65 (1H, dd, J = 10.2 and 3.0 Hz, HC=C-C_q), 2.42 (1H, s, OH), 2.06 (1H, d, J = 3.1 Hz, CHOCH), 1.77–1.67 (2H, m, CH_2), 1.64 (1H, m, C=CCH), 1.54–1.46 (2H, m, CH_2), 1.32 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.25–1.16 (2H, m, CH_2), 0.94 (3H, s, CH_3), 0.90 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3 (CHO), 133.8 (C=CC_q), 127.7 (=CC_q), 70.5 (OC_q), 68.8 (CHO–CH),

54.10 (=C*C*H), 41.2 (CH_2), 37.7 (CH_2), 37.2 (C_q), 32.9 ($C_q(Me)_2$), 32.7 (CH_3), 30.7 (CH_3), 21.9 (CH_3), 18.1 (CH_2), 16.5 (CH_3).*



2,5,5,8a-Tetramethyl-2-((trimethylsilyl)oxy)-1,2,4a,5,6,7,8,8a octahydronaphthalen-1-yl)methanol 267

To a solution of diol **261** (320 mg, 1.34 mmol) in CH_2Cl_2 (5 mL) was added imidazole (1.37 g, 20.1 mmol), TMSCl (1.7 mL, 13.4 mmol) and DMAP (16 mg, 0.13 mmol). After stirring for 24 h, water (2 mL) was added. The seperated organic layer was washed with water (2 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo*, and then trimethylsilanol was removed by azeotroping with PhMe (20 mL) to give di-TMS substrate **266** as yellow oil which was used directly in. A stirred solution of di-TMS substrate **266** (410 mg, 1.07 mmol) was dissolved in anhydrous MeOH/petrol (15:1) (16 mL) and cooled to –15 °C. Upon cooling, oven dried K_2CO_3 (86 mg, 0.54 mmol) was added in one portion. The solution was warmed to –10 °C over 4 h, after which time the solution was diluted with Et_2O (20 mL) and then water (20 mL) was added. The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; 10% EtOAc in petrol) to give *the title compound* as white crystals (180 mg, 54% for 2 steps).

m.p 80–82 °C; ν_{max}/cm^{-1} 3333br (O–H), 3023w, 2951w, 2846w, 2810w, 1460w, 1438w, 1384w, 1369w, 1214s, 1144s, 1088s, 1057s, 1027s, 1000s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75–5.69 (2H, m, 2 × =CH), 4.05 (1H, apparent dt, J = 12.1 and

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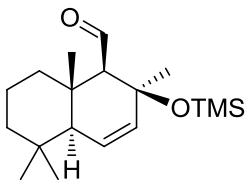
* Due to seeming instability of analogous substrates *m/z* was not analysed.

3.5 Hz, OCH_{a1}), 3.97 (1H, ddd, J = 12.1, 8.2 and 4.1 Hz, OCH_{b1}), 2.83 (1H, dd, J = 8.2 and 3.6 Hz, OH), 1.89–1.84 (1H, m, CH_{a2}), 1.74–1.64 (1H, m, CH_{b2}), 1.52 (1H, apparent brs, =CC*H*), 1.51–1.41 (2H, m, CH_2), 1.39 (3H, s, CH_3), 1.08–1.04 (6H, m, CH_2, HO–CC*H*, CH_3), 0.90 (3H, s, CH_3), 0.89 (3H, s, CH_3), 0.15 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1 (=C), 127.7 (=C), 75.7 (OC_q), 60.6 (OCH_2), 59.6 (OC*C*H), 55.2 (=C*C*H), 41.3 (CH_2), 37.7 (CH_2), 36.9 (C_q), 33.1 (CH_3), 32.8 (C_q), 31.3 (CH_3), 22.2 (CH_3), 18.4 (CH_2), 15.9 (CH_3), 2.7 (2 × $Si(CH_3)_3$); *m*/*z* the expected ions were not observed.

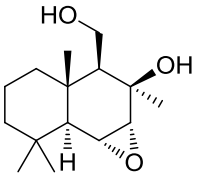


2,5,5,8a-Tetramethyl-2-((trimethylsilyl)oxy)-1,2,4a,5,6,7,8,8a octahydronaphthalene-1-carbaldehyde 268

To a stirred mixture of alcohol **267** (135 mg, 0.43 mmol), NaOAc (53 mg, 0.65 mmol) and 4 Å molecular sieves (approx. 100 mg) in CH_2Cl_2 (6 mL) was added PCC (157 mg, 0.65 mmol) at 0 °C. After warming to 23 °C over 1 h, the mixture was diluted with EtOAc (10 mL) and filtered over a 1 inch pad of silica gel. After washing the organic solution with water, the organic solvent was removed *in vacuo* to give *the title compound* as yellow oil (57 mg, 43%). *The compound showed degradation and was used immediately*.

ν_{max}/cm^{-1} 2950m, 2924m, 2871m, 2844m, 1710s (C=O), 1421m, 1391m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (1H, d, J = 4.6 Hz, CHO), 5.72 (2H, s, 2 × =CH), 1.73–1.41 (6H, m, CH_2, 4 × CH), 1.32 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.27–0.98 (2H, m, 2 × CH), 0.91 (6H, s, 2 × CH_3), 0.11 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$)

δ_C 207.9 (CHO), 134.0 (=C), 127.1 (=C), 73.6 (OC_q), 69.7 (OHC*C*), 54.0 (=C*C*H), 41.2 (CH_2), 37.7 (CH_2), 36.2 (C_q), 32.7 (CH_3), 30.8 (CH_3), 22.0 (CH_3), 18.0 (CH_2), 16.5 (C_q), 16.0 (CH_3), 2.5 ($Si(CH_3)_3$).



3-(Hydroxymethyl)-2,3a,7,7-tetramethyldecahydronaphtho[1,2-b]oxiren-2-ol

270

To a stirred solution of diol **261** (775 mg, 3.3 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (1.12 g, 6.5 mmol) with continued for 25 h. After this time the reaction mixture was vigorously washed with 1 M aq. sol. $NaHCO_3$ (2 × 5 mL). The separated organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo.* Purification of the crude residue by flash column chromatography (SiO_2; 50% EtOAc in petrol) gave the *title compound* as pale yellow crystals (475 mg, 58%).

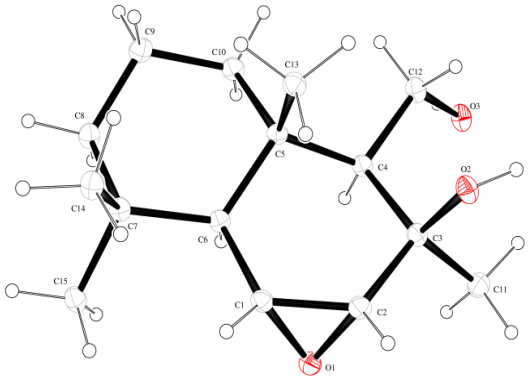
mp 66–75 °C; ν_{max}/cm^{-1} 3363br (OH), 2951m, 2925m, 2870m, 1706w, 1458m, 1392m, 1369m, 1262m, 1128m, 1070m, 1025m,; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.08 (1H, dd, J = 12.0 and 3.5 Hz, HOCH_a), 4.03 (1H, dd, J = 12.0 and 3.6 Hz, HOCH_b), 3.15 (1H, dd, J = 3.9 and 2.7 Hz, CHCOC*H*), 2.98 (1H, d, J = 3.9 Hz, $OCHC_q$), 2.96 (1H, s, OH), 2.36 (1H, s, OH), 1.76–1.63 (2H, m, CH_2), 1.54–1.46 (5H, m, CH_2, CH_3), 1.22 (3H, s, CH_3) 1.18–0.98 (8H, m, CH_2, 2 × CH_3), 0.95 (1H, d, J = 3.9 Hz, OCHC*H*), 0.88 (1H, t, J = 3.5 Hz, H_2CC*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 72.8 (OC_q), 60.3 (OCH_2), 59.6 (OepoxideC), 56.3 (OepoxideC), 55.0 (CH), 54.8 (CH), 41.5 (CH_2), 37.21 (C_q), 37.18 (CH_2), 33.2 (C_q), 32.8 (CH_3), 27.7

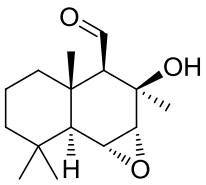
(CH_3), 22.5 (CH_3), 18.4 (CH_2), 18.2 (CH_3); *m/z* calculated for $[C_{15}H_{27}O_3 + NH_4]^+$ 272.2220 found $[M + NH_4]^+$ 272.2216.

X-Ray Crystallographic Data 270:

These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

CCDC 1043793 contains the supplementary crystallographic data for this compound.



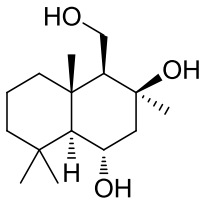


2-Hydroxy-2,3a,7,7 tetramethyldecahydronaphtho[1,2-b]oxirene-3-carbaldehyde 271

To a stirred solution of epoxide **270** (52 mg, 0.20 mmol) in $CHCl_3$ (1 mL) was added Dess-Martin periodinane[60] (190 mg, 0.45 mmol). After stirring for 24 h, 1 M (sat. aq.) $NaHCO_3$ (0.1 mL) was added, and the diluted organic layer ($CHCl_3$, 6 mL) was further washed with 1 M (sat. aq.) $NaHCO_3$ (2 mL). The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and purification

of the residue by flash column chromatography (SiO_2; 30% EtOAc in petrol) gave the *title compound* as colourless oil (15 mg, 23%).

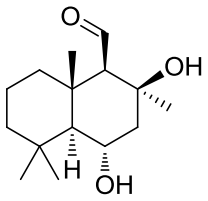
ν_{max}/cm^{-1} 3466br (O–H), 2952m, 2926m, 2870m, 2848m, 1709s (C=O), 1459m, 1391m, 1371m, 1204m, 1026m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (1H, d, J = 2.6 Hz, CHO), 3.37 (1H, s, OH), 3.14 (1H, dd, J = 3.9 and 2.4 Hz, CHCOC*H*), 2.99 (1H, d, J = 3.9 Hz, $OCHC_q$), 1.98 (1H, d, J = 2.6 Hz, *H*CCHO), 1.76–1.48 (4H, m, CH_2, CH_{a1}, CH_{a2}), 1.39 (3H, s, CH_3), 1.33–1.21 (5H, m, CH_{b1},CH_{b2}, CH_3), 1.18 (1H, d, J = 2.4 Hz, OCHC*H*), 1.08 (3H, s, CH_3), 1.03 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C=O), 70.6 (OC_q), 65.4 (CHO*C*H), 59.0 (OCH), 55.7 (OCH–*C*H), 54.1 (OCH), 41.3 (CH_2), 38.7 (C_q), 37.3 (CH_2), 33.2 (C_q), 32.6 (CH_3), 27.9 (CH_3), 22.2 (CH_3), 18.3 (CH_3), 18.0 (CH_2). *m*/*z* calculated for $[C_{15}H_{25}O_3]^+$ 253.1798 found $[M + H]^+$ 253.1798.



4-(Hydroxymethyl)-3,4a,8,8-tetramethyldecahydronaphthalene-1,3-diol 276

To a stirred solution of epoxide **270** (475 mg, 1.87 mmol) in PhMe (10 mL) was added Red-Al (2.0 mL, 65 wt% in PhMe, 5.6 mmol) at 23 °C. After 10 min the evolution of hydrogen had subsided and the solution was heated to reflux with continued stirring for 24 h. After this time NH_4Cl (aq. sat., 2 mL) was added and the mixture was filtered through a 1 inch pad of $MgSO_4$. The solvent was removed *in vacuo* to give a crude solid which was purified by flash column chromatography (SiO_2; 50% in petrol → EtOAc) to give the *title compound* as pale yellow needles (475 mg, 99%).

mp 190–192 °C; ν_{max}/cm^{-1} 3300br (O–H), 3004w, 2959m, 2926m, 2891m, 2872m, 2842m, 1461m, 1373s, 1190m, 1118m, 1047s; ^{1}H NMR (400 MHz, CD_3OD) δ 4.12 (1H, td, J = 11.0 and 4.0 Hz, OCH), 4.00 (1H, dd, J = 11.8 and 2.6 Hz, OCH_{a1}), 3.90 (1H, dd, J = 11.8 and 3.4 Hz, OCH_{b1}), 2.04 (1H, dd, J = 13.2 and 4.1 Hz, OC_qCHa2), 1.93–1.87 (1H, m, CH_{a3}), 1.75–1.65 (1H, m, CH_{a4}), 1.58 (1H, dd, J = 13.2 and 11.2 Hz, OC_qCH_{b2}), 1.50-1.38 (2H, m, CH_{b4}, CH_{a5}), 1.36 (3H, s, CH_3), 1.31-1.23 (1H, m, CH_{b5}), 1.21 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.06–0.99 (2H, m, CH_{b3}, HOCC*H*); ^{13}C NMR (101 MHz, CD_3OD) δ 75.2 (OC_q), 68.3 (OCH), 61.7 (OCCH), 60.4 (OCH_2), 59.9 (CH_2), 53.5 (CH_2), 45.1 (CH_2), 41.3 (CH_2), 41.0 (CH), 37.5 (CH_3), 34.7 (CH_3), 31.4 (CH_3), 22.8 (CH_3), 19.3 (CH_2), 18.1 (CH_3); *m/z* calculated for $[C_{15}H_{26}O_2 + NH_4 - H_2O]^+$ 256.2271 found $[M + NH_4 - H_2O]^+$ 256.2265



2,4-Dihydroxy-2,5,5,8a-tetramethyldecahydronaphthalene-1-carbaldehyde 277

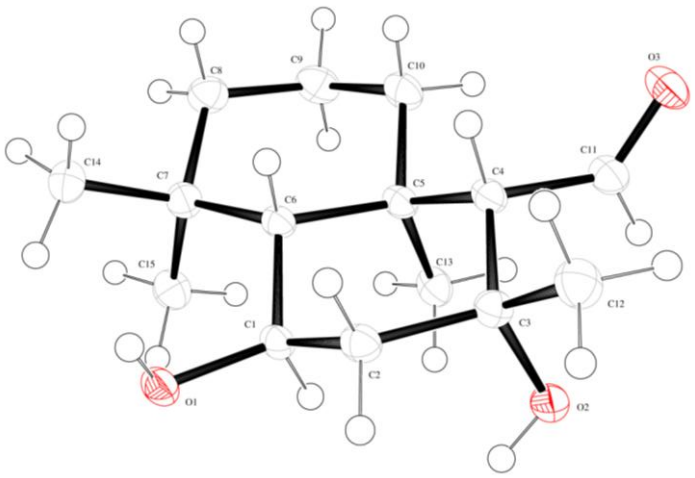
To a stirred mixture of triol **276** (475 mg, 1.85 mmol) in CH_2Cl_2 (5 mL) was added TEMPO (58 mg, 0.37 mmol) and $PhI(OAc)_2$ (715 mg, 2.2 mmol). After stirring for 5 h, the solution had become clear and $NaHCO_3$ (sat. aq., 1 mL) was added. The separated organic layer was then dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude solid which was purified by flash column chromatography (SiO_2; 30% EtOAc in petrol) to give the *title compound* as colourless crystals (339 mg, 72%).

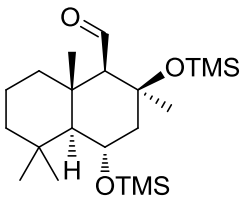
mp 144–147 °C; ν_{max}/cm^{-1} 3390br (O–H), 2969w, 2923w, 2906w, 2874w, 2846w, 1698s (C=O), 1459m, 1291m, 1175m, 1040s; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.04 (1H, d, *J* = 2.6 Hz, CHO), 4.20 (1H, td, *J* = 10.8 and 4.1 Hz, OCH), 3.06 (1H, s, OH), 2.18 (1H, d, *J* = 2.6 Hz, CHOC*H*), 2.09–2.03 (1H, m, CH_{a1}), 1.70–1.56 (2H, m, CH_{a2}, CH_{a3}), 1.47–1.22 (8H, m, CH_{b3}, CH_{b2}, CH_{b1}, CH_2, CH_3), 1.26 (3H, m, CH_3), 1.20 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.08−1.04 (4H, s, CH_3, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C=O), 72.7 (OC_q), 68.6 (O=C*C*H), 67.6 (HCO), 60.1 (CH), 52.3 (CH_2), 43.5 (CH_2), 41.8 (C_q), 40.9 (CH_2), 37.1 (CH_3), 33.9 (C_q), 31.2 (CH_3), 22.3 (CH_3), 18.2 (CH_3), 18.00 (CH_2); *m*/*z* calculated $[C_{15}H_{24}O_3]^+$ 253.1798 found $[M - H]^+$ 253.1796.

X-Ray Crystallographic Data 277:

These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

CCDC 1043794 contains the supplementary crystallographic data for this compound.

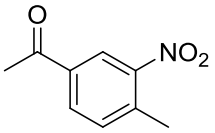




2,5,5,8a-Tetramethyl-2,4-bis((trimethylsilyl)oxy)decahydronaphthalene-1-carbaldehyde 280

To a stirred solution of aldehyde **277** (18 mg, 0.071 mmol) in CH_2Cl_2 (1 mL) cooled to –15 °C was added NEt_3 (200 µL, 1.4 mmol) and TMSOTf (≈30 µL, 0.17 mmol). After stirring for 30 min 1M $NaHCO_3$ (sat. aq., 5 mL) was added. After allowing to warm to 23 °C the organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; 5% Et_2O in petrol) to give the *title compound* as a pale yellow waxy oil (26 mg, 93%).

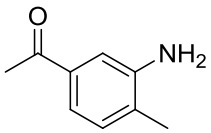
ν_{max}/cm^{-1} 2954m, 2928m, 2848m, 1715m (C=O), 1288s, 1105s, 1047m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (1H, d, J = 5.3 Hz, CHO), 4.32 (1H, td, J = 10.5 and 4.0 Hz, TMSOC*H*), 2.08 (1H, dd, J = 13.6 and 4.0 Hz, C_qCH_{a1}), 1.60–1.43 (3H, m, CHOC*H*, CH_{a2}, C_qCH_{b1}), 1.40–1.31 (6H, m, CH_{b2}, $CH_{a3,}$ CH_{a4}, CH_3), 1.23–1.01 (11H, 3 × $CH_{3,}$ CH_{b4}, CH_{b3}), 0.93 (1H, d, J = 10.5 Hz, CH), 0.18 (9H, s, $Si(CH_3)_3$), 0.16 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C=O), 75.8 (OC_q), 70.6 (CHOC*H*), 68.7 (TMSOC*H*), 60.0 (CH), 53.2 (CH_2), 44.1 (CH_2), 41.3 (CH_2), 39.6 (C_q), 36.9 (CH_3), 33.6 (C_q), 30.6 (CH_3), 22.6 (CH_3), 18.1 (CH_3), 17.9 (CH_2), 2.6 ($Si(CH_3)_3$), 1.2 ($Si(CH_3)_3$); *m*/*z* calculated $[C_{21}H_{40}O_3Si_2]^+$ 397.2589 found $[M - H]^+$ 397.2584.



3-Nitro-4-methylacetophenone 281

4-Methylacetophenone (10.0 g, 0.075 mol) was slowly added over 30 min to a stirring mixture of conc. HNO_3 (31 mL) and conc. H_2SO_4 (40 mL) cooled to 0 °C, maintaining the internal reaction temp below 10 °C. After continued stirring for 10 min, the solution was poured onto crushed ice and allowed to warm to 20 °C. The precipitate was collected by filtration and washed with copious amounts of water and then *n*-hexane (300 mL). The solid was collected and dried under high vacuum to give the *title compound* as a light yellow amorphous solid (8.1 g, 60 %) which was used without further purification. Data are consistent with those previously reported in the literature.[95]

mp 60–62 °C (lit[95] 60–61 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (1H, s, ArCH), 8.07 (1H, d, J = 8.0 Hz, ArCH), 7.46 (1H, d, J = 8.0 Hz, ArCH), 2.65 (3H, s, CH_3), 2.64 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0 (C=O), 149.4 (ArCH), 138.8 (ArCH), 136.1 (ArCH), 133.5 (Ar_q), 132.1 (Ar_q), 124.7 (Ar_q), 26.7 (CH_3), 20.7 (CH_3).



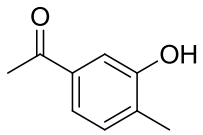
3-Amino-4-methylacetophenone 282

Preparation 1: To a stirring solution of 3-nitro-4-methylacetophenone (3.1 g, 17 mmol) in MeOH (60 mL) was added 5% Pd/C (500 mg) followed by vigorous stirring under 1 atm of hydrogen. After 1.5 h the mixture was filtered under vaccum. The filtrate was collected and the solvent was removed *in vacuo* to give the title

compound as cream-coloured crystals (2.40 g, 94%) which were used without further purification. Data are consistent with those previously reported in the literature. [95]

mp 78–79 °C (lit[95] 80–81 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, J = 1.7 Hz, ArCH), 7.26 (ArCH), 7.10 (1H, d, J = 7.5 Hz, ArCH), 3.75 (2H, s, NH_2), 2.53 (3H, s, CH_3), 2.20 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C=O), 145.0 (NC_q), 136.4 (OCC_q), 130.5 (ArCH), 128.1 (MeC_q), 119.1 (ArCH), 114.0 (ArCH), 26.6 (CH_3) , 17.6 ($ArCH_3$).

Preparation 2 (for >3 g)**:** To a stirred suspension of 3-nitro-4-methylacetophenone (14.0 g, 78 mmol) in 1.2 M HCl (100 mL) was added $SnCl_2 \cdot 2H_2O$ (53 g, 0.23 mol). The suspension was heated to 70 °C with continued stirring for 1 h. After cooling to 0 °C $NaHCO_3$ (sat. aq.) was added until neutralisation (judged as pH 7 by indicator paper). The tin by-products were removed by vacuum filtration and then rinsed with EtOAc (50 mL) to give a biphasic filtrate. The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the title compound as orange crystals (7.2 g, 62%) which were used without further purification. Data are consistent those previously reported in the literature.[95] Data were in accord to those reported for preparation 1.

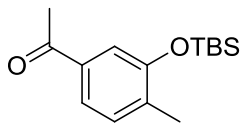


3-Hydroxy-4-methylacetophenone 283

To a stirred suspension of aniline **282** (15.8 g, 0.11 mol) in ice-cold water (200 mL) was slowly added conc. H_2SO_4 (54 mL). After 30 min the resultant clear solution was cooled to 0 °C. To the cooled solution was added $NaNO_2$ (9.0 g, 0.13 mol) in

water (30 mL).* After stirring for 10 min the solution was heated to reflux and stirring was continued for 5 h. After this time, the mixture was poured onto ice-cold water (50 mL) which was then allowed to warm to 23 °C over 17 h. After this time, the precipitate was filtered under vacuum. Dissolution of the collected solid in EtOAc (40 mL) was followed by washing with water (50 mL), $NaHCO_3$ (sat. aq., 20 mL), brine (20 mL), drying over $MgSO_4$ and filtering. The solvent was removed *in vacuo* to give the title compound as light brown crystals (16.3 g, 99%). The data are consistent with those previously reported in the literature.[95]

m.p 108–109 °C (lit[95] 110–111 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 1.6 Hz, ArCH), 7.45 (1H, dd, J = 7.7 and 1.6 Hz, ArCH), 7.20 (1H, d, J = 7.7 Hz, ArCH), 5.61 (1H, s, OH), 2.57 (3H, s, CH_3), 2.32 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C=O), 154.4 (Ar_q), 136.6 (Ar_q), 131.2 (ArCH), 130.8 (Ar_q), 121.5 (ArCH), 114.1 (ArCH), 26.7 (CH_3), 16.25 (CH_3).



3-(*tert*-Butyldimethylsiloxy)-4-methylacetophenone 284

To a stirred solution of 3-hydroxy-4-methylacetophenone **283** (16.3 g, 0.11 mol) in CH_2Cl_2 (100 mL) was added imidazole (22.2 g, 0.33 mol) and TBSCl (24 g, 0.16 mol). After stirring for 16 h, water (100 mL) was added. The separated organic layer was washed with NH_4Cl (sat. aq., 100 mL), water (5 × 300 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give *the title compound* as brown oil (18.3 g, 63%), which was used without further purification.

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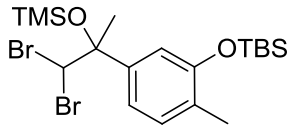
* Use a blast shield - potentially explosive diazonium salt!

ν_{max}/cm^{-1} 2956w, 2930w, 2858w, 1684s (C=O), 1602w, 1573w, 1500m, 1410m, 1356s, 1224s, 1193m, 1136w, 1068w; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, J = 7.8 and 1.6 Hz, ArCH), 7.36 (1H, d, J = 1.6 Hz, ArCH), 7.20 (1H, d, J = 7.8 Hz, ArCH), 2.55 (3H, s, CH_3), 2.26 (3H, s, CH_3), 1.03 (9H, s, $SiC(CH_3)_3$), 0.25 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7 (C=O), 154.3 (Ar_q), 136.5 (Ar_q), 135.4 (Ar_q), 131.0 (ArCH), 121.7 (ArCH), 117.7 (ArCH), 26.7 (CH_3), 25.9 ($SiC(CH_3)_3$), 18.4 (SiC), 17.3 (CH_3), –4.06 ($Si(CH_3)_2$): *m*/*z* calculated for $[C_{15}H_{25}O_2Si]^+$ 265.1618 found $[M + H]^+$ 265.1620.



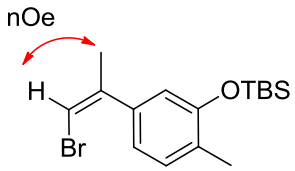
***tert*-Butyl(5-(1,1-dibromo-2-((trimethylsilyl)oxy)propan-2-yl)-2-methylphenoxy)dimethylsilane 290**

A solution of acetophenone **284** (1.0 g, 3.8 mmol) and dibromomethane (1.4 g, 7.9 mmol) in THF (10 mL) was transferred *via* cannula into an RBF containing a THF (10 mL) solution of freshly prepared lithium diisopropylamide (7.6 mmol) at –78 °C. After being stirred for 4 h at the same temperature, NH_4Cl aq. (2 mL) and Et_2O (20 mL) were added. The separated organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Volatiles were removed under high vacuum over 17 h. The crude residue (1.3 g) was dissolved in CH_2Cl_2 (20 mL) and imidazole (1.0 g, 14.9 mmol) and TMSCl (1.5 mL, 11.9 mmol) were added. After stirring for 4 h, water (10 mL) was added. The separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; petrol → 10% Et_2O in petrol) to give the *title compound* as brown thick oil (1.3 g, 66% for two steps)

ν_{max}/cm^{-1} 2956w, 2930w, 2897w, 2858w, 1609w, 1576w, 1502m, 1463m, 1251m, 1184m, 1065m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, J = 8.22 Hz, ArCH), 6.93–6.90 (2H, m, 2 × ArCH), 5.65 (1H, s, Br_2CH), 2.20 (3H, s, CH_3), 1.90 (3H, s, CH_3), 1.03 (9H, s, $SiC(CH_3)_3$), 0.23 (3H, s, $SiC(CH_3)_2$), 0.22 (3H, s, $SiC(CH_3)_2$), 0.10 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (ArCO), 141.8 (Ar_q), 130.5 (ArCH), 128.9 (Ar_q), 119.24 (ArCH), 117.42 (ArCH), 79.4 (CBr_2), 58.6 (*C*–OTMS), 26.0 ($SiC(CH_3)_3$), 23.7 (CH_3), 18.4 (SiC), 16.7 (CH_3), 2.2 ($Si(CH_3)_3$), –3.89 ($Si(CH_3)_2$), –3.96 ($Si(CH_3)_2$); *m*/*z* the expected ions could not be observed.

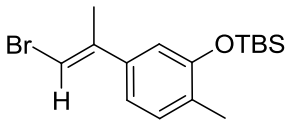
3-(*tert*-Butyldimethylsiloxy)-4-methylbromostyrene

To a solution of dibromo **290** (1.3 g, 2.5 mmol) in THF (10 mL) was added *n*-BuLi (1.1 mL, 2.8 mmol) at –78 °C. After stirring for 1 h the reaction was quenched with the addition of NH_4Cl (sat. aq., 1 mL) followed with the addition of Et_2O (15 mL) and warming to room temp. The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude mixture of *E*/*Z* alkenes determined by ^{1}H NMR as 1.0:1.3 ratio respectively. The isomers were separated by flash column chromatography (SiO_2; *n*-hexane) to give (*Z*)-alkene **285b** (140 mg, 16%) and (*E*)-alkene **285a** (100 mg, 12%) both as colourless oil. The geometry of each alkene was determined by NOESY experiments.

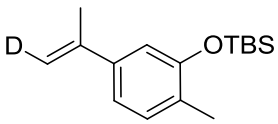


(*Z*)-Alkene 285b: ν_{max}/cm^{-1} 2955w, 2929w, 2858w, 1607w, 1566m, 1500m, 1250s, 1130m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (1H, d, J = 7.7 Hz, ArCH), 6.84 (1H, dd, J = 7.7 and 1.7 Hz, ArCH), 6.82 (1H, d, J = 1.7 Hz, ArCH), 6.19 (1H, q, J = 1.5 Hz,

=CH), 2.24 (3H, s, Ar*C*H$_3$), 2.11 (3H, d, *J* = 1.5 Hz, CH$_3$), 1.05 (9H ,s, SiC(CH$_3$)$_3$), 0.27 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 153.6 (ArCO), 141.3 (=C$_q$), 138.7 (Ar$_q$), 130.8 (ArCH), 128.6 (Ar$_q$), 120.2 (ArCH), 118.2 (ArCH), 101.1 (CBr), 25.9 (Si*C*(CH$_3$)$_3$), 25.15 (CH$_3$), 18.4 (SiC), 16.9 (CH$_3$), –4.0 (Si(CH$_3$)$_2$); *m*/*z* calculated for [C$_{16}$H$_{26}$BrSi]$^+$ 341.0931 found [M + H]$^+$ 341.0933.



(*E*)-Alkene 285a: ν_{max}/cm^{-1} 2956w, 2930w, 2887w, 2858w, 1608w, 1562w, 1510w, 1499w, 1402m, 1252s, 1180w, 1134w, 1001m; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (1H, d, *J* = 7.8 Hz, ArCH), 6.85 (1H, dd, *J* = 7.8 and 1.7 Hz, ArCH), 6.75 (1H, d, *J* = 1.7 Hz, ArCH), 6.40 (1H, q, *J* = 1.2 Hz, CH), 2.21 (3H, s, Ar*C*H$_3$), 2.20 (3H, d, *J* = 1.2 Hz, CH$_3$), 1.04 (9H, s, SiC(CH$_3$)$_3$), 0.24 (6H, s, Si(CH$_3$)$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.0 (ArCO), 141.4 (=C$_q$), 139.7 (Ar$_q$), 131.1 (ArCH), 128.9 (Ar$_q$), 118.8 (ArCH), 116.4 (ArCH), 104.7 (CBr), 25.9 (SiC(CH$_3$)$_3$), 19.8 (CH$_3$), 18.4 (SiC), 16.7 (CH$_3$), –4.0 (Si(CH$_3$)$_2$); *m*/*z* calculated for [C$_{16}$H$_{26}$BrSi]$^+$ 341.0931 found [M + H]$^+$ 341.0929.

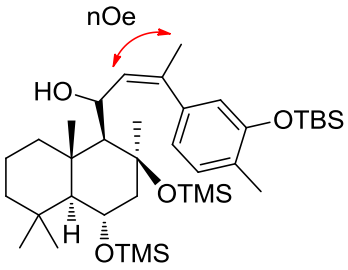


Deuterated-alkene 291

To a stirred solution of (*E*)-alkene **285a** (145 mg, 0.43 mmol) in THF (2 mL) at –78 °C was added *t*-BuLi (0.53 mL, 0.84 mmol) dropwise over 2 min. The resultant bright-yellow solution was stirred for a further 30 min and then a newly opened ampoule of CD$_3$OD (1 mL) was added, immeadiately followed by NH$_4$Cl (1 mL, sat.

aq.). The solution was allowed to warm to 23 °C and then diluted with Et_2O (5 mL). The organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was then removed *in vacuo* to give *the title compound* as pale yellow oil.

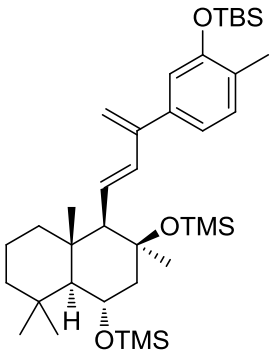
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, d, J = 7.8 Hz, ArCH), 7.00 (1H, dd, J = 7.8 and 1.8 Hz, ArCH), 6.91 (1H, d, J = 1.8 Hz, ArCH), 5.30 (1H, s, CH), 2.22 (3H, s, ArCH_3), 2.13 (3H, d, J = 0.66 Hz, CH_3), 1.05 (9H, s, $SiC(CH_3)_3$), 0.25 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (ArCO), 143.1 (=C_q), 140.1 (Ar_q), 130.7 (ArCH), 128.3 (Ar_q), 118.4 (ArCH), 116.0 (ArCH), 111.3 (t, J = 24 Hz, =CD), 26.0 ($SiC(CH_3)_3$), 21.9 (CH_3), 18.4 (SiC), 16.7 (CH_3), –4.0 ($Si(CH_3)_2$); *m/z* calculated for $[C_{16}H_{26}DOSi]^+$ 264.1888 found $[M + H]^+$ 264.1892.



(*Z*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)-4-methylphenyl)-1-((2,5,5,8a-tetramethyl-2,4-bis((trimethylsilyl)oxy)decahydronaphthalen-1-yl)but-2-en-1-ol 292

To a stirred solution of (*Z*)-bromoalkene **285b** (174 mg, 0.51 mmol) in THF (1 mL) at –78 °C was added *t*-BuLi (0.6 mL, 1.0 mmol) dropwise over 2 min. After stirring for 25 min a solution of aldehyde **280** (68 mg, 0.17 mmol) in THF (1 mL) was added dropwise to the bright-yellow solution. After continued stirring for 30 min the solution had become near-colourless and the reaction was quenched by the addition of NH_4Cl (sat. aq., 0.1 mL), and the mixture was diluted with Et_2O (5 mL). After warming to 23 °C the separated organic layer was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; petrol → 5% Et_2O in petrol) to give the *title compound* as pale yellow oil (60 mg, 53%).

ν_{max}/cm^{-1} 3518br (O–H), 2955m, 2929m, 2859m, 1503m, 1201s, 1081s; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, d, J = 7.6 Hz, ArCH), 6.66 (1H, dd, J = 7.6 and 1.3 Hz, ArCH), 6.57 (1H, d, J = 1.3 Hz, ArCH), 5.88 (1H, d, J = 8.3 Hz, =CH), 4.89–4.85 (1H, m, OHC*H*), 4.09 (1H, dt, J = 9.5 and 4.4 Hz, TMSOC*H*), 2.62 (1H, s, OH), 2.17 (3H, s, $ArCH_3$), 2.01 (1H, dd, J = 14.0 and 4.4 Hz, CH_{a1}), 1.97 (3H, s, =CC*H*$_3$), 1.89–1.83 (1H, m, CH_{a2}), 1.55–1.26 (6H, m, CH_2, CH_3, CH_{a3}), 1.22–1.06 (2H, m, $CH_{b3,}$ CH_{b2}), 1.03 (3H, s, CH_3), 1.02 (9H, s, $SiC(CH_3)_3$)), 0.99–0.95 (4H, m, CH_3, HOCC*H*), 0.92 (1H, d, J = 9.5 Hz, TMSOCC*H*), 0.89 (3H, s, CH_3), 0.22 (3H, s, $Si(CH_3)$), 0.20 (3H, s, $Si(CH_3)$), 0.130 (9H, s, $Si(CH_3)_3$), 0.126 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0 (ArCO), 140.9 (=C_q), 136.1 (Ar_q), 131.7 (=CH), 130.9 (ArCH), 127.3 (Ar_q), 120.6 (ArCH), 117.9 (ArCH), 79.7 (OC_q), 70.7 (HOCH), 68.8 (TMSOC*H*), 62.3 (HOCC*H*), 61.3 (TMSOCC*H*), 52.6 (CH_2), 43.8 (CH_2), 42.9 (CH_2), 41.3 (C_q), 36.7 (CH_3), 33.6 (C_q), 32.0 (CH_3), 26.3 (CH_3), 26.0 ($SiC(CH_3)_3$), 22.9 (CH_3), 18.9 (SiC), 18.4 (CH_2), 16.7 (CH_3), 2.8 ($Si(CH_3)_3$), 1.28 ($Si(CH_3)_3$), –3.85 ($Si(CH_3)$), –3.94 ($Si(CH_3)$); *m*/*z* calculated for $[C_{37}H_{68}O_4Si_3]^+$ 660.4365 found $[M]^+$ 660.4420.

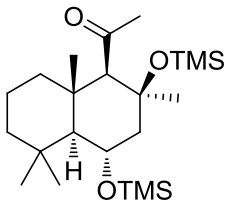


(*E*)-Ansellane diene 300

Ansellane alcohol **292** (approximately 60 mg) was left standing for several days in a fumehood at 23 °C, to give a mixture of degradation products. Purification of the mixture by flash column chromatography (SiO_2; petrol) gave *the title compound* as pale yellow oil (approximately 10 mg).

ν_{max}/cm^{-1} 2931m, 1860m, 1885m, 1836m, 1774m, 1411m, 1250m; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, J = 7.7 Hz, ArCH), 6.83 (1H, dd, J = 7.7 and 1.6 Hz, ArCH), 6.73 (1H, d, J = 1.6 Hz, ArCH), 6.14 (1H, d, J = 15.8 Hz, HC=C*H*C_q), 5.76 (1H, dd, J = 15.8 and 10.0 Hz, *H*C=CHC_q), 5.14 (1H, d, J = 1.9 Hz, C_q=CH), 5.04 (1H, d, J = 1.9 Hz, C_q=CH), 4.21 (1H, td, J = 10.6 and 4.0 Hz, TMSOC*H*), 2.20 (3H, s, ArC*H*$_3$), 2.07–2.01 (1H, m, CH_{a1}), 1.56–1.16 (7H, m, 2 × CH_2, CH_{b1}, CH_{a2}, C_qCH), 1.13 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.01 (10H, brs, SiC(CH_3)$_3$, C_qCH), 0.99 (6H, brs, 2 × CH_3), 0.20 (6H, s, Si(CH_3)$_2$), 0.16 (9H, s, Si(CH_3)$_3$), 0.00 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (ArCO), 148.2 (Ar$_q$), 139.6 (=C_q), 134.9 (C=*C*HC_q), 132.8 (H*C*=CHC_q), 130.5 (ArCH), 128.1 (Ar$_q$), 120.9 (ArCH), 118.4 (ArCH), 113.4 (=CH_2), 76.4 (OC_q), 69.0 (TMSO*C*), 64.5 (CH), 60.7 (CH), 53.8 (CH_2), 44.6 (CH_2), 41.9 (CH_2), 40.0 (C_q), 36.9 (CH_3), 33.8 (C_q), 30.9 (CH_3), 25.9 (Si(CH_3)$_3$), 22.5 (CH_3), 18.4 (SiC), 18.3 (CH_2), 17.2 (CH_3), 16.8 (CH_3), 2.6

($Si(CH_3)_3$), 1.2 ($Si(CH_3)_3$), –3.99 ($Si(CH_3)$), –4.01 ($Si(CH_3)$); *m/z* calculated for $[C_{37}H_{66}O_3Si_3]^+$ 642.4320 found $[M]^+$ 642.4316.

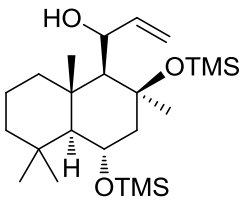


1-2,5,5,8a-Tetramethyl-2,4-bis((trimethylsilyl)oxy)decahydronaphthalen-1-yl)ethanone 306

To a stirred solution on aldehyde **280** (102 mg, 0.26 mmol) in THF (3 mL) was added MeLi (0.3 mL, 0.51 mmol) at –78 °C. After continued stirring for 1.5 h NH_4Cl (sat. aq., 0.2 mL) was added. Upon warming to 23 °C the mixture was diluted with Et_2O (5 mL) and the organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give alcohol **308** as pale yellow oil and a mixture two diastereomers (99 mg, 58%) which was used without further purification. To a stirred solution of DMSO (0.03 mL, 0.42 mmol) in CH_2Cl_2 (2 mL) was added $(COCl)_2$ (0.019 mL, 0.23 mmol). After stirring for 15 min a solution of alcohol **308** (50 mg, 0.076 mmol) in CH_2Cl_2 (1 mL) was added slowly. After a further 15 min NEt_3 (0.13 mL, 0.91 mmol) was added and the solution was allowed to warm to room temp over 1 h. After this time water (2 mL) was added and the organic layer was separated, dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give crude residue which was purified by flash column chromatography (SiO_2; petrol → Et_2O) to give the *title compound* as pale yellow oil (18 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (1H, dt, *J*= 10.6 and 4.1 Hz, TMSOC*H*), 2.19 (3H, s, O=CCH_3), 2.14 (1H, s, O=CCH), 2.00 (1H, dd, *J* = 13.2 and 4.0 Hz, CH_{a1}),

1.63–0.97 (20H, m, CH_{b1}, 4 × CH_3, 3 × CH_2, C_qCH), 0.17 (9H, s, $Si(CH_3)_3$), 0.15 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.0 (C=O), 74.9 (OC_q), 72.9 (O=CCH), 69.0 (TMSOC*H*), 61.0 (C_qCH), 53.9 (CH_2), 44.2 (CH_2), 41.3 (CH_2), 39.9 (C_q), 37.0 (O=C–CH_3), 33.6 (C_q), 30.4 (CH_3), 22.3 (CH), 18.0 (CH_2), 16.8 (CH_3), 14.2 (CH_3), 2.7 (($Si(CH_3)_3$), 1.2 (($Si(CH_3)_3$); *m/z* calculated for $[C_{22}H_{45}O_3Si_2]^+$ 413.2902 found $[M + H]^+$ 413.2894.

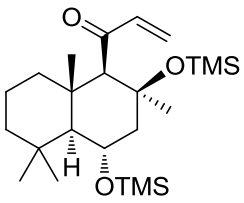


1,2,5,5,8a-Tetramethyl-2,4-bis((trimethylsilyl)oxy)decahydronaphthalen-1-yl)prop-2-en-1-ol 312

To a stirred solution of aldehyde **280** (11 mg, 0.04 mmol) in DME (1 mL) was added vinyl magnesium bromide (1M, 0.09 mL, 0.09 mmol) at –40 °C. After continued stirring for 1 h, the reaction was quenched with NH_4Cl (sat. aq., 0.2 mL) and, after warming to room temp, was diluted with Et_2O (4 mL). The organic layer was separated and dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude oil. Analysis of the crude oil by ^1H NMR indicated an 8:2 mixture of diastereomer products from which only the major diastereomer (5 mg, 44%) was isolated by flash column chromatography (SiO_2; 5% Et_2O in petrol). The stereochemistry of the newly formed carbinol chiral centre was not determined.

ν_{max}/cm^{-1} 3518br (O–H), 2954m, 2926m, 2871m, 1721w, 1250s, 1082s, 1030m; ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, ddd, J = 17.3, 10.7 and 4.2 Hz, HOCC*H*=C), 5.19 (1H, apt dt, J = 17.3 and 2.0 Hz, $C=CH_{trans}$), 4.99 (1H, apt dt, J = 10.7, 2.0 Hz, $=CH_{cis}$), 4.90–4.87 (1H, m, *H*COH), 4.15 (1H, td, J = 9.5 and 4.4 Hz, TMSOC*H*),

3.02 (1H, s, OH), 2.18 (1H, dd, J = 14.1 and 4.4 Hz, CH_{a1}), 2.03-1.98 (1H, m, CH_{a2}), 1.63 (1H, dd, J= 14.1 and 9.4 Hz, CH_{b1}), 1.54-1.42 (4H, m, CH_3, CH_{a3}), 1.37-1.25 (6H, m, CH_{b3}, CH_3, CH_{a4}), 1.18-0.93 (10H, m, CH_{b2}, CH_{b4}, 2 × CH, 2 × CH_3), 0.21 (9H, s, $Si(CH_3)_3$), 0.17 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (=CH), 111.0 (=CH_2), 79.6 (OC_q), 73.1 (HOCH), 68.7 (TMSO*C*H), 62.9 (CH), 61.5 (CH), 52.3 (CH_2), 43.7 (CH_2), 42.9 (CH_2), 41.7 (C_q), 36.7 (CH_3), 33.6 (CH_3), 32.7 (CH_3), 22.9 (C_q), 18.9 (CH_3), 18.3 (CH_2), 2.9 ($Si(CH_3)_3$), 1.3 ($Si(CH_3)_3$); *m/z* the expected ions were not observed.



1-2,5,5,8a-Tetramethyl-2,4-bis((trimethylsilyl)oxy)decahydronaphthalen-1-yl)prop-2-en-1-one 310

To a stirred solution of alcohol **312** (5 mg, 0.018 mmol) in CH_2Cl_2 (1 mL) was added MnO_2 (31 mg, 0.35 mmol). After stirring for 48 h, the mixture was diluted with Et_2O (6 mL) and filtered through a plug of SiO_2. The solvent was removed *in vacuo* to give a crude residue which was purified by flash column chromatography (SiO_2; 5% Et_2O in petrol) to give the *title compound* as colourless oil (<1 mg).*

^{1}H NMR (600 MHz, cryoprobe, $CDCl_3$) δ 6.63 (1H, dd, J = 17.2 and 10.7 Hz, =CH), 6.12 (1H, dd, J = 17.2 and 1.4 Hz, =CH), 5.57 (1H, dd, J = 10.7 and 1.4 Hz, =CH), 4.26 (1H, td, J = 10.6 and 4.0 Hz, OCH), 2.02 (1H, dd, J = 13.2 and 4.1 Hz, CH_{a1}), 1.55 (CH_{a2}), 1.48 (1H, dd, J = 13.2 and 10.7 Hz, CH_{b1}), 1.33–1.17 (11H, m, 2 × CH_3, C_qCH, CH_{b2}, CH_2, CH_{a3}), 1.09 (3H, s, CH_3), 1.08–1.01 (2H, m, CH_{b3}, O=CCH), 1.00

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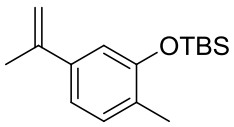
* Full characterisation was not attempted due to small quantity obtained.

(3H, s, CH_3), 0.17 (9H, s, $Si(CH_3)_3$), 0.15 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (101 MHz, cryoprobe, $CDCl_3$) δ 202.3 (C=O), 126.1 (2 × =C)*, 75.2 (OC_q), 69.0 (OCH), 61.0 (O=C*C*H), 54.0 (CH_2), 44.2 (CH_2), 41.3 (CH_2), 40.3 (C_q), 37.0 (CH_3), 33.6 (C_q), 30.4 (CH_3), 29.9 (CH), 22.4 (CH_3), 18.0 (CH_2), 17.1 (CH_3), 2.7 ($Si(CH_3)_3$), 1.2 ($Si(CH_3)_3$).



3-(*tert*-Butyldimethylsiloxy)-4-methylmethystyrene 311

To a stirred solution of methyltriphenylphosphonium bromide (1.35 g, 3.78 mmol) in PhMe (10 mL) was added KO^{t}Bu (318 mg, 2.84 mmol). After 30 min acetophenone **284** (500 mg, 1.89 mmol) in PhMe (5 mL) was added to the resultantly yellow solution. After a further 30 min NH_4Cl (sat. aq., 2 mL) was added. The crude mixture was directly placed onto a column (SiO_2; petrol) to give the *title compound* as pale yellow oil (231 mg, 47%).

ν_{max}/cm^{-1} 2957w, 2931w, 2859w, 1508w, 1253m; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, d, J = 7.8 Hz, ArCH), 6.91 (1H, dd, J = 7.8 and 1.8 Hz, ArCH), 6.83 (1H, d, J = 1.8 Hz, ArCH), 5.23 (1H, m , =CH), 4.96–4.94 (1H, m, =CH), 2.14 (3H, s, $ArCH_3$), 2.05 (3H, dd, J = 1.4, 0.8 Hz, CH_3), 0.97 (9H, s, $SiC(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (ArCO), 143.2 (Ar_q), 140.2 ($=C_q$), 130.8 (ArCH), 128.3 (Ar_q), 118.4 (ArCH), 116.0 (ArCH), 111.6 ($=CH_2$), 26.0 (($SiC(CH_3)_2$),), 22.0 (CH_3), 18.4 (SiC), 16.7 (CH_3), –4.0 ($Si(CH_3)_2$); *m/z* calculated for $[C_{16}H_{27}O_1Si]^+$ 263.1826 found $[M + H]^+$ 263.1827.

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† Co-resonant carbon signals confirmed by HSQC analysis.

5. References

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