Studies Towards the Synthesis of LL-Z1640-2 and Spirocyclic Systems

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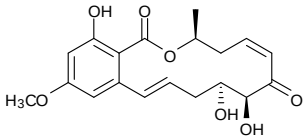
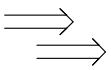
Abstract

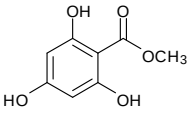
Resorcyclic acid lactones (RALs) are natural products, with some having been shown to be potent inhibitors of several protein kinases and mammalian cell proliferation and tumour growth in animals. LL-Z1640-2 (also known as 5Z-7-oxo-zeanol or C292) is a *cis*-enone RAL, isolated in 1978 from fungal broth and classified as an anti-protozoal agent. Later, in 1999, its cytokine releasing inhibiting activity was discovered, with subsequent data showing it could selectively and irreversibly inhibit transforming growth factor activating kinase-1 (TAK1) activity at low concentrations. It is also reported as having significant activity versus tumour necrosis factor-alpha (TNF-α) production in cells.

This thesis documents and describes the work undertaken towards a total synthesis of the 14-membered macrocycle, LL-Z1640-2. The presence of two internal bonds and three stereogenic centres poses a challenge synthetically, but this has been effectively overcome with the development of a flexible, economic and efficient synthesis, beginning from the commercially available starting materials, methyl 2,4,6-trihydroxybenzoate and 2-deoxy-D-ribose.

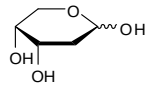


LL-Z1640-2





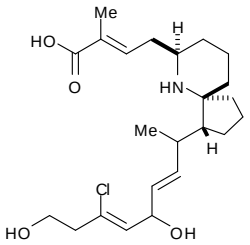
Methyl 2,4,6-trihydroxybenzoate



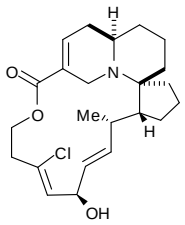
2-Deoxy-D-ribose

The original route relied on a Wittig olefination to introduce the *E*-double bond, with moderate selectivity and success. Later, an improved method was built upon, which utilised Grubbs mediated cross-metathesis to form the desired *E*-olefin in good yield and selectivity. Once the entire carbon framework had been established *via* a one-pot oxidation-Grignard adition of the appropriate alkyne unit, subsequent transformations enabled the formation of the *seco*-acid. This very successfully underwent Mitsunobu macrolactonisation, with complete inversion of the stereocentre, to afford the macrocyclic lactone. From this intermediate, the desired natural product LL-Z1640-2 could be generated in three steps.

A number of natural products and biologically important compounds contain spirocyclic pyran and piperidines ring systems as part of their overall structures. In 1996, pinnaic acid and halichlorine were isolated from their respective marine natural sources. It was subsequently shown that they exhibited inhibitory activity towards certain biological substances and for this reason they became targets for total synthesis. Characterised by an azaspiro[4.5]decane ring system, the difficulty in achieving total syntheses of such compounds is immense.

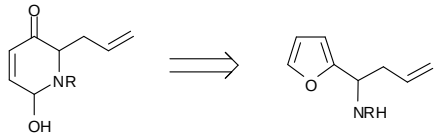


Pinnaic Acid



Halichlorine

The aim of the project was to develop a concise method towards the generation of highly functionalised spirocyclic piperidine units. The regioselective *aza*-Achmatowicz oxidative rearrangement was used as the key step to rearrange α-amino furan building blocks into their respective enones. Importantly, this rearrangement was proven to be viable and to proceed with compounds possessing a terminal olefin, with no over-oxidation observed.



This thesis also describes the investigation and efforts made into the production of more functionalised units, as well as studies into the synthesis of the cores of halichlorine and polymaxenolide, again using the *aza*-Achmatowicz and Achmatowicz rearrangement respectively.

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Acknowledgements

I would like to take this opportunity to extend my thanks to my supervisor, Dr Rudi Marquez, for all his support, encouragement and guidance throughout my PhD. Many thanks also to my second supervisor, Dr Andrew Sutherland, for his help and advice throughout my time in the department.

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I gratefully acknowledge Dr Ian Sword and the University of Glasgow for financial support.

Last, but by no means least, I must thank my family, especially Mum, Dad and Mark and also to Stephen, for being there every step of the way.

Suzannah

Author's Declaration

This thesis represents the original work of Suzannah Jane Harnor unless explicitly stated otherwise in the text. The research on which this thesis is based was carried out at the University of Glasgow in the Henderson and Raphael laboratories, under the supervision of Dr Rodolfo Marquez, during the period October 2006 to September 2009.

Suzannah J. Harnor

July 2010

Abbreviations

4Å MS	4 Angstrom molecular sieves
Å	Angstrom
Allyl	2-propenyl
aq.	aqueous
app.	apparent
approx.	approximately
Ar	aryl
atm	atmosphere(s)
bd	broad doublet
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
^{o}C	degrees Celsius
CAN	ceric ammonium nitrate
cat.	catalytic
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
cm^3	cubic centimetres
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
ddt	doublet of doublet of triplets
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement through polarisation transfer
DIPEA	*N,N'*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
EI	electron impact
eq.	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
FCC	flash column chromatography
g	gram(s)
h	hour(s)
HCl	hydrochloric acid
HF	hydrogen fluoride
HRMS	high resolution mass spectrometry

HSQC	heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
Hz	hertz
i	iso
IR	infrared
KHMDS	potassium *bis*(trimethylsilyl)amide
J	NMR spectra coupling constant
µL	microlitre(s)
L	litre(s)
lit.	literature
µM	micromolar
m	multiplet
M	molar (mol L^{-1})
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mM	millimolar
mol	mole(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectroscopy/spectrum
Ms	methanesulfonyl/mesyl
MW	molecular weight
*n*BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
oct.	octet
p	para
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
q	quartet
qn	quintet
R	alkyl chain
RCM	ring closing metathesis
rec.	recovered
rt	room temperature
s	singlet
sext.	sextet
t	tertiary
t	triplet
TBAF	*tetra*-butylammonium fluoride
TBAI	*tetra*-butylammonium iodide
TBDMS/TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide

TEA	triethylamine
tert	tertiary
TFAA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsily
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl/tosyl
UV	ultraviolet
$VO(acac)_2$	vanadyl acetylacetonate

1 Introduction

1.1 Macrolides

Macrolides are a biologically important class of natural products, but for many years the synthesis of such compounds posed an insurmountable challenge to chemists due to their often complex structures. Over the last 20-30 years, new synthetic methodologies have been pioneered, enabling the total synthesis and subsequent biological evaluation of many of these significant natural products. The key step in the majority of cases is the formation of the large ring (macrocycle) and to date there are several reliable methods to execute this. Generally, a macrolide is defined as a molecule containing a large ring lactone in its structure,[1] which can be thought of as being derived from *seco* acids through internal esterification (Figure 1). Additionally, those containing more than one ester linkage are also classified as macrolides.

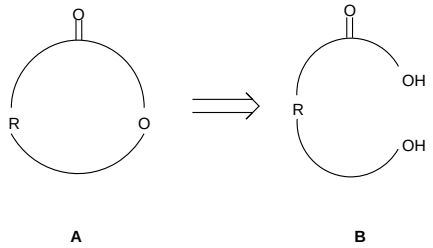


Figure 1: General Structure of Large Ring (Macrocyclic) Lactones (A) and *Seco* (Hydroxy) Acids (B).

A large amount of investigation has been devoted into this class of compounds. They have been found to possess significant biological and physiological properties and many have the potential to be drug leads. The macrolide antibiotics[2] feature a polysubstituted macrocyclic lactone, within a 12-16 membered framework. Examples of this class of antibiotics include erythromycin A and B, which both have 14-membered rings and leucomycin A, which has a 16-membered ring (Figure 2).

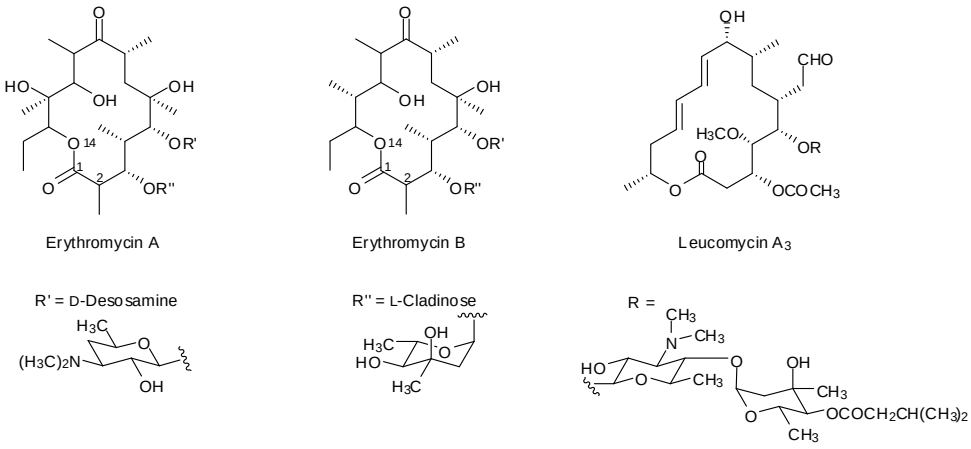


Figure 2: Structures of Erythromycin A and B and Leucomycin A_3.

There is a wealth of information regarding the different types and classes of macrolides, but it is not feasible to document it all within the length of this thesis. Briefly, the polyene macrolide antibiotics[3] possess strong anti-fungal activity, the cytochalasans[4] are active metabolites isolated from marine microorganisms and exhibit antibiotic, antitumour and cytostatic action, the macrodiilides contain within their structure two ester linkages and the macrotetrolides have four ester linkages and are antibiotic and ionophoric. Alkaloids also can contain macrocyclic lactones and so can be thought of as macrolides, for example carpaine[5] has a symmetrical 26-membered ring (Figure 3). ß-Resorcyclic acid macrolides also exist with many members, but as they are the group that LL-Z-1640-2 belongs to they will be discussed in further depth.

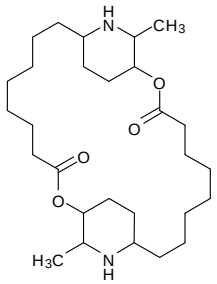


Figure 3: Structure of Carpaine.

1.2 Resorcyclic Acid Lactones

Resorcyclic acid lactones (RALs) have been known since 1953 when the first isolation of radicicol took place from *Monocillium nordinii*[6] and was termed

Monorden. The isolation of zearalenone,[7] LL-Z1640-2[8a] and hypothemycin[9] followed in subsequent years. Interestingly, the structures that were originally proposed for radicicol and hypothemycin were later found to be incorrect. When radicicol was isolated from *Nectria radicicola*[10] in 1964, the correct structure was elucidated and radicicol became the given name. In 2006, radicicol was found to be synthesised by fungi associated with a Sonoran desert plant.[11] Initially, the biological activity of early discovered RALs did not attract immediate attention and it was only in latter years that they were held in greater esteem.

1.3 Biosynthesis of RALs

RALs are mycotoxins which are produced by different fungal strains *via* polyketide synthesis (Figure 4).[12]

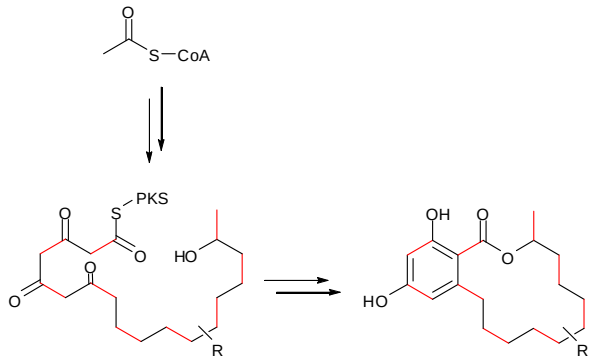


Figure 4: Biosynthesis of RALs. The red carbons represent the two-carbon units that are added in each reiterative condensation.

PKS's are type I polyketide synthases and are large multidomain enzymes that iteratively catalyse the condensation of nine units of malonates or thioacetates.[12] The product of each condensation can then be processed by different modules to either reduce or dehydrate the ß-ketone.

The biosynthesis involves two PKSs. The first assembles the first five acetate units, with further processing to arrive at the adequate oxidation state at each carbon and the second performs the remaining three condensations without carbonyl reduction. Ketones that are unreduced are highly reactive and take part in a cyclisation/aromatisation, the lactone then gets released *via* a

cyclisation module on the second PKS.[13] The functionality around the RAL macrocycle is dependent on the arrangement of modules in the first five condensations.

1.4 Biological Activity of the RALs

Originally, the properties of RALs did not attract much attention from chemists and it wasn't until the early 1990s that interest was renewed, mainly due to the selective kinase inhibitory action that some RALs possessed.

Zearalenone was found to have oestrogen agonistic properties, which were due to the direct interaction on the oestrogen receptor in competition with 17-estradiol.[14] Interestingly, the macrocycle was able to adopt a conformation that mimicked a steroid[15] and these properties further allowed it to be used as a bovine growth stimulant.

Radicicol has been found to be a potent and selective inhibitor of the molecular chaperone HSP90.[16,17] When there is no HSP90 chaperone activity, clients of HSP90 are unfunctional and targeted for degradation. It has been shown through co-crystallisation studies that even though radicicol and ATP are not structurally similar, radicicol is a competitive ligand for the ATP binding site of HSP90.[18]

There are some *cis*-enone RALs which irreversibly inhibit mitogen activated protein kinases (MAP kinases) and are competitive with ATP. The subject of protein kinases is vast and an immense amount of wide-ranging studies have been carried out in this field. Due to their importance and their biological connections with LL-Z1640-2, the protein kinases will be discussed in further depth.

1.5 Mitogen Activated Protein Kinases (MAP Kinases)

Protein phosphorylation of amino acids in the human body is catalysed by kinases and likewise, dephosphorylation is phosphatase catalysed (Figure 5).

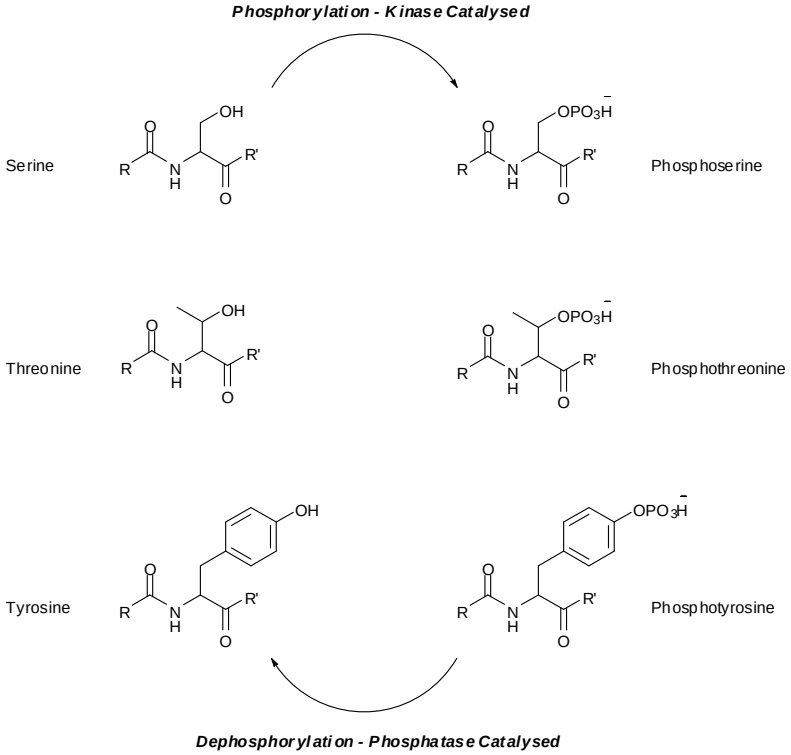


Figure 5: Protein Phosphorylation and Dephosphorylation.

Mitogen activated protein kinases (MAP kinases) belong to the family of kinases that are responsible for controlling many cellular events. Although each has a unique character, a number of features are shared by all MAP kinases. They are activated by protein kinase cascades that contain at least two upstream kinases (Figure 6). These upstream kinases are members of the MAP kinase/ERK (extracellular signal-regulated kinase) kinase or MEK family. In order for MAP kinases to become highly active, they require tyrosine and threonine phosphorylation (catalysed by MEKs).[19,20]

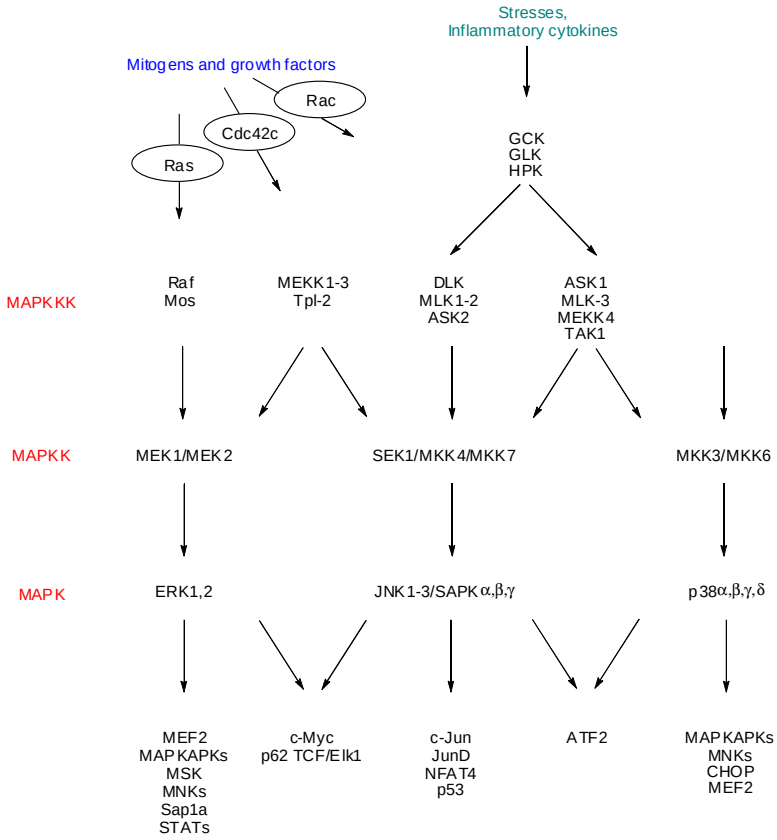


Figure 6: Excerpt from MAP Kinase Cascades. Reproduced from Elsevier Inc., 2003.

Inhibitors of MAP kinases are interesting as the MAP kinases relay, amplify and integrate signals from a range of extracellular stimuli, in so doing regulating a cell's response to its environment. The amplitude of the signal is controlled by three sequentially activated kinases, called a phosphorelay system. Generically, a stimulus turns on the activator which phosphorylates the first kinase (MAPKKK) which then phosphorylates the second kinase (MAPKK), which in turn phosphorylates the third kinase (MAPK) which phosphorylates a cytosolic protein or transcription factor.[21]

There are at least three subfamilies of MAP kinases (ERKs, JNKs and p38 enzymes), with at least seventeen MAPKKKs, seven MAPKKs and twelve MAPKs. Importantly, the specificity of the cascades needs to be regulated. This is achieved by scaffolding proteins which organise and localise the cascades to provide a combinatorial arrangement and down stream signal which is unique.[22] The MAP kinases are intensely important in regulating cellular responses and it is for this reason that they are prime, viable drug targets. They are also hugely

important in determining the functions of specific MAP kinases in complex networks.

Radicicol A (Figure 7) was the first RAL to show inhibitory action towards a kinase. The mode of action is that it accelerates the degradation of specific *m*RNA sequences containing AU-rich elements (AREs).[23,24]

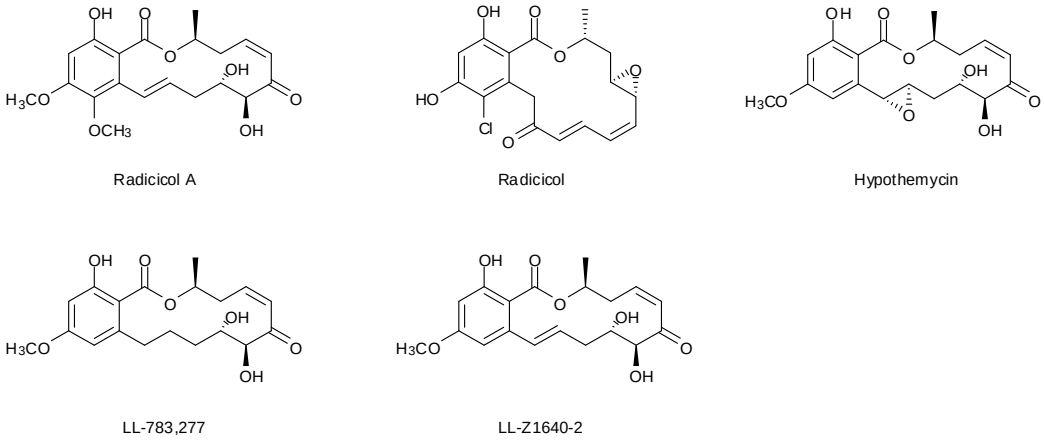


Figure 7: Structures of *cis*-enone Containing RALs.

Some macrolides contain an α,ß-unsaturated ketone in the macrocycle, for example the *cis*-enones which include hypothemycin, radicicol, radicicol A, LL-783,277 and LL-Z1640-2 (Figure 7). These *cis*-enone RALs have been shown to inhibit mammalian cell proliferation and tumour growth in animals,[25-27] with other reports suggesting that *cis*-enone RALs inhibit selected protein kinases.[28] Researchers at Merck found that LL-783,277 and hypothemycin were potent and irreversible inhibitors of MEK1 (4 nM and 15 nM respectively), with the presence of their *cis*-enone being essential for the activity.[29] The irreversible inhibition can be accredited to a Michael addition onto the *cis*-enone of a cysteine residue which is present in the ATP-binding pocket of a subset of kinases (Figure 8).[28] LL-Z1640-2 was found to be a potent and irreversible inhibitor of TAK1 (IC_{50} 8.1 nM).[30]

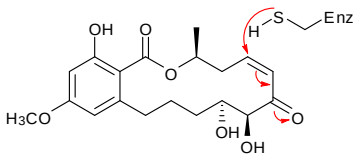


Figure 8: Proposed Mode of Action of the *cis*-enone RALs. LL-783,277 is given as the example in this case.

1.6 Chemical Synthesis of the RALs

Constructing natural products synthetically provides challenges, both intellectually and practically, which many thrive on in order to discover and even invent new chemical reactions and strategies. Since the syntheses of urea and acetic acid in the early 1800's, chemistry has evolved so much that high complexity of targets can be achieved. The macrolides have in general; a large macrocyclic ring fused to resorcyclic acid and for many years posed a challenge to synthetic chemists due to their complex structures. Over time, synthesis of these compounds has become more prevalent, with some having been synthesised and then re-synthesised to utilise new synthetic developments. As a consequence, long-standing, resistant molecules have finally succumbed to total synthesis.

Zearalenone[31] (Figure 9), due to its marked anabolic and uterotrophic activities, held great interest and a number of syntheses to this molecule have been reported. Indeed, it was perhaps the first naturally occurring macrolide to be synthesised, with the first total synthesis published by chemists at Merck in 1968.[32]

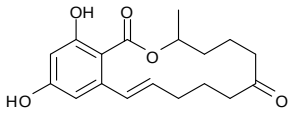
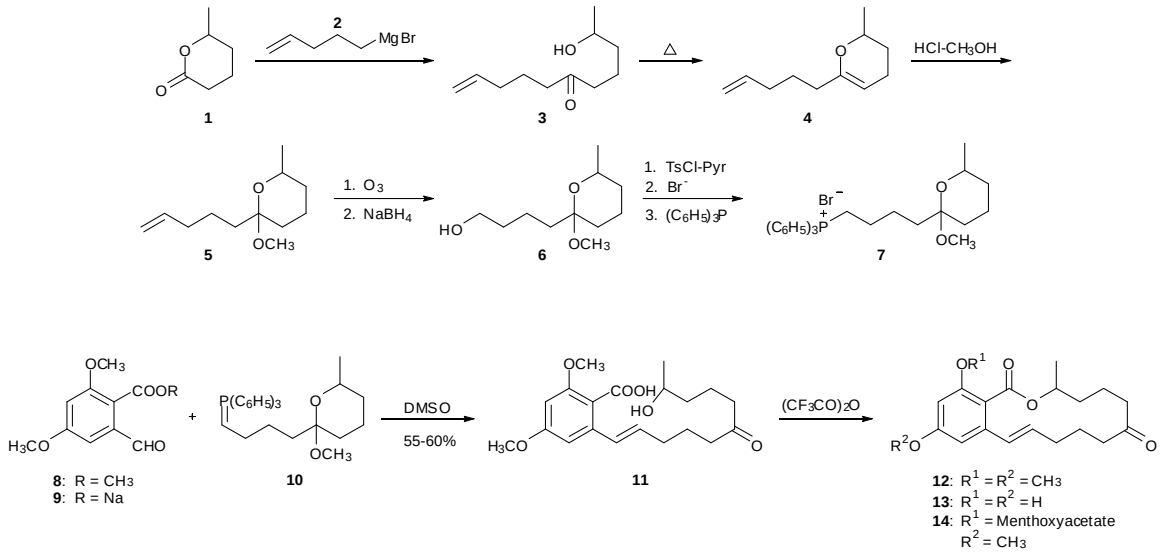


Figure 9: Structure of Zearalenone.

Leading up to the total synthesis of zearalenone, the Merck group investigated whether the macrocyclic ring could be formed by esterification of the *seco*-acid and from this, whether the natural product could be obtained. In order to test their hypothesis, they took natural zearalenone and prepared from it, the *seco*-acid derivative, by methylation of both phenolic groups and saponification. Preliminary experiments led to the knowledge that zearalenone could be obtained from the acyclic precursor by lactonisation followed by protection group removal. With the final stages completed, work began on the construction of the fragments which would join to form the *seco*-acid (Scheme 1).



Scheme 1: The Merck Synthesis of Zearalenone.

The aliphatic unit was obtained by condensation of **1** with 1-pentenylmagnesium bromide **2** followed by exposure to methanolic hydrogen chloride to afford the ketal **5**, *via* **3** and **4**. Reductive ozonolysis of the double bond and tosylation of the resulting alcohol **6** was followed by displacement of the tosylate with bromide ion and heating with triphenylphosphine to give the phosphonium salt **7**. The aromatic unit, as its sodium salt, was obtained from 2,4-dimethoxyphthalic anhydride by partial reduction with lithium tri-*t*-butoxyaluminium hydride followed by diazomethane to afford the methyl ester **8**, which was then converted to its sodium salt **9**.

The phosphorane **10** and aldehyde **9** in DMSO were condensed to afford the *seco*-acid **11** in 55-60% yield. Cyclisation proceeded using trifluoroacetic anhydride in dilute benzene to give **12**, which then underwent liberation of the phenolic group. The authors reported that this group was used as a handle to resolve the racemate **13** as 2-*l*-menthoxyacetate **14** gave natural zearalenone **13** after removal of the menthoxyacetate and the methyl ether (BBr_3).

1.7 LL-Z1640-2

LL-Z1640-2 (also known as C292[8b] or 5*Z*-7-oxo-zeaenol) is a *cis*-enone resorcyclic acid lactone that was first isolated in 1978 as an anti-protozoan agent from the culture broth of fungal strain f6024.[8a] As part of its structure it has a 14-

membered macrocycle, with two internal double bonds and three stereogenic centres (Figure 10).

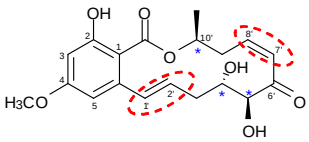


Figure 10: Structure of LL-Z1640-2 (C292 or 5*Z*-7-oxo-zeaenol). The internal double bonds and stereogenic centres are highlighted.

1.8 Biological Activity of LL-Z1640-2

Originally, this compound did not capture a great deal of attention as it held no particularly interesting properties; it had no anabolic or oestreogen-like activity. However, a major breakthrough came when a screen for TAK1 inhibition revealed that this compound had an IC_{50} of 8.1 nM.[30] Conversely, zearalenone and radicicol showed no appreciable activity. The same authors then proceeded to show that LL-Z1640-2 was competitive with ATP, as it targeted the ATP-binding pocket of kinases,[12] as well as being an irreversible inhibitor of a specific mitogen activated protein kinase, TAK1. On topical application to an animal model, LL-Z1640-2 was shown to effectively prevent inflammation.[30]

1.9 Transforming Growth Factor Activating Kinase-1 (TAK1)

TAK1 is transforming growth factor activating kinase-1 and is a MAPKKK involved in the p38 signalling cascade for proinflammation signals such as cytokines (Figure 6 and Figure 11). LL-Z1640-2 is 50-fold less active against MEK1 (411 nM), whilst having no inhibitory effect on other MAP kinases, such as ASK1.[33-35] This renders this RAL a promising specific inhibitor of TAK1.

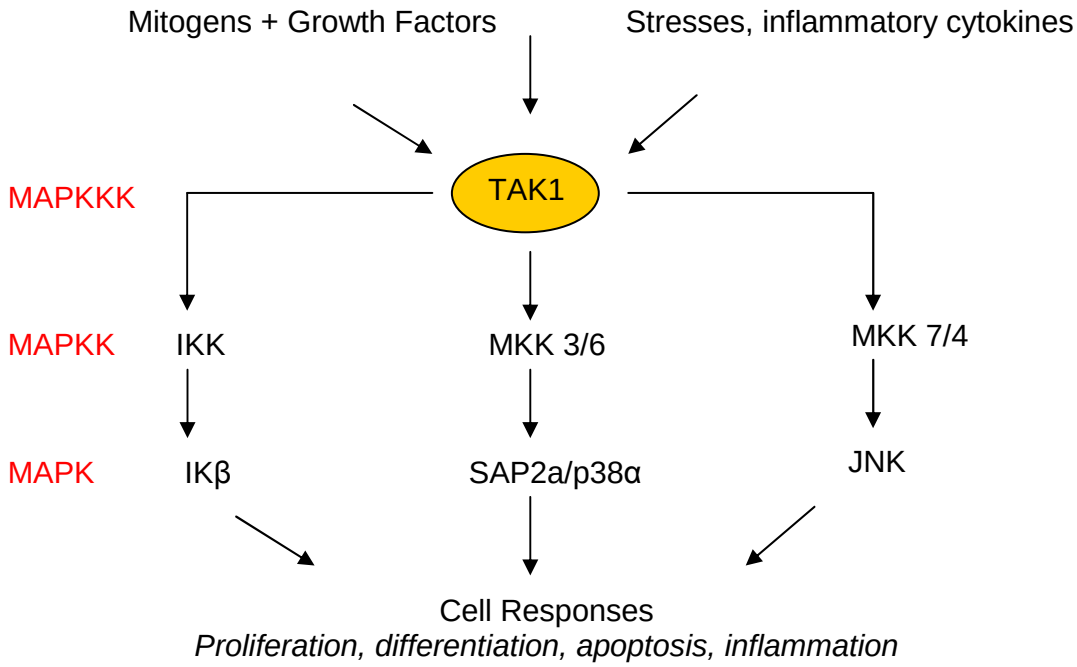


Figure 11: Position of TAK1 in a Summary of the Protein Kinase Cascade.

1.10 IC_{50}

For competition binding assays and functional antagonist assays the most common summary measure of the dose-response curve is IC_{50}. The IC_{50} is defined as the half-maximal inhibitory concentration and it serves to measure how much of a particular substance/molecule is needed to inhibit a biological process by 50%. It is commonly used in pharmacological research as a measure of antagonist drug potency and is comparable with EC_{50} for agonists. This is the concentration giving 50% of that compound's maximal response. The IC_{50} of a compound is calculated by plotting a dose-response curve relating concentration of the compound to the activity of the biological process. An example of a dose response cure is shown below (Figure 12).

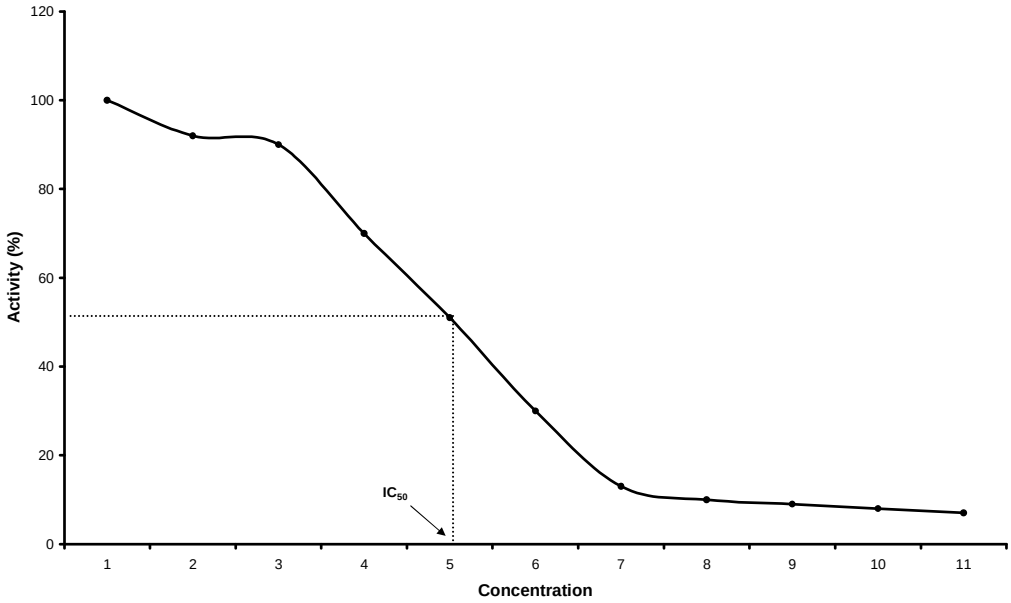
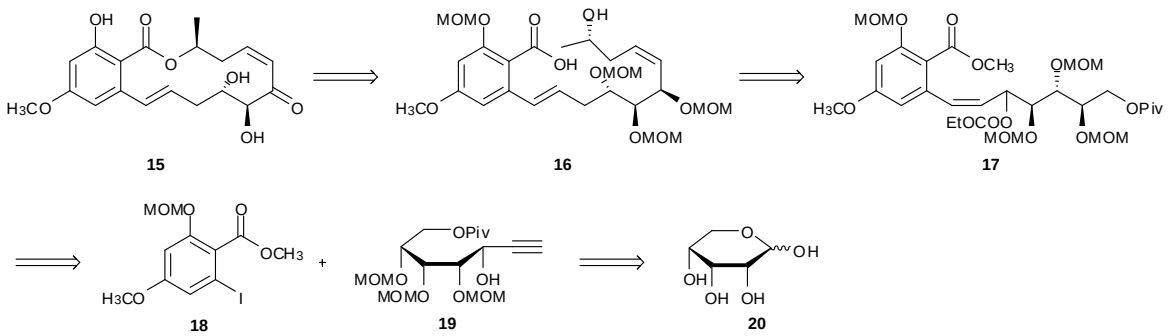


Figure 12: Dose-response Curve.

1.11 Previous Syntheses of LL-Z1640-2

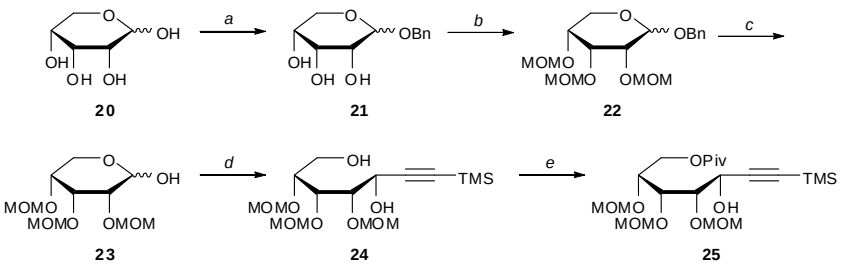
1.11.1 The First Total Synthesis - Tatsuta

Tatsuta, Takano, Sato and Nakano published the first total synthesis of LL-Z1640-2 in 2001[36], beginning from a carbohydrate starting material. In terms of the retrosynthesis (Scheme 2) they visualised the lactone core as originating from the Mukaiyama cyclisation[37] of *seco*-acid **16**. They foresaw that a Tsuji hydrogenolysis[38] would enable them to reach the *seco*-acid. **17** is prepared through Sonogashira coupling[39] of **18** and **19**. **19** is made from D-ribose **20** – the carbohydrate starting material and it was envisioned that the required stereochemistry of the two alcohols present in the final product would come from this compound.



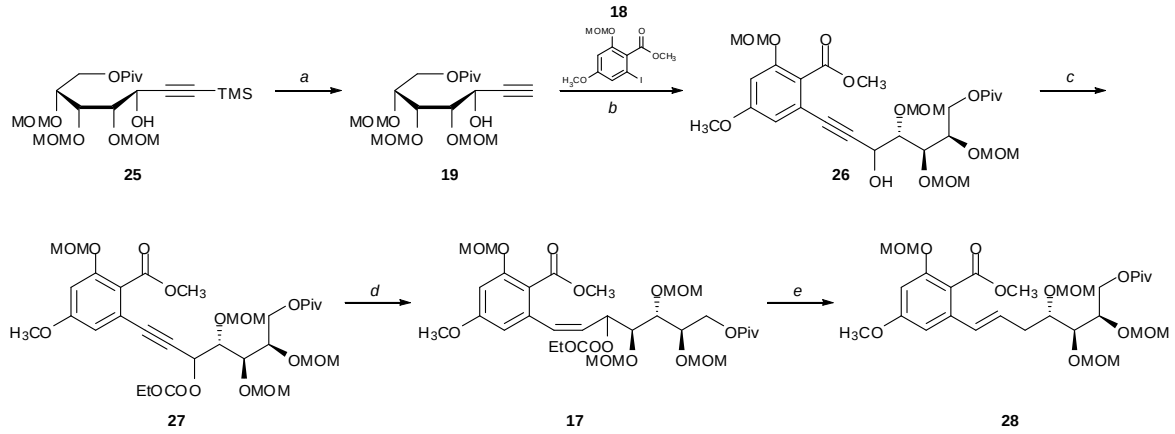
Scheme 2: Tatsuta's Retrosynthetic Analysis.

Tatsuta's synthesis began with D-ribose **20** in which the anomeric hydroxyl was protected as a benzyl ether and the resulting triol **21** globally protected as MOM ethers to generate **22**. Removal of the benzyl group, followed by reaction of the resulting lactol **23** with the lithiated acetylide, afforded diol **24**. Selective pivaloylation of diol **24**, yielded **25** as a single product. The authors note that only a trace of its diastereoisomer was observed.



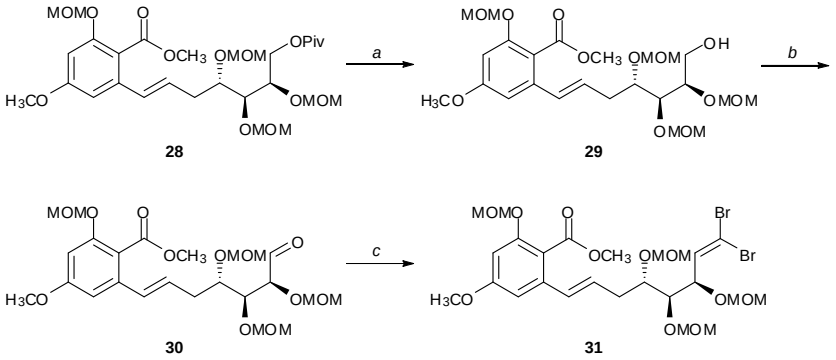
Scheme 3: Tatsuta's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) CSA/BnOH, 80 ^{o}C, 89%; (b) MOMCl, *i*-Pr_2Net, MeCN, 50 ^{o}C, 4 h, 85%; (c) H_2, $Pd(OH)_2$, EtOH, 3 h, quant.; (d) TMS-acetylene, *n*BuLi, $BF_3{\cdot}OEt_2$, THF, –78 ^{o}C → rt; (e) PivCl, pyridine, 0 ^{o}C, 1 h, 2 steps 48%.

Following TMS removal, the terminal alkyne **19** was coupled with iodobenzene **18** under palladium(0) mediated conditions to afford **26** (Scheme 4). Alkynol **26** was protected as the ethoxycarbonate **27** and then reduced with Lindlar's catalyst to give the desired *Z*-olefin **17**. Tsuji's hydrogenolysis conditions[38] cleanly isomerised the olefin to yield the *E*-alkene **28.**



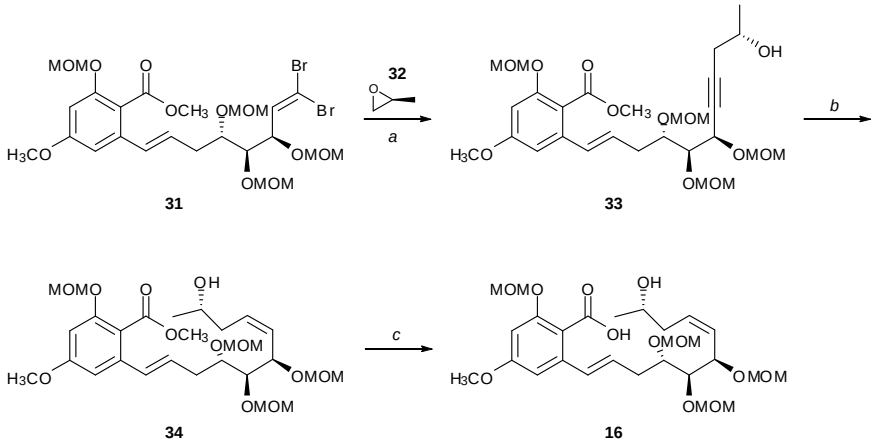
Scheme 4: Tatsuta's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) TBAF, AcOH, THF, 2 h, quant.; (b) $Pd(OAc)_2$, CuI, PPh_3, Et_3N, 2 h, 85%; (c) $ClCO_2Et$, pyridine, 0 ^{o}C, 1 h, 98%; (d) H_2, $Pd/BaCO_3$, quinoline, EtOH, 30 min; (e) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, $HCOONH_4$, 1,4-dioxane, 95 ^{o}C, 1 h, 2 steps 96%.

Pivaloyl group removal yielded the primary alcohol **29**, which was oxidised to aldehyde **30**. Treatment of aldehyde **30** with carbon tetrabromide and triphenylphosphine proceeded to give the dibromoolefin **31** (Scheme 5).



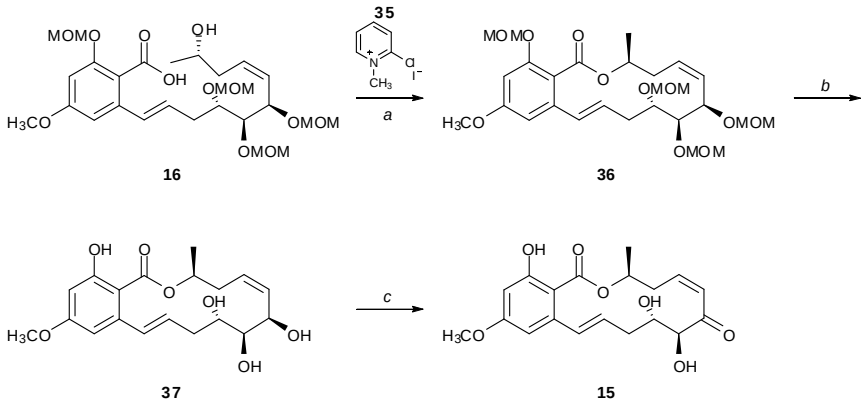
Scheme 5: Tatsuta's Synthesis of LL-Z1640-2. Reagents and conditions: (a) NaOMe, MeOH, 50 °C, 3 h, 95%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → rt; (c) PPh_3, CBr_4, CH_2Cl_2, 0 °C, 15 min, 2 steps 85%.

The dibromoolefin **31** was treated with *n*BuLi and the lithiated acetylide firstly produced; was captured with (*S*)-propylene oxide **32** to afford alcohol **33** (Scheme 6).



Scheme 6: Tatsuta's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) *n*BuLi, $BF_3{\cdot}OEt_2$, THF, –78 °C → rt, 45%; (b) H_2, $Pd/BaCO_3$, quinoline, AcOEt, 30 min; (c) 2 M, NaOH, MeOH, 1,4-dioxane, 90 °C.

Lindlar's reduction of alkyne **33** yielded *Z*-olefin **34**. Saponification of the ester gave the *seco*-acid **16**, which was cyclised under Mukaiyama conditions,[37] to afford the lactone **36** in 50% yield over 3 steps (Scheme 7). Removal of the MOM protecting groups generated tetraol **37**.

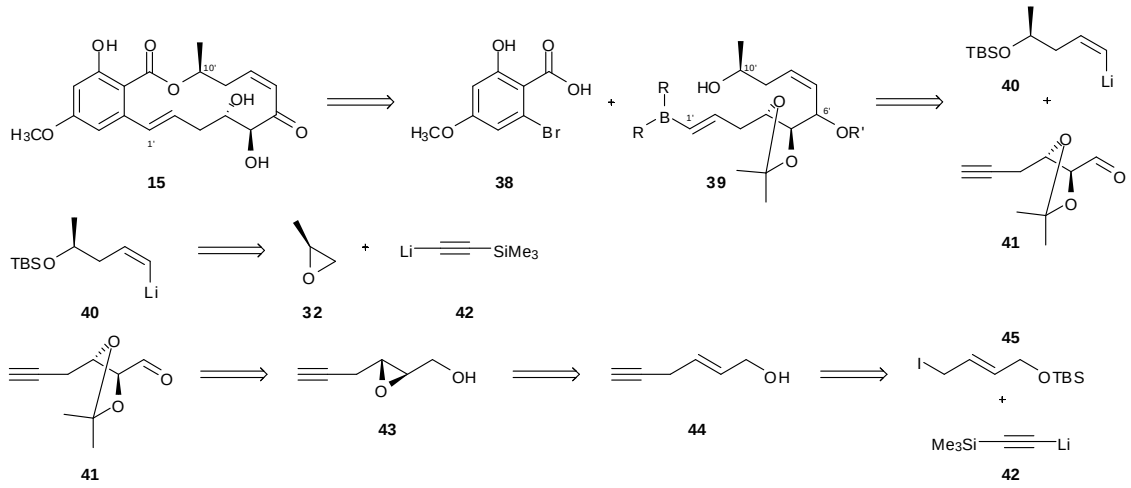


Scheme 7: Completion of Tatsuta's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Et_3N, MeCN, 50 ^oC, 1 h, 3 steps, 47%; (b) 5% HCl-MeOH, 50 ^oC, 2 h, 76%; (c) Dess-Martin periodinane, CH_2Cl_2, 15 min, 62%.

The final step involved the selective oxidation of the allyl alcohol. Interestingly, the authors reported, after extensive experimentation, that DDQ and Dess-Martin periodinane were the only reagents found to selectively oxidise the alcohol in yields of 20% and 62% respectively. The authors claimed that ketone **15** was identical in all respects to the naturally isolated LL-Z1640-2.

1.11.2 The Second Total Synthesis – Sellès and Lett

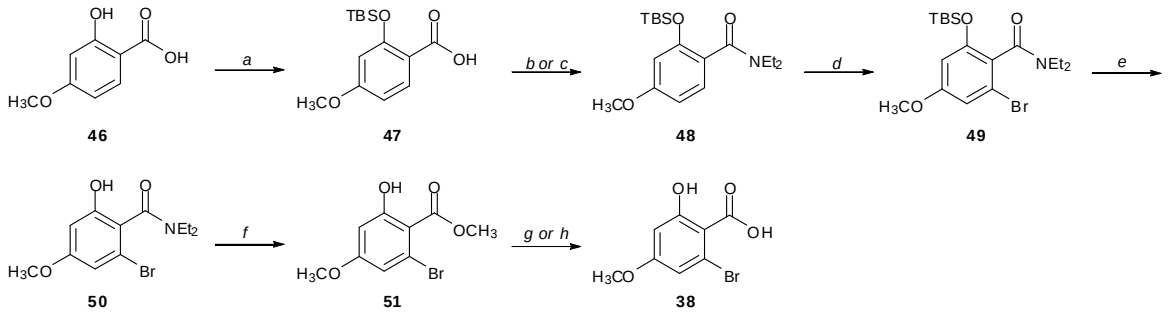
In 2002, the second total synthesis of LL-Z1640-2 was published in two parts by Sellès and Lett.[40,41] The first part focused on the stereospecific convergent synthesis of the precursors required for the formation of the 14-membered ring, either *via* intramolecular Suzuki coupling or an intermolecular Suzuki coupling followed by a macrolactonisation.[40] The retrosynthetic analysis (Scheme 8) led to three subunits: the aromatic unit **38** and two enantiopure units **40** and **41**.



Scheme 8: Lett's Retrosynthetic Scheme.

The hypothesised approach is flexible and the 14-membered macrocycle can be formed either by an intramolecular Suzuki coupling or by a macrolactonisation (via acyl activation or Mitsunobu). The enantiopure units draw from readily available starting materials. The $C_{4'}$-$C_{5'}$-diol would come from the regio- and stereospecific opening of the epoxide by a carbamate derived from **43**. This epoxy alcohol could be obtained through a Sharpless asymmetric epoxidation of the *trans*-disubstituted allylic alcohol.

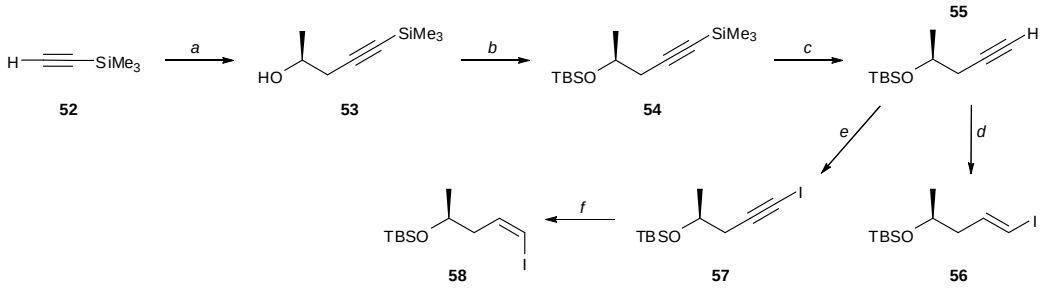
Synthesis of the aromatic unit **38** began with 4-methoxysalicyclic acid **46**, which was selectively protected as the silyl ether **47**, then treated with oxalyl chloride followed by diethylamine, to generate amide **48** (Scheme 9).



Scheme 9: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) TBDMSCl, *i*-Pr_2NEt, DMF, rt, 2 h; (b) oxalyl chloride, DMF, CH_2Cl_2, –10 °C → rt, overnight, then Et_2NH, 1 h, rt; (c) Et_2NAlMe_2 from Me_3Al and Et_2NH, toluene, –60 °C → rt, 45min, *then bis*-OTBS from **46**, reflux, overnight; (d) *t*BuLi, pentane, Et_2O, –78 °C, 10 min, then Br_2; (e) Me_3O^+, BF_4^-, CH_2Cl_2, rt, overnight, then evaporation; (f) aq. satd Na_2CO_3/MeOH (1/1), rt, 6 h; (g) conc. NaOH:DME (1:1), reflux, overnight; (h) TMSOK, DME, reflux, overnight.

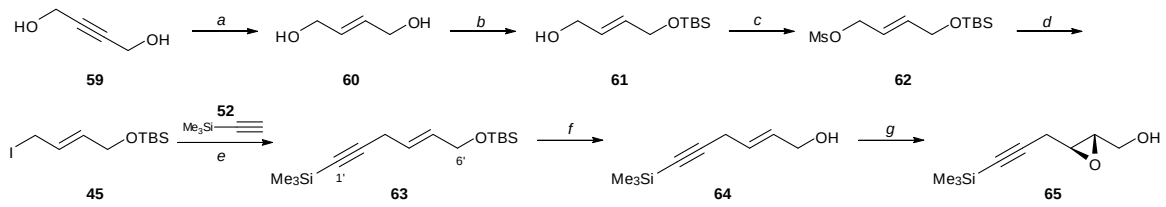
The presence of the TBS protective group prevented *o*-metallation at position 3 of amide **48** by its steric effect and allowed conversion of the amide **48** into the methyl ester **51**. The final aromatic unit **38** was obtained using conditions that avoided decarboxylation.

The synthesis of the enantiopure $C_{7'}$—$C_{10'}$ subunit began with ethynyltrimethylsilane **52**, which was lithiated and used to open the enantiopure (*S*)-propylene oxide **32**. The free alcohol **53** was protected as the TBS ether **54** and specific deprotection of the TMS-alkyne using potassium carbonate in methanol gave alkyne **55** in a 76% overall yield (Scheme 10). Hydrozirconation with Schwartz' reagent[42] was used to generate the (*S*)-*E*-vinyl iodide **56**. Hydroboration of iodoalkyne **57** with Sia_2BH generated the (*S*)-*Z* vinyl iodide **58**.



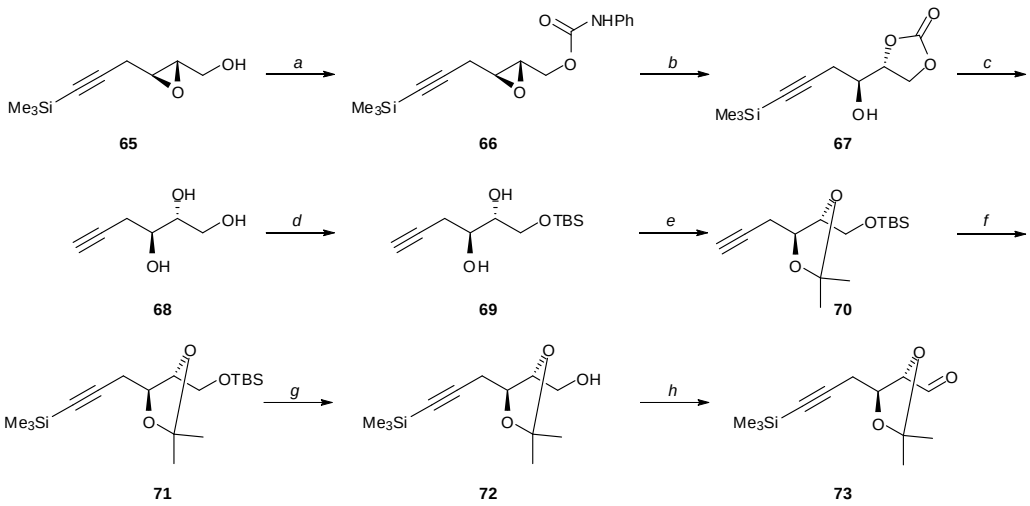
Scheme 10: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Et_2O, –78 °C, *n*BuLi, 30 min, then (*S*)-propylene oxide **32** and further addition of $BF_3{\cdot}OEt_2$, in 50 min, –78 °C; (b) TBDMSCl, imidazole, DMF, rt; (c) K_2CO_3, MeOH, rt, 5 h; (d) Cp_2ZrCl_2, $LiBHEt_3$, THF, rt, then **55**, rt, 15 min and I_2 in THF; (e) *n*BuLi, THF, hexane, –78 °C, 15 min, then I_2 in THF; (f) Sia_2BH, THF, –20 °C → 0 °C, 3 h then AcOH, 65 °C, 3 h.

Epoxide **65** was obtained in seven steps from 2-butyne-1,4-diol **59** (Scheme 11). The authors note that the selective deprotection of TBS ether **63** was best carried out using DDQ.



Scheme 11: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Red-Al®, toluene, THF, 0 °C–rt, overnight, 81%; (b) NaH, THF, rt, 1 h, then –78 °C, TBDMSCl, 36 h, 74%; (c) MsCl, Et_3N, CH_2Cl_2, –10 °C → rt, 30 min; (d) NaI, acetone, rt, 1 h; (e) TMS-alkyne **52**, THF, *n*BuLi, –78 °C, 30 min, then **45** and HMPA (THF:HMPA = 10:1), rt, 4 h; (f) DDQ, MeCN:H_2O (9:1), rt, 2 h; (g) $Ti(O\textit{i}Pr)_4$, (+)-DET, anhydrous CH_2Cl_2, *t*-BuOOH (~ 3 M in isooctane), –25 °C, overnight.

Sharpless asymmetric epoxidation of ene-yne **64** with (+)-DET afforded the desired epoxyalcohol **65**, as a single enantiomer. The epoxide **66** was opened in the presence of $BF_3{\cdot}OEt_2$ to afford carbonate **67** in high yield (Scheme 12).



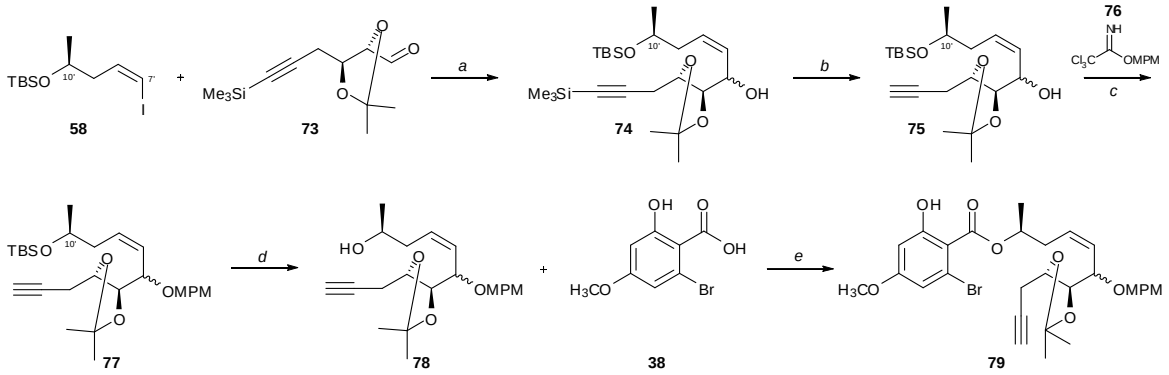
Scheme 12: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) PhNCO, CH_2Cl_2, pyridine, rt, 1 h; (b) $BF_3{\cdot}OEt_2$, Et_2O, –20 °C, 2 h, then 1 N H_2SO_4, rt, overnight; (c) NaOMe, MeOH, rt, 8 h, then DOWEX 50 WX8 column eluted with MeOH; (d) TBDMSCl, imidazole, DMF, rt, 1 h; (e) 2-methoxypropene, TsOH, CH_2Cl_2, rt, 1 h; (f) *n*BuLi, hexane, Et_2O, –30 °C, 30 min, then TMSCl, –30 °C → 10 °C, 98%; (g) DDQ, MeCN:H_2O (9:1), rt, 2 h, 73%; (h) oxalyl chloride, DMSO, CH_2Cl_2, –78 °C, 30 min, then **72**, 30 min and Et_3N, –78 °C → 0 °C.

Simultaneous hydrolysis of the carbonate and TMS deprotection was achieved using sodium methoxide in methanol, to afford triol **68** in 93% yield. TBS protection (→**69**) and acetonide formation, followed by reprotection of terminal alkyne **70** with a TMS group (→**71**) all proceeded readily. Once again, DDQ was used to bring about the selective deprotection of TBS ether **72**. These conditions minimised cleavage of the acetonide and TMS groups. Finally, the alcohol was converted to the aldehyde **73** under standard Swern conditions.

The synthesis of the $C_{1'}$—$C_{10'}$ fragment **79** began with the condensation of the two enantiopure fragments **58** and **73** to give a 60:40 mixture of the two $C_{6'}$ epimeric diastereoisomers **74** (Scheme 13). Following deprotection of TMS-alkyne **74**, the $C_{6'}$-OH **75** was protected as the MPM ether **77**. As the diastereoisomers were not easily separated, the authors carried forward this mixture to the macrocyclisation precursors.

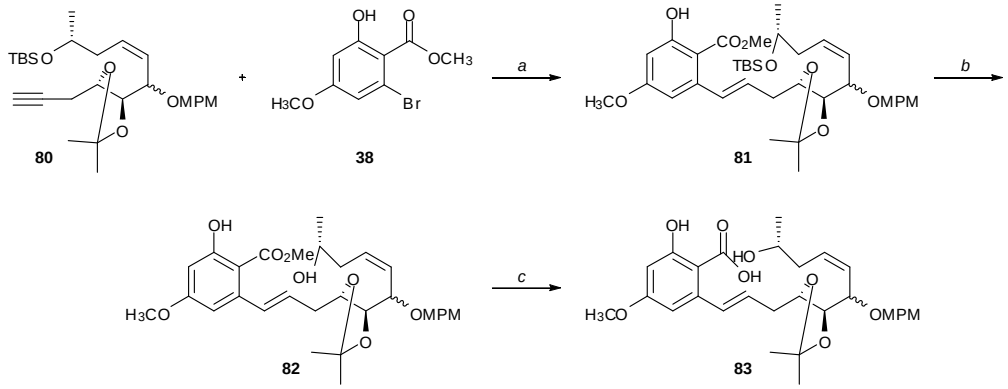
As pointed out previously, the hypothesised approach was flexible and the macrocycle can be formed by one of two methods. If an intramolecular Suzuki

coupling[43] were to be used for the formation of the macrocycle, then precursor **79** is needed. TBS ether **77** was deprotected using TBAF in THF and resulting alcohol **78** was coupled with benzoic acid **38** with DCC. The required ester **79** was obtained in 76% overall yield.



Scheme 13: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Et_2O, –78 °C, then *t*BuLi/pentane, 15 min and further addition of **73** in pentane, –78 °C → 0 °C; (b) K_2CO_3, MeOH, rt, 5 h; (c) Et_2O, CF_3SO_3H, rt, 4 h; (d) TBAF, THF, rt, 10 h; (e) DCC, DMAP, CH_2Cl_2, rt, 5 h.

For the alternative Mitsunobu macrolactonisation[44] reaction, precursor **83** was required (Scheme 14).

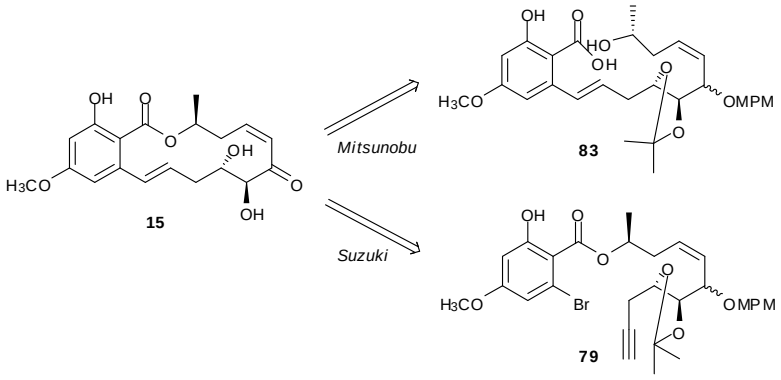


Scheme 14: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Sia_2BH, THF, –25 °C → rt, 2 h, then aq. 2 M K_3PO_4, further addition of that mixture *via* cannula at rt to a solution of **51** and 15 mol% [$Pd(OAc)_2$+4TFP] in DME; DME:H_2O (~7:1), reflux, 8 h; (b) TBAF, THF, rt, 6 h, 93%; (c) 2 N NaOH:MeOH (1:3), reflux, overnight, 71%.

Aryl bromide **38** underwent an intermolecular Suzuki coupling with the vinyldisiamylborane, prepared *in situ* from alkyne **80**. In comparison to the previous method, the aromatic hydroxy acid is not used, but rather its precursor, the methyl ester **81** is used. Interestingly, the final methyl ester cleavage proved less than straight forward. This was eventually achieved in 71% yield

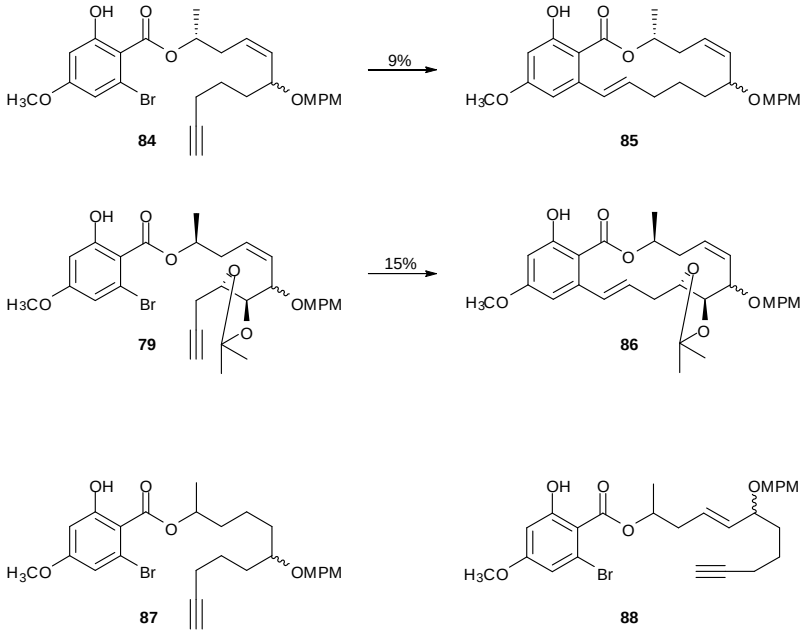
from **82**, using 13 equivalents of 2 N aq. NaOH in methanol under reflux to yield **83**.

Once both cyclisation precursors were available, the cyclisation reactions were attempted. In the completion of the total synthesis, published as Part 2,[41] the authors reported that the 14-membered macrocycle was achieved much more efficiently through the use of an intermolecular Suzuki coupling, followed by an intramolecular Mitsunobu macrolactonisation (Scheme 8 and Scheme 15).



Scheme 15: Retrosynthetic Analysis for Completion of the Synthesis.

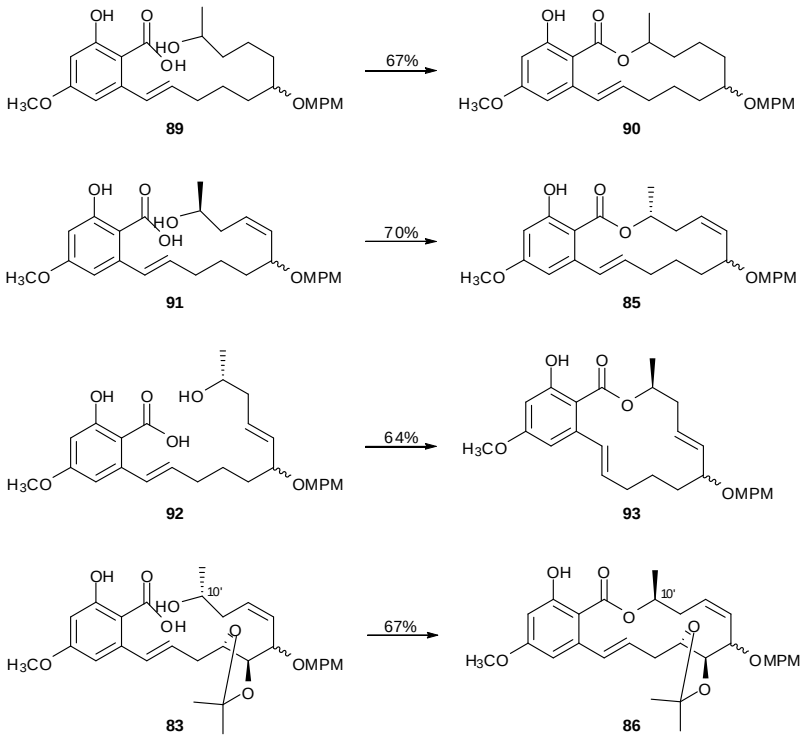
Using a model system **84**, the intramolecular Suzuki coupling of vinyldisiamylborane (generated *in situ*) derived from the alkyne **79,** was tested (Scheme 16). The best results were observed when acetone was added to destroy, *in situ*, any excess Sia_2BH that remained after hydroboration. Using these conditions, the macrolides **85** and **86** were obtained in 9% and 15% respectively. When the same conditions were applied to **87** and **88**, no corresponding macrolides were seen.



Scheme 16: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: Sia_2BH, THF, –20 $^oC \rightarrow$ rt, 2 h, then addition of acetone and afterwards 2 M aq. K_3PO_4 at –10 $^oC \rightarrow$ rt, further addition of that mixture *via* cannula to a solution of 4 mol% [$Pd(OAc)_2$+4TFP] in DME, i.e. substrate 0.034 M in DME:H_2O (~30:1), reflux, 6 h.

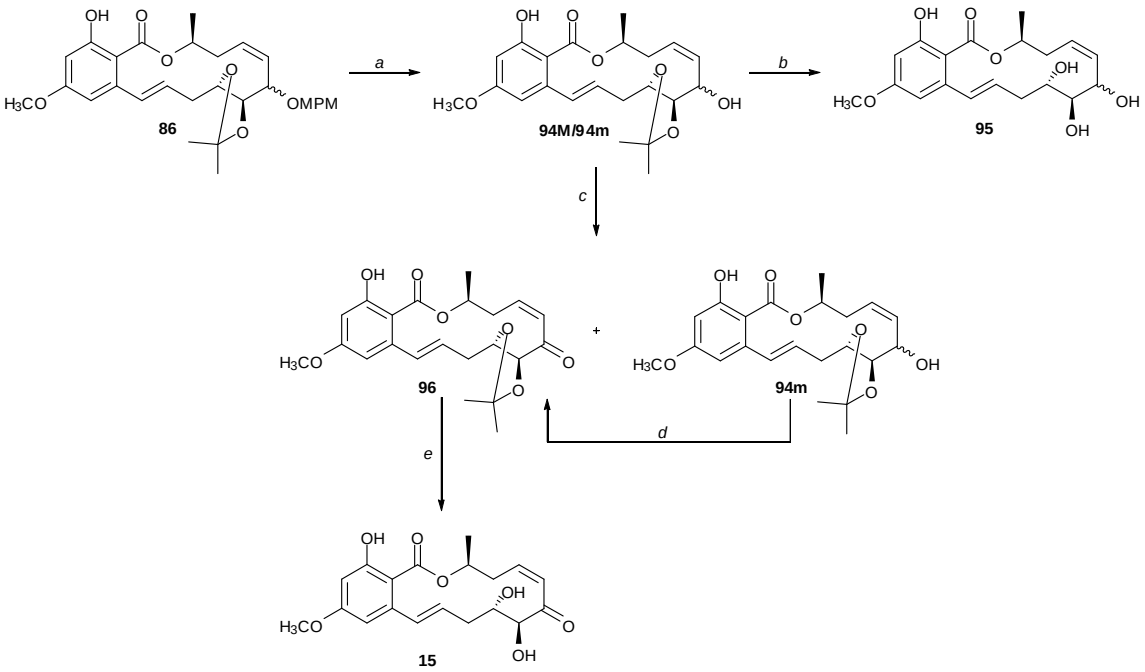
The macrolactonisations were far more successful when using the Mitsunobu reaction and its associated conditions (Scheme 17). The transformations were all achieved at room temperature, under low dilution (0.007-0.01 M), with yields ranging from 64-70%. In these cases there were no inhibitory factors arising from steric interactions or ring strain. In the case of the macrolactonisation of **83**, this proceeded readily in 67% yield.

As expected there was complete inversion of configuration at $C_{10'}$, further exemplified by comparison of the ^1H NMR spectra for product **86**, being derived from either intramolecular Suzuki coupling or Mitsunobu macolactonisation.



Scheme 17: Lett's Synthesis of LL-Z1640-2. Reagents and Conditions: hydroxy acid 0.007 M in anhydrous toluene, PPh_3, DEAD, rt, 15 min.

All that remained was the conversion of **86** into the final target compound **15** (Scheme 18).



Scheme 18: Lett's Completion of the Synthesis. Reagents and Conditions: (a) DDQ, CH_2Cl_2:pH 7 buffer (9:1), rt, 30 min, 94%; (b) *p*-TsOH, MeOH, rt, 4 h, 68%; (c) PCC, 2,5-DMP, CH_2Cl_2, 0 ^oC, 6 h; (d) Jones' reagent, acetone, 0 ^oC, 10 min, 35%; (e) *p*-TsOH, CH_2Cl_2:MeOH (1:1), rt, 3 h, 30 min, 76%.

Firstly, MPM ether **86** was deprotected using DDQ in buffered conditions to afford the alcohols **94M** and **94m** (60:40) in 94% yield. When using a model system, the authors were readily able to oxidise the 6'-OH into the corresponding enone using activated MnO_2 in 70% yield, disappointingly, this could not be transferred to the 'real' system. The mixture of the epimers could not be oxidised even when using a large excess of active MnO_2 or by DDQ. An alternative was to prepare **95**, but even this triol led to complex mixtures on oxidation with MnO_2. Fortunately, the authors tried PCC and on reacting **94M/94m** with PCC in the presence of 2,5-dimethylpyrazole they observed a clear difference in the reactivity of the diastereoisomers. The major epimer **94M** was converted quantitatively into the *Z*-enone **96** in 62% yield after chromatography, while the minor epimer **94m** was unchanged and isolated in 23% yield after chromatography. The pure minor diastereoisomer was reacted under Jones' oxidation conditions to form the *Z*-enone **96** in 35% yield. Overall the *Z*-enone was isolated in 74% yield from **94** (60:40) mixture. Surprisingly, Swern oxidation of **94M** gave the *Z*-enone **96** in 30% yield after chromatography. Finally, the acetonide was cleaved using *p*-TsOH in a 1:1 mixture of dichloromethane:methanol at room temperature, to generate LL-Z1640-2 **15** in 76% yield (20% of **96** also recovered).

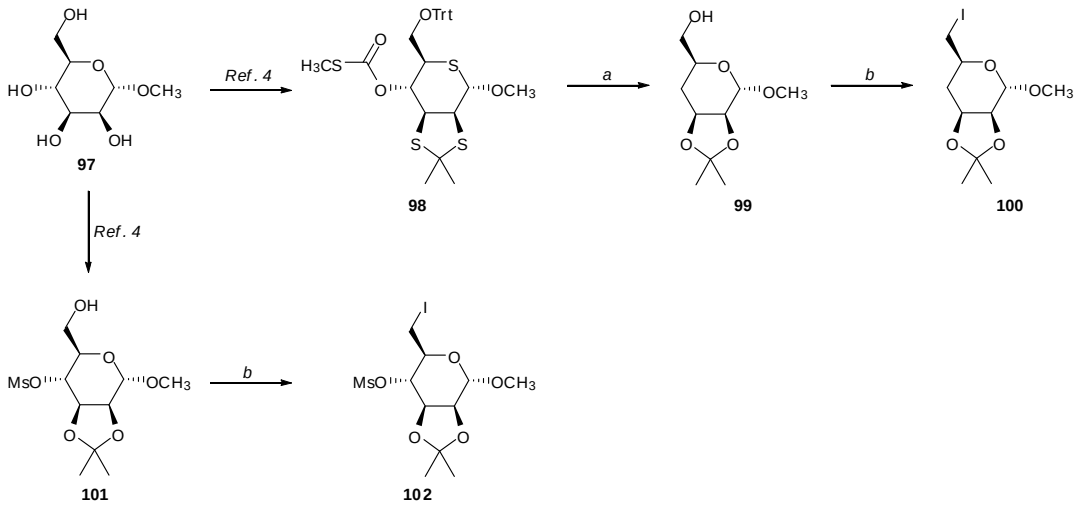
The syntheses presented by these two sets of authors are lengthy, containing steps that have needed careful establishment and much optimisation. At no time is there any mention of whether the steps that involve intricate conditions are readily reproducible, giving comparable yields. To their credit the syntheses are stereospecific, convergent and flexible. Indeed, Sellès and Lett go on to epoxidise the $E_{7',8'}$-enone to afford hypothemycin. Another additional benefit is that they are able to carry through their 60:40 mixture of the two diastereoisomers **94M/94m**, epimeric at $C_{6'}$, through all the steps until the oxidation, which is the penultimate step of the synthesis, where they could isolate each epimer after chromatography.

1.11.3 Synthesis of the Aliphatic Subunit from Mannose

In 2007, Krohn and Shukov published their synthesis of the aliphatic subunit of LL-Z1640-2.[45] This particular synthesis incorporated the Vasella reaction as a

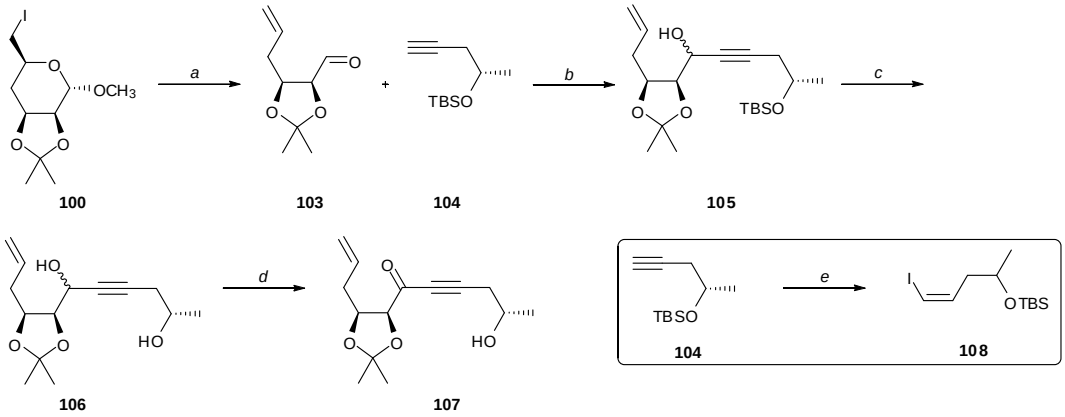
key step and the synthesis proceeded *via* the ring-opening of a 6-iodo-4-deoxy-D-mannose unit. The Vasella reaction[46] allows the conversion of halosugars into components having a carbonyl group tethered to an olefinic bond. The Vasella reaction is not uncommon and has been incorporated into previous total syntheses; of pentenomycin[47] for example.

The authors hypothesised that mannose could be used to provide two of the required stereocentres present in LL-Z1640-2. Mannose is a simple and inexpensive, commercially available compound and as such is an ideal choice as a starting material for a total synthesis. For this particular synthesis, the authors prepared two 6-deoxy-6-iodomannose derivatives **100** and **102** from methyl-α-D-mannopyranoside **97** (Scheme 19). This has been documented in depth in a previous publication by the same authors.[48] The alcohols formed were then treated with iodine and triphenylphosphine to give 6-iodo sugars **100** and **102**.



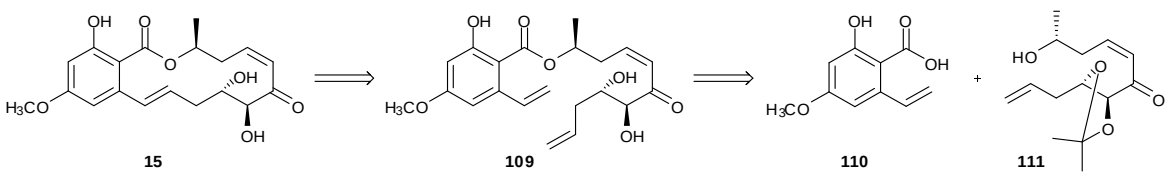
Scheme 19: Krohn's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) i) H_3PO_2/AIBN, Et_3N, dioxane, reflux, 90%; ii) *p*-TsOH, acetone, 90%; (b) Ph_3P, I_2, rt, 90%.

The iodo sugars **100** and **102** were then treated with activated zinc to initiate the Vasella ring-opening. Reaction of the deoxysugar **100** proceeded smoothly and gave aldehyde **103** in good yield using sonication (reaction of the mesylate **102**, under the same conditions, gave a mixture of products, presumably due to an interaction of zinc with the mesylate group) (Scheme 20).



Scheme 20: Krohn's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) activated zinc, *i*-PrOH, sonication, 50 ^{o}C, 60%; (b) *n*BuLi, THF, –78 ^{o}C, 50%; (c) Py–HF, THF, rt, 73%; (d) MnO_2, benzene, rt, 80%; (e) (i) *n*BuLi, I_2; (ii) $N_2(CO_2K)_2$, 50%.

From their retrosynthesis the authors envisaged that the aldehyde could be coupled with either acetylene **104** or vinyl iodide **108**. The acetylene unit was easily obtained and the *Z*-vinyl iodide could be accessed from the alkyne **104** through iodination and then stereoselective diimide reduction. The vinyl iodide and alkyne were each reacted *in situ* with *n*BuLi and then these lithium reagents reacted with the aldehyde **103**. When the aldehyde **103** and vinyl lithium were reacted a complex mixture of products was seen. Conversely, when the aldehyde and lithiated alkyne were reacted a mixture of diastereomeric propargyl alcohols **105** was observed (1:2.3 by ^{1}H NMR). Cleavage of the terminal TBS protecting group, followed by selective oxidation of the resulting diol **106**, afforded ketone **107**. Though not presented in the published paper, the authors identify this ketone as a late-stage building block towards **111** (Scheme 21). They predict that secondary alcohol **111** can be esterified with acid **110**, followed by *Z*-selective reduction of the acetylene. Ring-closing metathesis of **109** would close the macrocycle to produce and finalise the synthesis of the required LL-Z1640-2.

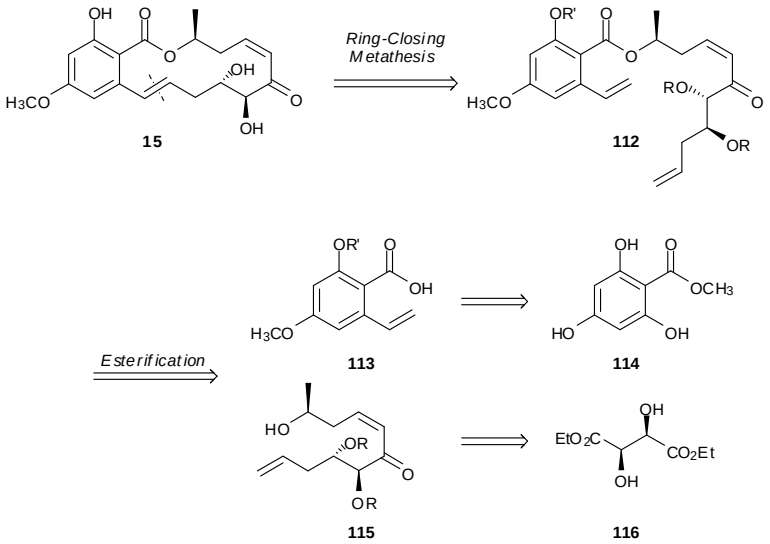


Scheme 21: Krohn and Shukov's Proposed Completion of the Synthesis of LL-Z1640-2.

The synthetic steps presented in this publication are neat and time efficient. The 6-iodo-4-deoxymannose derivative **100** was subjected to the Vasella ring-opening reaction, affording the *δ,ε*-hexenal **103**. Coupling of the aldehyde to the acetylene is reliable and two subsequent, straightforward steps produces propargylic ketone **107**.

1.11.4 Synthesis of the Complete LL-Z1640-2 Framework

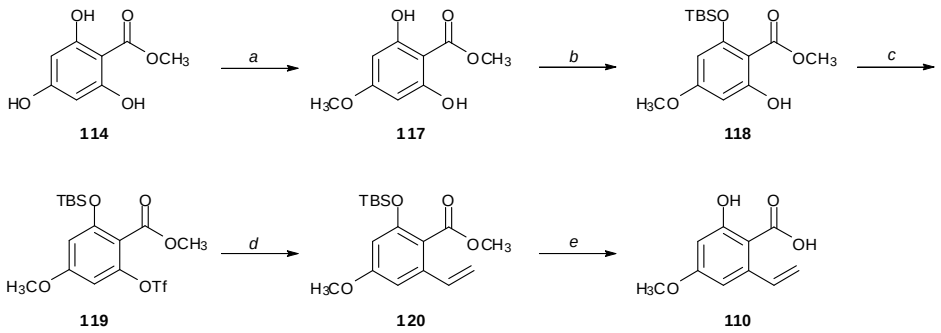
In 2007, Marquez, Henry and Robertson published their fast and efficient, convergent synthesis of the complete LL-Z1640-2 framework.[49] Their retrosynthetic analysis (Scheme 22) envisioned cleavage of the ester functionality and of the aryl double bond of the macrocyclic ring to produce the vinyl benzoic acid **113** and alcohol **115**.



Scheme 22: Marquez's Retrosynthetic Analysis.

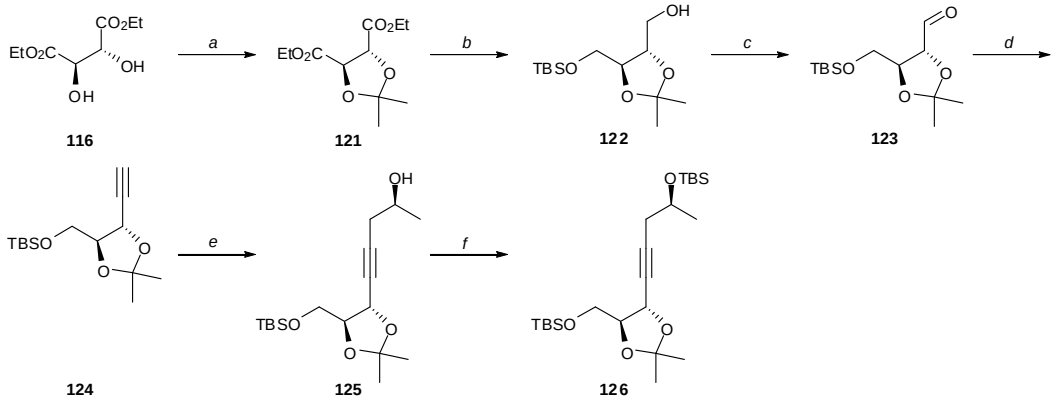
The commercially available and relatively inexpensive, methyl 2,4,6-trihydroxybenzoate **114** was used as the starting material for the synthesis of the vinyl benzoic acid unit **110** (Scheme 23). The C_4 position was methylated selectively through treatment with trimethylsilyl diazomethane to afford diol **117** in high yield. Monosilylation of the diol under standard conditions produced the TBS silyl ether **118**, which was treated with triflic anhydride to yield triflate **119**. The vinyl unit **120** was synthesised by subjecting the aryl triflate to a Stille coupling with vinyltributyltin. Saponification of the methyl ester **120** proceeded

to generate the free benzoic acid **110**. Spontaneous desilylation was also observed during this step.



Scheme 23: Marquez's Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) TMS–CH_2N_2, Et_2O, 90%; (b) TBDMSCl, Et_3N, CH_2Cl_2, 80%; (c) Tf_2O, pyridine, 100%; (d) vinyltributyltin, $Pd(PPh_3)_4$, CH_2Cl_2, 100%; (e) NaOH, 1,4-dioxane, 96%.

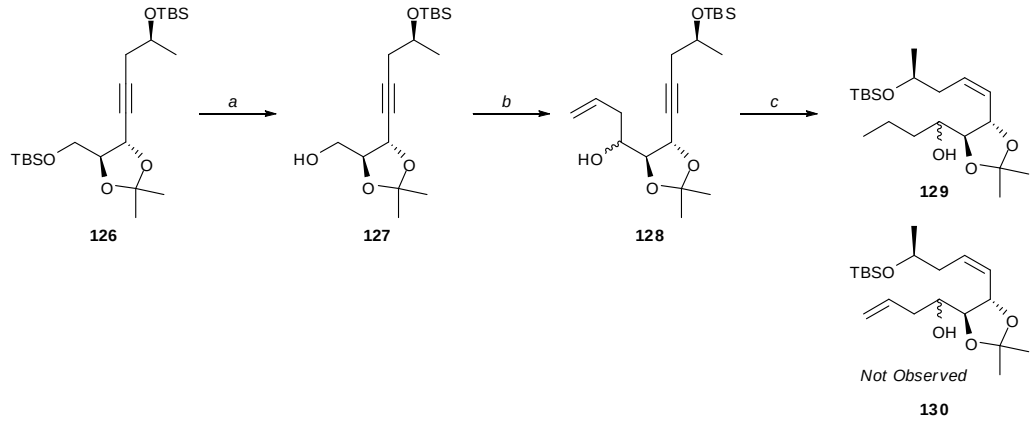
(L)-(+)-Diethyl tartrate **116** was used as the starting material for the synthesis of the $C_{1'}$—$C_{10'}$ aliphatic unit (Scheme 24). The tartrate was protected as the dimethyl ketal (→**121**) and then the diester reduced to the corresponding diol. Selective silylation provided TBS ether **122**, which then underwent Swern oxidation to generate aldehyde **123**. Corey-Fuchs olefination gave alkyne **124**, which was then alkynated with (*S*)-propylene oxide **32** under highly activated conditions. This resulted in the formation of internal alkynol **125** as a single diastereoisomer, after which silylation gave the *bis*-TBS silyl ether **126**.



Scheme 24: Marquez's Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) 2-Methoxypropene, *p*-TsOH, CH_2Cl_2, 97%; (b) i) $LiAlH_4$, THF; ii) NaH, TBDMSCl, THF, 89%; (c) Swern, 100%; (d) i) CBr_4, PPh_3, CH_2Cl_2; ii) *n*BuLi, Et_2O, 79%; (e) (*S*)-propylene oxide, *n*BuLi, $BF_3{\cdot}OEt_2$, THF, 76%; (f) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 97%.

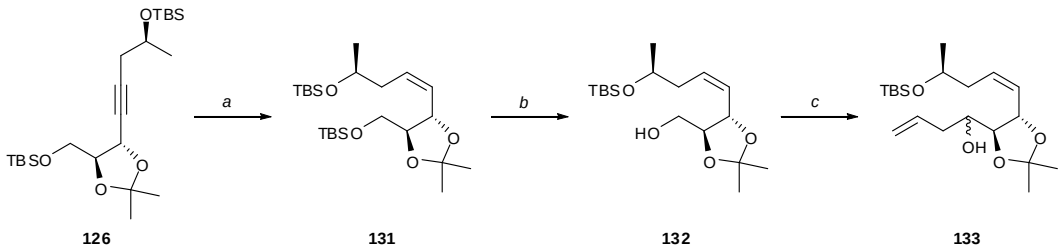
The outstanding steps of the $C_{1'}$—$C_{10'}$ unit started with the selective deprotection of the primary TBS silyl ether, which yielded the primary alcohol **127** (Scheme

25). A one-pot oxidation-allylation progressed to give the homoallylic alcohol **128** as a 1:1 mixture of diastereoisomers. At this stage the authors did not attempt to control the stereochemistry of allylation as the aim was to access LL-Z1640-2, as well as its $C_{9'}$ anomer for biological evaluation purposes. The next step was to convert the alkyne unit into the *Z*-alkene that is present in LL-Z1640-2. Attempts at hydrogenation using a $Pd/BaSO_4$ catalyst poisoned with quinoline, regrettably led to the over-reduced alkane **129**.



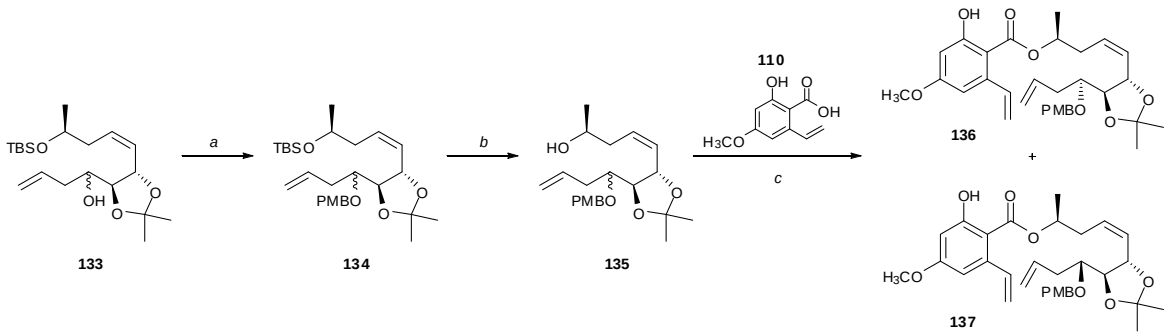
Scheme 25: Marquez's Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) HF–Pyr, Pyridine/THF, 85%; (b) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → rt; (ii) vinylmagnesium bromide, THF, 89%; (c) H_2, $Pd/BaSO_4$, quinoline, 99%.

The observed over-reduction prompted an assessment of the synthetic route and as a consequence changes were made. In the modified approach the *bis*-TBS ether **126** was selectively reduced to yield the *Z*-olefin **131** with complete stereocontrol (Scheme 26). Primary TBS removal (→**132**), followed by a one-pot oxidation-allylation procedure provided the required $C_{1'}$—$C_{10'}$ fragments **133** of LL-Z1640-2 and 9-*epi*- LL-Z1640-2.



Scheme 26: Marquez's Synthesis Towards LL-Z1640-2. Reagents and Conditions: (a) H_2, $Pd/BaSO_4$, quinoline, 100%; (b) HF–pyr/pyridine, 65% + SM; (c) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → rt, ii) vinylmagnesium bromide, THF, 96%.

In order to introduce the remaining units of the framework, the free alcohol **133** was protected as the PMB ether and the secondary TBS silyl ether carefully removed to afford the secondary alcohol **135** (Scheme 27). Reaction of alcohol **135** with vinyl benzoic acid **110** generated the esters **136** and **137** cleanly in good yield. This served to complete the entire frameworks of both LL-Z1640-2 and 9-*epi*-LL-Z1640-2 respectively.

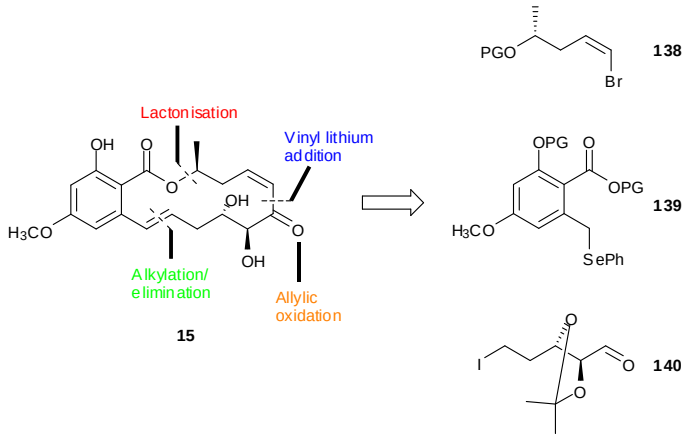


Scheme 27: Marquez's Synthesis Towards LL-Z1640-2. Reagents and conditions: (a) NaH, PMBCl, TBAI, THF, 100%; (b) HF–pyr/pyridine, 97%; (c) **110**, DCC, 67%.

The authors conclude that their two-directional chain functionalisation synthesis is fast, high-yielding and flexible, producing not only the complete framework of LL-Z1640-2 but also that of its C_9- epimer, 9-*epi*-LL-Z1640-2.

1.11.5 The Third Total Synthesis – Winssinger's Modular Approach

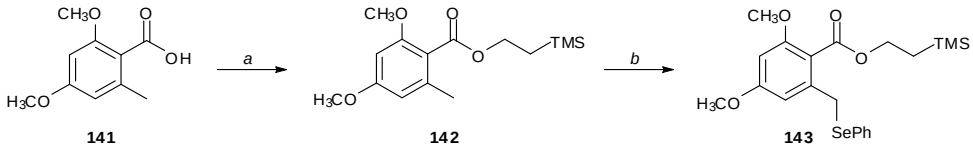
In 2007, a third total synthesis of LL-Z1640-2 was published, whereby a modular approach was developed.[50] The authors devised a retrosynthesis (Scheme 28) in which the enone would be introduced at a late stage to avoid isomerisation to the *trans*-isomer.



Scheme 28: Winssinger's Retrosynthetic Disconnection of LL-Z1640-2. Adapted from Reference 50.

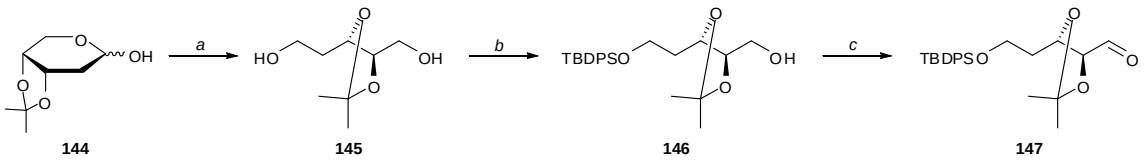
The *cis*-alkene would originate from a vinyl lithium addition onto an aldehyde. Three fragments, **138**, **139** and **140**, would be used to construct the main body of the structure, the order in which they could be coupled possible by means of any permutation. Despite this the authors needed a starting point and so rationally presumed that coupling the two non-aromatic fragments, **138** and **140**, first would allow them to use a fluorinated protecting group for the alcohol, facilitating the use of fluorous isolation technology. A distinct advantage of this technique is that multiple components can be tagged and taken through a synthesis as a mixture, with fluorous chromatography performed at the end to resolve the mixture.

For the synthesis of the aromatic fragment **143** (Scheme 29), carboxylic acid **141** was protected with a 2-(trimethylsilyl)ethyl group by esterification with 2(trimethylsilyl)ethanol. Selenide **143** was then formed by treatment of ester **142** with LDA and then coupled with diphenyldiselenide.



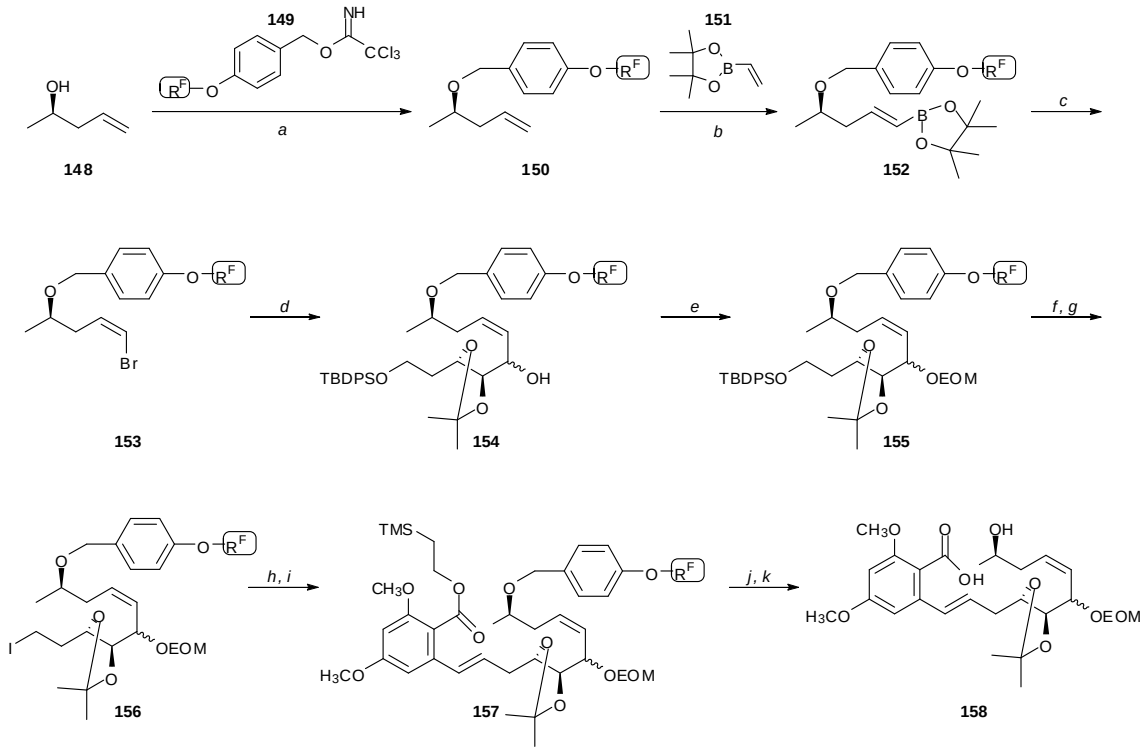
Scheme 29: Winssinger's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) Oxalyl chloride, DMF, CH_2Cl_2, 0 ^oC, 1 h, then 2-(trimethylsilyl)ethanol, Et_3N, DMAP, rt, 1 h, 96-98%; (b) LDA, diphenyldiselenide, THF, –78 ^oC, 1 h, 89-91%.

Aldehyde **147** was obtained from the ketal-protected deoxyribose **144**[51] by reduction with lithium aluminium hydride and the crude diol **145** selectively silylated on the less sterically hindered alcohol with a TBS protecting group (→**146**). The remaining alcohol was oxidised using an immobilised version of IBX, giving aldehyde **147,** which was used without work-up or purification (Scheme 30).



Scheme 30: Winssinger's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) $LiAlH_4$, THF, 0 $^oC \rightarrow$ rt, 2 h, 95%; (b) TBDPSCl, imidazole, DMF, 23 ^oC, 2 h, 66%; (c) PS-IBX, CH_2Cl_2, rt, 2 h, 100%.

The remaining fragment was synthesised beginning from (*R*)-2-hydroxypentane **148** with fluorous PMB trichloroacetimidate **149** to afford **150** (Scheme 31). Cross-metathesis of alkene **150** with vinyl borolane **151**, in the presence of Grubbs second generation catalyst, afforded the *trans*-product **152** in good selectivity (>20:1 *E:Z)*. The vinylborane could be transformed into the *cis*-vinyl bromide **153** through treatment with bromine and sodium methoxide.

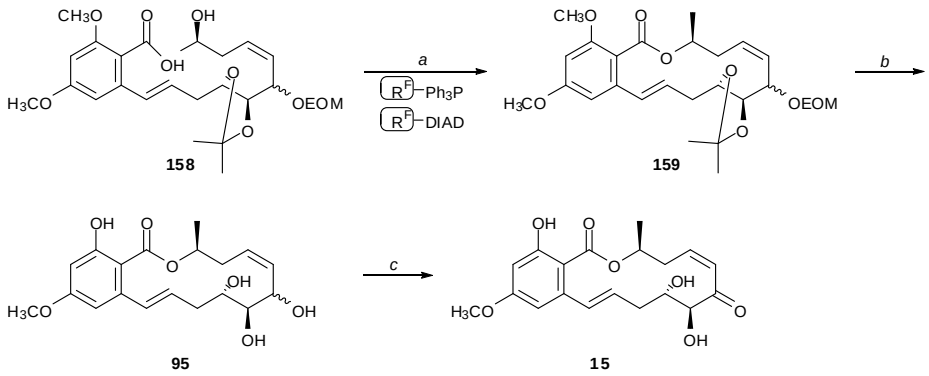


Scheme 31: Winssinger's Synthesis of LL-Z1640-2. Reagents and Conditions: (a) **149**, CSA, CH_2Cl_2, rt, 12 h, 92%; (b) **150**, Grubbs second generation catalyst, toluene, 80 ^oC, 12 h, 92%; (c) Br_2 (1 M in CH_2Cl_2), Et_2O, –20 ^oC, 10 min, then NaOMe (1 M in MeOH), –20 ^oC, 30 min, 89%; (d) *t*BuLi, THF/Et_2O, –100 ^oC, 15 min, then **147**, –100 ^oC, 15 min, 88%; (e) EOMCl, *i*Pr_2EtN, TBAI, DMF, rt, 12 h, 96%; (f) TBAF, THF, rt, 12 h, 92%; (g) PPh_3, I_2, imidazole, THF, 0 ^oC, 1 h, 91%; (h) **143**, LDA, THF/HMPA (10:1), –78 ^oC, 20 min, 88-91%; (i) H_2O_2, THF, rt, 2 h, 79-82%; (j) DDQ, CH_2Cl_2/H_2O (2:1), rt, 2 h, 70-80%; (k) TBAF, THF, rt, 2 h, 87%.

Transmetallation of the bromide with *t*BuLi and addition onto the crude aldehyde **155** afforded alcohol **154**, which was protected as the EOM ether to yield **155** as a mixture of diastereoisomers (3:1). Conversion of the silyl-protected hydroxyl group into the iodide proceeded smoothly to afford **156**, which was then alkylated with the aromatic fragment **143**. The resulting selenide was oxidised and eliminated to afford **157**. The crude reaction mixture was loaded onto a fluorous-silica column to remove the non-fluorous tagged components from the desired compound. The *seco*-acid **158** was obtained after the sequential removal of the PMB and TMSE ester protecting groups.

The final steps of the synthesis incorporate the key macrolactonisation which was accomplished through a Mitsunobu reaction using fluorous-tagged triphenyl phosphine and diazodicarboxylate (Scheme 32). The desired compound **159** was gained after a fluorous solid-phase extraction. The usage of boron trichloride enabled the simultaneous deprotection of the EOM and acetonide groups as well as the cleavage of the *ortho*-phenol. The formed allylic alcohol **95** was

selectively oxidised with a polymer-bound IBX to afford LL-Z1640-2 **15** after filtration.



Scheme 32: Winssinger's Completion of the Synthesis of LL-Z1640-2. Reagents and Conditions: (a) R^FPh_3P, R^FDEAD, toluene (10 mM), rt, 2 h, 81%; (b) BCl_3, CH_2Cl_2, 0 ^oC, 15 min, 86%; (c) PS-IBX, CH_2Cl_2, rt, 1 h, >90%.

This synthesis is concise and advantageous in its use of fluoro chemistry and polymer-bound reagents, enabling the process to be suitable for high-throughout synthesis.

1.12 Inflammation

Inflammation is the body's immediate response to damage to its tissues and cells by pathogens (infection), noxious stimuli (chemicals) or physical injury. It is characterised by redness, swelling, heat and pain in a tissue.[52]

There are two classifications of inflammation: acute and chronic. Acute inflammation is a short-term response, resulting in healing. Leukocytes penetrate the damaged region, repairing the tissue. Chronic inflammation is a prolonged response that involves active inflammation, tissue destruction and attempts at tissue repair. The persistency is associated with many chronic human conditions, including allergy, cancer, arthritis and autoimmune diseases,[52] some of which can be treated with non-steroidal anti-inflammatory drugs (NSAIDs).[53]

In response to damage of body tissues, mast cells release histamine. Although there are other substances involved in the inflammatory response, histamine is thought to be responsible for most of the effects. Histamine acts to increase

blood flow to damaged tissues, causing the heat and redness. It also makes the blood capillaries more 'leaky', resulting in fluid oozing out of them and into the tissues, causing localised swelling. The pain associated with inflammation is attributed to the stimulation of nerve endings by inflammatory chemicals.

1.13 Inflammatory Disorders

1.13.1 Rheumatoid Arthritis

Rheumatoid arthritis is a non-specific autoimmune disorder, where the immune system acts against and damages joints and surrounding soft tissues. The reasons why these autoimmune disorders develop are unclear, but genetic factors may play a role. An autoimmune disorder may primarily affect a specific organ or cell type, or may affect various organs. In the case of arthritis, it is the inflammation of a joint, characterised by pain, swelling and stiffness. The arthritis may involve one joint or many and can vary in severity from a mild ache and stiffness to severe pain and joint deformity. Rheumatoid arthritis is the most severe type of inflammatory joint disease and as shown in Figure 13, the joints most commonly affected are those in the hands, wrists, feet and arms, which become extremely stiff, painful and deformed.

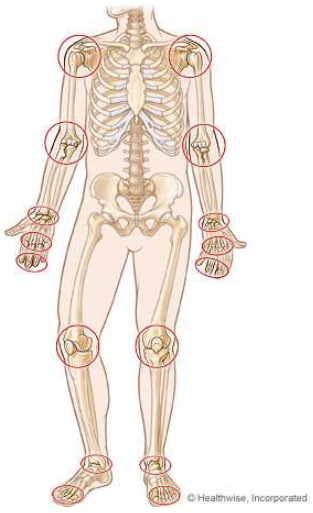


Figure 13: Common Target Sites for Rheumatoid Arthritis.[54]

The symptoms occur most commonly in women but can also arise in younger people. Overall, women are affected two to three times more than men. The

onset of the disease is gradual, with mild fever and aches and pains preceding specific joint symptoms, though in some, joint inflammation can develop suddenly. As well as the joint being affected, the structures around the joint may also become inflamed, resulting in weakness of the tendons, ligaments and surrounding muscles. The finger joints are the most commonly affected, resulting in a weak grip.[55]

With respect to the pathogenesis of rheumatoid arthritis,[56] monocytes are attracted to the affected joint, where they differentiate into macrophages and become activated. In addition to interleukin-1 (IL-1), they also secrete tumour-necrosis factor (TNF), which increases the expression of adhesion molecules on endothelial cells, which recruit more cells to the joint. IL-1 and TNF induce synovial fibroblasts to express cytokines, chemokines and growth factors, which contribute to cartilage and bone destruction (Figure 14).

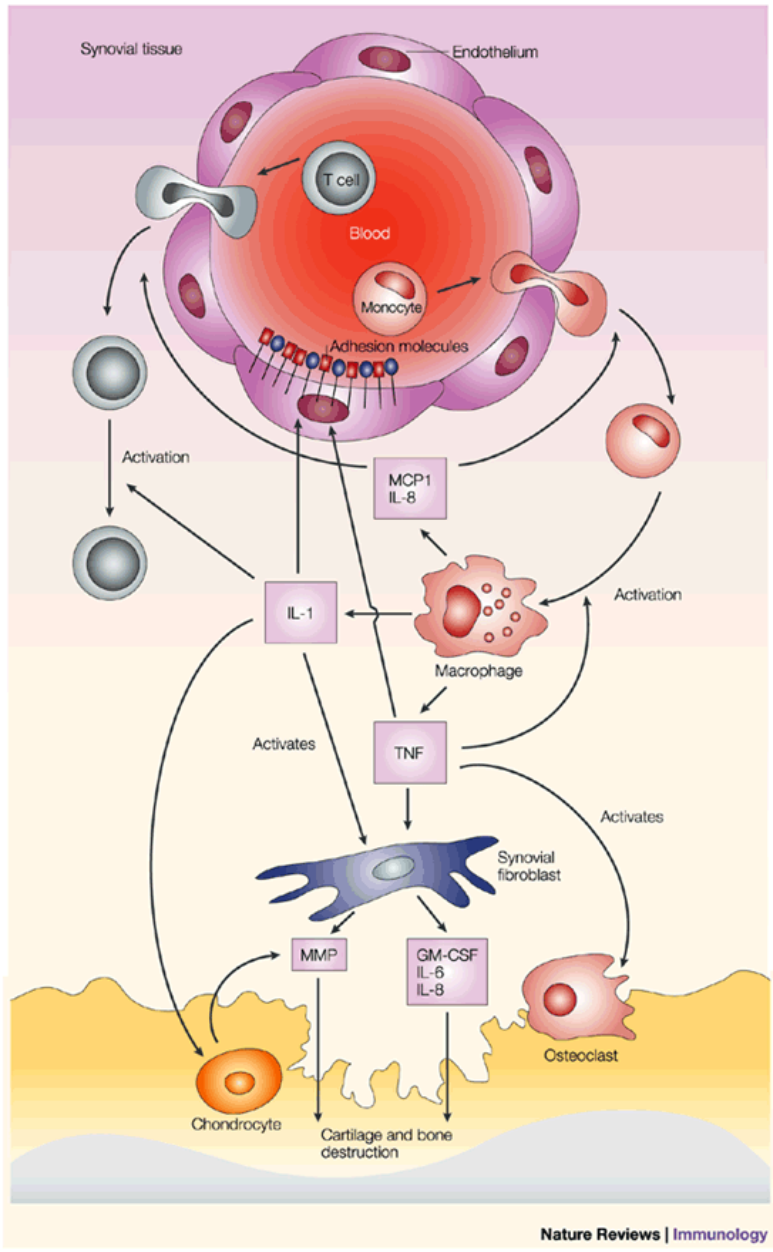


Figure 14: Overview of the Pathogenesis of Rheumatoid Arthritis.[56] Reproduced with permission.

1.13.2 Osteoarthritis

Osteoarthritis (OA) is a form of arthritis also known as degenerative arthritis and is the most common type, resulting from general mechanical stress and 'wear and tear' on the joints. It is thought that metabolic and genetic factors may also contribute. It is characterised by degeneration and degradation of the cartilage that lines joints which leads to joint space narrowing (JSN), painful joint disruption and loss of function or by formation of osteophytes (bony outgrowths), which lead to pain and stiffness of the affected joint.[55,57] It

generally evolves in middle age, but it most prevalently troubles the older generation, affecting three times as many women as men. Injury to a joint in earlier life can attribute to the development of osteoarthritis. Osteoarthritis causes pain, swelling, creaking and stiffness of one or more joints, the hands, hips, knees and spine being most commonly affected as shown in Figure 15.

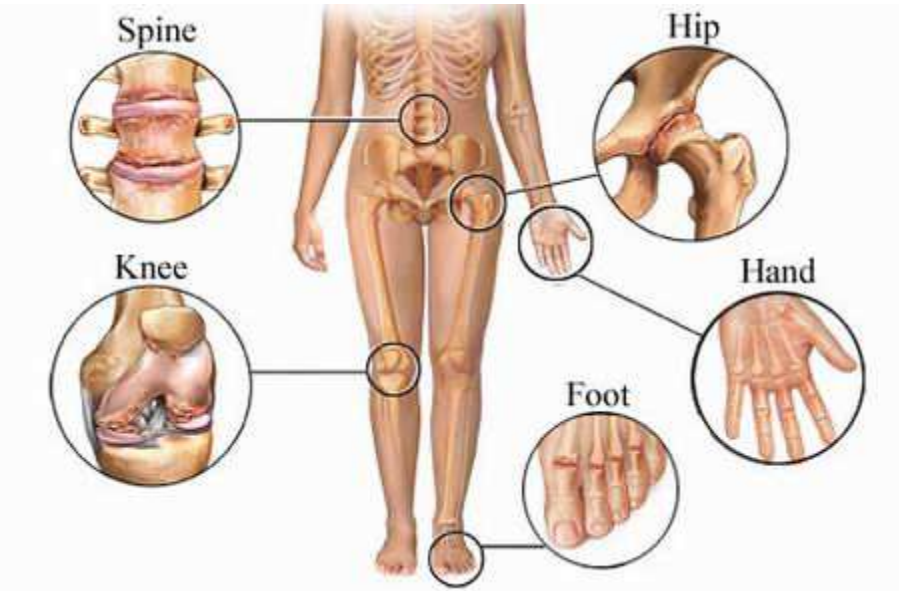


Figure 15: Common target sites for Osteoarthritis.[58]

OA involves the entire joint organ, including the subchondral bone, menisci, ligaments, muscle, capsule and synovium. If pain prevents the joint from being used regularly, weakness and shrinkage of the muscles surrounding the joint results. The affected joints become enlarged and distorted by osteophytes, which are responsible for the characteristic gnarled appearance of hands affected by osteoarthritis. In the United Kingdom, there are an estimated 8.5 million people affected by OA.[59] In the United States there are an estimated 20-40 million people affected; with over 250,000 knee replacements and over 150,000 hip replacements carried out annually.[57] Due to improvements in MRI imaging, there is an increased understanding of the other tissues in the pathophysiology of OA (Figure 16).

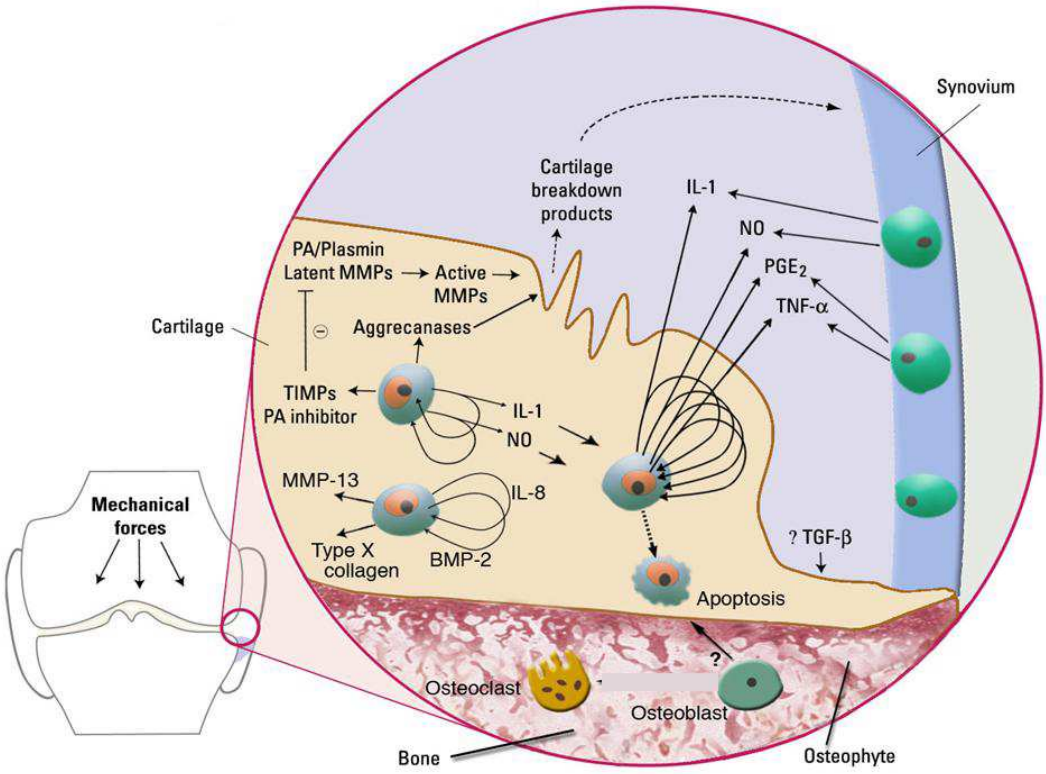


Figure 16: Molecular Pathogenesis of Osteoarthritis. A Schematic representation of key pathological events and some of the potential targets considered for disease modification.[57] Reproduced with permission.

Traditionally thought of as a non-inflammatory disease, Dr. Abramson and colleagues at NYU Medical Centre in the United States have reported that "OA cartilage produces inflammatory mediators such as nitric oxide, prostaglandin E2 and other pro-inflammatory cytokines locally which leads to joint deterioration."[57] There is a general belief that interleukin-1 (IL-1) plays a central role in the pathogenesis, with data being retrieved from animal susceptibility models, models of IL-1-targeted therapy, genetic association studies and elevated IL-1 gene expression in whole blood from patients with multi-joint osteoarthritis.

1.13.3 Crohn's disease

Inflammatory bowel disease is a general term for chronic inflammatory disorders affecting the small and/or large intestine. Crohn's disease most commonly affects those in adolescence and early adulthood and arises due to specific conditions – inflammation affecting any part of the gastrointestinal tract from the mouth to the anus, causing pain, fever, diarrhoea and loss of weight. The

site of inflammation is most commonly the terminal ileum, which becomes thick due to continued chronic inflammation and deep, penetrating ulcers may form. The disease tends to be irregular; areas of the intestine that lie between diseased areas may appear normal but in fact could be mildly affected. The cause is unknown, but it may arise from an abnormal allergic reaction or response to a viral or bacterial agent. The diagnosis can be determined firstly by displayed symptoms of spasmic pain in the abdomen, diarrhoea and sickness, followed by a physical examination which could reveal tender abdominal swellings. The disease is chronic and the symptoms fluctuate over years, in some cases eventually subsiding. Many other patients require surgery, whilst some remain in normal health with the disease being localised.

1.13.4 Cancer and Inflammation

The recognised connection between the development of cancer and inflammation has long been known.[60,61] Long-term inflammation leads to the development of dysplasia, an abnormal alteration in a tissue owing to abnormality in the function of the component cells, leading to cancer. Epidemiological studies estimate that nearly 15% of worldwide cancer cases can be related to microbial infections.[62,63] Further evidence has come from the use of NSAIDs in the prevention of spontaneous tumour formation in people with familial adenomatous polyposis (FAP), an autosomal dominant genetic disorder.[64]

The formation of reactive oxygen and nitrogen species can occur at the site of inflammation. These species have the potential to damage DNA, proteins and cell membranes, favouring carcinogenesis. It is also known that chronic inflammation often results in repeated cycles of damage and compensating cell proliferation. As a consequence, the number of cells that are dividing increases and therefore there are more cells that are available for DNA damage, promoting the growth of malignant cells.[65] In the article, *Why Cancer and Inflammation?*[66] it is suggested that cancer and inflammation are related by epidemiology, histopathology, inflammatory profiles and the efficacy of anti-inflammatory drugs in prophylaxis. The association is non-trivial and therefore

cannot be reduced to one theory, but lines of evidence show that the inflammatory system positively affects tumour development and growth.

1.14 Tumour Necrosis Factor-alpha (TNF-α) and Alzheimer's Disease

In the brains of those patients with Alzheimer's disease, neuroinflammation with over-expression of cytokines is a standard characteristic. Tumour necrosis factor-alpha (TNF-alpha or TNF-α) is a proinflammatory cytokine and numerous studies have proven it be involved in the pathogenesis of the disease.[67] Over recent years it has become known that excess TNF-alpha plays a pivotal role in Alzheimer's disease.[68] Etanercept, a potent anti-TNF therapeutic, was firstly used to treat rheumatoid arthritis, acting by binding to TNF-alpha and blocking its interaction with cell surface TNF-alpha receptors. The result is that the effects that excess TNF-alpha exerts are reduced. The drug has duly been used to treat other inflammatory disorders in which TNF-alpha takes part.

In 2006, in a pilot study, it was reported that treatment with Etanercept was effective in the treatment of mild to severe Alzheimer's.[69] These findings encouraged further studies and new, exceptional conclusions were reported in 2008.[68] In the study by Tobinick and Gross in 2006,[69] there was noticeable clinical improvement in Alzheimer's disease patients within minutes of administration of the drug. It is important to note that a novel method of administration was used called perispinal extrathecal into the posterior neck. This serves to improve delivery of the drug to the brain via the cerebrospinal venous system.

In the most recently published study,[68] Tobinick and Gross were able to take an individual patient with late onset Alzheimer's disease and use cognitive tests to evaluate the rapid effect after treatment. The most obvious sign of an improvement came when observing the results of the Montreal cognitive assessment. One day before treatment the patient was unable to complete parts of the test; becoming agitated and overwhelmed by his inability to do so. His score was seven out of a possible thirty. Two hours after administration, his score increased to fifteen out of thirty and he was able to answer questions with

less frustration and perform simple calculations. Seven weeks and fourteen days after receiving his last dose of perispinal Etanercept, his score was fourteen, with noticeable improvement in the tasks (Figure 17).

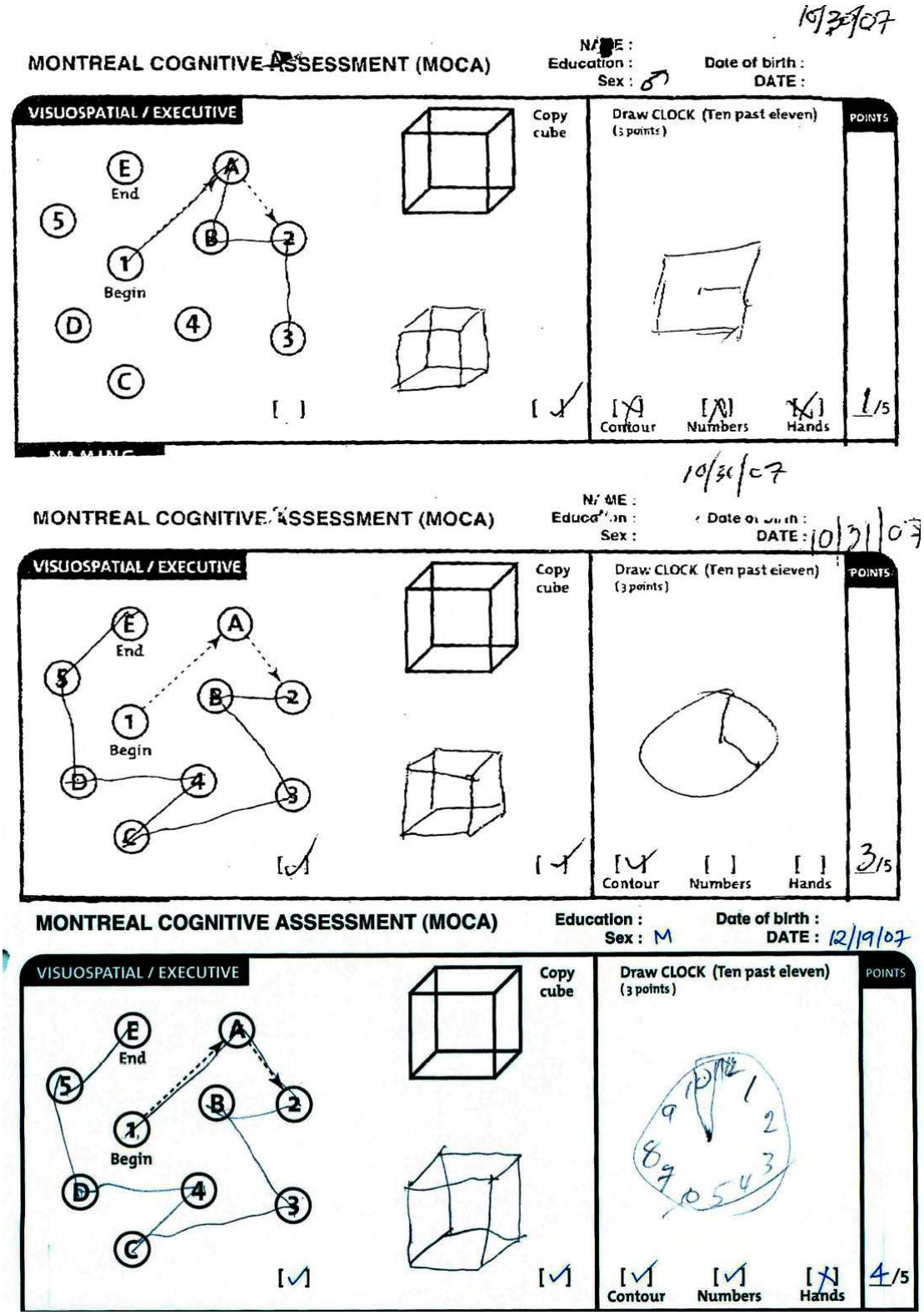


Figure 17: Tobinick and Gross' Most Definitive Study Results. The Montreal Congnitive Assessment shows rapid and sustained improvement in Visuospatial/Executive function following perispinal etabercept administration. Reproduced from Reference 68 with permission from the original publisher (BioMed Central).

Tobinick and Gross conclude that TNF-alpha is of critical importance in the regulation of synaptic transmission in the brain. They attribute this to the extreme rapidity of the effect and the potency and selectivity of Etanercept as an anti-TNF-alpha agent. Synaptic dysfunction is important in the pathogenesis of Alzheimer's disease and TNF-alpha mediates this and the associated cognitive and behavioural impairment. By using Etanercept they can rapidly neutralise the excess TNF-alpha and bring it to normal physiological levels, thereby alleviating the cognitive difficulties in patients by allowing normal cross-talk between regions of the brain. Clearly this is an intensely significant breakthrough in the study of Alzheimer's disease and the results presented can be utilised to set up further studies.

It has been shown that LL-Z1640-2 has significant activity versus TNF-alpha production in cells, with an IC_{50} of 6 nM.[70] This leads to the hypothesis that LL-Z1640-2 could be an antagonist and as such, a possible drug lead for the treatment of Alzheimer's disease. If it can indeed reduce the levels of TNF-alpha in cells, then this is analogous to the mode of action of Etanercept, proven to be successful in improving the cognitive function in patients with Alzheimer's disease.

1.15 Targeting TAK1

One of the major roles of TAK1 is to mediate some of the intracellular actions of proinflammatory cytokines. When it becomes activated, TAK1 is believed to switch on several protein-kinase cascades, including those that activate stress-activated protein kinase 2a, which is also called p38α, but is more often abbreviated to SAPK2a/p38α.

At the head of three proinflammatory kinase cascades lie TAK1 and its associated regulatory subunits TAB1 and TAB2 and the structurally related TAB3.[71,72] In 2003, Cohen and colleagues showed that SAPK2a/p38α exerted feedback control on TAK1 via TAB1.[72] They also discovered that the down regulation of TAK1 by SAPK2a/p38α was not just a feedback control device for limiting the activation of SAPK2a/p38α, but could also limit the activation of IKK

and JNK. This would synchronise three signalling pathways that play key roles in the inflammatory response.

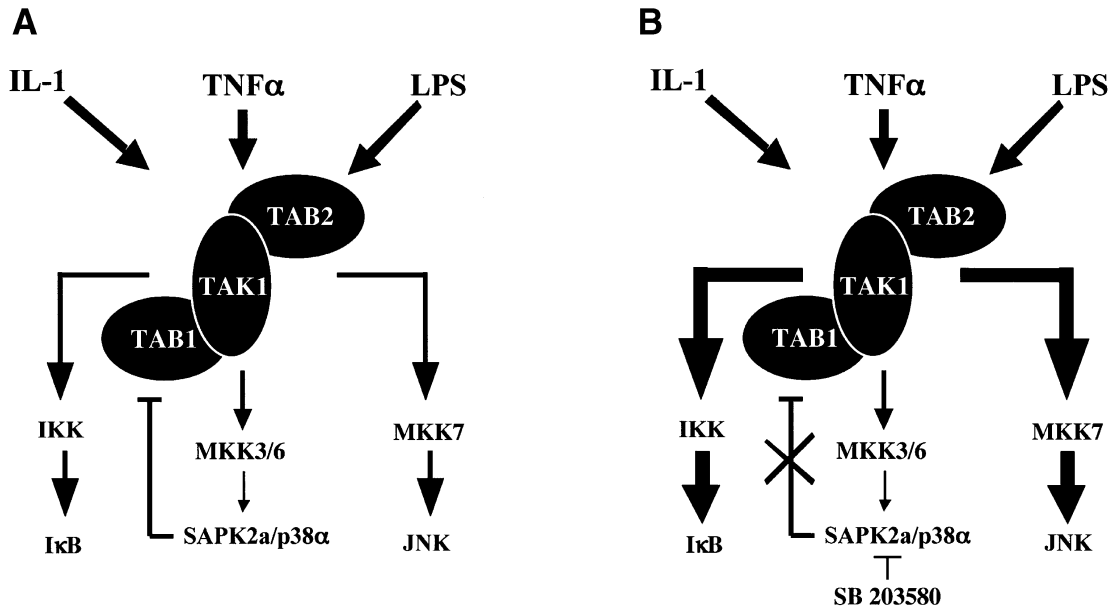


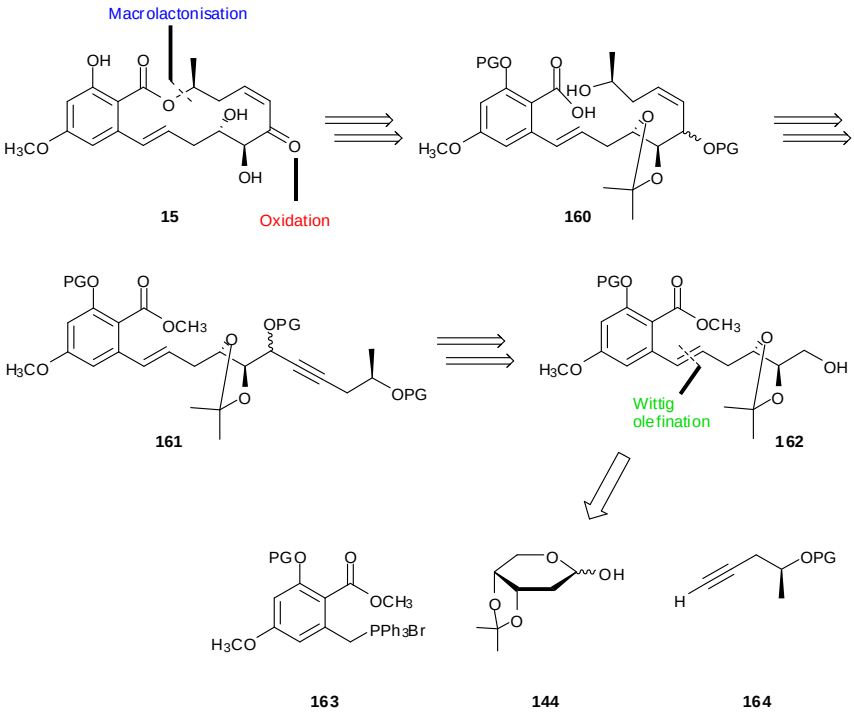
Figure 18: A representation of the feedback control of TAK1 activity by SAPK2a/p38α, highlighting how it implicates the regulation of JNK and NF-κB.[71] Reproduced with permission.

Figure 18A, shows how SAPK2a/p38α downregulates TAK1, via the phosphorylation of TAB1. In Figure 18B, SAPK2a/p38α is inhibited by SB203580, which stops the feedback control of TAK1. This causes the upregulation of the JNK and IKK pathways. These findings and those in associated publications, has led to the belief that the downregulation of TAK1 by SAPK2a/p38α may be a critical factor for the development of anti-inflammatory drugs. Presently, there are compounds that are more potent than SB 203580, which are undergoing clinical trials for the treatment of rheumatoid arthritis and other chronic inflammatory diseases.[50,73,74] Ultimately, it is reasonable to suggest that the inhibition of TAK1 activity may be effective in preventing inflammation and tissue destruction endorsed by proinflammatory cytokines.

1.16 Retrosynthetic Analysis

For this approach towards the total synthesis of LL-Z1640-2, it was important to utilise and build upon findings obtained through previous work carried out by past members of the Marquez research group.[49] The retrosynthetic analysis is

shown in Scheme 33, highlighting the key disconnections. A distinct advantage is that the synthesis begins from readily available starting materials, which are easily handled and manipulated to form the key fragments required for the coupling reactions.



Scheme 33: Initial Retrosynthetic Analysis.

An efficient approach was envisaged that would afford the final product **15** from the macrolactonisation of *seco*-acid **160**. No issues were forseen with this type of lactonisation, despite it serving to form a large-ring macrocycle. The precedent in the literature for this has already been demonstrated and discussed previously in this introduction.[36,41,50] *Seco*-acid **160** could result from a series of transformations from alkyne **161**. Alkyne **161** is obtained through the addition of alkyne **164** to terminal alcohol **162**, itself a product of a Wittig olefination between aromatic fragment **163** and sugar moiety **144**. It is hoped that this choice of reaction would enable to key *trans*-alkene to be formed in high selectivity.

The aromatic fragment **163** could be synthesised from the readily available starting material, methyl 3-oxobutanoate, in five steps, while the sugar moiety **144** could also be easily prepared in one protection step from 2-deoxy-D-ribose. The alkyne unit **164** is available from *S*-(+)-propylene oxide **32**, with the added

advantage that the second protection step is carried out on the crude material, so discarding the need for any purification on a highly volatile material.

The proposed route is robust and allows flexibility in the choice of orthogonal protecting group on fragments **163** and **164**. Following the Wittig olefination and introduction of the alkyne unit, the target compound **15** should be accessible in seven steps.

2 Results and Discussion

2.1 General Information

For the purposes of the following results and discussion section, the carbon atoms in the structure of the final product have been assigned accordingly. This enables the reader to interpret and distinguish between the correct fragments and specific parts of the molecule being discussed. The assignment is documented in Figure 19 below.

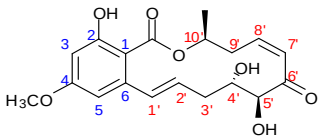
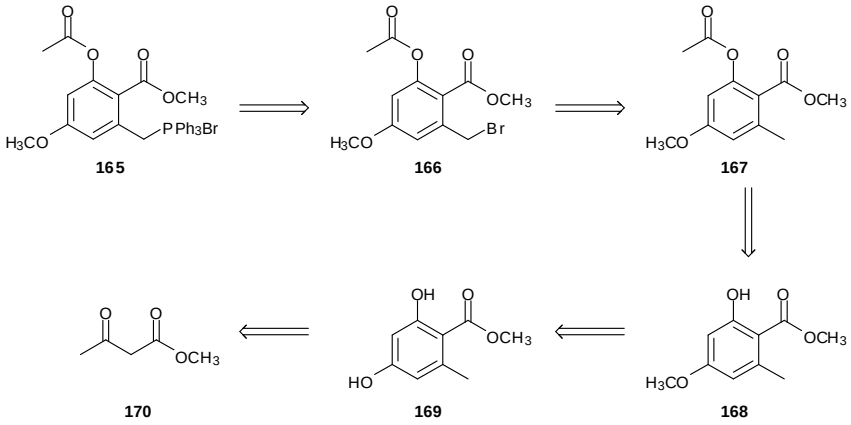


Figure 19: Structural Assignment of LL-Z1640-2.

2.2 Synthesis of the Aromatic Fragment

2.2.1 Retrosynthetic Analysis of (3-Acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide, 165

The proposed retrosynthetic analysis of (3-acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide **165** is shown in Scheme 34. The salt was thought of as originating from the bromide **166**, which in turn could originate from the methoxy unit **167**. Methoxy unit **167** is a result of acetate protection of phenol **168**, itself a product of selective capping of the *para*-hydroxyl of diol **169** with a methyl group. The diol could be prepared from the cyclisation and aromatisation of methyl acetoacetonate **170**.

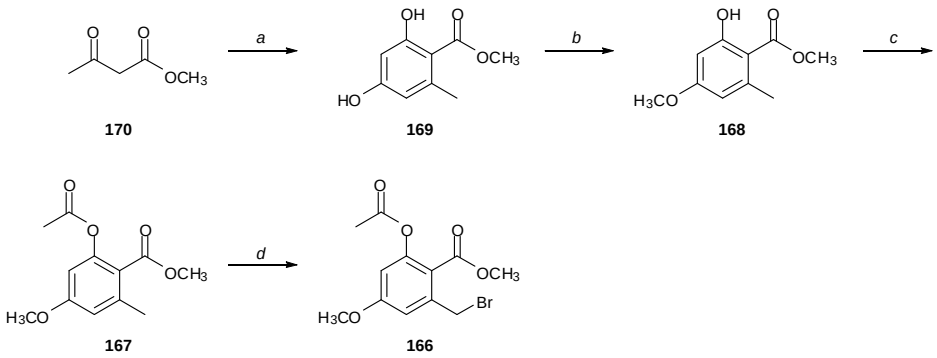


Scheme 34: Retrosynthetic Analysis of the Aromatic Fragment

Thus, the key step in this synthetic strategy is the first reaction, whereby methyl acetoacetonate is used to produce the aromatic product. The next four steps after aromatisation were thought to be straightforward and no potential pitfalls were envisioned.

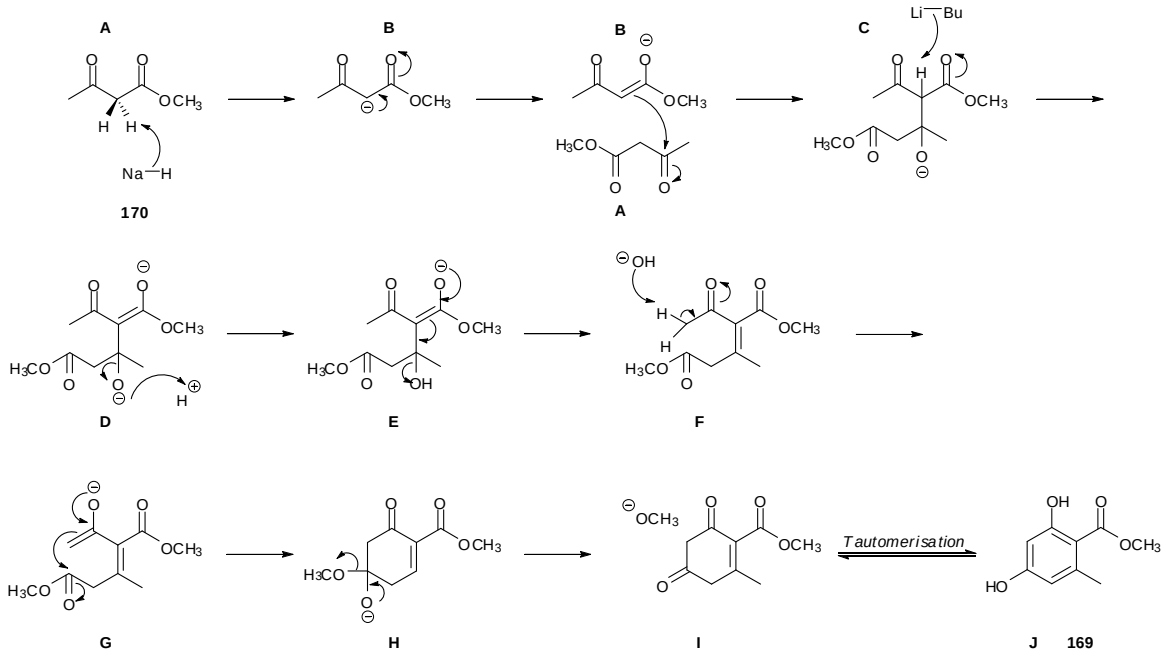
2.2.2 Synthesis of Methyl 2-acetoxy-6-bromomethyl-4-methoxybenzoate, 166

The synthesis of the aromatic fragment **166** began with methyl acetoacetonate **170**, which was efficiently converted into the aromatic unit **169** using established conditions.[49b] This reaction proceeded well and resulted in high yields.



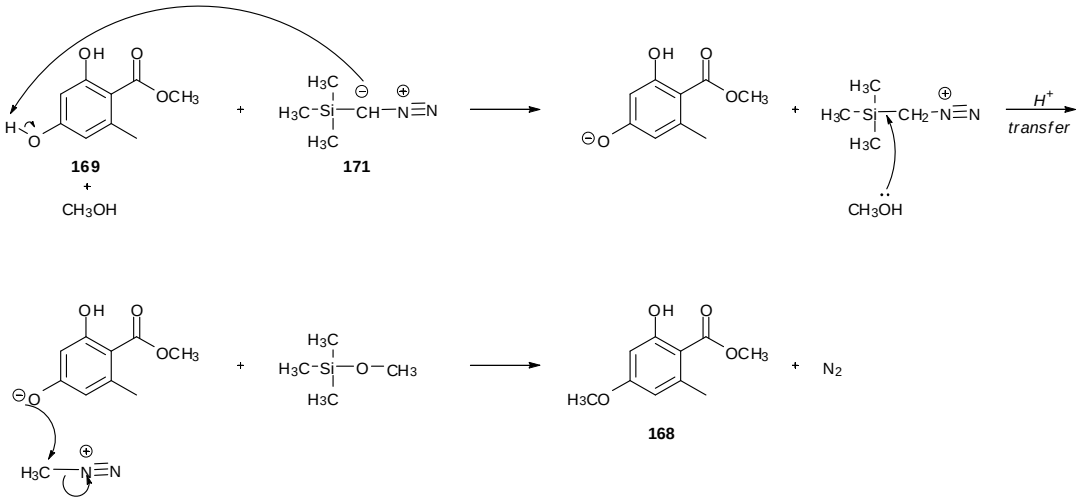
Scheme 35: Synthesis of the Aromatic Fragment 166. Reagents and Conditions: (a) NaH, *n*BuLi, THF, –78 °C → rt–reflux, 16 h, 65%; (b) TMS diazomethane, $CHCl_3$:MeOH, 0 °C, 3 h then rt, 16 h, 89%; (c) Ac_2O, pyridine, DMAP, Et_3N, CH_2Cl_2, 0 °C → rt, 2 h, 97%; (d) 1,3-dibromo-5,5-dimethylhydantoin, benzoylperoxide, CCl_4, reflux, 3.5 h, 95%.

The mechanism for this first transformation is worth discussing due to its relative complexity (Scheme 36). Deprotonation of ß-ketoester **A** gives enolate **B**, which can attack the ketone of a second ß-ketoester unit. Treatment of intermediate anion **C** with *n*-butyllithium removes the acidic hydrogen α to the ketone to give **D**. B-elimination of the hydroxyl group of **E** then gives the condensation product **F**. Deprotonation then generates enolate **G**, which upon attack onto the adjacent ester gives cyclic hemiacetal intermediate **H**, which then collapses into the tricarbonyl unit **I**. Compound **J** is formed by tautomerisation of the 1,3-dione **I**.



Scheme 36: Mechanism by which Methyl 2,4-dihydroxy-6-methylbenzoate (169) is Formed.

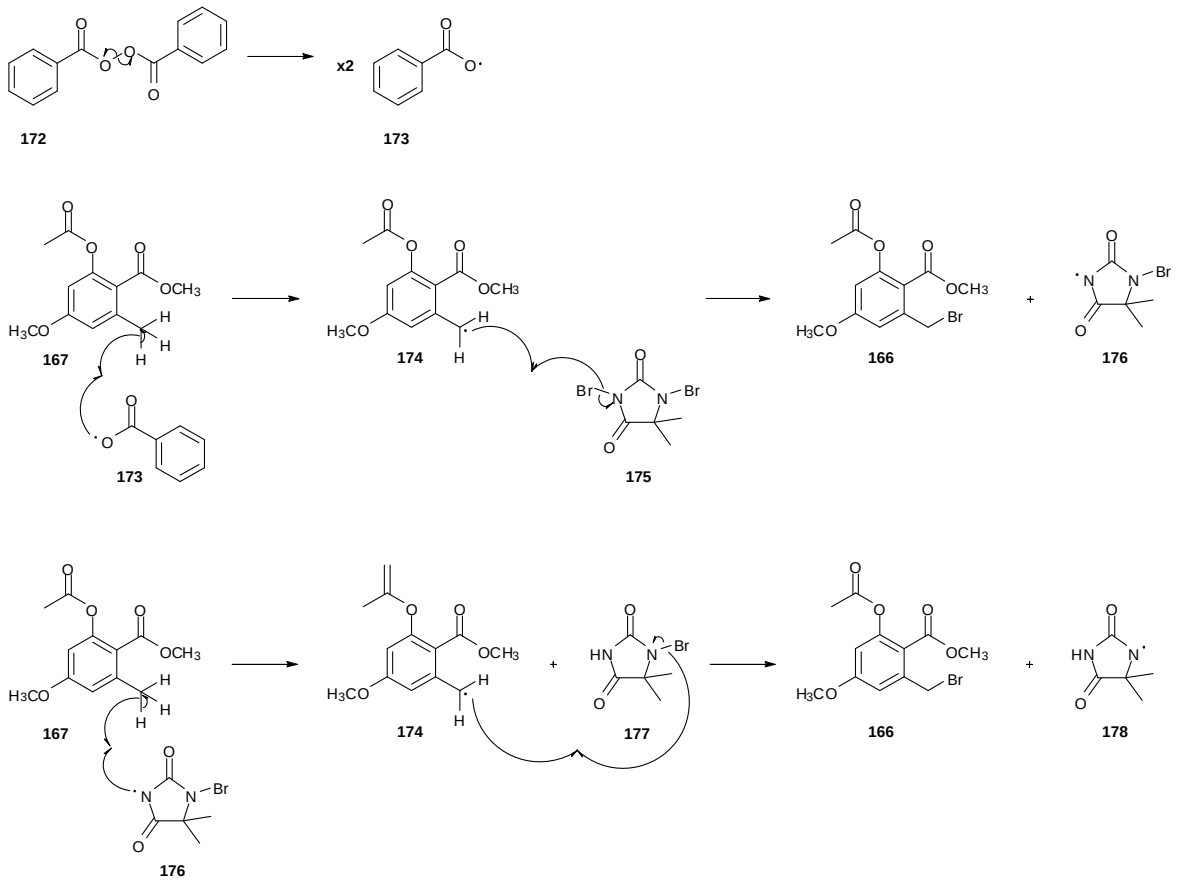
Selective methylation of **169** was achieved in 89% yield with TMS diazomethane in a mixture of chloroform and methanol.[49b] The mechanism is thought to proceed as shown in Scheme 37. TMS diazomethane **171** deprotonates the alcohol *para* to the ester functionality (presumably due to less steric hindrance and lack of H-bonding) and methanol attacks the δ^+ silicon. Hydrogen transfers from oxygen to diazomethane as silicon leaves. The phenolic anion then attacks the CH_3 group, giving product **168** and releasing nitrogen.



Scheme 37: Mechanism of TMS-diazomethane Mediated Methylation.

Protection of the remaining phenol proceeded under standard acetylation conditions to afford the fully protected aryl unit **167** in 97% yield. The final step was bromination of the methyl group, which proceeded using 1,3-dibromo-5,5-dimethylhydantoin to afford **166** in 95% yield.[49b]

The proposed mechanism is shown in Scheme 38 and the first step is the homolytic cleavage of the radical initiator, benzoyl peroxide **172**, to give two radical units **173**. Radical **173** reacts with aryl unit **167** to generate radical **174**. This goes on to react with 1,3-dibromo-5,5-dimethylhydantoin **175** to give desired product **166** and new radical **176**, which can go on to react with a second molecule of **167** to form radical **174** and **177**. These react together to generate product **166** and new radical **178**.

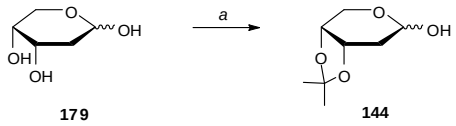


Scheme 38: Radical Bromination of 167.

2.3 Synthesis of the Sugar Fragment

The synthesis of the carbohydrate unit **144** was previously established[75] and began with 2-deoxy-D-ribose **179**, which initially was ketal protected (Scheme 39) using Horton's conditions.[51] However, their high yields were not reproducible, although the ratio of α- and ß-anomers matched those reported. In Horton's procedure, dimethylformamide is used as the solvent due to the poor solubility of 2-deoxy-D-ribose. This suffices to an extent for those reactions on a smaller scale, but as this is one of the initial steps in a total synthesis, the reaction calls to be carried out a large scale. Evidently, using vast volumes of DMF is prohibitive, both in terms of its toxicity but also due to the difficulty in removing it from the final product. In due course, it was discovered that switching to ethyl acetate as the solvent for the reaction, greatly improved the yields. In addition, ethyl acetate is readily removed under vacuum, circumventing any unnecessary decomposition of product. The protection yield was significantly improved when a catalytic amount of pyridinium *p*-

toluenesulfonate (PPTS) was used and ethyl acetate was employed as the solvent.[75,76] After purification, the desired ketal protected product **144** was isolated in 62% yield.



Scheme 39: Ketal Protection of 2-deoxy-D-ribose. Reagents and Conditions: (a) 2-Methoxypropene, PPTS, EtOAc, –10 ^{o}C, 2.5 h *then* rt, 16 h, 62%.

2.4 Coupling of the Aromatic and Sugar Fragments

The $C_{1'}$—$C_{2'}$ olefin present in the target compound possesses the *E*-configuration and whilst there are many ways by which olefins can be formed it is essential in this case that the chosen reaction generates an olefin with high *E*-selectivity.

2.4.1 Controlling the Geometry of Olefins

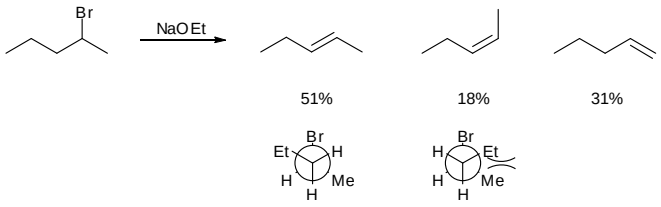
Geometrical isomers of alkenes are different compounds and they often have very different biological, chemical and physical properties. Experimentally they pose problems as they can be very difficult to separate by chromatography or distillation and as a consequence chemists have discovered and developed methods to make olefins as single isomers.

There are elimination reactions that can be employed to give single geometrical isomers as the product and they fall into four main classes:

1. Only one geometrical isomer is possible, for example, in a six-membered ring only a *cis*-double bond can exist.
2. The geometrical isomers are in equilibrium and the more stable *E*-alkene is formed.
3. The reaction is stereoselective and the *E*-alkene is formed as the main product by kinetic controls.
4. The reaction is stereospecific and the alkene geometry depends on the stereochemistry of the starting materials and the mechanism of the reaction.

Most common are reactions that fall into class 3 in the above list. Predominantly *E*-alkenes can be formed by stereoselective elimination reactions.

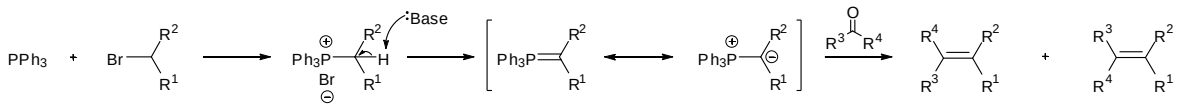
E1 elimination reactions give mainly the *E*-alkene as the transition state is lower in energy than that leading to the *Z*-alkene. An example is the treatment of 2-pentyl bromide with base (Scheme 40), which leads to three times as much *E*-alkene as *Z*-alkene, due to the lower energy of the transition state.



Scheme 40: Stereoselective Formation of *E*-Alkenes. Adapted from Reference 119.

2.4.2 Wittig Olefination

The Wittig reaction is arguably the most important and effective reaction used to generate *E*- and *Z*-alkenes.[77,78] The formation of the olefin comes from the reaction of aldehydes (fast) and ketones (slow) with the ylide generated from a phosphonium salt (Scheme 41).



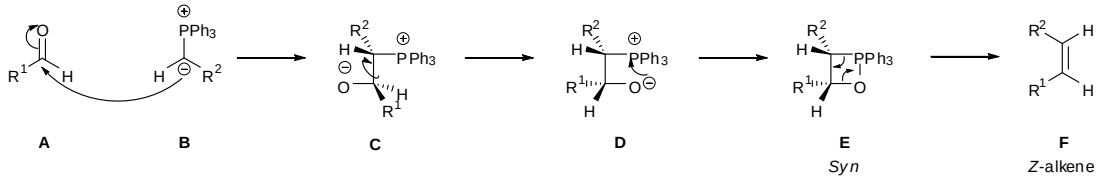
Scheme 41: General Scheme for the Wittig Olefination

The phosphorus ylide is prepared from a triaryl- or trialkylphosphine and a primary or secondary alkyl halide, followed by deprotonation with a suitable base. Depending on the nature of the *R* substituents, there are three different types of ylide:

Type 1 – "*Stabilised*" – The alkyl halide has at least one strong electron withdrawing group
Type 2 – "*Semi-stabilised*" – Have at least one aryl or alkenyl substituents as the R groups
Type 3 – "*Unstabilised*" – Have only alkyl substituents.

The overall geometry of the olefin is dependent on the reactivity of the ylide. "Stablilised" ylides give rise to predominantly *E*-alkenes with aldehydes and are not as reactive as "unstabilised" ylides, which give rise mainly to *Z*-alkenes. "Semi-stabilised" ylides generate alkenes with intermediate selectivity.

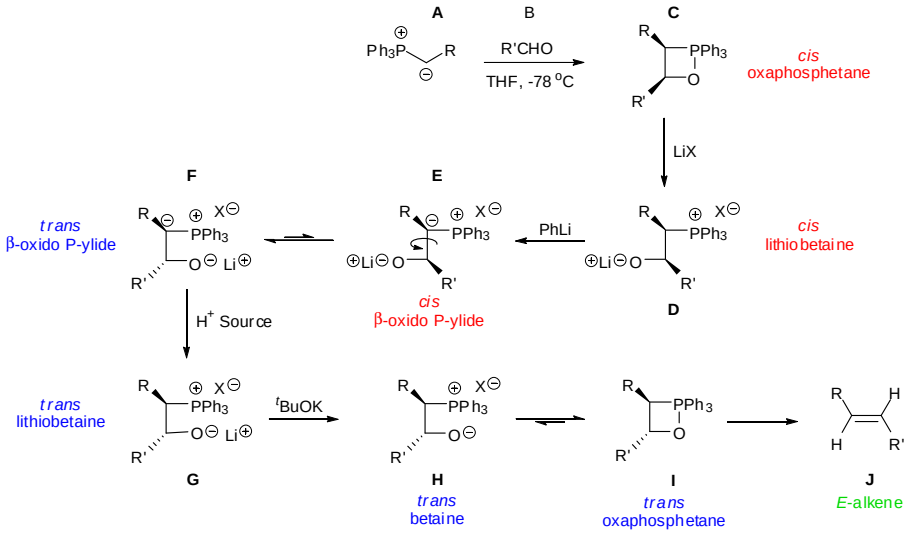
Mechanistically, the addition of the ylide **B** to the carbonyl **A** is thought to lead to a zwitterionic intermediate betaine **D**, which closes to the four-membered cyclic oxaphosphetane **E**. If the betaine possesses the *cis*-configuration the reaction from the reactive ylide to the *cis*-oxaphosphetane, then the major *Z*-alkene **F** is fast. The reaction to the *trans*-betaine is slower, but the collapse is fast to form the minor *E*-alkene.



Scheme 42: General Mechanism for the Wittig Reaction.

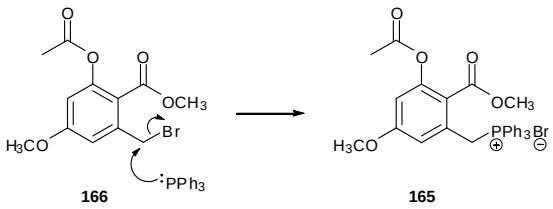
Improvements have been established to enable better selectivity of the Wittig reaction. In the Schlosser modification of Wittig,[79,80] *E*-alkenes are made in a one-pot synthesis from "unstabilised" ylides and carbonyl compounds.

Mechanistically (Scheme 43), the addition of the ylide **A** to the carbonyl compound **B**, at −78 °C, leads to the formation of the cyclic *cis*-oxaphosphetane **C**. *Cis*-oxaphosphetane **C** is deprotonated with alkyl/aryl lithium to give the *cis*-lithiobetaine **D**. Treatment of **D** with phenyllithium generates the *cis*-ß-oxido P-ylide **E**, which equilibrates to the *trans*-ß-oxido P-ylide **F**, which is more thermodynamically stable. The *trans*-ylide **F** is then treated with an H^+ donor to give the pure *trans*-lithiobetaine **G** and then with ^{t}BuOK to generate the *trans*-oxaphosphetane **I** *via* the *trans*-betaine **H**. This *trans*-oxaphosphetane **I** then collapses to the desired *E*-alkene **J**.



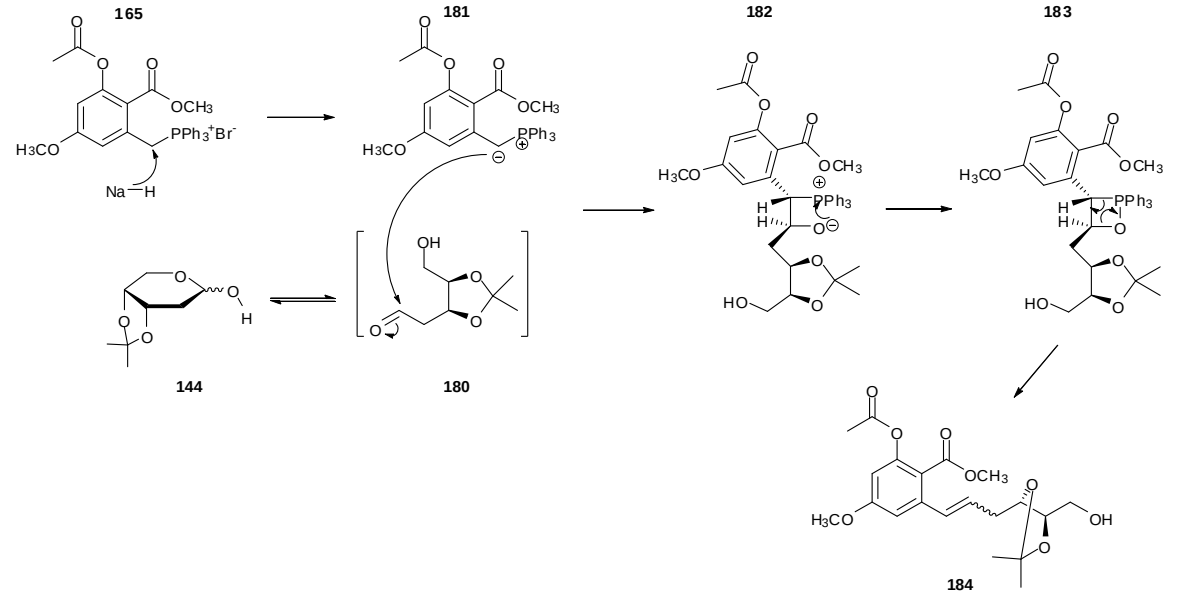
Scheme 43: Mechanism of the Schlosser Modification of Wittig.

When it came to the coupling of the aromatic fragment and the sugar derivative, the choice of method was considered carefully. It was decided that a Wittig olefination using a stabilised ylide would yield the desired double bond geometry. The corresponding Wittig salt **165** was generated in one step from the bromide **166** (Scheme 44).



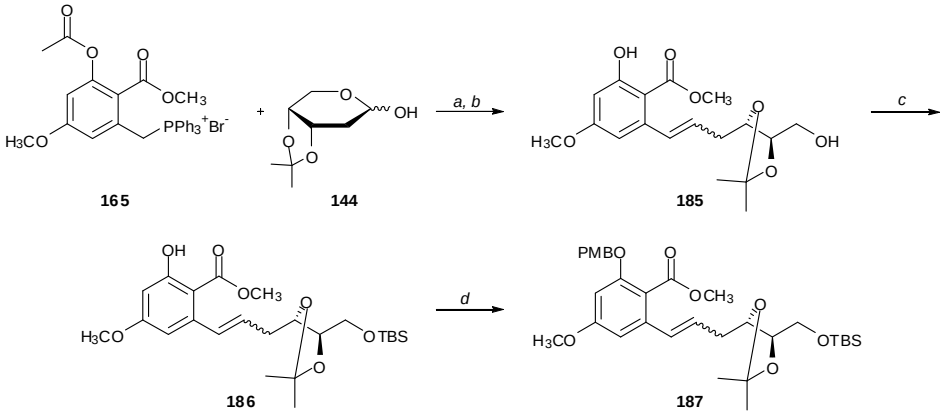
Scheme 44: Generation of the Wittig Salt 165. Reagents and Conditions: PPh_3, toluene, reflux, 24 h, 65%.

Triphenylphosphonium salt **165** is a stabilised ylide due to the negative charge being stabilised by further conjugation and by the phosphorus atom. This stabilised ylide is not very reactive and as a consequence the reaction progresses slowly, *via* the *trans*-oxaphosphetane, to generate the *E*-alkene. Stabilised ylides have been shown to react with lactols efficiently and the concept of carrying out Wittig chemistry on lactols is well known. Wittig approaches and reactions of stabilised ylides with lactols have been commonly used to form C-glycosides[81] and to synthesise lactones[82] and 2-substituted tetrahydrofurans.[83] The protected sugar **144** has masked aldehyde character of C_1, which is exploited under Wittig conditions (Scheme 45).



Scheme 45: Mechanism of Formation of 184.

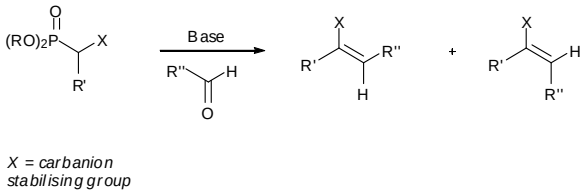
Reaction of ylide **165** and lactol **144** afforded the desired alkene **184**. However, the selectivity was disappointing and as determined by ^{1}H NMR spectroscopy the *E*:*Z*-ratio was 3:2, matching preliminary results obtained within the group.[49b] Unfortunately, the isomers were inseparable and in addition, it was discovered that approximately 10% of a deacetylated side-product **185**, was also present in the inseparable mixture. The instability of the acetate group to the reaction conditions meant that our choice of protection group had to be modified. In an alternative approach, the Wittig olefination reaction was repeated, but on this occasion sodium methoxide was added directly to the reaction mixture in order to ensure complete cleavage of the acetate protecting group. The overall yield over the 2 steps was determined as 40%. With diol **185** in hand, the primary hydroxyl was protected selectively as its silyl ether **186** in 65% yield. This then enabled the protection of the remaining aryl hydroxyl as the PMB ether **187** in excellent 90% yield using standard conditions (Scheme 46).



Scheme 46: Wittig Olefination of 165 and 144. Reagents and Conditions: (a) NaH, THF:DMF, 80 °C, 30 min; (b) NaOMe, rt, 15 min, 40%; (c) TBDMSCl, imidazole, DMF, rt, 3 h, 65%; (d) PMBCl, TBAI, K_2CO_3, DMF, 80 °C, 18 h, 90%.

2.4.3 Horner-Wadsworth-Emmons Olefination

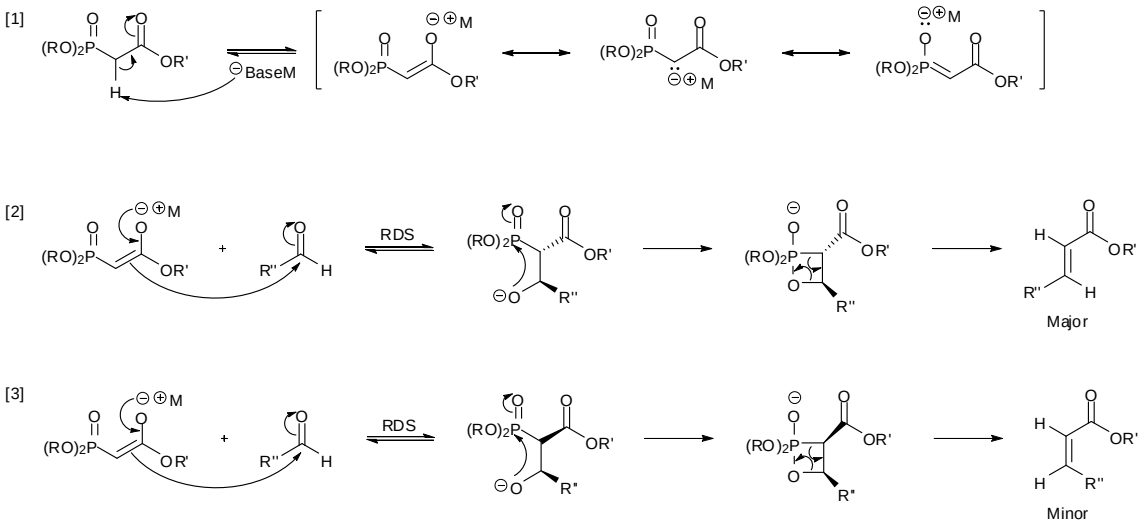
The Horner-Wadsworth-Emmons olefination[84] is another reaction that can be used to generate alkenes with excellent *E*-selectivity. In general terms, it is the reaction between an aldehyde or ketone and a phosphonate ester (Scheme 47). It is important to note that the reaction does not proceed in the case of ß-hydroxy phosphonates as no elimination takes place.



Scheme 47: General Reaction Scheme for the Horner-Wadsworth-Emmons Olefination.

The first step of the mechanism shown in Equation [1], Scheme 48, is the formation of the phosphonate carbanion from the phosphonate ester. The base can be *n*BuLi, NaH or NaOMe for example, which deprotonates the acidic hydrogen first, to then allow the addition of the aldehyde or ketone. The addition of the carbanion to the carbonyl can occur *syn*- or *anti*-periplanar, to form either the *trans*- (Equation [2]) or *cis*-oxaphosphetane (Equation [3]) intermediate. The formation of the *trans*-oxaphosphetane is favoured as the bulky substituents are kept as far apart as possible on opposite sides of the ring. Elimination gives the *E*-alkene and is faster than elimination to the *Z*-alkene by

way of the steric crowding in the *syn*-transition state. Equilibration of the two oxaphosphetane diasteroisomers as a result of the starting material replenishing the supply of *anti*-diasteroisomer, causing the *E*-alkene to be formed almost exclusively. The *E*-selectivity is further maximised by increasing the size of the alkyl group of the phosphonate.[85]

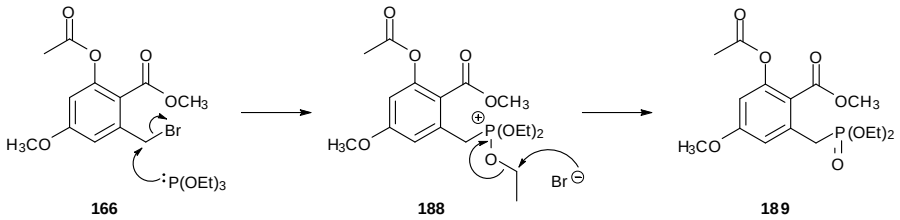


Scheme 48: General Mechansim for the Horner-Wadsworth-Emmons Olefination.

In an attempt to improve the *E*-selectivity of the reaction a Horner-Wadsworth-Emmons olefination was carried out. This first required the generation of the phosphonate ester, which would then be coupled with lactol **144**.

The phosphonate ester was obtained via an Arbuzov (or Michaelis-Arbuzov) reaction,[86] whereby the bromide **166** was treated with triethyl phosphite under microwave irradiation conditions to obtain phosphonate ester **189** in 58% yield. The choice to use microwave chemistry was advantageous in this case as it reduced not only the reaction time, but also reduced the safety risk associated with heating a reaction to elevated temperature for a prolonged period.

Mechanistically, nucleophilic attack (S_N2) by the phosphorus on the alkyl halide of **166** is followed by dealkylation of the trialkoxyphosphonium salt **188** to generate phosphonate ester **189** (Scheme 49).



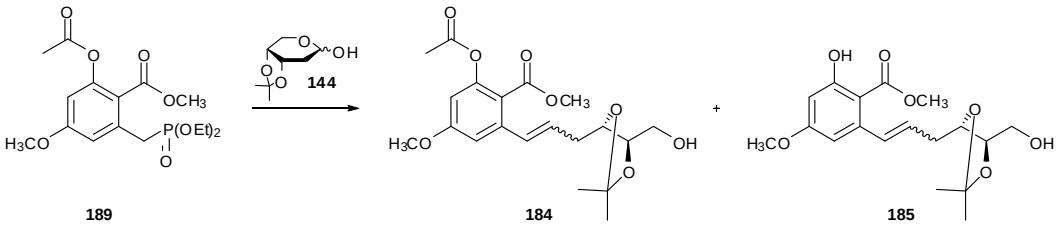
Scheme 49: Mechanism of Formation of 189 via the Arbuzov Reaction.

2.4.4 Microwave Reactions

Microwave chemistry originated in the 1950s, but only gained prominence in 1986.[87] Microwave methodology is the application of microwave irradiation to a reaction. It has become increasingly popular due to benefits such as reaction rate acceleration, shorter reaction times, milder reaction conditions and higher yields, as well as operational simplicity and lower energy usage.

Microwaves act as high frequency electric fields and usually will heat polar molecules in a solvent or conducting ions in a solid. With conventional heating the walls of the reactor heat quickly, but the core takes a prolonged time to achieve the target temperature. Microwave heating directly targets the compounds in the mixture throughout their volume, enabling the advantages mentioned above. The modern microwaves, manufactured by companies such as Biotage, are powerful but safe and easy to use, indeed some are even automated. The temperature range is typically 40 to 250 ^{o}C, with a pressure range of 0-20 bar. Different vial sizes are available enabling the user to begin with milligrams and scale up to grams if necessary.

With the phosphonate ester **189** in hand, the Horner-Wadsworth-Emmons reaction was attempted under conditions published by Schauer and Helquist.[88] Helquist's reaction conditions have the advantage of being mild and require a tertiary amine base in the presence of a Lewis acid, instead of the strong bases originally used. Helquist's work revealed that zinc(II) triflate is an effective promoter of mild Horner-Wadsworth-Emmon reactions with diprotic substances.



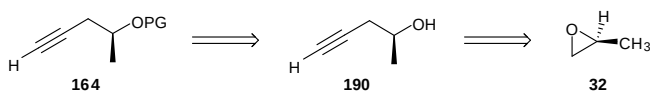
Scheme 50: Horner-Wadsworth-Emmons of Phosphonate Ester 189 and Lactol 144. Reagents and Conditions: $Zn(OTf)_2$, DBU, TMEDA, THF, rt, 18 h.

Unfortunately, the HWE coupling under Helquist's optimised conditions gave mixed results. The ^{1}H NMR spectrum showed that **184** was present as a mixture of inseparable *E*- and *Z*-isomers in low yield, together with the deacetylated product **185**. This disappointing result prompted us to pursue the initial Wittig olefination approach. This provided us with a way to carry material forward in an attempt to progress with the total synthesis. The differentially protected diol **187** gave us an excellent starting point from which to incorporate the entire carbon framework of LL-Z1640-2.

2.5 Synthesis of the Alkyne Fragment

2.5.1 Retrosynthetic Analysis of (*S*)-(-)-*tert*-butyldimethyl(pent-4-yn-2-yloxy)silane, 55

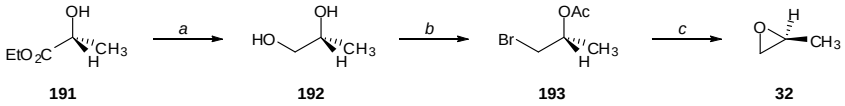
From our original retrosynthesis of LL-Z1640-2, we had realised the importance that the alkyne unit to be coupled to the aldehyde had the correct stereochemistry already in place. Literature precedent indicated that this would be easily achievable through a straightforward approach (Scheme 51).[89]



Scheme 51: Retrosynthetic Analysis of the Alkyne Fragment 164. PG equals a suitable protecting group.

2.5.2 Synthesis of (*S*)-(-)-*tert*-butyldimethyl(pent-4-yn-2-yloxy)silane, 55

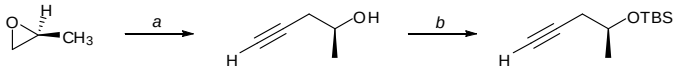
(*S*)-(+)-Propylene oxide is commercially available, but extremely hazardous and particular care is needed when handling this compound. (*S*)-(+)-Propylene oxide **32** can be synthesised from ethyl (*S*)-lactate **191**, according to Golding's procedure (Scheme 52).[90] We chose not to do this, as we were mindful of the safety aspects in producing such a compound.



191 **192** **193** **32**

Scheme 52: Golding's Synthesis of (*S*)-(+)-Propylene oxide.[90] Reagent and Conditions: (a) $LiAlH_4$; (b) 33% HBr in AcOH; (c) $C_5H_{11}ONa$, $C_5H_{11}OH$.

Commercially sourced (*S*)-propylene oxide **32** was added to a stirred suspension of lithium acetylide ethylenediamine complex to afford the crude alcohol **190** in quantitative yield. In order to maintain our orthogonal protecting group strategy, the free alcohol was protected as its TBS silyl ether to generate the desired optically pure alkyne fragment **55** in 78% yield.



32 **190** **55**

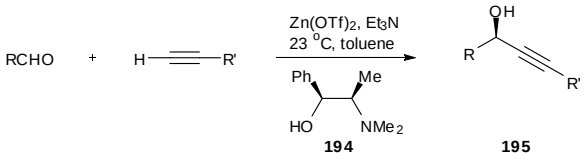
Scheme 53: Synthesis of the Alkyne Fragment 55. Reagents and Conditions: (a) lithium acetylide ethylenediamine complex, DMSO, 0 ^{o}C → rt, 48 h, 100%; (b) TBDMSCl, imidazole, DMF, rt, 16 h, 78%.

2.6 Synthesis of the $C_{1'}$—$C_{10'}$ Carbon Framework

2.6.1 Addition of the Alkyne Fragment

There is literature precedent for the enantioselective synthesis of propargylic alcohols by the direct addition of terminal alkynes to aldehydes and this had the potential to be exploited in this synthesis.

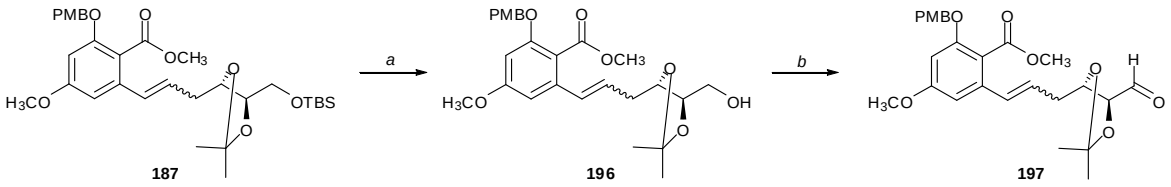
Before Carreira published his conditions,[91,92] the methods available for asymmetric synthesis of optically active propargylic alcohols were nucleophilic addition of metallated acetylenes to aldehydes or ynone reduction, with both the metallated acetylene and ynone requiring prior preparation. In 2000, Carreira published the synthesis of optically active propargylic alcohols **195** (up to 99% *e.e.*) under mild conditions at room temperature using *N*-methylephedrine **194** as a chiral additive (Scheme 54).[91]



Scheme 54: Carreira's Synthesis of Propargylic Alcohols Using a Chiral Additive.

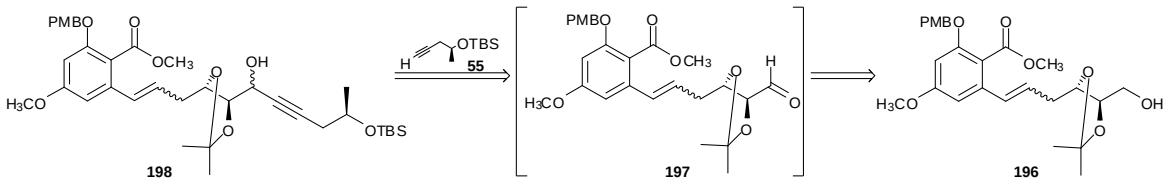
The authors initially found that in the presence of $Zn(OTf)_2$ and an amine base, terminal acetylenes underwent addition to aldehydes at room temperature in good yields. They hypothesised that a zinc(II) alkynylide was generated *in situ*, comparing it to the reaction of Cu(I) salts and amine bases with terminal acetylenes. With this success, they then went on to use inexpensive, commercially available chiral additives as ligands for Zn(II). In summary, they found that *N*-methylephidrine, an amino alcohol, was the most effective to give the optically active adduct.

The coupling sequence began with protected compound **187** which was deprotected using TBAF to generate alcohol **196** in 94% yield (Scheme 55). Alcohol **196** was then subjected to standard Swern conditions to produce aldehyde **197**, confirmed by the strong, characteristic signal in the ^1H NMR spectrum.



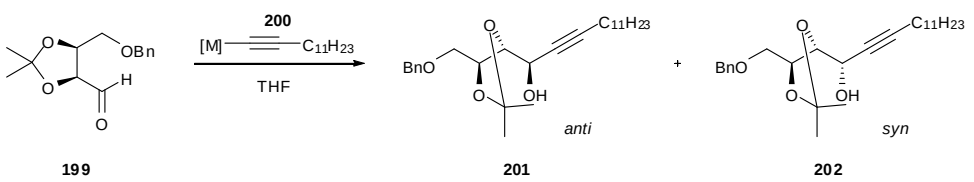
Scheme 55: Synthesis of Aldehyde 197. Reagents and Conditions: (a) TBAF, THF, 0 °C → rt, 2 h, 94%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → rt.

Unfortunately, this particular aldehyde proved unstable and started decomposing almost immediately, rendering it unusable for the addition to the alkyne unit. It also meant that large quantities could not be made and then stored for future use. In order to circumvent this problem, a new method was devised. As part of the new Swern oxidation procedure, triethylamine would be added at −78 °C and the reaction mixture allowed to warm to room temperature before being stirred for a further 30 minutes. It was hypothesised that at this stage the aldehyde need not be isolated, but rather it could be added directly to a second, simultaneously running reaction. This second reaction would contain the other reagents needed for the overall addition reaction (Scheme 56). The freshly prepared aldehyde **197** was added to a mixture of $Zn(OTf)_2$, *N*-methylephidrine **194** and alkyne **55**. Unfortunately, despite the reported success in the literature, the reaction did not work in our hands.



Scheme 56: Proposed One-pot Oxidation-Grignard Addition Reaction.

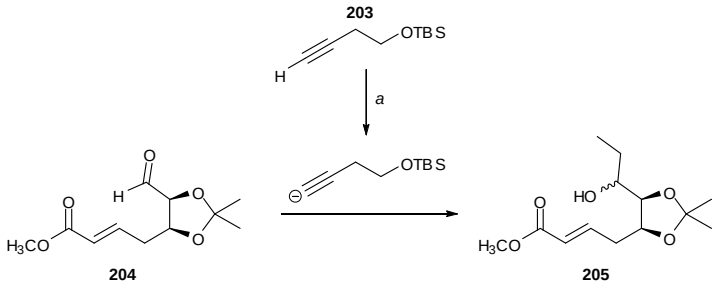
This set-back prompted us to search the literature for alternative procedures. In 1999, the *anti*-selective addition of tri*iso*propoxytitanium acetylide **200** to aldehyde **199** was published. It was reported that this alkyne addition afforded the *anti*-product **201** in 98% yield and as a single diastereoisomer (Scheme 57).[93] The improved procedure is analogous to that employed previously without success in Scheme 56. The only major difference was the use of chloroisopropoxytitanium (IV). Unfortunately, the reaction was not successful and NMR spectroscopy of the isolated compound showed it not to be the desired product.



Scheme 57: Addition of Triisopropoxytitanium Acetylide 200 to Chiral Aldehyde 199.

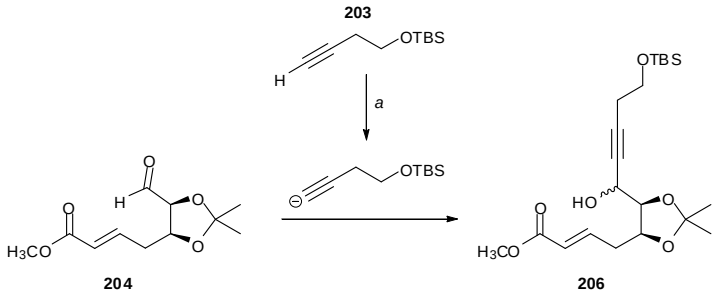
2.6.2 One-Pot Oxidation-Alkyne Coupling

The failure of the alkyne to couple to the aldehyde under titanium or zinc-promoted conditions drove us to consider an alternative metal counterion during the addition process. It was discovered in our laboratory that treatment of alkyne **203** with ethylmagnesium bromide at −78 °C did not proceed to generate the expected product. On its addition to the aldehyde **204**, it gave instead the ethyl addition product **205** (Scheme 58).[75]



Scheme 58: Addition of Acetylide 203 to Aldehyde 204. Reagents and Conditions: (a) EtMgBr, THF, –78 °C, 94%.

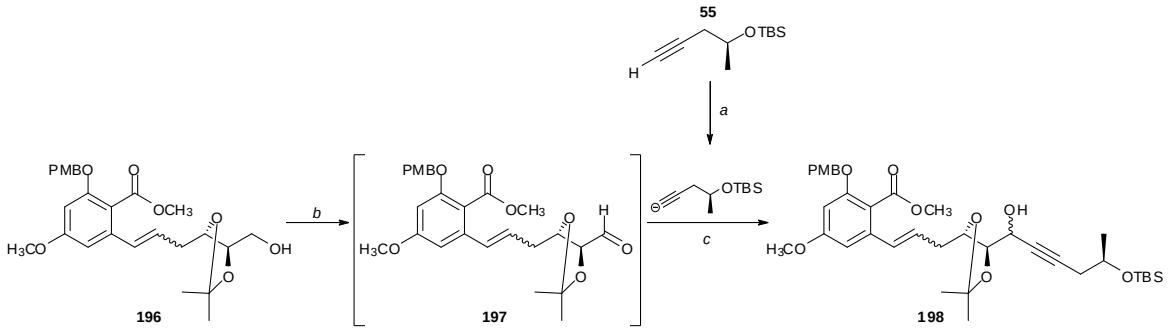
However, when the alkyne was treated with ethylmagnesium bromide at room temperature, the required magnesium acetylide was generated. Trapping of the aldehyde **204** afforded the alkynol product **206** in 88% yield (50:50 mixture of diastereoisomers) (Scheme 59).[75]



Scheme 59: Trapping of Acetylide 203 with Aldehyde 204. Reagents and Conditions: (a) EtMgBr, THF, rt, 88%.

Thus, alkyne **55** was treated with ethylmagnesium bromide at room temperature and was then added to crude aldehyde **197**. It was pleasing to see that the coupling did take place and the desired product **198** was obtained in 30% yield as a mixture of diastereoisomers (Scheme 60). It is worth pointing out that this

yield was for an initial, test-scale reaction and so it is fair to say that some material could potentially have been lost during work-up or purification. TLC analysis however proved the reaction to be efficient, with the clean conversion of the alcohol to the aldehyde and then to the final product.



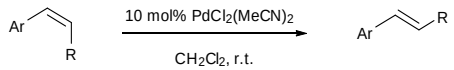
Scheme 60: One-Pot Oxidation Alkyne Coupling. Reagents and Conditions: (a) EtMgBr, THF, rt, 3 h; (b) $(COCl)_2$, DMSO, Et_3N, THF, –78 $^oC \rightarrow$ rt; (c) **55**, THF, –78 $^oC \rightarrow$ rt, 18 h, 30%.

Though the success of this reaction was appreciated and the gaining of the $C_{1'}$—$C_{10'}$ skeleton was welcomed, it was not advantageous to have an inseparable mixture of diastereoisomers. As can be appreciated, the ^1H and ^{13}C NMR spectra of such a compound is very complex and the ratio of diastereoisomers is not determinable. It can be postulated that a mixture is obtained due to the stereocentre α (alpha) to the aldehyde not being sufficient to fully direct the addition to the expected face. From the Felkin-Anh model, the outcome of the nucleophilic addition to the carbonyl compound can be predicted. When the large group is placed perpendicular to the carbonyl group, the expected face is the addition of the alkyne unit between the two hydrogen atoms (the two small groups and the least hindered trajectory). The *syn*-product is the expected product, while the *anti*-product is formed when the addition occurs between the large group and hydrogen of the aldehyde. In order to progress forward, the situation was reluctantly accepted and it was understood that NMR analysis of subsequent compounds would be difficult. Time was of the essence and we knew we could not afford the time at this stage to go back and test further enantioselective conditions.

2.7 Isomerisation Attempts

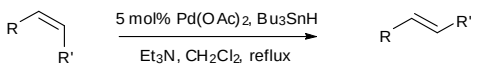
In the preparation of carbon-carbon double bonds, the isomerisation of a mixture of *Z*- and *E*-olefins to the geometrically pure *E*-isomer is highly significant and valuable. Over time, radical,[94] photochemical[95] and organometallic[96] reagents have been part of the conditions developed to isomerise olefins. Though successful, they are not without their disadvantages. Radical and photochemical techniques often require harsh conditions and in a number of photochemical reactions the reverse isomerisation is seen.

Recently, Yu and co-workers[97] prepared *E*-arylakenes *via* a mild, palladium(II)-catalysed isomerisation of *Z*-arylalkenes (Scheme 61). The method was limited to double bonds conjugated to aromatic systems, but this wasn't a hindrance as the double bond to be isomerised in our case is conjugated to an aromatic unit. What made the method even more attractive was that the reaction required only 10% loading of the chosen palladium catalyst, bis(acetonitrile)palladium(II) chloride, which is also commercially available and relatively inexpensive. The authors found that *cis*- and *trans*-methyl styrenes and styrenes with more bulky substituents were converted to the *trans*-isomer in good yield.



Scheme 61: Yu's Palladium(II)-Catalysed Isomerisation of *E*-arylalkenes.

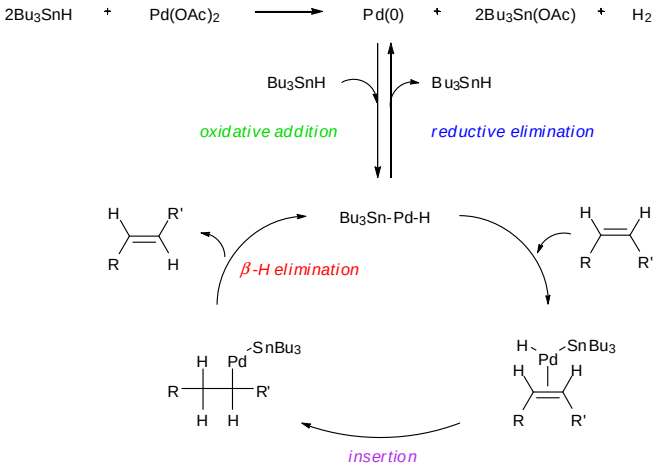
In 2007, Jung and colleagues[98] reported their efforts into the development of mild and efficient methods for olefin isomerisation, to generate geometrically pure *E*-alkenes using palladium acetate, tributyltinhydride and triethylamine (Scheme 62).



Scheme 62: Jung's Palladium(II)-Catalysed Isomerisation of Olefins.

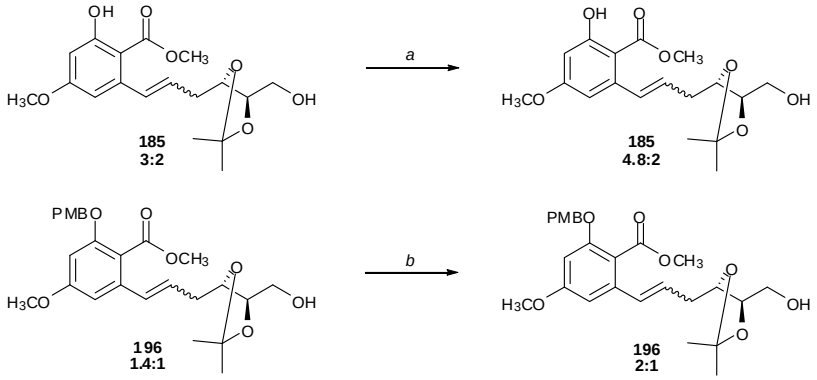
Jung found his conditions to be general for the isomerisation of *Z*-alkenes with allylic hydrogens and conjugated *Z*-arylakenes. The authors found that the

nature of the alkene substituents controlled the result of the isomerisation, for example, stabilisation by a phenyl group facilitated the reaction. The authors proposed a possible mechanism (Scheme 63) for the isomerisation and postulated that the Pd(0), formed by reduction of palladium(II) acetate with tributyltinhydride, would serve as an active catalyst for the isomerisation. The oxidative addition of tributyltinhydride to Pd(0) affords the palladium-tin complex which undergoes insertion. The *E*-olefin is generated following ß-H elimination and Pd(0) is regenerated from $Bu_3Sn—Pd—H$.



Scheme 63: Proposed Mechanism of Pd-Catalysed Isomerisation with Bu_3SnH. Adapted from Reference 98.

The fact that the Wittig olefination gave a 3:2 mixture of isomers, presented an opportunity for us to attempt an olefin isomerisation. If successful, the Wittig reaction could be scaled up with the knowledge that the *E*:*Z*-mixture of isomers could be readily isomerised into the geometrically pure *E*-isomer. Hence, Jung's conditions were tried on a simple model system **185** (Scheme 64). Due to the fact that the isomers were inseparable, it made it difficult to follow the reaction by TLC. To monitor the reaction it became necessary to take an aliquot of reaction mixture, allow it to cool, filter it through Celite® to remove the solids and concentrate it before running a ^1H NMR to observe any isomerisation to the *E*-isomer. After 45 hours under reflux it became apparent that no further isomerisation of the *Z*-isomer to the *E*-isomer was occurring so the above work-up was performed, followed by column purification and analysis by NMR. Although not wholly successful, some isomerisation had taken place and from the spectra the mixture was now 4.8:2 from 3:2 (*E*:*Z*).



Scheme 64: Isomerisation attempts. Reagents and Conditions: (a) $Pd(OAc)_2$ (5 mol%), Bu_3SnH, Et_3N, CH_2Cl_2, reflux, 45 h, 33%; (b) $Pd(OAc)_2$ (5 mol%), Bu_3SnH, Et_3N, $CHCl_3$, reflux, 50 h then rt, 74 h, 54%.

A second test reaction attempt was run, treating alcohol **196** under the same conditions, but switching the solvent to chloroform. Taking into account the prolonged reaction time needed for this kind of transformation, on this occasion the reaction mixture was heated under reflux for 50 hours and then cooled to room temperature, with stirring continued for a further 74 h. Again the same problem of inseparable isomers was encountered, rendering TLC analysis ineffective. The ^1H NMR spectrum showed a slight improvement from 1.4:1 to 2:1 (*E*:*Z*).

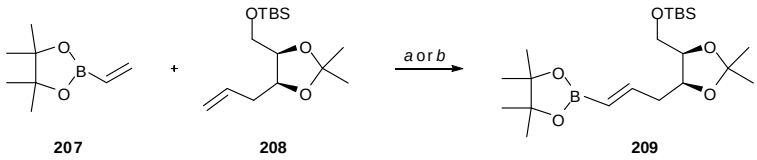
The failure of the palladium(II) catalysed isomerisation conditions to generate geometrically pure *E*-olefins meant that we had to seriously rethink our synthetic strategy to LL-Z1640-2. Whilst the Wittig olefination allowed us to garner material to test conditions for ensuing reactions in our proposed synthesis, it was becoming clear that this particular olefination to form the $C_{1'}$—$C_{2'}$ double bond in the *trans*-configuration was not suitable and another, significantly improved method was required.

2.8 Additional Studies

2.8.1 Cross-coupling Reactions

At this point a fellow PhD student in the research group found that a cross-metathesis between vinylboronic acid pinacol ester **207** and alkene **208** was achievable (Scheme 65).[75] He found that Grubbs first or second generation

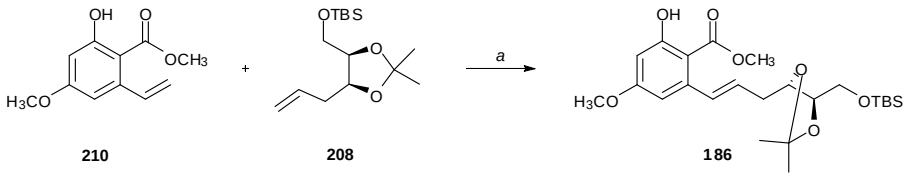
catalyst afforded alkene **209** in 71% or 73% yield respectively, as a 4:1 separable mixture of *E*:*Z*-isomers. Aside from proceeding with the desired Suzuki coupling, the success opened up the possibility of using alkene **208** as a partner in other Grubbs-mediated cross-metathesis reactions.



207 **208** **209**

Scheme 65: Successful Cross-metathesis of Alkene 208. Reagents and Conditions: (a) Grubbs second generation catalyst (5 mol%), CH_2Cl_2, reflux, 13 h, 73%; (b) Grubbs first generation catalyst (5 mol%), CH_2Cl_2, reflux, 13 h, 71%.

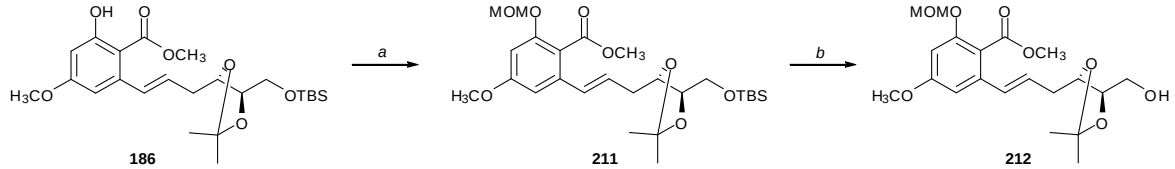
My fellow PhD student then went on to investigate the possibility of a cross-metathesis reaction between aromatic alkene **210** and alkene **208**. Following intense screening and optimisation, he found that the best reaction conditions were using Hoveyda-Grubbs second generation catalyst, with 30% loading and a ratio of 1:2 of aromatic alkene **210** and alkene **208** respectively (Scheme 66). The desired heterodimer **186** was obtained as a 9:1 mixture of *E*:*Z*. The additional formation of the homodimer could not be prevented and was isolated in an amount proportional to the success of formation of the heterodimer.



210 **208** **186**

Scheme 66: Successful Cross-metathesis of Aromatic Alkene 210 and Alkene 208. Reagents and Conditions: (a) Hoveyda-Grubbs second generation (30 mol%), CH_2Cl_2, reflux, 48 h, 73%.

My colleague was able to protect the free hydroxyl of **186** as its MOM ether **211** and remove the silyl ether protecting group to reveal the free alcohol **212** (Scheme 67), at which stage the isomers became separable. Due to time constraints enforced upon my colleague, the project was left at this stage, but a synthetic path of this type is highly attractive and something that would be worthwhile pursuing.



Scheme 67: Formation of Free Alcohol 212. Reagents and Conditions: (a) bromomethyl methyl ether, DIPEA, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 19 h, 90%; (b) TBAF, THF, rt, 30 min, 100%.

2.8.2 Continuation of the Synthesis Towards LL-Z1640-2

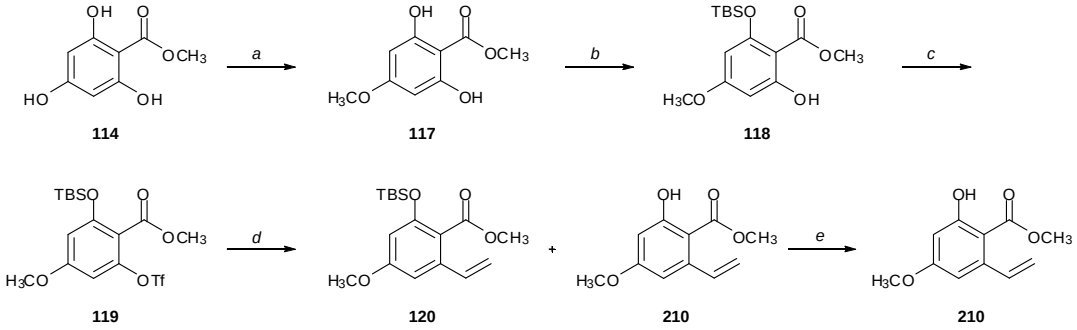
Taking into account all the investigations carried out towards the total synthesis of LL-Z1640-2 thus far, it was necessary to decide on a suitable path to follow. It was known from one angle that the Wittig olefination wasn't going to be productive in carrying the synthesis forward, due to the difficulties with the poor selectivity. Whilst all the possibilities for producing products with excellent *E*-selectivity had by no means been exhausted, we were now aware of the success with Grubbs-mediated cross-metathesis between alkenes **210** and **208**.[75]

2.9 New Synthetic Route to LL-Z1640-2

For completeness, it is necessary to highlight the routes that have already been established towards aromatic alkene **210** and alkene **208**. They are similar to those already described, but in order to present the revised synthesis towards LL-Z1640-2 in its entirety they will be discussed further.

2.9.1 Synthesis of the New Aromatic Fragment, 210

Aromatic fragment **210** was synthesised following the approach initially developed by Dr M. N. Robertson, a fellow member of the research group (Scheme 68).[49a,75,98]

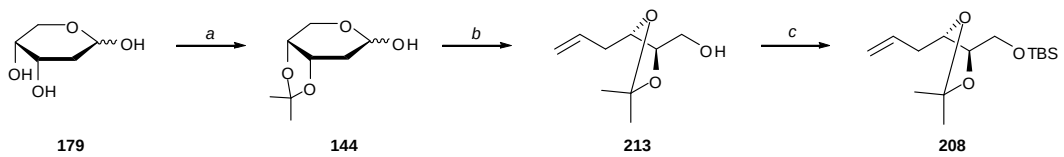


Scheme 68: Synthesis of Aromatic Fragment 210. Reagents and Conditions: (a) TMS–CH_2N_2, Et_2O, 90%; (b) TBDMSCl, Et_3N, CH_2Cl_2, 80%; (c) Tf_2O, pyridine, 100%; (d) vinyltributyl tin, $Pd(PPh_3)_4$, CH_2Cl_2; (e) TBAF, THF, 0 $^oC \rightarrow$ rt, 2 h; 74% *(over 2 steps)*.

2,4,6-Trihydroxybenzoate **114** was selectively methylated to afford diphenol **117**. Diol **117** was then mono-protected to generate silyl ether **118**. The remaining hydroxyl group was converted to the corresponding triflate **119**, under carefully controlled conditions.[75] The triflate was then subjected to Stille coupling[99] with vinyltributyltin. This proceeded in good yield to afford **120**, but also partially cleaved the silyl ether protecting group, giving phenol **210**. A decision was taken to treat the mixture of **120** and **210** with TBAF to deprotect fully the TBS group, affording aromatic fragment **210** in 74% yield over two steps.

2.9.2 Synthesis of the Alkene Coupling Fragment, 208

2-Deoxy-D-ribose **179** was ketal protected using 2-methoxypropene (Section 2.3). Wittig olefination of lactol **144** using methyltriphenylphosphonium iodide proceeded to give terminal alkene **213** in an acceptable 60% yield.[76] The primary alcohol was protected as its TBS silyl ether in 87% yield under standard conditions to give the desired alkene cross-metathesis coupling partner **208**.



Scheme 69: Synthesis of Alkene 208. Reagents and Conditions: (a) 2-Methoxypropene, PPTS, EtOAc, –10 ^oC, 2.5 h *then* rt, 16 h, 62%; (b) $(Ph_3P\text{-}CH_3)I$, KHMDS, THF, –78 $^oC \rightarrow$ rt, 17 h, 60%; (c) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 18 h, 87%.

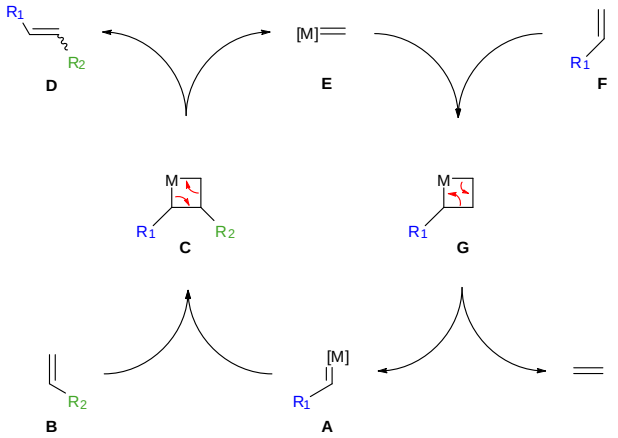
2.9.3 Olefin Metathesis

Olefin metathesis is one of the most powerful synthetic methods in organic chemistry. The definition of metathesis is change position, *meta* meaning change and *thesis* meaning position. In metathesis reactions double bonds are broken and made between carbon atoms in ways that cause atom groups to change places. In the 1950s, Du Pont, Standard Oil and Phillips Petroleum reported catalysed metathesis reactions when propene led to ethylene and 2-butenes on heating with molybdenum.[100]

Olefin cross-metathesis is the intermolecular mutual exchange of alkylidene (or carbene) fragments between two olefins promoted by metal-carbene complexes (Scheme 70).[101] The process is catalytic, typically requiring 1-5 mol% of catalyst, with high yields readily achievable.

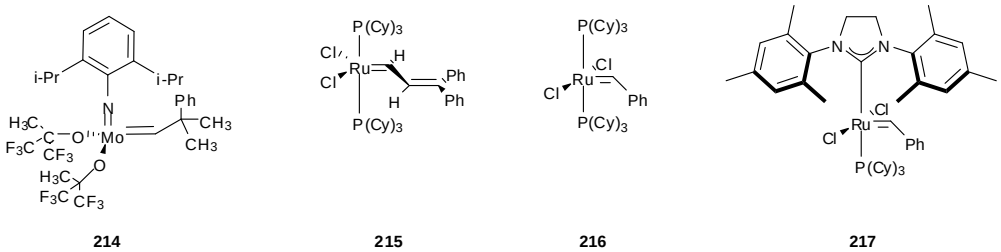
Scheme 70: General Scheme of Cross-Metathesis.[101]

In 1971, Chauvin and Hérisson published their widely accepted transition metal alkene metathesis mechanism (Scheme 71).[102] The reaction is reversible, but the gaseous ethylene produced drives the reaction to completion. A [2+2] cycloaddition between olefin **B** and a transition metal carbene **A** forms a metallocyclobutane intermediate **C**. This collapses in a productive fashion to afford the first olefin product **D** and a new metal alkylidene **E**. This metal alkylidene can react with a molecule of **F** via metallocyclobutane **G** to yield **A**, which re-enters the catalytic cycle.



Scheme 71: Mechanism of Olefin Cross-Metathesis.

In 2005, the Nobel Prize in Chemistry was jointly awarded to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock, "for the development of the metathesis method in organic synthesis."[103] They each contributed to the field of metathesis in their own way. To summarise, in 1971 Chauvin explained how metatheses reactions function and types of metal compound that act as catalysts, in 1990 Schrock was the first to produce an efficient metal-compound catalyst for metathesis (Figure 20, **214**) and in 1992 Grubbs reported his development of a superior ruthenium catalyst (Figure 20, **215**) for metathesis. Modifications of his catalysts came in 1995 (First Generation) and 1999 (Second Generation) (Figure 20, **216** and **217** respectively). Their research and findings combined allowed synthetic methods that were more efficient, simpler to use and more environmentally friendly.



214 **215** **216** **217**

Figure 20: Commonly Used Metathesis Catalysts.

2.9.4 Coupling of Fragments 210 and 208

The cross-coupling between the aromatic alkene **210** and alkene **208** was attempted using Hoveyda-Grubbs second generation catalyst (Figure 21) under the established conditions (Scheme 72).[75]

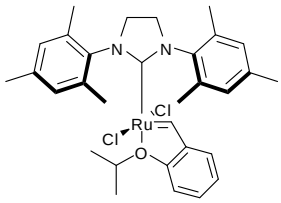
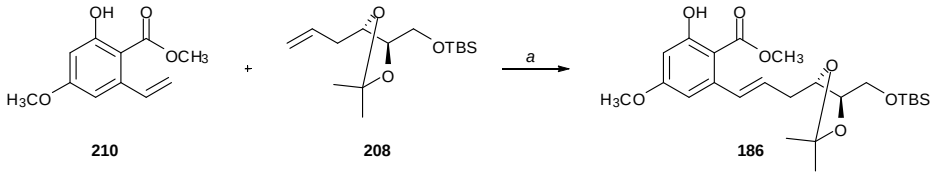


Figure 21: Hoveyda-Grubbs Second Generation Catalyst.

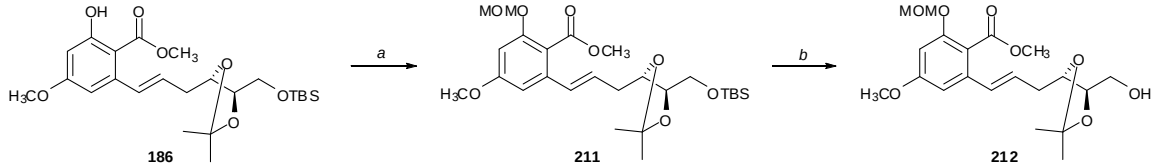
With a 30 mol% loading of catalyst and a 2:1 ratio of **208** to **210**, the desired product **186** was obtained in 65% yield after refluxing in the dark for 48 h in dichloromethane. Despite repeated attempts the yield obtained was not quite as high as reported previously in the group,[75] though more than acceptable to proceed. The product was still a mixture of *E*- and *Z*- isomers, but had vastly improved to 9:1 (*E*:*Z*), as opposed to 3:2 obtained following the Wittig olefination.



Scheme 72: Cross-metathesis of 210 with 208. Reagents and Conditions: (a) Hoveyda-Grubbs second generation catalyst (30 mol%), CH_2Cl_2, reflux, 48 h, 65%.

From earlier work, a TBS silyl ether positioned on the aryl ring was found to be labile and as such was ruled out as the choice of protecting group for the aromatic hydroxyl. In addition, there was a TBS group already present in the molecule which could potentially make the mono-deprotection slightly troublesome. A MOM ether was chosen as the protecting group for the phenolic alcohol of coupled product **186**. It was envisaged that the MOM group would stay in place throughout the remainder of the synthesis, while its cleavage could be performed simultaneously with the acetonide protecting group at the end of

the synthesis. The MOM group was introduced, using MOMBr and Hunig's base,[75] generating **211** in 60% yield (Scheme 73). This lower than expected yield was a surprise and it was originally assumed that the MOMBr could also be damaging the substrate. Removal of the TBS group with TBAF generated the free alcohol **212**, which could be used directly in our previously established one-pot alkyne coupling reaction.

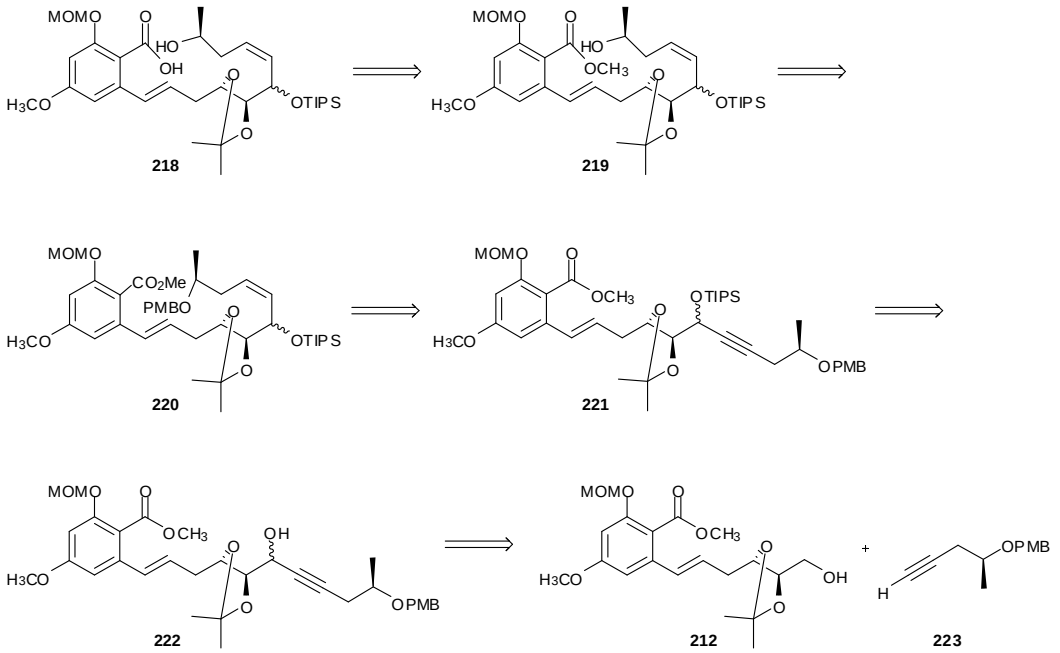


Scheme 73: Formation of Alcohol 212. Reagents and Conditions: (a) MOMBr, DIPEA, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 18 h, 60%; (b) TBAF, THF, 0 $^oC \rightarrow$ rt, 1.5 h, 93%.

2.10 Synthesis of the *Seco*-Acid

2.10.1 Retrosynthetic Analysis of 2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*S*-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoic acid, 218

As demonstrated in the retrosynthetic analysis shown in Scheme 74, *seco*-acid **218** was envisioned as originating from the base-catalysed hydrolysis of ester **219**. Compound **219** would be the result of PMB deprotection at the terminus of the structure. *Z*-Alkene **220** can be gained *via* selective hydrogenation of the alkyne **221**. Alkynol **222** comes from the one pot oxidation-acetylide addition of **212** and **223**.

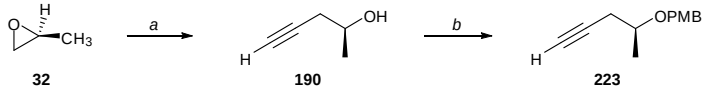


Scheme 74: Retrosynthetic Route to *Seco*-Acid 218.

2.10.2 Synthesis of 2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*S*)-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoic acid, 218

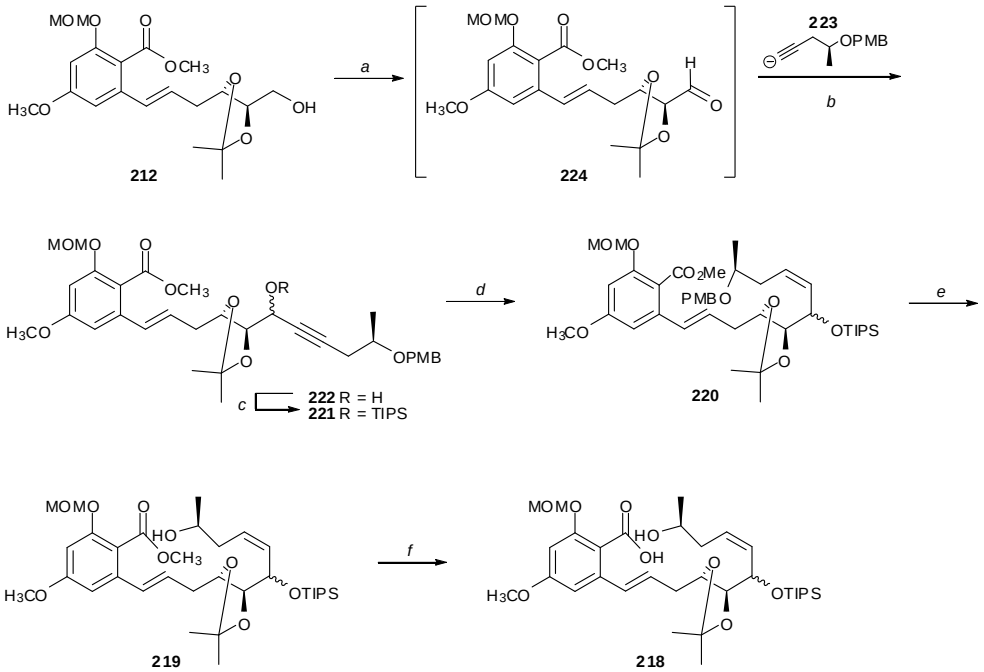
Alcohol **212** was subjected to the same one-pot Swern oxidation-Grignard acetylide coupling as described previously. This time it was decided to use an alternative protecting group for the hydroxyl group of the alkyne unit. The experiences encountered with cleavage of previous TBS groups under regular reaction conditions prompted us to change our strategy with regards to orthogonal protection. It was assumed that the more stable PMB ether would withstand the conditions employed in the three reactions up to its cleavage.

As shown in Scheme 75, lithium acetylide complex was coupled with (*S*)-(+)-propylene oxide to afford alcohol **190**. The crude alcohol was then protected as the PMB ether to afford alkyne **223** in 40% over two steps.



Scheme 75: Synthesis of 1-Methoxy-4-((*S*)-1-methyl-but-3-ynyloxymethyl)-benzene. Reagents and Conditions: (a) lithium acetylide ethylenediamine complex, DMSO, 0 ^{o}C → rt, 48 h, 100%; (b) PMBCl, DMF, 0 ^{o}C → rt, 17 h, 40%.

Alkyne **223** was treated with ethylmagnesium bromide and the resulting anion was added directly to a solution of freshly generated aldehyde **224** in THF. It was pleasing to see that once again the Grignard acetylide had added cleanly to the aldehyde, affording **222** in an acceptable 65% yield, as an inseparable mixture of diastereoisomers (Scheme 76).



Scheme 76: Synthesis of *Seco*-Acid 218. Reagents and Conditions: (a) $(COCl)_2$, DMSO, Et_3N, –78 °C → rt; (b) THF, –78 °C → rt, 14 h, 65%; (c) TIPSCl, imidazole, DMF, rt, 24 h, 83% (based on starting material consumed); (d) H_2, $Pd/BaSO_4$, quinoline, MeOH, rt, 4 h, 85%; (e) DDQ, CH_2Cl_2, pH 7 buffer, rt, 20 h, 79%; (f) 2 N KOH, EtOH, 80 °C, 48 h, 57%.

Having successfully introduced the alkyne unit, a triisopropylsilyl (TIPS) ether was chosen as the protection group for the newly created secondary alcohol **222**. In 1974, Ogilvie and colleagues[104] reported their experiments aimed at selective protection and deprotection of OH groups using the TIPS group. Due to its bulk, the isopropyl units of the TIPS group provide steric screening for the silicon they are attached to (and the atom to which the silicon is connected),[105] but also slow down reactions at silicon compared to TMS or TBDMS groups.

The TIPS ether was expected to remain in place for the duration of our synthesis until its cleavage in readiness for the final oxidation to the ketone. TIPS is more resistant to fluoride than TBS, but can be removed using standard conditions such as TBAF, so we didn't foresee any issues with its removal.[106] Protection of secondary alcohol **222** using TIPSCl and imidazole proceeded slowly as expected

and did not go to completion despite multiple attempts. Fortunately, the transformation was clean and no other products were formed. In 2000, a group published their findings in the efficient and selective protection of alcohols and phenols with TIPSCl/imidazole using microwave irradiation.[105] The method is solventless, so the alcohol **222**, imidazole and TIPSCl were added to a dry reaction vessel and subjected to microwave irradiation. The pattern of irradiation is shown below in Table 1.

Round	*Irradiation Condition*	
	Time (s)	Power (W)
1	15	300
2	15	300
3	30	400
4	40	400
5	90	400

Table 1: Irradiation Conditions for the TIPS Protection of Alcohol 222.

After each irradiation a sample of the reaction mixture was taken and TLC analysis performed. After the second round of irradiation, the desired product was observed (run against an authentic sample), with the reaction having progressed approximately 30%. After round three, the reaction had progressed further but after round four, the situation had changed. The reaction had progressed further still but there were three visible spots by TLC, starting material **222**, product **221** and a previously unseen spot. We continued with round five and it was found that the starting material had still not been consumed, the formation of the unknown had increased and there was no distinct change in the desired product. It was postulated that proceeding with microwave irradiation would have only increased the percentage of the unknown, with no guaranteed consumption of alcohol **222**. With these findings we reverted back to our standard protection conditions.

With the fully protected compound **221** in hand we turned our attention to the selective hydrogenation of the alkyne to generate the *cis*-alkene. Usual

palladium catalysts are so effective in promoting the addition of hydrogen to both triple and carbon-carbon bonds that the alkene intermediate formed by hydrogen addition to an alkyne cannot be isolated. Lindlar's catalyst[107] is a less efficient catalyst and allows the isolation of the intermediate alkene. The addition of hydrogen is *syn* and the alkene formed has the *cis*-configuration. Hydrogenation of alkyne **222** using $Pd/BaSO_4$ poisoned with lead(II) acetate and quinoline under a hydrogen atmosphere generated the *Z*-olefin **220** in variable yields of 77-85%.

Removal of the PMB protecting group, to generate **219**, was successfully achieved using DDQ, in a yield of 77%. However, some problems were encountered and on occasion the reaction did not proceed and it was necessary to work-up the reaction mixture and repeat the procedure. For this reason attempts were made to remove the PMB ether under different conditions.

In 2000, Yu and co-workers reported the chemo- and regio-selective cleavage of the PMB group at low temperature in the presence of tin(IV) chloride and thiophenol.[108] With the authors statement of the reaction being fast and high yielding and with further encouragement from the fact that these conditions had been employed successfully already in our group[109] we proceeded to test the reagents for the removal of the PMB group of **220**. Unfortunately, ^{1}H NMR of the crude residue suggested that the desired product had not been formed and it was not deemed fruitful to continue with any purification. Alternatively, it is well known that CAN (ammonium cerium(IV) nitrate) can be used to oxidatively cleave PMB ethers.[110] The reaction was continuously monitored by TLC and after 20 minutes it was clear that the reaction was progressing cleanly, with the formation of only one new spot. Disappointingly, over the course of 7 hours, additional new spots began to appear and the decision was taken to work-up the reaction without the complete consumption of starting material. It was disappointing to see that after purification, the desired deprotected product **219** was obtained in only 16% yield. The additional spots formed were isolated but found to be unidentifiable by NMR. Consequently, it was decided to continue with the use of DDQ as other PMB removal conditions reported in the literature were deemed unsuitable, based on the functionality present in our substrate.

For our first attempt at saponification of the ester we chose to use 2 N KOH in ethanol[111] and found that the reaction proceeded well over the course of 48 hours under reflux to generate the *seco*-acid **218** in 57% yield. Taking guidance from reports where other groups have used base-catalysed ester saponification on large molecules, the yield gained was comparable and no optimisation attempts were performed.

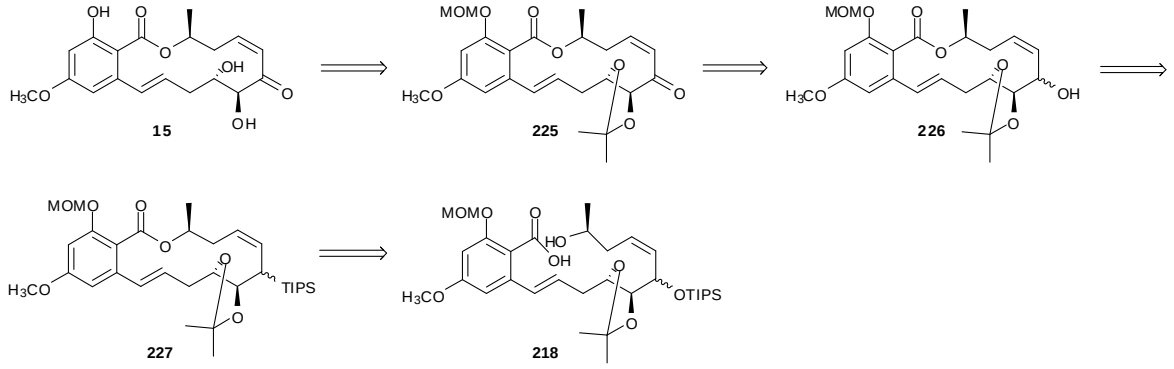
2.11 Completion of the Synthesis

With a robust and reliable synthesis to *seco*-acid **218** established and subjected successfully to scale-up, we could now proceed with the key macrolactonisation step. The construction of macrocyclic structures is a recurrent and testing problem in synthesis. Macrocyclic systems can be generated by cyclisation of open, long chain precursors, but the ring closure is disfavoured entropically, due to loss of entropy associated with the formation of the usually more rigid, cyclic structure. There are two methods which are frequently used for macrolactonisation, acid activation and alcohol activation. Studies carried out by Illuminati and colleagues[112] and Stoll and colleagues[113] showed that for successful ring formation there are two types of energy to take into account, the enthalpy and entropy. For medium ring formation entropy<enthalpy and for large ring formation entropy>enthalpy. The most difficult ring size to form is *n* = 8-11.

Over time, new synthetic methods have been developed which readily allow the formation of macrolides. The methods that appeal most in respect to our synthesis are discussed accordingly.

2.11.1 Retrosynthetic Analysis for the Final Steps to LL-Z1640-2

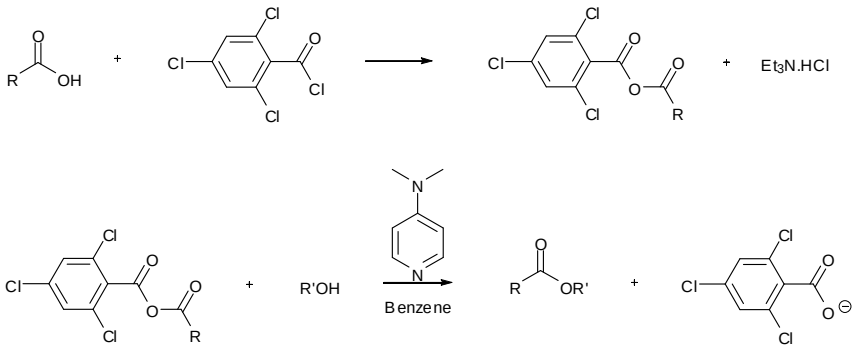
As demonstrated in Scheme 77, the final step to the natural product LL-Z1640-2 is achieved through global deprotection. The protected compound **225** is a direct result of oxidation of the secondary alcohol **226**, itself formed from the deprotection of the TIPS ether. Compound **227** is the product of the macrolactonisation.



Scheme 77: Retrosynthetic Analysis to LL-Z1640-2 from *Seco*-Acid 218.

2.11.2 Towards the Total Synthesis of LL-Z1640-2

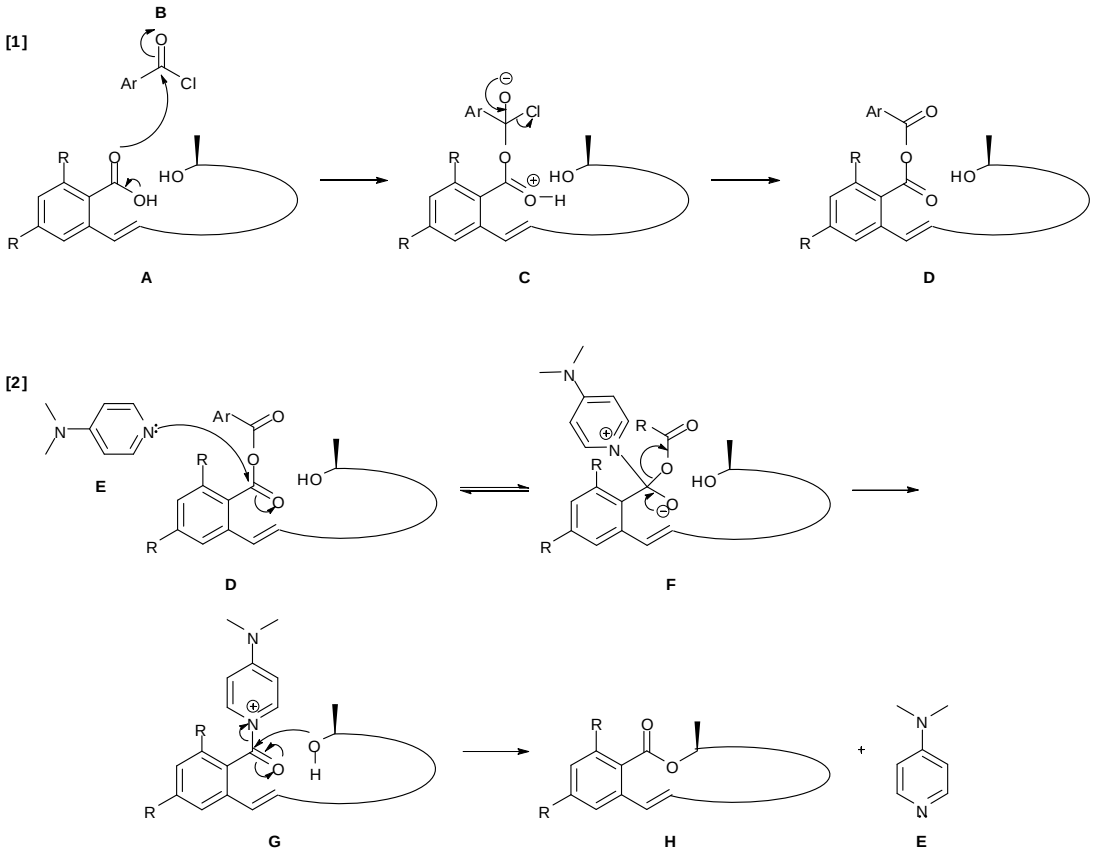
The first attempt at forming macrocycle **227** was made using the well known Yamaguchi esterification.[114] The Yamaguchi esterification allows the synthesis of highly functionalised esters and lactones *via* the alcoholysis of the corresponding mixed anhydrides. The conditions are mild, making it compatible with compounds which may have sensitive functionalities. The high catalytic activity of DMAP in acyl transfer reactions attracted the attention of the authors and they used it in esterifications with mixed anhydrides to investigate the synthesis of macrocyclic lactones. They found that 2,4,6-trichlorobenzoyl chloride and DMAP under high dilution was the best combination to give a high reaction rate and yield.



Scheme 78: General Formula for the Yamaguchi Esterification.

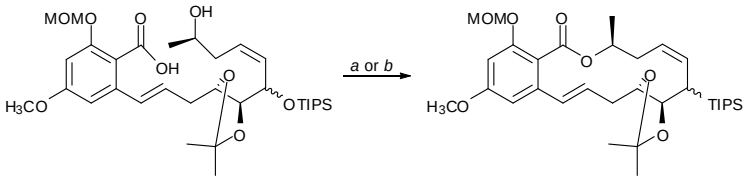
Yamaguchi took an acid sensitive *seco*-acid and treated it with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine, removing the triethylamine hydrochloride by-product. The mixed anhydride was diluted with

toluene and slowly added to a refluxing solution of DMAP in toluene *via* syringe pump in high dilution (0.002 M). The macrolactone was seen to form with no decomposition product. The mechanism for forming a macrolactone is shown in Scheme 79, using simplified models to demonstrate the order of events. The first step (Equation [1]) is the addition of the carboxylate **A** to the carboxylic acid chloride **B**, forming the tetrahedral intermediate **C**, which on addition of triethylamine eliminates triethylamine hydrochloride to form the mixed anhydride **D**. In Equation [2], DMAP **E** attacks at the least hindered carbonyl site of **D**. As it is a stronger nucleophile than the alcohol, the newly formed intermediate is less hindered and DMAP **E** leaves, generating the product **H**.



Scheme 79: General Mechanism of the Yamaguchi Macrolactonisation.

With the success experienced by other groups in utilising the Yamaguchi protocol for forming macrolactones,[115] we were confident that this procedure would be more than suitable for use with our *seco*-acid. Treatment of *seco*-acid **218** under standard Yamaguchi conditions afforded the desired macrolactone **227** in 37% yield (Scheme 80). This was an excellent result for a first attempt and for a reaction performed on a test scale.



218 **227**

Scheme 80: Yamaguchi Macrolactonisation of 218. Reagents and Conditions: (a) Trichlorobenzoyl chloride, Et_3N, rt, 2 h *then* DMAP, toluene, reflux, 6 h, 37%; (b) MNBA, DMAP, 4Å MS, toluene, rt, 6 h, 28%.

In an attempt to increase the macrolactonisation yield, we explored the use of MNBA. 2-Methyl-6-nitrobenzoic anhydride (MNBA, Figure 22) is an effective condensation reagent for the DMAP promoted lactonisation of ω-hydroxycarboxylic acids, as reported by Shiina and co-workers.[116] The reagents can produce comparable yields to the Yamaguchi conditions[117] but the experimental procedure is far simpler. Unfortunately, cyclisation of *seco*-acid **218** to **227** could only be achieved in 28% yield using MNBA (Scheme 80).

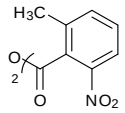
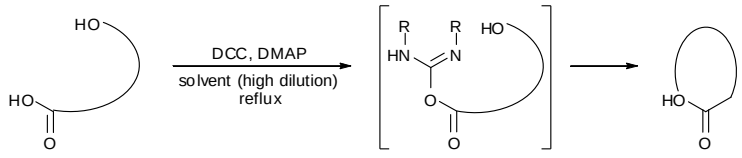


Figure 22: Structure of MNBA.

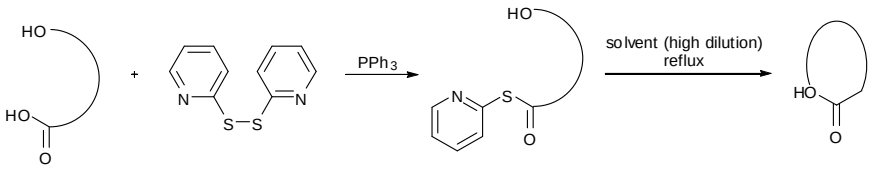
There are other potential methods that would allow the macrolactonisation of *seco*-acid **218**. The Keck coupling[118a] uses a combination of a dialkyl carbodiimide, an amine hydrochloride and an amine base under high dilution to form the activated ester intermediate which then macrolactonises, generating *N, N'*-dialkyurea as a by-product.



Scheme 81: General Formula for the Keck Macrolactonisation.

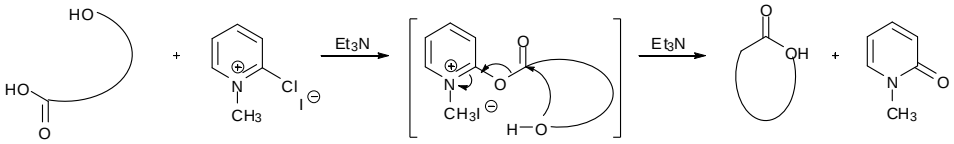
Another alternative is the Corey-Nicolaou macrolactonisation. [118b] This is a double activation method which forms the lactone from its *seco*-acid *via* 2-pyridinethiol esters. The reaction occurs under neutral and aprotic conditions

and under high dilution to keep the undesired intermolecular ester formation low (Scheme 82).



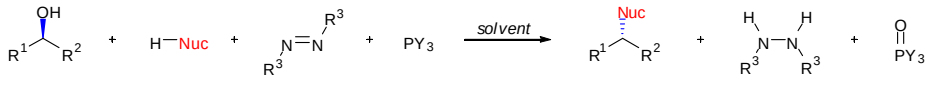
Scheme 82: General Formula for the Corey-Nicolaou Macrolactonisation.

Mukaiyama's lactonisation conditions[37] (Scheme 83) were employed by Tatsuta and colleagues[36] in the final stages of their total synthesis of LL-Z1640-2 to generate the lactone from the *seco*-acid (Chapter 1, Scheme 7). 1-Methyl-2-chloropyridinium iodide (4 eq.) in anhydrous acetonitrile is stirred and a solution of *seco*-acid and triethylamine (8 eq.) in acetonitrile added over 8 hours under high dilution.



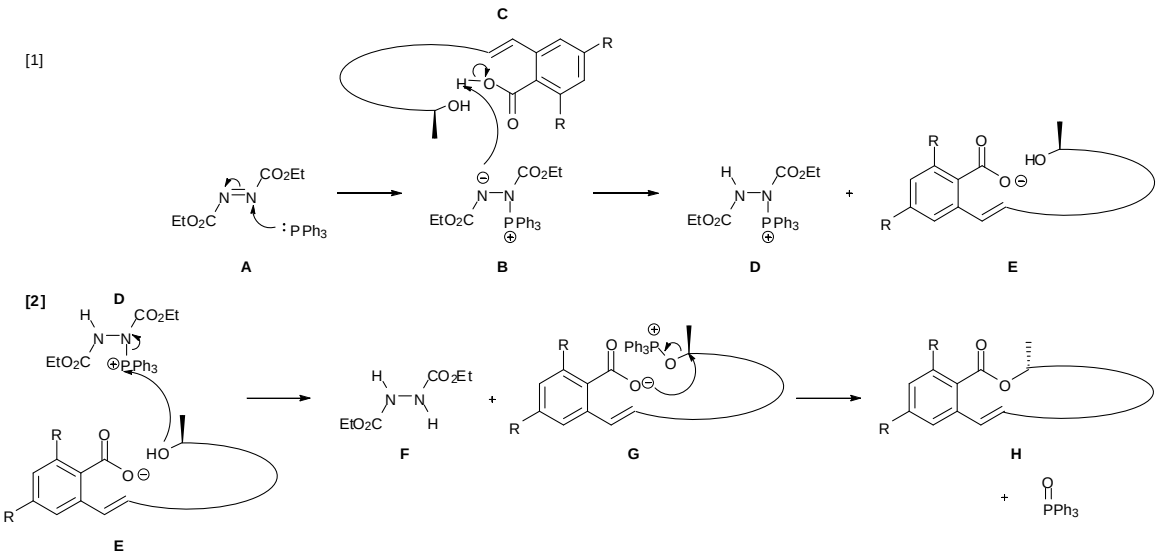
Scheme 83: General Formula for the Mukaiyama Macrolactonisation.

The Mitsunobu reaction is a versatile and effective reaction used extensively in organic synthesis (Scheme 84). It was reported in 1967[44] that secondary alcohols could be acylated with carboxylic acid in the presence of DEAD and triphenylphosphine and later that optically active secondary alcohols underwent complete inversion of configuration under the conditions. Currently, the Mitsunobu reaction is widely known and described as the substitution of primary and secondary alcohols with nucleophiles in the presence of a dialkyl azodicarboxylate and a trialkylphosphine.



Scheme 84: General Scheme for the Mitsunobu Reaction.

The first step of the assumed mechanism for the lactonisation is the irreversible addition of triphenylphosphine to DEAD (Scheme 85, Equation [1], **A**). The phosphine adds to the weak N=N π bond to give an anion stabilised by one of the ester groups. The zwitterionic adduct **B** formed is basic enough to then be able to abstract a proton from the carboxylic acid of hydroxy acid **C**, which substitutes as the strong nucleophile, to form products **D** and **E**.

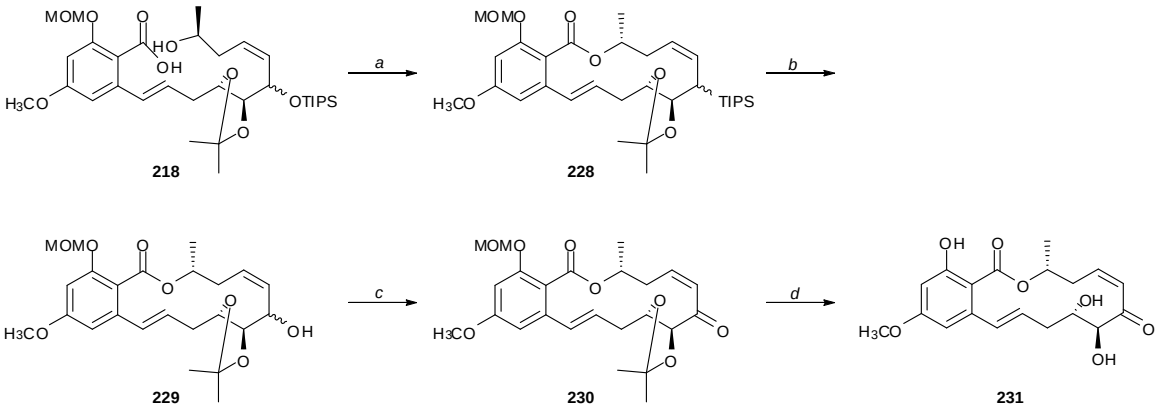


Scheme 85: General Mechanism of Macrolactonisation *via* a Mitsunobu Reaction.

Oxygen and phosphorus have a strong affinity and so the alcohol of **E** immediately attacks the positively charged phosphorus atom of **D** (Scheme 85, Equation [2]). The anion of the nucleophile attacks the phosphorus derivative of the alcohol **G** in a normal S_N2 reaction at carbon, with phosphine oxide as the leaving group. This furnishes the lactone product **H** with inversion of the methyl group and phosphine oxide as the side-product.

Sellès and Lett[41] used a Mitsunobu reaction to carry out the macrolactonisation of their hydroxy acid. At room temperature at 0.007 M the desired macrolide was obtained in a good yield of 67%. Importantly there was complete inversion of configuration at $C_{10'}$, with no change of configuration at $C_{6'}$ (MPM protected in their case). The simple experimental procedure associated with the Mitsunobu reaction makes it attractive and it was considered useful to attempt the reaction with our hydroxy acid to test the procedure in our hands. Treatment of *seco*-acid **218** under Mitsunobu conditions afforded the desired macrolide **228** in

71% yield (Scheme 86). Despite being run on a small scale there was enough material to progress with and test the following transformations.

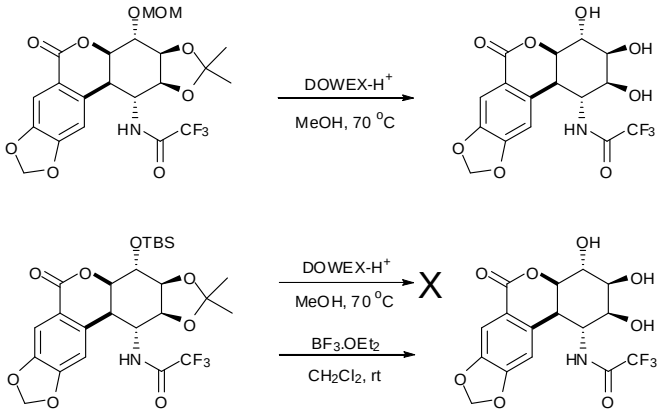


Scheme 86: Final Steps to LL-Z1640-2. Reagents and Conditions: (a) DEAD, PPh_3, toluene, 0 $^oC \rightarrow$ rt, 30 min, 71%; (b) TBAF, THF, 0 $^oC \rightarrow$ rt, 1.25 h, 100%; (c) PCC, CH_2Cl_2, rt, 3.5 h, 20%; (d) 1 N HCl, MeOH, rt, 46 h.

Removal of the TIPS ether was undertaken with TBAF, cleanly generating secondary alcohol **229** in quantitative yield. Due to the small scale and from the relatively clean ^1H NMR spectrum, it was decided not to proceed with any purification and the crude product was carried directly to the next step. Turning our attention to the oxidation of the secondary alcohol **229**, we chose to firstly attempt the reaction using pyridinium chlorochromate (PCC). Chromium (IV) reagents are conveniently used to oxidise alcohols to their corresponding aldehydes or ketones. They are convenient to use as they are soluble in dry organic solvents, usually dichloromethane for PCC, under anhydrous conditions. Alcohol **229** was treated with PCC and careful TLC analysis mapped the reaction, showing it to be progressing well over time, with the disappearance of the starting material and the gradual appearance of ketone **230**. Following purification, ketone **230** was isolated in 20% yield. Regrettably, the lack of material prevented the acquisition of a full data set to absolutely confirm the product.

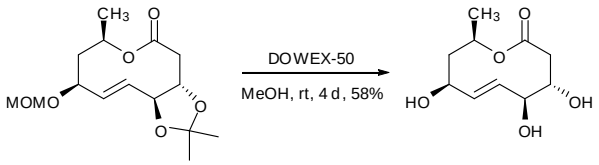
It was envisaged from the beginning that the MOM ether and acetonide protecting groups could be cleaved simultaneously under mild acidic conditions, with literature precedent reinforcing this theory. Keck and co-workers[120] have reported using DOWEX-H^+ resin in methanol at 70 ^oC to remove MOM and acetonide groups. Though they had experienced success previously, they found

that in the reported case the conditions did not achieve the deprotection, even under higher temperatures and longer reaction times. They went on to find that $BF_3 \cdot OEt_2$ in CH_2Cl_2 was effective at removing both groups (Scheme 87).



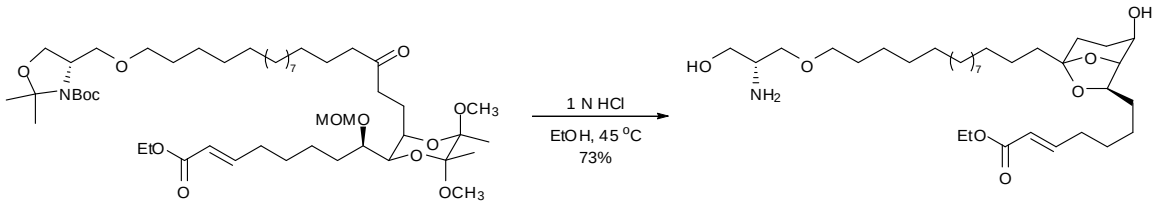
Scheme 87: Keck's Removal of Acetonide and MOM Protection Using DOWEX-H$^+$.

Andrus and Shih[121] also reported their use of DOWEX resin in methanol, but at room temperature, to achieve the one step removal of both groups (Scheme 88).



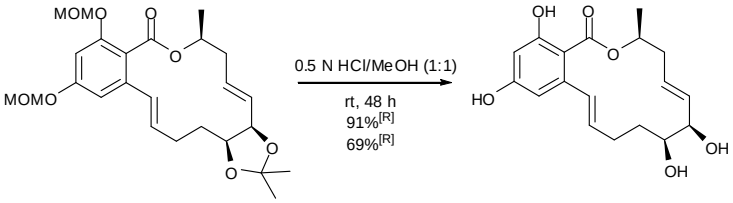
Scheme 88: Andrus and Shih's Removal of Acetonide and MOM Protection Using DOWEX-50.

In 2002, Kiyota, Ley and co-workers[122] reported, as part of their efforts to the synthesis, structure revision and absolute configuration of (+)-didemniserinolipid B, the simultaneous removal of the acetonide, BDA, Boc and MOM protecting groups. This was accomplished in one step using 1 N HCl in ethanol at 45 ºC to obtain the fully deprotected target compound (Scheme 89).



Scheme 89: Kiyota and Ley's Simultaneous Removal of Acetonide, BDA, Boc and MOM Protection Using 1 N HCl.

In his total synthesis of aigialomycin D, Danishefsky successfully performed the final global acidic deprotection (two MOM functions and an acetonide) using 0.5 N HCl in methanol.[76] Vu also used HCl in methanol for global deprotection of the same compound, in his approach to the natural product.[100] The reaction was slow and extended into days for completion, but ultimately was successful with Danishefsky reporting a yield in excess of 90% (Scheme 90).



Scheme 90: Generation of Aigialomycin D *via* Global Acidic Deprotection.

For our first attempt at the global deprotection of **230**, we chose the milder conditions of 1 N HCl in methanol at room temperature. Acutely aware of the long reaction time that may be required for the completion of the deprotection, it was thought responsible to start out with the mildest conditions, which may allow us to see clearly the deprotection proceeding by TLC. It also gave us the option of heating the reaction to accelerate a slow rate. Over the course of 46 hours, careful TLC analysis showed disappearance of the protected compound **230** and appearance of two new spots. It was presumed that cleavage of one protecting group was occurring faster than the other. Unfortunately, the small scale of the reaction and the lack of material prevented us from performing FCC to isolate each spot and hence determine the structure of the compound corresponding to each spot. Likewise, the lack of material prevented the acquisition of adequate NMR spectra for analysis.

It goes without saying that for a total synthesis to a natural product to be as successful as possible, as many methods as possible affording the best reliability and yields need to incorporated. With this in mind and taking into account the outcome of the Mitsunobu reaction, it naturally prompted us to seriously review our strategy as it became clear that a minor change in our already established synthesis could enable the very successful Mitsunobu reaction to be integrated into the route to LL-Z1640-2. Although we were able to generate the required product with the correct stereochemistry at $C_{10'}$, *via* the Yamaguchi protocol in

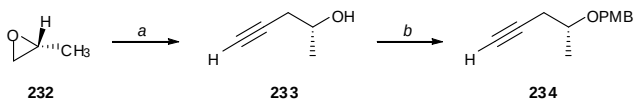
acceptable yield and later *via* a procedure using MNBA in lower yield, we were disappointed that our pivotal step was not as fruitful as first hoped. The Mitsunobu protocol has several distinct advantages over other macrolactonisation methods:

1. Fast reaction time
2. Simple procedure
3. High dilution
4. High yield
5. Clean conversion
6. No side-products
7. Complete inversion of stereochemistry

2.12 Final Synthetic Route to LL-Z1640-2

The stereochemistry at $C_{10'}$ is introduced as a direct result of the one pot Swern oxidation-Grignard acetylide addition of alkyne **223**. The Mitsunobu reaction later in the synthesis then serves to completely invert the stereochemistry of the methyl group at $C_{10'}$. Quite reasonably, if the stereochemistry of **223** was changed from *S* to *R*, then the already proven higher yielding Mitsunobu lactonisation would not only generate the macrolide, but in doing so would simultaneously invert the stereochemistry to afford the desired *S*-configuration. TIPS ether cleavage, oxidation and global deprotection would complete the total synthesis of LL-Z1640-2.

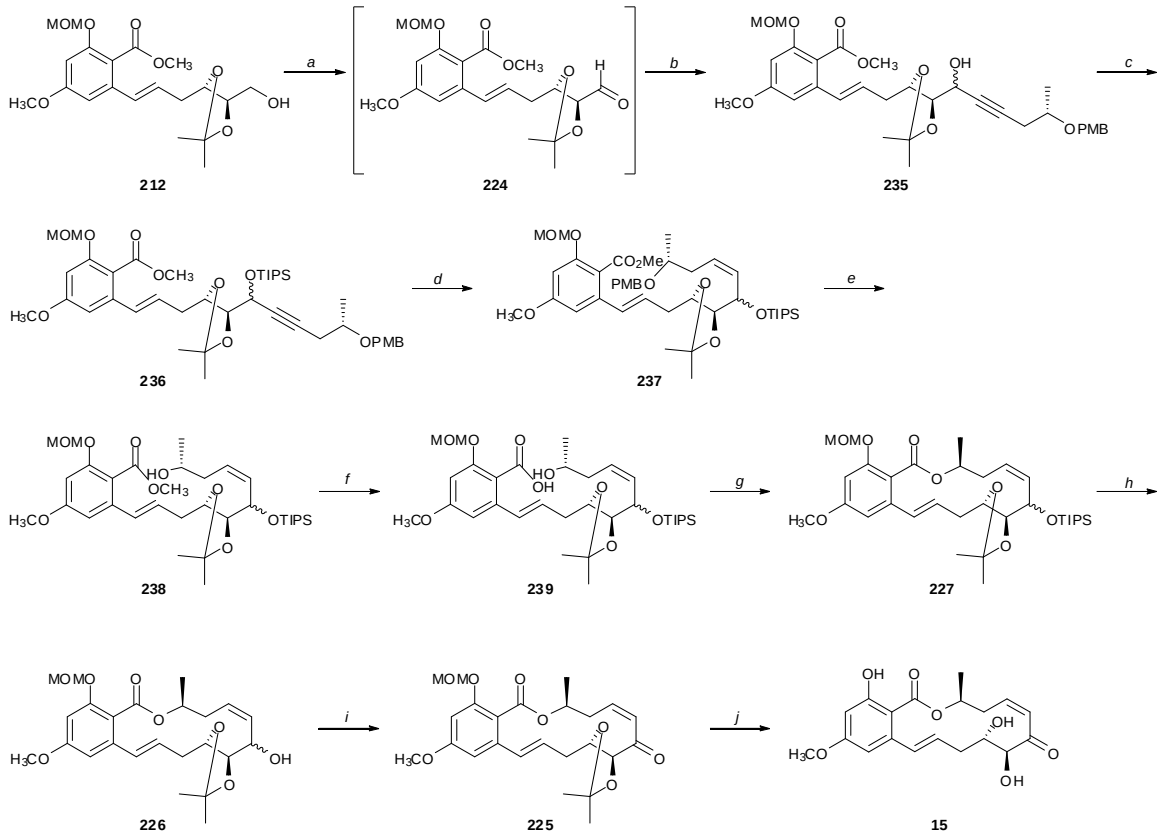
The synthesis of the *seco*-acid epimer **239** began with lithium acetylide ethylenediamine, which was treated with *(R)*-(+)-propylene oxide **232** to afford the crude alcohol **233** (Scheme 91). The crude alcohol was then immediately protected to generate terminal alkyne **234** in 40% over two steps. We chose to continue with the PMB protecting group due to its proven stability throughout the remainder of the synthesis and its relative ease of cleavage.



232 **233** **234**

Scheme 91: Synthesis of 1-Methoxy-4-((*R*)-1-methyl-but-3-ynyloxymethyl)-benzene. Reagents and conditions: (a) lithium acetylide ethylenediamine complex, DMSO, 0 °C → rt, 48 h; (b) NaH (60% in mineral oil), PMBCl, DMF, 0 °C → rt, 17 h, 40% *(over 2 steps)*.

Alkyne **234** was deprotonated with ethylmagnesium bromide and the resulting anion was added directly to a solution of freshly generated aldehyde (**212**→**224**) at −78 °C. Pleasingly, the Grignard acetylide added cleanly to the aldehyde, affording propargylic alcohol **235** in 75% yield, an increase of 10% from the previous addition. Similarly, the product was an inseparable mixture of diastereoisomers (Scheme 92). A TIPS ether was again used as the protecting group for the newly formed secondary alcohol as it had proven to be stable to later conditions and was easily removed using TBAF. Protection of alcohol **235** using TIPSCl and imidazole proceeded slowly like before and did not go to completion despite multiple attempts and a "recycling" procedure was employed. With the fully protected compound **236** in hand, selective hydrogenation was performed to generate the *Z*-olefin **237** in an excellent 89% yield. Removal of the PMB protecting group with DDQ in CH_2Cl_2 and pH 7 buffer at room temperature afforded alcohol **238** in 87% yield, which was a much more acceptable yield than the 77% gained previously. Saponification of the ester was again achieved using 2 N KOH in ethanol and after 48 hours under reflux, *seco*-acid **239** was generated in 61% yield.



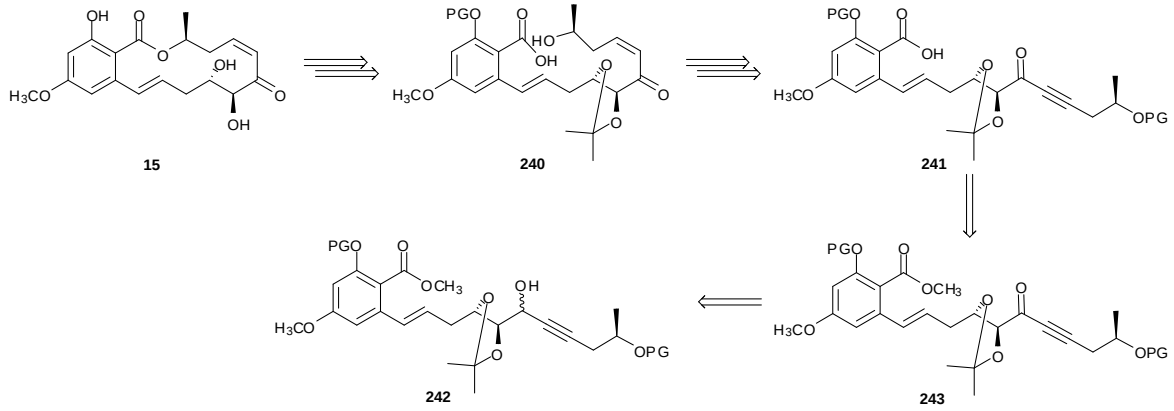
Scheme 92: Final Synthesis to LL-Z1640-2. Reagents and Conditions: (a) $(COCl)_2$, DMSO, Et_3N, –78 °C → rt; (b) **234**, THF, –78 °C → rt, 16 h, 75%; (c) TIPSCl, imidazole, DMF, rt, 19 h, 80%; (d) H_2, $Pd/BaSO_4$, quinoline, MeOH, rt, 2 h, 89%; (e) DDQ, CH_2Cl_2, pH 7 buffer, rt, 18 h, 87%; (f) 2 N KOH, EtOH, 80 °C, 48 h, 61%; (g) DEAD, PPh_3, toluene, 0 °C → rt, 10 min, 73%; (h) TBAF, THF, 0 °C → rt, 1 h; (i) PCC, CH_2Cl_2, rt, 18 h, 34%; (j) 1 N HCl, MeOH, rt, 5 d.

Mitsunobu macrolactonisation of *seco*-acid **239** afforded the macrocyclic lactone **227** in 73% yield. Cleavage of the TIPS ether was undertaken using TBAF to unmask the secondary alcohol **226**, which was used without further purification. Oxidation of **226** with PCC generated lactone **225** in 34% yield, but once again the small quantities of material obtained prevented the attainment of a complete data set. This extreme lack of material meant that treatment of lactone **225** with 1 N HCl was not fruitful. It could be seen by TLC that a reaction was occurring, with two new spots forming like before, but the reaction did not go to completion. ^{1}H NMR was not able to clarify if any of the globally deprotected product **15** had formed. Due to time constraints we were unable to synthesise more compound **225** and had to relinquish the opportunity to test the global deprotection further.

2.13 Further Investigation and Additional Studies

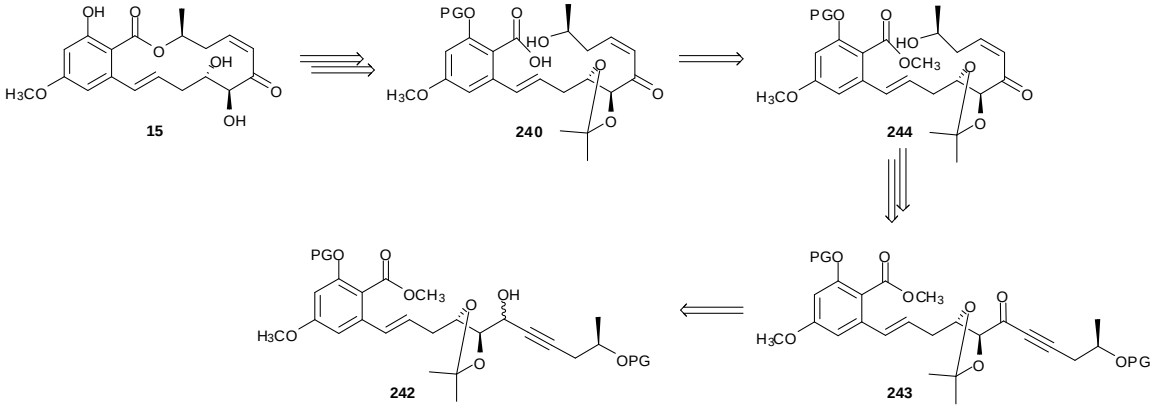
2.13.1 Alternative Retrosyntheses to LL-Z1640-2

As an alternative retrosynthesis to that shown in Scheme 74, we hypothesised that following the one-pot oxidation-alkyne coupling, the free hydroxyl of **242** could be oxidised readily to ketone **243**. This could be followed by saponification of the ester to afford acid **241** (Scheme 93). The reduction of the alkyne and removal of the PMB ether would afford the *seco*-acid **240**, which after macrolactonisation would yield the desired macrocycle with the lactone already in place. All that would remain would be removal of the MOM ether and acetonide protection groups, achievable in one step. The only concern was regarding whether the saponification would proceed in the presence of the ketone as deprotonation may occur at the position α to the ketone.



Scheme 93: First Possible Route.

In the second possible route (Scheme 94) it was envisaged that the free hydroxyl of **242** could be oxidised readily to the ketone **243**, after which the proceeding transformations would take place, culminating in the saponification of the ester to the carboxylic acid **240**. This *seco*-acid would then undergo macrolactonisation and the enone would already be in place.



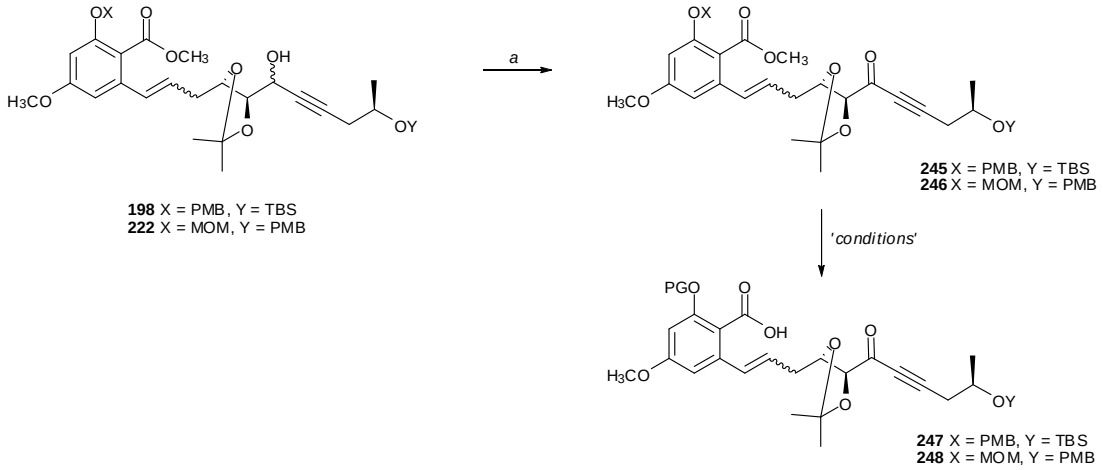
Scheme 94: Second Possible Route.

Both methods described above are advantageous. The benefits of oxidising the alcohol at position $C_{6'}$ earlier on in the synthesis, include the loss of a stereocentre and simplification of the NMR spectra.

The final option is the direct saponification of secondary alcohol **242**. There were concerns about this method in the guise of whether the secondary alcohol could be oxidised in the presence of a carboxylic acid. There was also some apprehension regarding the possibility of spontaneous cyclisation of the alcohol moiety onto the acid functionality.

2.13.2 Practical Studies

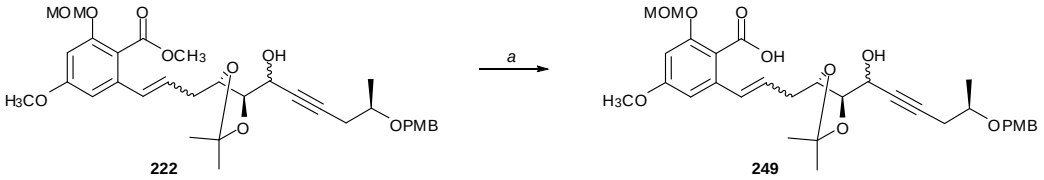
Oxidation of secondary alcohol **198** or **222** to ketone **245** or **246** respectively, proceeded smoothly and quantitatively under Swern oxidation conditions, with no need for any purification following work-up (Scheme 95). In the ^{1}H and ^{13}C NMR spectra both showed clearly the disappearance of the alcohol and the newly formed carbonyl function of the ketone. Ester hydrolysis was then attempted.



Scheme 95: Oxidation then Saponification Method. Reagents and Conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 2 h, –78 °C → rt, quant..

Alkali metal trimethylsilanolates ($TMSO^-M^+$) have been used widely for the efficient conversion of methyl esters to their acid salts under mild, non-aqueous conditions. In comparison with other oxygen anions they are advantageous in that they have good solubility in organic solvents, such as dichloromethane and diethyl ether. Encouraged by this and also the work published by Still and co-workers[123] which shows the hydrolysis of esters using TMSOK. Unfortunately the saponification of ketone **245** was unsuccessful under TMSOK conditions. A characteristic colour change was observed on addition of TMSOK, but after prolonged stirring at room temperature no product **247** was witnessed. This was confirmed after work-up when ^1H NMR analysis still showed the clear presence of the methyl ester signal at 3.87 ppm. Treatment of ester **246** under basic hydrolysis conditions (aq. KOH) also failed to hydrolyse the group to form **248**. Despite this, it was pleasing to see that the TBS ether was unaffected by both sets of conditions and remained in place throughout.

We tested whether the ester functionality of the newly generated secondary alcohol **222** can be directly saponified to allow the acid to be in place throughout the future transformations (Scheme 96). Even after 48 hours under reflux there was no reaction observed, likewise there was no appearance of spontaneous cyclisation or side reactions and the unreacted starting material was recovered.



Scheme 96: Direct Saponification of 222. Reagents and Conditions: (a) 2 N KOH, EtOH, 82 ^{0}C, 48 h.

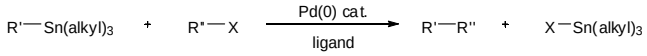
During the studies described thus far we have simultaneously been considering and reviewing each step of the synthesis in order to determine whether it could be improved upon. The routes to aromatic fragment **210** and alkene **208** are well established and robust and although the cross-metathesis step between the two is successful, there are disadvantages associated with it:

- Long reaction time, 48 hours
- Difficult and time consuming purification requiring two successive flash column chromatography steps
- High catalyst loading
- High cost of catalyst

It has been found when repeating the reaction that the yields were not consistent and so this step was identified as holding potential for improvement. We did not wish to deviate from our original synthesis too much, so bearing this in mind we envisaged a Stille coupling between tin derivative **250** and aromatic unit **257**. The tin derivative is easily prepared in four steps from alkene **208**, which has already been efficiently made. A version of the aromatic fragment has already been made and only simple deviation from the original route is necessary.

2.13.3 Stille Coupling

The Stille reaction is one of the most influential synthetic tools in organic chemistry. First reported in 1978,[124] the Stille coupling is the coupling between an organostannane and an organic electrophile to form a new C—C sigma bond and has been widely used for the palladium(0)-catalysed coupling of both aromatic and vinylic units (Scheme 97).



Scheme 97: General Formula of the Stille Coupling.

There are numerous advantages associated with the Stille coupling including the mild conditions and the fact that the precursor organotin compounds tolerate a wide variety of functional groups and are not sensitive to moisture or oxygen. On the other hand there is a distinct disadvantage due to their toxicity and the difficulty in removing all traces of tin from the reaction mixture and also the major side reaction of homocoupling of the organostannane reagent.

The detailed mechanism is still prone to discussion but the basic catalytic cycle (Figure 23) was proposed in 1979.[125] Oxidative addition of the vinyl/aromatic triflate/halide gives a palladium(II) intermediate, which undergoes transmetallation with the prepared organostannane. This gives an organopalladium intermediate which then undergoes a reductive elimination step, releasing the product and palladium(0) catalyst.

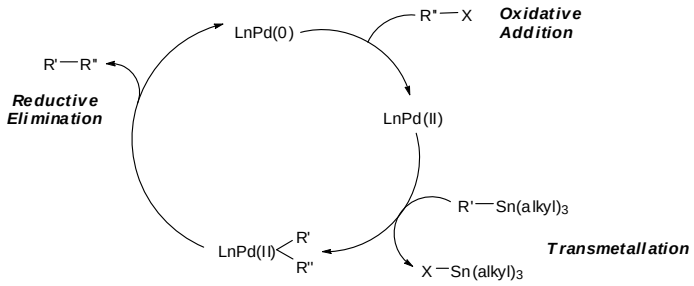
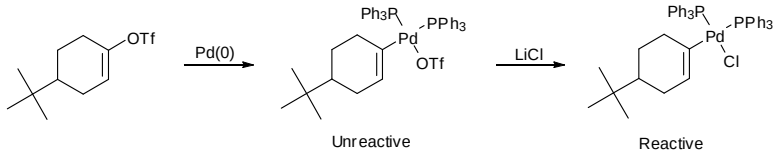


Figure 23: Catalytic Cycle for the Stille Coupling.

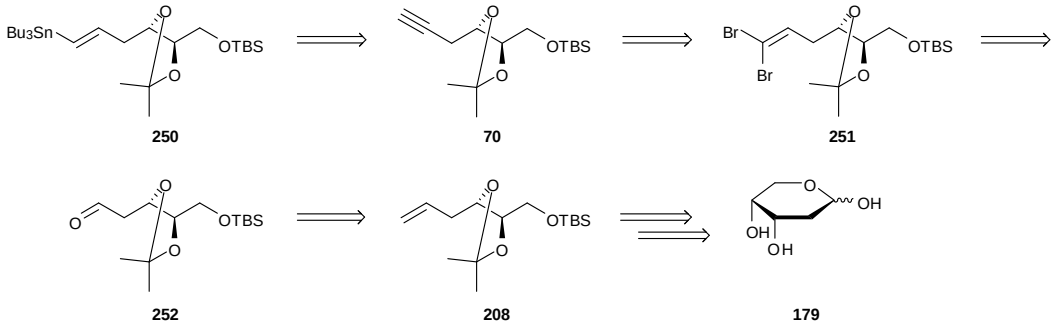
Triflates are often used due to their ease of preparation, but typically lithium chloride is added to the reaction mixture because the triflate is a counter ion and is not bound to the metal as a ligand (Scheme 98). If transmetallation is to occur another ligand must be added to give the necessary square coplanar geometry. The catalyst is a 14 e^-, Pd(0) complex and those used commonly are $Pd(PPh_3)_4$, $Pd(dba)_2$ and Pd(II) catalysts such as $Pd(OAc)_2$, $PdCl_2(MeCN)_2$ and $PdCl_2(PPh_3)_2$ can also be used as precursors.



Scheme 98: Stille Couplings with Triflates require the addition of LiCl.[119]

2.13.4 Retrosynthetic Analysis to *tert*-Butyl-[(4*R*,5*S*)-2,2-dimethyl-5-((*E*)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane, 250

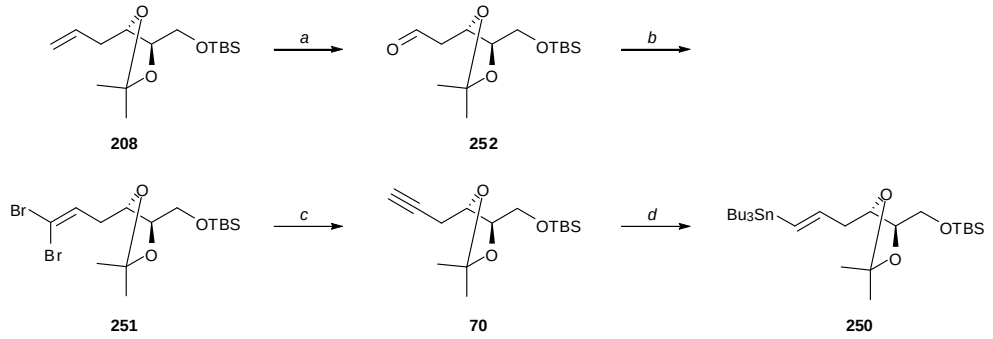
As demonstrated in Scheme 99, it was hypothesised that vinylstannane could come from hydrostannylation of alkyne **70** which is the product of a Corey-Fuchs procedure from aldehyde **252** via dibromoolefin **251**. Aldehyde **252** is the direct result of ozonolysis of alkene **208**.



Scheme 99: Retrosynthetic Analysis of tributylstannane 250.

2.13.5 Synthesis of *tert*-Butyl-[(4*R*,5*S*)-2,2-dimethyl-5-((*E*)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane, 250

As discussed previously, silyl-protected alkene **208** can be made readily in three steps from 2-deoxy-D-ribose **179**. Continuation of the synthesis from alkene **208** is shown in Scheme 100.



Scheme 100: Synthesis of tributylstannane 250. Reagents and Conditions: (a) O_3, CH_2Cl_2, –78 °C, 15 min *then* DMS, –78 °C → rt, h, 100%; (b) CBr_4, PPh_3, Zn dust, CH_2Cl_2, rt, 1.5 h, 100%; (c) *n*BuLi, THF, –78 °C, 2 h *then* H_2O, –78 °C → 0 °C–rt, 61%; (d) $PdCl_2(PPh_3)_2$), Bu_3SnH, THF, 30 min, rt, 79%.

The first step following formation of the alkene is the formation of the aldehyde unit **252**. A classic method of transforming terminal olefins to aldehydes is through ozonolysis. Ozonolysis is a 1,3-diolar cycloaddition, which cleaves π bonds oxidatively so two carbonyl groups are formed. The procedure uses ozone which is a symmetrical molecule with a positively charged oxygen and two terminal oxygen atoms which share a negative charge (Figure 24).

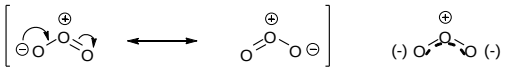
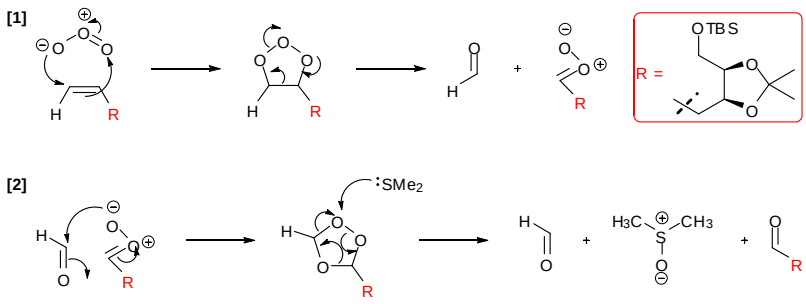


Figure 24: Structure of Ozone.

Mechanistically, the first step involves a 1,3-dipolar cycloaddition to generate molozonide. The unstable molozonide decomposes instantly by a reverse 1,3-dipolar cycloaddition (Scheme 101, Equation [1]). The newly formed 1,3-dipole adds to the aldehyde in a second cycloaddition step to generate an ozonide. Dimethylsulfide is typically used to reduce the ozonide to give DMSO and two molecules of aldehyde (Scheme 101, Equation [2]).



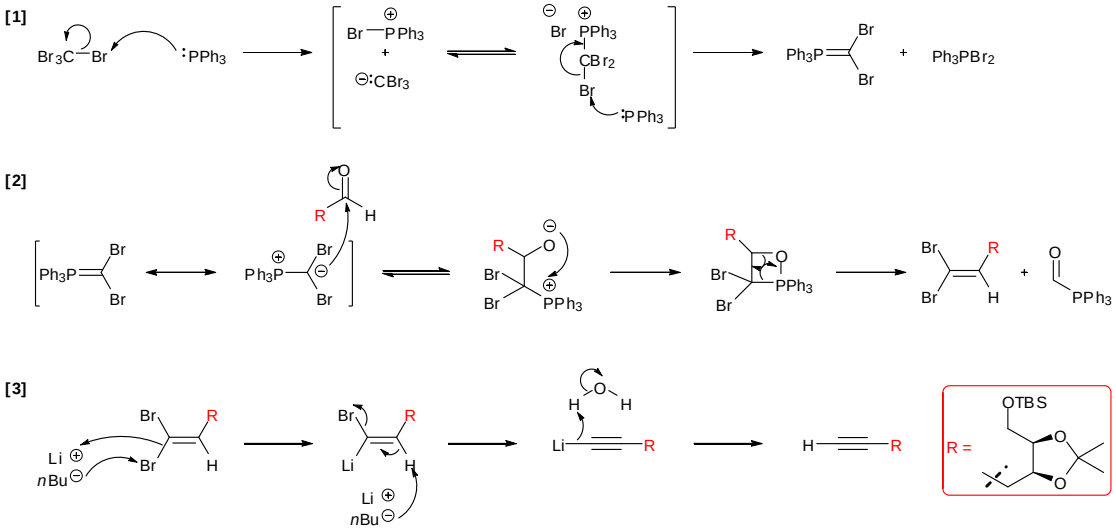
Scheme 101: Mechanism of Ozonolysis.

Ozonolysis of alkene **208** gave the desired aldehyde **252** with no need for purification, based on ^{1}H analysis of the crude material. The ozonolysis has been carried out on both milligram and multigram scales, with the unstable ozonide quenched with dimethylsulfide. This was a lengthy process and required a high excess of DMS (approximately 450-500 equivalents), added periodically over a prolonged period (typically 3-5 days), in order for complete conversion to the aldehyde. With aldehyde **252** in hand the next step was the transformation into terminal alkyne **70**, utilising the well-known and reliable Corey–Fuchs reaction.[126]

The Corey-Fuchs conversion of an aldehyde into a terminal alkyne calls for two steps, initial generation of the dibromoolefin and the sequential elimination of HBr and reduction of the bromoalkyne. The first step can be achieved in two possible ways: (1) the aldehyde is added to a mixture of PPh_3 and CBr_4 in CH_2Cl_2 at 0 ^oC; (2) zinc dust, PPh_3 and CBr_4 are mixed together in CH_2Cl_2 at ambient temperature and then the aldehyde is added to this mixture. This first step is comparable to the Wittig reaction and yields are generally high (80-90%).

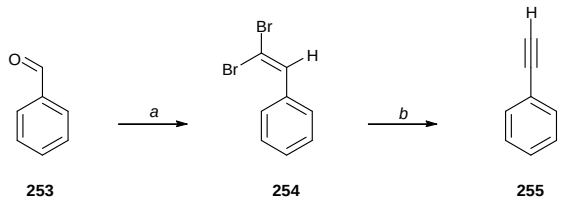
The second step of the procedure is the conversion of the dibromoolefin to the terminal alkyne which is achieved by treatment with *n*BuLi in THF at −78 ^oC to promote lithium-halogen exchange. This firstly rapidly forms the lithio derivative of the alkyne (lithium acetylide) which upon protonation produces the desired terminal alkyne.

Scheme 102, Equation [1] shows the first steps of the mechanism in which the phosphorus ylide is generated and then Equation [2] shows reaction of this ylide with the aldehyde in a manner analogous to the Wittig reaction. The mechanism for the conversion of the dibromoolefin to the alkyne is for the most part unknown but is thought to proceed as shown in Equation [3]. The sequential attack of two equivalents of *n*BuLi forms the lithium acetylide which after hydrolysis generates the terminal alkyne.



Scheme 102: Mechanism of the Corey-Fuchs Reaction.

To begin with, an aldehyde model system was used to test and establish the conditions required for formation of the alkyne. Gratifyingly, the Corey-Fuchs reaction of the model system **253** proceeded cleanly to generate alkyne **255**, *via* the dibromoolefin **254** (Scheme 103).[127]



Scheme 103: Test Corey-Fuchs Reaction. Reagents and Conditions: (a) PPh_3, CBr_4, CH_2Cl_2, 20 h, 0 °C → rt, 98%; (b) *n*BuLi, –78 °C → rt, 2 h *then* H_2O, rt, 1 h, 85%.

Unfortunately, under the same conditions, aldehyde **252** proved slightly more troublesome than expected and required a little optimisation. However, treatment of aldehyde **252** under the zinc-mediated olefination conditions[128] afforded the dibromoolefin **251** in quantitative yield. The newly generated dibromoolefin was treated with *n*BuLi to generate alkyne **70** in 61% yield after purification. It is worth mentioning that column purification is not required in every instance. The decision on whether to perform FCC was taken after viewing the ^{1}H NMR spectrum of the crude residue.

2.13.6 Hydrostannylation

Organostannanes are of tremendous synthetic utility as building blocks in organic chemistry due to the considerable number of C—C bond forming reactions these intermediates undergo. There are three main ways of forming a carbon-tin (C—Sn) bond:

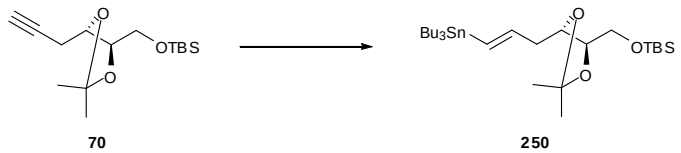
1. Reaction of a tin-metal compound (R_3-SnM) with an alkyl halide
2. Reaction of an organometallic with a tin halide
3. Overall addition of a tin-hydride to an alkyne, alkene or allene.

Method three is widely used due to the mild, neutral conditions and consequently there are multiple ways for addition of tin hydride:

1. Hydrostannylation under free-radical conditions
2. Stannylmetallation-protonation of an alkyne or alkene
3. Metal-catalysed hydrostannylation of an alkyne or alkene.

Tributyltinhydride was first synthesised in 1947 by Finholt[129] and has since become one of the most popular organometallic and hydrostannation reagents in organic synthesis for the formation of vinyl- and allyl- stannanes, mainly due to its price and reactivity.[130] The main problems for the stannylation of alkynes are the regio- and stereo-controls of the addition of the stannyl residue to the triple bond. Bu_3SnH is commercially available or can be prepared *in situ* from Bu_3SnCl and Et_3SiH in the presence of Lewis acid catalysts.[131]

Beginning from commercially available 2-deoxy-D-ribose, alkyne **70** can be readily obtained in six robust steps in 47% overall yield. With the desired alkyne in hand it was thought that it could undergo hydrostannylation to afford the *E*-vinylstannane **250** (Scheme 104).



70 **250**

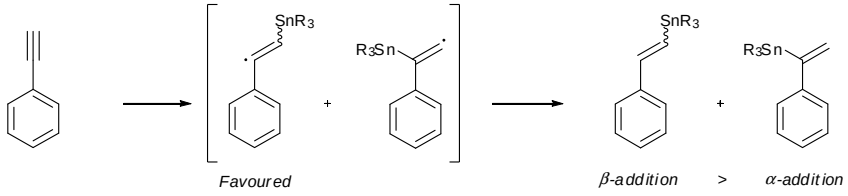
Scheme 104: Formation of *E*-Vinylstannane 250.

Disappointingly and frustratingly, this proved to be more problematic than initially anticipated and as a result various reaction conditions were attempted (Table 2).

Entry	*Reagents*	*Solvent*	*Temperature*	*Time*	*Result*
1	AIBN Bu_3SnH	Toluene	95 °C	24 h	85% *E*:*Z* + alkene **208**
2	$Pd(PPh_3)_4$ Bu_3SnH	CH_2Cl_2	0 °C to rt	20 min	68% *E*:*Z* + alkene **208**
3	$PdCl_2(PPh_3)_2$ Bu_3SnH	THF	Room Temperature	20 min	79% *E*:*Z*

Table 2: Attempted Conditions for the Formation of *(E)*-Vinylstannane 250.

Radical hydrostannylation has been greatly studied and in general gives a mixture of stereoisomers with the regiochemistry controlled by the relative stability of the two possible intermediate ß-stannyl radicals (Scheme 105).[129] The method is now less employed for the hydrostannylation of alkynes as the regio- and stereo-selectivities cannot be anticipated in advance, but it is still a popular radical cyclisation reaction.[130]

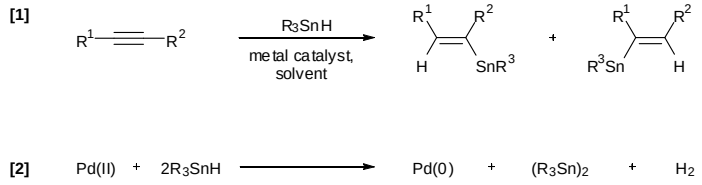


Scheme 105: Radical Hydrostannylation.

Addition of azobis(isobutyronitrile) (AIBN) and tributyltinhydride (Bu_3SnH) to alkyne **70** resulted in the formation of an *E*:*Z*-mixture of vinylstannane **250** and an unknown compound, later found to be alkene **208**. The isomers and the alkene were inseparable, although the yield was a reasonable 85%, suggesting no loss of product through side reactions or degradation.

Stannylmetallation of alkynes can be separated into stoichiometric stannylcupration and stannymetallation in the presence of a transition-metal catalyst (Scheme 106, Equation [1]). In the case of alkynes, metal-catalysed

hydrostannylation usually occurs with *cis*-stereoselectivity and good regioselectivity. Palladium is the most widespread catalyst for the hydrostannylation and under the reaction conditions, palladium(II) complexes are reduced to the catalytically active palladium(0) species (Scheme 106, Equation [2]).

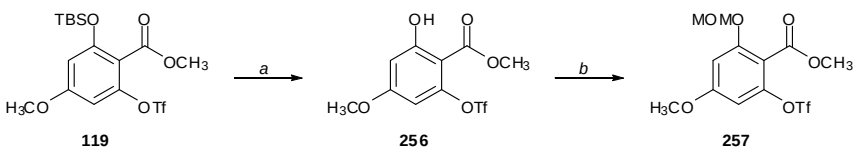


Scheme 106: General Equation for the Hydrostannylation of Alkynes.

In the first instance, stannylmetallation of alkyne **70** was attempted using tributyltinhydride (Bu_3SnH) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$). This also resulted in an inseparable *E*:*Z*-mixture of product **250** and alkene **208**, in slightly lower yield of 68%. Additionally, $PdCl_2(PPh_3)_2$ was utilised as the catalyst and Bu_3SnH added. By this stage, after intense investigation, a solvent system had been found to enable the separation of the *E*:*Z*-product **250** from the alkene **208**. As a result, a final yield of 79% was obtained.

2.13.7 Synthesis of Methyl 4-methoxy-2-(methoxymethoxy)-6-(trifluoromethylsulfonyloxy)benzoate, 257

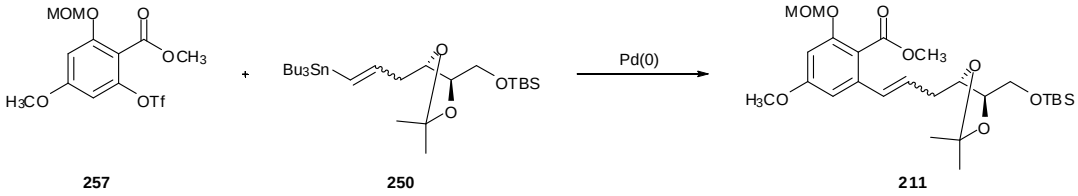
With the kind provision of gram quantities of fully protected aromatic compound **119** by Dr M. N. Robertson we were able to by-pass the initial stages of the synthesis. Deprotection of silyl ether **119** under standard conditions afforded phenol **256** in high yield (Scheme 107). Reprotection of the alcohol as its MOM ether, using MOMBr and Hunig's base, was extremely fruitful and the desired fully protected aromatic unit **257** was obtained in 90% yield.



119 **256** **257**

Scheme 107: Synthesis of Aromatic Fragment 257. Reagents and Conditions: (a) TBAF, THF, 0 ^{o}C → rt, 2 h, 83%; (b) MOMBr, DIPEA, CH_2Cl_2, 0 ^{o}C → rt, 18 h, 90%.

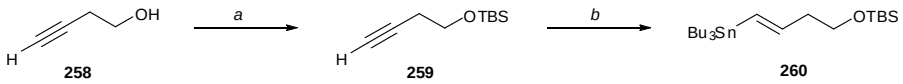
Despite the mixture obtained as result of hydrostannylation of alkyne **70**, it was decided that, rather than disregard the material, it would be used in an attempt to couple the triflate **257** (Scheme 108). In 2004, Baldwin[132] reported that combining copper(I) iodide and cesium fluoride can significantly enhance the Stille reaction coupling with aryl halides and triflates. These conditions were employed for our coupling partners, but despite promising TLC analysis, filtration of the reaction through Celite® was non-trivial and the subsequent ^{1}H NMR spectrum of the crude material showed no coupled product. Disappointingly, none of the other attempted modified procedures gave any of the desired product. In addition, the attempted coupling of triflate **257** and vinylstannane **250** with $Pd(PPh_3)_4$ and lithium chloride in 1,4-dioxane at 100 °C, was also unsuccessful.



257 **250** **211**

Scheme 108: Attempted Stille Coupling of Triflate 257 and Vinylstannane 250.

Faced with a rapidly depleting supply of alkyne **70**, we chose to use 3-butyn-1-ol **258** as a model system. The primary alcohol was protected as its TBS silyl ether under standard conditions in 82% yield (Scheme 109). TBS alkyne **259** was then subjected to a number of conditions to introduce the stannyl unit (Table 3).



258 **259** **260**

Scheme 109: Synthesis of *E*-Vinylstannane 260. Reagents and Conditions: (a) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 18 h, 82%; (b) 'conditions', see Table 3.

The most successful conditions were using AIBN and Bu_3SnH (Table 3, Entry 5) giving vinylstannane **260** as an *E:Z*-ratio of 79:21 and quantitative yield. This result is comparable to the literature,[133] where the authors achieved an inseparable 90:10 mixture of the *E*- and *Z*-vinylstannanes.

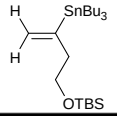
Entry	*Reagents*	*Solvent*	*Temperature*	*Time*	*Result*
1	CuCN, *n*BuLi, Bu_3SnH	THF	–78 °C	~2 h total	
2	Bistributyl tin, CuCN, *n*BuLi, MeOH	THF	–78 °C	18 h	No product
3	$Pd(PPh_3)_4$, Bu_3SnH	CH_2Cl_2	Room Temperature	10 min	Mix 3 products
4	$Pd(PPh_3)_4$, Bu_3SnH	THF	Room Temperature	10 min	Mix 3 products
5	AIBN, Bu_3SnH	Toluene	80 °C	1.5 h	100% 79:21 *E:Z*

Table 3: Attempts at the Synthesis of 260.

When palladium-catalysed conditions were employed (Table 3, Entry 3 and 4), a quick reaction time was observed. Unfortunately, the crude ^1H NMR spectrum showed a mixture of three products **261**, **262** and **263** (Figure 25).

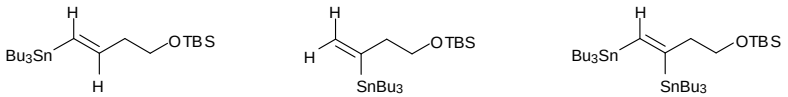
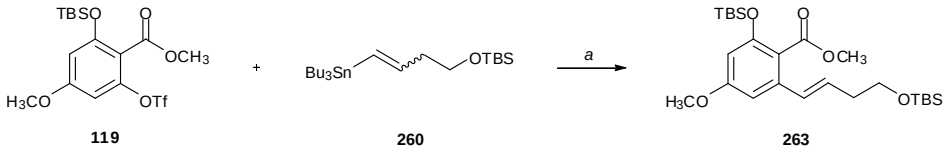


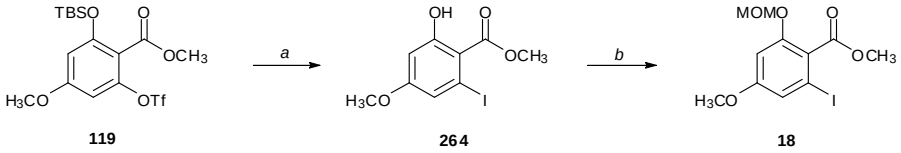
Figure 25: Products Obtained When Using Palladium-Catalysed Conditions.

The stannylcupration of acetylenes was first discovered in 1981 when Piers and colleagues found that a trimethylstannyl copper or cuprate reagent added to acetylenic esters.[134] Reaction of (trialkylstannyl)cuprates with terminal alkynes proceeds with high regio- and stereoselectivity *via* a vinylcopper intermediate. Stannylcupration of terminal alkyne **259** with the mixed organocuprate $Bu_3Sn(Bu)CuCNLi_2$,[130] using two different reaction conditions gave mixed results. Both methods are involved and intricate procedures and while CuCN, *n*BuLi and Bu_3SnH in THF gave exclusively **262**, CuCN, *n*BuLi, *bis*tributyltin and methanol in THF gave no product whatsoever. Despite this, ongoing thought and investigation led to the attempt of the Stille coupling of vinylstannane **260** with aromatic triflate **119**.



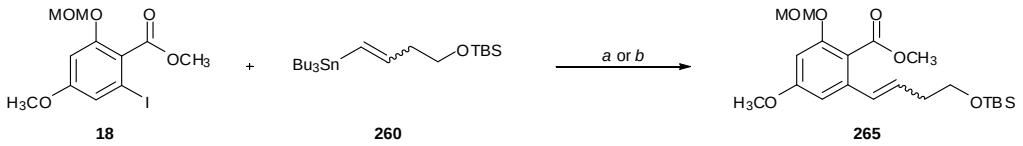
Scheme 110: Successful Coupling to Generate 263. Reagents and Conditions: (a) LiCl, $Pd(PPh_3)_4$, 1,4-dioxane, 100 ^oC, 4 d, 21%.

The reaction proceeded with 3 mol% of $Pd(PPh_3)_4$ in 1,4-dioxane at 100 ^oC over four days. The product was obtained as the pure *E*-isomer but disappointingly, the yield of product **263** was only 21%. However, we were optimistic about the potential of the conditions. As well as using triflates for palladium(0) catalysed couplings, iodides are also widely used. With this in mind, studies commenced into determining whether the corresponding aryl iodide would be a more effective coupling partner than the aryl triflate **119**. Aryl triflates can be readily converted into iodides through treatment with NaI in DMF at 80 ^oC.[135] Upon applying these conditions to aryl triflate **119**, the TBS protecting group was also cleaved during the transformation. Taking advantage of this, phenol **264** was protected as its MOM ether **18** in 98% yield (Scheme 111).



Scheme 111: Formation of Aryl Iodide 18. Reagents and Conditions: (a) NaI, DMF, 80 ^oC, 4 h; (b) MOMBr, DIPEA, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 24 h, 98%.

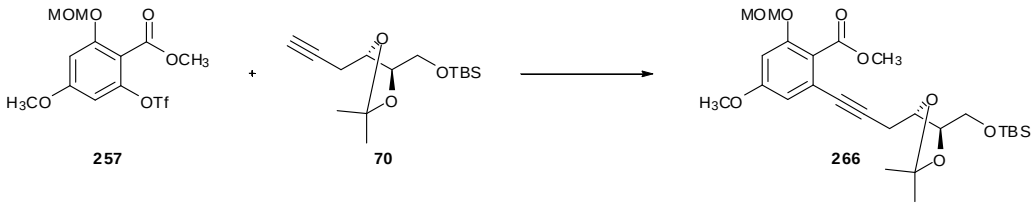
Both $PdCl_2(PPh_3)_4$ and $Pd(PPh_3)_4$ were used in our attempts to couple iodide **18** and vinylstannane **260** (Scheme 112**).** Progression of the reactions was followed by TLC analysis and to begin with there appeared to be the formation of a new product with the slow consumption of starting materials. Despite the promising beginning, after work-up and subsequent FCC to isolate the newly formed spot, no desired product was identified.



Scheme 112: Coupling of Aryl Iodide 18 and Vinylstannane 260. Reagents and Conditions: (a) $PdCl_2(PPh_3)_2$, DMF, 80 ^oC, 4 d; (b) $Pd(PPh_3)_4$, toluene, 100 ^oC, 3 d.

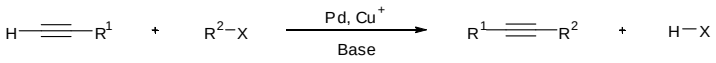
2.13.8 Sonogashira Couplings

An alternative to using a Stille coupling involved the use of a Sonogashira coupling.[39] This would directly couple alkyne **70** to aryl triflate **257** (Scheme 113).



Scheme 113: Sonogashira Coupling of Aryl Triflate 257 and Terminal Alkyne 70.

We were extremely hopeful about the Sonogashira coupling as there is ample literature precedence demonstrating its usefulness in coupling terminal alkynes and aryl/vinyl halides (Scheme 114).

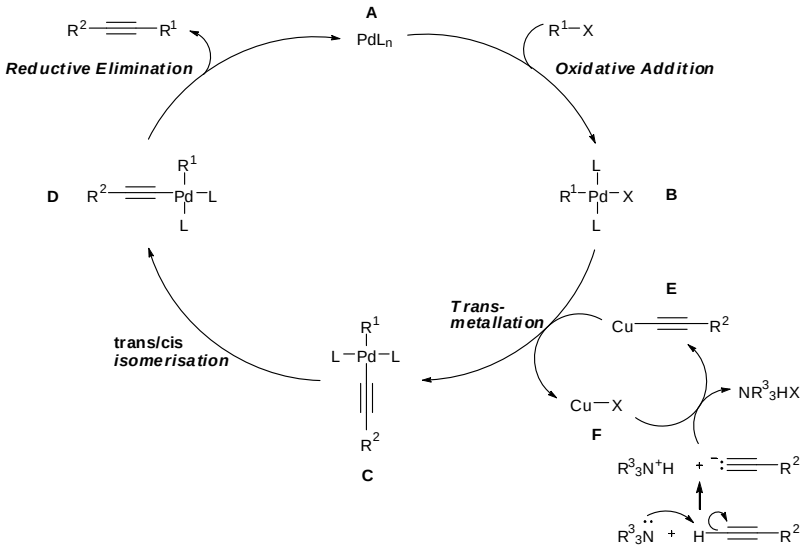


Scheme 114: General Scheme for the Sonogashira Coupling.

The Sonogashira coupling is catalysed by two catalysts; a palladium(0) complex and a copper(I) co-catalyst. The palladium complex activates the organic halides by oxidative addition into the carbon-halogen bond. The copper co-catalyst reacts with the terminal alkyne and produces copper(I) acetylide, which acts as an activated species for the coupling reactions. The reaction conditions must be anhydrous, although newer procedures have been developed that increase its versatility. Liang and co-workers,[136] have developed a copper-free procedure where the Sonogashira coupling takes place with $PdCl_2$ in water under

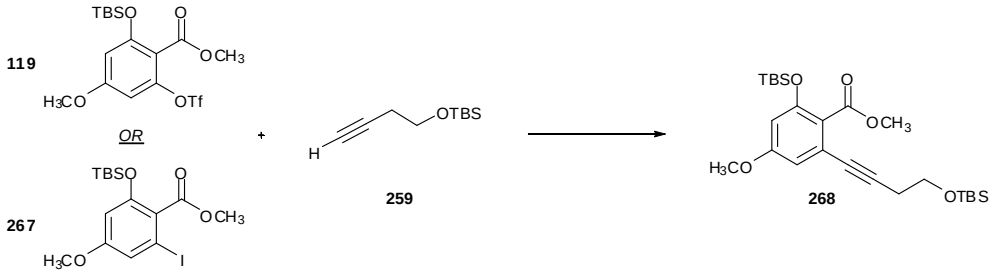
aerobic conditions. Mori's procedure,[137] on the other hand, is carried out in aqueous ammonia, $PdCl_2(PPh_3)_2$ and copper iodide in THF. So as to neutralise the hydrogen halide by-product the reaction must be basic. Triethylamine and diethylamine are often used as solvents, though DMF and diethyl ether are also suitable.

The mechanistic cycle of the Sonogashira coupling is shown in Scheme 115. The first step involves the oxidative addition of palladium(0) **A** with the aryl halide/triflate to generate the Pd(II) complex **B**. The complex reacts in a transmetallation with the copper acetylide (produced in the copper cycle) to complex **C**, ejecting the copper halide **F**. *Trans-cis* isomerisation of the ligands form complex **D**.



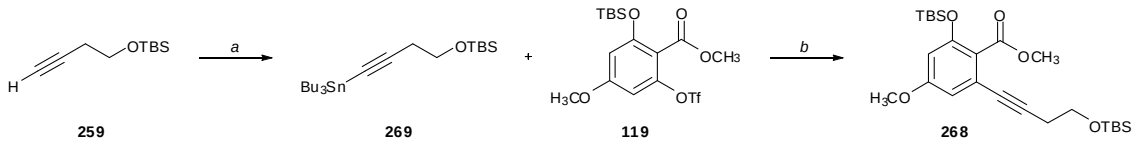
Scheme 115: Mechanism of the Sonogashira Coupling.[138]

Regrettably, all coupling attempts using alkyne **70** and aryl triflate **257** failed to yield any of the desired product (Scheme 113). Interestingly, the Sonogashira coupling of the silyl-protected alkyne model system **259**, with either aryl triflate **119** or aryl iodide **267**, proved futile (Scheme 116). It served only to afford unreacted starting materials.



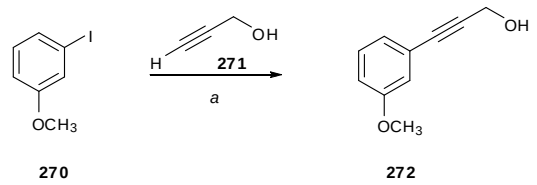
Scheme 116: Sonogashira Coupling of Aryl Triflate 119 or Aryl Iodide 267 and Terminal Alkyne 259. Reagents and Conditions: $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, rt.

The fact that the Stille couplings were more promising than the Sonogashira couplings, made us hopeful that a tributylstannane might prove more reactive.[139] Treatment of alkyne **259** with *n*BuLi and Bu_3SnCl gave the desired stannane **269**, which was found to be unstable and had to be used immediately in the next step (Scheme 117).



Scheme 117: Activation of Alkyne 259 and Subsequent Coupling Attempt. Reagents and Conditions: (a) *n*BuLi, THF, 0 °C, 1 h *then* Bu_3SnCl, 0 °C → rt, 19 h, 69%; (b) LiCl, $Pd(PPh_3)_4$, 1,4-dioxane, 100 °C, 4.5 h, 33%.

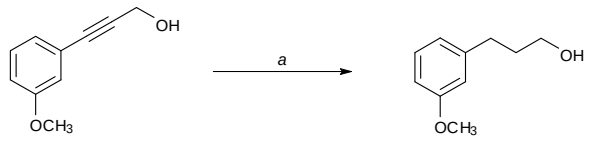
Stannane **269** was successfully coupled with aryl triflate **119** to afford the desired coupled product **268** in 33% yield. Despite the relatively low yield, the result was both pleasing and encouraging. With this product in hand, our attention could now turn to reduction of the triple bond to the *E*-double bond. Unfortunately, literature searches did not yield any procedures for doing this. A possibility was to use Na/NH_3, but due to the functionality already present and the nature of the compound this was not deemed suitable. As an alternative, the triple bond could be reduced to the *Z*-alkene using Lindlar's catalyst. Once the *Z*-double bond has been generated, a double bond isomerisation could be performed.[36,97,98] Once again we elected to use a model substrate in order to test the reaction conditions (Scheme 118). 3-Iodoanisole **270** was coupled with propargyl alcohol **271** in the presence of $PdCl_2(PPh_3)_2$, copper(I) iodide and triethylamine[140] to afford the desired internal alkyne **272** in 82% yield.



270 272

Scheme 118: Synthesis of Alkynol 272. Reagents and Conditions: (a) **271**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, CH_3CN, rt, 16 h, 82%.

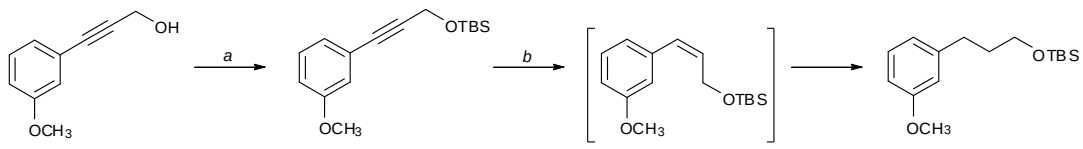
The reduction of alkynol **272** proved to be slightly more complicated than originally expected. Treatment of alkynol **272** with $Pd/BaSO_4$ and quinoline led to over-reduction to give the completely saturated product **273** (Scheme 119). Reduction of alkynol **272** using $Pd(OAc)_2$, NaOMe and PPh_3 also failed to give any of the desired product.[141]



272 273

Scheme 119: Over-reduction of Alkynol 272 to Alkane 273. Reagents and Conditions: (a) H_2, $Pd/BaSO_4$, quinoline, MeOH, 2 h, 72%.

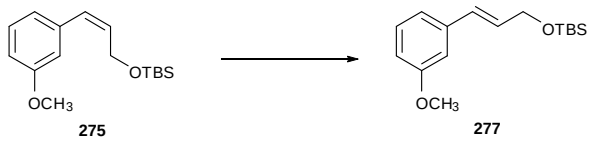
Seeking to remove the risk of the hydroxyl group coordinating to the palladium and aiding in the over-reduction, the hydroxyl group was protected as its silyl ether (Scheme 120). Hydrogenation of the silyl ether **274** was then carried out in two simultaneous reactions. One reaction was stopped after 30 minutes and the other after 60 minutes. After 30 minutes, the ^1H NMR spectrum showed an inseparable mixture of starting alkyne **274**, desired alkene **275** and alkane **276**. After 60 minutes alkane **276** was the only product.



272 274 275 276

Scheme 120: Protection of Alkynol 272 and Reduction of Alkyne 274. Reagents and Conditions: (a) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 18 h, 78%; (b) H_2, $Pd/BaSO_4$, quinoline, MeOH, 30 min *or* 1 h.

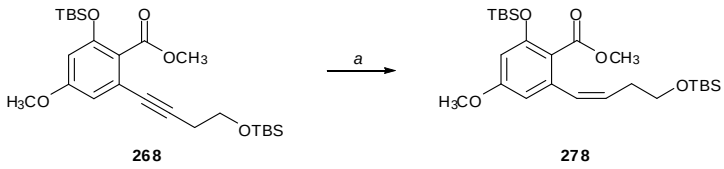
Despite being a mixture, the reaction material isolated following the 30 minute procedure was taken in order to attempt isomerisation reactions (Scheme 121).



Scheme 121: Double bond Isomerisation of Alkene 275.

None of the conditions tried ($PdCl_2(CH_3CN)_2$ and $Pd(OAc)_2/Bu_3SnH/Et_3N$) were successful and didn't provide much scope for using this method as part of our synthesis. The $C_{1'}$—$C_{2'}$ double bond has been successfully isomerised successfully by Tatsuta and co-workers[36] in their synthesis of LL-Z1640-2, though the palladium catalyst employed is expensive and time constraints prevented us from attempting this procedure.

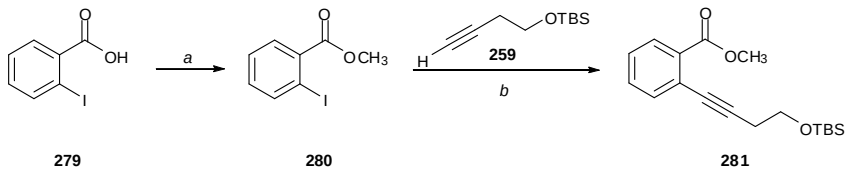
As we had our Sonogashira product **268** in hand, we wanted to proceed and attempt the hydrogenation (Scheme 122). Treatment of alkyne **268** with Lindlar's catalyst afforded *Z*-olefin **278** in 52% yield, as confirmed by ^1H and HRMS.



Scheme 122: Reduction of Alkyne 268. Reagents and Conditions: (a) H_2, $Pd/BaSO_4$, quinoline, MeOH, rt, 2 h, 52%.

At this point in the investigation, this particular route seemed to have hit a stumbling block due to the failure of the isomerisation reaction and so it was necessary to investigate alternative ways of introducing the *E*-double bond. Although Sonogashira product **268** can be achieved, the yield is low and it was postulated whether the aromatic ring may be too substituted. To test this theory, iodobenzoate **280** was synthesised from 2-iodobenzoic acid **279** using Fischer esterification[142] and then coupled with alkyne **259** *via* a Sonogashira

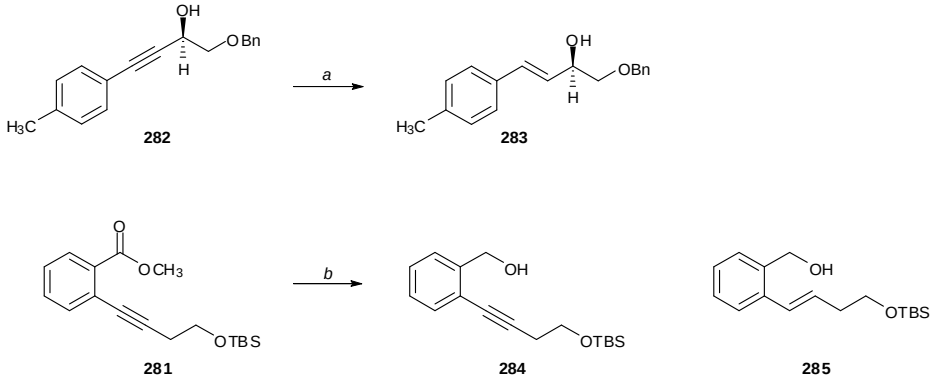
coupling. The desired coupled product **281** was obtained in 71% yield (Scheme 123).



279 **280** **281**

Scheme 123: Formation of Iodobenzoate 280 and Subsequent Coupling. Reagents and Conditions: (a) H_2SO_4, MeOH, reflux, 7 h, 82%; (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, MeCN, rt, 2 h, 71%.

Takano and co-workers[143] showed that $LiAlH_4$ could selectively transform their alkyne **282** into the corresponding *E*-olefin **283** (Scheme 124). In our case, this would reduce the ester functionality, but if the alkyne could be reduced selectively then the formed alcohol could be converted back to the ester. In our hands the procedure wasn't successful, with only trace amounts of alcohol **284** recovered from the reaction. The desired *E*-olefin **285** was not generated.



282 **283** **281** **284** **285**

Scheme 124: Alkyne Reduction Using $LiAlH_4$. Reagents and Conditions: (a) $LiAlH_4$, THF, reflux, 75 min; (b) $LiAlH_4$, THF, reflux, 24 h.

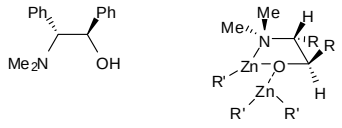
It was at this stage that time restraints were encountered and with no additional progress having been made, the focus turned to areas which could be further investigated and the practical work that could be pursued in the future.

2.14 Future Work

As noted previously, Carreira and colleagues published their facile synthesis of optically active propargylic alcohols **195** from aldehydes, using *N*-

methylephedrine **194** as the chiral additive, with 99% *e.e.* and good yields.[91] When we came to employ these conditions for the addition of alkyne **55**, we encountered problems regarding the stability of aldehyde **197**. This was solved and overcome with the development of the one-pot procedure. The one pot oxidation-Grignard addition procedure, allowing the addition of the required alkyne unit to the freshly generated aldehyde, was highly successful but the ^{1}H NMR spectra for this and subsequent reactions were rather complicated to interpret and assign. An ideal situation would be to enhance and improve the total synthesis by exploring further methods that would allow an asymmetric synthesis of propargylic alcohol **235**. Following a search of the literature we became interested in two methods.[144]

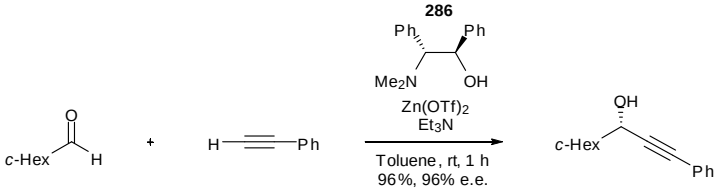
In 2005, Yamashita[144a] published their findings based on the catalytic asymmetric alkynylation of aldehydes with terminal alkynes by chiral alcohol (1*R*,2*R*)-2-(dimethylamino)-1,2-diphenylethanol **286** (Figure 26), which forms a more stable bimetallic complex **287** (than (+/-)-*N*-methylephidrine) with no steric interactions.



286 **287**

Figure 26: Structure of (1R,2R)-2-(dimethylamino)-1,2-diphenylethanol 286 and its Bimetallic Complex 287.

The authors concluded that by employing a straightforward procedure and using 0.22 equivalents of chiral amino alcohol **286**, zinc triflate (0.2 eq.) and triethylamine (0.5 eq.) in toluene at room temperature, they could bring about the asymmetric addition with the enantioselectivity reaching up to 98% (Scheme 125).



Scheme 125: Example of Chiral Amino Alcohol Mediated Catalytic Asymmetric Alkynylation.

In 1994, Fujisawa[144b] reported the use of zinc(II) bromide in the highly diastereoselective addition of acetylide to a chiral aldehyde. It is postulated that we could potentially apply the method to using our chiral terminal alkyne and aldehyde. The bromozinc acetylide is prepared from the lithium acetylide *via* transmetalation with $ZnBr_2$. The authors report a reaction time of 15 h, with an isolated yield of 81% and >99:1 *syn:anti*. Additionally, we would seek to investigate Carreira's method further in the hope that optimisation would allow the reaction to proceed.

It was touched upon in **2.13.1** and **2.13.2** that the free hydroxyl of **242** could be oxidised readily to the ketone, after which the proceeding transformations would take place, culminating in the saponification of the ester to the carboxylic acid. This *seco*-acid would then undergo macrolactonisation and the enone would already be in place. As time and quantities of material didn't allow the trial of this method but it would advantageous to attempt this in order to determine whether the enone can be in place throughout the following transformations. This would mean that when the *seco*-acid is subjected to macrolactonisation the product already has the enone in place and all that remains is the global deprotection.

3 Experimental

3.1 General Methods

All reactions were performed under an inert argon atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received, unless otherwise specified.

Anhydrous dichloromethane (DCM), diethyl ether, toluene and tetrahydrofuran (THF) were freshly obtained from in-house solvent purification system, Pure Solv 400-5MD (Innovative Technology, Inc). Anhydrous dimethylformamide (DMF) and triethylamine (TEA) were purchased from Aldrich Chemical Company. Petroleum ether refers to that with boiling fraction 40—60 ^{o}C. Solutions worked up were concentrated under reduced pressure at < 45 ^{o}C using a Buchi Rotavapor.

Melting points were determined using Stuart Scientific Melting Point SMP1 apparatus.

Optical rotations were determined as solutions irradiating with the sodium D line (λ = 598 nm) using an AA series automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Infrared (IR) spectra were recorded as thin films on sodium chloride (NaCl) plates using a JASCO FTIR 410 spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz using a Bruker DPX-400 spectrometer for sample solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration) (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext. = sextet, oct. = octet, m = multiplet, br = broad) (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz and (4) proton assignment. For relevant compounds, the OH signal was identified by D_2O exchange.

Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz using a Bruker DPX-400 spectrometer for sample solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. For larger, more complex compounds, the structure is shown with numbered carbon atoms to assist with the ^{13}C assignment.

Mass spectra were obtained using a JEOL JMS-700 spectrometer.

TLC was performed on aluminium backed plates pre-coated with silica gel 60 (Kieselgel 60 F_{254} aluminium plates, Merck) with *A*, petroleum ether-ethyl acetate (8:2); *B*, petroleum ether-ethyl acetate (7:3); *C*, petroleum ether-ethyl acetate (6:4); *D*, petroleum ether-ethyl acetate (9:1); *E*, petroleum ether-ethyl acetate (9.5:0.5); *F*, petroleum ether-diethyl ether (9.5:0.5); *G*, toluene-ethyl acetate (8:2); *H*, petroleum ether-ethyl acetate (2:8); *I*, petroleum ether-ethyl acetate (5:5); *J*, petroleum ether-ethyl acetate (3:7); *K*, chloroform-ethyl acetate (6:4); *L*, petroleum ether (10:0); *M*, petroleum ether-ethyl acetate (4:6); *N*, petroleum ether-diethyl ether (7:3); *O*, petroleum ether-ethyl acetate (2:8); *P*, petroleum ether-diethyl ether (9:1); *Q*, hexanes (10:0); *R*, petroleum ether-diethyl ether (8:2); *S*, petroleum ether-diethyl ether (5:5) as developers and detection under UV light (λ_{max} 254 nm) and/or by staining with anisaldehyde, unless otherwise specified, followed by heating.

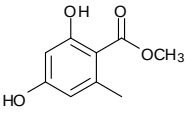
Flash column chromatography (FCC) was performed using Apollo Scientific silica gel 60 (0.040-0.063 mm), with the appropriate eluting solvent and elution gradient, shown in square brackets as part of the procedure, e.g. *purification by FCC [petroleum ether-ethyl acetate (85:15)→(75:25)→(60:40)→(50:50)] of the crude residue*....

The following chemicals were used at the concentrations given, unless otherwise stated:

- *tetra*-Butylammonium fluoride (TBAF), 1 M in tetrahydrofuran
- Oxalyl chloride, 2 M in dichloromethane
- Ethyl Magnesium Bromide (EtMgBr), 3 M in diethyl ether
- Potassium *bis*(trimethylsilyl)amide (KHMDS), 0.5 M in toluene
- *n*-Butyllithium (*n*BuLi), 2.5 M in hexanes.

3.2 Synthesis and Characterisation of Compounds

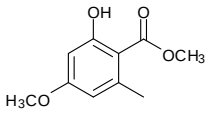
Methyl 2,4-Dihydroxy-6-methylbenzoate 169[145a]



Sodium hydride (5.16 g, 129 mmol, 60% dispersion in mineral oil) was washed with petroleum ether (2×10 cm^3), suspended in anhydrous THF (50 cm^3) and then cooled to 0 °C under an argon atmosphere. Methyl acetoacetonate (9.3 cm^3, 86.1 mmol) was then added dropwise, the solution cooled to −78 °C and *n*BuLi (32.7 cm^3, 81.8 mmol) was added. The reaction mixture was then allowed to warm up to room temperature overnight. The mixture was heated under reflux for 24 h, cooled to room temperature and acidified to pH 1-2 with 6 M aqueous hydrochloric acid. The mixture was stirred overnight and the biphasic mixture was extracted with ethyl acetate (3×50 cm^3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether–ethyl acetate (85:15)→(75:25)→(60:40)→(50:50)] of the crude residue afforded **169** (5.1 g, 65%) as a pale yellow solid; mp 130-132 °C (rec. from petroleum ether-ethyl acetate) (lit.,[145a] 136-138 °C); δ_H(400 MHz; $CDCl_3$) 2.44 (3 H, s, C*H*$_3$), 3.90 (3 H, s, CO_2CH_3), 6.05 (1 H, s, *H*C(COH)$_2$), 6.60 (1 H, s, *H*CCCH$_3$), 9.40 (1 H, s, O*H*) and 11.80 (1 H, s, O*H*). The spectral data matches that reported in the literature.[145a]

Also isolated was 2,4-dihyroxy-6-methyl benzoic acid (1.8 g, 25%) as a yellow solid; δ_H(400 MHz; $CDCl_3$) 2.46 (3 H, s, C*H*$_3$), 6.20 (1 H, s, *H*C(COH)$_2$), 6.77 (1 H, s, *H*CCCH$_3$), 9.45 (1 H, s, O*H*), 11.80 (1 H, s, O*H*) and 12.70 (1 H, s, COO*H*).

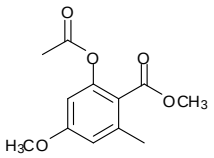
Methyl 2-hydroxy-4-methoxy-6-methylbenzoate 168[145b]



To a stirred solution of phenol **169** (1.3 g, 7.32 mmol) in a mixture of chloroform/methanol (3:1, 35 cm^3) at 0 °C was added (trimethylsilyl)diazomethane (4.4 cm^3, 8.78 mmol, 2 M in diethyl ether) under an argon atmosphere. The solution was stirred at 0 °C for 3 h and then allowed to

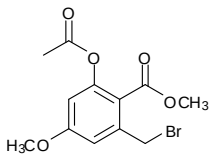
warm up to room temperature overnight. The solution was recooled to 0 °C and a second aliquot of (trimethylsilyl)diazomethane (2.2 cm^3, 4.39 mmol, 2 M in diethyl ether) was added. After 2 h at 0 °C, the solution was allowed to warm to room temperature overnight and the solvent was removed *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded methyl ether **168** (0.97 g, 89%) as a white solid; mp 130-132 °C (rec. from petroleum ether-ethyl acetate); ν_{max}(film)/cm^{-1} 3594 (OH), 1671 (C=O) and 1601 (C=C); δ_H(400 MHz; $CDCl_3$) 2.51 (3 H, s, CH_3), 3.74 (3 H, s, OCH_3), 3.93 (3 H, s, CO_2CH_3), 6.30 (1 H, dd, *J* 0.4 and 2.4, *H*COH), 6.34 (1 H, d, *J* 2.8, C*H*) and 11.78 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 22.1 (*C*H_3), 52.1 (COO*C*H_3), 55.7 (O*C*H_3), 101.0 (H*C*COH), 105.3 (*C*COOCH$_3$), 111.2 (H*C*CCH$_3$), 142.9 (HC*C*CH$_3$), 164.5 (*C*OH), 162.6 (*C*OCH$_3$) and 170.3 (*C*=O); MS (EI) *m*/*z* 197 $[M+H]^+$; HRMS *m*/*z* 197.0816 (197.0814 calcd for $C_{10}H_{13}O_4$, $M+H^+$). The spectral data matches that reported in the literature.[145b]

Methyl 2-acetoxy-4-methoxy-6-methylbenzoate <u>167</u>[146]



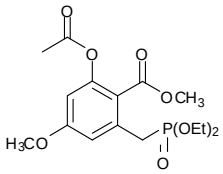
To a solution of methyl ether **168** (1.74 g, 8.89 mmol) in dry dichloromethane (45 cm^3) at 0 °C, was added sequentially pyridine (0.93 cm^3, 1.56 mmol), acetic anhydride (1.26 cm^3, 13.3 mmol) and dimethylaminopyridine (0.54 g, 4.44 mmol). The reaction mixture was stirred under argon for 2 h and then allowed to warm to room temperature, whereafter the solvent was removed *in vacuo*. Purification by FCC [petroleum ether-ethyl actetate (70:30)] of the crude residue afforded acetate **167** (2.05 g, 97%) as a pale yellow oil; R_f 0.31 (solvent *A*); ν_{max}(film)/cm^{-1} 1777 (C=O), 1609 (C=C), 1280 and 1151; δ_H(400 MHz; $CDCl_3$) 2.30 (3 H, s, OCOCH_3), 2.44 (3 H, s, CH_3), 3.30 (3 H, s, OCH_3), 3.88 (3 H, s, COOCH_3), 6.49 (1 H, d, *J* 2.4, C*H*) and 6.67 (1 H, d, *J* 2.4, C*H*); δ_C(100 MHz; $CDCl_3$) 20.1 (H_3*C*C=O), 22.1 (CH_3), 52.7 (C=OO*C*H_3), 55.9 (O*C*H_3), 108.8 (*C*H), 110.4 (*C*H), 114.7 (*C*C=OOCH$_3$), 140.1 (*C*CH$_3$), 151.4 (*C*OC=OCH$_3$), 161.6 (*C*OCH$_3$), 165.7 (CO*C*=OCH$_3$) and 169.8 (*C*=O). All spectral data matches that reported in the literature.[146]

Methyl 2-acetoxy-6-bromomethyl-4-methoxybenzoate <u>166</u>[147]



To a stirred solution of acetate **167** (2.05 g, 8.62 mmol) in carbon tetrachloride (200 cm^3) was added 1,3-dibromo-5,5-dimethylhydantoin (1.43 g, 4.99 mmol) and benzoyl peroxide (0.21 g, 0.86 mmol). The solution was heated under reflux under an argon atmosphere for 3.5 h and then cooled to room temperature, filtered and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (95:5)→(90:10)→(85:15)] of the crude residue afforded bromide **166** (2.58 g, 95%) as a yellow oil, which solidifies upon freezing; R_f 0.41 (solvent *A*); mp 49-51 °C (rec. from petroleum ether-ethyl acetate); δ_H(400 MHz;$CDCl_3$) 2.30 (3 H, s, OCOCH_3), 3.86 (3 H, s, OCH_3), 3.93 (3 H, s, COOCH_3), 4.71 (2 H, s, CH_2Br), 6.61 (1 H, d, *J* 2.5, C*H*) and 6.89 (1 H, d, *J* 2.5, C*H*); δ_C(100 MHz; $CDCl_3$) 20.3 (H_3*C*C=O), 30.9 (*C*H_2Br), 52.4 (C=OO*C*H_3), 55.7 (O*C*H_3), 108.9 (*C*H), 110.4 (*C*H), 114.6 (*C*C=OOCH_3), 140.1 (*C*CH_2Br), 151.1 (*C*OC=OCH_3), 161.6 (*C*OCH_3), 165.5 (CO*C*=OCH_3) and 169.1 (*C*=OOCH_3). All spectral data matches that reported in the literature.[147]

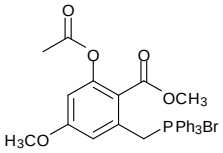
Methyl 2-acetoxy-6-(diethoxy-phosphorylmethyl)-4-methoxybenzoate <u>189</u>



Bromide **166** (350 mg, 1.10 mmol) was dissolved carefully in triethyl phosphite (0.23 cm^3, 1.35 mmol) and then heated in the microwave at 180 °C for 26 min. After cooling down to room temperature, water (10 cm^3) was added and then the solution was extracted with ethyl acetate (5×15 cm^3). The combined organic layers were washed with saturated sodium chloride (2×15 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Short pass distillation removed excess triethyl phosphite from the crude residue to afford phosphonate **189** (193 mg, 58%) as a yellow oil; R_f 0.41 (solvent *B*); ν_{max}(film)/cm^{-1} 2982, 1773, 1720, 1612 (C=C), 1192 (P=O) and 1151; δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, t, *J* 7.0 , CH_2CH_3), 1.30 (3 H, t, *J* 7.0, CH_2CH_3), 2.24 (3 H, s, OC=OCH_3), 3.50 (2 H, d, $^2J_{P\text{-}H}$ 22.5, CH_2), 3.79 (3 H, s, OCH_3), 3.83 (3 H, s,

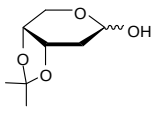
COOC*H*$_3$), 3.98 (2 H, q, *J* 7.0, C*H*$_2$CH$_3$), 4.07 (2 H, q, *J* 7.0, C*H*$_2$CH$_3$), 6.52 (1 H, d, *J* 1.8, C*H*) and 6.78 (1 H, d, *J* 1.8, C*H*); δ_C(100 MHz; $CDCl_3$) 14.5 (2×CH_2*C*H$_3$), 19.3 (*C*H$_3$C=OO), 30.4 (CH_2), 50.3 (COO*C*H$_3$), 53.8 (O*C*H$_3$), 60.4 (2×*C*H$_2$CH$_3$), 104.4 (*C*HAr), 106.0(*C*HAr), 116.4 (*C*COOCH$_3$), 138.9 (*C*CH$_2$), 149.2 (*C*O), 159.5 (*C*OCH$_3$), 164.3 (CH$_3$*C*=O) and 167.2 (*C*=OOCH$_3$); MS (EI) *m*/*z* 374 $[M]^+$; HRMS *m*/*z* 374.1125 (374.1131 calcd for $C_{16}H_{23}O_8P$, M^+)

(3-Acetoxy-5-methoxy-2-methoxycarbonylbenzyl)-triphenylphosphonium bromide <u>165</u>[147]



To a stirred solution of bromide **166** (2.08 g, 6.56 mmol) in toluene (33 cm^3) was added triphenylphosphine (1.89 g, 7.21 mmol) and the reaction mixture heated to 110 °C for 24 h under argon. After allowing the reaction to cool down to room temperature, the solid was filtered under vacuum, washed with petroleum ether and allowed to air dry to afford phosphonium salt **165** (2.48 g, 65%) as a cream solid; mp 183-186 °C (rec. from petroleum ether); δ_H(400 MHz; $CDCl_3$) 2.20 (3 H, s, OCOC*H*$_3$), 3.37 (3 H, s, OC*H*$_3$), 3.70 (3 H, s, COOC*H*$_3$), 5.90 (2 H, d, $^2J_{P\text{-}H}$ 15.1, C*H*$_2$), 6.55 (1 H, t, *J* 2.4, C*H*CCH$_2$), 7.38 (1 H, t, *J* 2.7, C*H*) and 7.60-7.80 (15 H, m, 3×Ph); δ_C(100 MHz; $CDCl_3$) 20.1 (OCO*C*H$_3$), 54.5 (CO_2*C*H$_3$), 55.7 (O*C*H$_3$), 60.0 (*C*H$_2$), 102.9 (*C*H), 110.0 (*C*H), 112.4 (*C*CO$_2$CH$_3$), 128.6 (9×*C*H), 136.1 (6×*C*H), 137.8 (3×P-*C*), 139.9 (*C*CH$_2$), 151.0 (*C*OCOCH$_3$), 165.6 (*C*OCH$_3$), 169.0 (O*C*OCH$_3$) and 171.2 (*C*O$_2$CH$_3$); δ_P 24.1. All spectral data matches that reported in the literature.[147]

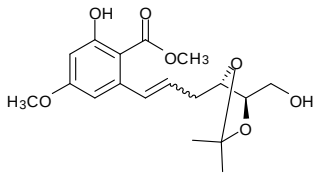
2-Deoxy-3,4-*O*-isopropylidene-D-pentopyranose <u>144</u>[51]



Under an argon atmosphere, a −10 °C stirred solution of 2-deoxy-D-ribose (3.0 g, 22.4 mmol) in ethyl acetate (150 cm^3) was treated with 2-methoxypropene (2.8 cm^3, 29.1 mmol) and pyridinium *p*-toluenesulfonate (224 mg, 0.694 mmol). The solution was allowed to stir at −10 °C for 2.5 h before allowing it to warm up to room temperature overnight. The reaction was quenched with triethylamine (1.5 cm^3) and then concentrated *in vacuo*. Purification by FCC [petroleum

ether-ethyl acetate (90:10)→(80:20)→(70:30)→(50:50)] of the crude residue afforded ketal **144** (2.39 g, 62%) as a white solid; R_f 0.30 (Solvent *M*); $[\alpha]_D^{20}$ -29.3 (*c* 1.1, $CHCl_3$) (lit.,[51] $[\alpha]_D^{21}$ -46.0 (*c* 0.1, water); ν_{max}(film)/cm^{-1} 2984 (OH), 2938, 1663, 1369; δ_H(400 MHz; $CDCl_3$) (major α anomer) 1.31 (3 H, s, C*H*$_3$), 1.48 (3 H, s, C*H*$_3$), 1.75 (1 H, ddd, *J* 4.2, 7.0 and 14.8, C*H*$_2$CHOH), 2.22 (1 H, dt, *J* 4.2 and 14.8, C*H*$_2$CHOH), 3.67 (1 H, dd, *J* 3.6 and 12.7, C*H*$_2$), 3.94 (1 H, dd, *J* 3.6 and 12.7, C*H*$_2$), 4.12-4.16 (1 H, m, C*H*OC), 4.41-4.47 (1 H, m, C*H*OC) and 5.23 (1 H, dd, *J* 4.2 and 7.2, CHO*H*); δ_C(100 MHz;$CDCl_3$) 25.4 (*C*H$_3$), 27.3 (*C*H$_3$), 32.1 (*C*H$_2$), 62.1 (*C*H$_2$COH), 70.8 (*C*H), 71.6 (*C*H), 90.9 (*C*OH) and 108.8 (*C*(CH$_3$)$_2$); MS (EI) *m*/*z* 197 $[M]^+$; HRMS *m*/*z* 197.0772 (197.0784 calcd for $C_8H_{14}NaO_4$, M^+); δ_H(400 MHz; $CDCl_3$) (minor ß anomer) 1.32 (3 H, s, C*H*$_3$), 1.57 (3 H, s C*H*$_3$), 2.10 (2 H, t, *J* 3.8, C*H*$_2$CHOH), 3.65-3.71 (1 H, m, C*H*$_2$), 3.95-4.02 (1 H, m, C*H*$_2$), 4.13-4.23 (1 H, m, C*H*OC), 4.43-4.45 (1 H, m, C*H*OC) and 5.09 (1 H, m, CHO*H*). All spectral data matches that reported in the literature.[51]

Methyl 2-hydroxy-6-{(*E*/*Z*)-3-[(4*S*,5*R*)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxybenzoate <u>185</u>



Procedure A

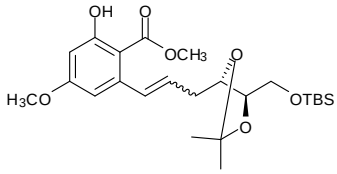
Sodium hydride (60% in mineral oil, 0.27 g, 6.65 mmol) was washed with petroleum ether (2×5 cm^3), suspended in dry tetrahydrofuran (13 cm^3) and added via cannula to a solution of phosphonium bromide **165** (3.70 g, 6.43 mmol) in dry tetrahydrofuran/dimethylformamide (5:1, 18:3.5 cm^3), all under an argon atmosphere. Stirring was continued for 45 min and then a solution of lactol **144** (0.75 g, 4.29 mmol) in dry tetrahydrofuran (13 cm^3) was added and the mixture heated at 80 °C for 30 min. The solution was allowed to cool down to room temperature and then sodium methoxide (25% solution in methanol, 1.02 cm^3, 4.72 mmol) was added and the stirring continued for a further 15 min. The reaction mixture was diluted with water (50 cm^3) and extracted with ethyl acetate (3×50 cm^3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC

[petroleum ether-ethyl acetate (80:20)→(70:30)→(60:40)] of the crude residue afforded diol **185** (0.61 g, 40%) as a yellow oil and as a 3:2 (*E*:*Z*) inseparable mixture of isomers; $[\alpha]_D^{24}$ -1.2 (*c* 1.0, $CHCl_3$); δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 1.38 (3 H, s, CC*H*$_3$), 1.50 (3 H, s, CC*H*$_3$), 2.41-2.50 (2 H, m, C*H*$_2$), 3.71 (2 H, d, *J* 6.2, C*H*$_2$OH), 3.80 (3 H, s, OC*H*$_3$), 3.93 (3 H, s, COOC*H*$_3$), 4.12-4.19 (1 H, m, CH=CHCH$_2$C*H*), 4.33 (1 H, q, *J* 6.2, C*H*CH$_2$OH), 5.89-5.98 (1 H, m, CH=C*H*CH$_2$), 6.39 (1 H, d, *J* 2.6, C*H*Ar), 6.46 (1 H, d, *J* 2.6, C*H*Ar), 7.02 (1 H, d, *J* 15.5, C*H*=CHCH$_2$) and 11.58 (1 H, s, O*H*); *Z*-isomer (*inter alia*) 5.61-5.67 (1 H, m, CH=C*H*CH$_2$) and 6.76 (1 H, d, *J* 11.4, C*H*=CHCH$_2$); δ_C(100 MHz; $CDCl_3$) (*E*-isomer) 25.5 (2×*C*H$_3$), 32.9 (*C*H$_2$), 52.2 (O=CO*C*H$_3$), 55.5 (O*C*H$_3$), 61.6 (*C*H$_2$OH), 77.8 (CH=CHCH$_2$*C*HO and O*C*HCH$_2$OH), 99.8 (*C*Ar), 99.9 (*C*Ar), 108.3 (*C*C=O), 108.6 (O*C*O), 127.8 (CCH=*C*H), 132.9 (C*C*H=CH), 140.4 (*C*CH=CH), 162.9 (*C*OH), 164.3 (*C*OCH$_3$) and 171.5 (*C*=O); MS (FAB) *m*/*z* 353.5 $[M+H]^+$; HRMS *m*/*z* 353.1591 (353.1600 calcd for $C_{18}H_{25}O_7$, $M+H^+$).

Procedure B

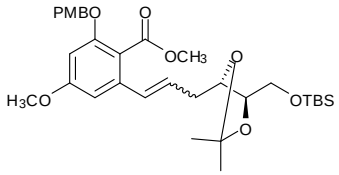
To a stirred solution of diol **185** (106 mg, 299 μmol) in dry dichloromethane (10 cm^3) was added palladium(II)acetate ($Pd(OAc)_2$) (3.4 mg, 14.9 μmol) and triethylamine (0.01 cm^3, 47.9 μmol) at room temperature under argon. To this mixture was added tributyltinhydride (70 μL, 0.258 mmol) dropwise and the reaction solution was heated under reflux for 45 h. The reaction was cooled down to room temperature, filtered through Celite® and the solvent concentrated carefully *in vacuo*. Purification by FCC [chloroform-ethyl acetate, (80:20)→(70:30)] of the crude residue afforded phenol **185** (35 mg, 33%); R_f 0.41 (solvent *K*); ^{1}H NMR spectroscopy showed a slight *Z* to *E* isomerisation of the double bond from 3:2 to 4.8:2; δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 1.38 (3 H, s, CC*H*$_3$), 1.50 (3 H, s, CC*H*$_3$), 2.34-2.40 (2 H, m, C*H*$_2$), 3.71 (2 H, d, *J* 6.2, C*H*$_2$OH), 3.79 (3 H, s, OC*H*$_3$), 3.93 (3 H, s, COOC*H*$_3$), 4.11-4.16 (1 H, m, CH=CHCH$_2$C*H*), 4.33 (1 H, q, *J* 6.2, C*H*CH$_2$OH), 5.87-5.93 (1 H, m, CH=C*H*CH$_2$), 6.38 (1 H, d, *J* 2.6, C*H*Ar), 6.47 (1 H, d, *J* 2.6, C*H*Ar), 7.02 (1 H, d, *J* 15.5, C*H*=CHCH$_2$) and 11.58 (1 H, s, O*H*); *Z*-isomer (*inter alia*) 5.60-5.65 (1 H, m, CH=C*H*CH$_2$) and 6.74 (1 H, d, *J* 11.4, C*H*=CHCH$_2$).

2-{(*E*/*Z*)-3-[(4*S*,5*S*)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-methyl [1,3]dioxolan-4-yl]-propenyl}-6-hydroxy-4-methoxybenzoate <u>186</u>



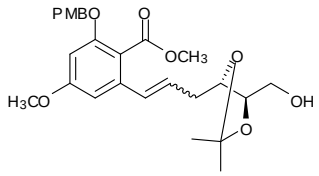
To a stirred solution of alcohol **185** (536 mg, 1.52 mmol) in dry dimethylformamide (30 cm^3) under argon was added *tert*-butyldimethylsilyl chloride (252 mg, 1.67 mmol) and imidazole (207 mg, 3.04 mmol). The solution was stirred for 3 h at room temperature and then diluted with distilled water (50 cm^3) and extracted with 50% diethyl ether in petroleum ether (3×150 cm^3). The combined organic layers were washed with water (50 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded silyl ether **186** (377 mg, 55%; *65% based on starting material consumed*) as a thick, colourless oil (recovered starting material 102 mg) and as a 7:5 (*E*:*Z*) mixture of isomers; R_f 0.56 (Solvent *D*); $[\alpha]_D^{20}$ -1.2 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2953 (OH), 2930, 1655 (C=O), 1610 (C=C), 1329, 1254, 1157 (O-Si) and 1074; δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 0.02 (6 H, s, Si(CH_3)$_2$), 0.80 (9 H, s, SiC(CH_3)$_3$), 1.25 (3 H, s, CCH_3), 1.46 (3 H, s, CCH_3), 2.35-2.50 (2 H, m, CH_2), 3.65 (2 H, d, 6.2, CH_2OTBS), 3.73 (3 H, s, OCH_3), 3.81 (3 H, s, COOCH_3), 3.96-4.05 (1 H, m, CH=CHCH$_2$C*H*), 4.18-4.22 (1 H, m, C*H*CH$_2$OTBS), 5.89-5.96 (1 H, m, CH=C*H*CH$_2$), 6.39 (1 H, d, *J* 2.6, C*H*Ar), 6.42 (1 H, d, *J* 2.6, C*H*Ar), 6.94 (1 H, d, *J* 15.5, C*H*=CHCH$_2$) and 11.57 (1 H, s, O*H*); *Z*-isomer (*inter alia*) 5.61 (1 H, m, CH=C*H*CH$_2$) and 6.68 (1 H, d, *J* 11.6, C*H*=CHCH$_2$); δ_C(100 MHz; CDC_3) (*E*-isomer) -5.7 (Si(*C*H_3)$_2$), 18.2 (Si*C*(CH$_3$)$_3$), 25.5 (2×*C*H$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 32.9 (*C*H$_2$), 52.2 (O=CO*C*H$_3$), 55.5 (O*C*H$_3$), 61.6 (*C*H$_2$OH), 77.8 (2×*C*O), 99.8 (*C*Ar), 99.9 (*C*Ar), 108.3 (*C*C=O), 108.6 (O*C*O), 127.8 (CCH=*C*H), 132.9 (C*C*H=CH), 140.4 (*C*CH=CH), 162.9 (*C*OH), 164.3 (*C*OCH$_3$) and 171.5 (*C*=O); MS (FAB) *m*/*z* 489.6 $[M+Na]^+$; HRMS *m*/*z* 489.2279 (489.2284 calcd for $C_{24}H_{38}NaO_7Si$, $M+Na^+$).

Methyl 2-{(*E*/*Z*)-3-[(4*S*,5*S*)-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-(4-methoxybenzyloxy)-benzoate 187



Alcohol **186** (377 mg, 0.808 mmol) was dissolved in anhydrous dimethylformamide (60 cm^3) and potassium carbonate (168 mg, 1.21 mmol), *p*-methoxybenzyl chloride (0.12 cm^3, 0.889 mmol) and *tetra*-butylammonium iodide (30 mg, 0.0808 mmol) were added sequentially at room temperature. The resulting yellow solution was heated at 80 °C overnight after which time TLC analysis showed the reaction to be complete. After cooling down to room temperature, the reaction mixture was diluted with diethyl ether (50 cm^3) and quenched with water (50 cm^3). The organic layer was separated, washed with water (3×80 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded PMB ether **187** (426 mg, 90%) as a thick, pale yellow oil and as a 6:4 (*E:Z)* mixture of isomers; R_f 0.34 (solvent *A*); $[\alpha]_D^{22}$ -1.5 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932, 1728 (C=O), 1599 (C=C), 1514, 1250, 1159 (O-Si) and 1099; δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 0.02 (6 H, s, Si(C*H*$_3$)$_2$), 0.81 (9 H, s, SiC(C*H*$_3$)$_3$), 1.23 (3 H, s, C*H*$_3$), 1.37 (3 H, s, C*H*$_3$), 2.34-2.50 (2 H, m, C*H*$_2$), 3.55-3.61 (2 H, m, C*H*$_2$OTBS), 3.71 (3 H, s, OC*H*$_3$), 3.79 (3 H, s, COOC*H*$_3$), 3.82 (3 H, s, OCH$_2$ArOC*H*$_3$), 3.96-4.19 (2 H, m, 2×C*H*O), 4.92 (2 H, d, *J* 3.3, OC*H*$_2$), 5.73-5.79 (1 H, m, CH=C*H*), 6.30-6.39 (2 H, m, 2×C*H*Ar), 6.84 (1 H, d, *J* 15.4, C*H*=CH) and 7.20-7.26 (4 H, m, 4×C*H*Ar); (*Z*-isomer) (*inter alia*) 5.72-5.81 (1 H, m, CH=C*H*CH$_2$) and 6.80 (1 H, d, *J* 11.5, C*H*=CHCH$_2$); δ_C(100 MHz; $CDCl_3$) (*E*-isomer) -5.4 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_2$), 33.3 (CH$_2$), 52.1 (CO$_2$*C*H$_3$), 55.3 (2×O*C*H$_3$), 61.9 (*C*H$_2$OTBS), 70.4 (O*C*H$_2$), 77.1 (H*C*CH$_2$OTBS), 77.7 (C=C*C*H$_2$*C*H), 99.4 (*C*H), 101.9 (*C*H), 106.5 (*C*CO$_2$CH$_3$), 108.0 (*C*(CH$_3$)$_2$), 113.9 (2×*C*H(Ph)), 128.3 (C=*C*), 128.6 (OCH$_2$*C* and 2×*C*H(Ph)), 130.3 (*C*=C), 137.5 (*C*C=C), 157.1 (*C*(Ph)OCH$_3$), 159.3 (*C*OPMB), 161.2 (*C*OCH$_3$) and 168.5 (*C*=O); MS (FAB) *m*/*z* 609.7 [M+Na]$^+$; HRMS *m*/*z* 609.2859 (609.2860 calcd for $C_{32}H_{46}O_8SiNa$, M+Na$^+$).

Methyl 2-{(*E*/*Z*)-3-[(4*S*,5*R*)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-(4-methoxybenzyloxy)-benzoate 196



Procedure A

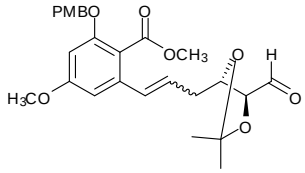
A solution of silyl ether **187** (426 mg, 0.725 mmol) in tetrahydrofuran (5 cm^3) was cooled to 0 °C and *tert*-butylammonium fluoride (1.45 cm^3, 1.5 mmol) was added. After 10 min, the ice-water bath was removed and stirring was continued for 2 h. Diethyl ether (50 cm^3) and water (50 cm^3) were then added and the layers separated. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (30:70)] of the crude residue removed the slight, unidentifiable impurity and afforded alcohol **196** (324 mg, 94%) as a thick yellow oil and as a 7:5 (*E:Z*) mixture of isomers; R_f 0.5 (solvent *H*); $[\alpha]_D^{20}$ +12.0 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2933 (OH), 1652 (C=O), 1607, 1254, 1156 and 1040 (C-O); δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 1.26 (3 H, s, C*H*$_3$), 1.38 (3 H, s, C*H*$_3$), 2.29-2.39 (2 H, m, CH=CHC*H*$_2$), 3.60 (2 H, d, *J* 5.6, C*H*$_2$OH), 3.70 (3 H, s, OC*H*$_3$), 3.73 (3 H, s, COOC*H*$_3$), 3.85 (3 H, s, OCH_2ArOCH_3), 4.02-4.21 (2 H, m, 2×C*H*O), 4.90 (2 H, s, OC*H*$_2$), 6.05-6.12 (1 H, m, CH=C*H*), 6.31 (1 H, d, *J* 2.2, C*H*Ar), 6.33 (1 H, d, *J* 2.2, C*H*Ar), 6.79 (1 H, d, *J* 15.7, C*H*=CH) and 7.18-7.22 (4 H, 2×d, *J* 6.0, 4×C*H*Ar); (*Z*-isomer) (*inter alia*) 5.66-5.71 (1 H, m, HC=C*H*CH_2), 6.89 (1 H, d, *J* 11.4, *H*C=$CHCH_2$); δ_C(100 MHz; $CDCl_3$) (*E*-isomer) 25.4 (OC*C*H$_3$), 28.1 (OC*C*H$_3$), 33.2 (CH=CH*C*H$_2$), 52.3 (COO*C*H$_3$), 55.3 (2×O*C*H$_3$), 61.6 (*C*H$_2$OH), 70.4 (O*C*H$_2$), 77.8 (*C*HO), 77.8 (*C*HO), 99.4 (*C*HAr), 102.2 (*C*HAr), 106.4 (*C*COOCH$_3$), 108.4 (O*C*(CH$_3$)$_2$), 113.9 (2×*C*HAr), 128.6 (*C*H=CH, *C*CH$_2$O, 2×*C*HAr), 129.2 (CH=*C*H), 137.5 (*C*CH=CH), 157.3 (*C*OCH$_3$), 159.3 (*C*OCH$_2$), 161.3 (*C*OCH$_3$) and 168.1 (*C*=O); MS (FAB) *m*/*z* 473.4 $[M+H]^+$; HRMS *m*/*z* 473.2171 (473.2175 calcd for $C_{26}H_{33}O_8$, $M+Na^+$).

Procedure B

To a stirred solution of PMB ether **196** (55.6 mg, 117 μmol) in chloroform (7 cm^3) was added palladium(II) acetate ($Pd(OAc)_2$) (1.3 mg, 58.8 μmol) and

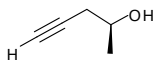
triethylamine (10 μL, 47.9 μmol) at room temperature under argon. To this mixture was added tributyltinhydride (0.07 cm^3, 0.258 mmol) dropwise and the reaction solution was heated under reflux for 50 h. The reaction was cooled down to room temperature and stirred for a further 74 h. The solvent was concentrated slowly *in vacuo,* then potassium fluoride (4 eq., 27 mg, 0.470 mmol), water (4 eq. 0.01 cm^3) and ethyl acetate (3 cm^3) were added and the reaction mixture stirred overnight. The potassium fluoride/tributyltinfluoride solid was filtered through Celite® with a little $MgSO_4$ added to absorb the water. The solvent was concentrated carefully *in vacuo* and the work-up procedure repeated on the now orange solution for 2 h. FCC [petroleum ether-ethyl acetate, (100:0)→(70:30)] of the residue afforded **196** (30 mg, 54%); ^1H NMR spectroscopy showed a slight *Z* to *E* isomerisation of the double bond from 7:5 to 2:1.

Methyl 2-{(*E*/*Z*)-3-[(4*S*,5*S*)-5-formyl-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-(4-methoxybenzyloxy)-benzoate <u>197</u>



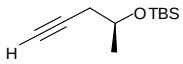
To a −78 °C solution of oxalyl chloride (0.10 cm^3, 0.203 mmol) in anhydrous dichloromethane (0.1 cm^3) was added dimethylsulfoxide (0.03 cm^3, 0.406 mmol). After stirring for 1 h, a solution of alcohol **196** in dichloromethane (0.7 cm^3) was added and stirring continued for a further 1 h. Triethylamine (0.08 cm^3, 0.609 mmol) was added and the reaction allowed to warm up to room temperature. The reaction was diluted with dichloromethane (7 cm^3), quenched with 1 M hydrochloric acid (7 cm^3) and then extracted with dichloromethane (2×10 cm^3). The combined organic layers were washed with saturated aqueous sodium chloride (10 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford aldehyde **197** as an unstable yellow oil; δ_H(400 MHz; $CDCl_3$) 9.72 (C*H*O).

(*S*)-(+)-Pent-4-yn-2-ol 190[89]



A stirred suspension of lithium acetylide ethylenediamine complex (4.74 g, 51.6 mmol) in anhydrous dimethylsulfoxide (100 cm^3) at 0 °C was treated with a solution of *S*-(+)-propylene oxide (3.0 cm^3, 43.0 mmol) dropwise. The reaction was then allowed to warm up to room temperature where it was stirred for 48 h. The suspension was poured onto ice (100 cm^3) and extracted with diethyl ether (4×70 cm^3). The combined ether extracts were washed with brine (6×30 cm^3), water (2×30 cm^3) and dried over anhydrous magnesium sulfate. Careful evaporation of the solvent under atmospheric pressure yielded the crude alcohol **190** (3.6 g, 100%) as a colourless liquid, which was taken on without any further purification; $[\alpha]_D^{22}$ +16.5 (*c* 1.0, $CHCl_3$) (lit.,[89] $[\alpha]_D^{26}$ +17.8 (*c* 0.2, $CHCl_3$)); ν_{max}(film)/cm^{-1} 3379 (OH), 3280 (C≡C) and 2340; δ_H(400 MHz; $CDCl_3$) 1.26 (3 H, d, *J* 6.0, C*H*$_3$), 2.08 (1 H, t, *J* 2.7, *H*C≡C), 2.33 (1 H, ddd, *J* 2.7, 5.3 and 16.0, C*H*$_2$), 2.42 (1 H, ddd, *J* 2.7, 6.2 and 16.0, C*H*$_2$) and 3.99-4.04 (1 H, m, *H*COH). All spectral data matches that reported in the literature.[89]

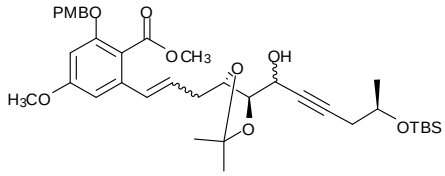
(*S*)-(-)-*tert*-Butyldimethyl(pent-4-yn-2-yloxy)silane 55[148]



A solution of alcohol **190** (3.6 g, 42.8 mmol) and imidazole (5.83 g, 85.6mmol) in dimethylformamide (215 cm^3) under argon was treated with *tert*-butyldimethylsilyl chloride (7.09 g, 47.1 mmol) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (70 cm^3) and the product extracted with diethyl ether (3×50 cm^3). The combined ether extracts were washed with brine (3×50 cm^3) then water (3×50 cm^3) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-diethyl ether (90:10)] of the crude residue afforded silyl ether **55** (6.6 g, 78%) as a colourless liquid; $[\alpha]_D^{23}$ -0.9 (*c* 1.0, $CHCl_3$) (lit.,[148] $[\alpha]_D^{25}$ -1.2 (*c* 10.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3309 (C≡C) and 1040 (C-O); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s Si(C*H*$_3$)$_2$), 0.90 (9 H, s, SiC(C*H*$_3$)$_3$), 1.22 (3 H, d, *J* 6.1, C*H*$_3$), 2.00 (1 H, t, *J* 2.7, *H*C≡C), 2.23 (1 H, ddd, *J* 2.7, 7.0 and 16.5, C*H*$_2$), 2.33 (1 H, ddd, *J* 2.7, 5.5 and 16.5, C*H*$_2$) and 3.98-4.03 (1 H, m, *H*COTBS); δ_C(100 MHz; $CDCl_3$) -5.0 (Si(*C*H$_3$)$_2$), 18.2 (Si*C*(CH$_3$)$_3$), 25.0 (*C*H$_3$), 25.8

(SiC(CH_3)$_3$), 31.1 (CH_2), 66.9 (*H*COTBS), 69.7 (H*C*≡C) and 82.2 (HC≡*C*). All spectral data matches that reported in the literature.[148]

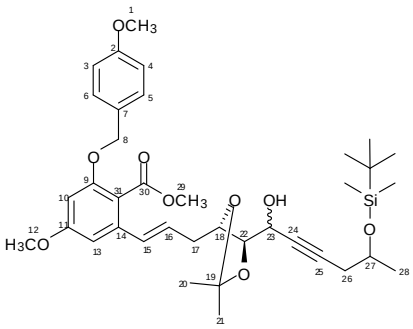
Methyl 2-(3-{(4*S*,5*R*)-5-[(*R*)-5-(*tert*-butyldimethylsilanyloxy)-1-hydroxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-4-methoxy-6-(4-methoxy-benzyloxy)-benzoate 198



A solution of alkyne **55** (29 mg, 0.155 mmol) in THF (1 cm^3) at room temperature was treated with ethylmagnesium bromide (0.04 cm^3, 0.124 mmol) and the resulting light brown mixture was stirred for 3 h.

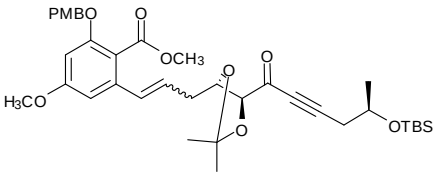
Whilst the above deprotonation was being carried out, a −78 °C solution of oxalyl chloride (0.10 cm^3, 0.207 mmol) in tetrahydrofuran (1 cm^3) at −78 °C was treated with dimethylsulfoxide (0.03 cm^3, 0.414 mmol). After stirring at −78 °C for 30 min, a solution of alcohol **196** (49 mg, 0.103 mmol) in tetrahydrofuran (0.5 cm^3) was added and stirring continued for 1 h. Triethylamine (0.12 cm^3, 0.829 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min at room temperature the reaction mixture was cooled back down to −78 °C and the deprotonated alkyne solution was added. The resulting mixture was allowed to warm up to room temperature and was stirred overnight. The reaction was then quenched with saturated aqueous ammonium chloride (10 cm^3) and extracted with ethyl acetate (3×15 cm^3). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl actetate (60:40)] of the crude residue afforded alcohol **198** (20 mg, 30%) as a thick, yellow oil and as an inseparable mixture of diastereoisomers; R_f 0.57 (solvent *I*); ν_{max}(film)/cm^{-1} 2925 (OH), 2841, 1732 (C=O), 1596 (C=C), 1258 and 1112 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(CH_3)$_2$), 0.79 (9 H, s, SiC(CH_3)$_3$), 1.18 (3 H, s, CH_3), 1.38 (3 H, s, CCH_3), 1.54 (3 H, s, CCH_3), 2.17-2.22 (2 H, m, CH_2), 2.42-2.48 (2 H, m, CH_2), 3.83-3.87 (1 H, m, C*H*OTBS), 3.79 (3 H, s, OCH$_2$PhOCH_3), 3.82 (3 H, s, OCH_3), 3.87 (3 H, s, CO_2CH_3), 4.24-4.35 (2 H, m, 2×OC*H*), 4.44-4.50 (3 H, m, C*H*OH and OCH_2PhOCH$_3$), 6.21-6.29 (1 H, m, CH=C*H*), 6.42-6.49 (1 H, m, C*H*=CH), 6.63 (1 H, s, C*H*), 6.71 (1 H, s, C*H*), 6.90 (2 H, d, *J* 8.5, 2×C*H*) and 7.30

(2 H, d, *J* 8.5, 2×C*H*); δ_C(100 MHz; $CDCl_3$) -4.8 (Si(CH_3)$_2$), 17.9 (Si*C*(CH_3)$_3$), 19.7 (C28), 25.3 (C20), 25.9 (SiC(CH_3)$_3$), 26.9 (C26), 27.7 (C21), 31.3 (C31), 33.5 (C17), 52.0 (C29), 55.3 (C1), 55.6 (C12), 62.4 (C22), 70.5 (C23), 73.0 (C8), 73.3 (C27), 79.9 (C18), 80.1 (C25), 84.5 (C24), 100.9 (C10), 103.8 (C13), 108.8 (C19), 113.7 (C3 and C4), 128.7 (C16), 129.3 (C15), 129.3 (C18), 130.2 (C5 and C6), 137.6 (C14), 155.6 (C2), 161.3 (C9), 168.2 (C11) and 171.3(C30); MS (CI) *m*/*z* 668 $[M]^+$; HRMS *m*/*z* 668.3375 (668.3381 calcd for $C_{37}H_{52}O_9Si$, M^+).



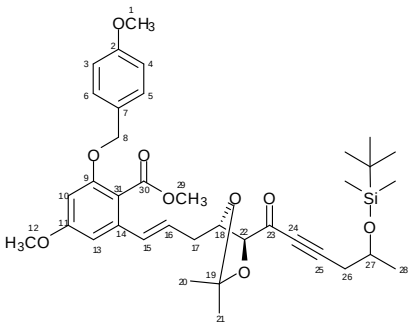
^{13}C assignment

Methyl 2-((*E*/*Z*)-3-{(4*S*,5*S*)-5-[(*R*)-5-(*tert*-butyldimethylsilyloxy)hex-2-ynoyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-4-methoxy-6-(4-methoxybenzyloxy)benzoate <u>245</u>



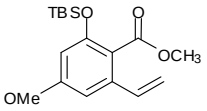
A solution of oxalyl chloride (30 µL, 59.8 µmol) in anhydrous dichloromethane (0.6 cm^3) was treated with dimethylsulfoxide (10 µL, 0.119 mmol) at −78 °C. After stirring at −78 °C for 30 min, a solution of alcohol **198** (20 mg, 29.9 µmol) in anhydrous dichloromethane (0.3 cm^3) was added and stirring continued for 1 h. Triethylamine (0.03 cm^3, 0.239 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min at room temperature the reaction mixture was diluted with dichloromethane (10 cm^3) and separated with 1 N hydrochloric acid (10 cm^3). The organic layers were washed with saturated aqueous sodium hydrogencarbonate (20 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford **245** (20 mg, 100%) as an off-white oil requiring no further purification; R_f 0.77 (Solvent *I*); δ_H(400 MHz; $CDCl_3$) 0.05 (6 H, s, Si(CH_3)$_2$), 0.86 (9 H, s, SiC(CH_3)$_3$), 1.22 (3 H, s, CH_3), 1.39 (3 H, s, CCH_3), 1.54 (3 H, s, CCH_3), 2.30-2.55 (4 H, m, 2×CH_2), 3.79 (6 H,

2×s, OCH_2PhOCH_3 and OCH_3), 3.84 (3 H, s, CO_2CH_3), 3.98-4.04 (1 H, m, CHOTBS), 4.24-4.35 (2 H, m, 2×OCH), 5.00 (2 H, s, OCH_2PhOCH_3), 5.78-5.82 (1 H, m, CH=CH), 6.18-6.22 (1 H, m, CH=CH), 6.40 (1 H, s, CH), 6.62 (1 H, s, CH), 6.90 (2 H, d, *J* 8.5, 2×CH) and 7.30 (2 H, d, *J* 8.5, 2×CH); δ_C(100 MHz; $CDCl_3$) -4.8 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 19.7 (C28), 25.3 (C20), 25.9 ($SiC(CH_3)_3$), 26.8 (C26), 27.7 (C21), 31.2 (C31), 33.6 (C17), 52.0 (C29), 55.3 (C1), 55.8 (C12), 62.4 (C22), 73.1 (C8), 73.3 (C27), 79.9 (C18), 80.0 (C25), 84.5 (C24), 101.0 (C10), 103.7 (C13), 108.8 (C19), 113.9 (C3 and C4), 128.8 (C16), 129.3 (C15), 129.4 (C18), 130.0 (C5 and C6), 137.8 (C14), 155.7 (C2), 161.3 (C9), 168.1 (C11),170.9.3(C30) and 185.7 (C23).



^{13}C Assignment

Methyl 2-(*tert*-butyldimethylsilanyloxy)-4-methoxy-6-vinyl-benzoate <u>120</u>



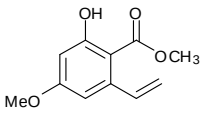
Lithium chloride (430 mg, 10.1 mmol) was dissolved in anhydrous dimethylformamide (24 cm^3) and then tri-2-furylphosphine (125 mg, 0.534 mmol) and tris[dibenzylideneacetone]dipalladium(0) ($Pd_2(dba)_3$) (62 mg, 0.0675 mmol) were added sequentially at room temperature followed by a solution of triflate **119** (1.5 g, 3.37 mmol) in anhydrous dimethylformamide (10 cm^3). The resulting reaction mixture was stirred for 30 min before tributylvinyl tin (1.2 cm^3, 4.05 mmol) was added. The reaction solution was heated to 60 °C for 3 h after which it was cooled down to room temperature, diluted with dichloromethane (40 cm^3) and water (40 cm^3). The aqueous layer was removed and the organic phase washed with 1 M potassium fluoride aqueous solution (3×50 cm^3). The reaction mixture was shaken in a separatory funnel for 1 minute each wash. After the first wash solid tributyltinfluoride precipitate formed at the interface and was filtered out through Celite®. The combined organic layers were washed with

brine (50 cm^3), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (100:0)→(95:5) *then* petroleum ether-diethyl ether (100:0)→(95:5)] of the crude residue afforded an inseparable mixture of alkenes **120**; R_f 0.60 (Solvent *A*) and **210**; R_f 0.59 (Solvent *A*) (736 mg) as a white solid.

Silylated compound **120**: δ_H(400 MHz; $CDCl_3$) 0.01 (6 H, s, $Si(CH_3)_2$), 0.76 (9 H, s, $SiC(CH_3)_3$), 3.82 (3 H, s, C*H*$_3$), 3.91 (3 H, s, COOC*H*$_3$), 5.21 (1 H, dd, *J* 1.6 and 10.8, CH=C*H*$_2$), 5.45 (1 H, dd, *J* 1.6 and 17.1, CH=C*H*$_2$), 6.30 (1 H, d, *J* 2.4, C*H*(OTBS)), 6.42 (1 H , d, *J* 2.4, C*H*($COCH_3$)) and 6.68-6.75 (1 H, m, C*H*=CH_2); δ_C(100 MHz; $CDCl_3$) -4.3 ($Si(CH_3)_2$), 17.8 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 52.0 (CO_2CH_3), 55.9 (OCH_3), 100.3 (*C*H), 103.5 (*C*H), 108.7 (CCO_2CH_3), 115.9 (HC=*C*H_2), 138.4 (H*C*=CH_2), 143.9 (*C*HC=CH_2), 164.3 (*C*OH), 165.0 ($COCH_3$) and 171.8 (*C*=O).

Desilylated compound **210**: δ_H(400 MHz; $CDCl_3$) 3.78 (3 H, s, C*H*$_3$), 3.87 (3 H, s, COOC*H*$_3$), 5.18 (1 H, dd, *J* 1.5 and 10.8, CH=C*H*$_2$), 5.42 (1 H, dd, *J* 1.5 and 17.1, CH=C*H*$_2$), 6.36 (1 H, d, *J* 2.6, C*H*(OH)), 6.46 (1 H , d, *J* 2.6, C*H*($COCH_3$)), 7.23-7.30 (1 H, m, C*H*=CH_2) and 11.61 (1 H, s, O*H*).

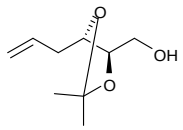
Methyl 2-hydroxy-4-methoxy-6-vinylbenzoate <u>210</u>[149]



A solution of alkenes **120** and **210** (736 mg, 2.28 mmol) in anhydrous tetrahydrofuran (10 cm^3) was cooled down to 0 °C. *tetra*-Butylammonium fluoride (4.5 cm^3, 4.56 mmol) was added and the ice-water bath was removed after 10 min, whereafter the reaction was allowed to warm up to room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (30 cm^3) and diluted with water (30 cm^3). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was passed through a pad of silica gel which was eluted with 20% diethyl ether-petroleum ether to remove excess TBS. The fractions were concentrated under reduced pressure to afford phenol **210** (517 mg, 74% *over two steps*) as a white solid; R_f 0.56 (Solvent *A*); mp 78-80 °C (from diethyl ether-petroleum ether) (lit.,[149] 75-76 °C); ν_{max} (film)/cm^{-1} 2925, 2854, 1733 (C=O), 1648 (C=C), 1437,

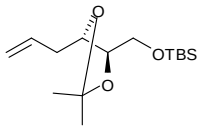
1328, 1257, 1159; δ_H(400 MHz; $CDCl_3$) 3.78 (3 H, s, OC*H*$_3$), 3.87 (3 H, s, COOC*H*$_3$), 5.18 (1 H, dd, *J* 1.6 and 10.8, CH=C*H*$_2$), 5.42 (1 H, dd, *J* 1.6 and 17.1, CH=C*H*$_2$), 6.36 (1 H, d, *J* 2.6, C*H*), 6.46 (1 H , d, *J* 2.6, C*H*), 7.23-7.33 (1 H, m, C*H*=CH_2) and 11.61 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 52.1 (CO_2CH_3), 55.5 (OCH_3), 100.3 (*C*H), 103.9 (*C*H), 108.3 (CCO_2CH_3), 115.8 (HC=CH_2), 138.4 (H*C*=CH_2), 143.6 ($CHC=CH_2$), 164.3 (*C*OH), 165.1 ($COCH_3$) and 171.7 (*C*=O); MS (EI) *m*/*z* 208.0 $[M]^+$; HRMS *m*/*z* 208.0734 (208.0736 calcd for $C_{11}H_{12}O_4$, M^+). All spectral data matches that reported in the literature.[149]

((4*S*,5*R*)-5-Allyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol 213[76]



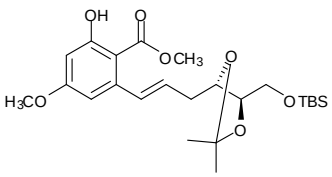
Potassium bis(trimethylsilyl)amide (32 cm^3, 16.1 mmol) was added to a −78 °C stirred suspension of methyl triphenylphosphonium iodide (8.74 g, 21.5 mmol) in anhydrous tetrahydrofuran (40 cm^3). The reaction was warmed up to 0 °C and stirred for 30 min before cooling back down to −78 °C. A solution of acetonide **144** (937 g, 5.38 mmol) in anhydrous tetrahydrofuran (10 cm^3) was added and the yellow solution was warmed up to room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (50 cm^3) and extracted with ethyl acetate (3×50 cm^3). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (100:0)→(70:30)→(60:40)] of the crude residue afforded alcohol **213** (557 g, 60%) as a yellow oil; R_f 0.54 (Solvent *M*); $[\alpha]_D^{19}$ -15.7 (*c* 1.0, $CHCl_3$) (lit.,[76] $[\alpha]_D^{25}$ +54.8 (*c* 0.26, $CHCl_3$); ν_{max} (film)/cm^{-1} 3450 (OH), 2987, 2853, 1643, 1457, 1379, 1235, 1217, 1045 (C-O); δ_H(400 MHz;$CDCl_3$) 1.37 (3 H, s, C*H*$_3$), 1.48 (3 H, s, C*H*$_3$), 2.23-2.32 (1 H, m, C*H*$_2$), 2.36-2.46 (1 H, m, C*H*$_2$), 3.64 (2 H, t, *J* 5.8, C*H*$_2$), 4.17 (1 H, q, *J* 5.9, C*H*CH_2), 4.25 (1 H, q, *J* 5.9, C*H*CH_2OH), 5.09-5.18 (2 H, m, C*H*$_2$=CH) and 5.78-5.90 (1 H, m, CH_2=C*H*); δ_C(100 MHz; $CDCl_3$) 25.4 (*C*H_3), 28.0 (*C*H_3), 33.5 (*C*H_2), 61.3 (*C*H_2OH), 76.2 (*C*H), 77.8 (*C*H), 108.1 (*C*$(CH_3)_2$), 117.2 (H*C*=$CHCH_2$) and 134.2 (HC=*C*HCH_2); MS (CI) *m*/*z* 173 $[M+H]^+$; HRMS *m*/*z* 173.1174 (173.1178 calcd for $C_9H_{17}O_3$, $M+H^+$). All spectral data matches that reported in the literature.[76]

((4*S*,5*S*)-5-Allyl-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-*tert*-butyldimethylsilane 208



Alcohol **213** (446 mg, 2.59 mmol) was dissolved in anhydrous dichloromethane (13 cm^3) and triethylamine (0.65 cm^3, 4.66 mmol) and dimethylaminopyridine (32 mg, 0.259 mmol) were added sequentially at room temperature. The reaction mixture was stirred for 5 min and then *tert*-butyldimethylsilyl chloride (507 mg, 3.37 mmol) was added. After 18 h, the reaction was quenched with saturated aqueous ammonium chloride (10 cm^3) and extracted with dichloromethane (3×10 cm^3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded silyl ether **208** (643 mg, 87%) as an orange oil; R_f 0.83 (Solvent *A*); $[\alpha]_D^{23}$ -0.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2954, 1643 (C=C), 1472, 1257 (Si-CH_3); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, Si(C*H*$_3$)$_2$), 0.89 (9 H, s, SiC(C*H*$_3$)$_3$), 1.34 (3 H, s, C*H*$_3$), 1.43 (3 H, s, C*H*$_3$), 2.29-2.46 (2 H, m, C*H*$_2$), 3.59-3.71 (2 H, m, C*H*$_2$OTBS), 4.03-4.07 (1 H, m, C*H*CH_2), 4.18-4.22 (1 H, m, C*H*CH_2OTBS), 5.00-5.16 (2 H, m, C*H*$_2$=CH) and 5.83-5.95 (1 H, m, CH_2=C*H*); δ_C(100 MHz; $CDCl_3$) -5.5 (Si*C*H$_3$), -5.4 (Si*C*H$_3$), 18.3 (*C*(CH$_3$)$_3$), 25.5 (*C*H$_3$), 25.9 (3×*C*H$_3$), 28.1 (*C*H$_3$), 33.8 (*C*H$_2$), 61.9 (*C*H$_2$OTBS), 76.7 (*C*H), 77.8 (*C*H), 107.9 (*C*(CH$_3$)$_2$), 116.8 (*C*H=CHCH_2) and 135.2 (CH=*C*HCH_2); MS (CI) *m*/*z* 287.1 $[M+H]^+$; HRMS *m*/*z* 287.2047 (287.2042 calcd for $C_{15}H_{31}O_3Si$, $M+H^+$).

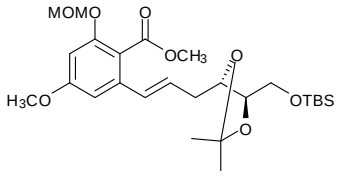
2-{(*E*)-3-[(4*S*,5*S*)-5-(*tert*-butyldimethylsilanyloxymethyl)-2,2-dimethyl-methyl [1,3]dioxolan-4-yl]-propenyl}-6-hydroxy-4-methoxybenzoate 186



A stirred solution of styrene **210** (966 mg, 4.64 mmol) and alkene **208** (2.66 g, 9.28 mmol) in anhydrous dichloromethane (75 cm^3) was treated with Hoveyda-Grubbs second generation catalyst (872 mg, 1.39 mmol) and the resulting mixture was heated to reflux in the dark for 48 h. The reaction mixture was allowed to cool down to room temperature and was filtered through silica gel

and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (95:5)→(90:10)] of the crude residue afforded alkene **186** (1.4 g, 65%) as a colourless oil; R_f 0.53 (Solvent *N*); $[\alpha]_D^{23}$ –1.3 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2930 (OH), 2856, 1655 (C=C), 1437, 1327, 1213, 1159 and 1097 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(C*H*$_3$)$_2$), 0.82 (9 H, s, SiC(C*H*$_3$)$_3$), 1.27 (3 H, s, C*H*$_3$), 1.37 (3 H, s, C*H*$_3$), 2.35-2.50 (2 H, m, C*H*$_2$), 3.55-3.69 (2 H, m, C*H*$_2$), 3.80 (3 H, s, OC*H*$_3$), 3.89 (3 H, s, COOC*H*$_3$), 4.12-4.30 (2 H, m, 2×OC*H*), 5.98 (1 H, dt, *J* 6.9 and 15.5, CH=C*H*), 6.36 (1 H, d, *J* 2.5, C*H*(Ar)), 6.48 (1 H, d, *J* 2.5, C*H*(Ar)), 7.01 (1 H, d, *J* 15.5, C*H*=CH) and 11.61 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) -5.3 (Si*C*H$_3$), -5.2 (Si*C*H$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 25.7 (*C*H), 26.0 (SiC(*C*H$_3$)$_3$), 28.3 (*C*H), 33.2 (*C*H$_2$), 52.1 (CO_2*C*H$_3$), 55.5 (O*C*H$_3$), 62.0 (*C*H$_2$OTBS), 77.3 (*C*H(O)), 77.8 (*C*H(O)), 99.9 (CH(Ar)), 103.8 (CH(Ar)), 108.1 (*C*CO_2CH_3), 116.6 (*C*(CH$_3$)$_2$), 129.2 (HC=*C*HCH$_2$), 133.0 (H*C*=CHCH$_2$), 143.2 (*C*HC=CHCH$_2$), 164.1 (*C*OH), 165.1 (*C*OCH3) and 171.9 (*C*=O); MS (CI) *m*/*z* 467 $[M+H]^+$; HRMS *m*/*z* 467.2466 (467.2465 calcd for $C_{24}H_{39}O_7Si$, $M+H^+$).

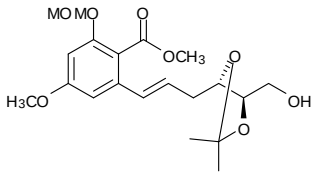
Methyl 2-{(*E*)-3-[(4*S*,5*S*)-5-(*tert*-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethyl-benzoate <u>211</u>



Phenol **186** (263 mg, 0.565 mmol) was dissolved in anhydrous dichloromethane (6 cm^3) and *N*,*N*'-diisopropylethylamine (DIPEA) (0.30 cm^3, 1.60 mmol) was added at room temperature. The reaction mixture was cooled down to 0 ^oC and bromomethyl methyl (MOMBr) ether (0.10 cm^3, 1.13 mmol) was slowly added. The ice-water bath was removed after 10 min and the reaction allowed to warm up to room temperature and stirred for 18 h. After this time, starting material was still present, so the above procedure was repeated and the reaction left for another 18 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (40 cm^3) and extracted with ethyl acetate (3×40 cm^3). The combined organic layers were washed with water (50 cm^3), then brine (50 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-diethyl ether (80:20)→(70:30)] of the crude residue afforded MOM ether **211** (170 mg, 60%) as a colourless oil; R_f 0.26

(Solvent *N*); $[\alpha]_D^{20}$ -29.3 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2984, 2938, 1663 (C=C), 1369; δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(CH_3)$_2$), 0.82 (9 H, s, SiC(CH_3)$_3$), 1.26 (3 H, s, OCCH_3), 1.36 (3 H, s, OCCH_3), 2.40-2.58 (2 H, m, CH=CHCH_2), 3.45 (3 H, s, OCH_2OCH_3), 3.63-3.71 (2 H, m, 2×C*H*OC), 3.80 (3 H, s, OCH_3), 3.89 (3 H, s, COOCH_3), 4.09-4.15 (1 H, m, CH_2), 4.18-4.23 (1 H, m, CH_2), 5.13 (2 H, s, OCH_2OCH_3), 6.21-6.31 (1 H, m, CH=C*H*CH_2), 6.42 (1 H, d, *J* 15.7, C*H*=$CHCH_2$), 6.59 (1 H, d, *J* 2.2, C*H*(Ar)) and 6.69 (1 H, d, *J* 2.2, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) -5.3 (Si*C*H_3), -5.2 (Si*C*H_3), 18.4 (Si*C*(CH_3)$_3$), 25.7 (*C*H), 26.0 (SiC(*C*H_3)$_3$), 28.3 (*C*H), 33.4 (*C*H_2), 52.2 ($CO_2C$$H_3$), 55.5 (O$CH_3$), 56.3 ($OCH_2OC$H3), 62.0 (*C*$H_2$OTBS), 77.3 (*C*H(O)), 77.8 (*C*H(O)), 95.9 (OCH2OCH3), 100.0 (*C*HAr), 103.8 (*C*HAr), 108.1 (*C*CO_2CH_3), 116.6 (*C*(CH_3)$_2$), 129.2 (HC=*C*HCH_2), 130.6 (H*C*=$CHCH_2$), 137.7 (*C*HC=$CHCH_2$), 155.7 (*C*OCH_2OCH_3), 161.4 (*C*OCH_3) and 168.5 (*C*=O); MS (EI) *m*/*z* 197 $[M]^+$; HRMS *m*/*z* 197.0772 (197.0784 calcd for $C_8H_{14}NaO_4$, M^+).

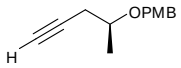
Methyl 2-[(*E*)-3-((4*S*,5*R*)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-propenyl]-4-methoxy-6-methoxymethylbenzoate <u>212</u>



MOM ether **211** (373 mg, 0.730 mmol) was dissolved in anhydrous tetrahydrofuran (5 cm^3) and cooled down to 0 °C before the addition of *tetra*-butylammonium fluoride (1.5 cm^3, 1.46 mmol). After 10 min, the ice-water bath was removed and the reaction allowed to warm up to room temperature. After 1.5 h, the reaction was diluted with ethyl acetate (10 cm^3) and water (10 cm^3) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (30:70)] of the crude residue afforded alcohol **212** (268 mg, 93%) as an off white oil; R_f 0.40 (Solvent *O*); $[\alpha]_D^{20}$ -6.0 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2988, 2937, 1601 (C=C), 1433; δ_H(400 MHz; $CDCl_3$) 1.35 (3 H, s, OCCH_3), 1.48 (3 H, s, OCCH_3), 2.37-2.47 (1 H, m, CH=CHCH_2), 2.49-2.58 (1 H, m, CH=CHCH_2), 3.45 (3 H, s, OCH_2OCH_3), 3.67 (2 H, t, *J* 5.8, CH_2OH), 3.79 (3 H, s, OCH_3), 3.88 (3 H, s, COOCH_3), 4.20 (1 H, q, *J* 5.8, CH_2C*H*), 4.28 (1 H, dt, *J* 5.8 and 8.0, C*H*CH_2OH), 5.13 (2 H, s, OCH_2OCH_3), 6.18 (1 H, ddd, *J* 6.1, 7.8 and 15.6, CH=C*H*CH_2), 6.43 (1 H, d, *J* 15.6, C*H*=$CHCH_2$), 6.59 (1 H, d, *J* 2.1, C*H*(Ar)) and

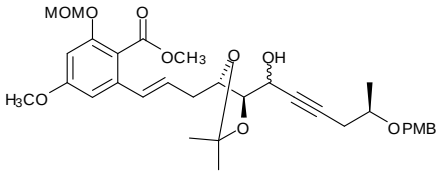
6.69 (1 H, d, *J* 2.1, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 25.4 (C(*C*H_3)), 28.0 (C(*C*H_3)), 33.2 (*C*H_2), 52.2 (CO_2*C*H_3), 55.4 (O*C*H_3), 56.1 (OCH_2OCH_3), 61.3 (*C*H_2OH), 76.3 (*C*H(O)), 77.8 (*C*H(O)), 94.7 OCH_2OCH_3), 100.6 (*C*HAr), 103.6 (*C*HAr), 108.2 (*C*CO_2CH_3), 116.2 (*C*$(CH_3)_2$), 128.8 (HC=*C*HCH_2), 129.6 H*C*=$CHCH_2$), 137.3 (*C*HC=$CHCH_2$), 155.5 *C*OCH_2OCH_3), 161.2 (*C*OCH_3) and 168.3 (*C*=O); MS (EI) *m*/*z* 396 $[M]^+$; HRMS *m*/*z* 396.1787 (396.1784 calcd for $C_{20}H_{28}O_8$, M^+).

1-Methoxy-4-((*S*)-1-methyl-but-3-ynyloxymethyl)-benzene <u>223</u>[150]



To a suspension of 60% NaH in mineral oil (2.51 g, 62.9 mmol) in anhydrous dimethylformamide (70 cm^3) at 0 °C was added a solution of the freshly generated crude alcohol **190** (4.81 g, 57.2 mmol) in anhydrous dimethylformamide (70 cm^3). The reaction mixture was stirred for 15 min, then *p*-methoxybenzyl chloride (11.6 cm^3, 85.8 mmol) was added and the reaction mixture allowed to warm up to room temperature and stirred for 17 h. The reaction mixture was poured onto brine (400 cm^3) and extracted with diethyl ether (3×100 cm^3). The combined organic layers were concentrated under reduced pressure, then washed with brine (300 cm^3), dried over anhydrous magnesium sulfate, filtered through cotton wool and the solvent removed under vacuum. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded PMB ether **223** (5.26 g, 45%) as a colourless oil; $[\alpha]_D^{20}$ –8.8 (*c* 1.0, $CHCl_3$) (lit.,[150] $[\alpha]_D^{26}$ +6.5 (*c* 1.04, $CHCl_3$); ν_{max}(film)/cm^{-1} 3294 (C≡C), 1511 (C=C), 1243 and 1033 (C-O); δ_H(400 MHz; $CDCl_3$) 1.34 (3 H, d, *J* 6.0, C*H*$_3$), 2.08 (1 H, s, *H*C), 2.35-2.42 (1 H, m, HCC*H*$_2$), 2.51-2.58 (1 H, m, HCC*H*$_2$), 3.71 (1 H, app. sext, *J* 6.0 and 12.3, C*H*CH_3), 3.82 (3H, s, OC*H*$_3$), 4.53 (2 H, s, OC*H*$_2$), 6.91 (2 H, d, *J* 8.6, 2×C*H*Ar) and 7.32 (2 H, d, *J* 8.6, 2×C*H*Ar); δ_C(100 MHz; $CDCl_3$) 19.5 (CH_3), 26.0 (CH_2), 55.2 (OCH_3), 70.1 (*C*HCH_3), 70.3 (H*C*CCH_2), 72.8 (OCH_2), 81.3 (HC*C*CH_2), 113.8 (2×CHAr), 129.3 (2×CHAr), 130.6 (OCH_2*C*) and 159.2 (*C*OCH_3). All ^{1}H and ^{13}C data matches that reported in the literature.[150]

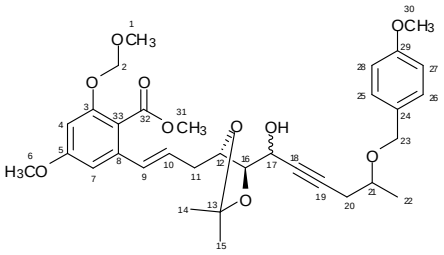
Methyl 2-((*E*)-3-{(4*S*,5*R*)-5-[(*R*)-1-hydroxy-5-(4-methoxybenzyloxy)-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-4-methoxy-6-methoxymethylbenzoate <u>222</u>



A solution of alkyne **223** (466 mg, 2.43 mmol) in anhydrous tetrahydrofuran (9.5 cm^3) was treated with ethylmagnesium bromide (0.76 cm^3, 2.27 mmol) at room temperature and the resulting solution was stirred for 5 h.

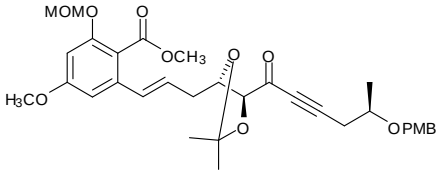
Whilst the above deprotonation was being carried out, a −78 °C solution of oxalyl chloride (1.52 cm^3, 3.03 mmol) in anhydrous tetrahydrofuran (15 cm^3) was treated with dimethylsulfoxide (0.47 cm^3, 6.06 mmol). After 30 min, a solution of alcohol **212** (560 mg, 1.52 mmol) in anhydrous tetrahydrofuran (7 cm^3) was added and the reaction was stirred at −78 °C for 1 h. After this time, triethylamine (1.69 cm^3, 12.1 mmol) was added and the reaction was allowed to warm up to room temperature. After 30 min, the reaction was cooled back down to −78 °C and a solution of the deprotonated alkyne was added. The reaction mixture was allowed to warm to room temperature and stirring continued for 14 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 cm^3) and extracted with ethyl acetate (2×40 cm^3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded propargylic alcohol **222** (585 mg, 65%) as a thick, yellow oil and as an inseparable mixture of diastereoisomers; R_f 0.33 (Solvent *I*); $[\alpha]_D^{19}$ -0.9 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928, 1728 (C=O), 1601 (C=C), 1250, 1153 and 1034 (C-O); δ_H(400 MHz; $CDCl_3$) 1.30 (3 H, s, CH_3), 1.38 (3 H, s, CCH_3), 1.54 (3 H, s, CCH_3), 2.39-2.78 (4 H, m, 2×CH_2), 3.50 (3 H, s, OCH_2OCH_3), 3.69-3.71 (1 H, m, C*H*OPMB), 3.81 (3 H, s, OCH_2ArOCH_3), 3.83 (3 H, s, OCH_3), 3.91 (3 H, s, CO_2CH_3), 4.10-4.18 (1 H, m, OC*H*), 4.24-4.35 (1 H, m, OC*H*), 4.45-4.55 (3 H, m, C*H*OH and OCH_2ArOCH_3), 5.18 (2 H, s, OCH_2OCH_3), 6.19-6.29 (1 H, m, CH=C*H*), 6.49 (1 H, d, *J* 15.7, C*H*=CH), 6.62 (1 H, s, C*H*), 6.71 (1 H, s, C*H*), 6.89 (2 H, d, *J* 8.5, 2×C*H*) and 7.27 (2 H, d, *J* 8.5, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 19.8 (C22), 25.5 (C14), 26.5 (C20), 27.6 (C15), 31.0 (C33), 33.3 (C11), 52.3 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.1 (C16), 70.4 (C17), 72.9

(C23), 73.1 (C21), 79.7 (C12), 80.4 (C19), 84.5 (C18), 94.8 (C2), 100.7 (C4), 103.8 (C7), 108.6 (C13), 113.8 (C27 and C28), 128.7 (C10), 129.2 (C9), 129.3 (C24), 130.2 (C25 and C26), 137.6 (C8), 155.6 (C29), 161.3 (C3), 168.0 (C5) and 171.1 (C32); MS (FAB) *m*/*z* 599.3 $[M+H]^+$; HRMS *m*/*z* 599.2862 (599.2856 calcd for $C_{33}H_{43}O_{10}$, $M+H^+$).



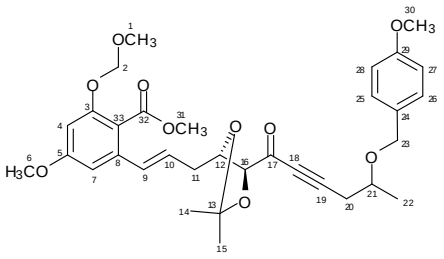
^{13}C Assignment

Methyl 4-methoxy-2-((*E*)-3-{(4*S*,5*S*)-5-[(*R*)-5-(4-methoxybenzyloxy)-hex-2-ynoyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate <u>246</u>



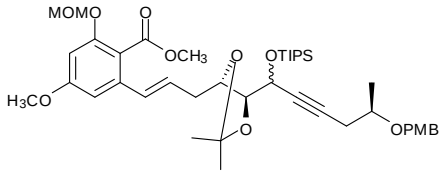
A solution of oxalyl chloride (0.19 cm^3, 0.376 mmol) in anhydrous dichloromethane (2 cm^3) was treated with dimethylsulfoxide (0.06 cm^3, 0.752 mmol) at −78 °C. After 30 min, a solution of alcohol **222** (112 mg, 0.188 mmol) in anhydrous dichloromethane (1 cm^3) was added and the reaction mixture stirred at −78 ° for 1 h. After this time, triethylamine (0.21 cm^3, 1.50 mmol) was added and the reaction was allowed to warm to room temperature, where it was stirred for a further 30 min. The reaction mixture was diluted with dichloromethane (10 cm^3) and quenched with 1 N hydrochloric acid (10 cm^3). The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogencarbonate (20 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded ketone **246** (95 mg, 85%) as a thick, yellow oil; R_f 0.53 (Solvent *I*); $[\alpha]_D^{23}$ -3.1 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2203, 1714 (C=O), 1575 (C=C) and 1100; δ_H(400 MHz; $CDCl_3$) 1.23 (3 H, d, *J* 6.1, CH_3), 1.32 (3 H, s, CCH_3), 1.56 (3 H, s, CCH_3), 2.27-2.66 (4 H, m, 2×CH_2), 3.39 (3 H, s, OCH_2OCH_3), 3.71 (3 H, s, OCH_2ArOCH_3), 3.65-3.73 (1 H, m,

C*H*OPMB), 3.74 (3 H, s, OC*H*$_3$), 3.81 (3 H, s, CO_2CH_3), 4.36-4.43 (3 H, m, OC*H* and OCH_2ArOCH_3), 4.50 (1 H, d, *J* 7.3, OC*H*), 5.08 (2 H, s, OCH_2OCH_3), 6.08-6.18 (1 H, m, CH=C*H*), 6.38 (1 H, d, *J* 15.8, C*H*=CH), 6.54 (1 H, s, C*H*), 6.61 (1 H, s, C*H*), 6.79 (2 H, d, *J* 8.5, 2×C*H*) and 7.19 (2 H, d, *J* 8.5, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 18.89 (C22), 24.3 (C15), 25.9 (C20), 26.0 (C14), 33.0 (C11), 51.2 (C31), 54.23 (C30), 54.4 (C6), 55.1 (C1), 69. 6 (C23), 71.3 (C21), 76.9 (C12), 80.5 (C19), 82.1 (C16), 93.8 (C18), 95.2 (C2), 99.7 (C4), 102.8 (C7), 109.8 (C33), 112.8 (C27 and C28), 115.5 (C13), 128.0 (C10), 128.2 (C25 and 26), 128.3 (C9), 129.1 (C24), 136.2 (C8), 154.5 (C29), 158.2 (C3), 160.2 (C5), 167.3 (C32) and 185.5 (C17); MS (FAB) *m*/*z* 597.3 $[M+H]^+$; HRMS *m*/*z* 597.2712 (597.2699 calcd for $C_{33}H_{41}O_{10}$, $M+H^+$).



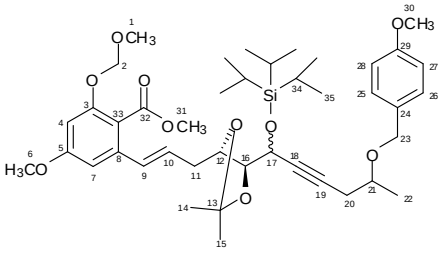
^{13}C Assignment

Methyl 4-methoxy-2-((*E*)-3-{(4*S*,5*S*)-5-[(*R*)-5-(4-methoxybenzyloxy)-1-triisopropylsilanyloxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate 221



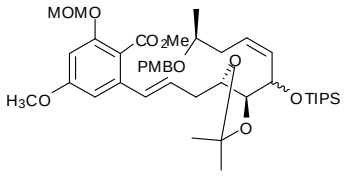
To a solution of alcohol **222** (585 mg, 0.977 mmol) in anhydrous dimethylformamide (10 cm^3) was added imidazole (199 mg, 2.93 mmol) and stirred until homogenous. Triisopropylsilyl chloride (0.25 cm^3, 1.17 mmol) was then added at room temperature and the reaction was stirred for 16 h. The reaction mixture was then diluted with ethyl acetate (30 cm^3) and quenched with water (40 cm^3). The organic phase was washed with water (4×100 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded silyl ether **221** (386 mg, 52%, *83% based on starting material consumed*) as a yellow oil (recovered starting material 216 mg); R_f 0.66 (Solvent *I*); $[\alpha]_D^{24}$ -

27.0 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2942, 2865, 1731 (C=O), 1600 (C=C), 1247, 1152 and 1048 (C-O); δ_H(400 MHz; $CDCl_3$) 1.01-1.12 (21 H, m, 3×SiC*H*(CH_3)$_2$), 1.29 (3 H, d, *J* 6.1, CH_3), 1.37 (3 H, s, CCH_3), 1.50 (3 H, s, CCH_3), 2.34 (1 H, dd, *J* 7.6 and 16.5, C≡CCH_2), 2.51-2.74 (3 H, m, CH=CHCH_2 and C≡CCH_2), 3.46 (3 H, s, OCH_2OCH_3), 3.60-3.67 (1 H, m, C*H*OPMB), 3.76 (3 H, s, OCH_2ArOCH_3), 3.81 (3 H, s, OCH_3), 3.88 (3 H, s, COOCH_3), 4.09-4.29 (2 H, m, 2×C*H*O), 4.48 (2 H, d, *J* 6.7, OCH_2ArOCH_3), 4.53 (1 H, d, *J* 6.8, *H*COTIPS), 5.14 (2 H, s, OCH_2OCH_3), 6.18-6.25 (1 H, m, CH=C*H*), 6.40 (1 H, dd, *J* 4.4 and 15.6, C*H*=CH), 6.60 (1 H, s, C*H*(Ar)), 6.69 (1 H, d, *J* 3.3, C*H*(Ar)), 6.87 (2 H, t, *J* 6.8, 2xC*H*(Ar)) and 7.24-7.28 (2 H, m, 2xC*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.3 (C34), 17.7 (C35), 19.8 (C22), 25.7 (C15), 26.5 (C20), 27.8 (C14), 34.0 (C11), 52.2 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.7 (C17), 70.3 (C23), 73.2 (C21), 77.3 (C12), 80.4 (C16), 80.7 (C19), 83.9 (C18), 94.8 (C2), 100.7 (C4), 103.5 (C7), 108.6 (C33), 109.0 (C13), 113.8 (C27 and C28), 128.2 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C10), 137.1 (C8), 156.1 (C29), 159.0 (C3), 161.2 (C5) and 168.0 (C32); MS (FAB) *m*/*z* 777.3 $[M+Na]^+$; HRMS *m*/*z* 777.4014 (777.4010 calcd for $C_{42}H_{62}NaO_{10}Si$, $M+Na^+$).



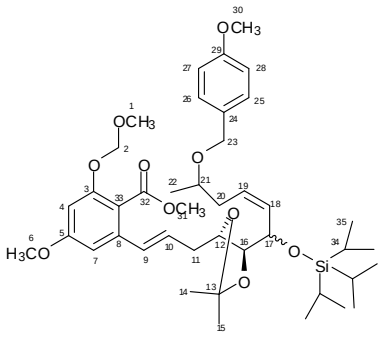
^{13}C Assignment

Methyl 4-methoxy-2-((*E*)-3-{(4*S*,5*S*)-5-[(*Z*)-(*S*)-5-(4-methoxybenzyloxy)-1-triisopropylsilanyloxy-hex-2-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate <u>220</u>



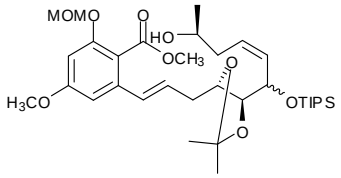
A solution of alkyne **221** (270 mg, 0.357 mmol) in methanol (7 cm^3) was treated with a catalytic amount of Pd/$BaSO_4$ catalyst and poisoned with quinoline (0.05 cm^3, 0.45 mmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 4 h at room temperature. TLC analysis deemed the reaction

complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alkene **220** (225 mg, 83%) as a pale yellow oil; R_f 0.72 (Solvent *I*); $[\alpha]_D^{24}$ +26.7 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2963, 2918, 2851, 2363, 1969, 1734 (C=O), 1259,1014 and 793; δ_H(400 MHz; $CDCl_3$) 1.04 (3 H, s, 3×SiC*H*$(CH_3)_2$), 1.09 (18 H, s, 3×SiCH(C*H*$_3)_2$), 1.23 (3 H, d, *J* 6.1, C*H*$_3$), 1.32 (3 H, s, CC*H*$_3$), 1.42 (3 H, s, CC*H*$_3$), 2.22-2.69 (4 H, m, 2×C*H*$_2$), 3.45 (3 H, s, OCH_2OCH_3), 3.58-3.63 (1 H, m, C*H*OPMB), 3.77 (3 H, s, OCH_2ArOCH_3), 3.81 (3 H, s, OC*H*$_3$), 3.87 (3 H, s, COOC*H*$_3$), 3.92-4.16 (2 H, m, 2×C*H*O), 4.36-4.52 and 4.61-4.70 (3 H, m, OC*H*$_2$ArOCH$_3$ and *H*COTIPS), 5.14 (2 H, s, OC*H*$_2$OCH$_3$), 5.48-5.68 (2 H, m, C*H*=C*H*), 6.20-6.30 (1 H, m, CH=C*H*), 6.44-6.47 (1 H, m, C*H*=CH) 6.59 (1 H, s, C*H*(Ar)), 6.74 (1 H, s, C*H*(Ar)), 6.85 (2 H, t, *J* 6.7, 2xC*H*(Ar)) and 7.24-7.27 (2 H, m, 2xC*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.3 (C34), 17.7 (C35), 19.8 (C22), 25.6 (C15), 26.9 (C20), 27.4 (C14), 33.7 (C11), 52.0 (C31), 55.3 (C30), 55.4 (C6), 56.2 (C1), 60.4 (C17), 70.2 (C23), 74.3 (C21), 77.8 (C12), 80.5 (C16), 94.8 (C2), 99.2 (C4), 107.6 (C33), 107.8 (C7), 113.8 (C27 and C28), 117.3 (C13), 127.9 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C19), 131.5 (C10), 132.3 (C18), 142.4 (C8), 155.5 (C29), 159.1 (C3), 161.2 (C5) and 168.7 (C32); MS (FAB) *m*/*z* 781.2 $[M+Na]^+$; HRMS *m*/*z* 779.4157 (779.4169 calcd for $C_{42}H_{64}NaO_{10}Si$, $M+Na^+$).

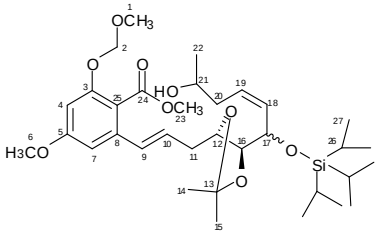


^{13}C Assignment

Methyl 2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*S*)-5-hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoate 219

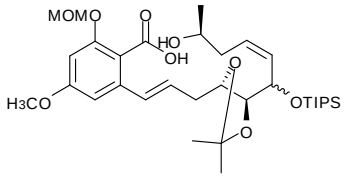


To a solution of PMB ether **220** (246 mg, 0.325 mmol) in dichloromethane (7 cm^3) and pH 7 buffer (7 cm^3) at 0 °C was added dichlorodicyanobenzoquinone (96 mg, 0.422 mmol). The reaction was allowed to warm to room temperature over 16 h. The reaction was then diluted with dichloromethane (30 cm^3) and quenched with saturated aqueous sodium hydrogencarbonate (30 cm^3). The aqueous layer was extracted with dichloromethane (3×30 cm^3) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded free alcohol **219** (160 mg, 77%) as a thick, yellow oil; R_f 0.24 (Solvent *B*); $[\alpha]_D^{24}$ -19.0 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2928, 2867, 1732 (C=O), 1601 (C=C), 1464, 1264, 1154 and 1048 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, s, 3×SiC*H*$(CH_3)_2$), 1.07 (18 H, s, 3×SiCH(C*H*$_3)_2$), 1.19 (3 H, dd, *J* 3.9 and 6.1, C*H*$_3$), 1.32 (3 H, s, CC*H*$_3$), 1.40 (3 H, s, CC*H*$_3$), 2.14-2.70 (4 H, m, 2C*H*$_2$), 3.46 (3 H, s, OCH_2OCH_3), 3.75 (3 H, s, OC*H*$_3$), 3.86 (3 H, s, COOC*H*$_3$), 3.91-4.19 (3 H, m, 2×C*H*O and C*H*OH), 4.66-4.78 (1 H, m, C*H*OTIPS), 5.12 (2 H, s, OCH_2OCH_3), 5.48-5.71 (2 H, m, C*H*=C*H*), 6.25-6.28 (1 H, m, CH=C*H*), 6.38-6.42 (1 H, m, C*H*=CH), 6.41 (1 H, d, *J* 2.2, C*H*(Ar)), and 6.54 (1 H, d, *J* 2.2, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.4 (C26), 18.2 (C27), 23.4 (C22), 25.5 (C15), 27.1 (C20), 27.5 (C14), 33.5 (C11), 52.0 (C23), 55.4 (C6), 56.2 (C1), 66.4 (C17), 68.1 (C21), 77.9 (C12), 80.4 (C16), 94.9 (C2), 99.2 (C4), 107.6 (C25), 108.1 (C7), 116.6 (C13), 127.0 (C9), 128.7 (C19), 132.2 (C10), 134.7 (C18), 142.4 (C8), 155.5 (C3), 161.2 (C5), and 168.1 (C24); MS (FAB) *m*/*z* 637.2 $[M+H]^+$; HRMS *m*/*z* 637.3768 (637.3772 calcd for $C_{34}H_{57}O_9Si$, $M+H^+$).

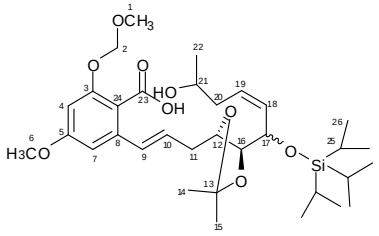


^{13}C Assignment

2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*S*)-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoic acid <u>218</u>

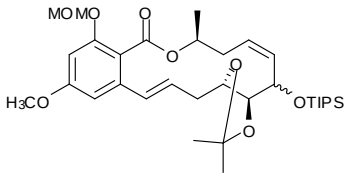


A solution of ester **219** (80 mg, 0.125 mmol) in ethanol (1 cm^3) was treated with the dropwise addition of 2 N potassium hydroxide (1 cm^3). The reaction mixture was heated under reflux for 48 h then cooled down to room temperature, diluted with water (5 cm^3) and acidified to pH 1 with 6 N hydrochloric acid. The organics were extracted with ethyl acetate (2×10 cm^3) and the combined organic phases were washed with water (7 cm^3) then brine (7 cm^3) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated *in vacuo*. Purification by FCC [ethyl acetate (100)] of the crude residue afforded acid **218** (33 mg, 57%) as a thick, yellow oil; R_f 0.1 (Solvent *I*); $[\alpha]_D^{22}$ -18.2 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2940, 1591, 1447, 1253 and 1148; δ_H(400 MHz: $CDCl_3$) 0.95 (3 H, s, 3×SiC*H*$(CH_3)_2$), 1.04 (18 H, s, 3×SiCH(C*H*$_3)_2$), 1.18 (3 H, dd, *J* 3.9 and 6.1, C*H*$_3$), 1.33 (3 H, s, CC*H*$_3$), 1.43 (3 H, s, CC*H*$_3$), 2.16-2.81 (4 H, m, 2xC*H*$_2$), 3.48 (3 H, s, OCH_2OCH_3), 3.82 (3 H, s, OC*H*$_3$), 3.97-4.36 (3 H, m, 2xC*H*O and C*H*OH), 4.70-4.76 (1 H, m, C*H*OTIPS), 5.20 (2 H, s, OCH_2OCH_3), 5.59-5.71 (2 H, m, C*H*=C*H*), 6.12-6.23 (1 H, m, CH=C*H*), 6.44-6.47 (1 H, m, C*H*=CH), 6.51 (1 H, s, C*H*(Ar)), and 6.72 (1 H, s, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.9 (C25), 18.2 (C26), 23.1 (C22), 25.8 (C15), 27.8 (C17), 29.7 (C14), 34.0 (C11), 37.9 (C20), 55.6 (C6), 56.5 (C1), 67.9 (C21), 77.4 (C12), 80.3 (C16), 95.4 (C2), 100.9 (C4), 105.6 (C24), 108.7 (C7), 113.4 (C13), 127.1 (C9), 129.9 (C19), 130.3 (C10), 132.4 (C18), 139.9 (C8), 156.0 (C3), 161.7 (C5), and 168.2 (C23); MS (EI) *m/z* 271.1 $[H_3CCH(OH)CH_2CH=CHCH(OTIPS)]^+$.



^{13}C Assignment

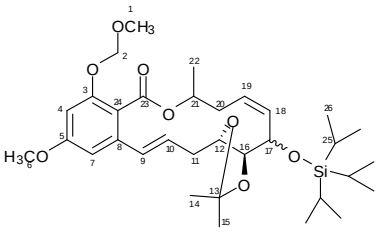
(2*E*,11*Z*)-(5*S*,9*S*,14*S*)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-10-triisopropylsilanyloxy-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one 227



Procedure A

Trichlorobenzoyl chloride (4.5 μL, 28.7 μmol) was added to a mixture of *seco*-acid **218** (17.9 mg, 28.7 μmol) and triethylamine (4.4 μL, 31.5 μmol) and the reaction mixture stirred at room temperature under argon for 2 h. The resulting mixture was filtered through a short pad of Celite®, diluted with toluene (15 cm^3) and added to a refluxing solution of dimethylaminopyridine (21 mg, 0.172 mmol) in toluene (15 cm^3) over a period of 6 h. The reaction was then cooled down to room temperature, then diluted with diethyl ether (15 cm^3) and washed sequentially with 1 *N* hydrochloric acid (15 cm^3), saturated aqueous sodium hydrogencarbonate (2×15 cm^3) and brine (15 cm^3). The solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded lactone **227** (6.5 mg, 37%) as a thick, yellow oil; R_f 0.61 (Solvent *I*); $[\alpha]_D^{22}$ -1.8 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2935, 1269 and 1089 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.09 (3 H, s, 3×SiC*H*(CH_3)$_2$), 1.05 (18 H, s, 3×SiCH(C*H*$_3$)$_2$), 1.22-1.24 (3 H, m, C*H*$_3$), 1.32 (3 H, s, CC*H*$_3$), 1.48 (3 H, s, CC*H*$_3$), 2.18-2.21 (2 H, m, C*H*$_2$), 2.47-2.54 (2 H, m, C*H*$_2$), 3.42 (3 H, s, OCH_2OCH_3), 3.83 (3 H, s, OC*H*$_3$), 3.94-4.05 (3 H, m, 2×C*H*O and C*H*CH_3), 4.74-4.78 (1 H, m, C*H*OTIPS), 5.20 (2 H, s, OCH_2OCH_3), 5.61-5.76 (2 H, m, C*H*=C*H*), 6.44-6.47 (1 H, m, CH=C*H*), 6.65-6.69 (1 H, m, C*H*=CH), 6.61 (1 H, d, *J* 2.1, C*H*), and 6.78 (1 H, s, C*H*); δ_C(100 MHz; $CDCl_3$) 12.8 (C25), 18.3 (C26), 23.8 (C22), 26.4 (C15), 28.9 (C17), 29.7 (C14), 30.4 (C11), 38.7 (C20), 55.4 (C6),

56.2 (C1), 68.2 (C21), 77.4 (C12), 81.4 (C16), 94.7 (C2), 100.6 (C4), 104.9 (C24), 107.8 (C7), 113.7 (C13), 128.8 (C9), 130.1 (C19), 131.0 (C10), 132.5 (C18), 137.8 (C8), 156.1 (C3), 161.4 (C5), and 167.8 (C23). The compound failed to ionise under all mass spectrometry conditions attempted.

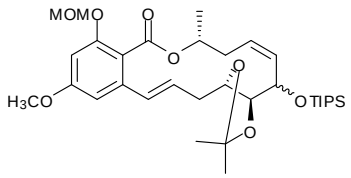


^{13}C Assignment

Procedure B

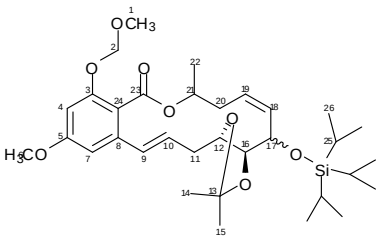
A mixture of 2-methyl-6-nitrobenzoic anhydride (15.2 mg, 44 μmol), dimethylaminopyridine (16.2 mg, 132 μmol) and powdered activated 4Å molecular sieves in dry toluene (10 cm^3) was stirred at room temperature for 30 min. A solution of *seco*-acid **218** (18.4 mg, 29 μmol) in dry toluene (6 cm^3) was then added slowly over 4 h. After the addition was complete, the reaction mixture was stirred for 2 h at room temperature. The mixture was then diluted with ethyl acetate (5 cm^3), passed through a pad of Celite® and then washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), water (10 cm^3) and brine (10 cm^3). The solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded lactone **227** (5 mg, 28%) as a thick, yellow oil; R_f 0.57 (Solvent *C*). ^{1}H and ^{13}C match that reported for Procedure A.

(2*E*,11*Z*)-(5*S*,9*S*,14*R*)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-10-triisopropylsilanyloxy-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one <u>228</u>



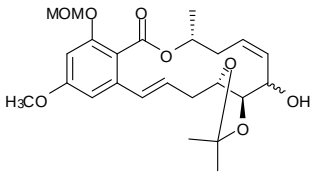
To a solution of *seco*-acid **218** (27.5 mg, 44.1 μmol) in anhydrous toluene (6.3 cm^3) was added triphenylphosphine (23 mg, 88.3 μmol) and the solution stirred until dissolved. The mixture was cooled to 0 °C and diethyl azodicarboxylate

(DEAD) (14 μL, 88.3 μmol) was added slowly. After 5 min, the ice-water bath was removed and the reaction allowed to warm up to room temperature. After 30 min, the reaction was diluted with toluene (10 cm^3) and the solvent then evaporated slowly under vacuum to leave an orange viscous mass. Purification by FCC [petroleum ether–ethyl acetate (50:50)] of the residue afforded lactone **228** (19 mg, 71%) as a yellow oil; R_f 0.67 (Solvent *M*); $[\alpha]_D^{22}$ +2.0 (*c* 1.1, $CHCl_3$); ν_{max}(film)/cm^{-1} 2929, 1262, 1089 (O-Si) and 1028; δ_H(400 MHz; $CDCl_3$) 0.94 (3 H, s, 3×SiC*H*$(CH_3)_2$), 1.02 (18 H, s, 3×SiCH(C*H*$_3)_2$), 1.26 (3 H, d, *J* 7.0, C*H*$_3$), 1.38 (3 H, s, CC*H*$_3$), 1.45 (3 H, s, CC*H*$_3$), 1.80-2.05 (2 H, 2×m, C*H*$_2$), 2.40-2.60 (2 H, m, C*H*$_2$), 3.44 (3 H, s, OCH_2OCH_3), 3.78 (3 H, s, OC*H*$_3$), 3.90-4.00 (2 H, m, 2×C*H*O), 4.22 (1 H, dd, *J* 1.7 and 7.0, C*H*CH_3), 4.52 (1 H, dd, *J* 8.2 and 9.3, C*H*OTIPS), 5.12 (2 H, s, OCH_2OCH_3), 5.42-5.90 (4 H, m, 2×C*H*=C*H*), 6.34 (1 H, d, *J* 2.2, C*H*), and 6.54 (1 H, d, *J* 2.2, C*H*); δ_C(100 MHz; $CDCl_3$) 12.6 (C25), 18.1 (C26), 24.6 (C22), 26.9 (C15), 28.1 (C17), 29.6 (C14), 29.9 (C11), 36.7 (C20), 55.4 (C6), 56.2 (C1), 68.9 (C21), 77.3 (C12), 81.3 (C16), 94.6 (C2), 99.4 (C4), 107.4 (C24), 107.5 (C7), 116.9 (C13), 128.5 (C9), 130.5 (C19), 131.3 (C10), 132.5 (C18), 141.2 (C8), 155.3 (C3), 161.0 (C5), and 167.6 (C23). The compound failed to ionise under all mass spectrometry conditions attempted.



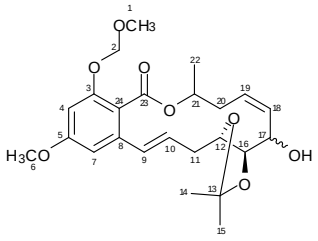
^{13}C Assignment

(2*E*,11*Z*)-(5*S*,9*R*,14*R*)-10-Hydroxy-20-methoxy-18-methoxymethyl-7,7,14-trimethyl-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one <u>229</u>



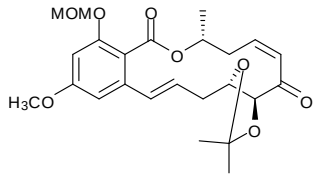
Tetra-butylammonium fluoride (60 μL, 62.4 μmol) was added to a solution of TIPS ether **228** (19 mg, 31.2 μmol) in anhydrous tetrahydrofuran (1 cm^3). The reaction mixture was stirred at 0 °C for 10 min and was then allowed to warm up

to room temperature. After 1.25 h the reaction was diluted with diethyl ether (5 cm^3) and quenched with water (5 cm^3). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield alcohol **229** as a yellow, thick oil; R_f 0.32 (Solvent *M*); $[\alpha]_D^{22}$ +2.5 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 1670 (C=O), 1159 and 1012; δ_H(400 MHz; $CDCl_3$) 1.24 (3 H, d, C*H*$_3$), 1.35 (3 H, s, CC*H*$_3$), 1.44 (3 H, s, CC*H*$_3$), 1.80-2.05 (2 H, m, C*H*$_2$), 2.50-2.80 (2 H, m, C*H*$_2$), 3.45 (3 H, s, OCH_2OCH_3), 3.77 (3 H, s, OC*H*$_3$), 3.90-4.04 (2 H, m, 2×C*H*O), 4.27-4.29 (2 H, m, C*H*CH_3 and C*H*OH), 5.12 (2 H, s, OCH_2OCH_3), 5.20-5.50 (2 H, m, C*H*=C*H*), 5.70-5.99 (2 H, m, C*H*=C*H*), 6.34 (1 H, d, *J* 2.0, C*H*) and 6.53 (1 H, d, *J* 2.0, C*H*); δ_C(100 MHz; $CDCl_3$) 24.3 (C22), 26.3 (C15), 28.2 (C17), 29.3 (C14), 29.7 (C11), 35.2 (C20), 55.4 (C6), 56.2 (C1), 68.9 (C21), 77.6 (C12), 80.4 (C16), 94.5 (C2), 99.2 (C4), 107.4 (C24), 107.9 (C7), 116.9 (C13), 128.5 (C9), 130.1 (C19), 131.7 (C10), 132.1 (C18), 141.3 (C8), 154.9 (C3), 161.0 (C5), and 167.6 (C23).



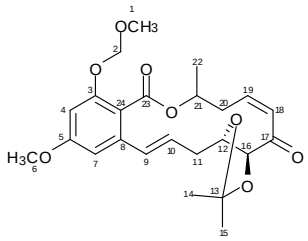
^{13}C Assignment

(2*E*,11*Z*)-(5*S*,9*S*,14*R*)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaene-10,16-dione 230



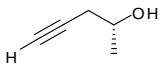
A solution of pyridinium chlorochromate (16 mg, 77.4 μmol) in anhydrous dichloromethane (1 cm^3) was treated with a solution of alcohol **229** (16.7 mg, 37.2 μmol) in anhydrous dichloromethane (1 cm^3) at room temperature. After 3.5 h, the reaction mixture was diluted with dichloromethane (2 cm^3) and passed through a short column of SiO_2, eluting with dichloromethane. The solvent was concentrated *in vacuo* to leave enone **230** (3.3 mg, 20%) as a thick, orange viscous mass; R_f 0.71 (Solvent *M*); δ_H(400 MHz; $CDCl_3$) 1.24 (3 H, d, *J* 6.4, C*H*$_3$),

1.38 (3 H, s, CC*H*$_3$), 1.45 (3 H, s, CC*H*$_3$), 2.08-2.12 (2 H, m, C*H*$_2$), 2.46-2.50 (2 H, m, C*H*$_2$), 3.40 (3 H, s, OCH$_2$OC*H*$_3$), 3.73 (3 H, s, OC*H*$_3$), 4.30-4.55 (2 H, m, CC*H*$_3$ and CH$_2$C*H*O), 4.72 (2 H, s, OC*H*$_2$OCH$_3$), 5.00-5.03 (1 H, m, C*H*O), 5.37-5.43 (2 H, m, C*H*=C*H*), 6.05-6.12 (2 H, m, C*H*=C*H*), 6.17 (1 H, d, *J* 2.8, C*H*), and 6.23 (1 H, d, *J* 2.8, C*H*). The lack of material prevented the acquisition of a full data set.



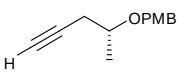
^{13}C Assignment

(*R*)-(-)-Pent-4-yn-2-ol **233**



A stirred suspension of lithium acetylide ethylenediamine complex (5.7 g, 62.0 mmol) in anhydrous dimethylsulfoxide (110 cm^3) at 0 °C was treated dropwise with *R*-(+)-propylene oxide (3.6 cm^3, 51.6 mmol). The reaction was then allowed to warm up to room temperature, where it was stirred for 48 h. The suspension was poured onto ice (100 cm^3) and extracted with diethyl ether (4×80 cm^3). The combined ether extracts were washed with brine (6×30 cm^3), water (2×30 cm^3) and dried over anhydrous magnesium sulfate. Careful evaporation of the solvent at atmospheric pressure yielded the crude alcohol **233** which was taken on without any purification; $[\alpha]_D^{22}$ -18.0 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3340 (OH), 3301 (C≡C) and 2360; δ_H(400 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.0, C*H*$_3$), 2.10 (1 H, t, *J* 2.7, *H*C≡C), 2.33 (1 H, ddd, *J* 2.7, 5.3 and 16.0, C*H*$_2$), 2.42 (1 H, ddd, *J* 2.7, 6.2 and 16.0, C*H*$_2$) and 4.02-4.04 (1 H, m, *H*COH); δ_C(100 MHz; $CDCl_3$) 24.7 (*C*H$_3$), 32.8 (*C*H$_2$), 67.2 (H*C*OH), 71.1 (H*C*≡C) and 85.1 (HC≡*C*); MS (CI) *m*/*z* 67 [M-OH]$^+$; HRMS *m*/*z* 67.0550 (67.0548 calcd for C_5H_7, M-OH$^+$).

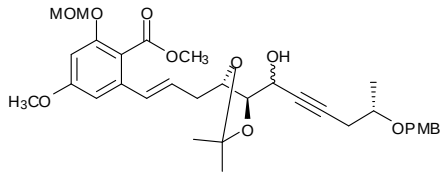
1-Methoxy-4-((*R*)-1-methyl-but-3-ynyloxymethyl)-benzene **234**



A suspension of 60% in mineral oil NaH (2.27 g, 56.7 mmol) at 0 °C, was diluted with anhydrous dimethylformamide (65 cm^3) and a solution of the freshly

generated crude alcohol **233** (4.34 g, 51.6 mmol) in anhydrous dimethylformamide (65 cm^3) was added. The reaction mixture was stirred for 15 min, then *p*-methoxybenzyl chloride (10.5 cm^3, 77.4 mmol) was added and the reaction mixture was allowed to warm up to room temperature and stirred for 17 h. The solution was then poured onto brine (400 cm^3) and extracted with diethyl ether (3×100 cm^3). The combined organic layers were concentrated under reduced pressure, then washed with brine (300 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent concentrated. Purification by FCC [petroleum ether-ethyl acetate (95:5)] of the crude residue afforded PMB ether **234** (4.13 g, 40%) as a colourless oil; R_f 0.69 (Solvent *A*); $[\alpha]_D^{19}$ +11.2 (*c* 1.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2253, 911 and 739; δ_H(400 MHz; $CDCl_3$) 1.32 (3 H, d, *J* 6.0, C*H*$_3$), 2.04 (1 H, t, *J* 2.6, *H*C≡C), 2.38 (1 H, ddd, *J* 2.6, 7.0 and 16.6, C*H*$_2$), 2.52 (1 H, ddd, *J* 2.6, 4.9 and 16.6, C*H*$_2$), 3.70 (1 H, sext., *J* 6.0, C*H*), 3.86 (3 H, s, OC*H*$_3$), 4.53 (2 H, s, OC*H*$_2$), 6.91 (2 H, d, *J* 8.6, Ar) and 7.31 (2 H, d, *J* 8.6, Ar); δ_C(100 MHz; $CDCl_3$) 19.5 (*C*H$_3$), 26.0 (*C*H$_2$), 55.3 (O*C*H$_3$), 69.9 (*C*H), 70.3 (H*C*≡C), 72.8 (O*C*H$_2$), 81.3 (HC≡*C*), 113.8 (2×*C*H), 129.2 (2×*C*H), 130.6 (*C*) and 159.1 (*C*OCH$_3$); MS (EI) *m*/*z* 204.04 $[M]^+$; HRMS *m*/*z* 204.1146 (204.1150 calcd for $C_{13}H_{16}O_2$, M^+).

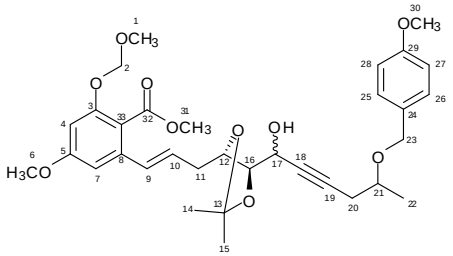
Methyl 2-((*E*)-3-{(4*S*,5*R*)-5-[(*S*)-1-hydroxy-5-(4-methoxybenzyloxy)-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-4-methoxy-6-methoxymethylbenzoate <u>235</u>



A solution of alkyne **234** (82.4 mg, 0.403 mmol) in anhydrous tetrahydrofuran (2 cm^3) was treated with ethyl magnesium bromide (0.13 cm^3, 0.378 mmol) at room temperature and the resulting solution was stirred for 5.5 h.

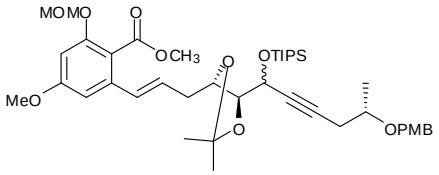
Whilst the above deprotonation was being carried out, a −78 °C solution of oxalyl chloride (0.25 cm^3, 0.504 mmol) in anhydrous tetrahydrofuran (3 cm^3) was added dimethylsulfoxide (70 μL, 1.00 mmol). After stirring for 30 min a solution of alcohol **212** (100 mg, 0.252 mmol) in anhydrous tetrahydrofuran (1.5 cm^3) was added and stirring continued for 1 h at −78 °C. After this time, triethylamine (0.28 cm^3, 2.02 mmol) was added and the reaction allowed to warm up to room

temperature. After 30 min the reaction was cooled back down to −78 °C and a solution of the deprotonated alkyne was added. The mixture was then allowed to warm up to room temperature overnight. The reaction was then quenched with saturated aqueous ammonium chloride (10 cm^3) and extracted with ethyl acetate (3×20 cm^3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded propargylic alcohol **235** (113 mg, 75%) as a pale yellow oil and as an inseparable mixture of diastereoisomers; R_f 0.27 (Solvent *I*); $[\alpha]_D^{25}$ +0.04 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 3434, 3019, 1720 (C=O), 1602 (C=C), 1215, 765, 669; δ_H(400 MHz; $CDCl_3$) 1.30 (3 H, s, CH_3), 1.38 (3 H, s, CCH_3), 1.54 (3 H, s, CCH_3), 2.39-2.78 (4 H, m, 2×CH_2), 3.50 (3 H, s, OCH_2OCH_3), 3.60-3.70 (1 H, m, C*H*OPMB), 3.81 (3 H, s, OCH_2ArOCH_3), 3.83 (3 H, s, OCH_3), 3.91 (3 H, s, CO_2CH_3), 4.20-4.30 (1 H, m, OC*H*), 4.43-4.47 (1 H, m, OC*H*), 4.45-4.55 (3 H, m, C*H*OH and OCH_2ArOCH_3), 5.18 (2 H, s, OCH_2OCH_3), 6.23-6.29 (1 H, m, CH=C*H*), 6.49 (1 H, d, *J* 15.7, C*H*=CH), 6.62 (1 H, s, C*H*), 6.71 (1 H, s, C*H*), 6.89 (2 H, d, *J* 8.5, 2×C*H*) and 7.27 (2 H, d, *J* 8.5, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 19.8 (C22), 25.5 (C14), 26.5 (C20), 27.6 (C15), 31.0 (C33), 33.3 (C11), 52.3 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.1 (C16), 70.4 (C17), 72.9 (C23), 73.1 (C21), 79.7 (C12), 80.4 (C19), 84.5 (C18), 94.8 (C2), 100.7 (C4), 103.8 (C7), 108.6 (C13), 113.8 (C27 and C28), 128.7 (C10), 129.2 (C9), 129.3 (C24), 130.2 (C25 and C26), 137.6 (C8), 155.6 (C29), 161.3 (C3), 168.0 (C5) and 171.1 (C32); MS (FAB) *m*/*z* 599.3 $[M+H]^+$; HRMS *m*/*z* 599.2843 (599.2857 calcd for $C_{33}H_{43}O_{10}$, $M+H^+$).

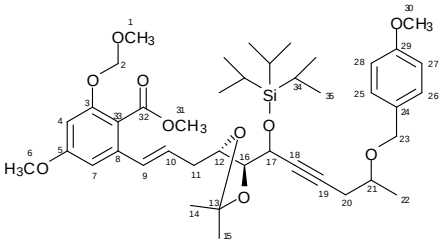


^{13}C Assignment

Methyl 4-methoxy-2-((*E*)-3-{(4*S*,5*S*)-5-[(*S*)-5-(4-methoxybenzyloxy)-1-triisopropylsilanyloxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate <u>236</u>

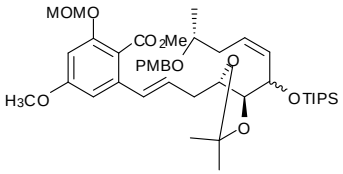


Propargylic alcohol **235** (113 mg, 0.188 mmol) was dissolved in anhydrous dimethylformamide (2 cm^3), imidazole (38 mg, 0.566 mmol) added and the solution was stirred until homogenous. Triisopropylsilyl chloride (0.05 cm^3, 0.226 mmol) was then added at room temperature and the reaction left to stir overnight. The reaction mixture was diluted with ethyl acetate (10 cm^3) and quenched with water (10 cm^3). The organic layer was separated, extracted with water (3×30 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (50:50)] of the crude residue afforded TIPS ether **236** (114 mg, 80%) as a yellow oil; R_f 0.60 (Solvent *I*); $[\alpha]_D^{19}$ -2.2 (*c* 1.13, $CHCl_3$); ν_{max}(film)/cm^{-1} 2943, 2866, 1725 (C=O), 1601 (C=C), 1513, 1266, 1215, 1154, 757; δ_H(400 MHz; $CDCl_3$) 1.01-1.12 (21 H, m, TIPS), 1.29 (3 H, s, C*H*$_3$), 1.37 (3 H, s, CC*H*$_3$), 1.50 (3 H, s, CC*H*$_3$), 2.34 (1 H, dd, *J* 7.6 and 16.5, C≡CC*H*$_2$), 2.51-2.74 (3 H, m, CH=CHC*H*$_2$ and C≡CC*H*$_2$), 3.46 (3 H, s, OCH_2OCH_3), 3.61-3.67 (1 H, m, C*H*OPMB), 3.76 (3 H, s, OCH_2ArOCH_3), 3.81 (3 H, s, OC*H*$_3$), 3.88 (3 H, s, COOC*H*$_3$), 4.09-4.29 (2 H, m, 2×C*H*O), 4.48 (2 H, d, *J* 6.7, OC*H*$_2$PhOCH$_3$), 4.53 (1 H, d, *J* 6.4, *H*COTIPS), 5.14 (2 H, s, OC*H*$_2$OCH$_3$), 6.22-6.31 (1 H, m, CH=C*H*), 6.40 (1 H, dd, *J* 4.4 and 15.6, C*H*=CH), 6.60 (1 H, s, C*H*(Ar)), 6.69 (1 H, d, *J* 3.3, C*H*(Ar)), 6.87 (2 H, t, *J* 6.8, 2×C*H*(Ph)) and 7.22-7.27 (2 H, m, 2×C*H*(Ph)); δ_C(100 MHz; $CDCl_3$) 12.3 (C34), 17.7 (C35), 19.8 (C22), 25.7 (C15), 26.5 (C20), 27.8 (C14), 34.0 (C11), 52.2 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 62.8 (C17), 70.3 (C23), 73.2 (C21), 77.3 (C12), 80.5 (C16), 80.7 (C19), 83.7 (C18), 94.8 (C2), 100.7 (C4), 103.6 (C7), 108.5 (C33), 109.0 (C13), 113.8 (C27 and C28), 128.3 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C10), 137.1 (C8), 156.1 (C29), 159.0 (C3), 161.2 (C5) and 168.0 (C32); MS (FAB) *m*/*z* 777.7 $[M+Na]^+$; HRMS *m*/*z* 777.4019 (777.4012 calcd for $C_{42}H_{62}NaO_{10}Si$, $M+Na^+$).



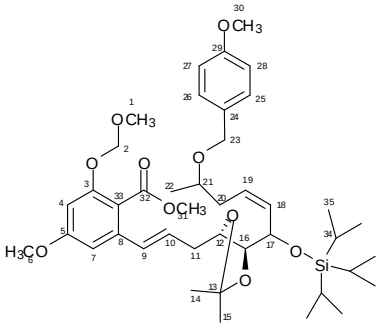
^{13}C Assignment

Methyl 4-methoxy-2-((*E*)-3-{(4*S*,5*S*)-5-[(*Z*)-(*R*)-5-(4-methoxy-benzyloxy)-1-triisopropylsilanyloxy-hex-2-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-propenyl)-6-methoxymethylbenzoate 237



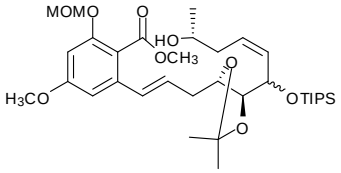
A solution of TIPS ether **236** (59 mg, 0.0779 mmol) in methanol (1.5 cm^3) was treated with a catalytic amount of $Pd/BaSO_4$ catalyst and poisoned with quinoline (0.01 cm^3, 97.3 μmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alkene **237** (53 mg, 89%) as a pale yellow oil; R_f 0.68 (Solvent *I*); $[\alpha]_D^{26}$ -2.4 (*c* 0.9, $CHCl_3$); ν_{max}(film)/cm^{-1} 2943, 2865, 1729 (C=O), 1602 (C=C), 1513; δ_H(400 MHz; $CDCl_3$) 1.04 (3 H, s, 3×C*H*$(CH_3)_2$), 1.09 (18 H, s, 3 CH(C*H*$_3)_2$), 1.23 (3 H, d, *J* 6.1, C*H*$_3$), 1.32 (3 H, s, CC*H*$_3$), 1.42 (3 H, s, CC*H*$_3$), 2.22-2.69 (4 H, m, 2×C*H*$_2$), 3.45 (3 H, s, OCH_2OCH_3), 3.56-3.60 (1 H, m, C*H*OPMB), 3.77 (3 H, s, OCH_2ArOCH_3), 3.81 (3 H, s, OC*H*$_3$), 3.87 (3 H, s, COOC*H*$_3$), 3.92-4.16 (2 H, m, 2×C*H*O), 4.36-4.52 (2 H, m, OC*H*$_2$ArOCH_3), 4.61-4.70 (1 H, m, *H*COTIPS), 5.14 (2 H, s, OC*H*$_2OCH_3$), 5.48-5.68 (2 H, m, C*H*=C*H*), 6.25-6.31 (1 H, m, CH=C*H*), 6.43-6.47 (1 H, m, C*H*=CH) 6.59 (1 H, s, C*H*(Ar)), 6.74 (1 H, s, C*H*(Ar)), 6.85 (2 H, d, *J* 6.7, 2×C*H*(Ar)) and 7.24-7.27 (2 H, m, 2×C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.8 (C34), 17.7 (C35), 19.8 (C22), 25.6 (C15), 27.0 (C20), 27.5 (C14), 34.0 (C11), 52.1 (C31), 55.3 (C30), 55.5 (C6), 56.2 (C1), 68.1 (C17), 70.1 (C23), 74.3 (C21), 77.6 (C12), 80.3 (C16), 94.8 (C2), 100.7 (C4), 108.2 (C33), 108.3 (C7), 113.8 (C27 and C28), 117.0 (C13), 128.2 (C9), 129.2 (C25 and C26), 130.9 (C24), 131.0 (C19), 131.2 (C10), 132.3

(C18), 142.4 (C8), 155.5 (C29), 159.1 (C3), 161.2 (C5) and 168.7 (C32); MS (FAB) *m/z* 779.7 $[M+Na]^+$; HRMS *m/z* 779.4168 (779.4169 calcd for $C_{42}H_{64}NaO_{10}Si$, $M+Na^+$).



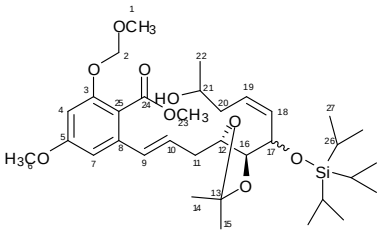
^{13}C Assignment

Methyl 2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*R*)-5-hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoate <u>238</u>



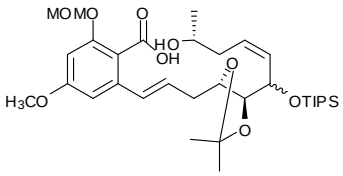
PMB ether **237** (148 mg, 0.195 mmol) was dissolved in a mixture of dichloromethane (2 cm^3) and pH 7 buffer (2 cm^3) and cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (58 mg, 25.4 μmol) was then added with vigorous stirring and the reaction allowed to warm up to room temperature overnight. After this time, the reaction was re-cooled to 0 °C and further 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (58 mg, 25.4 μmol) was added. After allowing the reaction to warm up to room temperature overnight, the reaction mixture was diluted with dichloromethane (15 cm^3) and quenched with saturated aqueous sodium hydrogen carbonate (15 cm^3). The aqueous layer was separated and extracted with dichloromethane (3×40 cm^3). The combined organic layers were washed with brine (40 cm^3), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (60:40)] of the crude residue afforded alcohol **238** (108 mg, 87%) as a yellow oil; R_f 0.52 (Solvent *I*); $[\alpha]_D^{26}$ -0.03 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3450, 2942, 2865, 1721 (C=O), 1598, 1150; δ_H(400 MHz; $CDCl_3$) 0.93 (3 H, s, 3×C*H*$(CH_3)_2$), 1.06 (18 H, s, 3×CH(C*H*$_3)_2$), 1.18 (3 H, d, *J* 6.1, C*H*$_3$), 1.31 (3 H, s, CC*H*$_3$), 1.46 (3 H, s, CC*H*$_3$), 2.12-2.18 (1 H, m, C*H*$_2$), 2.23-2.32 (1 H, m, C*H*$_2$), 2.45-2.63 (2 H, m, C*H*$_2$),

3.45 (3 H, s, OCH_2OCH_3), 3.80 (3 H, s, OCH_3), 3.86 (3 H, s, $COOCH_3$), 3.96-4.02 (1 H, dd, *J* 5.6 and 8.9, C*H*O), 4.22-4.29 (1 H, m, C*H*OH), 4.73 (1 H, t, *J* 8.5, C*H*OTIPS), 5.12 (2 H, s, OCH_2OCH_3), 5.56-5.67 (2 H, m, C*H*=C*H*), 6.23-6.30 (1 H, m, CH=C*H*), 6.40 (1 H, d, *J* 15.7, C*H*=CH), 6.57 (1 H, d, *J* 2.2, C*H*(Ar)) and 6.71 (1 H, d, *J* 2.2, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.9 (C26), 18.2 (C27), 23.8 (C22), 26.1 (C15), 28.1 (C17), 29.7 (C14), 34.4 (C11), 38.7 (C20), 52.1 (C23), 55.4 (C6), 56.2 (C1), 66.7 (C21), 77.7 (C12), 80.3 (C16), 94.8 (C2), 100.7 (C4), 103.7 (C25), 108.8 (C7), 116.5 (C13), 128.7 (C9), 129.9 (C19), 130.4 (C10), 133.8 (C18), 137.5 (C8), 155.5 (C3), 161.2 (C5), and 168.4 (C24); MS (EI) *m*/*z* 636.6 $[M]^+$; HRMS *m*/*z* 636.3699 (636.3694 calcd for $C_{34}H_{56}O_9Si$, M^+).



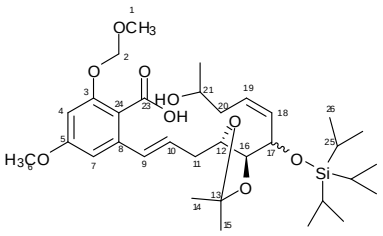
^{13}C Assignment

2-{(*E*)-3-[(4*S*,5*S*)-5-((*Z*)-(*R*)-5-Hydroxy-1-triisopropylsilanyloxy-hex-2-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-propenyl}-4-methoxy-6-methoxymethylbenzoic acid <u>239</u>



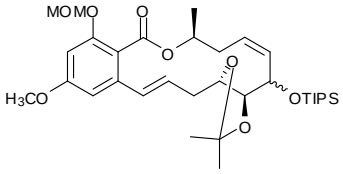
Methyl ester **238** (79 mg, 0.124 mmol) was dissolved in ethanol (1.5 cm^3) and 2 *N* potassium hydroxide (1.5 cm^3) was added dropwise. A colour change from yellow to orange was observed after the addition of base. The reaction was heated under reflux for 48 h whereafter it was cooled down to room temperature and diluted with water (10 cm^3). The solution was acidified to pH 1-2 using 6 *N* hydrochloric acid and was then extracted with ethyl acetate (3×15 cm^3). The combined organic layers were washed with water (20 cm^3), then brine (20 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded *seco*-acid **239** (47 mg, 61%) as a thick, pale orange oil; R_f 0.17 (Solvent *I*); $[\alpha]_D^{21}$ -0.1 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3447, 2941, 2866, 2359,

1724 (C=O), 1604 (C=C), 1248, 1155 and 1041 (C-O); δ_H(400 MHz; $CDCl_3$) 0.94 (3 H, s, 3×C*H*(CH_3)$_2$), 1.02 (18 H, s, 3×CH(C*H*$_3$)$_2$), 1.21 (3 H, d, *J* 6.1, C*H*$_3$), 1.30 (3 H, s, CC*H*$_3$), 1.47 (3 H, s, CC*H*$_3$), 2.08-2.45 (2 H, m, C*H*$_2$), 2.80-3.00 (2 H, m, C*H*$_2$), 3.52 (3 H, s, OCH_2OCH_3), 3.82 (3 H, s, OC*H*$_3$), 3.94-4.20 (3 H, m, 2×C*H*O and C*H*OH), 4.63-4.67 (1 H, m, C*H*OTIPS), 5.23 (2 H, s, OCH_2OCH_3), 5.59-5.71 (2 H, m, C*H*=C*H*), 6.20-6.27 (1 H, m, CH=C*H*), 6.42-6.48 (1 H, m, C*H*=CH), 6.51 (1 H, s, C*H*(Ar)), and 6.72 (1 H, s, C*H*(Ar)); δ_C(100 MHz; $CDCl_3$) 12.5 (C25), 18.2 (C26), 23.5 (C22), 26.0 (C15), 28.0 (C17), 29.7 (C14), 34.4 (C11), 38.7 (C20), 55.4 (C6), 56.5 (C1), 67.0 (C21), 77.5 (C12), 80.3 (C16), 95.3 (C2), 100.7 (C4), 105.5 (C24), 108.9 (C7), 114.0 (C13), 128.7 (C9), 130.2 (C19), 131.0 (C10), 133.0 (C18), 139.7 (C8), 156.2 (C3), 161.7 (C5), and 169.0 (C23); MS (FAB) *m*/*z* 645.6 $[M+Na]^+$; HRMS *m*/*z* 645.3436 (645.3437 calcd for $C_{33}H_{54}NaO_9Si$, $M+Na^+$).



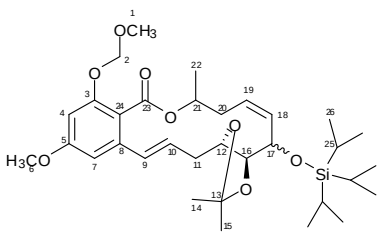
^{13}C Assignment

(2*E*,11*Z*)-(5*S*,9*S*,14*S*)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-10-triisopropylsilanyloxy-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one <u>227</u>



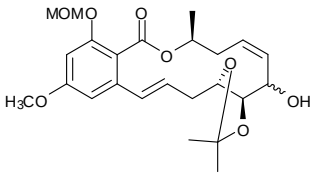
Seco-acid **239** (45 mg, 72.4 μmol) was dissolved in anhydrous toluene (10 cm^3) and triphenylphosphine (38 mg, 145 μmol) was added at room temperature. The mixture was stirred until homogenous and then the reaction mixture was cooled down to 0 °C at which stage, diethyl azodicarboxylate (20 μL, 145 μmol) was added dropwise. The ice-water bath was removed after 5 min and after a further 5 min, TLC analysis (solvent *M*) showed the total consumption of starting material. The solvent was then carefully evaporated *in vacuo*. Purification by FCC [petroleum ether – ethyl acetate (70:30)] of the crude residue afforded lactone **227** (31 mg, 73%) as a yellow oil; R_f 0.87 (Solvent *M*); $[\alpha]_D^{21}$ –1.6 (*c* 1.0,

$CHCl_3$); ν_{max}(film)/cm^{-1} 3439, 2941, 2866, 1725 (C=O), 1606 (C=C), 1249; δ_H(400 MHz; $CDCl_3$) 0.80 (3 H, s, 3×C*H*$(CH_3)_2$), 0.99 (18 H, s, 3×CH(C*H*$_3)_2$), 1.18 (3 H, s, C*H*$_3$), 1.26 (3 H, s, CC*H*$_3$), 1.42 (3 H, s, CC*H*$_3$), 2.02-2.70 (4 H, m, 3×C*H*$_2$), 3.38 (3 H, s, OCH_2OCH_3), 3.70 (3 H, s, OC*H*$_3$), 3.75-4.05 (3 H, m, 2×C*H*O and C*H*CH_3), 4.73-4.76 (1 H, m, C*H*OTIPS), 5.08 (2 H, s, OC*H*$_2$OCH$_3$), 5.47-5.76 (2 H, m, C*H*=C*H*), 6.07-6.13 (1 H, m, CH=C*H*), 6.25-6.29 (1 H, m, C*H*=CH), 6.45 (1 H, s, C*H*), and 6.51 (1 H, s, C*H*); δ_C(100 MHz; $CDCl_3$) 12.8 (C25), 18.3 (C26), 23.8 (C22), 26.4 (C15), 28.9 (C17), 29.7 (C14), 30.4 (C11), 38.7 (C20), 55.5 (C6), 56.2 (C1), 68.2 (C21), 77.2 (C12), 81.4 (C16), 94.7 (C2), 100.6 (C4), 104.9 (C24), 107.8 (C7), 113.7 (C13), 128.8 (C9), 130.1 (C19), 131.0 (C10), 132.5 (C18), 137.8 (C8), 156.1 (C3), 161.4 (C5), and 167.8 (C23); MS (FAB) *m*/*z* 627 $[M+Na]^+$; HRMS *m*/*z* 627.3324 (627.3329 calcd for $C_{33}H_{52}NaO_8Si$, $M+Na^+$).



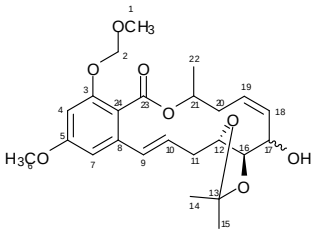
^{13}C Assignment

(2*E*,11*Z*)-(5*S*,9*R*,14*S*)-10-Hydroxy-20-methoxy-18-methoxymethyl-7,7,14-trimethyl-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaen-16-one <u>226</u>



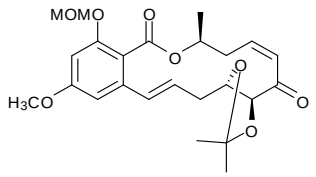
Lactone **227** (31 mg, 51.9 μmol) was dissolved in anhydrous tetrahydrofuran (2 cm^3) and the solution was cooled down to 0 °C. *tetra*-Butylammonium fluoride (0.1 cm^3, 0.104 mmol) was added and the ice-water bath removed after 10 min. After 1 h, the reaction mixture was diluted with ethyl acetate (10 cm^3) and water (10 cm^3). The organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*, to afford alcohol **226** which was used without any further purification; R_f 0.18 (Solvent *C*); $[\alpha]_D^{24}$ -2.8 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3360 (OH), 2922, 2851, 1720 (C=O), 1661 (C=C), 1468, 1155 and 1043 (C-O); δ_H(400 MHz; $CDCl_3$) 1.16 (3 H, s, C*H*$_3$), 1.22 (3 H, s, CC*H*$_3$),

1.40 (3 H, s, CCH_3), 2.00-2.63 (4 H, m, 2×CH_2), 3.38 (3 H, s, OCH_2OCH_3), 3.68 (3 H, s, OCH_3), 3.75-4.00 (3 H, m, 2×C*H*O and C*H*CH_3), 4.33-4.37 (1 H, m, C*H*OH), 5.10 (2 H, s, OCH_2OCH_3), 5.47-5.76 (2 H, m, 2×C*H*=CH), 5.90-6.10 (2 H, m, 2×CH=C*H*), 6.45 (1 H, s, C*H*), and 6.51 (1 H, s, C*H*); δ_C(100 MHz; $CDCl_3$) 23.8 (C22), 26.5 (C15), 28.9 (C17), 29.7 (C14), 30.4 (C11), 38.8 (C20), 55.4 (C6), 56.2 (C1), 68.2 (C21), 77.2 (C12), 81.4 (C16), 94.7 (C2), 100.6 (C4), 104.9 (C24), 107.9 (C7), 113.7 (C13), 128.8 (C9), 130.1 (C19), 131.0 (C10), 132.5 (C18), 137.8 (C8), 156.1 (C3), 161.4 (C5), and 168.0 (C23).



^{13}C Assignment

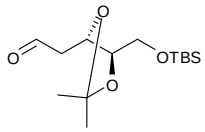
(2*E*,11*Z*)-(5*S*,9*S*,14*S*)-20-Methoxy-18-methoxymethyl-7,7,14-trimethyl-6,8,15-trioxa-tricyclo[15.4.0.05,9]henicosa-1(21),2,11,17,19-pentaene-10,16-dione 225



Pyridinium chlorochromate (29 mg, 132 μmol) was dissolved in anhydrous dichloromethane (1.6 cm^3) and a solution of alcohol **226** (30 mg, 66 μmol) in anhydrous dichloromethane (1.6 cm^3) was added at room temperature. The reaction was stirred for 18 h and then decanted into a clean flask and the residue washed with dichloromethane (2×10 cm^3). The solvent was concentrated *in vacuo* and the residual material diluted with diethyl ether (20 cm^3). The suspension was filtered through cotton wool to remove the chromium salts. The ethereal component was washed with 1 M sodium hydroxide (15 cm^3), then brine (15 cm^3) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to leave an orange/brown residue. Purification by FCC [petroleum ether – ethyl acetate (50:50)] of the crude residue afforded protected LL-Z1640-2 **225** (10 mg, 34%); R_f 0.38 (Solvent *C*); $[\alpha]_D^{22}$ -0.16 (*c* 1.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 2952 (C-H), 1760 (C=O), 1599 (C=C), 1019 and 979; δ_H(400 MHz; $CDCl_3$) 1.24 (6

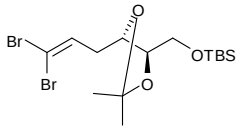
H, s, 2×CC*H*$_3$), 1.32 (3 H, d, *J* 12.6, C*H*$_3$), 2.45-2.70 (4 H, m, 2×C*H*$_2$), 3.43 (3 H, s, OCH$_2$OC*H*$_3$), 3.75 (3 H, s, OC*H*$_3$), 4.41-4.43 (1 H, m, CH$_2$C*H*O), 4.53-4.56 (1 H, m, *H*CCH$_3$), 4.63 (1 H, d, *J* 7.8, C*H*O), 5.08-5.15 (1 H, m, CH=C*H*), 5.29 (2 H, s, OC*H*$_2$OCH$_3$), 5.43-5.48 (1 H, m, CH=C*H*(C=O)), 6.01-6.05 (1 H, m, C*H*=CH(C=O)), 6.30-6.54 (2 H, m, C*H*=CH and C*H*) and 6.54 (1 H, m, C*H*). The lack of material prevented the acquisition of a full data set.

2-[(4*S*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde <u>252</u>



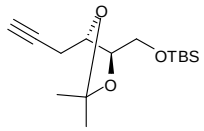
Alkene **208** (620 mg, 2.16 mmol) was dissolved in dichloromethane (15 cm^3) and ozone was bubbled through the solution at −78 °C until the blue colour persisted (15 min). The reaction was quenched with dimethylsulfide (500 eq., 80 cm^3, 1.08 mol; added periodically in 20 cm^3 aliquots) and the resulting solution warmed up to room temperature and stirred until the disappearance of the ozonide (approx. 4 d). The reaction mixture was washed with water (25 cm^3) and the organic layers separated. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford aldehyde **252** (650 mg, 100%) as a colourless oil; R_f 0.44 (Solvent *E*); $[\alpha]_D^{22}$ +1.9 (*c* 1.0, CHCl$_3$) (lit.,[151] $[\alpha]_D^{23}$ +2.2 (*c* 5.0, CHCl$_3$); δ_H(400 MHz; CDCl$_3$) 0.00 (6 H, s, Si(C*H*$_3$)$_2$), 0.82 (9 H, s, SiC(C*H*$_3$)$_3$), 1.30 (3 H, s, C*H*$_3$), 1.36 (3 H, s, C*H*$_3$), 2.68 (1 H, dd, *J* 7.8 and 16.8, C*H*$_2$), 2.80 (1 H, dd, *J* 5.6 and 16.8, C*H*$_2$), 3.52-3.56 (2 H, m, C*H*$_2$OTBS), 4.11 (1 H, dd, *J* 5.6 and 12.1, C*H*CH$_2$), 4.65 (1 H, dd, *J* 6.2 and 12.6, C*H*CH$_2$OTBS) and 9.74 (1 H, s, C*H*O); δ_C(100 MHz; CDCl$_3$) -5.5 (Si(*C*H$_3$)$_2$), 18.2 (Si-*C*), 25.3 (*C*H$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 27.9 (*C*H$_3$), 43.7 (*C*H$_2$), 61.5 (*C*H$_2$OTBS), 71.9 (*C*H), 108.3 (*C*(CH$_3$)$_2$) and 200.1 (*C*=O). All spectral data matches that reported in the literature.[151]

tert-Butyl{[(4*S*,5*S*)-5-(3,3-dibromoallyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dimethylsilane 251



A solution of aldehyde **252** (656 mg, 2.18 mmol) in anhydrous dichloromethane (27 cm^3) at room temperature was treated sequentially with carbon tetrabromide (2.9 g, 8.73 mmol), zinc dust (571 mg, 8.73 mmol) and triphenylphosphine (2.3 g, 8.73 mmol). The addition of triphenylphosphine was done in portions so as to keep the reaction temperature at 25 °C. Over the reaction time, the colour changed from a green solution to a pinkish brown colour. After 1.5 h, the reaction was diluted with hexanes (100 cm^3), passed through a pad of silica gel and washed with diethyl ether. The solvent was concentrated *in vacuo* to afford dibromide **251** (995 mg, 100%) as a colourless oil, which was used without any further purification; R_f 0.79 (Solvent *A*); $[\alpha]_D^{20}$ -0.14 (*c* 1.4, $CHCl_3$); ν_{max} (film)/cm^{-1} 2486, 2071, 1193 and 1121 (C-O); δ_H(400 MHz; $CDCl_3$) 0.05 (6 H, s, Si(CH_3)$_2$), 0.85 (9 H, s, SiC(CH_3)$_3$), 1.31 (3 H, s, CH_3), 1.41 (3 H, s, CH_3), 2.22-2.30 (1 H, m, CH_2), 2.36-2.43 (1 H, m, CH_2), 3.64 (2 H, d, *J* 6.0, CH_2OTBS), 4.10 (1 H, q, *J* 6.0, $CHCH_2$), 4.18-4.23 (1 H, m, $CHCH_2$OTBS) and 6.54 (1 H, t, *J* 6.8, CH=Br_2); δ_C(100 MHz; $CDCl_3$) -2.5 (Si(CH_3)$_2$), 19.1 (SiC(CH_3)$_3$), 26.3 (2×CH_3), 26.5 (SiC(CH_3)$_3$), 36.3 (CH_2), 64.7 (CH_2OTBS), 71.8 (CH), 75.9 (CH), 90.1 (C=CBr_2), 108.0 ((C(CH_3)$_2$) and 137.6 (C=CBr_2); MS (CI) *m*/*z* 310.2 [M-OTBS]$^+$; HRMS *m*/*z* 310.9284 (310.9282 calcd for $C_9H_{13}Br_2O_2$, M-OTBS$^+$).

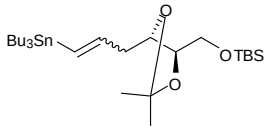
tert-Butyl[(4*S*,5*S*)-2,2-dimethyl-5-prop-2-ynyl-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane 70



Dibromoolefin **251** (1.0 g, 2.19 mmol) was dissolved in anhydrous tetrahydrofuran (27 cm^3), cooled down to −78 °C and treated with *n*BuLi (1.6 M in hexanes, 2.7 cm^3, 4.38 mmol). The reaction was kept at −78 °C for 2 h and then quenched with water (40 cm^3). The mixture was stirred for 15 min at −78 °C and then allowed to warm up slowly to 0 °C and then room temperature. The reaction mixture was extracted with ethyl acetate (3×40 cm^3) and the combined

organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether – ethyl acetate (97:3)] of the crude residue afforded alkyne **70** (395 mg, 61%) as a yellow oil; R_f 0.57 (Solvent *D*); $[\alpha]_D^{20}$ –0.2 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 2477 (C≡C), 2051, 1201 and 1120 (C-O); δ_H(400 MHz; $CDCl_3$) 0.15 (6 H, s, Si(C*H*$_3$)$_2$), 0.88 (9 H, s, SiC(C*H*$_3$)$_3$), 1.34 (3 H, s, C*H*$_3$), 1.45 (3 H, s, C*H*$_3$), 2.02 (1 H, t, *J* 2.6, C≡C*H*), 2.44-2.62 (2 H, m, C*H*$_2$), 3.71 (2 H, dd, *J* 5.0 and 6.8, C*H*$_2$OTBS), 4.15 (1 H, q, *J* 6.0, C*H*CH$_2$OTBS) and 4.30-4.34 (1 H, m, C*H*CH$_2$); δ_C(100 MHz; $CDCl_3$) -5.4 (Si(*C*H$_3$)$_2$), 20.1 (Si*C*(CH$_3$)$_3$), 25.4 (*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 27.8 (*C*H$_3$), 29.7 (*C*H$_3$), 61.5 (*C*H$_2$OTBS), 69.7 (H*C*≡C), 75.7 (HC≡C*C*H$_2$*C*), 77.4 (*C*CH$_2$OTBS), 81.2 (HC≡*C*) and 108.6 (*C*(CH$_3$)$_2$); MS (CI) *m/z* 153.1 [M-OTBS]$^+$; HRMS *m/z* 153.0912 (153.0916 calcd for $C_9H_{13}O_2$, M-OTBS$^+$).

tert-Butyl-[(4*S*,5*S*)-2,2-dimethyl-5-((*E*/*Z*)-3-tributylstannyl-allyl)-[1,3]-dioxolan-4-ylmethoxy]-dimethylsilane <u>250</u>



Procedure A

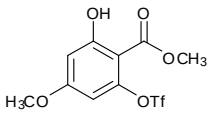
A solution of alkyne **70** (40 mg, 0.135 mmol) and *bis*(triphenylphosphine)palladium dichloride ($(Ph_3P)_2PdCl_2$) (catalytic amount) in anhydrous tetrahydrofuran (2 cm^3) at room temperature, was treated by the slow addition of a solution of tributyltinhydride (40 µL, 142 µmol) in tetrahydrofuran (0.2 cm^3). Upon addition, the colour of the solution changed from pale yellow to orange-brown. After 20 min, the now brown coloured reaction was complete and the mixture was concentrated *in vacuo*. Purification by FCC [petroleum ether-diethyl ether (95:5)] of the crude residue afforded stannane **250** (62 mg, 79%) as a colourless oil and as an inseparable *trans:cis* mixture; R_f 0.83 (Solvent *E*); $[\alpha]_D^{20}$ –1.8 (*c* 0.7, $CHCl_3$); ν_{max} (film)/cm^{-1} 2928, 2362 and 1255; δ_H(400 MHz; $CDCl_3$) (*trans*) 0.04 (6 H, s, Si(C*H*$_3$)$_2$), 0.80-0.92 (24 H, m, SiC(C*H*$_3$)$_3$, (C*H*$_3$)$_3$, (C*H*$_2$)$_3$), 1.20-1.36 (9 H, m, C*H*$_3$, (C*H*$_2$)$_3$), 1.38 (3 H, s, C*H*$_3$), 1.40-1.60 (6 H, m, (C*H*$_2$)$_3$), 2.22-2.45 (2 H, m, (C*H*$_2$)$_3$), 3.53-3.70 (2 H, m, C*H*$_2$OTBS), 4.03-4.09 (1 H, m, C*H*CH$_2$OTBS), 4.14-4.20 (1 H, m, C*H*CH$_2$), 5.05 (1 H, d, *J* 19.0, C*H*=CH) and 5.81-5.83 (1 H, m, CH=C*H*); (*cis*) (*inter alia*) 5.08 (1 H, d,

J 11.5, C*H*=CH). MS (CI) *m*/*z* 291.3 $[Bu_3Sn]^+$, 361.5 $[Bu_3SnCH{=}CHCH_2CH_2OH]$, 461.4 $[M\text{-}TBS]^+$ and 577.6 $[M+H]^+$.

Procedure B

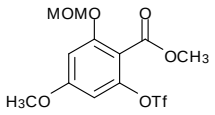
Alkyne **70** (41.6 mg, 0.1403 mmol) in toluene (5 cm^3) was treated with 2,2'-azobis(2-methyl)propionitrile (AIBN) (1.2 mg, 7 μmol) and Bu_3SnH (0.04 cm^3, 0.154 mmol) under argon. The mixture was heated to 95 °C for 24 h. The reaction mixture was then cooled down to room temperature and the solvent evaporated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (100:0)→(98.5:1.5)] of the crude residue afforded an inseparable mixture of *E:Z*-stannane **250** and alkene **208** (70 mg, 85%) as a colourless oil; R_f 0.54 (Solvent *E*). The spectral data matches that for Procedure A.

Methyl 2-hydroxy-4-methoxy-6-(trifluoromethylsulfonyloxy)benzoate <u>256</u>



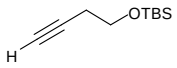
A solution of triflate **119** (1.23 g, 2.77 mmol) in anhydrous tetrahydrofuran (15 cm^3) at 0 °C, was treated with *tetra*-butylammonium fluoride (5.5 cm^3, 5.53 mmol) and the ice-water bath was removed after 10 min. After 2 h, the reaction mixture was diluted with ethyl acetate (20 cm^3) and quenched with water (20 cm^3). The phases were separated and the aqueous layer was extracted with ethyl acetate (20 cm^3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether–ethyl acetate (80:20)] of the crude residue afforded phenol **256** (754 mg, 83%) as a white solid; R_f 0.62 (Solvent *A*); mp 35-38 °C (from petroleum ether-ethyl acetate); ν_{max} (film)/cm^{-1} 3367, 1671 (C=O), 1635 (C=C), 1570, 1427, 1341, 1219; δ_H(400 MHz; $CDCl_3$) 3.74 (3 H, s, OC*H*$_3$), 3.88 (3 H, s, CO_2CH_3), 6.25 (1 H, s, C*H*), 6.39 (1 H, s, C*H*) and 11.59 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 52.5 (CO_2CH_3), 56.0 (OCH_3), 100.3 (*C*COH), 100.9 (CCO_2CH_3), 103.2 (H*C*COTf), 149.5 (*C*OTf), 164.5 (*C*OH), 165.3 ($COCH_3$) and 168.8 (CO_2CH_3); MS (CI) *m*/*z* 331.2 $[M+H]^+$; HRMS *m*/*z* 331.0100 (331.0100 calcd for $C_{10}H_{10}F_3O_7S$, $M+H^+$).

Methyl 4-methoxy-2-(methoxymethyl)-6-(trifluoromethylsulfonyloxy)-benzoate 257



Phenol **256** (412 mg, 1.25 mmol) was dissolved in anhydrous dichloromethane (7 cm^3) and *N,N*-diisopropylethylamine (0.65 cm^3, 3.74 mmol) was added at room temperature. The reaction mixture was cooled to 0 °C and bromomethyl methyl ether (0.2 cm^3, 2.50 mmol) was added. After 10 min, the the ice-water bath was removed and the reaction mixture allowed to warm up to room temperature overnight. The now yellow solution was poured into saturated aqueous sodium hydrogen carbonate (30 cm^3) and extracted with ethyl acetate (3×40 cm^3). The combined organic layers were washed sequentially with brine (30 cm^3) then water (30 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether–ethyl acetate (80:20)] of the crude residue afforded MOM ether **257** (421 mg, 90%) as a pale yellow solid; R_f 0.24 (Solvent *A*); mp 26-28 °C (from petroleum ether-ethyl acetate); ν_{max}(film)/cm^{-1} 3434, 1630, 1425; δ_H(400 MHz; $CDCl_3$) 3.53 (3 H, s, OCH_2OCH_3), 3.86 (3 H, s, OCH_3), 3.94 (3 H, s, CO_2CH_3), 5.24 (2 H, s, CH_2), 6.52 (1 H, s, C*H*) and 6.79 (1 H, s, C*H*); δ_C(100 MHz; $CDCl_3$) 52.5 (CO_2CH_3), 55.9 (OCH_2OCH_3), 56.5 (OCH_3), 95.2 (OCH_2OCH_3), 101.0 (CCO_2CH_3), 101.5 (2×*C*H(Ar)), 149.3 (*C*OTf), 157.5 ($COCH_2OCH_3$), 157.4 ($COCH_3$) and 162.3 (*C*=O); MS (CI) *m/z* 375.3 $[M+H]^+$; HRMS *m/z* 375.0359 (375.0362 calcd for $C_{12}H_{14}F_30_8S$, $M+H^+$).

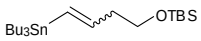
***tert*-Butyl-but-3-ynyloxy-dimethylsilane 259**



A solution of 3-butyn-1-ol (2.0 g, 28.5 mmol) in dichloromethane (140 cm^3) at room temperature, was treated with dimethylaminopyridine (348 mg, 2.85 mmol) and triethylamine (7 cm^3, 51.3 mmol). After 5 min, *tert*-butyldimethylsilyl chloride (5.6 g, 37.1 mmol) was added and the colourless solution was stirred for 18 h. The reaction was quenched with saturated aqueous ammonium chloride (100 cm^3) and extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether–diethyl ether (90:10)] of the crude residue afforded **259** (4.3 g, 82%) as a

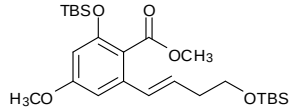
colourless oil; R_f 0.87 (Solvent *A*); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, Si(CH_3)$_2$), 0.88 (9 H, s, SiC(CH_3)$_3$), 1.94 (1 H, t, *J* 2.6, H), 2.39 (2 H, dt, *J* 2.4 and 7.2, CH_2) and 3.71 (2 H, t, *J* 7.2, CH_2OTBS). All spectral data matches that reported in the literature.[152]

tert-Butyl-[(*E*/*Z*)-4-(dibutylethylstannanyl)-but-3-enyloxy]-dimethylsilane 260[133]



A neat mixture of alkyne **259** (103 mg, 0.559 mmol) and 2,2'-azobis(2-methyl)propionitrile (AIBN) (5 mg, 27.9 μmol) under argon was heated to 80 °C for 1.5 h. The reaction mixture was then cooled down to room temperature and the excess alkyne **259** was removed under high vacuum to yield (265 mg) as an *E*:*Z*-mixture (79:21) of stannane **260** in quantitative yield and as a colourless oil. No separation was necessary and the mixture was used in the next step without any further purification; R_f 0.89 (Solvent *D*); ν_{max}(film)/cm^{-1} 2924, 2855, 1464 and 1100 (O-Si); δ_H(400 MHz; $CDCl_3$) (*E*-isomer) 0.05 (6 H, s, Si(CH_3)$_2$), 0.89 (9 H, s, SiC(CH_3)$_3$), 1.21-1.34 (9 H, m, 3×CH_3), 1.42-1.55 (18H, m, 9×CH_2), 2.34-2.36 (2 H, m, CH_2), 3.64 (1 H, t, *J* 6.8, CH_2OTBS) and 5.93 (2 H, s, *H*C=C*H*); (*Z*-isomer) 0.06 (6 H, s, Si(CH_3)$_2$), 0.91 (9 H, s, SiC(CH_3)$_3$), 1.21-1.34 (9 H, m, 3×CH_3), 2.24-2.27 (2 H, m, CH_2), 3.66 (1 H, t, *J* 7.0, CH_2OTBS), 5.89 (1 H, dt, *J* 1.2 and 12.4, *H*C=CH) and 6.53 (1 H, dt, *J* 6.8 and 12.8, HC=C*H*); MS (CI) *m*/*z* 419 [M-C(CH_3)$_3$]$^+$; HRMS *m*/*z* 419.1800 (419.1792 calcd for $C_{18}H_{39}OSiSn$, M-C(CH_3)$_3^+$). All spectral data matches that reported in the literature.[133]

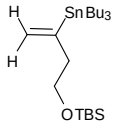
Methyl 2-(_tert_-butyldimethylsilanyloxy)-6-[(*E*)-4-(_tert_-butyldimethylsilanyloxy)-but-1-enyl]-4-methoxybenzoate 263



A solution of triflate **119** (127 mg, 286 μmol) in dioxane (6 cm^3) was treated with stannane **260** (163 mg, 343 μmol), lithium chloride (36 mg, 857 μmol) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (10 mg, 8.57 μmol). The mixture was heated to 100 °C for 24 h and then treated with a further portion of lithium chloride (36 mg, 857 μmol) and $Pd(PPh_3)_4$ (10 mg, 8.57 μmol). The reaction mixture was then heated under reflux for 3 d and then cooled down to room temperature and concentrated *in vacuo*. Purification by FCC [petroleum

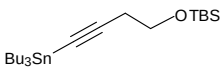
ether – diethyl ether (100:0)→(97:3)→(95:5)] of the crude residue afforded alkene **263** (29 mg, 21%) as colourless oil; R_f 0.5 (Solvent R); ν_{max}(film)/cm^{-1} 2931, 1730 (C=O) and 1257; δ_H(400 MHz; $CDCl_3$) 0.04 (6 H, s, Si(CH_3)$_2$), 0.20 (6 H, s, Si(CH_3)$_2$), 0.89 (9 H, s, SiC(CH_3)$_3$), 0.94 (9 H, s, SiC(CH_3)$_3$), 2.40 (2 H, q, *J* 6.7, CH_2), 3.69 (2 H, t, *J* 6.7, CH_2OTBS), 3.77 (3 H, s, OCH_3), 3.83 (3 H, s, CO_2CH_3), 6.15-6.18 (1 H, m, HC=C*H*), 6.25 (1 H, d, *J* 2.0, C*H*), 6.39 (1 H, d, *J* 15.7, *H*C=CH), 6.60 (1 H, d, *J* 7.0, C*H*); δ_C(100 MHz; $CDCl_3$) -5.3 (Si(*C*H$_3$)$_2$ (CH_2OTBS), -4.4 (Si(*C*H$_3$)$_2$ (OTBS), 18.0 (Si*C*(CH$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), 25.5 (SiC(*C*H$_3$)$_3$ (CH_2OTBS), 25.9 (SiC(*C*H$_3$)$_3$ (OTBS)), 36.7 (*C*H$_2$), 52.0 (CO_2*C*H$_3$), 55.3 (O*C*H$_3$), 62.8 (*C*H$_2$OTBS), 102.8 (*C*H), 104.5 (*C*H), 118.3 (*C*COOCH$_3$), 128.4 (HC=CH), 130.4 (HC=CH), 137.9 (*C*HC=CH), 154.0 (*C*OTBS), 160.8 (*C*OCH$_3$) and 168.6 (*C*=O); MS (EI) *m*/*z* 480.16 [M]$^+$; HRMS *m*/*z* 480.2725 (480.2727 calcd for $C_{25}H_{44}O_5Si_2$, M^+), 481.2775 (481.2806 calcd for $C_{25}H_{45}O_5Si_2$, M+H$^+$).

tert-Butyldimethyl-(3-(tributylstannyl)but-3-enyloxy)silane **262**[153]



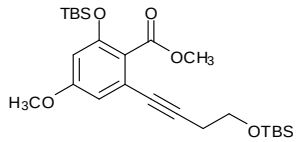
To a suspension of copper cyanide (194 mg, 2.17 mmol) in anhydrous tetrahydrofuran (8.5 cm^3) was added *n*BuLi (1.6 M in hexanes, 2.8 cm^3, 4.54 mmol) at −78 °C. The solution was warmed up to −40 °C and stirred for 10 min (pale yellow colour). The mixture was cooled back down to −78 °C and tributyltinhydride (1.2 cm^3, 4.54 mmol) was added. The solution was warmed up to −40 °C and stirred for 10 min (yellow/gold colour). The solution was cooled back down to −78 °C and a solution of alkyne **259** (200 mg, 1.08 mmol) in anhydrous tetrahydrofuran (1 cm^3) was added. The reaction mixture was allowed to warm up to −30 °C for 1 h and was then poured into a saturated aqueous ammonium chloride solution (10 cm^3) at −10 °C. After 30 min, the reaction mixture was extracted with diethyl ether. The combined organic layers were washed with brine (20 cm^3), dried over magnesium sulfate, filtered and the solvent concentrated *in vacuo* to afford stannane **262** quantitatively as a colourless oil; R_f 0.66 (Solvent *E*); δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(CH_3)$_2$), 0.72-0.92 (24 H, m, SiC(CH_3)$_3$, (CH_3)$_3$, (CH_2)$_3$), 1.20-1.30 (6 H, m, (CH_2)$_3$), 1.39-1.49 (6 H, m, (CH_2)$_3$), 2.28-2.30 (2 H, m, CH_2), 3.60 (2 H, t, *J* 7.2, CH_2OTBS) and 5.90 (2 H, s, C=CH_2). All spectral data matches that reported in the literature.[153]

***tert*-Butyl-dimethyl-(4-tributylstannanyl-but-3-ynyloxy)-silane 269**[139]



Alkyne **259** (225 mg, 1.22 mmol) was dissolved in anhydrous tetrahydrofuran (10 cm^3) and cooled to 0 °C. *n*BuLi (0.9 cm^3, 1.46 mmol) was then added and the reaction mixture stirred for 10 min before it was allowed to warm up to room temperature, where it was stirred for 1 h. After this time, the reaction was cooled back down to 0 °C and tributyltinchloride (0.4 cm^3, 1.46 mmol) added. The pale yellow solution was stirred overnight at room temperature and then diluted with dichloromethane (20 cm^3). The mixture was washed with water (20 cm^3) and the phases separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [hexanes (100) *then* ethyl acetate (100)] of the crude residue afforded alkyne **269** (397 mg, 69%) as a yellow oil; R_f 0.07 (Solvent *Q*); δ_H(400 MHz; $CDCl_3$) 0.08 (6 H, s, Si(CH_3)$_2$), 0.85-0.91 (24 H, m, SiC(CH_3)$_3$ and (CH_3)$_3$ and (CH_2)$_3$), 1.22-1.27 (6 H, m, (CH_2)$_3$), 1.46-1.49 (6 H, m, (CH_2)$_3$), 2.39 (2 H, t, *J* 7.3, CH_2) and 3.66 (2 H, t, *J* 7.3, CH_2OTBS). All spectral data matches that reported in the literature.[139]

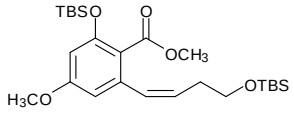
Methyl 2-(*tert*-butyl-dimethyl-silanyloxy)-6-[4-(*tert*-butyl-dimethyl-silanyloxy)-but-1-ynyl]-4-methoxybenzoate 268



A mixture of triflate **119** (310 mg, 0.699 mmol), lithium chloride (89 mg, 2.10 mmol), stannane **269** (397 mg, 0.838 mmol) and *tetra*kis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (24 mg, 20.9 μmol) in 1,4-dioxane (15 cm^3) was heated at 100 °C for 4.5 h. The reaction was then cooled down to room temperature and the solvent was removed under reduced pressure. Initial purification by FCC [petroleum ether – diethyl ether (90:10)] followed by a second purification by FCC [petroleum ether – diethyl ether (95:5)] afforded alkyne **268** (111 mg, 33%) as a yellow oil; R_f 0.6 (Solvent *P*); ν_{max}(film)/cm^{-1} 2931, 1732 (C=O) and 1265; δ_H(400 MHz;$CDCl_3$) 0.00 (6 H, s, Si(CH_3)$_2$), 0.12 (6 H, s, Si(CH_3)$_2$), 0.82 (9 H, s, SiC(CH_3)$_3$), 0.88 (9 H, s, SiC(CH_3)$_3$), 2.52 (2 H, t, *J* 7.4, CH_2), 3.68 (3 H, s, OCH_3), 3.70 (2 H, t, *J* 7.8, CH_2OTBS), 3.76 (3 H, s, CO_2CH_3), 6.24 (1 H, d, *J* 2.1, C*H*) and 6.50 (1 H, d, *J* 2.1, C*H*); δ_C(100 MHz;$CDCl_3$) –5.3 (Si(CH_3)$_2$ *from* CH_2OTBS), -4.4 (Si(CH_3)$_2$ *from* OTBS), 18.1 (Si*C*

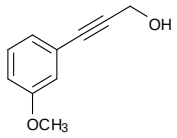
from OTBS), 18.4 (Si*C* *from* CH_2OTBS), 23.9 (*C*H_2), 25.5 (SiC(*C*H_3)$_3$ *from* OTBS), 25.9 (SiC(*C*H_3)$_3$ *from* CH_2OTBS), 52.1 (CO_2*C*H_3), 55.4 (O*C*H_3), 61.9 (*C*H_2OTBS), 79.8 (*C*≡C(CH_2)$_2$), 90.1 (C≡*C*(CH_2)$_2$), 106.5 (*C*H), 109.8 (*C*H), 121.9 (*C*(CO_2CH_3)), 123.6 (*C*(C≡C)), 153.2 (*C*(OTBS)), 160.7 (*C*(OCH_3)) and 167.3 (CO_2CH_3); MS (CI) *m/z* 479.4 $[M+H]^+$; HRMS *m/z* 479.2644 (479.2650 calcd for $C_{25}H_{43}O_5Si_2$, $M+H^+$).

Methyl 2-(*tert*-butyl-dimethyl-silanyloxy)-6-[(*Z*)-4-(*tert*-butyldimethylsilanyloxy)-but-1-enyl]-4-methoxybenzoate <u>278</u>



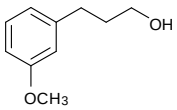
A solution of alkyne **268** (111 mg, 0.232 mmol) in methanol (2 cm^3) was treated with a catalytic amount of Pd/$BaSO_4$ catalyst and poisoned with quinoline (30 µL, 289 µmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through silica gel to remove the catalyst and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-diethyl ether (95:5)→(90:10)] of the crude residue afforded (*Z*)-alkene **278** (58 mg, 52%) as a yellow oil; R_f 0.63 (Solvent *R*); ν_{max}(film)/cm^{-1} 3055, 1734 (C=O) and 1255; δ_H(400 MHz;$CDCl_3$) 0.02 (6 H, s, Si(C*H*$_3$)$_2$), 0.20 (6 H, s, Si(C*H*$_3$)$_2$), 0.87 (9 H, s, SiC(C*H*$_3$)$_3$), 0.95 (9 H, s, SiC(C*H*$_3$)$_3$), 2.38 (2 H, q, *J* 6.5, C*H*$_2$), 3.62 (2 H, t, *J* 6.5, C*H*$_2$OTBS), 3.75 (3 H, s, OC*H*$_3$), 3.79 (3 H, s, CO_2C*H*$_3$), 5.67-5.73 (1 H, m, HC=C*H*), 6.24 (1 H, d, *J* 2.0, C*H*), 6.43-6.49 (2 H, d, *J* 11.0, *H*C=CH); δ_C(100 MHz;$CDCl_3$) -5.3 (Si(*C*H_3)$_2$ (CH_2OTBS), -4.4 (Si(*C*H_3)$_2$ (OTBS), 18.1 (Si*C*(CH_3)$_3$), 18.4 (Si*C*(CH_3)$_3$), 25.5 (SiC(*C*H_3)$_3$ (CH_2OTBS), 26.0 (SiC(*C*H_3)$_3$ (OTBS), 32.2 (*C*H_2), 51.9 (CO_2*C*H_3), 55.3 (O*C*H_3), 62.8 (*C*H_2OTBS), 104.0 (*C*H), 108.5 (*C*H), 118.9 (*C*COOCH_3), 128.1 (HC=*C*H), 130.7 (H*C*=CH), 137.9 (*C*HC=CH), 154.0 (*C*OTBS), 160.6 (*C*OCH_3) and 168.4 (C=O); MS (FAB) *m/z* 481.3 $[M+H]^+$; HRMS *m/z* 481.2810 (481.2806 calcd for $C_{25}H_{45}O_5Si_2$, $M+H^+$).

3-(Methoxy-phenyl)-prop-2-yn-1-ol 272[140]

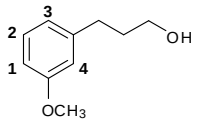


3-Iodoanisole (1.0 g, 4.27 mmol) in anhydrous acetonitrile (40 cm^3) was treated with $PdCl_2(PPh_3)_2$ (375 mg, 0.534 mmol), copper iodide (203 mg, 1.07 mmol) and triethylamine (3 cm^3, 21.3 mmol). To this was added propargyl alcohol (287 mg, 5.12 mmol) and the reaction stirred in the dark for 16 hours at room temperature. The solids were removed by filtration, washed with diethyl ether (2×60 cm^3) and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the crude residue afforded alkynol **272** (567 mg, 82%); R_f 0.31 (Solvent *S*); δ_H(400 MHz;$CDCl_3$) 1.71 (1 H, s, O*H*), 3.80 (3 H, s, OCH_3), 4.49 (2 H, s, CH_2OH), 6.88 (1 H, ddd, *J* 0.6, 2.8 and 8.4, C*H*), 6.98 (1 H, dd, *J* 1.2 and 2.4, C*H*), 7.03 (1 H, dt, *J* 0.8 and 7.6, C*H*) and 7.21 (1 H, dd, *J* 0.8 and 8.0, C*H*). The spectral data matches that reported in the literature.[140]

3-(3-Methoxy-phenyl)-propan-1-ol 273[154]

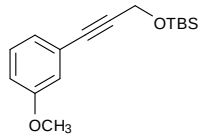


Alkynol **272** (114 mg, 0.703 mmol) was dissolved in methanol (10 cm^3) and was treated with a catalytic amount of Pd/$BaSO_4$ catalyst and poisoned with quinoline (0.10 cm^3, 0.879 mmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 2 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of silica gel and the solvent concentrated *in vacuo*. Purification by FCC [diethyl ether (100)] of the crude residue afforded alkane **273** (83 mg, 72%) as a pale yellow oil; R_f 0.23 (Solvent *A*); δ_H(400 MHz;$CDCl_3$) 1.80 (1 H, *br* s, O*H*), 2.39 (2 H, dd, *J* 6.4 and 14.2, $CH_2CH_2CH_2$), 3.19 (2 H, t, *J* 6.4, $CH_2CH_2CH_2$), 4.17 (2 H, t, *J* 6.4, $CH_2CH_2CH_2$), 4.29 (3 H, s, OCH_3), 7.20-7.32 (2 H, m, C*H*1 and C*H*3), 7.68 (1H, t, *J* 7.6, C*H*2) and 7.74 (1 H, s, C*H*4); MS (EI) *m*/*z* 166 $[M]^+$; HRMS *m*/*z* 166.0996 (166.0994 calcd for $C_{10}H_{14}O_2$, M^+). All spectral data matches that reported in the literature.[154]

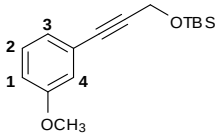


^{1}H Assignment

***tert*-Butyl-[3-(3-methoxyphenyl)-prop-2-ynyloxy]-dimethylsilane 274**

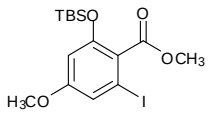


Alkynol **272** (200 mg, 1.23 mmol) was dissolved in dichloromethane (10 cm^3) at room temperature and dimethylaminopyridine (15 mg, 0.123 mmol) and triethylamine (0.31 cm^3, 2.22 mmol) were added successively. *tert*-Butyldimethylsilyl chloride (242 mg, 1.60 mmol) was added and the reaction stirred at room temperature for 18 h. The cloudy, yellow solution was quenched with saturated aqueous ammonium chloride (20 cm^3) and extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded alkyne **274** (264 mg, 78%) as a pale orange oil; R_f 0.67 (Solvent *A*); ν_{max}(film)/cm^{-1} 2928 and 1257; δ_H(400 MHz; $CDCl_3$) 0.17 (6 H, s, Si(C*H*$_3$)$_2$), 0.93 (9 H, s, SiC(C*H*$_3$)$_3$), 3.80 (3 H, s, C*H*$_3$), 4.52 (2 H, s, C*H*$_2$), 6.85 (1 H, d, *J* 8.3, C*H*1), 6.93 (1 H, s, C*H*4), 7.00 (1 H, d, *J* 7.5, C*H*3) and 7.19 (1 H, t, *J* 8.0, C*H*2); δ_C(100 MHz; $CDCl_3$) -5.0 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 52.3 (*C*H$_2$OTBS), 55.3 (O*C*H$_3$), 84.8 (*C*≡C), 87.8 (C≡*C*), 114.8 (C1 and C3), 116.5 (C4), 124.2 (*C*C≡CCH$_2$OTBS), 129.3 (C2) and 159.3 (*C*OCH$_3$); MS (EI) *m*/*z* 276.1 $[M]^+$, 261.0 $[M\text{-}CH_3]^+$, 145.0 [M-OTBS]$^+$; HRMS *m*/*z* 276.1543 (276.1546 calcd for $C_{16}H_{24}O_2Si$, M^+), 277.1483 (277.1625 calcd for $C_{16}H_{25}O_2Si$, $M+H^+$).



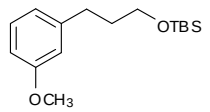
^{1}H and ^{13}C Assignment

Methyl 2-(*tert*-Butyldimethylsilanyloxy)-6-iodo-4-methoxybenzoate 267



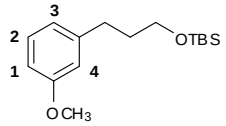
A dry flask was charged with triflate **119** (242 mg, 0.544 mmol) and sodium iodide (163 mg, 1.09 mmol). The reaction flask was flushed with argon and dry dimethylformamide (5 cm^3) was injected. The heterogeneous solution was heated to 80 ^oC for 17.5 h. After cooling down to room temperature, the reaction was poured into a mixture of saturated sodium thiosulphate (20 cm^3) and ethyl acetate (20 cm^3). The organic layer was separated and then washed with water (2×40 cm^3) and brine (30 cm^3), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded **267** (99 mg, 43%) as a colourless oil; R_f 0.43 (Solvent *R*); ν_{max}(film)/cm^{-1} 1265; δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(CH_3)$_2$), 0.82 (9 H, s, SiC(CH_3)$_3$), 3.75 (3 H, s, OCH_3), 3.88 (3 H, s, CO_2CH_3), 6.32 (1 H, d, *J* 2.4, C*H*) and 6.47 (1 H, d, *J* 2.4, C*H*); δ_C(100 MHz; $CDCl_3$) –3.6 (Si(*C*H_3)$_2$), 18.1 (Si*C*(CH$_3$)$_3$), 25.7 (SiC(*C*H_3)$_3$), 52.5 (CO_2*C*H_3), 56.0 (O*C*H_3), 100.0 (*C*I), 100.9 (H*C*COTBS), 103.3 (HICI), 133.7 (*C*COOCH$_3$), 164.7 (*C*OTBS), 165.4 (C=O) and 168.9 (*C*OCH$_3$). The compound failed to ionise under all mass spectrometry conditions attempted.

***tert*-Butyl-[3-(3-methoxyphenyl)-allyloxy]-dimethylsilane 276**



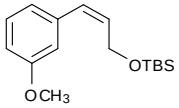
Alkyne **274** (130 mg, 0.470 mmol) was dissolved in methanol (6 cm^3) and was treated with a catalytic amount of Pd/$BaSO_4$ catalyst and poisoned with quinoline (0.07 cm^3, 0.588 mmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 1 h at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® and the solvent concentrated *in vacuo*. Purification by FCC [diethyl ether (100)] of the crude residue afforded alkane **276** (92 mg, 70%) as a pale yellow oil; R_f 0.23 (Solvent *A*); ν_{max}(film)/cm^{-1} 2951, 2857, 1258 and 1100 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.09 (6 H, s, Si(CH_3)$_2$), 0.91 (9 H, s, SiC(CH_3)$_3$), 1.78-1.82 (2 H, m, CH_2C$H_2$$CH_2$), 2.62 (2 H, t, *J* 7.6, C$H_2$$CH_2$$CH_2$), 3.61 (2 H, t, *J* 6.3, $CH_2$$CH_2CH_2$),

3.76 (3 H, s OC*H*$_3$), 6.70 (1 H, d, *J* 7.7, C*H*1), 6.73 (1 H, s, C*H*4), 6.78 (1 H, dd, *J* 7.7, C*H*3) and 7.20 (1 H, t, *J* 7.7, C*H*2); δ_C(100 MHz; $CDCl_3$) -5.3 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 32.2 (*C*H$_2$CH$_2$CH$_2$OTBS), 34.4 (CH$_2$*C*H$_2$CH$_2$OTBS), 55.1 (O*C*H$_3$), 62.4 (CH$_2$CH$_2$*C*H$_2$OTBS), 111.0 (*C*1), 114.2 (*C*4), 121.1 (*C*3), 128.7 (*C*2), 142.0 (*C*) and 162.2 (*C*OCH$_3$); MS (CI) *m*/*z* 281 [M+H]$^+$; HRMS *m*/*z* 281.1934 (281.1937 calcd for $C_{16}H_{29}O_2Si$, M+H$^+$).



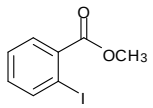
^{1}H and ^{13}C Assignment

***tert*-Butyl-[(*Z*)-3-(3-methoxyphenyl)-allyloxy]-dimethylsilane 275**

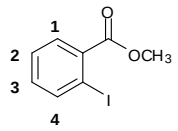


Alkyne **274** (130 mg, 0.470 mmol) was dissolved in methanol (6 cm^3) and was treated with a catalytic amount of Pd/$BaSO_4$ catalyst and poisoned with quinoline (0.07 cm^3, 0.588 mmol). The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 30 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether - diethyl ether (90:10)] of the crude residue afforded **274** and **275** and **276** (114 mg, 87%, 4:89:7) as an inseparable mixture and as a yellow oil; R_f 0.61 (Solvent *P*); δ_H(400 MHz; $CDCl_3$) (*Z*-Alkene) 0.05 (6 H, s, Si(C*H*$_3$)$_2$), 0.87 (9 H, s, SiC(C*H*$_3$)$_3$), 3.78 (3 H, s, OC*H*$_3$), 4.43 (2 H, d, *J* 5.9, C*H*$_2$), 5.80 (1 H, dt, *J* 5.9 and 11.8, CH=C*H*CH$_2$), 6.41 (1 H, d, *J* 11.8, C*H*=CH), 6.69-6.80 (3 H, m, 3×C*H*) and 7.15-7.21 (1 H, m, C*H*); (Alkane) 0.09 (6 H, s, Si(C*H*$_3$)$_2$), 0.91 (9 H, s, SiC(C*H*$_3$)$_3$), 1.77-1.81 (2 H, m, CH$_2$C*H*$_2$CH$_2$), 2.62 (2 H, t, *J* 7.6, C*H*$_2$CH$_2$CH$_2$), 3.61 (2 H, t, *J* 6.3, CH$_2$CH$_2$C*H*$_2$), 3.76 (3 H, s OC*H*$_3$), 6.69-6.80 (3 H, m, 3×C*H*) and 7.15-7.21 (1 H, m, C*H*).

Methyl 2-iodo-benzoate 280[155]

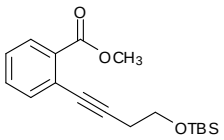


To a solution of 2-iodobenzoic acid (1.0 g, 4.03 mmol) in methanol (4 cm^3) was added concentrated sulphuric acid (0.24 cm^3). The reaction mixture was heated under reflux for 7 h, then cooled down to room temperature, diluted with water (10 cm^3) and extracted several times with chloroform (5×30 cm^3). The combined organic layers were washed with water (40 cm^3), 5% saturated aqueous sodium hydrogen carbonate (2×40 cm^3), water (40 cm^3) and brine (2×40 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether–diethyl ether (70:30)] of the crude residue afforded iodide **280** (868 mg, 82%) as a colourless oil; R_f 0.43 (Solvent *R*); ν_{max}(film)/cm^{-1} 1725 (C=O), 1582 (C=C), 1430, 1249, 1100 and 1013; δ_H(400 MHz; $CDCl_3$) 3.96 (3 H, s, C*H*$_3$), 7.18 (1 H, dt, *J* 1.8 and 7.8, H1), 7.44 (1 H, dt, *J* 1.2 and 7.6, H3), 7.82 (1 H, dd, *J* 1.7 and 7.8, H4) and 8.04 (1 H, dd, *J* 1.1 and 8.0, H1); δ_C(100 MHz; $CDCl_3$) 52.5 (*C*H$_3$), 94.1 (*C*-I), 127.9 (C2), 130.9 (C1), 132.6 (C3), 135.1 (*C*(CO_2CH_3), 141.3 (C4) and 166.9 (C=O); MS (CI) *m*/*z* 262 $[M+H]^+$; HRMS *m*/*z* 262.9566 (262.9569 calcd for $C_8H_8IO_2$, $M+H^+$). All spectral data matches that reported in the literature.[155]



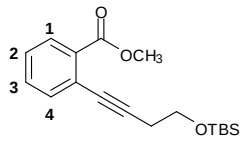
^{1}H and ^{13}C Assignment

Methyl 2-[4-(*tert*-Butyldimethylsilanyloxy)-but-1-ynyl]-benzoate 281



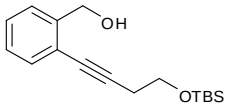
To a mixture of iodobenzoate **280** (300 mg, 1.14 mmol), alkyne **259** (253 mg, 1.37 mmol), bis(triphenylphosphine)palladium dichloride ($PdCl_2(PPh_3)_2$) (80 mg, 0.114 mmol) and copper iodide (22 mg, 0.114 mmol) in anhydrous acetonitrile (11 cm^3) under argon was added triethylamine (0.80 cm^3, 5.72 mmol) at room temperature. The reaction mixture was stirred in the dark for 2 h, then filtered through Celite® to remove the solids and washed with diethyl ether. The solvent was concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether

(90:10) of the crude residue afforded **281** (260 mg, 71%) as a yellow oil; R_f 0.39 (Solvent *R*); ν_{max}(film)/cm^{-1} 2929, 1728 (C=O) and 1255; δ_H(400 MHz; $CDCl_3$) 0.09 (6 H, s, Si(C*H*$_3$)$_2$), 0.90 (9 H, s, SiC(C*H*$_3$)$_3$), 2.68 (2 H, t, *J* 7.3, C*H*$_2$), 3.84 (2 H, t, *J* 7.3, C*H*$_2$OTBS), 3.89 (3 H, s, C*H*$_3$), 7.31 (1 H, dt, *J* 1.4 and 7.8, H2), 7.41 (1 H, dt, *J* 1.4 and 7.8, H3), 7.50 (1 H, dd, *J* 1.1 and 7.7, H4) and 7.88 (1 H, dd, *J* 1.1 and 7.7, H1); δ_C(100 MHz; $CDCl_3$) -5.3 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 24.2 (C≡C*C*H$_2$), 25.9 (SiC(*C*H$_3$)$_3$), 52.0 (COO*C*H$_3$), 61.9 (*C*H$_2$OTBS), 80.2 (*C*≡C), 92.5 (C≡*C*), 124.2 (*C*COOCH$_3$), 127.3 (C2), 130.2 (C1), 131.5 (C3), 132.2 (*C*C≡C), 134.3 (C4) and 167.21 (C=O); MS (FAB) *m*/*z* 319.2 [M+H]$^+$; HRMS *m*/*z* 319.1727 (319.4906 calcd for $C_{18}H_{27}O_3Si$, M+H$^+$).



^{1}H and ^{13}C Assignment

[2-(4-(*tert*-Butyldimethylsilyloxy)but-1-ynyl)phenyl]-methanol <u>284</u>

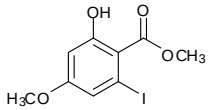


To a solution of alkyne **281** (91 mg, 0.286 mmol) in anhydrous tetrahydrofuran (3 cm^3) was added lithium aluminium hydride (17 mg, 0.457 mmol) under argon. The resulting grey solution was heated under reflux for 23 h. The reaction mixture was cooled down to room temperature and then 0 °C, before the careful addition of diethyl ether (3 cm^3) and then water dropwise with stirring. As a white precipitate was formed, the water was added more quickly until approximately 10 cm^3 had been added. The resulting mixture was left to stir for 20 min at 0 °C, until no grey lithium aluminium hydride was visible. The entire solution was poured into a separating funnel and washed with 1 M sodium hydroxide (20 cm^3). The aqueous layer was separated and extracted with diethyl ether (2×15 cm^3). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether (90:10)] of the crude residue afforded alcohol **284** (4.3 mg) as an oil and an unknown compound (8.1 mg).

Alcohol **284**: R_f 0.2 (Solvent *R*); ν_{max}(film)/cm^{-1} 3365 (OH), 2929, 1265 and 1105 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.10 (6 H, s, Si(C*H*$_3$)$_2$), 0.89 (9 H, s, SiC(C*H*$_3$)$_3$), 2.65 (2 H, t, *J* 6.7, C*H*$_2$), 3.62 (2 H, t, *J* 6.7, C*H*$_2$OTBS), 4.77 (2 H, d, *J* 5.4, C*H*$_2$OH) and 7.19-7.46 (4 H, m, 4×CH); δ_C(100 MHz; $CDCl_3$) -5.2 (Si(CH_3)$_2$), 18.4 (SiC(CH_3)$_3$), 24.0 (CH_2), 25.9 (SiC(CH_3)$_3$), 62.0 (CH_2OTBS), 64.3 (CH_2OH), 79.8 (C≡C), 92.5 (C≡C), 122.1 (C2), 127.5 (C4), 128.1 (C6), 132.1 (C5), 139.2 (C3) and 142.8 (C1); MS (CI) *m*/*z* 291.1 [M+H]$^+$; HRMS *m*/*z* 291.1779 (291.1781 calcd for $C_{17}H_{27}O_2Si$, M+H$^+$).

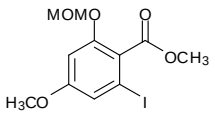
Unknown: R_f 0.8 (Solvent *R*); δ_H(400 MHz; $CDCl_3$) 0.09 (6 H, s, Si(C*H*$_3$)$_2$), 0.88 (9 H, s, SiC(C*H*$_3$)$_3$), 2.55 (1 H, t, *J* 7.2), 2.64 (1H, t, *J* 7.2), 3.75 (2 H, dt, *J* 7.2 and 12.5), 7.23-7.32 (2 H, m), 7.43 (1 H, d, *J* 7.0) and 7.50 (1 H, t, *J* 7.0).

Methyl 2-hydroxy-6-iodo-4-methoxybenzoate <u>264</u>



A dry flask was charged with triflate **119** (447 mg, 1.00 mmol) and sodium iodide (301 mg, 2.01 mmol). The reaction flask was flushed with argon and anhydrous dimethylformamide (10 cm^3) was injected. The heterogeneous solution was heated to 80 ^{o}C for 4 h. After cooling down to room temperature, the reaction was poured into a mixture of saturated sodium thiosulphate (20 cm^3) and ethyl acetate (20 cm^3). The organic layers were washed with water (2×40 cm^3) and brine (30 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded iodide **264** (99 mg, 43%) as a colourless oil; ν_{max}(film)/cm^{-1} 1739 (C=O) and 520; δ_H(400 MHz; $CDCl_3$) 3.88 (3 H, s, OC*H*$_3$), 4.02 (3 H, s, CO_2C*H*$_3$), 6.38 (1 H, s, C*H*) and 6.53 (1 H, d, *J* 2.2, C*H*) and 7.29 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 52.5 (CO_2*C*H$_3$), 56.0 (O*C*H$_3$), 100.0 (*C*I), 101.9 (H*C*COH), 103.9 (H*C*CI), 133.6 (*C*COOCH$_3$), 164.9 (*C*OH), 165.4 (C=O) and 168.9 (*C*OCH$_3$). The compound failed to ionise under all mass spectrometry conditions attempted.

Methyl 2-iodo-4-methoxy-6-methoxymethylbenzoate 18[36]



Phenol **264** (160 mg, 0.519 mmol) was dissolved in dichloromethane (5 cm^3) and *N,N*-diisopropylethylamine (0.27 cm^3,1.56 mmol) was added at room temperature. The reaction mixture was cooled down to 0 °C and bromomethyl methyl ether (0.10 cm^3, 1.04 mmol) was added. After 10 min, the ice-water bath was removed and the reaction allowed to warm to room temperature overnight. After this time, further *N,N'*-diisopropylethylamine (0.27 cm^3,1.56 mmol) and bromomethyl methyl ether (0.10 cm^3, 1.04 mmol at 0 °C) were added. After 2 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate (20 cm^3) and extracted with ethyl acetate (3×20 cm^3). The combined organic layers were washed with water (20 cm^3), then brine (20 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether – diethyl ether (80:20)] of the crude residue afforded MOM ether **18** (179 mg, 98%) as a colourless oil; R_f 0.11 (Solvent *R*); ν_{max}(film)/cm^{-1} 1737 (C=O), 1620 (C=C), 1213, 1149, 1024 and 513; δ_H(400 MHz; $CDCl_3$) 3.49 (3 H, s, OCH_2OCH_3), 3.81 (3 H, s, OCH_3), 3.90 (3 H, s, CO_2CH_3), 5.19 (2 H, s, OCH_2OCH_3), 6.47 (1 H, d, *J* 2.2, C*H*) and 6.73 (1 H, d, *J* 2.2, C*H*); δ_C(100 MHz; $CDCl_3$) 52.3 (CO_2CH_3), 56.0 (OCH_2OCH_3), 56.6 (OCH_3), 95.2 (OCH_2OCH_3), 101.0 (*C*-I), 101.5 (*C*H), 110.8 (*C*H), 147.5 ($COCH_3$), 157.5 ($COCH_2OCH_3$), 162.4 (CCO_2CH_3) and 163.1 (C=O); MS (CI) *m/z* 375.2 $[M+Na]^+$; HRMS *m/z* 374.9700 (374.9705 calcd for $C_{11}H_{13}INaO_5$, $M+Na^+$). All spectral data matches that reported in the literature.[36]

4 Introduction

4.1 Natural Products

A natural product can be described as a chemical compound or substance that is created by a living organism. In the pharmaceutical industry, these compounds are often isolated and characterised, with specific focus on whether they possess any biological activity, which would render them of interest as a potential drug lead.

For many years numerous compounds have been isolated through tissue extraction of plants, animals and microorganisms. Through the use of highly specialised techniques, their novel chemical structures have been elucidated and solved.

Most biologically active natural products are secondary metabolites with highly complex structures hence; the construction of natural products synthetically provides challenges, both intellectually and practically. Since the synthesis of urea and acetic acid in the early 1800's, chemistry has evolved so that highly complex targets are now achievable.

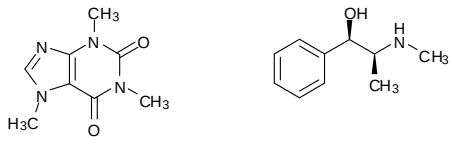
4.2 Alkaloids

The alkaloids are a family of naturally occurring heterocyclic organic compounds which contain nitrogen and an alkaline pH. Alkaloids can be produced by plants, bacteria, fungi or animals and many have been found to exert pharmacological effects and are now used as medicines, for example morphine, or in some cases as recreational drugs such as cocaine. The alkaloids have been further classified by way of their structure, chemical features, biological origin and the biogenetic origin if known,[156] culminating in a quite exhaustive classification:

- Pyridine group
- Pyrrolidine group
- Tropane group
- Indolizidine
- Quinoline
- Isoquinoline

- Phenanthrene
- Phenethylamine
- Indole
- Purine
- Terpenoid
- Quaternary
- Miscellaneous

Some well known examples are caffeine, which is a purine alkaloid and further classified as a xanthine and ephedrine, a phenethylamine alkaloid (Figure 27).



288 289

Figure 27: Structure of Caffeine 288 and Ephedrine 289.

The total synthesis of alkaloids is prevalent in the literature and some of these often fascinating and hugely important, complex molecules have been synthesised and re-synthesised to take advantage of new synthetic developments. In addition, molecules that were previously resistant, have at long last succumbed to total synthesis.

4.3 Spirocyclic Pyrans and Piperidines

A number of natural products and biologically important compounds contain spirocyclic pyran and piperidine ring systems as part of their overall structures.[157] In the past it was common that the difficulty in achieving the total synthesis of such natural products was the formation of the spirocyclic core structures. As a result, numerous synthetic approaches have been developed towards their generation, however most of these tend to be substrate specific and afford a limited number of functional handles from which synthetic diversification can take place.

4.4 Pinnaic Acid

In 1996, Uemura reported the isolation of pinnaic acid and tauropinnaic acid from the Okinawan bivalve *Pinna muricata* (Figure 28).[158]

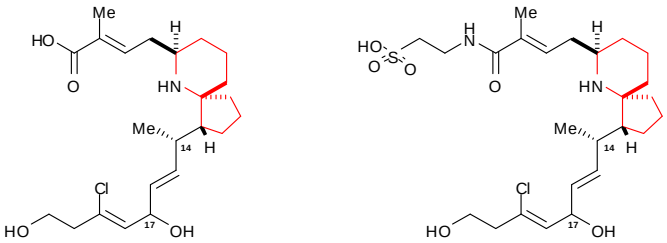


Figure 28: Structures of Pinnaic Acid 290 and Tauropinnaic Acid 291.

These compounds were the first members of a novel class of alkaloids, characterised by an azaspiro[4.5]decane ring system (highlighted in red). Subsequent research showed that pinnaic acid and tauropinnaic acid were found to exhibit inhibitory activity towards cytosolic phospholipase A_2 ($cPLA_2$). The phospholipase A_2 (PLA_2) family consists of lipolytic enzymes whose constituents catalyse the hydrolysis of intra- and extra-cellular membrane phospholipids.[159] Cytosolic phospholipase A_2 ($cPLA_2$) is an 85 kDa phospholipase which is important in the family as it has a significant role in the generation of free arachiodonic acid from cellular phospholipids in mammalian cells.[160] This acid can then go on to mediate the biosynthesis of, for example, prostaglandins and thromboxanes. These biological messengers influence cell proliferation and inflammatory responses and it is for this reason that selective $cPLA_2$ inhibitors are potential targets for the development of novel anti-inflammatory drugs. Pinnaic acid inhibits $cPLA_2$ *in vitro*, with an IC_{50} of 0.2 mM and as a result of this anti-inflammatory activity, suspicion arose that pinnaic acid may be a potential drug for the treatment of inflammation.[158,161]

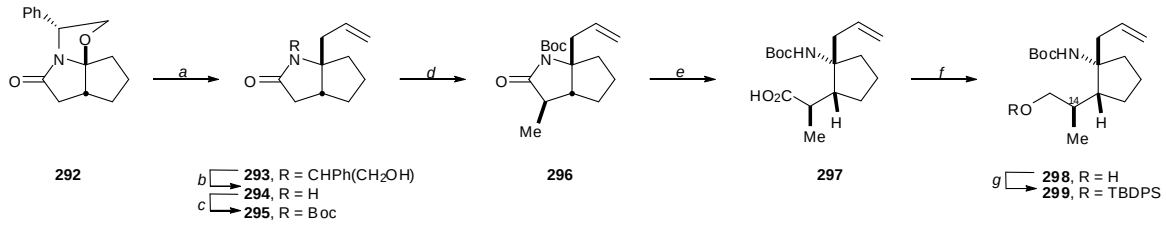
Shortly after its isolation in 1996, the configuration at C_{14} of pinnaic acid was assigned to be *R*, *via* magnetic resonance methods, though this was never conclusive. The stereochemistry at C_{17} was not assigned at all.[158] The isolation process yielded only several milligrams of the natural material, preventing further pharmacological and structural studies meaning only total synthesis of the natural product would provide a resolution to the initial speculation over the assignment, as well as determining the configuration at C_{17}.

There have been numerous research groups who have become intensely motivated to study the synthetic chemistry of pinnaic acid, with the work summarised in a review published in 2005 by Clive and colleagues.[162] By this

stage there were three total syntheses of pinnaic acid,[159,163-165] and two further formal syntheses of this alkaloid.[166,167,168]

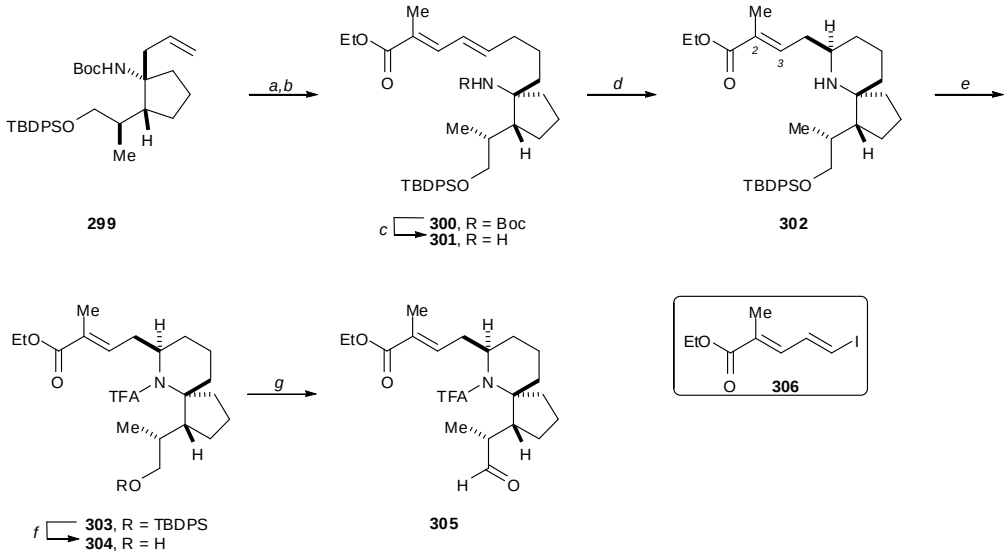
4.4.1 Danishefsky's Total Synthesis of Pinnaic Acid

In 2001, Danishefsky and co-workers published the first total synthesis of pinnaic acid.[159,164] The synthesis is neat and concise and begins from Meyers' lactam (Scheme 126). Meyers' lactam **292** was asymmetrically allylated to give bicyclic lactam **293**. After *N*-protection (Boc), stereoselective alkylation of the lithium enolate of **295** with methyl iodide gave **296**. Base-induced hydrolysis of **296** and reduction of the anhydride intermediate gave alcohol **298** as the major product. Subsequent protection gave the protected amino alcohol **299**.



Scheme 126: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, –78 °C → rt, 18 h, 98%; (b) Na, EtOH, NH_3/THF, –33 °C, 1 h, 88%; (c) Boc_2O, DMAP, THF, rt, 18 h, 93%; (d) LiHMDS, hexanes/THF, –78 °C → –40 °C, 1.5 h, *then* MeI, –40 °C, 1 h; (e) LiOH, THF/H_2O, rt, 18 h; (f) $ClCO_2Et$, Et_3N, THF, –10 °C, 1 h, *then* $NaBH_4$, MeOH, 0 °C → rt, 1 h, 39% over three steps; (g) TBDPSCl, Et_3N, DMAP, 0 °C → rt, 96%.

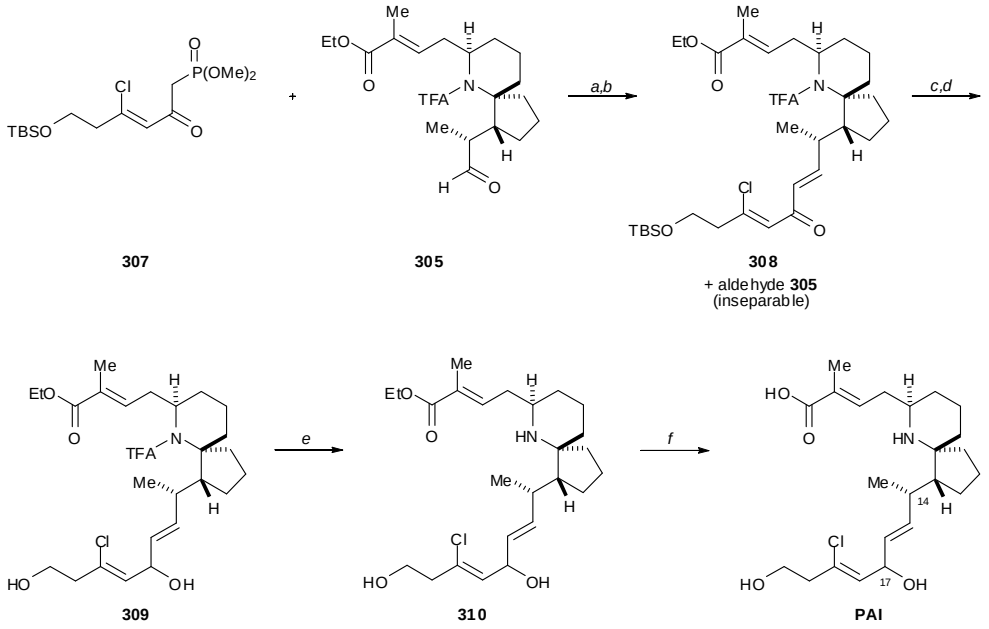
The next series of transformations culminated in the generation of the azaspiro core. The alkylborane of **299** was coupled with vinyl iodide **306**, itself generated from the corresponding vinyl stannane, to give **300** in 75% yield (Scheme 127). The removal of the Boc protecting group enabled the free amine **301** to undergo a base-induced cyclisation to afford desired piperidine **302** with good diastereoselectivity and as the exclusive *E*-isomer at C_2—C_3.



Scheme 127: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) 9-BBN, THF, rt, 1.5 h; (b) **306**, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $AsPh_3$, Cs_2CO_3, DMF/H_2O, rt, 3 h, 75%; (c) CF_3CO_2H, CH_2Cl_2, rt, 1 h; (d) DBU, rt, 18 h, 81% over two steps; (e) TFAA, DIPEA, 1,2-CH_2ClCH_2Cl, 0 ^oC, 5 min, 88%; (f) HF-pyridine, THF/pyridine, 0 $^oC \rightarrow$ rt, 18 h, 91%; (g) TPAP, NMO, 3Å MS, MeCN, 30 min, 84%.

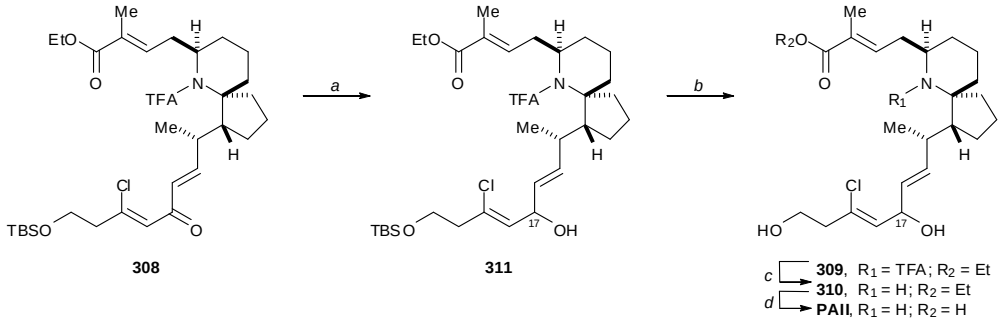
Following removal of the TBDPS protecting group, the free alcohol **304** was subjected to oxidation conditions, but as the authors report, this was troublesome and the desired aldehyde could not be generated. It was eventually found that continued nitrogen protection was necessary, protection that would not be affected by proceeding transformations, but likewise would be readily removed at a later stage. In the end, the authors settled on the trifluoroacetyl derivative and created **303**, following which the TBDPS protection was removed using HF-pyridine. The free alcohol **304** was then readily oxidised to aldehyde **305** in 84% yield using TPAP and NMO.

Base-mediated reaction of **305** with phosphonate **307** produced an inseparable mixture of product **308** and starting aldehyde **305**. Despite this, the authors advanced with the mixture and following reduction with either *R*- or *S*-alpine borane, the alcohol was gained in 30% isolated yield over two steps (Scheme 128). Silyl deprotection gave diol **309** and cleavage of the TFA (→**310**) and ethyl ester functions gave what the authors believed to be pinnaic acid (**PAI**). The signals in the high field of the NMR spectrum were comparable with Uemura's, but the lack of authentic natural product was a disadvantage as the synthetic and natural compounds could not be directly compared by NMR.



Scheme 128: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) LiHMDS, THF, –78 °C, 30 min; (b) **305**, THF/HMPA, –78 °C → rt, 2 d; (c) *(R)*- or *(S)*-alpine hydride, 30% over two steps; (d) HF-pyridine, THF/pyridine, 0 °C, 1 h, 95%; (e) $NaBH_4$, EtOH, rt, 18 h, 93%; (f) LiOH, THF/MeOH/H_2O, 4 h, 40 °C, 90%.

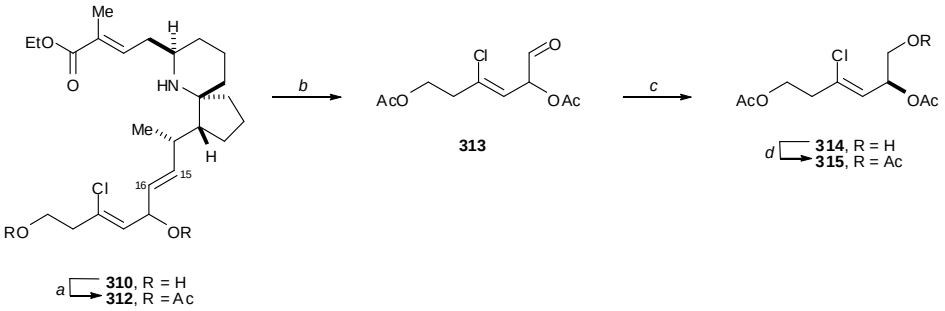
Shrewdly, the authors took **308** and reduced the carbonyl to the alcohol **311** using $NaBH_4$ (Scheme 129). This was then used to generate a different form of pinnaic acid which differed only in the configuration at C_{17}. Alcohol **311** was desilylated (→**309**) and the TFA (→**310**) and ester groups removed. This new pinnaic acid, **PAII**, exhibited an NMR spectrum which was vastly different in the high field area to the spectrum of natural pinnaic acid (from Uemura's work).



Scheme 129: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) $NaBH_4$, $CeCl_3 \cdot H_2O$, MeOH, rt, 30 min, 23%; (b) HF-pyridine, THF/pyridine, 0 °C, 1 h, 71%; (c) $NaBH_4$, EtOH, rt, 18 h, 90%; (d) LiOH, THF/MeOH/H_2O, 40 °C, 4 h, 97%.

After additional synthetic studies (not discussed here), the authors had strong evidence that compound **PAI** matched the natural pinnaic acid, making the configuration at C_{14} *S*. To determine the configuration at C_{17}, diol **310** was exposed to acetic anhydride/pyridine and catalytic DMAP for two hours at room temperature (Scheme 130). This capped the free hydroxyls (→**312**) and

subsequent ozonolysis of the C_{15}=C_{16} bond gave chloroaldehyde **313**. Reduction (→**314**) followed by acetylation afforded **315**. The degradation product **315** was consistent with the *R* configuration at C_{17}.

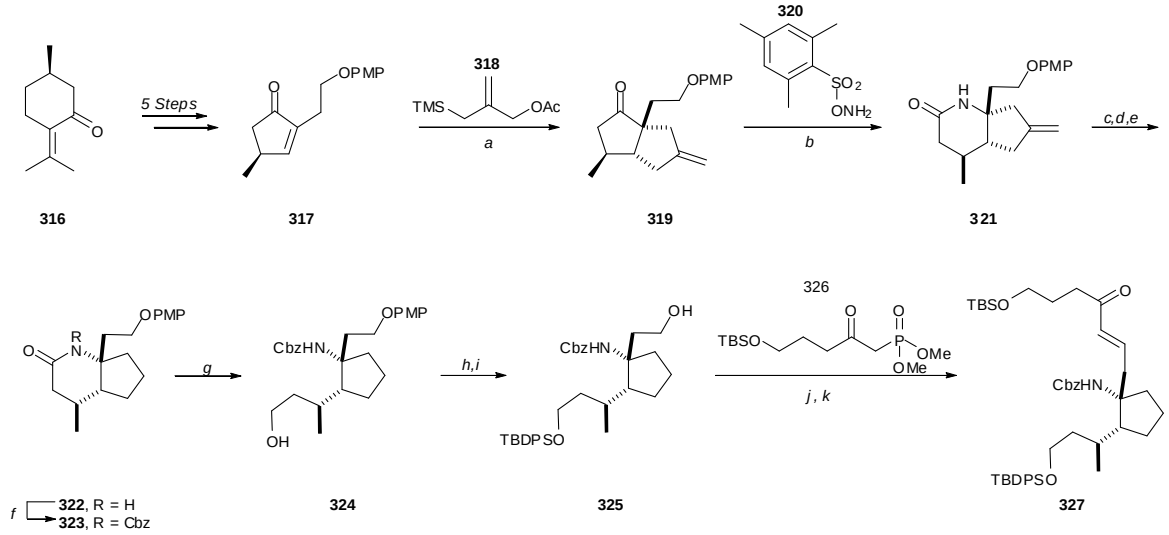


Scheme 130: Danishefsky's Synthesis of Pinnaic Acid. Reagents and Conditions: (a) Ac_2O, pyridine, DMAP, rt, 2 h, 80%; (b) O_3, MeOH, –40 ^{o}C, then Me_2S; (c) $NaBH_4$, $CeCl_3 \cdot H_2O$, MeOH; (d) Ac_2O, Et_3N, rt, 35% over three steps.

4.4.2 Uemura's Asymmetric Synthesis of Pinnaic Acid

In 2007, Uemura and co-workers reported their asymmetric total synthesis of pinnaic acid.[169] The synthesis began from a chiral cyclopentanone, developed especially for the investigation, with the overall route being neat and concise, incorporating impressive and intricate transformations.

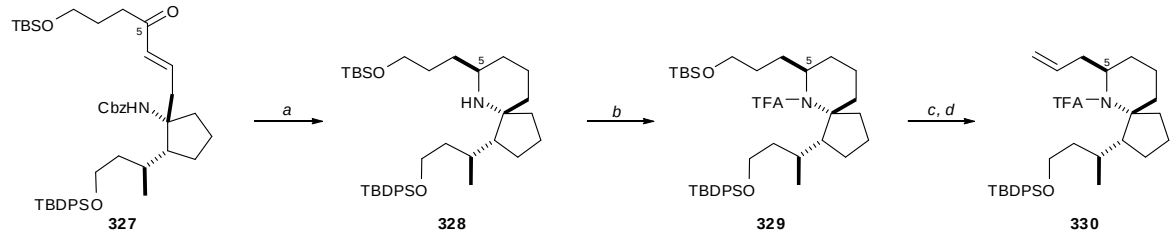
In Uemura's synthesis, (*R*)-(+)-pulegone **316** was transformed into chiral compound **317** in five steps, with an overall yield of 41%.[169] Enone **317** then underwent a key Pd-TMM (trimethylenemethane) [3+2]-cyclisation in high yield and high stereoselectivity to afford the *anti*-adduct **319** (Scheme 131).



Scheme 131: Uemura's Asymmetric Synthesis of Pinnaic Acid. Reagents and Conditions: (a) $Pd(OAc)_2$, (iPrO)$_3$P, THF, reflux, 80%; (b) 4Å MS, alumina, CH_2Cl_2, rt, 43% (100% based on recovered starting material); (c) O_3, MeOH, –78 ^oC; then Me_2S, –78 ^oC, 82%; (d) $TsNHNH_2$, MeOH, 50 ^oC; (e) $NaBH_3CN$, TsOH, THF, reflux, 60% over two steps; (f) NaH, CbzCl, THF, reflux, 87%; (g) $NaBH_4$, LiBr, THF, 50 ^oC, quant.; (h) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, rt; i) CAN, MeCN/H_2O (1:1), 0 ^oC, 76% over two steps; (j) SO_3·pyridine, Et_3N, DMSO, rt; (k) **326**, Et_3N, LiCl, THF, 30 ^oC, quant. in two steps.

Lactam **321** was obtained from lactone **319** through a Beckman rearrangement using *O*-mesitylsulfonylhydroxylamine (MSH, **320**). Ozonolysis of the *exo*-olefin, hydrazone formation and deoxygenation gave **322**. Alcohol **324** was obtained following amide protection (→**323**) and reductive opening of lactam **322**. Interestingly, Uemura reported that no racemisation had occurred from cyclopentanone **317**. Silyl protection of the primary alcohol, followed by PMP ether removal gave alcohol **325**. Oxidation of alcohol **325** into the corresponding aldehyde, followed by a HWE reaction with phosphonate **326** furnished enone **327** as the *E*-isomer.

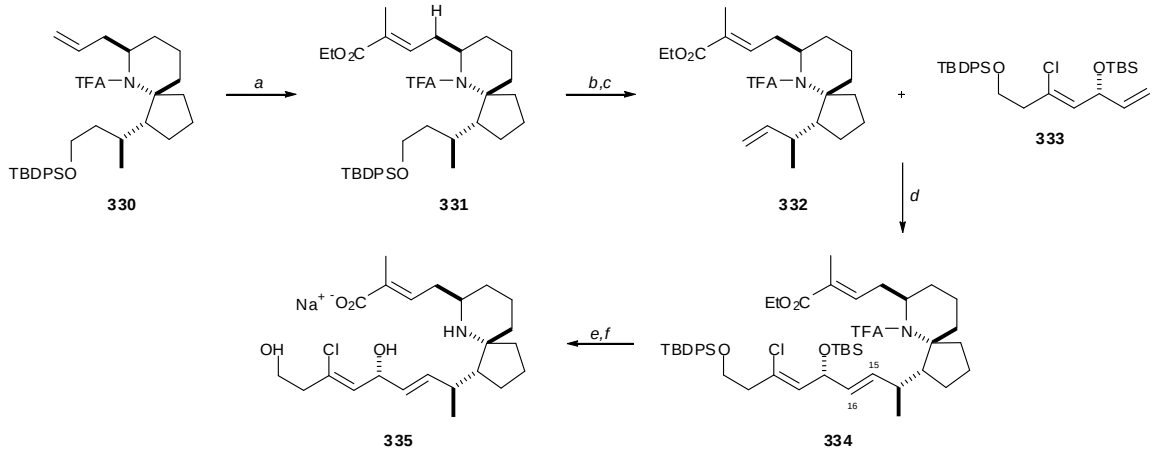
To construct the piperidine ring with the correct configuration at C_5 the authors use an innovative tandem hydrogenation-cyclisation procedure. This consists of four, one-pot transformations: (1) alkene saturation; (2) Cbz removal; (3) intramolecular cyclic imine and/or enamine formation and (4) stereoselective reduction of imine/enamine intermediate (Scheme 132).



Scheme 132: Uemura's Asymmetric Synthesis of Pinnaic Acid. Reagents and Conditions: (a) H_2, $Pd(OH)_2/C$ (20 mol%), HOAc (7 equiv), EtOH, 25 °C; (b) TFAA, iPr$_2$NEt/ClCH$_2$CH$_2$Cl (1:5), 0 °C, 81% over two steps; (c) PPTS, EtOH, 25 °C; (d) o-NO$_2$PhSeCN, nBu$_3$P, THF, rt; then mCPBA, rt, 88% over two steps.

Piperidine **328** was formed by reaction of enone **327** with 20 mol% palladium catalyst. Protection of the amino group (→**329**) and selective deprotection of the TBS group followed by a Grieco elimination[170] led to olefin **330**.

Installation of the side chain was completed successfully *via* cross-metathesis of olefin **330** using Hoveyda-Grubbs second generation catalyst, with ethyl methacrylate as the solvent (Scheme 133). Hence, trisubstituted alkene **331** was obtained exclusively as the *E*-isomer.



Scheme 133: Completion of Uemura's Asymmetric Synthesis of Pinnaic Acid. Reagents and Conditions: (a) ethyl methacrylate, Hoveyda-Grubbs second generation catalyst (10 mol%), neat, reflux, 74%; (b) HF·pyridine, 45 °C; (c) o-NO$_2$PhSeCN, nBu$_3$P, THF, rt; then mCPBA, rt, 90% over two steps; (d) **333** (5.5 equiv), Grubbs second generation catalyst (80 mol%), toluene, 90 °C, 40%; (e) HF·pyridine/pyridine (1:3), 25 °C; (f) $NaBH_4$, EtOH, 25 °C; then NaOH (1.6 M in 1:2 EtOH/H_2O), 40 °C, 86% over two steps.

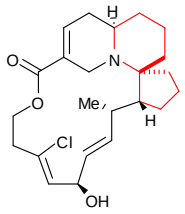
Treatment of **331** with HF·pyridine afforded the terminal alcohol, which upon a second Grieco elimination gave terminal alkene **332**. In this strategy the authors installed the C_{17} centre as part of **333** and then introduced it to the spirocyclic core, *via* cross-metathesis. As expected, the terminal olefins were more reactive than the internal double bonds and the cross-metathesis proceeded in 69% yield to furnish **334** as the single *trans*-isomer (C_{15}—C_{16} bond).

After removal of the two silyl groups, TFA amide and the ethyl ester, the chiral pinnaic acid was obtained as its sodium salt **335**. ^{1}H NMR comparison of this and the racemic form proved to be identical.

The method developed by Uemura and colleagues is advanced and relies heavily on the success of some intricate and complex reactions. Despite this, all the stereochemistry (apart from C_{17}) can be efficiently controlled from the methyl group in cyclopentone **317**.

4.5 Halichlorine

In 1996, as well as reporting the isolation of pinnaic acid, Uemura also isolated the novel marine alkaloid, halichlorine, from the Japanese black marine sponge *Halichondria okadai* (Figure 29).[158] It is an interesting compound in that it shares the same azaspiro[4.5]decane core with pinnaic acid.



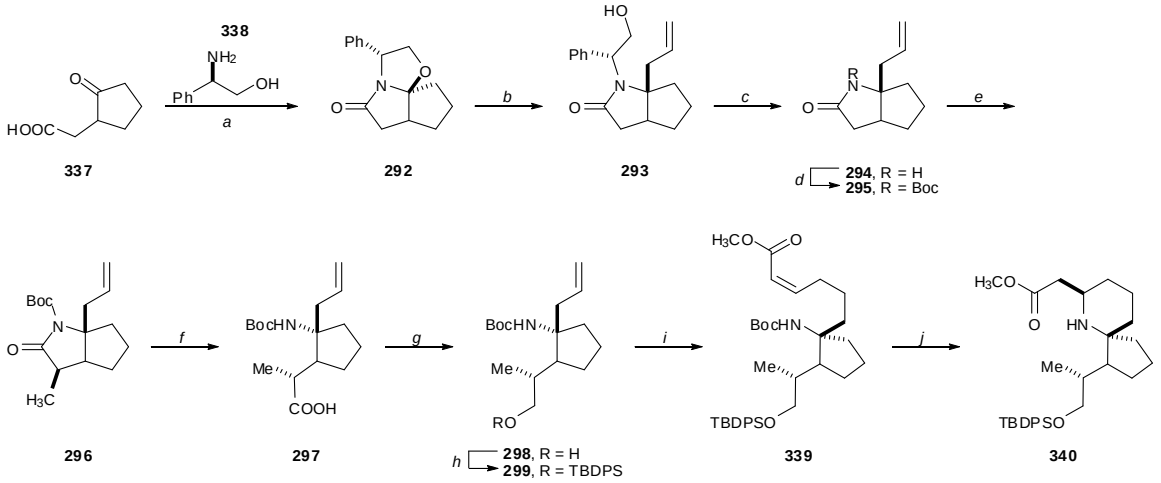
336

Figure 29: Structure of Halichlorine 336.

Halichlorine is a crystalline compound and its structure was assigned only after extensive NMR studies; structurally it possesses 23 carbon atoms and five stereocentres. Halichlorine selectively inhibits induced expression of vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} of 7 μg/mL. VCAM-1 is a member of the immunoglobulin superfamily and is expressed on the surface of endothelium cells. VCAM-1 monitors and regulates leukocyte recruitment into inflamed tissue.[163,171] Since leukocyte recruitment is involved in allergic inflammatory disorders, VCAM-1 has been identified as a target for drug discovery.

4.5.1 First Total Synthesis of (+)-Halichlorine

With its interesting biological profile, halichlorine was the subject of study in numerous groups but it wasn't until three years after its isolation that it finally succumbed to total synthesis. In 1999, Danishefsky and colleagues discussed their studies towards and most importantly, the first total synthesis of halichlorine.[171-173] In their initial publication[171] they discussed the stereoselective, asymmetric synthesis of the spiroquinolizidine subunit **344**, which contains 17 out of the 23 carbon's and four of the five stereocentres. Danishefsky's synthesis began with Meyers lactam **292** which was made by heating racemic carboxylic acid **337** with D-(—)-phenylglycinol **338** (Scheme 134). Treatment of the Meyers lactam **292** with allyl TMS in the presence of Lewis acid gave bicyclolactam **293**. After debenzylation (→**294**) and nitrogen protection, the bicyclic *N*-Boc-lactam **295** was stereoselectively methylated from the convex face to afford **296**. This compound was hydrolysed (→**297**) and then reduced. The resulting primary alcohol **298** was protected to afford silyl ether **299**.

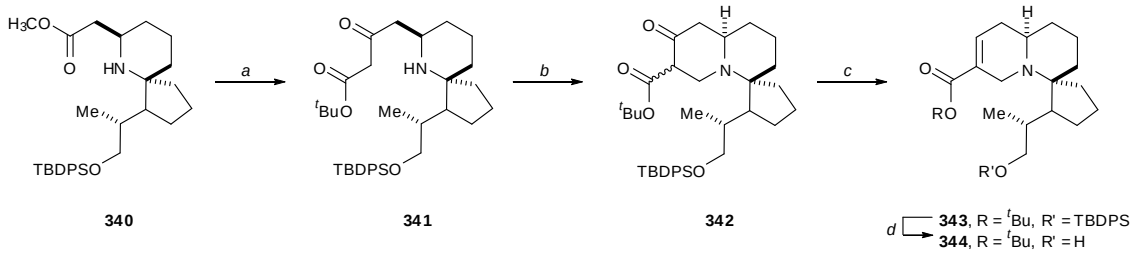


Scheme 134: Danishefsky's Synthesis of the Spiroquinolizidine Core of Halichlorine. Reagents and Conditions: (a) PhMe, reflux, 95%; (b) allyl TMS, $TiCl_4$, CH_2Cl_2, –78 °C → rt, 99%; (c) Na, NH_3, THF, EtOH, –78 °C, 92%; (d) Boc_2O, DMAP, THF, 96%; (e) (i) LiHMDS, THF, –40 °C; (ii) MeI, –78 °C → 0 °C, 90%; (f) LiOH, THF, H_2O, 89%; (g) (i) ClCOOEt, Et_3N, THF; (ii) $NaBH_4$, MeOH, 82%; (h) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 95%; (i) (i) 9-BBN, THF; (ii) *Z*-I-CH=CH=COOMe, $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, DMF, H_2O; (j) (i) TFA, CH_2Cl_2; (ii) H_2O, K_2CO_3, 77%.

At this juncture, three of the stereogenic centres had been introduced and the next stage was the formation of the C_5 stereocentre. Hydroboration of alkene **299** and subsequent palladium mediated Suzuki coupling of the resulting borane with *Z*-3-iodoacrylate allowed elongation of the allylic side chain to generate

unsaturated ester **339**. Deprotection of the amino function and basification allowed an intramolecular Michael addition to take place and generate piperidine **340**. The authors discuss the stereochemical control of this transformation as originating from the chair-conformation transition state, whereby the larger substituent adopts a pseudoequatorial position.

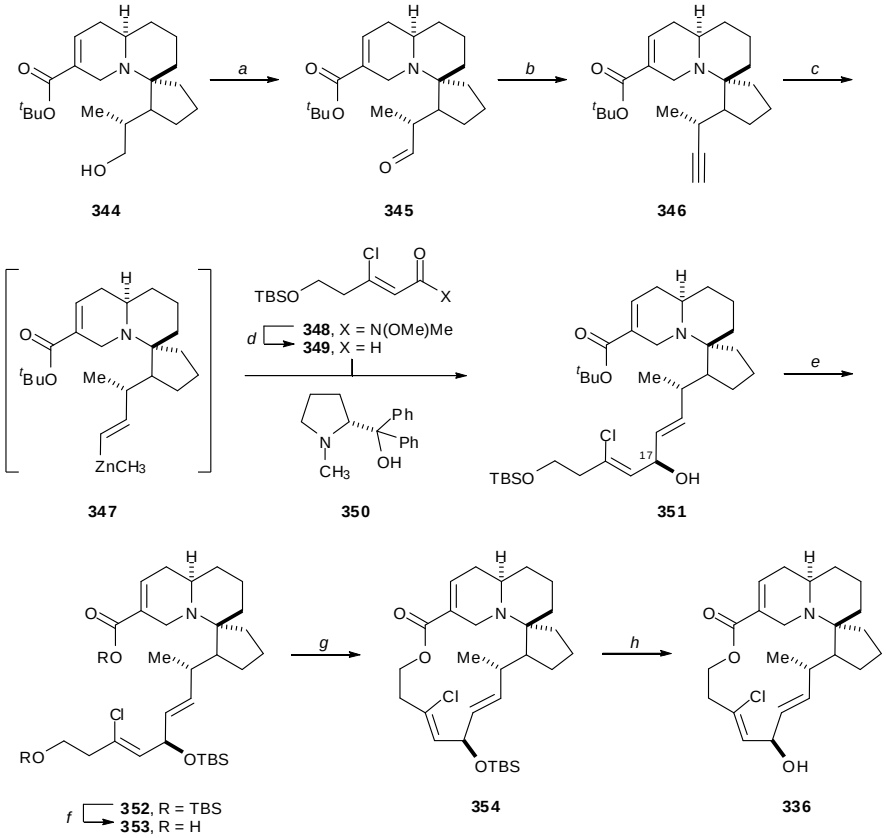
As shown in Scheme 135, crossed Claisen condensation of **340** with *tert*-butyl acetate produced the ß-keto ester **341**. Quinolizidine ring closure was then effected by a Mannich reaction with formaldehyde. Tricycle **342** was then converted into the α,ß-unsaturated ester **343**, which after deprotection gave spiroquinolizidine **344**.



340 **341** **342**

Scheme 135: Danishefsky's Synthesis of the Spiroquinolizidine Core of Halichlorine. Reagents and Conditions: (a) ^{t}BuOAc, LiHMDS, THF, –50 ^{o}C → rt, 86%; (b) H_2CO, EtOH, 73%; (c) (i) LiHMDS, THF, 0 ^{o}C; (ii) $Cp_2Zr(H)Cl$, rt, 91%; (d) HF-pyridine, THF, 94%.

Alcohol **344** was oxidised to aldehyde **345** using TPAP/NMO and then treated with Gilbert's reagent[174] to produce alkyne **346** in reasonable yield. Hydrozirconation, followed by transmetallation gave zincate **347**, which was then coupled to aldehyde **349** (aldehyde **349** was prepared from the known Weinreb amide **348**[175]). The reaction was carried out in the presence of amino alcohol **350**, which led to a 4:1 mixture of the desired 17*R* epimer **351**. Treatment of the mixture with TBSOTf generated both the silyl ester of the carboxylic acid and the protection of the secondary alcohol (→**352**). Simultaneous cleavage of the carboxyl and primary silyl groups (→**353**) was brought about by the addition of ammonium fluoride in aqueous methanol. Crucially, the secondary TBS group remained intact. Macrolactonisation under Keck conditions enabled the formation of 17-TBS-halichlorine **354** and importantly allowed the separation of the 17*R* and 17*S* epimers. The final step entailed deprotection at C_{17} with HF-pyridine to afford halichlorine **336**. The spectral data of the 17*R* synthetic material matched that of an authentic specimen.

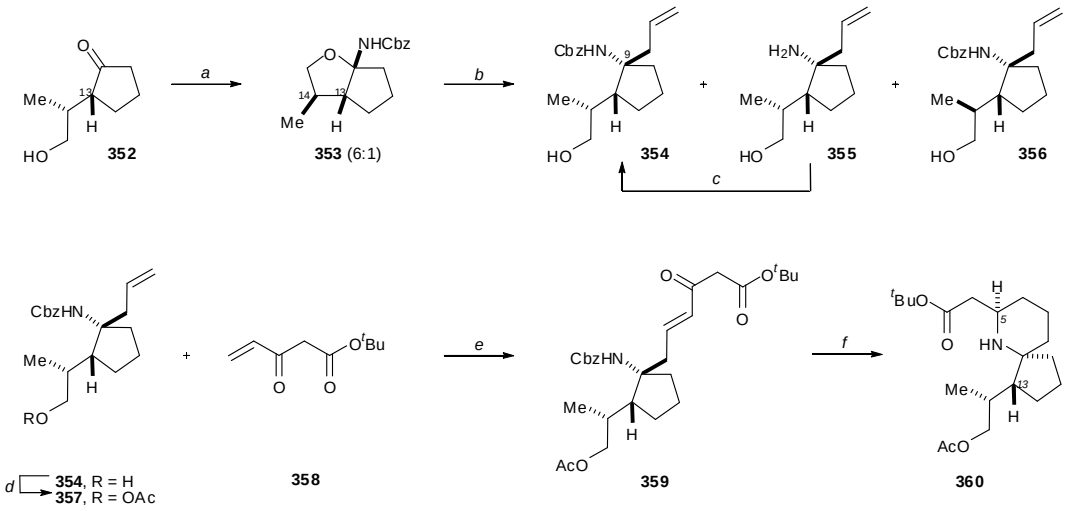


Scheme 136: Completion of Danishefsky's Synthesis of Halichlorine. Reagents and Conditions: (a) TPAP, NMO, MeCN, rt; (b) $N_2CHP(O)(OMe)_2$, KO^{t}Bu, THF, –78 ^{o}C, 57% over two steps; (c) (i) [$Cp_2Zr(H)Cl$], CH_2Cl_2; (ii) Zn_2Me, heptane, –65 ^{o}C; (iii) **350** (10 mol%), –65 ^{o}C → –30 ^{o}C; (iv) **349**, –30 ^{o}C → rt, 67% overall; (d) DIBAH, PhMe, CH_2Cl_2, –78 ^{o}C, 82%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 ^{o}C → rt; (f) NH_4F, MeOH, H_2O, 66% overall from **351**; (g) EDCI, DMAP, DMAP·HCl, $CHCl_3$, THF, reflux, 54%; (h) HF-pyridine, pyridine, THF, 95%.

4.6 Christie and Heathcock's Total Synthesis of (±)-Pinnaic Acid and (±)-Halichlorine

In 2004, PNAS published a fascinating report by Christie and Heathcock in which they reported the synthesis of both pinnaic acid and halichlorine, from a common late-stage intermediate.

As shown in Scheme 137, acylimmonium precursor **353** was prepared from keto-alcohol **352**. Condensation of ketone **352** with benzyl carbamate gave the *cis*-fused bicyclic carbamate **353** as a 6:1 ratio of diastereoisomers. The structure was epimeric at C_{14}, with the major compound being the isomer with the methyl group on the convex face.

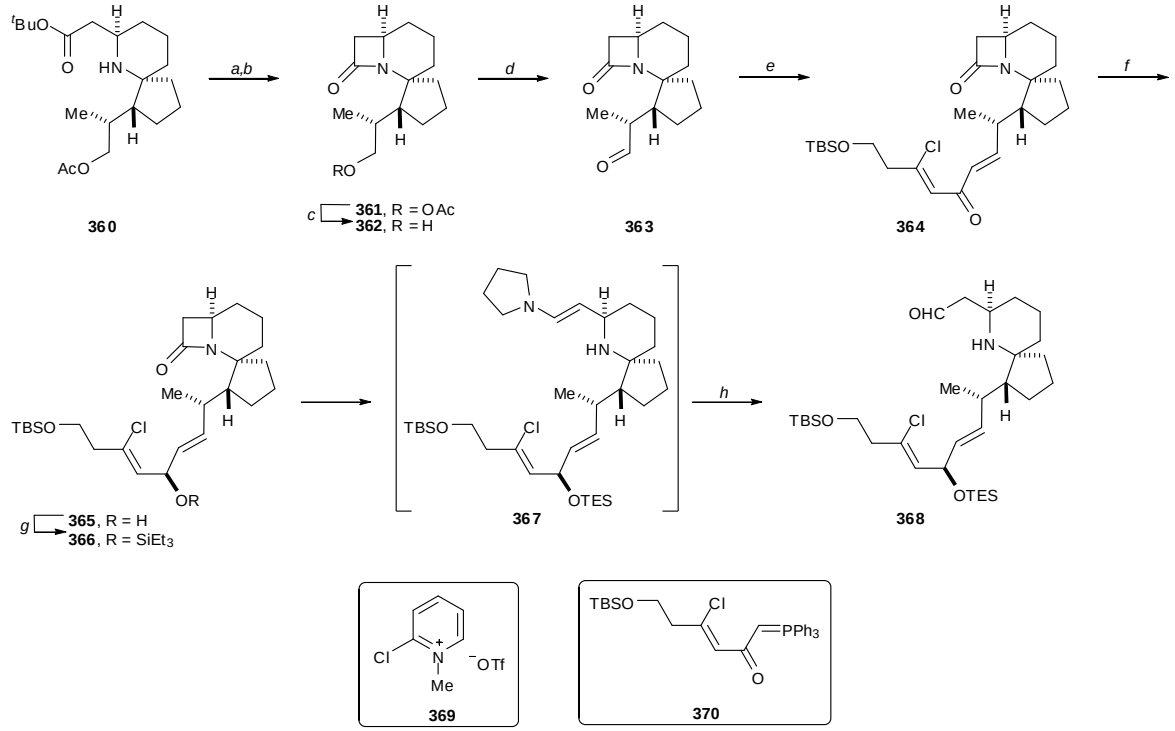


Scheme 137: Christie and Heathcock's Synthesis. Reagents and Conditions: (a) Benzyl carbamate, Amberlyst-15, benzene, reflux, 2 h, 91%; (b) $TiCl_4$, $H_2C{=}CHCH_2SiMe_3$, CH_2Cl_2, –50 °C → –20 °C, 7 h, 53%; (c) (i) recrystallise as the hydroacetate salt; (ii) CbzCl, NaOH, H_2O, 15 h; (iii) MeOH, K_2CO_3, overnight; (d) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 1 h; (e) Grubbs second generation catalyst, CH_2Cl_2, 40 °C, 3.5 h; (f) 55 psi H_2, Pd/C, EtOAc, rt, 50 h.

Carbamate **353** was treated with allyl TMS and $TiCl_4$ to afford alcohol **354** in 53% yield, together with free amine **355**. Amine **355** could be reprotected hence, increasing the allylation yield to 65%. Acetylation of the primary hydroxyl of **354** afforded **357**, which underwent cross-metathesis with Nazarov ester **358**[176] in the presence of Grubbs second generation catalyst, to produce enone **359**. Reduction of enone **359** generated piperidine **360** as a single isomer at C_5.

With the core in place, the focus turned to functionalisation of the side chains. Protection of the nitrogen atom and C_5 side chain function was achieved through treatment of amino acid (obtained from amino ester **360**) with the modified Mukaiyama reagent **369** (Scheme 138).

Cleavage of the acetate group of ß-lactam **361**, gave alcohol **362**, which was then oxidised to aldehyde **363**. Aldehyde **363** was then treated with phosphorane **370** to yield dienone **364** in 77% yield.

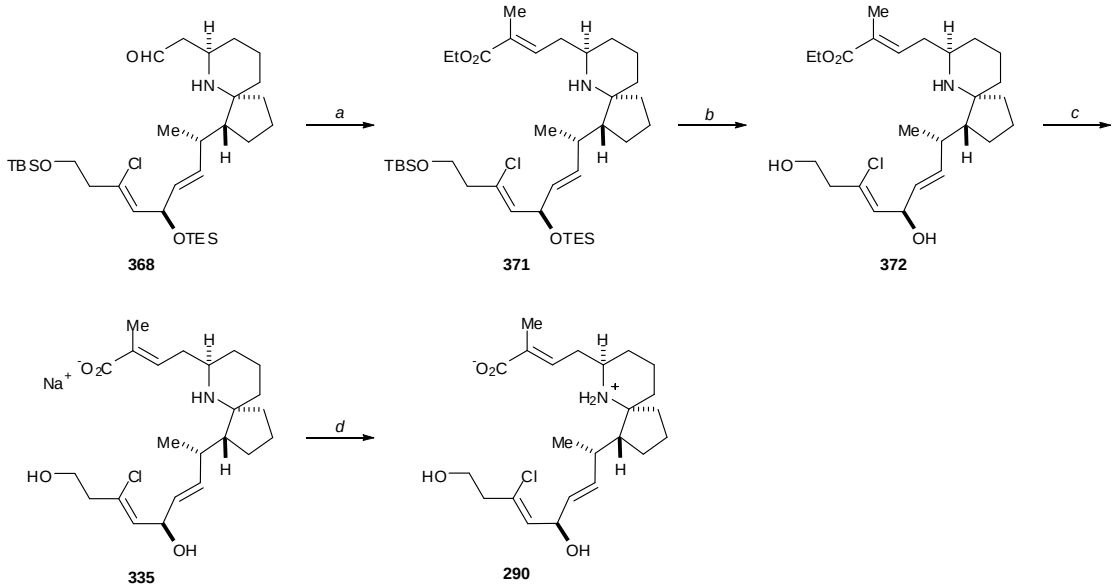


Scheme 138: Christie and Heathcock's Synthesis. Reagents and Conditions: (a) TFAA, rt, 35 min; (b) *i*-Pr_2Net, **369**, MeCN, 70 °C, 80%; (c) K_2CO_3, MeOH, rt, 2 h, 97%; (d) tetrapropylammonium perruthenate, *N*-methylmorpholine *N*-oxide, CH_2Cl_2, rt, 10 min, 92%; (e) **370**, MeOH, 65 °C, 3 d, 77%; (f) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 90% (5:2); (g) TESCl, DMAP, *i*-Pr_2Net, CH_2Cl_2, –78 °C → 0 °C, 92%; (h) Red-Alp/*t*BuOK, methyl *tert*-butyl ether, rt, 3 h, 78%.

Reduction of ketone **364** gave alkenol **365** as a 5:2 mixture of diastereoisomers, which upon TES protection gave the fully protected compound **366**. Cleavage of the ß-lactam proceeded best when using "Red-Alp", a pyrrolidine-modified Red-Al reagent,[177] to enable the formation of aldehyde **368** *via* the decomposition of enamine **367** on silica gel. This amino aldehyde became the precursor for both pinnaic acid and halichlorine.

4.6.1 Completion of Pinnaic Acid

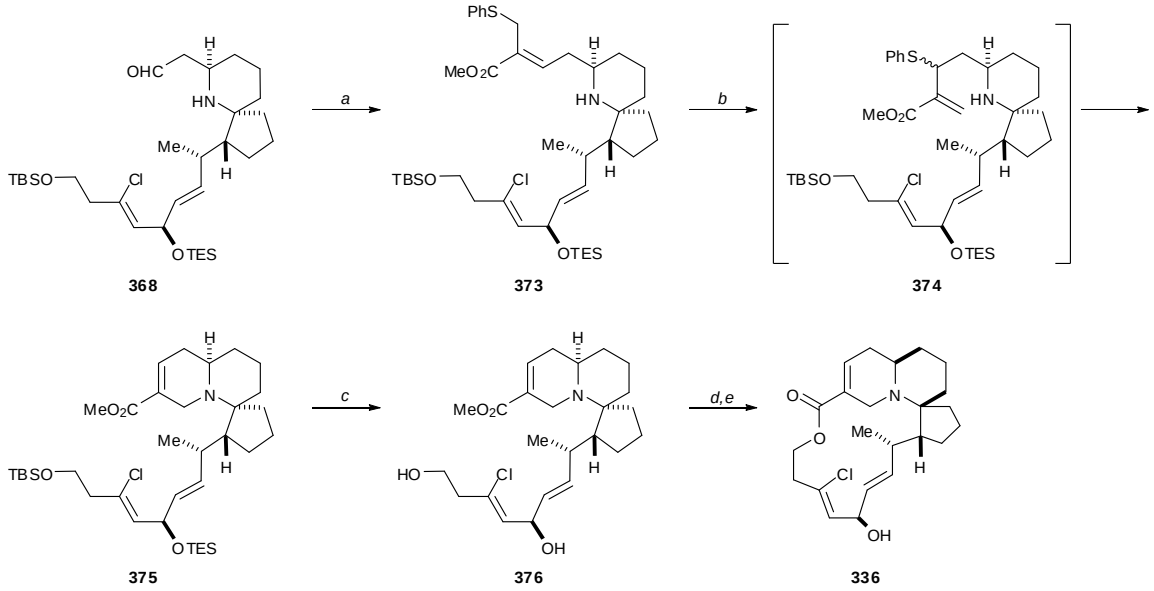
HWE reaction of aldehyde **368** afforded the entire carbon skeleton of pinnaic acid, in 54% yield. The authors make no mention of the obtained *E*:*Z*-selectivity in their publication. The silicon protecting groups were readily removed under standard conditions to afford diol **372** in 85% yield. Ester hydrolysis afforded the carboxylate salt **335**, which upon treatment with pH 7 buffer allowed its purification as its zwitterion **290** by reverse-phase HPLC.



Scheme 139: Completion of the Synthesis of Pinnaic Acid. Reagents and Conditions: (a) $(EtO)_2P(O)CH(CH_3)CO_2Et$, LiCl, DBU, MeCN, rt, 12 h, 54%; (b) TBAF, THF, 0 ^oC, 2 h, 85%; (c) NaOH, MeOH, H_2O, rt → 45 ^oC, 4 h, 90%; (d) pH 7 buffer/*n*BuOH extract.

4.6.2 Completion of Halichlorine

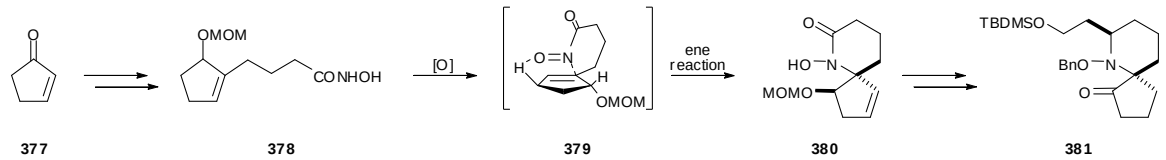
To enable the conversion of aldehyde **368** into halichlorine **336**, a new 6-membered ring fused to the spirocyclic core had to be created as well as the generation of the 15-membered macrocycle. Aldehyde **368** was treated with trimethyl phosphonoacrylate and lithium thiophenoxide to afford a mixture of the desired *E:Z*-thioether **373**. Interestingly, when the *E*-isomer was treated with excess thiophenoxide a mixture was obtained that contained predominantly the *Z*-isomer. Heating of either the *E:Z*-mixture or the pure *Z*-isomer in a basic thiophenoxide solution resulted in the formation of dehydroquinolizidine **375**. By allowing the nitrogen atom to add to the unsaturated ester of intermediate **374**, addition/elimination of thiophenoxide could occur to form the dehydroquinolizidine. The silyl protecting groups were cleaved using TBAF (→**376**) and the resulting ester was saponified to give the sodium salt. Application of Keck's macrolactonisation conditions allowed the formation of (±)-halichlorine **336**. The NMR spectra of the synthetic material were identical to that of the authentic material.



Scheme 140: Completion of the Synthesis of Halichlorine. Reagents and Conditions: (a) Trimethyl phosphonoacrylate, PhSLi, THF, 0 °C → rt, 12 h, 71%; (b) K_2CO_3, PhSH, DMF, 55 °C, 35 h, 48-61%; (c) TBAF, THF, 0 °C, 3 h, 77%; (d) NaOH, MeOH, H_2O, 55 °C, 2 h, then rt, overnight; (e) *N*-(3-methylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride, *N*-dimethylaminopyridine·HCl, $CHCl_3$, THF, reflux, 10 h, 32%.

4.7 Kibayashi's Synthesis of (±)-Pinnaic Acid and (±)-Halichlorine

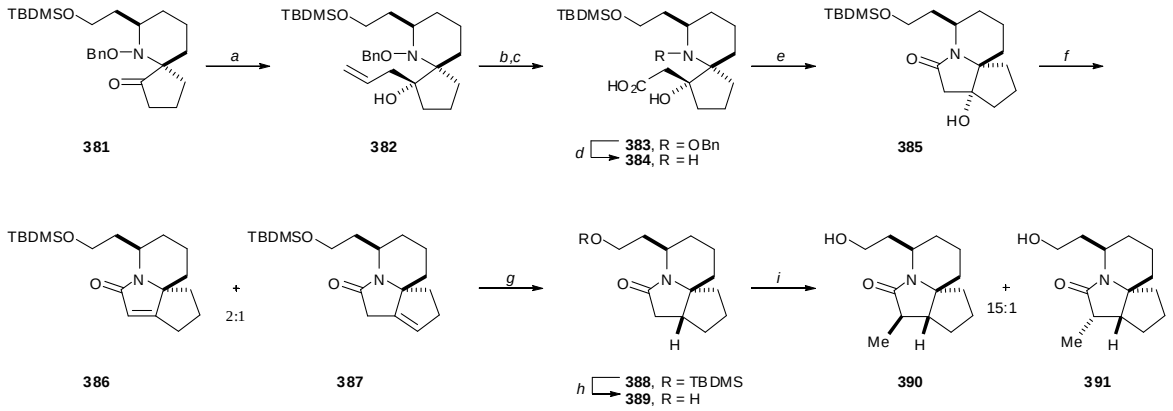
Kibayashi's laboratory reported the efficient synthesis of ketone **381** incorporating the azaspirobicyclic core, *via* the 6-azaspiro[4.5]decane skeleton **380** (Scheme 141).[178] In a subsequent publication by the same authors,[166] ketone **381** was able to be used as a precursor in the synthesis of Danishefsky intermediate **303** and **401** (the ethyl ester of Danishefsky intermediate **344**), to further enable a formal total synthesis of (±)-halichlorine and (±)-pinnaic acid.



Scheme 141: Summary of the Synthesis to Kibayashi's Common Precursor 381.

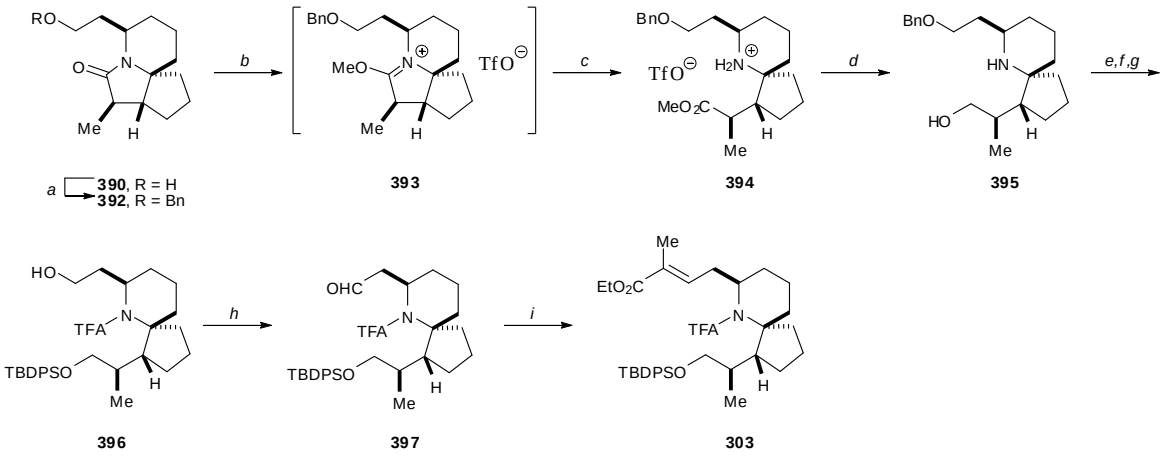
Addition of allylmagnesium bromide to ketone **381** gave the tertiary alcohol **382**. The allylation is directed to the less hindered face by the *N*-benzyloxy group. Oxidative cleavage of alkene **382** gave carboxylic acid **383**, which upon cleavage of the benzyloxy group (→**384**), followed by lactam cyclisation gave the hydroxy tricyclic lactam **385**. Dehydration of lactam **385** yielded a 2:1

mixture of the α,β- and β,γ-lactams **386** and **387** respectively. Catalytic hydrogenation of the mixture gave the tricyclic lactam **388** as a single product. Removal of the silyl group afforded alcohol **389** which upon C_7 methylation from the ß-face gave **390** and **391** with 15:1 selectivity.



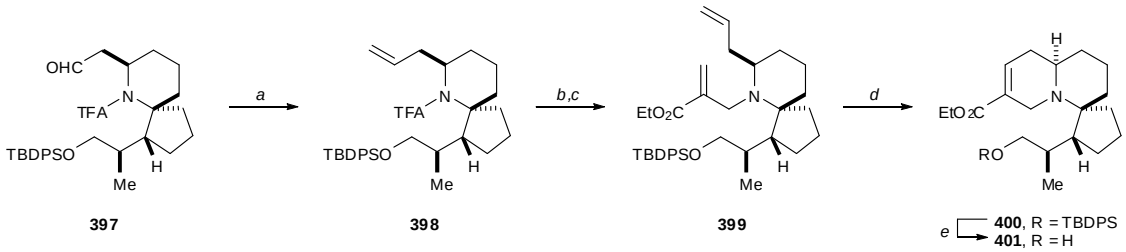
Scheme 142: Kibayashi's Synthesis towards Pinnaic Acid. Reagents and Conditions: (a) $H_2C{=}CHCH_2MgBr$, THF, 0 °C, 99%; (b) OsO_4, $NaIO_4$, H_2O, THF, rt, 82%; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, *t*-BuOH, rt, 95%; (d) H_2, Pd-C, EtOH, 97%; (e) $ClCO_2CH_2CHMe_2$, Et_3N, toluene, rt, 90%; (f) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 92%; (g) H_2, Pd-C, MeOH, 99%; (h) 1 M HCl, THF, rt, 99%; (i) MeI, LDA, THF, –78 °C, 78%.

Protection of the primary alcohol **390** as the benzyl ether **392**, was followed by lactam cleavage to produce amino ester **394** using methyl triflate (Scheme 143), *via* iminium intermediate **393**. The 1,7-disubstituted spirobicyclic compound underwent ester reduction to yield alcohol **395**, which was converted to **396** by TBDPS protection, *N*-trifluoroacetylation and *O*-debenzylation. Dess–Martin oxidation of alcohol **396** gave the corresponding aldehyde **397**, which after HWE homologation provided the TBDPS-protected Danishefsky intermediate **303**. This intermediate had previously been converted to pinnaic acid (see Section 4.4.1) and thus constituted a formal synthesis of (±)-pinnaic acid by Kibayashi and co-workers.



Scheme 143: Kibayashi's Synthesis towards Pinnaic Acid. Reagents and Conditions: (a) BnBr, NaH, THF, rt, 90%; (b) TfOMe, $ClCH_2CH_2Cl$, 60 ^oC; (c) H_2O, THF, rt; (d) $LiAlH_4$, THF, 0 ^oC, 74% over 2 steps; (e) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 95%; (f) TFAA, *i*-PrNEt, $ClCH_2CH_2Cl$, 0 ^oC, 99%; (g) H_2, $Pd(OH)_2$-C, MeOH, 99%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (i) $EtO_2CCH(Me)P(O)(OEt)_2$, NaH, THF, –78 ^oC, 76%.

Wittig methylenation, *N*-protection and introduction of the alkenyl chain into the secondary amine allowed the azaspirobicyclic aldehyde **397** to be converted into diene **399** (Scheme 144). Ring-closing metathesis with Grubbs second generation catalyst enabled the formation of **400** in high yield. Finally, removal of the silyl protection furnished intermediate **401** (the ethyl ester of Danishefsky intermediate **344**). Similarly this intermediate had been transformed into halichlorine (see Section 4.5.1) and so a formal synthesis of racemic halichlorine had also been achieved by Kibayashi and co-workers.



Scheme 144: Kibayashi's Synthesis towards Halichlorine. Reagents and Conditions: (a) $Ph_3P^+MeBr^-$, BuLi, THF, 0 ^oC, 80%; (b) $NaBH_4$, EtOH, rt, 83%; (c) $H_2C=C(CH_2Br)CO_2Et$, K_2CO_3, MeCN, 60 ^oC, 88%; (d) Grubbs second generation catalyst, CH_2Cl_2, reflux, 99%; (e) TREAT·HF, Et_3N, MeCN, rt, 94%.

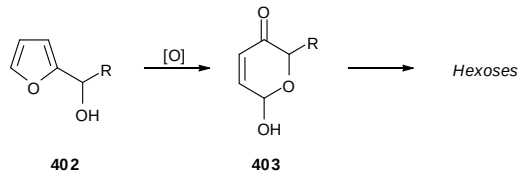
4.8 Investigation of Alternative Routes to the Spirocyclic Core of Pinnaic Acid and Halichlorine

The unique azaspiro[4.5]decane core structure present in both pinnaic acid and halichlorine has imparted challenges to synthetic chemists, who have strived for an easily accessible and reliable route to the core structure. As a consequence

many authors have described their synthetic approaches.[178-183] In addition to those methods already described herein, it is not feasible and in the scope of this thesis to discuss every approach in depth. However, the work of many groups is portrayed in the informative review by Clive, Yu, Wang, Yeh and Kang in 2005.[162]

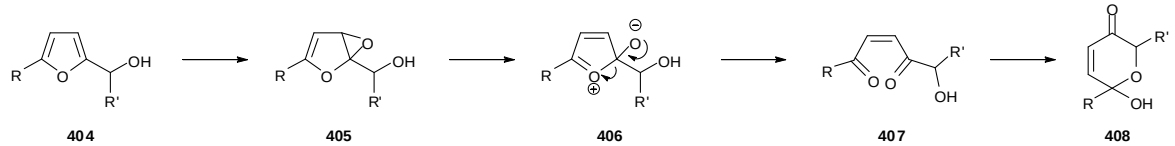
4.9 The Achmatowicz and *aza*-Achmatowicz Oxidative Rearrangement

Hexoses have been successfully synthesised by routes which incorporate oxidative rearrangement of furylcarbinols **402** to pyranones **403**, with chirality at the furylic position being conserved during the rearrangement (Scheme 145). This transformation has been termed the Achmatowicz rearrangement as a result of the pioneering work of O. Achmatowicz.[184]



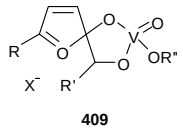
Scheme 145: The Achmatowicz Rearrangement.

*m*CPBA is most commonly used as the peracid needed for the rearrangement to take place, though other reagents such as vanadyl acetylacetonate ($VO(acac)_2$) and *N*-bromosuccinimide (NBS) have also been reported as suitable. In a quest for 2-(1-hydroxyalkyl)-3(2*H*)-furanones Ho and Sapp[185] investigated the epoxidation of 2-furancarbinols **404** with *tert*-butyl hydroperoxide in the presence of $VO(acac)_2$. It was expected that the double bond linked directly to the hydroxyalkyl chain would undergo the reaction regioselectively, with the resultant dioxabicyclo(3.1.0)hexane derivative rearranging to furanone **408** (Scheme 146). Oxidation was reasonably rapid and the 3(2*H*)-pyranones were obtained in acceptable yield.



Scheme 146: Formation of Furanones 408 from 2-Furancarbinols.

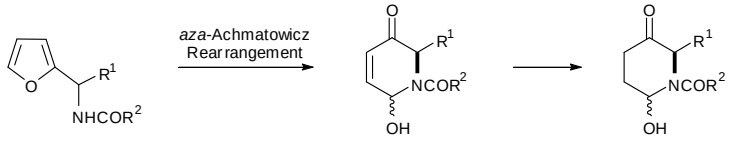
These compounds underwent epoxide ring opening in a direction governed by the relative stability of the cyclic vanadate intermediate **409**. Vanadates derived from the *vic*-glycol systems are the most favourable (Figure 30).



409

Figure 30: Cyclic Vanadate Intermediate 409.

Efforts to develop new routes to nitrogen bearing substances have been of considerable interest to synthetic chemists for some time. The *aza*-Achmatowicz rearrangement emerged in the 1980s in response to the synthetic problems the indolizidine and quinolizidine structures posed. Ciufolini and Wood[186] reasoned that ketone **412** may be accessible from the enone **411**. Enone **411** is in turn accessible through an *aza*-Achmatowicz rearrangement, starting from a substrate such as **410** (Scheme 147).



410 **411** **412**

Scheme 147: The *aza*-Achmatowicz Rearrangement.

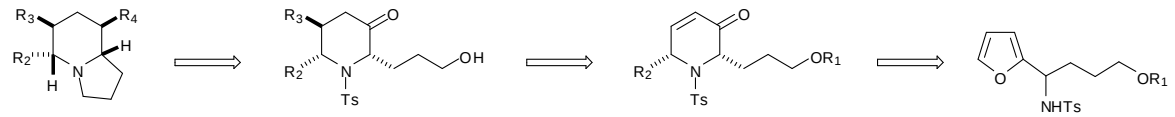
A hypothesis emerged that if similarly protected furfurylamines could be oxidised to nitrogen heterocycles, then they could be used as building blocks to readily incorporate nitrogen-containing heterocycles into natural product synthesis. Ciufolini reported that carbamate protected furfurylamines were unstable and readily hydrolysed to 3-hydroxypyridines under oxidation conditions. Further investigation by Zhou[187] and Altenbach[188] established that sulphonamide protection was well-suited under *aza*-Achmatowicz oxidation conditions and consequently the *N*-tosyl group is regularly used as a protecting group.

Since its conception, the *aza*-Achmatowicz reaction has been further developed and applied to the synthesis of a number of classes of compounds including piperidine alkaloids, azasaccharides and izidines. For the scope of this thesis it is not appropriate to discuss all of the synthetic situations in which the *aza*-

Achmatowicz has been used, but nevertheless some important and interesting examples are highlighted below.

4.9.1 Formation of Substituted Piperidines *via* the *aza*-Achmatowicz Rearrangement

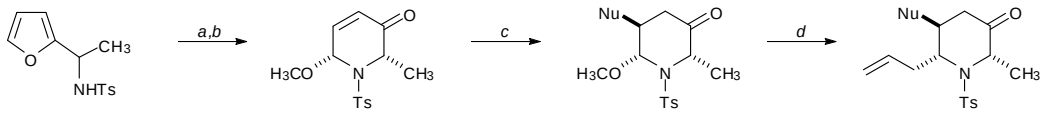
In 2002, Harris and Padwa published their short and concise route to 2,5,6-trisubstituted piperidines, which incorporated an *aza*-Achmatowicz oxidation.[189] They postulated that this specific reaction could be used to prepare indolizidine systems such as **413** from furylamides **416** and subsequently a variety of piperidines-based alkaloids (Scheme 148).



413 **414** **415** **416**

Scheme 148: Padwa's Synthesis of 2,5,6-Trisubstituted Piperidines 413.

To enable the formation of systems such as **413**, a 1,4-conjugate addition to **415** is necessary to introduce the R_3 substituent. To investigate the stereochemical aspects of this addition, **418** was prepared from furyl sulphonamide **417** and from NOE evaluation was assigned as the *cis*-isomer (Scheme 149). The authors reason that the "exclusive formation of **418** can be rationalised by assuming that $A^{1,3}$-strain between the two substituents and the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation."[189]



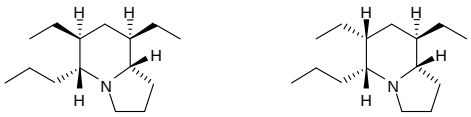
417 **418** **419** **420**

Scheme 149: Padwa's Synthesis of 2,5,6-Trisubstituted Piperidines. Reagents and Conditions: (a) *m*CPBA, CH_2Cl_2, 2 h, rt, 85%; (b) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ^oC, 3 h, 85%; (c) cuprate reagent, 85-90%; (d) allyl TMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ^oC.

When enone **418** was treated with various cuprate reagents the reaction proved to be stereospecific, providing the corresponding Michael adducts in pure diastereomeric form. The stereochemistry is a result of axial attack from the face that is opposite to the diaxial substituents at C_2 and C_6. This may occur due to steric hindrance between the pseudoaxial 2,6-substituents and the equatorial

approach of the nucleophile, thus forming the kinetically favoured 1,4-adduct. Following this, the pyridinone ring can be functionalised at C_6 by treatment of **419** with allyl trimethylsilane and $BF_3{\cdot}OEt_2$ at 0 °C. The product **420** is a single diastereoisomer with 2,6-*cis*-disubstituted stereochemistry as dictated by the tosyl group which shields the opposite face of the molecule as a result of the $A^{1,3}$-strain between the tosyl and methyl groups. The size of the tosyl group directs nucleophile attack on the iminium ion to the side of the C_2 methyl, generating the *cis*-product.

In 2003, Padwa applied his methodology towards trisubstituted piperidines, which culminated in the synthesis of 6-*epi*-indolizidine 223A.[190] A number of indolizidine alkaloids have been isolated from neotropical frogs, with a new subclass called 223A identified in 1997, after its extraction from a skin extract of the frog Dendrobatidae.[191] The actual structure of 223A was finally elucidated in 2002 and was shown to contain an atypical 5,6,8-trisubstituted indolizidine ring (Figure 31).[192]

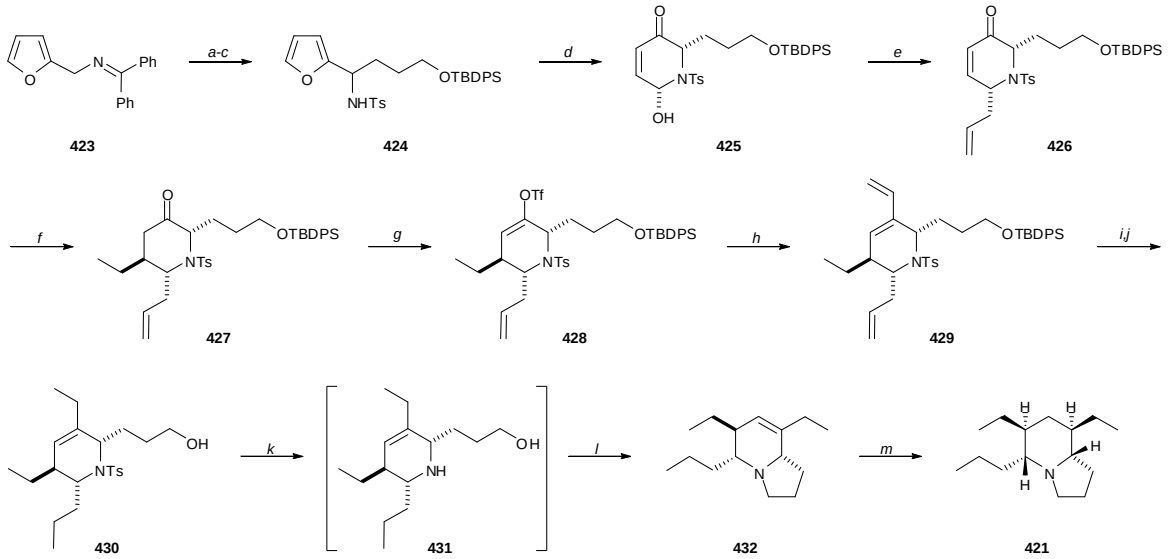


421 422

Figure 31: Indolizidine Alkaloid 223A. The originally proposed structure[191] is shown (**421**), along with the revised structure[192] (**422**).

A taxing problem in the synthesis of indolizidine alkaloids is the creation of the correct stereocentres in the piperidine ring, but Padwa envisioned that the *aza*-Achmatowicz reaction could be utilised to solve this issue and enable a synthesis of 6-*epi*-indolizidine 223A. At the outset of their work the revised structure had not been published, so the synthesis is directed towards the originally proposed structure **421**.

The more complex dihydro-2*H*-pyridone **426** was synthesised from benzophenone-derived imine **423**, which was alkylated, hydrolysed and the amine treated with tosyl chloride to generate **424** (Scheme 150). Oxidative rearrangement of **424** using *m*CPBA gave the desired 6-hydroxy-2,6-dihydropyridinone **425** as a single diastereoisomer, which was then transformed into alkene **426** through reaction with allylsilane.



Scheme 150: Synthesis of 6-*epi*-Indolizidine 223A. Reagents and Conditions: (a) *n*-BuLi, THF, $BrCH_2CH_2CH_2OTBDPS$, 86%; (b) 1 N HCl, acetone, 95%; (c) TsCl, Et_3N, CH_2Cl_2, 90%; (d) *m*CPBA, CH_2Cl_2, rt, 4 h; (e) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 64% over two steps; (f) $(Et)_2CuMgBr$, THF, 0 °C, 90%; (g) $PhNTf_2$, NaHMDS, –78 °C, 95%; (h) $CH_2{=}CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, 85%; (i) PtO_2, H_2, EtOH, 95%; (j) TBAF, THF, 90%; (k) Na, $C_{10}H_8$, –78 °C; (l) CBr_4, PPh_3, Et_3N, 50% over three steps; (m) PtO_2, H_2, EtOH, 90%.

The synthesis afforded 6-*epi*-indolizidine 223A **421** in eight further steps, making the total synthesis thirteen steps long; with an overall yield of 13.1%. The incorporation of the *aza*-Achmatowicz oxidative rearrangement allows the 5,6,8-trisubstituted core structure to be easily obtainable, from which further functionalisation can take place.

4.9.2 Towards Hydroxylated Piperidine Alkaloids

In 2004, Cassidy and Padwa[193] utilised the *aza*-Achmatowicz oxidative rearrangement as the crucial step in their synthesis of *cis*-2,3,6-trisubstituted piperidines. Padwa then proceeded to demonstrate its use in the synthesis of the biologically active alkaloids (±)-azimic acid and (±)-deoxocassine. Both compounds are 2,6-disubstituted piperidin-3-ol alkaloids, with azimic acid **434** being a product of the hydrolysis of azimine **433**. Azimic acid, azimine and deoxocassine **435** (Figure 32) have attracted a great deal of attention since their isolation.

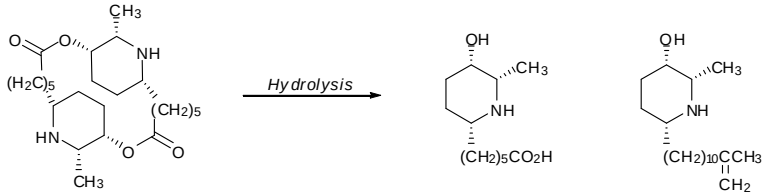
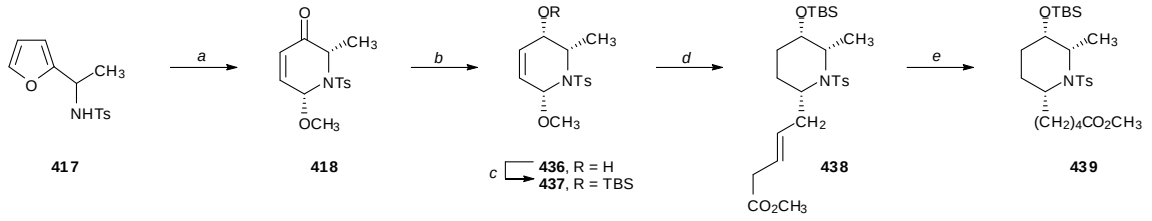


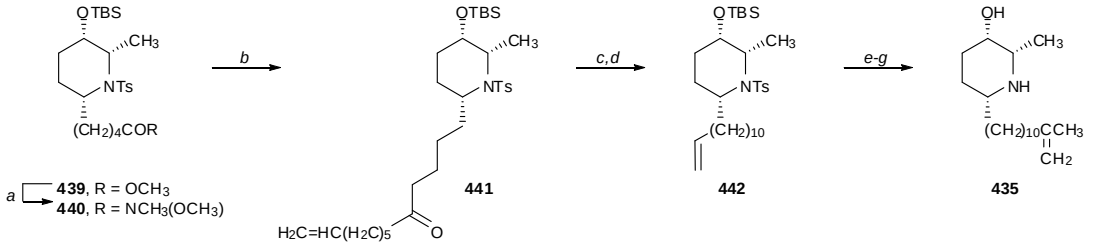
Figure 32: Structures of Azimic Acid 434 and Deoxocassine 435.

In Padwa's synthesis of (±)-azimic acid and (±)-deoxocassine,[189] furyl sulphonamide **417** was oxidatively ring expanded with *m*CPBA, followed by treatment with trimethyl orthoformate and $BF_3{\cdot}OEt_2$ to generate aminal **418** (Scheme 151). Reduction under Luche conditions gave the *cis*-alcohol **436** as a single diastereoisomer. Following TBS protection (→**437**), addition of methyl 3-(trimethylsilyl)-4-pentenoate, led to the formation of piperidine intermediate **438**. The *cis*-substitution can be explained by assuming that the steric bulk of the tosyl group directs the allylsilane attack on the iminium ion to the side of the C_2-methyl group, leading to *cis*-stereochemistry.



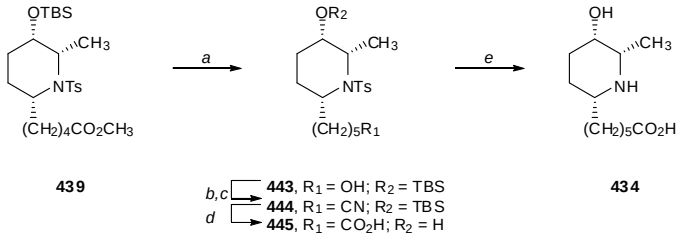
Scheme 151: Formation of Functionalised Piperidino Ester 439. Reagents and Conditions: (a) (i) *m*CPBA, CH_2Cl_2, 2 h, rt, 85%; (ii) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 3 h, 85%; (b) $NaBH_4$, $CeCl_3$, MeOH, –40 °C, 60%; (c) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 82%; (d) methyl 3-(trimethylsilyl)-4-pentenoate, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C; (e) H_2, PtO_2, MeOH, rt, 57%.

To complete the synthesis of deoxocassine, ester **439** was converted to the Weinreb amide **440** in high yield (Scheme 152). Treatment of amide **440** with 6-heptenyllithium gave ketone **441**. Ketone reduction *via* the corresponding tosylhydrazone afforded **442**. Hydrogenation, followed by global deprotection, resulted in the formation of deoxocassine **435** in an excellent 92% over the final three steps.



Scheme 152: Completion of (±)-Deoxocassine. Reagents and Conditions: (a) MeNH(OMe)·HCl, ^{i}PrMgCl, THF, –20 ^{o}C, 85%; (b) CH_2=CH$(CH_2)_5$I, *t*-BuLi, heptane, –78 ^{o}C, 56%; (c) $TsNHNH_2$, EtOH, rt; (d) DIBAH, NaOH, CH_2Cl_2, 0 ^{o}C; (e) H_2, PtO_2, MeOH; (f) TBAF, THF, 0 ^{o}C; (g) Li, NH_3, THF, –78 ^{o}C, 92%.

The synthesis of azimic acid began from the same precursor **439** (Scheme 153). Ester **439** was reduced with LAH and the resulting alcohol **443** was converted to the mesylate before cyanide displacement resulted in the formation of nitrile **444**. Hydrolysis of the nitrile, with consequential TBS cleavage, generated carboxylic acid **445**. Finally, removal of the tosyl group afforded azimic acid **434**.



Scheme 153: Completion of (±)-Azimic Acid. Reagents and Conditions: (a) $LiAlH_4$, THF, 0 ^{o}C, 97%; (b) MsCl, Et_3N, CH_2Cl_2, 0 ^{o}C; (c) NaCN, DMF, 50 ^{o}C; (d) NaOH, MeOH, 70 ^{o}C, 89%; (e) Li, NH_3, THF, –78 ^{o}C, 70%.

The routes reported provide an efficient synthesis of two hydroxlated piperidine alkaloids. They both rely on the *aza*-Achmatowicz rearrangement as the pivotal step to provide the key *N*-tosyl-*O*-methylaminal from which the necessary functionalisation can take place.

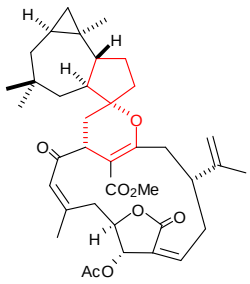
4.10 Polymaxenolide

A coelenterate is an invertebrate of the phylum *Coelenterata*, which has a saclike body with a single mouth, which occurs in polyp and medusa forms. The group includes jellyfish, sea anemones and corals. A cnidarian is any coelenterate of the subphylum *Cnidaria* and the soft corals are a group of cnidarians that make up a large part of the biomass in tropical reefs. A good number of soft corals are of the genus *Sinularia*, which are inclined to form large

monospecific 'carpets' of up to 10 m^2.[194] It is known that the soft corals produce multiple classes of unique secondary metabolites such as sesquiterpenes and diterpenes, with a broad range of carbon skeletons and biological activities.

The effects of natural hybridisation on secondary metabolite production and diversification has been largely ignored in marine organisms, despite the fact that it appears to be a widespread occurrence, having a bearing on the evolution of marine organisms. In 2004, Kamel and co-workers discovered hybridisation between *Sinularia maxima* and *Sinularia polydactyla* and reported the isolation (from Piti bomb holes in Guam) of a novel metabolite they termed polymaxenolide. Later, in 2009, Kamel and colleagues[195] further examined the CH_2Cl_2/MeOH extracts and isolated additional related metabolites, 7*E*-polymaxenolide, 7*E*-5-epipolymaxenolide and polymaxenolides A—C.

The structure of polymaxenolide was resolved *via* mass spectrometry, IR spectrometry and extensive and intricate 1D and 2D NMR experiments. Fortunately for the authors, the isolated compound was in solid form, so x-ray crystallography was used to further determine the structure. The outcome of this investigation revealed that polymaxenolide **446** was composed of a fusion of a cembrane diterpene with an africanane-type sesquiterpene with the skeleton joined *via* a C—C bond (Figure 33).

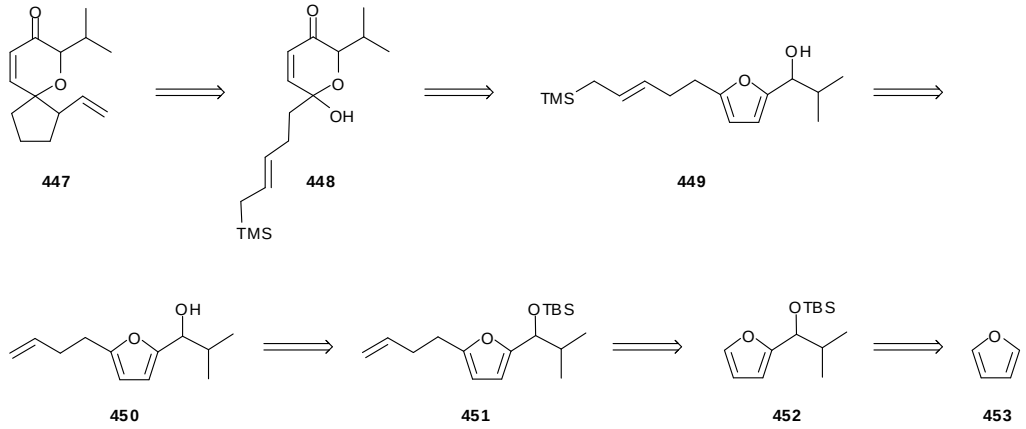


446

Figure 33: Structure of Polymaxenolide 446. The spirocyclic core structure is highlighted in red.

Other than the accounts documenting its isolation and structural determination, there have been no biological or synthetic studies of polymaxenolide reported. Therefore, as a result of our interest in the synthesis of the spirocyclic piperidine and spirocyclic pyran core of natural products, we believed that we could use our prior synthetic experience and knowledge to establish a route to the spirocyclic core of polymaxenolide.

In our proposed approach, Lewis acid mediated ring-closing of **448** enables the formation of spirocyclic structure **447** (Scheme 154). Spirocycle **448** is the result of Achmatowicz rearrangement of TMS alkene **449**, which itself is a product of Grubbs-mediated cross-metathesis of allyl TMS with terminal alkene **450**. The known alkene **450** can be easily accessible from furan **453** in three steps.



Scheme 154: Retrosynthetic Analysis to Polymaxenolide 446.

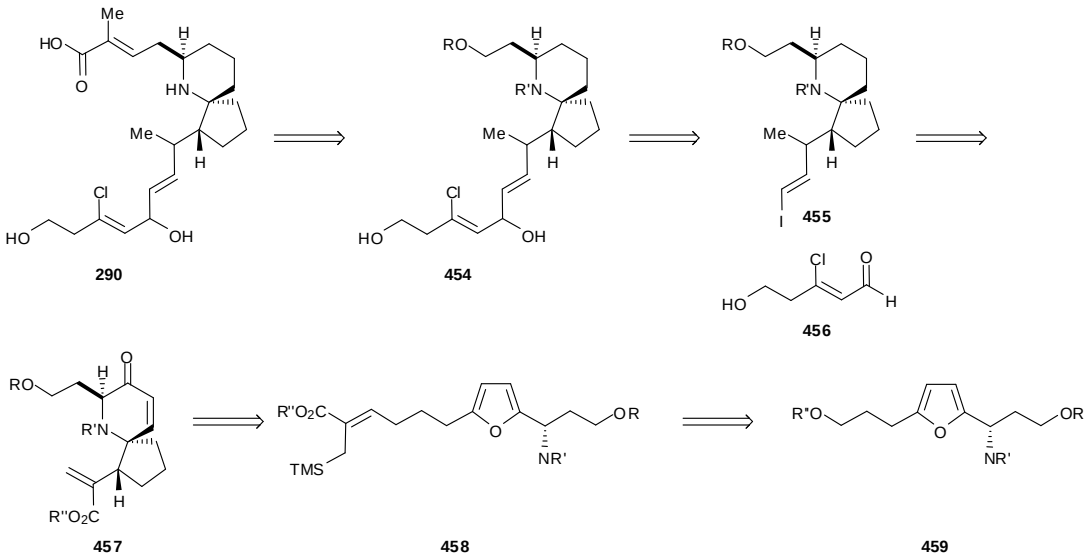
In conclusion, the Achmatowicz and *aza*-Achmatowicz rearrangement reactions have become integral steps in the synthesis of natural products. With this in mind, we hope to build upon prior knowledge from our own laboratories and the chemistry community, to allow the use of this powerful rearrangement in our efforts towards the synthesis of the azaspiro cores of pinnaic acid and halichlorine, with the potential to develop a total synthesis of these alkaloids. We also believe that the rearrangement can be used to reach the spirocyclic core of polymaxenolide, with the view to then focus on a first total synthesis of this natural product.

5 Results and Discussion

At the outset of this project we envisioned that the work would ultimately lead towards a total synthesis of the marine natural product, pinnaic acid.

5.1 Retrosynthetic Analysis to Pinnaic Acid

As shown in Scheme 155, we envisaged pinnaic acid as having originated from spirocyclic piperidine **454**, which could be obtained from the Nozaki coupling of vinyl iodide **455** and aldehyde **456**. Vinyl iodide **455** is derived from conjugated ester **457**. The fundamental spiropiperidine core **457** is thought to originate from *aza*-Achmatowicz rearrangement-intramolecular cyclisation sequence of allylsilane **458**. This allylsilane could be generated from amino furan **459**.

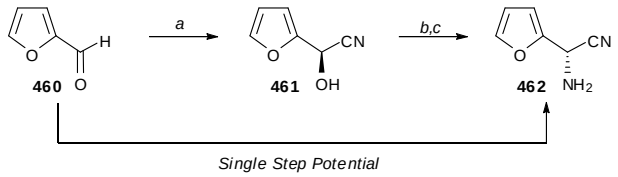


Scheme 155: Retrosynthetic Analysis to Pinnaic Acid 290.

5.2 Previous Work

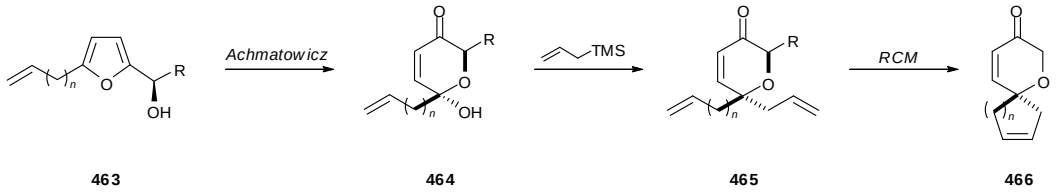
The *aza*-Achmatowicz rearrangement has been explored in recent times by groups such as Ciufolini, Nelson and Padwa[193,196,197] as a method of generating *aza*-saccharides and polysubstituted piperidine units. The generation of the enantiomerically pure furanyl alcohol limits the use of the rearrangement and though various approaches have been broached, we chose to take advantage of readily available oxynitrilases to introduce the desired hydroxyl functionality. It has formerly been demonstrated within the Marquez group that trimethylsilyl

cyanohydrins can be treated with ammonia and transformed into their amine derivatives with complete inversion of configuration. We tentatively hypothesised that amino unit **462** could be obtained in a single step from aldehyde **480** by introduction of the appropriate ammonium salt into the enzymatic step (Scheme 156).



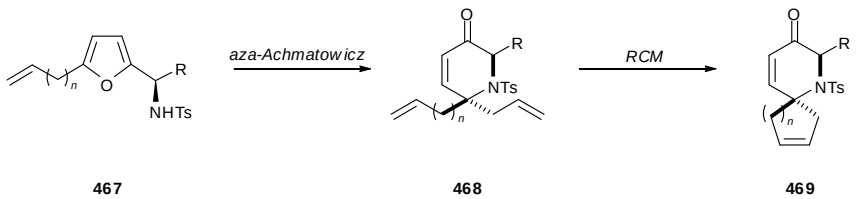
Scheme 156: Conversion of TMS Cyanohydrins into their Corresponding Amino Units. Reagents and Conditions: (a) *(S)*-Oxynitrilase, HCN; (b) TMSCl, Et_3N, DMAP, CH_2Cl_2; (c) NH_3.

In addition, it has previously been demonstrated in our laboratory that highly functionalised spirocyclic pyrans can be obtained *via* the Achmatowicz rearrangement of furyl carbinols (Scheme 157).[157] This methodology, which takes advantage of the different rates of reaction for epoxidation and nucleophilic addition, has allowed spirocyclic units of different sizes to be selectively generated with complete stereocontrol.



Scheme 157: Synthesis of Highly Functionalised Spirocyclic Pyrans *via* Achmatowicz Rearrangement.

It is thought that the methodology established can be applied to the synthesis of both natural and unnatural spirocyclic piperidines beginning from the corresponding furfuryl amines (Scheme 158). Although it had been formerly shown that the rearrangement of α-hydroxyfurans could take place in the presence of olefins, there were concerns about the rearrangement of α-amino furans in the presence of double bonds.

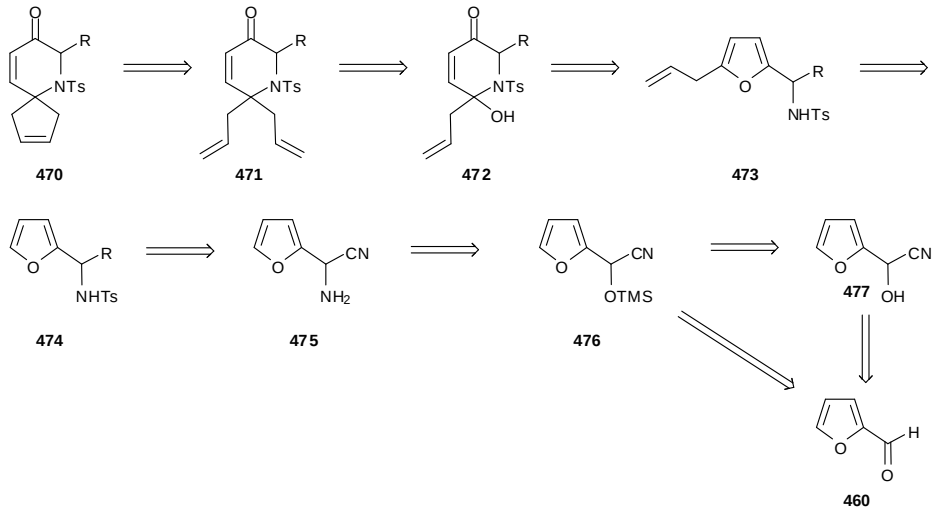


Scheme 158: Proposed Synthesis of Spirocyclic Piperidines from Furfuryl Amines.

5.3 Synthesis of the Spirocyclic Core

5.3.1 Retrosynthetic Analysis

Before progressing to the commencement of reactions that involved compounds that necessitated the incorporation of stereochemistry, the decision was made to work with racemic material first, to test procedures and conditions and to allow evaluation of the results. A suitable retrosynthetic analysis was devised and is revealed in Scheme 159.

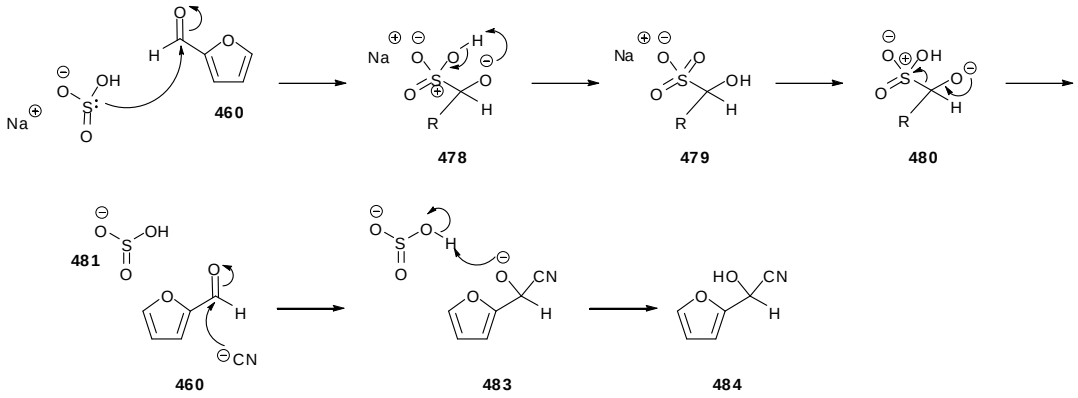


Scheme 159: Retrosynthetic Analysis to Spirocyclic Piperidine Core 470 *via* a Racemic Route.

Retrosynthetically, spirocyclic compound **470** could be achieved *via* a Grubbs-mediated ring-closing metathesis of **471**, itself generated from diastereoselective allylation of **472** with allyl TMS. Hemi-aminal **472** is the product of the *aza*-Achmatowicz rearrangement of **473**, which is flexible in having an alkyl side-chain which can vary in length and nature. Tosylate **474** could be generated through nitrogen protection of amine **475**, the result of conversion from TMS-cyanohydrin **476**. Cyanohydrin **476** can be formed directly from 2-furaldehdye or *via* cyanohydrin **477**, itself made from 2-furaldehdye **460**. The presence of CN as a leaving group allows the introduction of a yet to be determined side-chain. The proposed route is novel, flexible and versatile and we aimed to demonstrate improvement over existing methodologies. Following the ring-closing metathesis step there is the opportunity to form spirocyclic cores with different ring sizes.

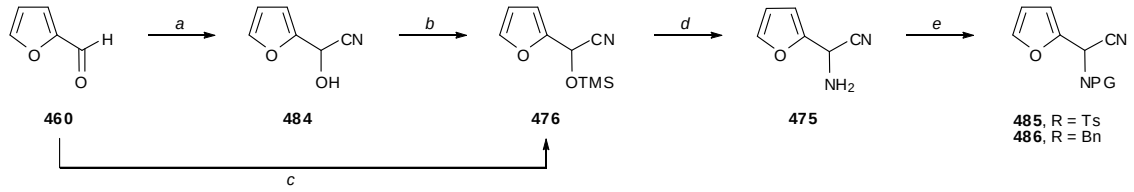
5.3.2 Studies Towards the Synthesis of the Spirocyclic Core

The synthesis began with the commercially available and inexpensive starting material, 2-furaldehyde which was treated with 10% aqueous sodium hydrogen sulphite solution and 20% sodium cyanide solution. $NaHSO_3$ is a nucleophile which adds to aldehydes to give the bisulfite addition compound **479** *via* the mechanism detailed in Scheme 160. Nucleophilic attack of the sulphur lone pair on the carbonyl group of **460**, leaves a positively charged sulphur atom which upon proton transfer leads to the bisulfite addition compound **479**. When sodium cyanide is added, the formation of the bisulfite compound is reversed. Bisulfite then provides the single proton required to re-install the hydroxyl group of **484** at the end of the reaction.



Scheme 160: Mechanism for the Formation of Cyanohydrin 484. Adapted from Reference 119.

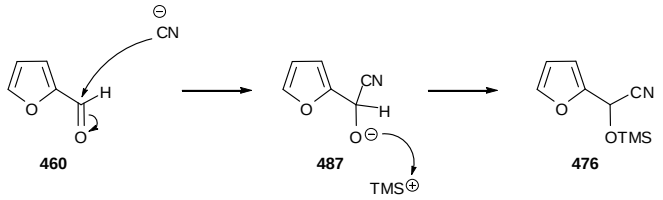
After 2 hours, the reaction had reached completion, but flash column purification proved to be troublesome due to crude product insolubility. Pre-adsorption onto silica gel also failed to yield any product. Modification of the work-up isolation allowed normal flash column chromatography to be carried out, affording the desired cyanohydrin **484** as a viscous, brown oil in 94% yield (Scheme 161). Protection of the alcohol as its TMS ether (**476**) using TMSCl failed to achieve completion, hence an alternative method was found.



Scheme 161: Synthesis of the Protected Amine. Reagents and Conditions: (a) 10% aq. $NaHSO_3$, 10% aq. NaCN, 0 $^oC \rightarrow$ rt, 3.5 h, 94%; (b) TMSCl, pyridine, Et_2O, 0 ^oC, 22 h; (c) TMSCN, Et_3N, 1.5 h, 99%; (d) 2 M NH_3, EtOH, 40 ^oC, 2 h, 61%; (e) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 18 h, 12% *or* BnBr, DMAP, Et_3N, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 16 h, 27%.

2-Furaldehyde was treated carefully with TMSCN, which showed complete conversion after 2 hours. However, column chromatography proved troublesome and no desired product could be retrieved from the column. The reaction was repeated and the crude ^1H NMR spectra showed that other than excess triethylamine being present, the required product was clean, requiring no purification. The triethylamine was simply evaporated off the residue, yielding the TMS cyanohydrin **476** in 99%. This procedure was advantageous due to the fact that the starting aldehyde could be directly transformed into the TMS-cyanohydrin in one step,[198] avoiding the intermediate cyanohydrin altogether.

In terms of the mechanism (Scheme 162) the reaction is a nucleophilic addition reaction to the carbonyl group. As the reaction is run with TMSCN, the TMS is present in the reaction mixture, which is then able to be attacked by the alkoxide **487**, to generate the final TMS-cyanohydrin **476**.

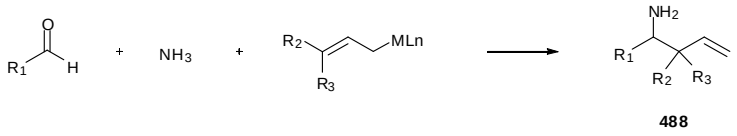


Scheme 162: Mechanism for the Formation of TMS-Cyanohydrin 476.

With TMS-cyanohydrin **476** in hand, conversion to the amino cyanohydrin was attempted. Treatment of TMS-cyanohydrin **476** with ammonia in ethanol generated amino cyanohydrin **475**, with ^1H NMR spectroscopy of the crude residue showing that no further purification was necessary. A tosylate protecting group was chosen to mono-protect the nitrogen. It was found by Ciufolini[186,197,199] that carbamate protected furfurylamines were unstable and readily hydrolysed to 3-hydroxypyridines under typical oxidation conditions. Sulphonamide protecting groups don't display this instability and are compatible

with the *aza*-Achmatowicz oxidation reaction. Amine **475** was treated with tosyl chloride and the desired protected compound **485** was isolated in 14% yield. Following a published procedure,[200] the crude material was treated to precipitate any remaining impurities, affording tosyl amine **485** with only slight improvement in purity. This result was disappointing due to the relative simplicity of the reaction and on further attempts at protection with other groups similar results were also obtained. Some improvement was noted when using a benzyl ether protection, with mono-benzyl protected **486** isolated in 27% yield, a two-fold improvement in yield compared to the tosyl protection. Boc protection and benzoyl mono-protection of amine **475** was unsuccessful in both cases. At this stage it was clear that the protection step was hindering the synthesis, certainly insufficient product was always obtained which meant that the synthesis could not go forward as first planned.

Having had no success with the cyanohydrin approach, a new strategy was devised to generate the desired furfuryl amine. It has been reported that aldehydes can be aminoallylated using ammonia and allylating agents to give homoallylic primary amines with high chemoselectivity (amine *vs.* alcohol) (Scheme 163).[201-203] This method affords α-amino furan units such as **488**, while simultaneously incorporating a useful synthetic handle onto which further functionality could be added. This method is also advantageous as it avoids the use and handling of cyanide and cyano-containing compounds.

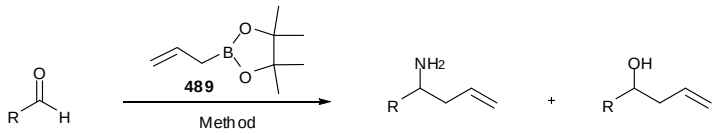


488

Scheme 163: α-Aminoallylation Using Ammonia.

Ammonia is a versatile and inexpensive nitrogen source and has been used as a nucleophile to incorporate nitrogen into organic molecules. The α-aminoalkylation of carbonyl compounds using ammonia has been reported, however, low yields have been the norm. Kobayashi and colleagues utilised the potential of ammonia and investigated α-aminoallylation of carbonyl compounds, using allylating agents as the carbon nucleophiles. It was Kobayashi who first described the novel three-component reactions of aldehydes, ammonia and

allylboronates to yield homoallylic primary amines with high chemo- and stereo-selectivities (Scheme 164).[201]



Scheme 164: α-Aminoallylation of Aldehydes.

Kobayashi reported that since solvent has no effect in the reaction outcome, ethanol was chosen for its high solubility of ammonia and limited environmental impact. Variations of the allylboronated species also had little effect and pinacol allylboronate **489** was selected due to its high stability. Experimentally, Kobayashi found that a large excess of liquid ammonia was necessary to obtain high chemoselectivity of amine *versus* alcohol.

In subsequent communications Kobayashi reported the use of aqueous ammonia for the α-aminoallylation, making it an easy and convenient procedure.[202] Although initial results had shown that the use of aqueous ammonia led to a decrease in chemoselectivity (84:3 to 80:8, amine *vs.* alcohol). The inclusion of dodecylbenzenesulfonic acid (DBSA, Figure 34) as an additive was effective in improving the chemoselectivity. Since toluenesulfonic acid demonstrated much lower activity, it was thought that the hydrophobic element of DBSA played an important role.[202] Further optimisation by the authors determined that α-aminoallylations carried out with 10 mol% of DBSA in aqueous ammonia at room temperature for 6-12 hours, provided the best yields and selectivity.

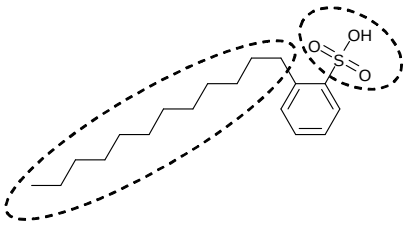
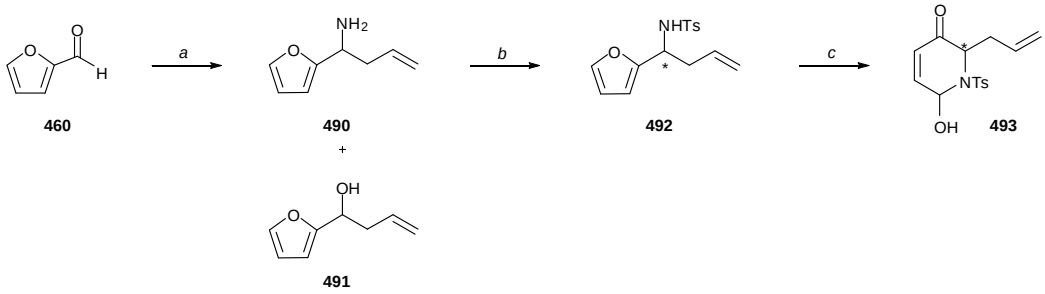


Figure 34: Structure of Dodecylbenzenesulfonic acid. The hydrophobic and acidic elements are highlighted.

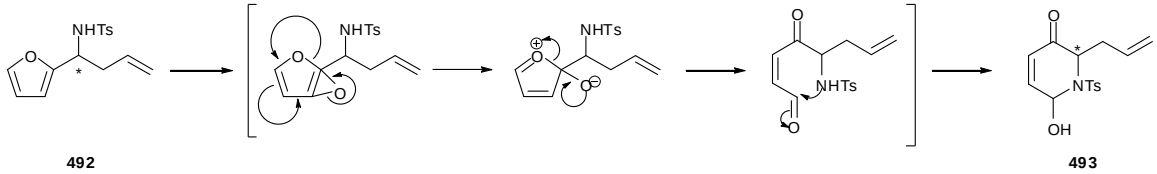
In our hands, the α-aminoallylation of 2-furaldehyde turned out to be an exceptionally reliable reaction, with identical yields obtained every time the reaction was carried out. The homoallylic amine **490** was reliably obtained in 55% yield and the matching alcohol side-product **491** in 3% yield (Scheme 165).



Scheme 165: Synthesis of Rearrangement Product 493. Reagents and Condition: (a) allyl boronic acid pinacol ester, DBSA, 25wt% aq. NH_3, rt, 2 h, 55%; (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 ^oC → rt, 18 h, 100%; (c) *m*CPBA, CH_2Cl_2, 0 ^oC → rt, 18 h, 48%.

Despite the disappointing result with mono-tosylation of amine **475,** we were optimistic about the chances of success with protection of homoallylic amine **490**. Treatment of amine **490** with tosyl chloride gave a spot to spot conversion to yield tosyl amine **492** in quantitative yield. NMR spectroscopy confirmed the product as being extremely clean and impurity free.

We were delighted with the successful α-aminoallylation reaction as it meant we were now in a strong position to proceed with the pivotal *aza*-Achmatowicz rearrangement.[184] We were extremely pleased when treatment of tosyl amine **492** with *m*CPBA afforded the desired enone **493** in 59% yield. To our knowledge, this is the first example of a successful *aza*-Achmatowicz rearrangement in the presence of an olefin, the mechanism for which is demonstrated in Scheme 166.

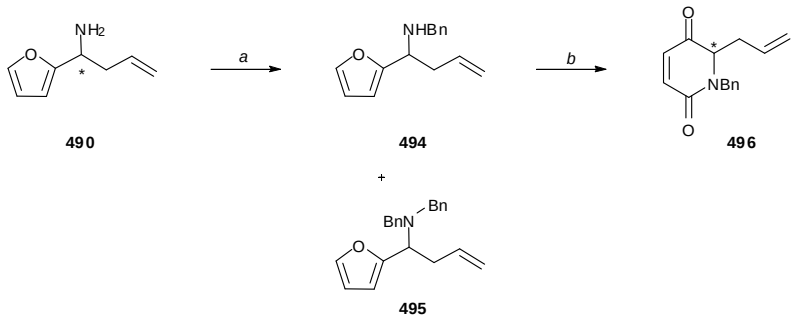


Scheme 166: Mechanism of Formation of 493 *via* the *aza*-Achmatowicz Rearrangement.

Attempts to optimise the rearrangement yields by using purified *m*CPBA[204] failed to increase the yield of the reaction. Also, it has been found through multiple reactions on similar scales that the yield is not consistent and fluctuates between 26% and 48%.

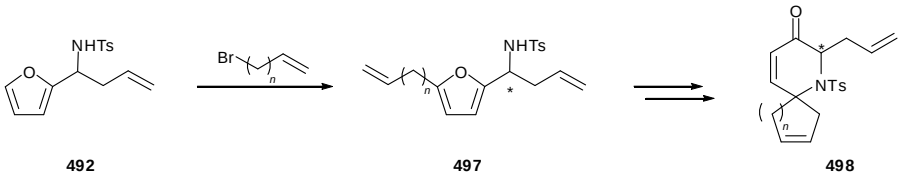
It was hypothesised that replacing the tosyl group on the amine with an electron donating group might improve the overall efficiency of the rearrangement. Treatment of amine **490** with benzyl bromide afforded the mono-protected

amine **494** in 43% yield, together with 10% of di-benzylated product **495** (Scheme 167). Interestingly, *aza*-Achmatowicz rearrangement of **494** gave dione **496**, rather than the expected enone. The yield for the transformation was 26%, with the product being confirmed by NMR and mass spectrometry.



Scheme 167: Synthesis of Rearrangement Product 496. Reagents and Conditions: (a) BnBr, Et_3N, DMAP, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 18 h, 43%; (b) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 19 h, 26%.

Knowing that the rearrangement was viable without affecting the terminal double bond, our attention focused on introducing the functionality at position C_5 of the furyl ring. It was envisaged that deprotonation of **492** and addition of the appropriate bromoalkene would lead to addition product **497**. The length of the chain introduced would dictate the final obtained ring size of product **498**, following ring-closing metathesis (Scheme 168).

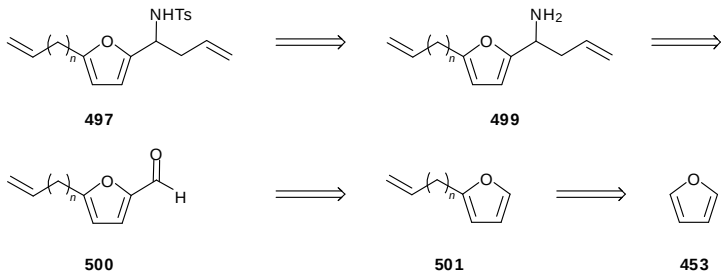


Scheme 168: Formation of 498 *via* Addition Product 497.

Hence, tosyl amine **492** was treated with *n*BuLi for 24 hours before being quenched with 6-bromo-1-hexene. After 24 hours the reaction afforded the desired disubstituted furan in 19% yield (48% based on starting material consumed). Unfortunately, despite extensive experimentation, which took into account equivalents, reaction times and bases, the reaction yield failed to improve.

Due to these difficulties an alternative route to **497** was explored, whereby the C_5 side chain would be installed first (→**501**), followed by the introduction of the aldehyde at the C_2 position (→**500**) by deprotonation and trapping with DMF.

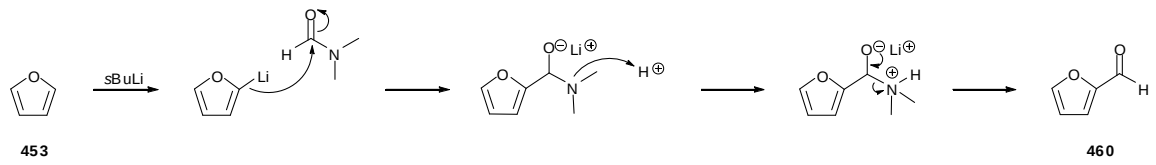
As shown in Scheme 169, this then sets the molecule up for the reactions that have already been performed and shown to work.



Scheme 169: Alternative Route to 497.

Treatment of furan **453** with *n*BuLi and quenching with 4-bromo-1-butene afforded the desired alkenyl furan **501**, ***n*=2** in a disappointing 12% yield after purification. The low yield observed is presumably due to the relative volatility of the compound and the fact that two purification procedures were required. Similarly, freshly distilled furan was treated with *n*BuLi and 5-bromo-1-pentene to generate alkenyl furan **501**, ***n*=3**. A decision was taken not to purify the crude residue as the ^{1}H NMR spectrum showed it to be sufficiently clean to be taken on to the next step.

The Bouveault synthesis of aldehydes[205] is well known (Scheme 170) and following a procedure reported by Marshall and colleagues,[206] formylation of the furfuryl alkene was attempted. Unfortunately, treatment of alkenes **501** (***n*=1** and ***n*=3**) with *s*BuLi and quenching with DMF failed to generate the desired aldehydes. Alternative procedures were explored in the alkenes were treated with *n*BuLi and quenched with ethyl formate. However, despite repeated attempts no product could be detected, with the starting material remaining unaffected.

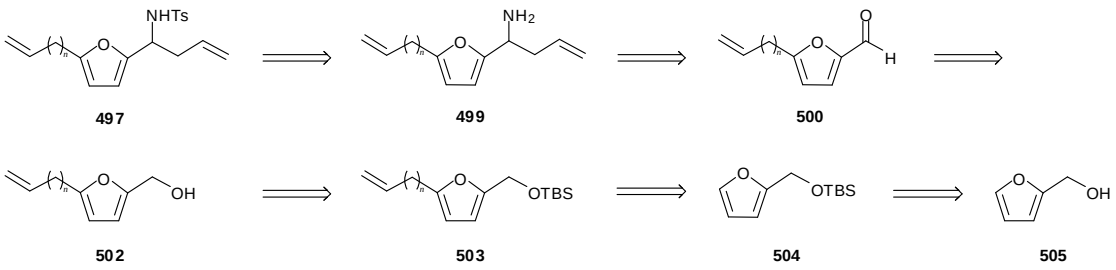


Scheme 170: Bouveault Synthesis of Aldehydes.

To check that deprotonation was taking place and the effect of the C_5 substituent in the reaction, freshly distilled furan was treated with *n*BuLi then quenched with DMF. NMR analysis of the crude reaction mixture showed that 2-

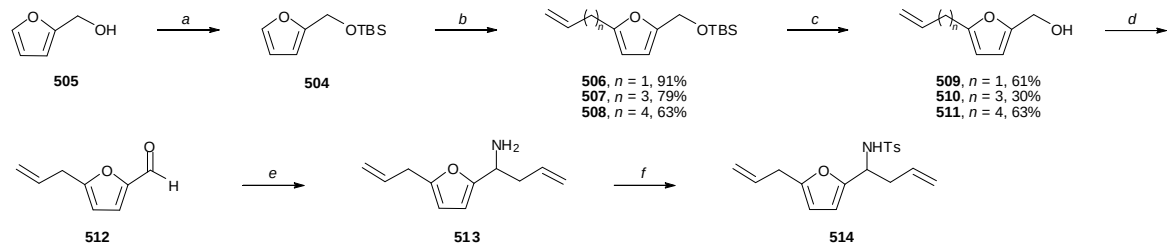
furaldehyde had been formed by the appearance of the characteristic aldehyde signal at 9 ppm (together with an unknown side-product). Likewise, when freshly distilled furan was treated with *n*BuLi and quenched with freshly distilled ethyl formate, NMR analysis of the crude product once again showed the presence of 2-furaldehyde. From these particular results it seemed that the procedure employed was suitable for the installation of the aldehyde at the C_2 position and perhaps it was the presence of the side chain at C_5 that was causing the reaction not to proceed. Additionally, the fact that the material was used crude in some cases, may have an impact on the success of the reaction.

As the main problem seemed to be the addition of the C_5 alkenyl chain, a new strategy had to be devised which would allow for the effective introduction of both side chains (Scheme 171). In a new approach, the disubstituted furan **497** originates from the tosyl protection of amine **499,** itself a result of α-aminoallylation of aldehyde **500**. The aldehyde **500** is a product of oxidation of primary alcohol **502** which is the result of TBS cleavage of **503**. Silyl ether **503** is the product of alkenyl chain addition onto **504** which comes from the TBS protection of the readily available furfuryl alcohol **505**.



Scheme 171: New Retrosynthesis to Furfuryl Compound 497.

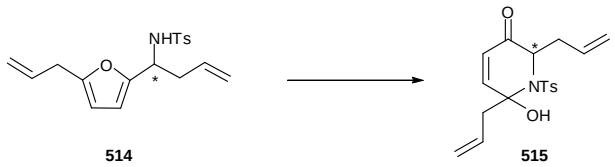
The first step of the synthesis (shown in Scheme 172) is the straightforward TBS protection of furfuryl alcohol **505** which was achieved in quantitative yield after only 10 minutes, to afford the silyl ether **504**. There was no need for further purification.



Scheme 172: Alternative Synthesis of 514. Reagents and Conditions: (a) TBDMSCl, imidazole, DMF, rt, 10 min, 100%; (b) alkenyl bromide, *n*BuLi, THF, 0 °C → rt, 18–24 h, 63-91%; (c) HF:Pyr, pyridine, THF, rt, 2 h *or* TBAF, THF, 0 °C → rt, 1.5 h, 30–63%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C → rt, 2 h, 87%; (e) allylboronic acid pinacol ester, DBSA, 25 wt% aq. NH_3, rt, 2 h, 76%; (f) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C → rt, 20 h, 35%.

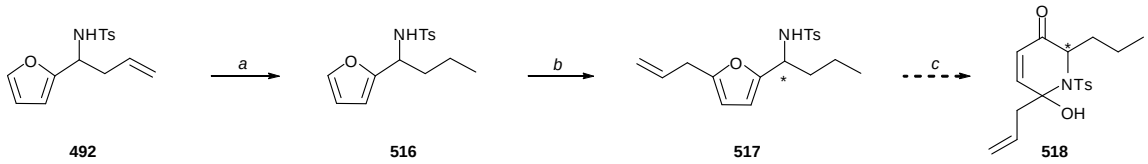
The introduction of the C_5 alkenyl substituent was attempted using conditions which had been successfully employed for the synthesis of 2-(5-(allyl)-furylmethanol **509**.[207] Hence, TBS ether **504** was treated with *n*BuLi and quenched with freshly distilled allyl bromide. ^{1}H NMR analysis of the crude residue showed the formation of a clean product but a short column was undertaken to remove the excess silyl product remaining from the protection step. This meant that the desired compound **506** was isolated in an excellent 91% yield. Switching the solvent from tetrahydrofuran to diethyl ether resulted in an incomplete conversion of starting material to product. TBAF deprotection of the TBS ether proved not as reliable as expected and the desired primary alcohol **509** was isolated in 54%. The addition of 1% triethylamine to the column eluent failed to improve the yield. Switching the fluoride source from TBAF to hydrogen fluoride in pyridine was more successful, affording alcohol **509** in 61% yield after purification. Swern oxidation of alcohol **509** afforded the crude aldehyde **512** in 87%. The potential instability of this compound and the clean nature of the ^{1}H NMR spectrum, showing the characteristic aldehyde signal at 9.49 ppm, meant that the product was not purified and taken on crude to the next step. With great satisfaction we now had the alkenyl chain in place at position C_5 and the aldehyde at the C_2 furan position, which left us in prime position to perform the α-aminoallylation. Due to the reliable success of this transformation previously, we were confident that the reaction would provide us with the correct adduct. This indeed turned out to be the case, with the reaction proceeding smoothly to afford the required amine **513** in 76% yield, with no purification required. Surprisingly, the tosylation of amine **513** only gave the required nitrogen protected compound **514** in a mere 35%. With this we could now proceed with the *aza*-Achmatowicz rearrangement of **514** (Scheme 173). In anticipation of the planned synthesis being successful, we synthesised

the additional compounds **507** and **508** with varying chain length at the C_5 position. The TBS ether was removed in each case using TBAF to afford the corresponding alcohols **510** and **511** (Scheme 172).



Scheme 173: *aza*-Achmatowicz Rearrangement of 515.

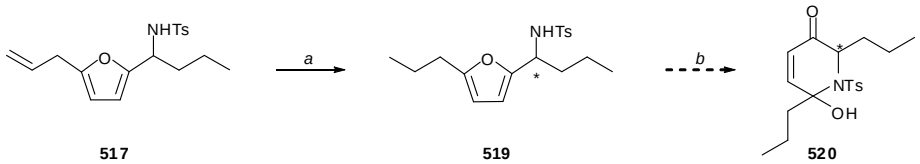
A number of different oxidative conditions and methods were attempted, including vanadyl acetoacetonate ($VO(acac)_2$),[208] however, none of them yielded the desired product **515**. It was postulated that a possible reason why the rearrangement was not working could be due to the multiple double bonds present in the molecule. In order to test this hypothesis, the decision was made to remove the double bond on the C_2 substituent of **492**. Synthetically, this meant reverting back to a modified version of a previously attempted synthesis, whereby the C_5 substituent is installed and then rearrangement performed. Hydrogenation of furan **492** using palladium on carbon was extremely successful, giving the required alkane **516** in 99% yield (Scheme 174). Deprotonation using *n*BuLi and trapping of the resulting lithiate with allyl bromide gave the di-substituted furan **517** in good yield, together with 44% of unreacted starting material.



Scheme 174: Hydrogenation of Furan 492. Reagents and Conditions: (a) H_2, Pd/C, MeOH, 40 min, rt, 99%; (b) allyl bromide, *n*BuLi, THF, 16 h, 0 ^{o}C → rt, 66% based on starting material consumed; (c) 'oxidative conditions'.

Unfortunately, the same problems with the rearrangement were encountered, with *m*CPBA, $VO(acac)_2/^{t}$BuOOH and NBS all failing to promote the desired rearrangement to generate spirocyclic piperidine **518**. We were particularly disappointed as NBS has been reported to give good yields *via* a very simple procedure. Although NBS has been successfully used, as the oxidative reagent for the Achmatowicz rearrangement, in synthesis by Couladouros[209] and O'Doherty,[210,211] their reported conditions were unsuccessful in our hands.

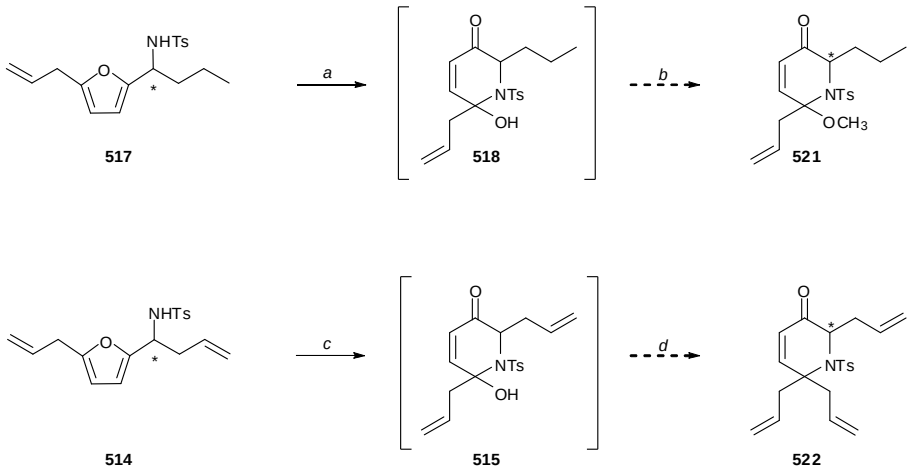
Faced with this lack of success, we sought to remove the remaining terminal olefin of **517** to discover whether the dialkyl derivative **519** would then be able to oxidise successfully. Hydrogenation of alkene **517** proceeded in 98% yield to yield dialkane **519**, which was subjected to the oxidative conditions. Once again there was no positive outcome, with no formation of **520**.



Scheme 175: Hydrogenation of 517 and attempted *aza*-Achmatowicz Rearrangement. Reagents and Conditions: (a) H_2, Pd/C, MeOH, 45 min, rt, 98%; (b) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt.

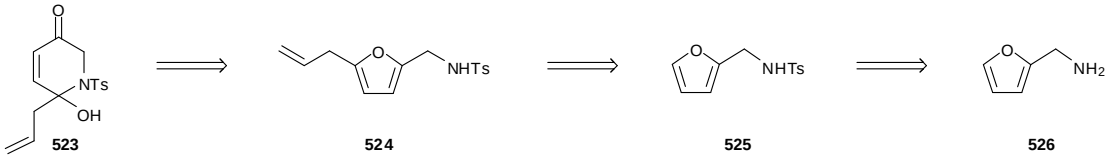
Although until this point the assumption had been made that the oxidative conditions used were not rearranging our substrates, there was also the possibility that the desired aminal might be formed under our conditions, but not able to withstand work-up and purification. For this reason it was decided to cap the aminal's hydroxyl group with a methyl unit. Reactions of this type have been demonstrated successfully by Padwa[189], so furyl sulphonamide **517** was oxidatively rearranged with *m*CPBA and the crude residue treated with trimethyl orthoformate and $BF_3 \cdot OEt$ (Scheme 176). Unfortunately, TLC analysis showed no clear appearance of product **521** and resulted in the eventual degradation of all starting material.

Intriguingly, there are reports of the *aza*-Achmatowicz oxidative rearrangement being performed at elevated temperatures (up to 60 ^oC). Following helpful discussions with Dr D. P. Furkert[212] a solution of furyl sulphonamide **521** in chloroform was treated with *m*CPBA at 55 ^oC. After 6 hours, the starting material seemed to have been consumed by TLC, together with the faint appearance of a possible product. Taking precedent from work by Padwa,[190] the crude product was treated with allyl trimethylsilane and $BF_3 \cdot OEt_2$. NMR spectroscopy of the crude residue was not conclusive and at this stage time did not permit repeated attempts at this transformation as we wished to progress to trial supplementary ideas. This area of investigation is worth revisiting in the future with respect to applying efforts towards optimising reaction conditions.



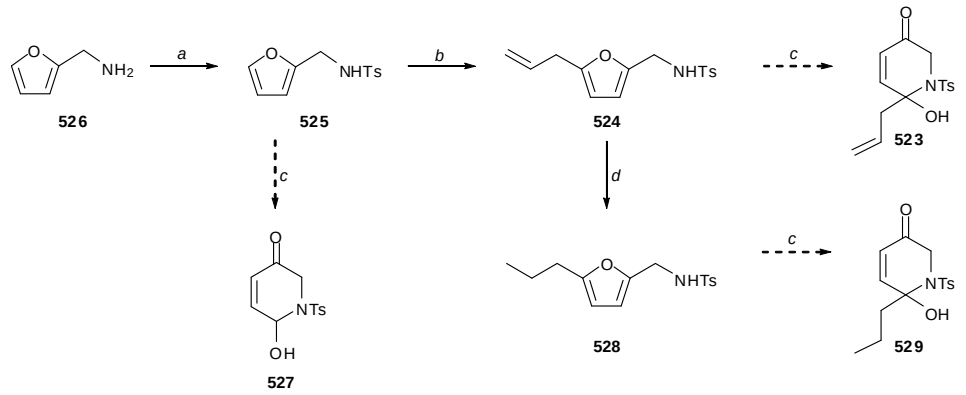
Scheme 176: Additional Rearrangement Studies. Reagents and Conditions: (a) *m*CPBA (2.3 eq.), CH_2Cl_2, 0 $^oC \rightarrow$ rt, 2.5 h *then m*CPBA (1.9 eq.), 2.5 h, rt; (b) $(MeO)_3CH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 ^oC, 24 h; (c) *m*CPBA (2.3 eq.), CH_2Cl_2, 55 ^oC, 6 h; (d) Allyl TMS, $BF_3{\cdot}OEt_2$, 4Å MS, CH_2Cl_2, –78 $^oC \rightarrow$ 0 $^oC \rightarrow$ rt, 2.5 h.

The findings thus far, suggested that the rearrangement proceeded well in the presence of the alkenyl chain at the C_2 position as long as there were no substituents at C_5. Substitution at both C_2 and C_5 caused the oxidative *aza*-Achmatowicz rearrangement to not proceed. Furthermore, hydrogenation of one or both of the terminal olefins did not aid the rearrangement in either case. As a result, we contemplated whether the oxidation would come about if the C_5 substitution was in place but the C_2 substitution was simplified. This would require the synthesis of the simplified analogue **524** (Scheme 177).



Scheme 177: Retrosynthesis to Rearrangement Product 523 *via* Simplified Furyl Sulfonamide 524.

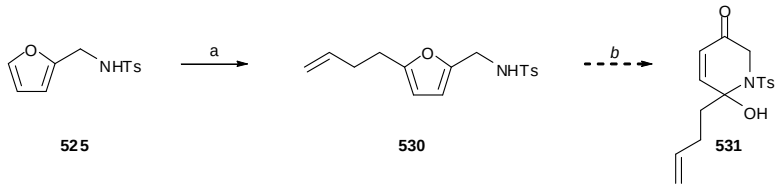
Synthetically, furfurylamine **526** was monoprotected in quantitative yield and the resulting tosylate **525** was treated sequentially with *n*BuLi and allyl bromide (Scheme 178). Gratifyingly, allyl furan **524** was obtained in 88% yield, with no need for purification. Treatment of tosyl amine **524** with excess *m*CPBA consumed the starting material, however the ^1H NMR showed that no desired product **523** was present.



Scheme 178: Synthesis Towards 523. Reagents and Conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 1 h, 100%; (b) *n*BuLi, allyl bromide, THF, 0 $^oC \rightarrow$ rt, 20 h, 88%; (c) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt; (d) H_2, Pd/C, MeOH, 45 min, rt, 92%.

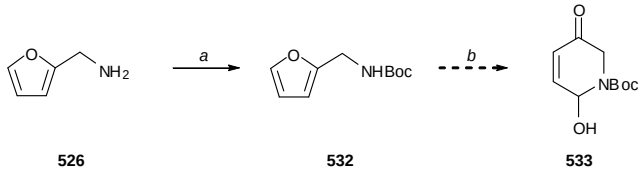
Out of interest, the terminal olefin was removed using palladium on carbon to generate **528** in 92% yield with no column purification needed. Once again the *aza*-Achmatowicz reaction let us down and the rearrangement product **529** was not formed. Rearrangement of protected amine **525** also failed, with no reaction occurring the simple starting material was recovered after work-up.

Additionally, protected amine **525** was taken and deprotonated at C_5 to enable the addition of 4-bromo-1-butene to form **530** in 43% yield, which was then treated with *m*CPBA, but again the reaction failed (Scheme 179).



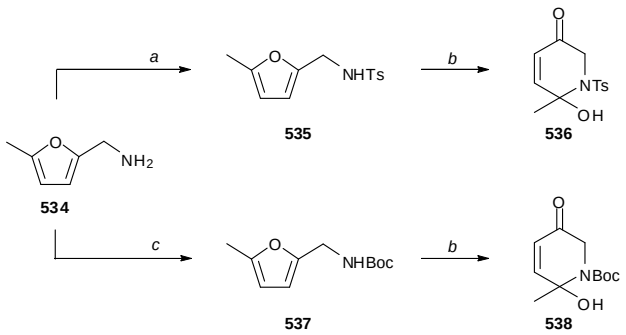
Scheme 179: Attempts with Longer Chain Substituent at C_5 Position. Reagents and Conditions: (a) *n*BuLi, 4-bromo-1-butene, THF, 0 $^oC \rightarrow$ rt, 20 h, 43%; (b) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt.

An attempt was also made with the Boc protected amine (Scheme 180). Oxidative rearrangement of Boc protected furfuryl amine **532** with *m*CPBA also caused the starting material to disappear by TLC, although ^1H NMR spectra showed a mixture of unknown signals.



Scheme 180: Investigation with Boc Protected Amine. Reagents and Conditions: (a) $(Boc)_2O$, H_2O, rt, 40 min, 97%; (b) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt.

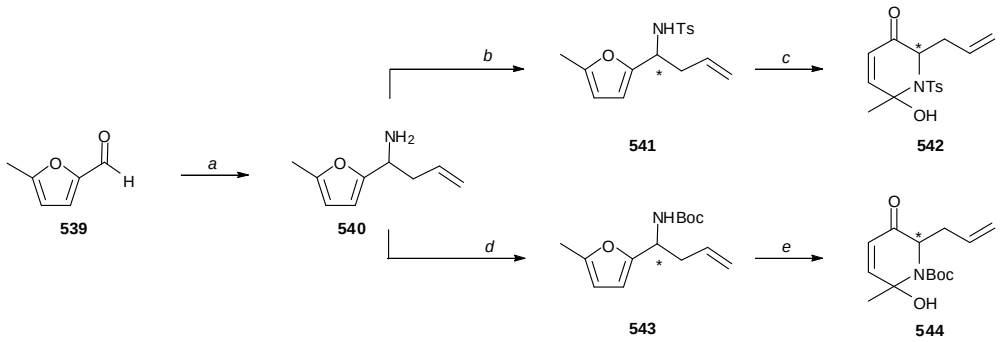
The most interesting set of results were obtained when methyl furfurylamine was used as our starting substrate (Scheme 181). Methyl furfurylamine **534** was protected to afford the desired mono-tosylated product **535** in quantitative yield after purification. Tosyl amine **535** was treated with *m*CPBA under similar conditions to those used for all the previous rearrangement attempts. On this occasion we were delighted to see the successful *aza*-Achmatowicz reaction product **536**, which was isolated in quantitative yield after work-up. ^{1}H NMR analysis showed that no purification was required. Simultaneously, methyl furfurylamine was protected as the Boc amine **537** in quantitative yield. The rearrangement proceeded well by TLC but surprisingly; the product **538** was not easily isolated and after work-up NMR spectroscopy showed a significant number of additional signals that could not be attributed to any other realistic compound. Due to the great success of the tosylated compound the Boc analogue was abandoned.



Scheme 181: Successful *aza*-Achmatowicz Reactions. Reagents and Conditions: (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 1 h, 100%; (b) *m*CPBA, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 4 h, 100%; (c) $(Boc)_2O$, H_2O, rt, 40 min, 82%.

Though we were thrilled with this success, we were intrigued as to why the rearrangement would now proceed with presence of a methyl group at C_5, when it would not proceed with a longer chain or no substituent at all. To supplement our existing knowledge, the same process was executed with 5-methylfuraldehyde (Scheme 182).

5-Methylfuraldehyde **539** was subjected to the same α-aminoallylation reaction in aqueous ammonia described previously, which provided homoallylic amine **540** in 77% yield. Amine **540** was then monoprotected as either the tosyl amine **541** or Boc amine **543** in 93% yield and 81% yield respectively.



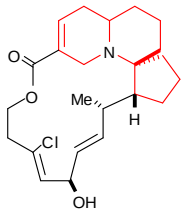
Scheme 182: Reaction with 5-methylfuraldehyde. Reagents and Conditions: (a) allyl boronic acid pinacol ester, DBSA, 25wt% aq. NH_3, rt, 2 h, 77%; (b) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 $^oC \rightarrow$ rt, 1 h, 93%; (c) *m*CPBA, CH_2Cl_2, rt, 40 min, 99%; (d) $(Boc)_2O$, H_2O, rt, 30 min, 81%; (e) *m*CPBA, CH_2Cl_2, rt, 1 h, 88%.

Treatment of amines **541** and **543** under the same oxidative rearrangement conditions led to the clean formation of enones **542** and **544** in 99% yield and 88% yield respectively, with no need for further purification. No additional products were seen by ^1H NMR spectroscopy proved the result, with no need for any purification.

5.4 Efforts Towards the Synthesis of the Tricyclic Core of Halichlorine

5.4.1 Retrosynthetic Analysis

We envisaged that the results and information gained, as part of the previous studies described above, could be utilised to develop a short, concise route to the tricyclic core of halichlorine (Figure 35).

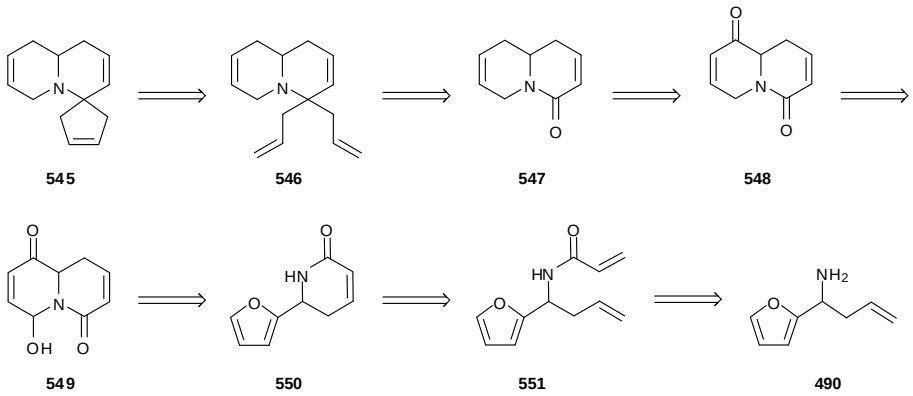


336

Figure 35: Structure of Halichlorine 336. The tricyclic core is highlighted in red.

A retrosynthetic route was devised as shown in Scheme 183. It was hypothesised that the basic, initial tricyclic core **545**, from which further functionalisation could be introduced, is the product of ring-closing metathesis of diene **546**. Diene **546** was thought of as being a product of treatment of **547** with

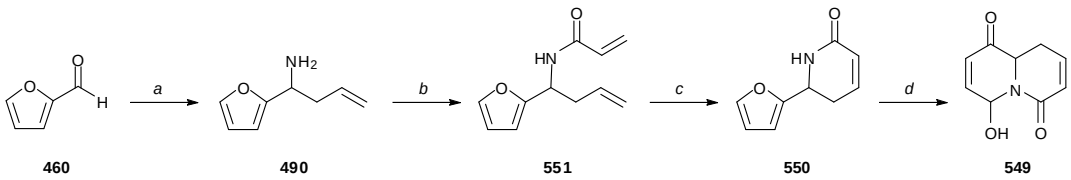
allylstannane. Bicyclic structure **547** is generated from the reduction of dicarbonyl **548**. This dicarbonyl is afforded after removal of the hydroxyl function of **549** using triethylsilane and a Lewis acid. **549** is a result of the *aza*-Achmatowicz oxidative rearrangement of **550**, which in turn is gained from ring-closing metathesis of diene **551**. Diene **551** could in turn be obtained through the protection of previously generated homoallylic amine **490**, itself obtained *via* α-aminoallylation of 2-furaldehyde.



Scheme 183: Retrosynthetic Analysis to Tricyclic Core 545.

5.4.2 Initial Synthetic Investigations

Our synthesis began with homoallylic amine **490**, which was prepared using the procedure described previously. Homoallylic amine **490** was treated with acryloyl chloride to generate amide **551** in a non-reproducible 63% yield after purification (Scheme 184). We were surprised that the yield was not higher for such a simple transformation, but a minor modification of the reaction conditions[213] allowed us to obtain vastly improved and reliable quantitative yields.

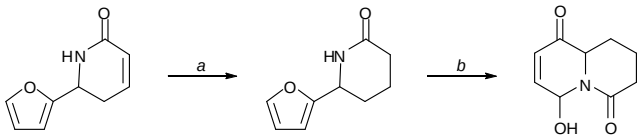


Scheme 184: Synthesis of Bicyclic Structure 549. Reagents and Conditions: (a) allylboronic acid pinacol ester, DBSA, 25wt% aq. NH_3, rt, 2 h, 55%; (b) CH_2=CHCOCl, DIPEA, CH_2Cl_2, rt, 2 h, 100%; (c) Grubbs first generation catalyst (10 mol%), CH_2Cl_2, reflux, 18 h, 84%; (d) *m*CPBA, $CHCl_3$, 60 ^{o}C, 3.5 h *then* rt, 18 h, 70%.

Ring-closing metathesis of diene **551** using Grubbs first generation catalyst afforded lactam **550** in reproducible 76-84% yields. Disappointingly, *aza*-

Achmatowicz rearrangement of **550** failed to generate the desired product under a variety of conditions. We were delighted when the reaction was run with *m*CPBA at 60 °C in chloroform. In this case, the desired bicyclic lactam **549** was isolated in 70% yield, together with traces of unreacted starting material **550**. Unfortunately, this reaction could not be repeated to reproduce the successful result and for the most part, no reaction was seen to occur at all.

Out of interest, to determine the effect of the double bond on the success of the reaction, the double bond of **550** was hydrogenated using palladium on activated carbon to generate **552** in 70% yield (Scheme 185). Regrettably, time constraints meant that only one attempt was made at the rearrangement to form **553** and it was disappointing to see no observed reaction and the starting material was recovered.



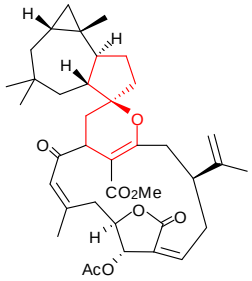
550 **552** **553**

Scheme 185: Attempted Rearrangement of 662. Reagents and Conditions: (a) H_2, Pd/C, MeOH, 35 min, rt, 70%; (b) *m*CPBA, $CHCl_3$.

5.5 Efforts Towards the Synthesis of the Spirocyclic Core of Polymaxenolide

5.5.1 Retrosynthetic Analysis

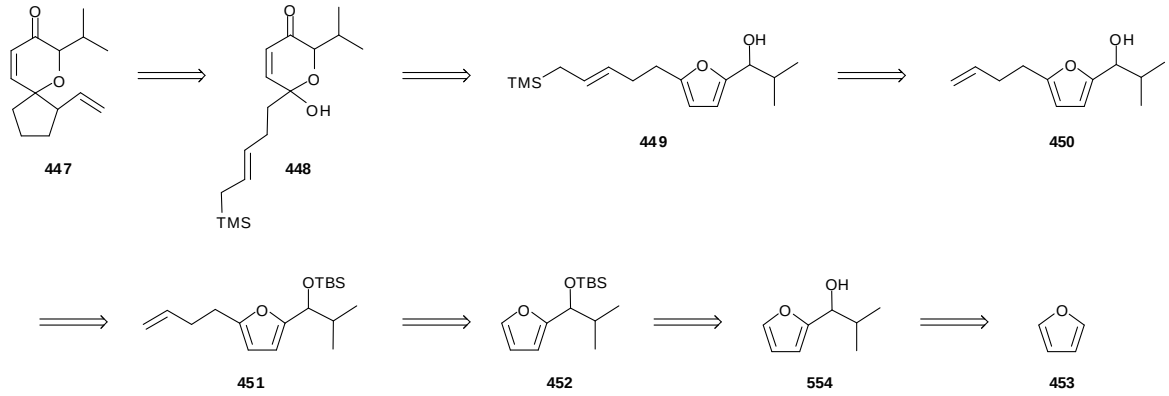
As a result of our continued interest in the synthesis of the spirocyclic cores of natural products, we believed that we could utilise our learned knowledge and apply it further. Drawing from our synthetic experience thus far, we wanted to establish a route to the spirocyclic unit of polymaxenolide **446** (Figure 36), a route that would incorporate the Achmatowicz rearrangement.



446

Figure 36: Structure of Polymaxenolide 446. The spirocyclic unit is highlighted in red.

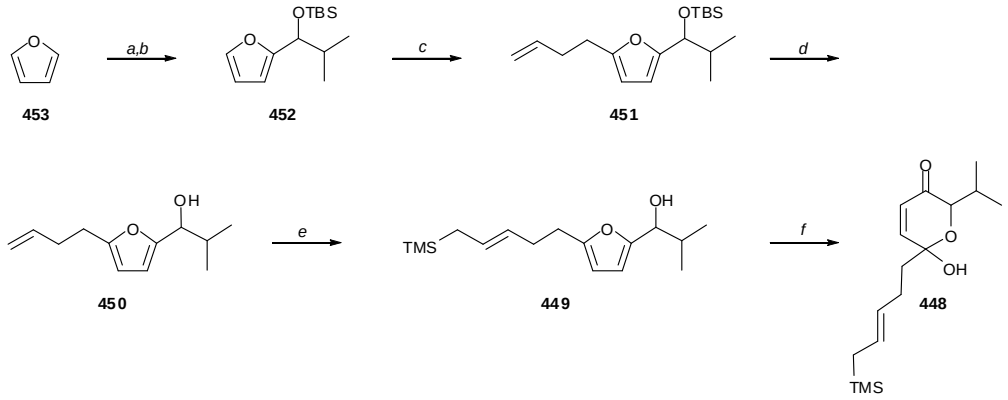
It was visualised that the spirocyclic unit **447** could be the product of Lewis acid-mediated ring-closing of **448**, itself a product of the Achmatowicz rearrangement of **449** (Scheme 186). Grubbs-mediated cross-metathesis of alcohol **450** with allyltrimethylsilane could afford **449**, with the alcohol a result of the silyl group removal in **451**. The C_5 addition of an alkenyl chain of varying length to **452** gives **451**, while **452** is prepared from the addition of *iso*butyraldehyde to furan **453**, followed by silyl protection.



Scheme 186: Retrosynthetic Analysis to 447.

5.5.2 Initial Synthetic Investigations

The synthesis began with 2-lithiofuran which was trapped with *iso*butyraldehyde to generate the furfuryl alcohol **554** in 96% yield. Alcohol **554** was then protected as its corresponding TBS ether to give the desired protected compound **452** in 84% yield.



Scheme 187: Synthesis of Spirocyclic Compound 448. Reagents and Conditions: (a) *n*BuLi, TMEDA, *iso*butyraldehyde, 0 °C → –78 °C, 3 h, 96%; (b) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 16 h, 84%; (c) *n*BuLi, 4-bromo-1-butene, 0 °C → rt, 16 h, 91%; (d) TBAF, THF, 0 °C → rt, 19 h, 81%; (e) allyltrimethylsilane, Grubbs second generation catalyst, reflux, 48 h, 52%; (f) $VO(acac)_2$, TBHP, CH_2Cl_2, 0 °C, 2 h, 9 %.

Deprotonation of **452** at C_5 with *n*BuLi, followed by the addition of 4-bromo-1-butene enabled the formation of **451** in excellent yield. Removal of the silyl protection group with TBAF then afforded the corresponding secondary alcohol **450** in 81% yield. Cross-metathesis of alkene **450** with allyltrimethylsilane in the presence of Grubbs second generation catalyst[214] converted the terminal double bond into the allylsilane **449** in 52% yield (Entry 2, Table 4). ^1H NMR analysis showed that **449** was formed as an inseparable mixture of *E*:*Z*-isomers (6.15:1). The remainder of the yield can be attributed to the formation of the homodimer. Efforts to improve the yield of the cross-metathesis reaction using alternative catalysts concluded in mixed results (Table 4).

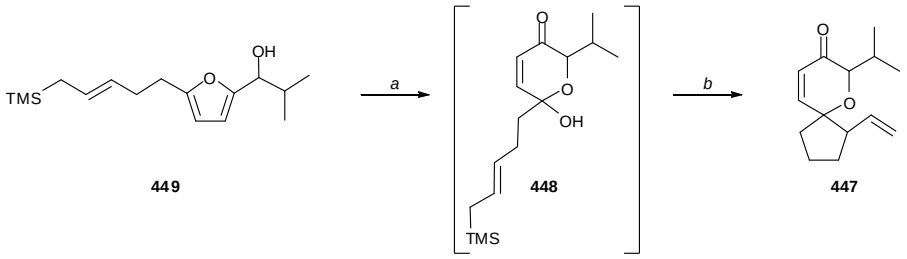
Entry	Catalyst	Conditions	Result
1	Grubbs 1st Gen. (5 mol%)	Allyl TMS (3 eq.) CH_2Cl_2, reflux, 48 h	43%
2	Grubbs 2nd Gen. (5 mol%)	Allyl TMS (3 eq.) CH_2Cl_2, reflux, 48 h	52%
3	Hoveyda-Grubbs 2nd Gen. (5 mol%)	Allyl TMS (3 eq.) CH_2Cl_2, reflux, 48 h	27%

Table 4: Cross-Metathesis of 450 with Allyltrimethylsilane.

The Achmatowicz rearrangement of alkene **449** was initially attempted with the addition of *m*CPBA in two portions. Initially, the TLC of the reaction mixture gave cause to be optimistic about the success of the reaction, with the appearance of a major new spot thought to be the desired rearranged product. However, after work-up a second precautionary TLC showed the appearance of additional spots, bringing the total number to seven spots, with one being a

trace amount of remaining starting material. The spot thought to be the product was still the major spot and FCC was performed to isolate as many as possible. Unfortunately, even though the isolation was successful, ^{1}H NMR spectroscopy showed a compound that had clearly degraded. As an alternative oxidising agent, $VO(acac)_2$[208] was used and this proved to be a significant improvement. TLC anlaysis showed a clean, spot to spot conversion with the only other spot being a faint showing at the baseline. FCC of the residue afforded the desired product **448** in 9% yield. It was postulated that degradation may be occurring on the silica column, therefore the feasibility of a one-pot, two-step procedure was investigated.

It was known from TLC analysis that the rearrangement product **448** was being formed cleanly as the major product. It was tentatively thought that filtering the reaction through Celite® would not greatly affect the compound. Therefore, a second method was tried in which **448** was not purified but used immediately in the second cyclisation procedure (Scheme 188). With the knowledge that $VO(acac)_2$ was the superior oxidising agent for the Achmatowicz rearrangement, the same procedure was carried out as described above. The reaction was filtered through Celite® and the solvent was concentrated to approximately 1 cm^3 and then fresh, anhydrous CH_2Cl_2 added and the solution cooled to −78 °C. The BF_3 complex, $BF_3{\cdot}OEt_2$, was slowly added and then the stirring continued for 30 minutes at −78 °C. Disappointingly, the yield was very low (~1%) and only ^{1}H NMR spectroscopy was able to be performed on such a small amount. Despite this, we believe that the desired product was indeed formed and isolated.

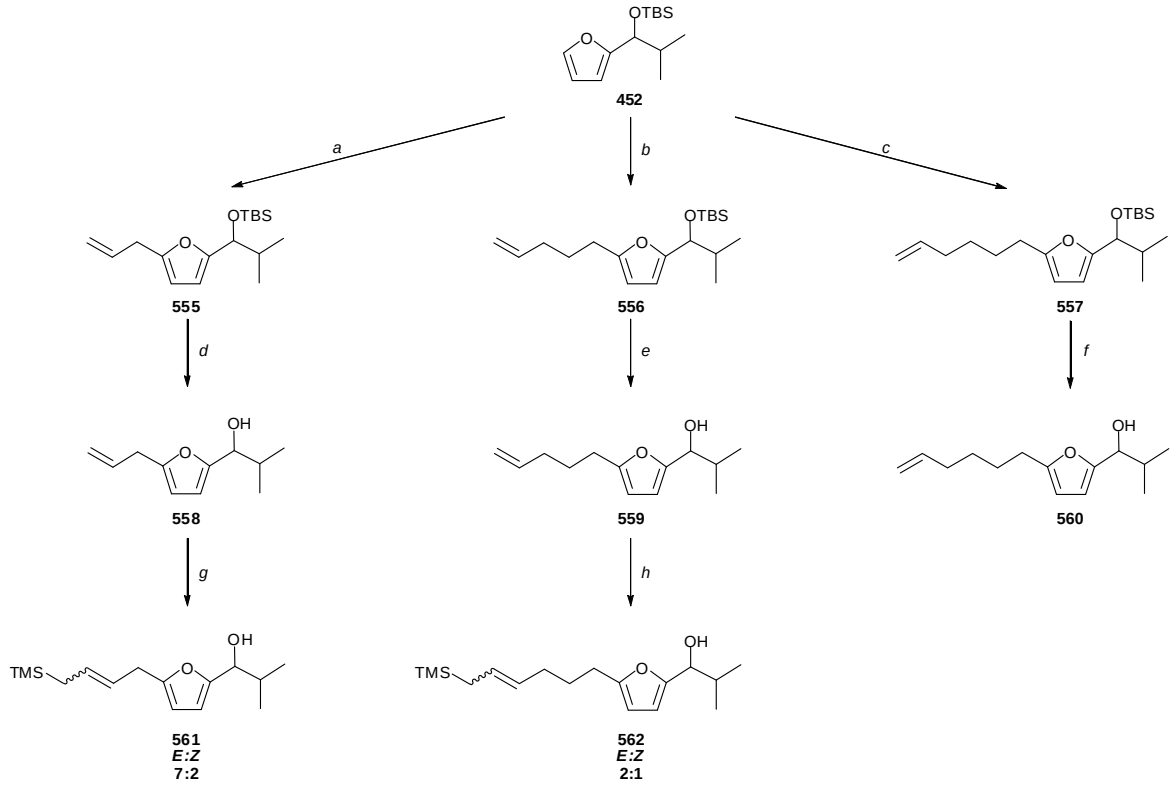


Scheme 188: One-pot, two-step Procedure. Reagents and Conditions: (a) $VO(acac)_2$, TBHP, CH_2Cl_2, 0 °C, 2 h, 9 %; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 30 min, ~1%.

Due to time restraints this method was only carried out once, but we believe that we have identified a novel route to the spirocyclic structure of polymaxenolide **447**, incorporating the Achmatowicz rearrangement as the key

step. In addition we consider the one-pot method to be the correct reaction for the transformations and reason that further investigation will optimise the yield.

In addition to carrying out the above investigation into the synthesis of the spirocyclic core of polymaxenolide, we simultaneously began the synthesis of the additional units that would be needed. In readiness for the synthesis of spirocyclic core units with different ring sizes the appropriate compounds were prepared as shown below in Scheme 189, with no difficulties encountered. Once again, an inseparable *E*:*Z*-mixture of isomers of allylsilanes **561** and **562** was obtained.



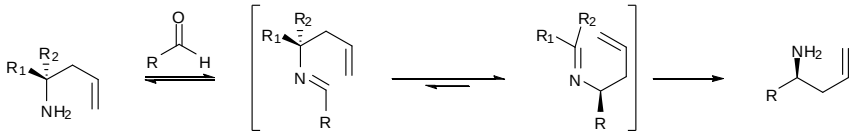
Scheme 189: Synthesis of Compounds with Different C_5 Substitution. Reagents and Conditions: (a) *n*BuLi, allyl bromide, THF, 0 °C → rt, 16 h, 92%; (b) *n*BuLi, 5-bromo-1-pentene, THF, 0 °C → rt, 16 h, 86%; (c) *n*BuLi, 6-bromo-1-hexene, THF, 0 °C → rt, 16 h, 100%; (d) TBAF, THF, 0 °C → rt, 19 h, 87%; (e) TBAF, THF, 0 °C → rt, 19 h, 81%; (f) TBAF, THF, 0 °C → rt, 19 h, 80%; (g) Grubbs second generation catalyst, allyl TMS, CH_2Cl_2, reflux, 48 h, 36%; (h) Grubbs second generation catalyst, allyl TMS, CH_2Cl_2, reflux, 48 h, 45%.

We are encouraged by all of the progress that has been made in the three areas of our interest in spirocyclic piperidines and pyrans, but realise that further investigation is necessary in each area in order to progress further. This will mostly involve the testing of new reagents and optimisation of reaction conditions.

5.6 Future Work

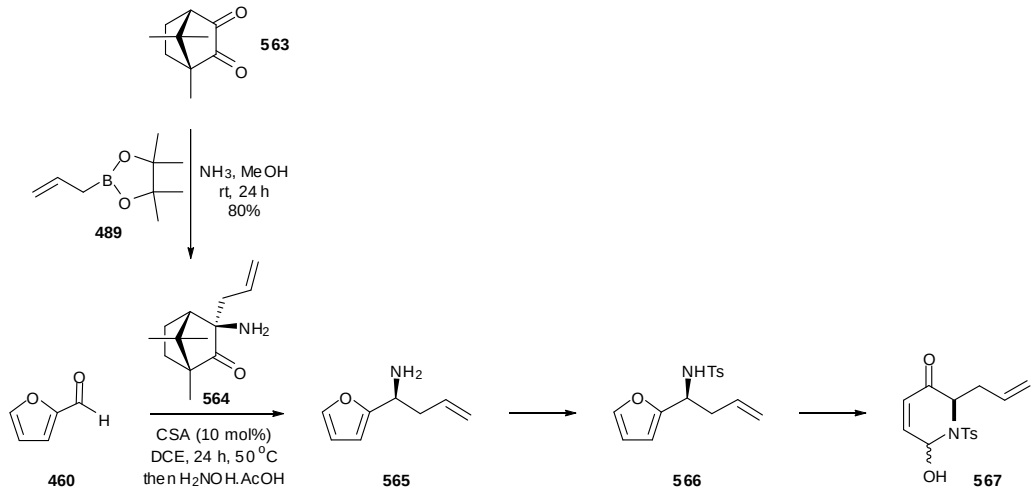
5.6.1 Enantioselective α-Aminoallylation

The enantioselective synthesis of homoallylic primary amines has been reported.[202] The synthesis is based on asymmetric 2-azonia-Cope rearrangement (Scheme 190). The authors term this transfer aminoallylation as "both the amino and the allyl groups are incorporated into the product".



Scheme 190: Transfer Aminoallylation.

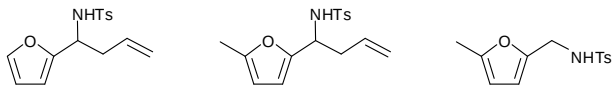
α-Aminoketone **564** was readily synthesised from (1*R*)-camphorquinone **563** in 80%, with >99% *d.e.* and then used for the transfer aminoallylation of 2-furaldehyde (Scheme 191).[202] The desired optically active amine was obtained in 60% yield and 97% *e.e.*. It would be interesting to carry out this transfer aminoallylation on 2-furaldehyde to obtain the primary amine **565**, which after mono-tosylation (→**566**) could be subjected to the *aza*-Achmatowicz rearrangement. This would generate lactone **567**.



Scheme 191: Synthesis of α-Aminoketone 564 and Transfer Aminoallylation of 2-Furaldehyde.

5.6.2 Pinnaic Acid

It has been determined in the studies described that the *aza*-Achmatowicz rearrangement is highly successful for compounds that have either no substitution or methyl substitution at position C_5. This holds true for tosyl (or Boc) protected compounds with a terminal olefin, produced as a result of an α-aminoallylation reaction, or for the simpler tosyl protected amine (Figure 37).



492 541 535

Figure 37: C_5 Substitution Enabling a Successful *aza*-Achmatowicz Rearrangement.

For clarification it is vital that the rearrangement of **514** is further investigated. From experience in trying various conditions for a variety of rearrangements, there is the belief that from the analysis of TLC's of various reactions, the rearrangement may be occurring and it is the work-up that is causing the product to be destroyed. Another possibility is that the product is extremely unstable and begins to decompose before it can be properly identified. In the future the solvent should not be evaporated to dryness unless the compound is stable. It was thought that **515** would be stable due to the hemiaminal being substituted. It is also possible that the residue may be undergoing rapid decomposition due to the peroxide reacting further with the hemiaminal.

Therefore, a sensible course of action would be to fully and rigorously investigate this particular reaction. This would involve complete examination of:

Reagents - with care taken to distill/purify any commercial reagents before use

Equivalents – trialling a range of equivalents from small to large, adding equivalents in one portion and/or portionwise

Temperature – adding reagents at a temperature lower/higher than room temperature, changing temperature throughout the course of the reaction, heating for prolonged period

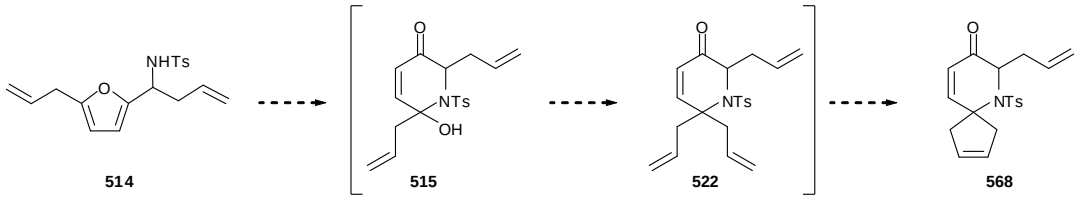
Time – allowing a reaction to run its course to allow full consumption of starting material, seemingly dormant reactions should be left for prolonged periods to ensure that they are not just slow running. Particular care and attention must be made to TLC analysis must be made in these cases.

Following oxidative rearrangement it would be necessary to either:

Perform work-up - followed by reduction of the reaction solvent to ~1 cm^3 and then carry out the Lewis acid mediated addition of allyltrimethylsilane to generate **522**. The first wash after this reaction would be a sat. aq. $NaHCO_3/NaSO_3$ to remove any residual peroxide.

Not perform work-up - followed by reduction of the reaction solvent to ~1 cm^3 and then carry out the Lewis acid mediated addition of allyltrimethylsilane. The first wash after this reaction would be a sat. aq. $NaHCO_3/NaSO_3$ to remove any residual peroxide.

If may also be necessary to perform the ring-closing metathesis immediately after the Lewis acid mediated addition, with careful work-up and no column purification (Scheme 192). If successful, the procedure could be applied to compounds with longer substitution at C_5, in order to generate larger ring sizes. Appropriate functionalisation could then take place utilising the terminal olefin.



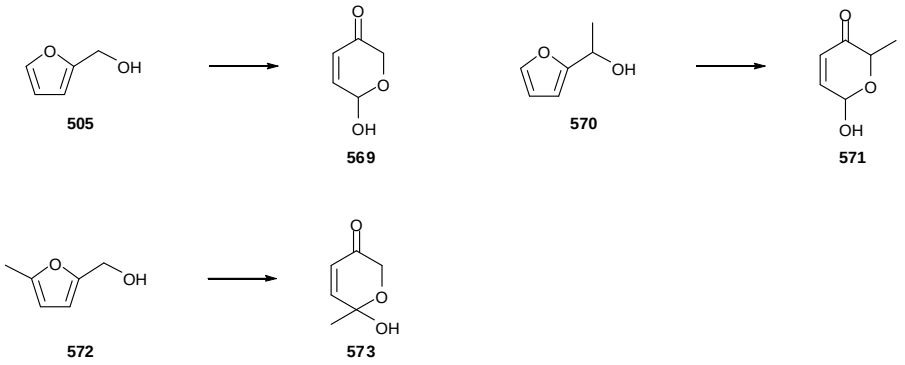
514 515 522 568

Scheme 192: Proposed Three-Step Procedure to 568.

5.6.3 Halichlorine

It is difficult to know how to progress with this area in as much as the conditions which worked once do not enable a repeat result. A possibility is to investigate an alternative oxidising agent such as dimethyldioxirane (DMDO), which should be more reactive than *m*CPBA. DMDO is easily generated[215] and used as a solution in acetone, with the products being only the oxidised compound and acetone. In 1991, Adger and colleagues reported their use of DMDO for the

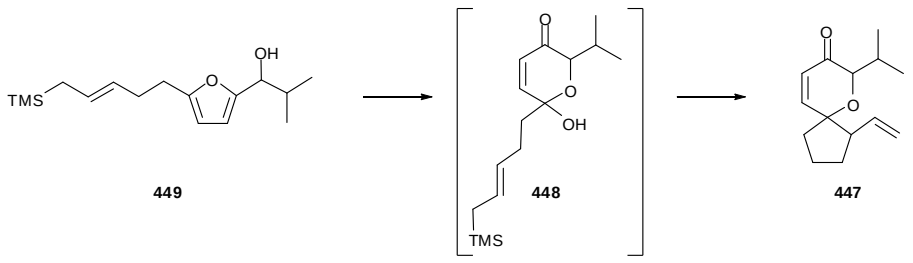
oxidation of furans.[216] With 1 equivalent of DMDO in acetone at room temperature they were able to successfully oxidise furfuryl alcohol **505** to 2*H*-pyran-3(6*H*)-one **569** and the substituted furfuryl alcohols **570** and **572** to their corresponding pyranones **571** and **573** respectively. No mention of yields is made in the publication.



Scheme 193: Oxidation of Furfuryl Alcohol with DMDO. Reagents and Conditions: DMDO (1 eq.) in acetone (0.05 mol dm^{-3}), acetone, rt.

5.6.4 Polymaxenolide

There is a desire to further develop the one-pot, two-step reaction sequence in order to generate the bicyclic core **447** in higher yield (Scheme 194). Although it has been shown that the Lewis acid, $BF_3{\cdot}OEt_2$ is effective to promote the cyclisation, there is a wish to perform a Lewis acid screen to test the effectiveness of other Lewis acids beginning with: $EtAlCl_2$, Et_2AlCl, $SnCl_4$, $TiCl_3(O^iPr)$, $TiCl_2(O^iPr)_2$ and $TiCl(O^iPr)_3$. In addition there would be an investigation into the effect of temperature on the reaction.



Scheme 194: Generation of 447.

6 Experimental

6.1 General Methods

All reactions were performed under an inert argon atmosphere unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used as received, unless otherwise specified.

Anhydrous dichloromethane (DCM), diethyl ether, toluene and tetrahydrofuran (THF) were freshly obtained from in-house solvent purification system, Pure Solv 400-5MD (Innovative Technology, Inc). Anhydrous dimethylformamide (DMF) and triethylamine (TEA) were purchased from Aldrich Chemical Company. Petroleum ether refers to that with boiling fraction 40–60 °C. Solutions worked up were concentrated under reduced pressure at < 45 °C using a Buchi Rotavapor.

Melting points were determined using Stuart Scientific Melting Point SMP1 apparatus.

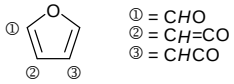
Optical rotations were determined as solutions irradiating with the sodium D line (λ = 598 nm) using an AA series automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Infrared (IR) spectra were recorded as thin films on sodium chloride (NaCl) plates using a JASCO FTIR 410 spectrometer. Only significant absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Proton magnetic resonance spectra (^1H NMR) were recorded at 400 MHz using a Bruker DPX-400 spectrometer for sample solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration) (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext. = sextet, oct. = octet, m = multiplet, br = broad) (3) coupling constant (*J*) quoted in Hertz to the nearest 0.1 Hz and (4) proton assignment. For relevant compounds, the OH signal was identified by D_2O exchange.

Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz using a Bruker DPX-400 spectrometer for sample solutions in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the residual solvent peak.

For convenient ^{1}H and ^{13}C NMR spectroscopy characterisation, furanyl compounds have been labelled as shown below:



Mass spectra were obtained using a JEOL JMS-700 spectrometer.

TLC was performed on aluminium backed plates pre-coated with silica gel 60 (Kieselgel 60 F_{254} aluminium plates, Merck) with *A*, petroleum ether-ethyl acetate (8:2); *B*, petroleum ether-ethyl acetate (7:3); *C*, petroleum ether-ethyl acetate (6:4); *D*, petroleum ether-ethyl acetate (9:1); *E*, petroleum ether-ethyl acetate (9.5:0.5); *F*, petroleum ether-diethyl ether (9.5:0.5); *G*, toluene-ethyl acetate (8:2); *H*, petroleum ether-ethyl acetate (2:8); *I*, petroleum ether-ethyl acetate (5:5); *J*, petroleum ether-ethyl acetate (3:7); *K*, chloroform-ethyl acetate (6:4); *L*, petroleum ether (10:0); *M*, petroleum ether-ethyl acetate (4:6); *N*, petroleum ether-diethyl ether (7:3); *O*, petroleum ether-ethyl acetate (2:8); *P*, petroleum ether-diethyl ether (9:1); *Q*, hexanes (10:0); *R*, petroleum ether-diethyl ether (8:2); *S*, petroleum ether-diethyl ether (5:5) as developers and detection under UV light (λ_{max} 254 nm) and/or by staining with anisaldehyde, unless otherwise specified, followed by heating.

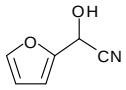
Flash column chromatography (FCC) was performed using Apollo Scientific silica gel 60 (0.040-0.063 mm), with the appropriate eluting solvent and elution gradient, shown in square brackets as part of the procedure, e.g. *purification by FCC [petroleum ether-ethyl acetate (85:15)→(75:25)→(60:40)→(50:50)] of the crude residue....*

The following chemicals were used at the concentrations given, unless otherwise stated:

- *tetra*-Butylammonium fluoride (TBAF), 1 M in tetrahydrofuran
- Oxalyl chloride, 2 M in dichloromethane
- Ethyl Magnesium Bromide (EtMgBr), 3 M in diethyl ether
- Potassium *bis*(trimethylsilyl)amide (KHMDS), 0.5 M in toluene
- *n*-Butyllithium (*n*BuLi), 2.5 M in hexanes.

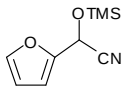
6.2 Synthesis and Characterisation of Compounds

Furan-2-yl-hydroxy-acetonitrile 477[217]



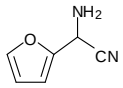
A mixture of 2-furaldehyde (1.00 g, 10.4 mmol) and 10% aqueous $NaHSO_3$ (15.6 cm^3) was stirred in diethyl ether at 0 °C for 1 h. 20% aqueous sodium cyanide (4.16 cm^3) was added and stirring continued, allowing the reaction to warm to room temperature over 2.5 h. The reaction was diluted with ethyl acetate (30 cm^3) and water (30 cm^3) was added. The phases were separated and the aqueous layer extracted with ethyl acetate (3×20 cm^3). The combined organic extracts were washed with brine (30 cm^3), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (80:20)→(70:30)→(60:40)] of the crude residue gave cyanohydrin **477** (1.20 g, 94%) as a thick brown oil; R_f 0.71 (solvent *C*); ν_{max}(film)/cm^{-1} 3360 (OH) and 2252 (C≡N); δ_H(400 MHz; $CDCl_3$) 5.21 (1 H, s, C*H*CN), 6.30 (1 H, dd, *J* 1.9 and 3.3, C*H*=CO), 6.48 (1 H, d, *J* 3.3, C*H*CO) and 7.40 (1 H, d, *J* 1.9, C*H*O). The spectral data matches that reported in the literature.[217]

Furan-2-yl-trimethylsilanyloxy-acetonitrile 476[198]



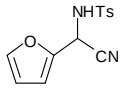
A stirred solution of 2-furaldehyde (2.00 g, 20.8 mmol) in triethylamine (1.45 cm^3, 10.4 mmol) at room temperature was treated by the careful dropwise addition of trimethylsilylcyanide (2.86 cm^3, 22.8 mmol). The reaction mixture was kept at room temperature for 1.5 h and the triethylamine was then evaporated under vacuum to afford TMS ether **476** (4.00 g, 99%) as a thick brown oil, with no need for further purification; R_f 0.82 (solvent *A*, PMBA); ν_{max}(film)/cm^{-1} 2960, 1669 (C=C) and 1394; δ_H(400 MHz; $CDCl_3$) 0.00 (9 H, s, 3×CH_3), 5.35 (1 H, s, C*H*CN), 6.20 (1 H, dd, *J* 1.9 and 3.3, C*H*=CO), 6.35 (1 H, d, *J* 3.3, C*H*CO) and 7.25 (1 H, d, *J* 1.9, C*H*O); δ_C(125 MHz; $CDCl_3$) 57.0 (*C*HCN), 108.8 (*C*HCO), 109.7 (*C*H=CO), 116.9 (CN), 142.7 (CHO) and 147.4 (CO); MS (EI) *m*/*z* 68.0 [M-C_5H_9ONSi]$^+$, 106.0 [M-C_3H_9OSi]$^+$, 180.0 [M-N]$^+$; HRMS *m*/*z* 195.0715 (195.0716 calcd for $C_9H_{13}O_2NSi$, M^+). The spectral data matches that reported in the literature.[198]

Amino-furan-2-yl-acetonitrile 475



Silyl ether **476** (1.50 g, 7.68 mmol) was dissolved in 2 M ammonia in ethanol (4.6 cm^3, 9.22 mmol) at room temperature and the reaction mixture was stirred at 40 ^oC for 2 h. The reaction was quenched with $CHCl_3$ (75 cm^3) and water (75 cm^3). The phases were separated and the organic layer was acidified with 1 M hydrochloric acid (50 cm^3). To the acid layer 2 M sodium hydroxide (200 cm^3) was added, followed by extraction with chloroform (3×75 cm^3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give amine **475** (0.58 g, 61%) as a thick brown oil, with no need for further purification; R_f 0.12 (solvent *B*); δ_H(400 MHz; $CDCl_3$) 1.95 (2 H, br s, NH_2), 4.90 (1 H, s, C*H*CN), 6.30 (1 H, dd, *J* 1.9 and 3.3, C*H*=CO), 6.40 (1 H, d, *J* 3.3, C*H*CO) and 7.40 (1 H, d, *J* 1.9, C*H*O).

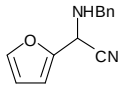
***N*-(Cyano-furan-2-yl-methyl)-4-methyl-benzenesulfonamide 485**[218]



A solution of amine **475** (50 mg, 0.387 mmol) in anhydrous CH_2Cl_2 (7 cm^3) at 0 ^oC, was treated with triethylamine (0.08 cm^3, 0.580 mmol), dimethylaminopyridine (14 mg, 0.116 mmol) and *p*-toluenesulfonyl chloride (111 mg, 0.580 mmol) successively. The reaction mixture was warmed to room temperature and stirred for 18 h, after which further portions of dimethylaminopyridine were added (0.116 mmol then 0.058 mmol) due to the slow progress of the reaction. The reaction was diluted with diethyl ether (10 cm^3) and the organic layer was washed sequentially with water (10 cm^3), saturated aqueous sodium hydrogen carbonate (10 cm^3) and dried over anhydrous sodium sulfate. The solution was filtered and concentrated *in vacuo* to give a crude residue which was purified by FCC [petroleum ether-ethyl acetate, (80:20)] to give tosylamine compound **485** (14 mg, 12%) together with a non-separable impurity. NMR spectrum shows required product plus impurity); R_f 0.44 (solvent *C*); δ_H(400 MHz; $CDCl_3$) 1.60 (1 H, br s, N*H*), 2.44 (3 H, s, CH_3), 5.23 (1 H, s, C*H*CN), 6.52 (1 H, dd, *J* 1.8 and 3.4, C*H*=CO), 6.82 (1 H, dd, *J* 0.7 and 3.4, C*H*CO), 7.32 (2 H, d, *J* 8.4, 2×CH), 7.53 (1 H, dd, *J* 0.7 and 1.8, C*H*O) and

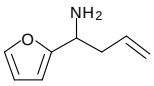
7.81 (2 H, d, *J* 8.4, 2×CH). The spectral data matches that reported in the literature.[218]

Benzylamino-furan-2-yl-acetonitrile 486



A solution of amine **475** (165 mg, 1.35 mmol) in anhydrous dichloromethane (7 cm^3) was cooled to 0 °C and treated with triethylamine (0.41 cm^3, 2.97 mmol) and dimethylaminopyridine (99 mg, 0.811 mmol). The reaction was stirred at 0 °C for 10 min before the addition of benzyl bromide (0.18 cm^3, 1.49 mmol). The solution was kept at 0 °C for 20 min and then was allowed to warm up to room temperature. The reaction was stirred for 16 h and then was diluted with dichloromethane (20 cm^3). The layers were separated and the organic layer was washed sequentially with water (2×20 cm^3), saturated aqueous sodium hydrogen carbonate (2×20 cm^3), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the crude residue by FCC [petroleum ether-ethyl acetate, (90:10)→(85:15)] gave the benzyl protected amine **486** (76 mg, 27%); ν_{max}(film)/cm^{-1} 2245 (C≡N), 1608 (C=C) and 1595; δ_H(400 MHz; $CDCl_3$) 3.50 (2 H, s, CH_2), 5.02 (1 H, s, C*H*), 6.18 (1 H, dd, *J* 1.6 and 3.2, C*H*=CO), 6.30 (1 H, dd, *J* 0.7 and 3.2, C*H*CO), 7.17-7.35 (5 H, m, ArC*H*) and 7.60 (1 H, dd, *J* 0.7 and 1.6, C*H*O); δ_C(100 MHz; $CDCl_3$) 45.0 (*C*H_2), 49.8 (*C*H), 106.4 (Ar*C*H), 111.1 (Ar*C*H), 118.2 (*C*≡N), 127.1 (Ph*p*CH), 127.5 (2×Ph*C*H), 128.2 (2×Ph*C*H), 141.9 (CH_2*C*), 139.0 (Ar*C*H) and 152.2 (O*C*); MS (EI) *m*/*z* 213 $[M+H]^+$; HRMS *m*/*z* 213.1031 (213.1028 calcd for $C_{13}H_{13}N_2O$, $M+H^+$).

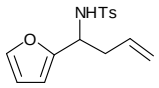
1-Furan-2-yl-but-3-enylamine 490[202]



A mixture of allylboronate pinacol ester (1.17 cm^3, 6.24 mmol) and dodecylbenzenesulfonic acid (0.17 cm^3, 0.520 mmol) in 25 wt% aqueous ammonia (10.4 cm^3) was stirred at room temperature for 30 min. To this suspension was added 2-furaldehyde (0.43 cm^3, 5.20 mmol) and the reaction mixture was stirred vigorously at room temperature for 2 h. The reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichloromethane (3×50 cm^3). The combined organic phases were dried over

anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the crude alcohol **491** (14.4 mg, 2%); R_f 0.59 (solvent *B*). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×50 cm^3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield amine **490** (392 mg, 55%) as an orange oil, with no need for further purification; R_f 0.21 (solvent *B*); ν_{max}(film)/cm^{-1} 2917, 1640 (C=C), 1438 and 1148; δ_H(400 MHz; $CDCl_3$) 1.80 (2 H, br s, NH_2), 2.20-2.30 (1 H, m, CH_2), 2.40-2.50 (1 H, m, CH_2), 3.85 (1 H, dd, *J* 5.9 and 7.2, C*H*N), 4.90-5.05 (2 H, m, CH=CH_2), 5.55-5.70 (1 H, m, C*H*=CH_2), 6.0 (1 H, dd, *J* 0.9 and 3.2, C*H*=CO), 6.15 (1 H, d, *J* 3.2, C*H*CO) and 7.20 (1 H, d, *J* 0.9, C*H*O); δ_C(100 MHz; $CDCl_3$) 40.9 (*C*H_2), 49.2 (*C*HNH_2), 104.4 (*C*H=CO), 110.0 (*C*HCO), 118.0 (HC=*C*H_2), 134.7 (H*C*=CH_2), 141.3 (*C*CHN) and 158.5 (*C*HO); MS (CI) *m*/*z* 96.97 $[M\text{-}CH_2CH{=}CH_2]^+$, 138.11 $[M+H]^+$; HRMS *m*/*z* 138.0917 (138.0920 calcd for $C_8H_{12}NO$, $M+H^+$).

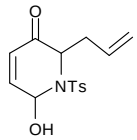
_N_-(1-Furan-2-yl-but-3-enyl)-4-methyl-benzenesulfonamide 492[219]



To a solution of allylic amine **490** (100 mg, 0.729 mmol) in anhydrous dichloromethane (7 cm^3) at 0 °C was added triethylamine (0.22 cm^3, 1.60 mmol), dimethylaminopyridine (53 mg, 0.437 mmol) and tosyl chloride (210 mg, 1.09 mmol). The reaction mixture was stirred at 0 °C for 30 min, then allowed to warm to room temperature and was then stirred for a further 18 h. The reaction was diluted with diethyl ether (20 cm^3) and the layers were separated. The organic phase was washed with water (2×20 cm^3) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm^3). The solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford tosylamine **492** (212 mg, 100%) as a brown crystalline solid with no need for further purification; R_f 0.64 (solvent *C*); mp 83-85 °C (from diethyl ether) (lit.,[219] 86.6-88.6 °C); ν_{max}(film)/cm^{-1} 3272, 1642 (C=C), 1430, 1328, 1158 and 1092; δ_H(400 MHz; $CDCl_3$) 2.22 (3 H, s, CH_3), 2.28-2.43 (2 H, m, CH_2), 4.50 (1 H, q, *J* 6.8, C*H*N), 5.02-5.07 (2 H, m, CH=CH_2), 5.53-5.58 (1 H, m, C*H*=CH_2), 5.97 (1 H, d, *J* 3.2, C*H*CO), 6.15 (1 H, dd, *J* 2.0 and 3.2, C*H*=CO), 7.17 (1 H, dd, *J* 0.4 and 2.0, C*H*O), 7.21 (2 H, d, *J* 8.4, 2×C*H*) and 7.63 (2 H, d, *J* 8.4, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.5 (*C*H_3), 39.0 (*C*H_2), 50.9 (*C*HN), 107.1 (*C*H=CO), 110.0 (*C*HCO), 119.3 (CH=*C*H_2), 127.0 (*C*H),

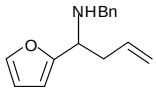
129.4 (*C*H), 132.6 (*C*H=CH_2), 137.5 (*C*CHN), 141.9 (*C*HO), 143.1 (*C*) and 152.8 (*C*); MS (FAB) *m*/*z* 292.2 $[M+H]^+$; HRMS *m*/*z* 292.1004 (292.1007 calcd for $C_{15}H_{18}NO_3S$, $M+H^+$). Spectral data matches that reported in the literature.[219]

2-Allyl-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one 493

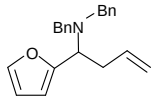


Homoallylic amine **492** (100 mg, 0.343 mmol) was dissolved in dry dichloromethane (1.7 cm^3) and cooled to 0 °C before being treated with *meta*-chloroperoxybenzoic acid (*m*CPBA) (84.4 mg, 0.489 mmol). The reaction was stirred at 0 °C for 30 min and then allowed to warm to room temperature where it was stirred for 18 h. The reaction was quenched by stirring with saturated aqueous sodium hydrogen carbonate (10 cm^3) for 1 h and was then diluted with dichloromethane (10 cm^3). The layers were separated and the organic phase was washed with saturated aqueous sodium hydrogen carbonate (2×10 cm^3), water (2×10 cm^3) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and FCC of the crude residue [petroleum ether-ethyl acetate, (80:20)→(70:30)→(65:35)] afforded hemi-aminal **493** (50.2 mg, 48%; 59% based on starting material consumed) as a yellow oil; R_f 0.39 (solvent *C*); ν_{max}(film)/cm^{-1} 3460 (OH), 2926, 1687, 1332, 1161, 1033 and 729; δ_H(400 MHz; $CDCl_3$) 2.30 (3 H, s, C*H*$_3$), 2.51-2.60 (1 H, m, C*H*$_2$), 2.66-2.75 (1 H, m, C*H*$_2$), 3.40 (1 H, d, *J* 4.5, OH), 4.35 (1 H, t, *J* 7.4, C*H*(N)), 5.00-5.10 (2 H, m, CH=C*H*$_2$), 5.71-5.82 (1 H, m, C*H*=CH_2), 5.77 (1 H, s, C*H*(OH)), 5.88 (1 H, dd, *J* 1.2 and 10.4, CH=C*H*), 6.70 (1 H, dd, *J* 4.4 and 10.4, C*H*=CH), 7.20 (2 H, d, *J* 6.6, 2×C*H*) and 7.50 (2 H, d, *J* 6.6, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.5 (*C*H_3), 40.0 (*C*H_2), 61.0 (*C*H(N)), 73.4 (*C*H(OH)), 118.9 (CH=*C*H_2), 126.7 (2×*C*H), 126.8 (CH=*C*H), 130.1 (2×*C*H), 133.2 (*C*H=CH_2), 136.6 (*C*), 143.0 (*C*H=CH), 144.3 (*C*) and 193.6 (*C*=O); MS (CI) *m*/*z* 290.3 $[M-OH]^+$, 308.3 $[M+H]^+$; HRMS *m*/*z* 308.0959 (308.0956 calcd for $C_{15}H_{18}NO_4S$, $M+H^+$).

Benzyl-(1-furan-2-yl-but-3-enyl)-amine 494[220]

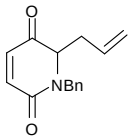


A mixture of homoallylic amine **490** (100 mg, 0.728 mmol), dimethylaminopyridine (53.4 mg, 0.437 mmol) and triethylamine (0.32 cm^3, 2.33 mmol) in anhydrous dichloromethane (7 cm^3) was stirred at 0 °C for 30 min before being treated with benzyl bromide (0.13 cm^3, 1.12 mmol). The reaction mixture was then allowed to warm to room temperature and was stirred for a further 18 h. The reaction was quenched with water (10 cm^3). The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)] of the crude residue afforded benzyl amine **494** (71 mg, 43%); R_f 0.57 (solvent *B*); ν_{max}(film)/cm^{-1} 908 and 734; δ_H(400 MHz; $CDCl_3$) 1.65 (1 H, br s, N*H*), 2.42-2.50 (2 H, m, CH_2), 3.52 (2 H, d, *J* 13.2, CH_2Ph), 3.66-3.69 (1 H, m, C*H*N), 4.92-5.04 (2 H, m, CH=CH_2), 5.57-5.70 (1 H, m, C*H*=CH_2), 6.09 (1 H, d, *J* 3.1, C*H*=CO), 6.24 (1 H, dd, *J* 1.8 and 3.1, C*H*CO), 7.11-7.25 (5 H, m, Ph) and 7.31 (1 H, dd, *J* 0.5 and 1.8, C*H*O); MS (CI) *m*/*z* 228.20 $[M+H]^+$; HRMS *m*/*z* 228.1394 (228.1389 calcd for $C_{15}H_{18}NO$, $M+H^+$). Spectral data matches that reported in the literature.[220]



The di-protected compound **495** was also isolated (16 mg, 10%); R_f 0.83 (solvent *B*); δ_H(400 MHz; $CDCl_3$) 2.47-2.52 (1 H, m, CH_2), 2.50-2.55 (1 H, m, CH_2), 3.01 (2 H, d, *J* 13.9, CH_2Ph), 3.55-3.59 (3 H, m, C*H*N and CH_2Ph), 4.88-4.97 (2 H, m, CH=CH_2), 5.60-5.73 (1 H, m, C*H*=CH_2), 6.07 (1 H, d, *J* 3.1, C*H*=CO), 6.30 (1 H, dd, *J* 1.9 and 3.1, C*H*CO), 7.40 (1 H, d, *J* 1.9, C*H*O) and 7.01-7.35 (10 H, m, 2×Ph).

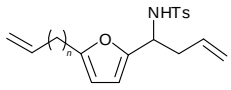
6-Allyl-1-benzyl-1,6-dihydropyridine-2,5-dione 496



meta-Chloroperoxybenzoic acid (*m*CPBA) (76 mg, 0.338 mmol) was added to a 0 °C solution of amine **494** (70 mg, 0.307 mmol) in anhydrous dichloromethane (1.5 cm^3). The reaction was stirred at 0 °C for 30 min before allowing it to warm

up to room temperature and stirring overnight. The reaction was then diluted with dichloromethane (5 cm^3) and quenched with saturated aqueous sodium hydrogen carbonate (5 cm^3). The organic layer was separated and was washed sequentially with saturated aqueous sodium hydrogen carbonate (2×10 cm^3) and water (10 cm^3). The solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)→(80:20)→(70:30)] of the crude residue afforded benzyl protected dione **496** (19.4 mg, 26%); R_f 0.34 (solvent *B*); ν_{max}(film)/cm^{-1} 2924, 1643, 1456, 1296, 1139, 1010 and 733; δ_H(400 MHz; $CDCl_3$) 2.82-2.89 (1 H, m, CH_2), 3.20-3.29 (1 H, m, CH_2), 5.04 (1 H, t, *J* 7.5, C*H*(N)), 5.11 (1 H, br d, *J* 10.3, CH=CH_2), 5.25 (1 H, dd, *J* 1.4 and 17.1, CH=CH_2), 5.79 (1 H, ddt, *J* 7.5, 10.3 and 17.1, C*H*=CH_2), 6.40 (1 H, dd, *J* 1.8 and 3.2, C*H*=CHCO), 6.56 (1 H, d, *J* 3.2, CH=C*H*(CO)), 7.38-7.45 (5 H, m, Ph) and 8.21-8.23 (2 H, m, CH_2Ph); δ_C(100 MHz; $CDCl_3$) 29.7 (*C*H_2CH=CH_2), 35.1 (*C*H_2Ph), 73.3 (H*C*N), 119.0 (CH=*C*H_2), 128.5 (2× *C*H(Ph)), 128.8 (2× *C*H(Ph)), 130.3 (*C*(Ph), 130.5 (*C*H(Ph), 132.7 (CH=*C*H), 133.7 (*C*H=CH_2), 143.1 (*C*H=CH), 149.8 (O=*C*-N) and 191.0 (*C*=O); MS (CI) *m*/*z* 242 $[M+H]^+$; HRMS *m*/*z* 242.1179 (242.1181 calcd for $C_{15}H_{16}NO_2$, $M+H^+$).

_N_-[1-(5-But-3-enyl-furan-2-yl)-but-3-enyl]-4-methyl-benzensulfonamide 497, (*n*=2)



Procedure A

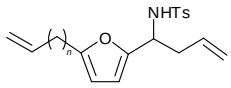
A solution of tosyl amine **492** (126 mg, 0.432 mmol) in anhydrous tetrahydrofuran (2.2 cm^3) was cooled to −20 °C and *n*BuLi (0.18 cm^3, 0.454 mmol) was slowly added. The solution was stirred for 30 min at −20 °C before being cooled to −78 °C. The reaction was stirred for 45 min before being treated with *t*BuLi (1.7 M in pentane, 0.28 cm^3, 0.475 mmol) and the resulting reaction was stirred at −78 °C for 1 h. The reaction was warmed up to −20 °C and was then treated with 4-bromo-1-butene (0.06 cm^3, 0.562 mmol). After 1 h at −20 °C, the reaction mixture was warmed to 0 °C and then room temperature where it was left to stir for 48 h. The reaction was quenched by being pouring onto ice (20 cm^3) and diluting with diethyl ether (10 cm^3). The phases were separated and the organic layer was washed with water (2×10 cm^3), saturated

aqueous sodium chloride (2×10 cm^3) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the crude residue was purified by FCC [petroleum ether-ethyl acetate (90:10→85:15→80:20)] to yield diene **497**, ***n*=2** (20.6 mg, 17%) as a yellow oil; R_f 0.60 (solvent *A*); ν_{max}(film)/cm^{-1} 2935, 1350, 1171 and 1020; δ_H(400 MHz; $CDCl_3$) 1.82-1.95 (1 H, m, CH_2CH_2), 2.10-2.20 (1 H, m, CH_2CH_2), 2.35 (3 H, s, CH_3), 2.48-2.52 (1 H, m, $CH_2CH{=}CH_2$), 2.64-2.70 (1 H, m, $CH_2CH{=}CH_2$), 2.96-3.04 (2 H, m, CH_2CH_2), 4.72-5.07 (5 H, m, 2×CH=CH_2 and CHN), 5.47-5.70 (2 H, m, 2×$CH{=}CH_2$), 6.01 (1 H, d, *J* 3.2, $CH{=}CO$), 6.20 (1 H, d, *J* 3.2, $CHCO$) and 7.20 (2 H, d, *J* 8.2, 2×CH) and 7.65 (2 H, d, *J* 8.2, 2×CH); δ_C(100 MHz; $CDCl_3$) 22.7 (CH_3), 27.7 ($H_2C{=}CHCH_2CH_2$), 29.1 ($H_2C{=}CHCH_2$), 41.4 ($CH_2CH{=}CH_2$), 55.1 (HCNH), 108.9 (2×CH), 117.8 (2×$H_2C{=}CH$), 127.4 (2×PhCH), 129.4 (2×PhCH), 134.2 ($CH{=}CH_2$), 136.7 (CCH_3), 138.5 ($H_2C{=}CH$), 140.5 (SO_2C), 147.8 (CCHNH) and 151.0 ($H_2C{=}CH(CH_2)_2C$); MS (CI) *m*/*z* 346.2 $[M+H]^+$; HRMS *m*/*z* 346.1480 (346.1477 calcd for $C_{19}H_{24}NO_3S$, $M+H^+$).

Procedure B

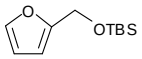
A solution of homoallylic amine **492** (112 mg, 0.384 mmol) in anhydrous tetrahydrofuran (2.0 cm^3) was cooled to −20 °C and *n*BuLi (0.16 cm^3, 403 μmol) was slowly added. The solution was stirred for 30 min at −20 °C and then *t*BuLi (1.7 M in pentane, 0.25 cm^3, 0.422 mmol) was added. The reaction was stirred at −20 °C for 1 h and then warmed to 0 °C before 4-bromo-1-butene (50 μL, 0.499 mmol) was added. After 1 h at 0 °C the reaction mixture was warmed to room temperature and stirred for 48 h. The reaction was quenched by pouring onto ice (20 cm^3) and diluting with diethyl ether (10 cm^3). The phases were separated and the organic layer was washed with water (2×10 cm^3) and saturated aqueous sodium chloride (2×10 cm^3). The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10→85:15→80:20)] of the crude residue yielded **497**, ***n*=2** (11.3 mg, 9%) as a yellow oil; R_f 0.68 (solvent *A*). The spectroscopic data obtained matches that for Procedure A.

***N*-[1-(5-Hex-5-enyl-furan-2-yl)-but-3-enyl]-4-methyl-benzenesulfonamide 497, *n*=4**



A solution of homoallylic amine **492** (106 mg, 0.363 mmol) in anhydrous THF (1.8 cm^3) was treated with *n*BuLi (0.15 cm^3, 0.363 mmol) at room temperature and the resulting solution was stirred for 24 h. 6-Bromo-1-hexene (0.049 cm^3, 0.363 mmol) was then added and the reaction mixture was stirred for a further 24 h. The reaction was quenched by pouring onto ice (20 cm^3) and diluting with diethyl ether (20 cm^3). The phases were separated and the organic layer was washed with water (2×10 cm^3) and saturated aqueous sodium chloride (2×10 cm^3). The solution was dried over anhydrous sodium chloride, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (90:10)→(80:20)] of the crude residue gave diene **497**, ***n*=4** (25.5 mg, 19%; 48% based on starting material consumed); R_f 0.65 (solvent *B*); ν_{max}(film)/cm^{-1} 2937, 1346, 1173 and 1020; δ_H(400 MHz; $CDCl_3$) 1.00-1.50 (8 H, m, 4×CH_2), 1.70-2.01 (2 H, m, CHNCH_2), 2.34 (3 H, s, CH_3), 4.05 (1 H, q, *J* 7.1, C*H*N), 4.58-5.0 (4 H, m, 2×CH=CH_2), 5.56-5.58 (2 H, m, 2×C*H*=CH_2), 6.00 (1 H, d, *J* 3.2, C*H*=CO), 6.17 (1 H, dd, *J* 1.6 and 3.2, CHCO), 7.20 (2 H, d, *J* 8.2, 2×CH) and 7.66 (2 H, d, *J* 8.2, 2×CH); δ_C(100 MHz; $CDCl_3$) 22.6 (*C*H_3), 27.7 (H_2C=$CHCH_2CH_2CH_2CH_2$), 27.9 (H_2C=$CHCH_2CH_2CH_2CH_2$), 28.5 (H_2C=$CHCH_2CH_2CH_2CH_2$), 29.1 (H_2C=$CHCH_2CH_2CH_2CH_2$), 41.3 (*C*H_2CH=CH_2), 55.1 (H*C*NH), 108.9 (2×*C*H), 117.6 (2×H_2C=CH), 127.4 (2×PhCH), 129.4 (2×PhCH), 134.3 (*C*H=CH_2), 136.9 (*C*CH_3), 138.4 (H_2C=*C*H), 140.5 (SO_2C), 147.8 (*C*CHNH) and 151.1 (H_2C=$CH(CH_2)_2C$); MS (CI) *m*/*z* 374.1 $[M+H]^+$; HRMS 374.1786 (374.1790 calcd for $C_{21}H_{28}NO_3S$, $M+H^+$).

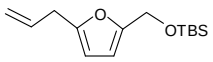
***tert*-Butyl-(furan-2-ylmethoxy)-dimethyl-silane 504**[207]



To anhydrous dimethylformamide (10 cm^3) was added furfuryl alcohol **505** (1.00 g, 10.1 mmol) at room temperature and the resulting solution was stirred for 10 min. Imidazole (2.08 g, 30.5 mmol) was then added and the mixture stirred until clear. *tert*-Butyldimethylsilyl chloride (2.30 g, 15.2 mmol) was added, with TLC analysis showing that the reaction was complete after 10 min. The mixture was diluted with diethyl ether (35 cm^3) and quenched with water (50 cm^3). The organic layer was washed with water (4×100 cm^3), dried over anhydrous sodium

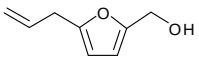
sulphate, filtered and concentrated *in vacuo*, to afford silyl ether **504** (1.59 g, 74%) as a colourless oil with no further purification, although excess, inseparable Si signals are seen in the NMR spectrum which equate to 570 mg, 26% of the obtained total mass of 2.16 g; R_f 0.80 (solvent *B*); δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(C*H*$_3$)$_2$), 0.83 (9 H, s, SiC(C*H*$_3$)$_3$), 4.56 (2 H, s, CH_2), 6.14 (1 H, d, *J* 3.1 Hz, C*H*=CO), 6.23 (1 H, dd, *J* 1.8 and 3.1, C*H*CO) and 7.28 (1 H, d, *J* 1.8, C*H*O). The spectral data matches that reported in the literature.[207]

(5-Allyl-furan-2-ylmethoxy)-*tert*-butyl-dimethyl-silane 506



A solution of crude silyl ether **504** (1.00 g, 4.70 mmol) in anhydrous tetrahydrofuran (23.5 cm^3) was stirred for 10 min before being cooled down to 0 ^{o}C and treated with *n*BuLi (2.25 cm^3, 5.17 mmol). The resulting mixture was stirred at 0 ^{o}C for 15 min and then it was allowed to warm up to room temperature. The reaction was stirred at room temperature for 15 min and then cooled back down to 0 ^{o}C, where it was stirred for a further 15 min. Freshly distilled allyl bromide (0.49 cm^3, 5.65 mmol) was then added and the reaction allowed to warm up to room temperature. After 18 h, the reaction mixture was diluted with diethyl ether (20 cm^3) and quenched with water (30 cm^3). The layers were separated and the organic phase was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford diene **506** (1.07 g, 91%) with no need for further purification; R_f 0.66 (solvent *F*); ν_{max}(film)/cm^{-1} 2929, 2858, 1255 and 1078 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, Si(C*H*$_3$)$_2$), 0.81 (9 H, s, SiC(C*H*$_3$)$_3$), 3.30 (2 H, dd, *J* 1.0 and 6.6, C*H*$_2$CH=CH$_2$), 4.51 (2 H, s, C*H*$_2$), 5.02-5.08 (2 H, m, CH=C*H*$_2$), 5.79-5.90 (2 H, m, C*H*=CH$_2$ and C*H*=CO) and 6.07 (1 H, d, *J* 3.1, C*H*CO); δ_C(100 MHz; $CDCl_3$) -5.2 (Si(*C*H$_3$)$_2$), 18.4 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 32.7 (*C*H$_2$), 58.2 (*C*H$_2$OTBS), 106.1 (*C*H), 108.1 (*C*H), 116.8 (H$_2$*C*=CH), 134.0 (H$_2$C=*C*H), 152.0 (*C*O) and 154.0 (*C*CH$_2$OTBS); MS (EI) *m*/*z* 121 [M-OTBS]$^+$; HRMS *m*/*z* 121.0656 (121.0653 calcd for C_8H_9O, M-OTBS$^+$).

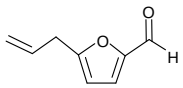
2-(5-Allyl)furyl methanol 509[207]



A solution of TBS ether **506** (2.73 g, 9.73 mmol) in anhydrous tetrahydrofuran (45 cm^3) and pyridine (20 cm^3) was treated with hydrogen fluoride in pyridine

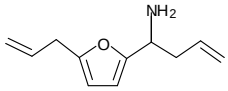
(10 cm^3) and the reaction stirred for 2 h at room temperature. The reaction was quenched by the careful addition of saturated aqueous sodium hydrogen carbonate (350 cm^3) with vigorous stirring. The mixture was stirred until the fizzing had subsided. After a further precautionary 30 min stirring, the reaction mixture was extracted with dichloromethane (2×70 cm^3) and the combined organic layers washed with water (100 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Pyridine was azeotroped from the crude residue with toluene (3×10 cm^3). Purification by FCC of the crude residue [petroleum ether-ethyl acetate (85:15)] afforded alcohol **509** (0.812 g, 61%) as a yellow oil; R_f 0.13 (solvent *A*), δ_H(400 MHz; $CDCl_3$) 2.00 (1 H, br s, O*H*), 3.42 (2 H, dd, *J* 0.7 and 6.6, CH_2CH=CH_2), 4.58 (2 H, s, CH_2), 5.12-5.22 (2 H, m, CH=CH_2), 5.89-6.03 (2 H, m, C*H*=CH_2 and C*H*=CO) and 6.20 (1 H, d, *J* 3.1, C*H*CO); MS(EI) *m/z* 138.1 $[M]^+$, 121.1 $[M\text{-}OH]^+$, 107.1 $[M\text{-}CH_2OH]^+$; HRMS *m/z* 138.0685 (138.0681 calcd for $C_8H_{10}O_2$). The spectral data matches that reported in the literature.[207]

5-Allyl-furan-2-carbaldehyde <u>512</u>[221]



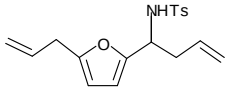
To a −78 °C solution of oxalyl chloride (0.17 cm^3, 2.00 mmol) in dry dichloromethane (10 cm^3) was added a solution of dimethylsulfoxide (0.28 cm^3, 4.00 mmol) in dichloromethane (1 cm^3). After 20 min at −78 °C, a solution of alcohol **509** (184.4 mg, 1.33 mmol) in dichloromethane (6.7 cm^3) was added and the reaction was stirred at −78 °C for a further 1 h, whereafter triethylamine (0.93 cm^3, 6.67 mmol) was added. The reaction was warmed up to 0 °C and stirred for 30 min. The reaction was then diluted with dichloromethane (10 cm^3) and treated with 1 M hydrochloric acid (10 cm^3). The layers were separated and the organic layer was washed sequentially with saturated aqueous sodium chloride (20 cm^3) and saturated aqueous sodium hydrogen carbonate (20 cm^3). The solution was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford aldehyde **512** (158.3 mg, 87%) as a brown oil with no further purification carried out; R_f 0.69 (solvent *C*); δ_H(400 MHz; $CDCl_3$) 3.32 (2 H, d, *J* 7.2, CH_2), 5.09-5.12 (2 H, m, CH_2=CH), 5.82-5.90 (1 H, m, CH_2=C*H*), 5.92 (1 H, d, *J* 3.3, C*H*=CO), 6.21 (1 H, d, *J* 3.3, C*H*CO) and 9.49 (1 H, s, C*H*O). The spectral data matches that reported in the literature.[221]

1-(5-Allyl-furan-2-yl)-but-3-enylamine 513



A mixture of allylboronic acid pinacol ester (0.14 cm^3, 0.759 mmol) and dodecylbenzenesulfonic acid (20 μL, 63.2 μmol) in 25 wt% ammonia (1.3 cm^3) was stirred at room temperature for 30 min before aldehyde **512** (86.2 mg, 0.632 mmol) was added. After stirring for 2 h, the reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the crude alcohol; R_f 0.84 (solvent *B*). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×20 cm^3). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford homoallylic amine **513** (86.1 mg, 76%) as a pale yellow oil with no further purification required; R_f 0.09 (solvent *B*); ν_{max}(film)/cm^{-1} 2999, 2931 and 1029; δ_H(400 MHz; $CDCl_3$) 1.90 (2 H, br s, NH_2), 2.29-2.35 (1 H, m, CH(NH_2)CH_2), 2.48-2.52 (1 H, m, CH(NH_2)CH_2), 3.28 (2 H, d, *J* 6.5, CH_2), 3.88 (1 H, dd, *J* 5.6 and 7.6, C*H*N), 5.00-5.11 (4 H, m, 2×CH=CH_2), 5.65-5.72 (1 H, m, CH(NH_2)CH_2C*H*=CH_2), 5.81-5.91 (1 H, m, C*H*=CH_2), 5.85 (1 H, d, *J* 3.0, C*H*=CO) and 5.96 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) 29.1 (H_2C=CH*C*H_2), 41.0 (*C*H_2), 49.3 (*C*HNH_2), 104.4 (*C*H=CO), 110.0 (*C*HCO), 118.0 (2×HC=*C*H_2), 134.6 (2×H*C*=CH_2), 141.5 (*C*CHN) and 158.5 (*C*HO); MS (CI) *m*/*z* 178 $[M+H]^+$; HRMS *m*/*z* 178.1235 (178.1232 calcd for $C_{11}H_{16}NO$, $M+H^+$).

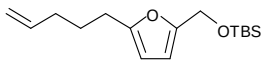
***N*-[1-(5-Allyl-furan-2-yl)-but-3-enyl]-4-methyl-benzenesulfonamide 514**



A solution of homoallylic amine **513** (26.5 mg, 0.149 mmol) in dry dichloromethane (1 cm^3) was stirred at 0 °C for 30 min before triethylamine (0.05 cm^3, 0.328 mmol), dimethylaminopyridine (11 mg, 0.0897 mmol) and *p*-toluenesulfonyl chloride (43 mg, 0.224 mmol) were sequentially added. After 30 min at 0 °C, the reaction was allowed to warm up to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether (5 cm^3) and H_2O (10 cm^3) and the layers separated. The organic layer was washed with water (2×10 cm^3), saturated aqueous sodium hydrogen carbonate (2×10 cm^3)

and dried over anhydrous sodium sulphate. The solution was concentrated *in vacuo* to afford crude tosylate **514** (17.4 mg, 35%) with no further purification carried out; R_f 0.78 (solvent *C*); ν_{max}(film)/cm^{-1} 2926, 1371, 1172 and 1010; δ_H(400 MHz; $CDCl_3$) 2.35 (3 H, s, C*H*$_3$), 2.50-2.60 (1 H, m, CH(NHTs)C*H*$_2$), 2.63-2.72 (1 H, m, CH(NHTs)C*H*$_2$), 3.50 (1 H, dd, *J* 7.1 and 16.4, H_2C=CHC*H*$_2$), 3.71 (1 H, dd, *J* 5.4 and 16.4, H_2C=CHCH_2), 4.88-5.09 (5 H, m, CH=C*H*$_2$, C*H*$_2$=CH, *H*C(NHTs)), 5.47-5.57 (1 H, m, CH_2=C*H*CH_2), 5.60-5.72 (1 H, m, (NHTs)CH_2CH=CH_2), 6.02 (1 H, dd, *J* 0.6 and 3.2, C*H*=CO), 6.17 (1 H, dd, *J* 1.8 and 3.2, CHCO), 7.18 (2 H, d, *J* 8.3, 2×CH) and 7.64 (2 H, d, *J* 8.3, 2×CH); δ_C(100 MHz; $CDCl_3$) 21.4 (*C*H$_3$), 29.5 (H_2C=CH*C*H$_2$), 39.0 (*C*H$_2$), 51.0 (*C*HN), 107.3 (*C*H=CO), 110.0 (*C*HCO), 119.3 (CH=*C*H$_2$), 118.5 (H_2*C*=CH), 127.0 (*C*H), 129.4 (*C*H), 132.8 (*C*H=CH$_2$), 133.9 (H_2C=*C*H), 137.5 (*C*CHN), 141.9 (*C*HO), 143.1 (*C*) and 152.8 (*C*) MS (CI) *m*/*z* 332.2 [M+H]$^+$; HRMS *m*/*z* 332.1323 (332.1321 calcd for $C_{18}H_{22}O_3NS$, M+H$^+$).

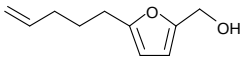
tert-Butyl-dimethyl-(5-pent-4-enyl-furan-2-ylmethoxy)-silane 507



A solution of furan **504** (322.2 mg, 1.52 mmol) in anhydrous tetrahydrofuran (8 cm^3) at 0 °C was treated with *n*BuLi (0.73 cm^3, 1.67 mmol). After 15 min at 0 °C the reaction mixture was allowed to warm to room temperature where it was stirred for a further 15 min. The solution was recooled to 0 °C and 5-bromo-1-pentene (0.22 cm^3, 1.82 mmol) was added. After 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and stirred for 18 hours. The reaction was diluted with diethyl ether (10 cm^3) and partitioned with water (10 cm^3). The layers were separated and the organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford alkene **507** (337 mg, 79%) as an oil; R_f 0.72 (solvent *F*); ν_{max}(film)/cm^{-1} 2929, 2858, 1701, 1253 and 1078 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.02 (6 H, s, Si(C*H*$_3$)$_2$), 0.83 (9 H, s, SiC(C*H*$_3$)$_3$), 1.63-1.66 (2 H, m, CH_2C*H*$_2$CH$_2$), 2.05-2.10 (2 H, m, C*H*$_2$CH$_2$CH$_2$), 2.54-2.56 (2 H, m, CH_2CH_2C*H*$_2$), 4.51 (2 H, s, C*H*$_2$OTBS), 4.90-4.99 (2 H, m, C*H*$_2$=CH), 5.70-5.75 (1 H, m, CH_2=C*H*), 5.80 (1 H, d, *J* 3.0, C*H*=CO) and 6.02 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) -5.9 (Si(*C*H$_3$)$_2$), 17.9 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 27.1 (CH_2*C*H$_2$CH$_2$), 28.9 (*C*H$_2$CH$_2$CH$_2$), 37.2 (CH_2CH_2*C*H$_2$), 60.7 (*C*H$_2$OTBS), 106.6 (H*C*), 109.6 (H*C*), 115.0 (H_2*C*=CH), 137.6 (H_2C=*C*H), 152.2

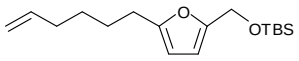
(*C*CH_2OH) and 156.5 (*C*); MS (CI) *m*/*z* 149.1 [M-OTBS]$^+$; HRMS *m*/*z* 149.0965 (149.0966 calcd for $C_{10}H_{13}O$, M-OTBS$^+$).

(5-Pent-4-enyl-furan-2-yl)-methanol 510



A 0 °C solution of silyl ether **507** (337 mg, 1.20 mmol) in tetrahydrofuran (10 cm^3) was added *tetra*-butylammonium fluoride (2.4 cm^3, 2.40 mmol) and the reaction was stirred at 0 °C for 15 min before allowing it to warm up to room temperature. After 1.5 h at room temperature the reaction mixture was diluted with diethyl ether (20 cm^3) and quenched with water (20 cm^3). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)→(75:25)] of the crude residue afforded alcohol **510** (60.4 mg, 30%) as a yellow oil; R_f 0.09 (solvent *F*); ν_{max}(film)/cm^{-1} 3470 (OH), 2852, 1260; δ_H(400 MHz; $CDCl_3$) 1.71-1.80 (2 H, m, $CH_2CH_2CH_2$), 2.13-2.20 (2 H, m, $CH_2CH_2CH_2$), 2.65 (2 H, t, *J* 7.6, $CH_2CH_2CH_2$), 4.59 (2 H, d, *J* 5.8, CH_2OH), 5.00-5.07 (2 H, m, CH_2=CH), 5.80-5.89 (1 H, m, CH_2=CH), 5.95 (1 H, d, *J* 3.0, CH=CO) and 6.21 (1 H, d, *J* 3.0, CHCO); δ_C(100 MHz; $CDCl_3$) 27.1 ($CH_2CH_2CH_2$), 27.5 ($CH_2CH_2CH_2$), 33.2 ($CH_2CH_2CH_2$), 57.7 (CH_2OH), 105.6 (HC), 108.6 ($HCCCH_2OH$), 115.0 (H_2C=CH), 138.2 (H_2C=CH), 152.2 ($HCCCH_2OH$) and 156.5 (HC*C*); MS (EI) *m*/*z* 82.96 [M-CH_2OH-CH_2=$CHCH_2CH_2$]$^+$, 111.07 [M-CH_2OH-CH_2CH], 124.08 [M-CH_2OH-CH_2]$^+$, 135.11 [M-CH_2OH]$^+$; HRMS *m*/*z* 166.0996 (166.2170 calcd for $C_{10}H_{14}O_2$, M$^+$).

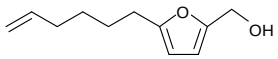
***tert*-Butyl-(5-hex-5-enyl-furan-2-ylmethoxy)-dimethyl-silane 508**



A 0 °C solution of silyl ether **504** (266.2 mg, 1.25 mmol) in anhydrous tetrahydrofuran (6.5 cm^3) was treated with *n*BuLi (0.73 cm^3, 1.67 mmol). After 15 min at 0 °C, the reaction mixture was allowed to warm up to room temperature and was stirred for a further 15 min, before being recooled back to 0 °C. 5-Bromo-1-hexene (0.2 cm^3, 1.50 mmol) was then added and the reaction was stirred for 15 min. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. The reaction was diluted with diethyl ether (10 cm^3) and quenched with water (10 cm^3). The layers were separated and the organic layer was dried over anhydrous sodium sulphate, filtered and

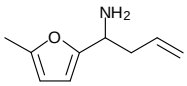
concentrated *in vacuo* to afford alkene **508** (231 mg, 63%) as a colourless oil with no further purification required; R_f 0.69 (solvent *F*); ν_{max}(film)/cm^{-1} 2934, 2860, 1699, 1258, 1159 and 1111; δ_H(400 MHz; $CDCl_3$) 0.00 (6 H, s, (Si(C*H*$_3$)$_2$), 0.83 (9 H, s, SiC(C*H*$_3$)$_3$), 1.33-1.62 (4 H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_2$), 2.00 (2 H, qn, *J* 6.7 and 13.8, CH$_2$=CHC*H*$_2$), 3.33 (2 H, t, *J* 6.8, (CH$_2$)$_3$C*H*$_2$), 4.51 (2 H, s, C*H*$_2$OTBS), 4.85-4.94 (2 H, m, C*H*$_2$=CH), 5.67-5.75 (1 H, m, CH$_2$=C*H*), 5.82 (1 H, d, *J* 2.9, C*H*=CO) and 6.02 (1 H, d, *J* 2.9 Hz, C*H*CO); δ_C(100 MHz, $CDCl_3$) -5.0 (Si(*C*H$_3$)$_2$), 15.5 (Si*C*(CH$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 25.9 (CH$_2$*C*H$_2$CH$_2$CH$_2$), 27.6 (CH$_2$CH$_2$*C*H$_2$CH$_2$), 32.4 (*C*H$_2$CH$_2$CH$_2$CH$_2$), 33.1 (CH$_2$CH$_2$CH$_2$*C*H$_2$), 68.2 (CH$_2$OTBS), 105.6 (HC), 108.2 (H*C*CCH$_2$OTBS), 115.3 (H$_2$*C*=CH), 138.3 (H$_2$C=*C*H), 152.7 (HC*C*CH$_2$OTBS) and 156.2 (HC*C*); MS (CI) *m*/*z* 163 [M-OTBS]$^+$; HRMS *m*/*z* 163.1120 (163.1123 calcd for $C_{11}H_{15}O$, M-OTBS$^+$).

(5-Hex-5-enyl-furan-2-yl)-methanol <u>511</u>



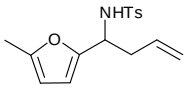
A 0 °C solution of silyl ether **508** (231.8 mg, 0.787 mmol) in tetrahydrofuran (5 cm^3) was treated with *tetra*-butylammonium fluoride (1.57 cm^3, 1.57 mmol) and the resulting reaction was stirred at 0 °C for 15 min, before being warmed up to room temperature. After 1.5 h at room temperature, the reaction mixture was diluted with diethyl ether (20 cm^3) and quenched with water (20 cm^3). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)→(75:25)] of the crude residue afforded alcohol **511** (89.1 mg, 63%) as a yellow oil; R_f 0.50 (solvent *C*); δ_H(400 MHz; $CDCl_3$) 1.32-1.38 (2 H, m, CH$_2$=CH(CH$_2$)C*H*$_2$), 1.53-1.61 (2 H, m, CH$_2$=CHCH$_2$C*H*$_2$), 1.95-2.01 (2 H, m, CH$_2$=CHC*H*$_2$), 2.51 (2 H, t, *J* 7.5, CH$_2$=CH(CH$_2$)$_3$C*H*$_2$), 4.45 (2 H, d, *J* 5.9, C*H*$_2$OH), 4.82-4.90 (2 H, m, C*H*$_2$=CH), 5.66-5.73 (1 H, m, CH$_2$=C*H*), 5.82 (1 H, d, *J* 3.1, C*H*=CO) and 6.08 (1 H, d, *J* 3.1 Hz, C*H*CO); δ_C(100 MHz, $CDCl_3$) 25.9 (CH$_2$*C*H$_2$CH$_2$CH$_2$), 26.2 (CH$_2$CH$_2$*C*H$_2$CH$_2$), 32.7 (*C*H$_2$CH$_2$CH$_2$CH$_2$), 33.2 (CH$_2$CH$_2$CH$_2$*C*H$_2$), 60.2 (*C*H$_2$OH), 105.6 (H*C*), 108.2 (H*C*), 115.3 (H$_2$*C*=CH), 138.3 (H$_2$C=*C*H), 152.2 (*C*CH$_2$OH) and 156.2 (*C*); MS (CI) *m*/*z* 163.2 [M-OH]$^+$; HRMS *m*/*z* 163.1126 (163.1123 calcd for $C_{11}H_{15}O$, M-OH$^+$).

1-(5-Methyl-furan-2-yl)-but-3-enylamine 540



A mixture of allylboronic acid pinacol ester (2.04 cm^3, 10.8 mmol) and dodecylbenzenesulfonic acid (0.3 cm^3, 0.90 mmol) in 25% aqueous ammonia (18 cm^3) was stirred for 30 min, before being treated with 5-methylfuraldehyde **539** (0.90 cm^3, 9.08 mmol) at room temperature. After 2 h, the reaction mixture was acidified to pH 1-2 with 3 N hydrochloric acid and extracted with dichlormethane (3×30 cm^3). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford the crude alcohol; R_f 0.68 (solvent *A*). The aqueous layer was basified to pH 12-13 with 6 N sodium hydroxide and extracted with dichloromethane (3×40 cm^3). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to yield amine **540** (1.05 g, 77%) as yellow oil with no need for further purification; R_f 0.16 (solvent *A*); δ_H(400 MHz; $CDCl_3$) 2.20 (3 H, s, C*H*$_3$), 2.33-2.40 (1 H, m, C*H*$_2$), 2.51-2.56 (1 H, m, C*H*$_2$), 3.90 (1 H, t, *J* 6.1, C*H*N), 5.03-5.10 (2 H, m, CH=C*H*$_2$), 5.68-5.79 (1 H, m, C*H*=CH$_2$), 5.82 (1 H, d, *J* 2.4, C*H*=CO) and 5.96 (1 H, d, *J* 2.4, C*H*CO); δ_C(100 MHz; $CDCl_3$) 13.5 (*C*H$_3$), 40.9 (*C*H$_2$), 49.2 (*C*HN), 105.1 (CH), 105.8 (CH), 117.8 (CH=*C*H$_2$), 134.9 (*C*H=CH$_2$), 150.8 (*C*CHN) and 156.6 (*C*CH$_3$); MS (CI) *m*/*z* 152.23 $[M + H]^+$; HRMS *m*/*z* 152.1074 (152.1075 calcd for $C_9H_{14}NO$, M+ H^+).

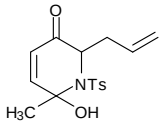
4-Methyl-*N*-[(1-(5-methyl-furan-2-yl)-but-3-enyl)]-benzenesulfonamide 541



A solution of homoallylic amine **540** (200 mg, 1.32 mmol) in dichloromethane (7 cm^3) was cooled to 0 °C and treated with dimethylaminopyridine (97 mg, 0.79 mmol) and triethylamine (0.41 cm^3, 2.90 mmol). After stirring for 10 min, *p*-toluenesulfonyl chloride (265 mg, 1.38 mmol) was added to the reaction mixture and the ice-water bath removed after a further 10 min. After 1 h, the reaction mixture was diluted with dichloromethane (10 cm^3) and quenched with water (10 cm^3). The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (2×10 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude residue was passed through a pad of silica gel (eluting with solvent *C*) to afford tosyl amine

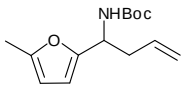
541 (376 mg, 93%) as a yellow oil; ν_{max}(film)/cm^{-1} 3054, 2986, 1598, 1265 and 1160; δ_H(400 MHz; $CDCl_3$) 2.00 (3 H, s, C*H*$_3$), 2.31 (3 H, s, C*H*$_3$(Ar)), 2.35-2.50 (2 H, m, C*H*$_2$), 4.36 (1 H, q, *J* 6.9, C*H*NH), 5.00-5.02 (2 H, m, CH=C*H*$_2$), 5.49-5.58 (1 H, m, C*H*=CH$_2$), 5.62 (1 H, dd, *J* 1.0 and 3.1, C*H*=CO), 5.78 (1 H, d, *J* 3.1, C*H*CO), 7.12 (2 H, d, *J* 8.0, 2×CH) and 7.57 (2 H, d, *J* 8.0, 2×CH); δ_C(100 MHz; $CDCl_3$) 13.3 (*C*H$_3$CO), 21.5 (*C*H$_3$), 39.1 (*C*H$_2$), 51.2 (*C*HN), 105.8 (*C*H), 108.0 (*C*H), 119.1 (CH=*C*H$_2$), 127.1 (2×*C*H), 129.3 (2×*C*H), 133.0 (*C*H=CH$_2$), 137.7 (*C*CH$_3$), 143.0 (*C*S), 150.6 (*C*CHN) and 151.6 (CH$_3$*C*O); MS (CI) *m*/*z* 306.3 [M+H]$^+$; HRMS 306.1165 (306.1164 calcd for $C_{16}H_{20}NO_3S$, M+H$^+$).

2-Allyl-6-hydroxy-6-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one 542



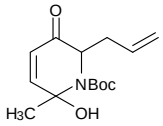
To a room temperature solution of tosyl amine **541** (103 mg, 0.337 mmol) in dichloromethane (1.7 cm^3) was added *meta*-chloroperoxybenzoic acid (*m*CPBA) (91 mg, 0.404 mmol). After stirring for 2 h, 10% aqueous sodium hydrogen carbonate (5 cm^3) was added to the pale yellow solution and the resulting mixture was stirred for 40 min. The biphasic mixture was transferred to a separating funnel and dichloromethane (10 cm^3) was added. The phases were separated and the organic layer was washed with saturated aqueous sodium hydrogen carbonate (4×15 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford hemi-aminal **542** (107 mg, 99%) as a pale yellow oil; R_f 0.10 (solvent *A*); ν_{max}(film)/cm^{-1} 2254, 1701, 1265 and 1164; δ_H(400 MHz; $CDCl_3$) 2.12 (3 H, s, C*H*$_3$), 2.43-2.50 (2 H, m, C*H*$_2$), 2.45 (3 H, s, CH$_3$(Ar)), 4.02-4.05 (1 H, m, C*H*(N)), 4.89-4.99 (2 H, m, CH=C*H*$_2$), 5.21 (1 H, d, *J* 7.6, CH=C*H*(C=O)), 5.41-5.51 (1 H, m, C*H*=CH$_2$), 6.30 (1 H, app. s, C*H*=CH(C=O)) and 7.21 (2 H, d, *J* 8.0, 2×CH) and 7.62 (2 H, d, *J* 8.0, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.6 (*C*H$_3$(Ar)), 29.6 (*C*H$_3$), 36.0 (*C*H$_2$), 60.6 (*C*H(N)), 119.9 (CH=*C*H$_2$), 127.2 (2×*C*H), 129.8 (2×*C*H), 131.5 (*C*H=CH$_2$), 132.6 (CH=*C*H(CO)), 137.0 (*C*), 138.4 (*C*), 143.8 (*C*H=CH(CO)), 199.3 (*C*=O), *plus* one unresolved carbon; MS (CI) *m*/*z* 322.2 [M+H]$^+$; HRMS *m*/*z* 322.1114 (322.1114 calcd for $C_{16}H_{20}NO_4S$, M+H$^+$).

[1-(5-Methyl-furan-2-yl)-but-3-enyl]-carbamic acid *tert*-butyl ester 543



To a stirred, room temperature solution of homoallylic amine **540** (200 mg, 1.32 mmol) in water (1.5 cm^3) was added di-*tert*-butyl dicarbonate ($(Boc)_2O$) (317 mg, 1.45 mmol). The pale yellow solution was stirred at for 30 min after which water (5 cm^3) was added and the mixture extracted with ethyl acetate (2×10 cm^3). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford Boc amine **543** (269 mg, 81%) as a colourless oil with further purification needed; R_f 0.67 (solvent *A*); ν_{max}-(film)/cm^{-1} 1709, 1498, 1265 and 1168; δ_H(400 MHz; $CDCl_3$) 1.45 (9 H, s, 3×CH_3), 2.27 (3 H, s, CH_3), 2.53-2.57 (2 H, m, CH_2), 4.80-4.83 (1 H, m, C*H*N), 5.05-5.12 (2 H, m, CH=CH_2), 5.65-5.73 (1 H, m, C*H*=CH_2), 5.88 (1 H, dd, *J* 1.0 and 3.0, C*H*=CO) and 6.03 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) 13.6 (*C*H_3), 28.4 (3×*C*H_3), 38.7 (*C*H_2), 48.3 (*C*HN), 85.2 (C$(CH_3)_3$), 105.9 (*C*H), 106.6 (*C*H), 118.1 (CH=*C*H_2), 133.9 (*C*H=CH_2), 146.7 (*C*CHN), 151.3 (CH_3*C*) and 155.2 (*C*=O); MS (CI) *m*/*z* 252.2 $[M+H]^+$; HRMS *m*/*z* 252.1602 (252.1599 calcd for $C_{14}H_{22}NO_3$, $M+H^+$).

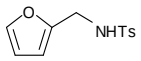
2-Allyl-6-hydroxy-6-methyl-3-oxo-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester 544



To a solution of Boc amine **543** (102 mg, 0.405 mmol) in dichloromethane (2 cm^3) at room temperature, was added *meta*-chloroperoxybenzoic acid (*m*CPBA) (109 mg, 0.486 mmol) at room temperature. After stirring for 1 h, 10% aqueous sodium hydrogen carbonate (5 cm^3) was added and the pale yellow biphasic solution was stirred for 1 h before being transferred to a separating funnel. Dichloromethane (10 cm^3) was added and the organic layer separated. The organic layer was washed with saturated aqueous sodium hydrogen carbonate (4×15 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford Boc aminal **544** (94.6 mg, 88%) as a white oil; R_f 0.18 (solvent *A*); ν_{max}(film)/cm^{-1} 3431 (OH), 2983, 2254, 1702 (C=O), 1165 and 907; δ_H(400 MHz; $CDCl_3$) 1.44 (9 H, s, 3×CH_3), 2.21 (3 H, s, CH_3), 2.37-2.42 (1 H, m, CH_2), 2.58-2.64 (1 H, m, CH_2), 4.37-4.41 (1 H, m, NC*H*), 5.02-5.09 (2 H, m, CH=CH_2), 5.60-5.71 (1 H, m, C*H*=CH_2), 6.32 (2 H, m, C*H*=C*H*); δ_C(100 MHz; $CDCl_3$) 28.2 (3×*C*H_3),

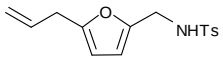
29.7 (*C*H_3), 35.5 (*C*H_2), 58.5 (N*C*H), 80.0 (*C*OH), 85.2 (*C*$(CH_3)_3$), 119.6 (CH=*C*H_2), 130.1 (CH=*C*H(C=O)), 133.2 (*C*H=CH_2), 146.7 (*C*H=CH(C=O)), 155.5 (N(*C*=O)O^{t}Bu) and 200.6 (C=O); MS (CI) *m*/*z* 268.3 $[M+H]^+$; HRMS *m*/*z* 268.1548 (268.1549 calcd for $C_{14}H_{22}NO_4$, $M+H^+$).

N-Furan-2-ylmethyl-4-methyl-benzenesulfonamide **525**[222,223]



To a stirred solution of furfurylamine (500 mg, 5.14 mmol) in dichloromethane (25 cm^3) at 0 °C, was added triethylamine (1.6 cm^3, 11.3 mmol) and dimethylaminopyridine (377 mg, 3.08 mmol). After 10 min, *p*-toluenesulfonyl chloride (1.03 g, 5.40 mmol) was added, following which, an immediate colour change from colourless to yellow was observed. The ice-water bath was then removed after 10 min and the reaction mixture was allowed to warm up to room temperature. After 1 h, the reaction was diluted with dichloromethane (20 cm^3), washed with water (2×20 cm^3) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm^3). The solution was then dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford tosyl amine **525** (1.29 g, 100%) as a yellow solid; R_f 0.35; mp 110-112 °C (from dichloromethane) (lit.,[12] 111-112 °C); δ_H(400 MHz; $CDCl_3$) 2.35 (3 H, s, CH_3), 4.09 (2 H, s, CH_2), 6.02 (1 H, dd, *J* 0.8 and 3.3, C*H*=CO), 6.15 (1 H, dd, *J* 1.9 and 3.3, C*H*CO), 7.18 (1 H, dd, *J* 0.8 and 1.9, C*H*O), 7.20 (2 H, d, *J* 8.3, 2×C*H*) and 7.65 (2 H, d, *J* 8.3, 2×C*H*). The spectral data matches that reported in the literature.[222,223]

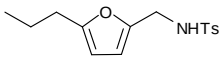
N-((5-allylfuran-2-yl)methyl)-4-methylbenzenesulfonamide **524**



A solution of tosyl amine **525** (259 mg, 1.02 mmol) in tetrahydrofuran (5 cm^3) was stirred for 10 min and then cooled to 0 °C before being treated with *n*BuLi (0.49 cm^3, 1.13 mmol). The resulting light brown solution was stirred at 0 °C for 15 min before being allowed to warm up to room temperature and stirred for 15 min. The solution was recooled down to 0 °C and allyl bromide (0.11 cm^3, 1.23 mmol) was added. The reaction was stirred for 10 min and the ice-water bath was removed to allow the reaction mixture to warm up to room temperature. After 20 h, the reaction mixture was diluted with diethyl ether (10 cm^3) and quenched with water (10 cm^3). The organic layer was separated, dried over

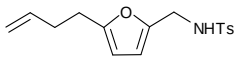
anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford alkene **524** (264 mg, 88%) as a dark brown thick oil; R_f 0.52 (solvent *A*); ν_{max}(film)/cm^{-1} 2253, 1159, 1093 and 908; δ_H(400 MHz; $CDCl_3$) 2.28 (3 H, s, CH_3), 3.62 (2 H, d, *J* 6.4, C*H*$_2$CH=CH$_2$), 4.25 (2 H, s, C*H*$_2$), 4.98-5.03 (2 H, m, CH=C*H*$_2$), 5.45-5.57 (1 H, m, C*H*=CH$_2$), 6.00 (1 H, dd, *J* 0.6 and 3.2, C*H*=CO), 6.12 (1 H, dd, *J* 1.8 and 3.2, C*H*CO), 7.11 (2 H, d, *J* 8.2, 2×C*H*) and 7.53 (2 H, d, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.5 (*C*H$_3$), 42.7 (CH$_2$=CH*C*H$_2$), 49.6 (*C*H$_2$N), 109.5 (*C*H), 110.3 (*C*H), 119.2 (*C*H$_2$=CH), 127.3 (2×CH), 129.5 (2×*C*H), 132.5 (CH$_2$=*C*H), 137.6 (*C*CH$_3$), 142.4 (*C*S), 143.1 (CH$_2$=CHCH$_2$*C*) and 149.7 (*C*CH$_2$); MS (CI) *m*/*z* 292.2 [M+H]$^+$; HRMS *m*/*z* 292.1006 (292.1007 calcd for $C_{15}H_{18}NO_3S$, M+H$^+$).

4-Methyl-*N*-((5-propylfuran-2-yl)methyl)benzenesulfonamide 528



A solution of alkene **524** (174 mg, 0.598 mmol) in methanol (3 cm^3) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 45 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated *in vacuo* to afford tosyl amine **528** (161 mg, 92%) as a thick, orange oil; R_f 0.52 (solvent *A*); ν_{max}(film)/cm^{-1} 2254, 1334, 1158 and 908; δ_H(400 MHz; $CDCl_3$) 0.72 (3 H, t, *J* 7.4, CH$_2$C*H*$_3$), 1.49 (2 H, sext., *J* 7.4, C*H*$_2$CH$_3$), 2.35 (3 H, s, C*H*$_3$), 3.00 (2 H, dd, *J* 7.4 and 9.2, C*H*$_2$CH$_2$CH$_3$), 4.31 (2 H, s, C*H*$_2$), 6.07 (1 H, dd, *J* 0.6 and 3.2, C*H*=CO), 6.18 (1 H, dd, *J* 1.9 and 3.2, C*H*CO), 7.17 (2 H, d, *J* 8.1, 2×C*H*) and 7.57 (2 H, d, *J* 8.1, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 11.0 (*C*H$_3$), 21.3 (*C*H$_3$(Ar)), 21.5 (CH$_3$*C*H$_2$), 43.7 (CH$_3$CH$_2$*C*H$_2$), 49.2 (*C*H$_2$), 109.3 (*C*H), 110.4 (*C*H), 127.2 (2×*C*H), 129.5 (2×*C*H), 137.0 (*C*CH$_3$), 142.4 (*C*S), 143.0 (*C*HCH$_2$) and 149.9 (CH$_2$*C*H); MS (CI) *m*/*z* 294.3 [M+H]$^+$; HRMS *m*/*z* 294.1161 (296.1164 calcd for $C_{15}H_{20}NO_3S$, M+H$^+$).

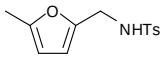
N-((5-(But-3-enyl)furan-2-yl)methyl)-4-methylbenzenesulfonamide 530



A solution of amine **525** (650 mg, 2.58 mmol) in tetrahydrofuran (10 cm^3) was stirred for 10 min, then cooled to 0 °C and treated with *n*BuLi (1.19 cm^3, 2.84

mmol). The resulting dark orange solution was stirred at this temperature for 15 min before being warmed up to room temperature and stirred for 15 min. The solution was recooled to 0 °C and 4-bromobutene (0.32 cm^3, 3.10 mmol) was added. After 10 min, the ice-water bath was removed to allow the reaction mixture to warm up to room temperature. After 20 h, TLC analysis showed there to be considerable remaining starting material, so the above procedure was repeated to add the same amount of reagents for a second time. After 8 h, the reaction had not proceeded, so the reaction mixture was diluted with diethyl ether (20 cm^3) and water (20 cm^3). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (70:30)] of the residue afforded alkene **530** (340 mg, 43%) as an orange oil; ν_{max}(film)/cm^{-1} 913; δ_H(400 MHz; $CDCl_3$) 2.05 (2 H, q, *J* 7.2, CH_2=CHCH_2), 2.25 (3 H, s, CH_3), 3.03 (2 H, t, *J* 7.2, CH_2=CHCH_2CH_2), 4.22 (2 H, s, CH_2), 4.82-4.88 (2 H, m, CH_2=CH), 5.51-5.62 (1 H, m, CH_2=C*H*), 6.00 (1 H, dd, *J* 0.6 and 3.2, C*H*=CO), 6.12 (1 H, dd, *J* 1.9 and 3.2, C*H*CO), 7.10 (2 H, d, *J* 8.4, 2×C*H*) and 7.51 (2 H, d, *J* 8.4, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.5 (*C*H_3), 32.8 (CH_2*C*H_2), 43.9 (*C*$H_2$$CH_2$), 46.9 (*C*$H_2$), 109.4 (*C*H), 110.4 (*C*H), 117.0 (*C*H_2=CH), 127.3 (2×*C*H), 129.5 (2×*C*H), 134.7 (*C*CH_3), 142.4 (CH_2=*C*H), 143.0 (*C*S), 149.8 (*C*CH_2), *plus* one unresolved carbon; MS (CI) *m*/*z* 306.2 $[M+H]^+$; HRMS *m*/*z* 306.1165 (306.1164 calcd for $C_{16}H_{20}NO_3S$, $M+H^+$).

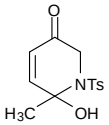
4-Methyl-*N*-(5-methylfuran-2-ylmethyl)-benzenesulfonamide 535[224]



To a stirred solution of methylfurfurylamine **534** (300 mg, 2.69 mmol) in dichloromethane (13 cm^3) at 0 °C was added triethylamine (0.83 cm^3, 5.93 mmol) and dimethylaminopyridine (198 mg, 1.61 mmol). After 10 min, *p*-toluenesulfonyl chloride (540 mg, 2.83 mmol) was added, following which an immediate colour change from colourless to yellow was observed. The cooling bath was removed after 10 min and the reaction mixture allowed to warm up to room temperature. After 1 h, the reaction was diluted with dichloromethane (20 cm^3), washed with water (2×20 cm^3) followed by saturated aqueous sodium hydrogen carbonate (2×20 cm^3). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residue was passed through a pad of silica gel to afford tosyl amine **535** (715 mg, 100%) as a yellow solid; R_f 0.31; mp 85-86 °C (from dichloromethane) (lit.,[224] 82-83 °C); δ_H(400

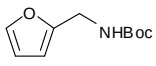
MHz; $CDCl_3$) 2.16 (3 H, s, CH_3), 2.46 (3 H, s, CH_3(Ph)), 4.13 (2 H, s, CH_2), 5.80 (1 H, d, *J* 3.0, C*H*=CO), 5.99 (1 H, d, *J* 3.0, C*H*CO), 7.30 (2 H, d, *J* 8.0, 2×C*H*) and 7.74 (2 H, d, *J* 8.0, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 13.4 (*C*H_3), 21.5 (*C*H_3(Ph)), 40.3 (*C*H_2), 106.2 (*C*H), 109.1 (*C*H), 127.2 (2×*C*H), 129.6 (2×*C*H), 136.9 (*C*CH_3), 143.4 (*C*S), 147.5 (*C*CH_2) and 152.3 (O*C*(CH_3)); MS (CI) *m*/*z* 266.2 $[M+H]^+$; HRMS *m*/*z* 266.0850 (266.0852 calcd for $C_{13}H_{16}NO_3S$, $M+H^+$). The spectral data matches that reported in the literature.[224]

6-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one <u>536</u>



To a 0 °C solution of amine **535** (360 mg, 1.35 mmol) in dichloromethane (7 cm^3) was added *meta*-chloroperoxybenzoic acid (*m*CPBA) (365 mg, 1.62 mmol) and the ice-water bath was removed after 10 min. The yellow reaction mixture was allowed to warm up to room temperature and quenched after 4 h with water (10 cm^3). The solution was transferred to a separating funnel and dichloromethane (15 cm^3) and water (10 cm^3) were added. The phases were separated and the organic layer was washed with water (10 cm^3) and saturated aqueous sodium hydrogen carbonate (4×15 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford **536** (381 mg, 100%) as a pale yellow oil; R_f 0.13 (solvent *G*); ν_{max}(film)/cm^{-1} 2253, 1160, 1090 and 910; δ_H(400 MHz; $CDCl_3$) 2.19 (3 H, s, CH_3), 2.36 (3 H, s, CH_3), 3.90 (2 H, s, *J* 5.2, CH_2), 5.23 (1 H, t, *J* 5.1, O*H*), 6.15 (1 H, d, *J* 11.9, CH=C*H*(C=O)), 6.35 (1 H, d, *J* 11.9, C*H*=CH(C=O)), 7.23 (2 H, d, *J* 8.2, 2×C*H*) and 7.66 (2 H, d, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 21.6 (*C*H_3), 29.7 (*C*H_3COH), 51.5 (*C*H_2), 77.0 (*C*OH), 127.1 (2×*C*H), 129.8 (2×*C*H), 133.2 (CH=*C*H(C=O)), 136.2 (*C*S), 137.3 (*C*CH_3), 143.9 *C*H=CH(C=O)) and 196.9 (*C*=O); MS (CI) *m*/*z* 282.2 $[M+H]^+$; HRMS 282.0807 (282.0800 calcd for $C_{13}H_{16}NO_4S$, $M+H^+$).

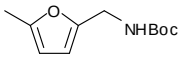
Furan-2-ylmethyl-carbamic acid *tert*-butyl ester <u>532</u>[225]



To a stirred mixture of furfuryl amine **526** (0.36 cm^3, 4.11 mmol) in water (4.2 cm^3) was added di-*tert*-butyl dicarbonate ($(Boc)_2O$) (988 mg, 4.43 mmol) at room temperature. After 40 min, the reaction was complete and was diluted with

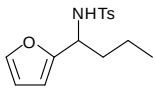
water (10 cm^3) and extracted with ethyl acetate (2×10 cm^3). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to afford Boc amine **532** (785 mg, 97%) as a clear oil; R_f 0.71; δ_H(400 MHz; $CDCl_3$) 1.45 (9 H, s, 3×CH_3), 4.30 (2 H, d, *J* 5.4, CH_2), 6.20 (1 H, d, *J* 2.8, C*H*=CO), 6.31 (1 H, dd, *J* 1.8 and 2.8, C*H*CO) and 7.32 (1 H, dd, *J* 0.8 and 1.8, C*H*O); δ_C(100 MHz; $CDCl_3$) 28.4 (3×CH_3), 37.7 (CH_2), 79.6 (CCH_3), 110.3 (2×CH), 142.0 (*C*HO), 146.7 (CCH_2) and 155.6 (*C*=O). The spectral data matches that reported in the literature.[225]

(5-Methyl-furan-2-ylmethyl)-carbamic acid *tert*-butyl ester 537



To a stirred mixture of methylfurfurylamine **534** (150 mg, 1.34 mmol) in water (1.35 cm^3) was added di-*tert*-butyl dicarbonate ($(Boc)_2O$) (324 mg, 1.48 mmol) at room temperature. Soon after, transparent liquid droplets were observed on the walls of the reaction vessel. After 40 min, water (5 cm^3) was added to the pale yellow solution and the reaction mixture extracted with ethyl acetate (2×5 cm^3). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo* to yield Boc amine **537** (233 mg, 82%) as a yellow oil; R_f 0.53 (solvent *A*); ν_{max}(film)/cm^{-1} 1701 and 1110; δ_H(400 MHz; $CDCl_3$) 1.48 (9 H, s, 3×CH_3), 2.27 (3 H, s, CH_3), 4.23 (2 H, d, *J* 5.2, CH_2), 5.88 (1 H, dd, *J* 0.8 and 2.9, C*H*=CO) and 6.08 (1 H, d, *J* 2.9, C*H*CO); δ_C(100 MHz; $CDCl_3$) 13.5 (CH_3), 28.4 (3×CH_3), 37.8 (CH_2), 79.5 ($C(CH_3)_3$), 106.1 (*C*H), 107.8 (*C*H), 150.0 (CCH_3), 151.7 (CCH_2) and 155.6 (C=O); MS (EI) *m*/*z* 211 $[M]^+$; HRMS *m*/*z* 211.1210 (211.2108 calcd for $C_{11}H_{17}NO_3$, M^+).

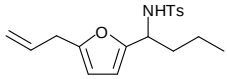
***N*-(1-furan-2-yl-butyl)-4-methyl-benzenesulfonamide 516**



To a solution of homoallylic amine **492** (275 mg, 0.943 mmol) in methanol (5 cm^3) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 40 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated *in vacuo* to afford alkane **516** (275 mg, 99%) as a white crystalline

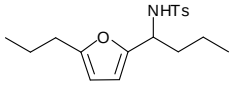
solid; R_f 0.59 (solvent *B*); mp 94-96 ^oC(from methanol); δ_H(400 MHz; $CDCl_3$) 0.78 (3 H, t, *J* 7.4, CH_2CH_3), 1.10-1.28 (2 H, m, CH_2CH_3), 1.67 (2 H, q, *J* 7.6, CH_2CH_2), 2.30 (3 H, s, CH_3(Ph)), 4.32 (1 H, t, *J* 7.6, CHN), 5.80 (1 H, d, *J* 3.2, CH=CO), 6.03 (1 H, dd, *J* 1.8 and 3.2, CHCO), 7.06 (1 H, dd, *J* 0.6 and 1.8, CHO), 7.11 (2 H, d, *J* 8.1, 2×CH) and 7.53 (2 H, d, *J* 8.1, 2×CH); δ_C(100 MHz, $CDCl_3$) 13.5 (CH_2CH_3), 18.9 (CH_2CH_3), 21.5 (CH_3), 37.1 (CH_2CH_2), 51.5 (CHN), 106.8 (CH=CO), 109.9 (CHCO), 127.0 (CH), 129.4 (CH), 137.7 (CCHN), 141.8 (CHO), 143.0 (*C*) and 153.0 (*C*); MS (EI) *m/z* 293.1 $[M]^+$, 250.1 $[M\text{-}CH_2CH_2CH_3]^+$, 155.0 $[M\text{-}(HTs)CH_2CH_2CH_3]^+$; HRMS 293.1084 (293.1086 calcd for $C_{15}H_{19}NO_3S$, M^+).

N-[1-(5-Allyl-furan-2-yl)-butyl]-4-methyl-benzenesulfonamide 517



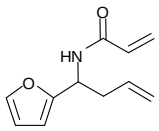
To a solution of amine **516** (704.8 mg, 2.40 mmol) in tetrahydrofuran (10 cm^3) at 0 ^oC, was added *n*BuLi (1.2 cm^3, 2.88 mmol). After stirring for 10 min at 0 ^oC and then 15 min at room temperature, the now yellow solution was recooled to 0 ^oC and allyl bromide (0.25 cm^3, 2.88 mmol) was added. After 15 min at 0 ^oC, the reaction mixture was allowed to warm up to room temperature once again and stirred for 16 h. The reaction was diluted with diethyl ether (10 cm^3) and water (10 cm^3) was added to separate the layers. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (85:15)→(80:20)] of the crude residue afforded alkene **517** (294 mg, 66% *based on starting material consumed*); R_f 0.65 (solvent *A*); ν_{max}(film)/cm^{-1} 2910, 2849, 1699 (C=C), 1455, 1262 and 1090; δ_H(400 MHz; $CDCl_3$) 0.85 (3 H, t, *J* 7.4, CH_3), 1.22-1.39 (2 H, m, CH_2CH_3), 1.71-1.87 (2 H, m, CH_2CH_2), 2.34 (3 H, s, CH_3), 3.46 (1 H, dd, *J* 7.6 and 16.4, CH_2), 3.65-3.70 (1 H, m, CH_2), 4.87-5.00 (3 H, m, CH_2=CH and CHN), 5.47-5.55 (1 H, m, CH_2=CH), 5.98 (1 H, dd, *J* 0.6 and 3.2, CH=CO), 6.15 (1 H, dd, *J* 1.8 and 3.2, CHCO), 7.18 (2 H, d, *J* 8.4, 2×CH) and 7.63 (2 H, d, *J* 8.4, 2×CH); δ_C(100 MHz; $CDCl_3$) 13.7 (CH_3), 19.5 (CH_2CH_3), 21.5 (CH_3), 33.9 (CH_2CH_2), 47.1 (CH_2=CHCH_2), 55.1 (CHN), 108.5 (CH=CO), 110.1 (CHCO), 116.8 (CH_2=CH), 127.5 (2×CH), 129.2 (2×CH), 135.6 (CHN), 137.9 (CCHN), 141.8 (CH_2=CH), 142.9 (*C*) and 152.8 (*C*); MS (CI) *m/z* 290.2 $[M\text{-}CH_2CH_2CH_3]^+$, 334.3 $[M+H]^+$; HRMS *m/z* 334.1481 (334.1478 calcd for $C_{18}H_{24}O_3NS$, $M+H^+$).

4-Methyl-*N*-[(1-(5-propylfuran-2-yl)butyl)]benzenesulfonamide <u>519</u>



To a solution of amine **517** (106 mg, 0.31 mmol) in methanol (2 cm^3) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 45 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent concentrated *in vacuo* to afford alkane **519** (104 mg, 98%) as an orange oil with no further purification performed; R_f 0.58 (solvent *A*); ν_{max}(film)/cm^{-1} 2254, 1160 and 908; δ_H(400 MHz; $CDCl_3$) 0.64 (3 H, t, *J* 7.4, CH_3), 0.84 (3 H, t, *J* 7.4, CH_3), 1.20–1.40 (4 H, m, 2×CH_2CH_3), 1.63-1.71 (1 H, m, NCHCH_2), 1.83-1.91 (1 H, m, NCHCH_2), 2.43 (3 H, s, CH_3), 2.75-2.80 (1 H, m, CH_2), 2.88-2.97 (1 H, m, CH_2), 4.90 (1 H, t, *J* 7.7, NC*H*), 5.92 (1 H, d, *J* 3.3, C*H*=CO), 6.13 (1 H, dd, *J* 1.9 and 3.3, *CHCO*), 7.17 (2 H, d, *J* 8.0, 2×C*H*) and 7.61 (2 H, d, *J* 8.0, 2×C*H*); δ_C(100 MHz; $CDCl_3$) 11.3 (CH_3), 13.8 ($HNCHCH_2CH_2CH_3$), 19.7 ($HNCHCH_2CH_2CH_3$), 21.5 ($PhCH_3$), 23.8 (H_3CCH_2), 34.2 ($H_3CCH_2CH_2$), 46.5 ($HNCHCH_2CH_2CH_3$), 55.0 ($HNCHCH_2CH_2CH_3$), 108.2 (*C*H), 110.1 (*C*H), 127.4 (2×*C*H), 129.2 (2×*C*H), 138.2 (CCH_3), 141.8 (SO_2C), 142.7 (*C*CHNH) and 153.0 ($CH_3CH_2CH_2C$); MS (CI) *m*/*z* 336.4 $[M+H]^+$; HRMS *m*/*z* 336.1637 (336.1634 calcd for $C_{18}H_{26}NO_3S$, $M+H^+$).

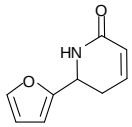
***N*-(1-Furan-2-yl-but-3-enyl)acrylamide <u>551</u>**[226]



To a stirring, room temperature, solution of acryloyl chloride (70 μL, 0.801 mmol) and diisopropylethylamine (0.14 cm^3, 0.801 mmol) in dry dichloromethane (4 cm^3) under argon, was added a solution of amine **490** (100 mg, 0.729 mmol) and diisopropylethylamine (0.13 cm^3, 0.729 mmol) in dry dichloromethane (7 cm^3). The resulting bright yellow solution was stirred for 2 h, whereafter it was quenched with saturated aqueous ammonium chloride (15 cm^3) and diluted with dichloromethane (15 cm^3). The organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (60:40)] of the crude residue afforded amide **551** (139 mg, 100%) as a pale yellow oil; R_f 0.52

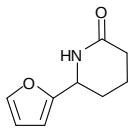
(solvent *I*); δ_H(400 MHz; $CDCl_3$) 2.61 (2 H, t, *J* 6.9, CH_2), 5.06-5.13 (2 H, m, CH=CH_2), 5.26-5.30 (1 H, m, C*H*N), 5.62-5.76 (2 H, m, CH_2CH=CH_2 and COCH=CH_2), 6.09-6.14 (1 H, m, COCH=CH_2), 6.20 (1 H, dd, *J* 0.6 and 3.0, C*H*=CO), 6.28 (1 H, d, *J* 1.4, C*H*CO), 6.31 (1 H, dd, *J* 1.4 and 3.0, COC*H*=CH_2) and 7.33 (1 H, d, *J* 0.9, C*H*O). The spectral data matches that reported in the literature.[226]

6-Furan-2-yl-5,6-dihydro-1*H*-pyridin-2-one 550



A solution of amide **551** (316 mg, 1.65 mmol) in dry dichloromethane (17 cm3) under argon was treated with Grubbs first generation catalyst (136 mg, 0.165 mmol). The reaction mixture was heated under reflux in the dark for 18 h, then concentrated under reduced pressure and the residue passed through a short column of silica gel, eluting with ethyl acetate, to give cyclic amide **550** (226 mg, 84%) as a brown solid with no further purification necessary; R_f 0.07 (solvent *C*); mp 96-98 °C (from ethyl acetate) (lit.,[226] 98-99 °C); δ_H(400 MHz; $CDCl_3$) 2.68-2.71 (2 H, m, CH_2), 4.80 (1 H, t, *J* 7.5, C*H*N), 5.97 (1 H, d, *J* 10.0, C*H*=$CHCH_2$), 6.25 (1 H, d, *J* 3.2, C*H*=CO), 6.34 (1 H, dd, *J* 1.8 and 3.2, C*H*CO), 6.61 (1 H, dt, *J* 4.2 and 10.0, CH=C*H*CH_2) and 7.39 (1 H, s, C*H*O); δ_C(100 MHz; $CDCl_3$) 27.6 (*C*H_2), 47.2 (*C*HN), 104.8 (*C*H), 108.9 (*C*H), 122.8 (*C*H=$CHCH_2$), 138.1 (CH=*C*HCH_2), 140.7 (*C*HO), 151.6 (*C*) and 164.2 (*C*=O); MS (CI) *m*/*z* 164.2 $[M+H]^+$; HRMS 164.0710 (164.0712 calcd for $C_9H_{10}NO_2$, $M+H^+$). The spectral data matches that reported in the literature.[226]

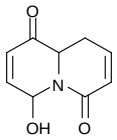
6-Furan-2-yl-piperidin-2-one 552[186]



To a solution of amide **550** (56 mg, 0.345 mmol) in methanol (2 cm^3) was treated with a catalytic amount of 10% palladium on activated carbon. The flask was evacuated and after purging three times with hydrogen gas *via* a balloon, the mixture was stirred under an atmosphere of hydrogen for 35 min at room temperature. TLC analysis deemed the reaction complete and the solution was filtered through a pad of Celite® to remove the catalyst and the solvent

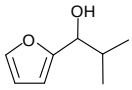
concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (20:80)] of the crude residue afforded lactam **552** (40 mg, 79%) as a white solid; R_f 0.24 (ethyl acetate); δ_H(400 MHz; $CDCl_3$) 1.76-1.87 (1 H, m, $OCCH_2CH_2$), 1.91-2.02 (2 H, m, $OCCH_2CH_2$ and $OCCH_2CH_2CH_2$), 2.11-2.20 (1 H, m, $OCCH_2CH_2CH_2$), 2.42-2.48 (2 H, m, $OCCH_2$), 4.67 (1 H, t, *J* 6.0, CHNH), 6.25 (1 H, d, *J* 3.2, CH=CO), 6.38 (1 H, dd, *J* 1.9 and 3.2, CHCO) and 7.40 (1 H, d, *J* 1.9, CHO); MS (CI) *m/z* 166.25 $[M+H]^+$; HRMS *m/z* 166.0864 (166.0868 calcd for $C_9H_{12}NO_2$, $M+H^+$). The spectral data matches that reported in the literature.[186].

4-Hydroxy-9,9a-dihydro-4*H*-quinolizine-1,6-dione 549



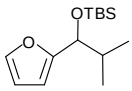
A solution of lactam **550** (46 mg, 0.218 mmol) in chloroform (10 cm^3) was treated with *meta*-chloroperoxybenzoic acid (*m*CPBA) (139 mg, 0.620 mmol) in one portion at room temperature. The reaction mixture was heated to 60 °C for 3.5 h, then cooled down to room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (10 cm^3) and saturated aqueous sodium hydrogen carbonate (10 cm^3) added. The organic layer was washed with a further amount of saturated aqueous sodium hydrogen carbonate (15 cm^3), water (15 cm^3) and saturated aqueous sodium chloride (15 cm^3). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate, (30:70)] of the crude residue afforded the bicyclic lactam **549** (40 mg, 70%) as a yellow oil; R_f 0.40 (solvent *J*); δ_H(400 MHz; $CDCl_3$) 2.70-2.75 (2 H, m, $H_2CCH=CH$), 4.44 (1 H, t, *J* 8.1, HCN), 5.90 (1 H, dt, *J* 1.9 and 10.0, $H_2CCH=CH$), 6.09 (1 H, d, *J* 10.1, O=CCH=CHCHOH), 6.14 (1 H, d, *J* 4.9, O=CCH=CHCHOH), 6.55-6.60 (1 H, m, $H_2CCH=CH$) and 6.99 (1 H, dd, *J* 4.9 and 10.1, O=CCH=CHCHOH); δ_C(100 MHz; $CDCl_3$) 22.7 (CH_2), 56.6 (CHN), 74.8 (HOCH), 122.9 ($CH_2CH=CH$), 126.9 (HOCHCH=CH), 138.5 (CH_2CH), 142.8 (HOCHCH), 157.9 (NCO) and 192.7 (C=O); MS (CI) *m/z* 162.19 $[M-OH]^+$, 180.21 $[M+H]^+$; HRMS 180.0675 (180.0660 calcd for $C_9H_{10}NO_3$, $M+H^+$).

1-Furan-2-yl-2-methyl-propan-1-ol 554[207]



To a solution of furan (5.0 g, 73.4 mmol) in diethyl ether (150 cm^3) at 0 °C, was added *N,N,N',N'*-tetramethylethylenediamine (11.0 cm^3, 73.4 mmol), followed by *n*BuLi (32.3 cm^3, 80.7 mmol). The reaction mixture was stirred at 0 °C for 1 h, then warmed up to room temperature and stirred for a further 1 h. After this time, the reaction mixture was cooled to –78 °C and *iso*butyraldehyde (7.33 cm^3, 80.7 mmol) was added. After 3 h at –78 °C, the reaction was diluted with diethyl ether (50 cm^3) and quenched with water (50 cm^3). The organic layer was separated, washed with water (3×50 cm^3), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. Purification by FCC [diethyl ether-petroleum ether (30:70)] of the crude residue afforded furfuryl alcohol **554** (9.82 g, 96%) as a pale yellow oil; δ_H(400 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 6.8, CH_3), 1.02 (3 H, d, *J* 6.8, CH_3), 1.94 (1 H, br s, OH), 2.10-2.13 (1 H, m, C*H*$(CH_3)_2$), 4.37 (1 H, d, *J* 6.8, C*H*OH), 6.27 (1 H, d, *J* 3.2, C*H*=CO), 6.33 (1 H, dd, *J* 1.8 and 3.2, C*H*CO) and 7.30 (1 H, d, *J* 1.8, C*H*O). The spectral data matches that reported in the literature.[207]

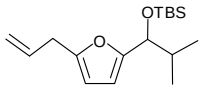
***tert*-Butyl-(1-furan-2-yl-2-methyl-propoxy)-dimethyl-silane 452**



To a solution of furfuryl alcohol **554** (5.90 g, 42.1 mmol) in dichloromethane (210 cm^3) at 0 °C, was added triethylamine (17.6 cm^3, 126.3 mmol) and the reaction mixture was stirred for 10 min. *tert*-Butyldimethylsilyl chloride (9.52 g, 63.1 mmol) and dimethylaminopyridine (2.57 g, 21.1 mmol) were added successively and the reaction was warmed up to room temperature. After 16 h, further portions of triethylamine (17.6 cm^3, 126.3 mmol), dimethylaminopyridine (2.57 g, 21.1 mmol) and *tert*-butyldimethylsilyl chloride (9.52 g, 63.1 mmol) were added and the mixture stirred for a further 24 h. The reaction was quenched with 1% hydrochloric acid (40 cm^3) and extracted with dichloromethane (50 cm^3). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (50 cm^3), water (2×50 cm^3) and saturated aqueous sodium chloride (50 cm^3). The solution was then dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification

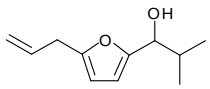
by FCC [diethyl ether-petroleum ether (20:80) *then* (5:95) *then* (0:100)] of the crude residue afforded silyl ether **452** (8.97 g, 84%) as a colourless oil; R_f 0.62 (solvent *L*); δ_H(400 MHz; $CDCl_3$) -0.18 (3 H, s, Si(CH_3)$_2$), 0.00 (3 H, s, Si(CH_3)$_2$), 0.77 (3 H, d, *J* 6.7, CH_3), 0.85 (9 H, s, SiC(CH_3)$_3$), 0.93 (3 H, d, *J* 6.7, CH_3), 1.98-2.01 (1 H, m, CH), 4.29 (1 H, d, *J* 6.8, OC*H*), 6.11 (1 H, d, *J* 3.1, C*H*=CO), 6.27 (1 H, dd, *J* 1.8 and 3.1, C*H*CO) and 7.30 (1 H, d, *J* 1.8, C*H*O); δ_C(100 MHz; $CDCl_3$) -5.9 (Si(*C*H$_3$)$_2$), 18.0 (Si*C*(CH$_3$)$_3$, 18.5 (CH*C*H$_3$), 19.0 (CH*C*H$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 35.2 (*C*H(CH$_3$)$_2$), 76.8 (*C*HOTBS), 108.8 (*C*H=CO), 109.7 (*C*HCO), 152.5 (*C*CHOTBS) and 155.5 (*C*); MS (EI) *m/z* 123.1 [M-OTBS]$^+$; HRMS *m/z* 123.0813 (123.0810 calcd for $C_8H_{11}O$, M-OTBS$^+$).

[1-(5-Allyl-furan-2-yl)-2-methyl-propoxy]-*tert*-butyl-dimethyl-silane <u>555</u>



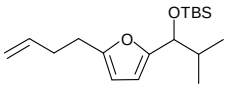
To a solution of silyl ether **452** (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 ^{o}C was added *n*BuLi (2.36 cm^3, 5.89 mmol). The resulting yellow solution was stirred at 0 ^{o}C for 15 min and then allowed to warm up to room temperature and stirred for 15 min. After recooling down to 0 ^{o}C, allyl bromide (0.41 cm^3, 4.71 mmol) was added and the mixture was stirred for 15 min. The reaction was allowed to warm up to room temperature and after 16 h, the reaction was diluted with diethyl ether (30 cm^3) and quenched with water (50 cm^3). The phases were separated and the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford alkene **555** (1.06 g, 92%) as a yellow oil with further purification necessary; R_f 0.70 (solvent *L*); ν_{max}(film)/cm^{-1} 2981, 1610 (C=C) and 1145 (O-Si); δ_H(400 MHz; $CDCl_3$) -0.16 (3 H, s, Si(CH_3)$_2$), 0.00 (3 H, s, Si(CH_3)$_2$), 0.77 (3 H, d, *J* 6.7, CHCH_3), 0.88 (9 H, s, SiC(CH_3)$_3$), 0.93 (3 H, d, *J* 6.7, CHCH_3), 1.94-2.02 (1 H, m, C*H*(CH$_3$)$_2$), 3.33 (2 H, d, *J* 6.4, CH_2), 4.22 (1 H, d, *J* 6.9, C*H*OTBS), 5.05-5.12 (2 H, m, CH_2=CH), 5.85-5.95 (1 H, m, C*H*=CH$_2$), 5.89 (1 H, d, *J* 3.1, C*H*=CO) and 6.02 (1 H, d, *J* 3.1, C*H*CO); δ_C(100 MHz; $CDCl_3$) -5.2 (Si(*C*H$_3$)$_2$), -4.9 (Si(*C*H$_3$)$_2$), 18.2 (Si*C*(CH$_3$)$_3$), 18.4 (CH*C*H$_3$), 18.9 (CH*C*H$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 32.6 (CH$_2$), 34.2 (*C*H(CH$_3$)$_2$), 74.2 (*C*HOTBS), 105.8 (*C*H=CO), 107.0 (*C*HCO), 116.5 (*C*H$_2$=CH), 134.3 (CH$_2$=*C*H), 152.3 (*C*CHOTBS) and 155.5 (CH$_2$=CHCH$_2$*C*); MS (CI) *m/z* 163 [M-OTBS]$^+$; HRMS *m/z* 163.1119 (163.1123 calcd for $C_{11}H_{15}O$, M-OTBS$^+$).

1-(5-Allyl-furan-2-yl)-2-methyl-propan-1-ol 558[157]



To a solution of silyl ether **555** (1.06 g, 4.19 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 °C, was added *tetra*-butylammonium fluoride (8.4 cm^3, 8.38 mmol). The ice-water bath was removed after 10 min and the reaction was left to stir overnight. The reaction mixture was then diluted with diethyl ether (30 cm^3) and water (30 cm^3) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded alcohol **558** (513 mg, 87%) as a colourless oil; R_f 0.26 (solvent *D*); ν_{max}(film)/cm^{-1} 3550 (OH), 2968, 2940 and 1459; δ_H(400 MHz; $CDCl_3$) 0.75 (3 H, d, *J* 6.7, CHCH_3), 0.91 (3 H, d, *J* 6.7, CHCH_3), 1.71 (1 H, d, *J* 5.2, OH), 1.98 (1 H, oct., *J* 6.8, CH(CH_3)$_2$), 3.28 (2 H, dd, *J* 0.7 and 6.5, CH_2=CHCH_2), 4.19 (1H, dd, *J* 5.2 and 7.0, CHOH), 4.98-5.06 (2 H, m, CH_2=CH), 5.78-5.89 (1 H, m, CH_2=CH), 5.85 (1 H, d, *J* 3.1, CH=CO) and 6.03 (1 H, d, *J* 3.1, CHCO); MS (EI) *m*/*z* 163 $[M\text{-}OH]^+$; HRMS *m*/*z* 181.1225 (181.1229 calcd for $C_{11}H_{17}O_2$, $M+H^+$). The spectral data matches that reported in the literature.[157]

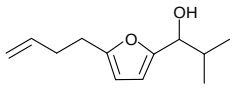
[1-(5-But-3-enyl-furan-2-yl)-2-methyl-propoxy]-*tert*-butyl-dimethyl-silane 451



To a solution of silyl ether **452** (1.2 g, 4.71 mmol) in anhydrous tetrahydrofuran (25 cm^3) at 0 °C, was added *n*BuLi (2.82 cm^3, 7.06 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0 °C, before 4-bromo-1-butene (0.59 cm^3, 5.65 mmol) was added. The reaction was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (40 cm^3) and water (60 cm^3), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford alkene **451** (1.32 g, 91%) as a yellow oil; R_f 0.72 (solvent *L*); ν_{max}(film)/cm^{-1} 2969, 1621 and 1152 (O-Si); δ_H(400 MHz; $CDCl_3$) -0.14 (3 H, s, Si(CH_3)$_2$), 0.00 (3 H, s, Si(CH_3)$_2$), 0.79 (3 H, d, *J* 6.7, CHCH_3), 0.86 (9 H, s, SiC(CH_3)$_3$), 0.93 (3 H, d,

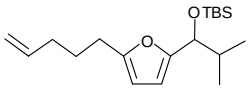
J 6.7, CHC*H*$_3$), 1.97-2.01 (1 H, m, C*H*(CH$_3$)$_2$), 2.28-2.32 (2 H, m, CH$_2$=CHC*H*$_2$), 2.93-2.95 (2 H, m, CH$_2$=CHCH$_2$C*H*$_2$), 4.20 (1 H, d, *J* 6.9, C*H*OTBS), 5.03-5.12 (2 H, m, C*H*$_2$=CH), 5.85-5.90 (1 H, m, CH$_2$=C*H*), 5.89 (1 H, d, *J* 3.2, C*H*=CO) and 6.02 (1 H, d, *J* 3.2, C*H*CO); δ_C(100 MHz; CDCl$_3$) -5.1 (Si(*C*H$_3$)$_2$), -4.8 (Si(*C*H$_3$)$_2$), 18.3 (Si*C*(CH$_3$)$_3$), 18.5 (CH*C*H$_3$), 19.0 (CH*C*H$_3$), 25.5 (C(*C*H$_3$)$_3$), 30.3 (CH$_2$*C*H$_2$), 32.6 (*C*H$_2$CH$_2$), 34.2 (*C*H(CH$_3$)$_2$), 74.0 (*C*HOTBS), 105.5 (*C*H=CO), 107.2 (*C*HCO), 116.6 (*C*H$_2$=CH), 134.5 (CH$_2$=*C*H), 152.1 (*C*CHOTBS) and 155.4 (CH$_2$=CHCH$_2$*C*); MS (CI) *m*/*z* 177 [M-OTBS]$^+$; HRMS *m*/*z* 177.1281 (177.1279 calcd for C$_{12}$H$_{17}$O, M-OTBS$^+$).

1-(5-But-3-enyl-furan-2-yl)-2-methyl-propan-1-ol 450[157]



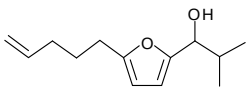
To a solution of silyl ether **451** (1.3 g, 4.21 mmol) in anhydrous tetrahydrofuran (20 cm^3) was added *tetra*-butylammonium fluoride (8.4 cm^3, 8.42 mmol) at 0 °C. The ice-water bath was removed after 10 min and the reaction was left to stir overnight at room temperature. The reaction mixture was then diluted with diethyl ether (30 cm^3) and water (30 cm^3) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue afforded alcohol **450** (818 mg, 81%) as a colourless oil; R_f 0.26 (solvent *D*); δ_H(400 MHz; CDCl$_3$) 0.71 (3 H, d, *J* 6.7, CHC*H*$_3$), 0.89 (3 H, d, *J* 6.7, CHC*H*$_3$), 1.67 (1 H, d, *J* 5.1, OH), 1.96 (1 H, oct., *J* 6.8, C*H*(CH$_3$)$_2$), 2.25 (2 H, q, *J* 7.6, CH$_2$=CHC*H*$_2$), 2.58 (2 H, t, *J* 7.6, CH$_2$=CHCH$_2$C*H*$_2$), 4.16 (1 H, dd, *J* 5.2 and 7.1, C*H*OH), 4.82-4.94 (2 H, m, C*H*$_2$=CH), 5.65-5.75 (1 H, m, CH$_2$=C*H*), 5.80 (1 H, d, *J* 3.0, C*H*=CO) and 6.02 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; CDCl$_3$) 18.4 (CH*C*H$_3$), 18.8 (CH*C*H$_3$), 27.6 (CH$_2$=CH*C*H$_2$), 32.1 (CH$_2$=CHCH$_2$*C*H$_2$), 33.3 (*C*H(CH$_3$)$_2$), 73.6 (*C*HOH), 105.4 (*C*H=CO), 107.1 (*C*HCO), 115.3 (*C*H$_2$=CH), 137.5 (CH$_2$=*C*H), 154.3 (*C*CHOH) and 154.9 (CH$_2$=CHCH$_2$CH$_2$*C*); MS (EI) *m*/*z* 177.0 [M-OH]$^+$; HRMS *m*/*z* 177.1281 (177.1279 calcd for C$_{12}$H$_{17}$O, M-OH$^+$). The spectral data matches that reported in the literature.[157]

[1-(5-Pent-4-enyl-furan-2-yl)-2-methyl-propoxy]-*tert*-butyl-dimethyl-silane 556



To a solution of silyl ether **452** (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 °C, was added *n*BuLi (2.35 cm^3, 5.89 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0 °C, before 5-bromo-1-pentene (0.56 cm^3, 4.71 mmol) was added. The reaction was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (40 cm^3) and water (50 cm^3), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford alkene **556** (1.09 g, 86%) as a yellow oil with no further purification carried out; R_f 0.71 (solvent *L*); δ_H(400 MHz; $CDCl_3$) -0.12 (3 H, s, Si(CH_3)$_2$), 0.00 (3 H, s, Si(CH_3)$_2$), 0.79 (3 H, d, *J* 6.7, CHCH_3), 0.86 (9 H, s, SiC(CH_3)$_3$), 0.93 (3 H, d, *J* 6.7, CHCH_3), 1.87-1.92 (2 H, m, CH_2=CHCH_2CH_2), 1.97-2.03 (1 H, m, C*H*(CH_3)$_2$), 2.18-2.21 (2 H, m, CH_2=CHCH_2), 2.92-2.97 (2 H, m, CH_2=CHCH_2CH_2CH_2), 4.20 (1 H, d, *J* 7.0, C*H*OTBS), 5.03-5.12 (2 H, m, CH_2=CH), 5.85-5.90 (1 H, m, CH_2=C*H*), 5.88 (1 H, d, *J* 3.2, C*H*=CO) and 6.02 (1 H, d, *J* 3.2, C*H*CO); δ_C(100 MHz; $CDCl_3$) -5.1 (Si(CH_3)$_2$), -4.8 (Si(CH_3)$_2$), 18.3 (Si*C*(CH_3)$_3$), 18.5 (CH*C*H_3), 19.0 (CH*C*H_3), 25.5 (C(*C*H_3)$_3$), 29.9 (CH_2*C*H_2CH_2), 32.6 (*C*H_2CH_2CH_2), 34.2 (*C*H(CH_3)$_2$), 38.4 (CH_2CH_2*C*H_2), 74.0 (*C*HOTBS), 105.5 (*C*H=CO), 107.2 (*C*HCO), 116.6 (*C*H_2=CH), 134.5 (CH_2=*C*H), 152.1 (*C*CHOTBS) and 155.4 (CH_2=CHCH_2*C*); MS (CI) *m/z* 191 [M-OTBS]$^+$; HRMS *m/z* 191.1433 (191.1436 calcd for $C_{13}H_{19}O$, M-OTBS$^+$).

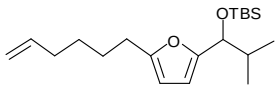
2-Methyl-1-(5-pent-4-enyl-furan-2-yl)-propan-1-ol 559



To a solution of silyl ether **556** (1.0 g, 3.10 mmol) in anhydrous tetrahydrofuran (15 cm^3) was added *tetra*-butylammonium fluoride (6.2 cm^3, 6.20 mmol) at 0 °C. The ice-water bath was removed after 10 min and the reaction left to stir overnight at room temperature. The reaction mixture was then diluted with diethyl ether (25 cm^3) and water (25 cm^3) was added. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in*

vacuo. Purification by FCC [petroleum ether-ethyl acetate (90:10)→(85:15)] of the crude residue afforded alcohol **559** (514 mg, 80%) as a pale yellow oil; R_f 0.45 (solvent *A*). Also obtained was a mixture of alcohol **559** and silyl ether **452** of which approximately 15% was silyl ether **452**; δ_H(400 MHz; $CDCl_3$) 0.75 (3 H, d, *J* 6.8, CHC*H*$_3$), 0.93 (3 H, d, *J* 6.8, CHC*H*$_3$), 1.64 (2 H, q, *J* 7.6, CH_2=CHCH$_2$C*H*$_2$), 1.93-2.06 (3 H, m, CH_2=CHC*H*$_2$ and C*H*(CH_3)$_2$), 2.51 (2 H, t, *J* 7.6, CH_2=CHCH$_2$CH$_2$C*H*$_2$), 4.19 (1 H, dd, *J* 3.6 and 6.4, C*H*OH), 4.86-4.97 (2 H, m, C*H*$_2$=CH), 5.68-5.76 (1 H, m, CH_2=C*H*), 5.81 (1 H, d, *J* 3.0, C*H*=CO) and 6.00 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) 18.4 (CH*C*H$_3$), 18.8 (CH*C*H$_3$), 27.2 (CH_2=CHCH$_2$*C*H$_2$), 27.4 (CH_2=CH*C*H$_2$), 33.2 (*C*H(CH_3)$_2$), 33.3 (CH_2=CHCH$_2$CH$_2$*C*H$_2$), 73.6 (*C*HOH), 105.3 (*C*H=CO), 107.1 (*C*HCO), 115.0 (*C*H$_2$=CH), 138.2 (CH_2=*C*H), 154.3 (*C*CHOH) and 155.3 (CH_2=CHCH$_2$CH$_2$CH$_2$*C*); MS (EI) *m*/*z* 191 $[M\text{-}OH]^+$; HRMS *m*/*z* 191.1433 (191.1436 calcd for $C_{13}H_{19}O$, $M\text{-}OH^+$).

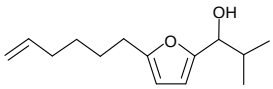
[1-(5-Hex-5-enyl-furan-2-yl)-2-methyl-propoxy]-*tert*-butyl-dimethylsilane
557



To a solution of silyl ether **452** (1.0 g, 3.93 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 °C, was added *n*BuLi (2.36 cm^3, 5.89 mmol). The resulting yellow solution was stirred at 0 °C for 15 min and then allowed to warm up to room temperature. The solution was stirred at room temperature for 15 min and then recooled back down to 0 °C, before 6-bromo-1-pentene (0.63 cm^3, 4.71 mmol) was added. The reaction was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 16 h, the reaction was diluted with diethyl ether (30 cm^3) and water (40 cm^3), the organic layers were separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford alkene **557**. ^{1}H NMR spectroscopy of the crude residue showed that approximately 19% of starting material **452** remained, which was inseparable from the product (R_f 0.58 (solvent *L*)) by FCC. Therefore alkene **557** was taken on crude to the next step; ν_{max}(film)/cm^{-1} 2929, 2857, 2251, 1676 (C=C), 1254 and 1068 (O-Si); δ_H(400 MHz; $CDCl_3$) -0.17 (3 H, s, Si(CH_3)$_2$), -0.09 (3 H, s, Si(CH_3)$_2$), 0.76 (3 H, d, *J* 6.8, CH_3), 0.82 (9 H, s, SiC(CH_3)$_3$), 0.94 (3 H, d, *J* 6.8, CH_3), 1.40 (1 H, dt, *J* 7.5 and 15.1, CH_2=CHCH$_2$C*H*$_2$), 1.60 (1 H, dt, *J* 7.5 and 15.1, CH_2=CHCH$_2$CH$_2$C*H*$_2$), 1.95-2.10 (3 H, m, C*H*(CH_3)$_2$ and CH_2=CHC*H*$_2$), 2.57 (2

H, t, *J* 7.5, CH_2=CHCH$_2$CH$_2$CH$_2$C*H*$_2$), 4.20 (1 H, d, *J* 7.1, C*H*OTBS), 4.88-5.01 (2 H, m, C*H*$_2$=CH), 5.72-5.80 (1 H, m, CH_2=C*H*), 5.83 (1 H, d, *J* 3.0, C*H*=CO) and 5.97 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) -5.3 (Si(*C*H$_3$)$_2$), -4.9 (Si(*C*H$_3$)$_2$), 18.3 (*C*H$_3$), 18.6 (*C*H$_3$), 18.8 (Si*C*(CH$_3$)$_3$), 25.7 (CH_2=CHCH$_2$*C*H$_2$), 25.8 (CH_2=CHCH$_2$CH$_2$*C*H$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 28.3 (CH_2=CH*C*H$_2$), 33.5 (CH_2=CHCH$_2$CH$_2$CH$_2$*C*H$_2$), 34.2 (*C*H(CH$_3$)$_2$), 74.3 (*C*HOTBS), 104.9 (*C*H=CO), 106.9 (*C*HCO), 114.4 (*C*H$_2$=CH), 138.8 (CH_2=*C*H), 154.8 (*C*CHOTBS) and 154.9 (CH_2=CH(CH$_2$)$_4$*C*); MS (CI) *m/z* 205 [M-OTBS]$^+$, 221 [M-TBS]$^+$; HRMS *m/z* 221.1546 (221.1542 calcd for $C_{14}H_{21}O_2$, M-TBS$^+$).

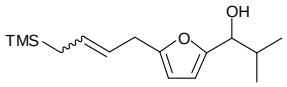
1-(5-Hex-5-enyl-furan-2-yl)-2-methyl-propan-1-ol <u>560</u>



To a stirred solution of silyl ether **557** (1.32 g, 3.91 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0 ^{o}C, was added *tetra*-butylammonium fluoride (7.82 cm^3, 7.82 mmol). The ice-water bath was removed after 10 min and the reaction allowed to warm up to room temperature, whereafter it was stirred for 16 h. Due to the remainder of some starting material, further *tetra*-butylammonium fluoride (1.10 cm^3, 1.10 mmol, 0.3 eq.) was added at 0 ^{o}C. After a further 4 h, there was still incomplete consumption of starting material so work up was carried out. The reaction was diluted with diethyl ether (30 cm^3) and water (30 cm^3), the organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-diethyl ether (90:10)→(85:15)] of the crude residue afforded **560** (494 mg, 57%) as a colourless oil; R_f 0.25 (solvent *D*); ν_{max}(film)/cm^{-1} 3387 (OH), 2931, 2870, 1643 (C=C), 1180, 1010 and 910; δ_H(400 MHz; $CDCl_3$) 0.74 (3 H, d, *J* 6.8, CHC*H*$_3$), 0.92 (3 H, d, *J* 6.8, CHC*H*$_3$), 1.33 (2 H, qn, *J* 7.6, CH_2=CH(CH$_2$)$_2$C*H*$_2$)), 1.52 (2 H, qn, *J* 7.6, CH_2=CHCH$_2$C*H*$_2$), 1.69 (1 H, d, *J* 5.1, C*H*(CH$_3$)$_2$), 1.98 (2 H, q, *J* 7.5, CH_2=CHC*H*$_2$), 2.50 (2 H, t, *J* 7.6, CH_2=CH(CH$_2$)$_3$CH$_2$), 4.19 (1 H, dd, *J* 5.3 and 7.2, C*H*OH), 4.81-4.92 (2 H, m, C*H*$_2$=CH), 5.64-5.75 (1 H, m, CH_2=C*H*), 5.80 (1 H, d, *J* 3.0, CH=CO) and 6.00 (1 H, d, *J* 3.0, CHCO); δ_C(100 MHz; $CDCl_3$) 18.4 (CH*C*H$_3$), 18.8 (CH*C*H$_3$), 24.5 (CH_2=CHCH$_2$*C*H$_2$), 27.9 (CH_2=CH(CH$_2$)$_2$*C*H$_2$), 28.4 (CH_2=CH*C*H$_2$), 33.3 (*C*H(CH$_3$)$_2$), 33.5 (CH_2=CH(CH$_2$)$_3$*C*H$_2$), 73.6 (CHOH), 105.1 (*C*H=CO), 107.1 (*C*HCO), 114.5 (*C*H$_2$=CH), 138.7 (CH_2=*C*H), 154.1 (*C*CHOH) and 155.7 (CH_2=CH(CH$_2$)$_4$*C*); MS (EI)

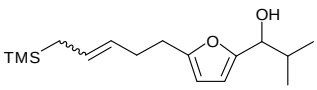
m/*z* 222.1 $[M]^+$; HRMS *m*/*z* 222.1618 (222.1620 calcd for $C_{14}H_{22}O_2$, M^+). The spectral data matches that reported in the literature.[157]

(*E*/*Z*)-2-Methyl-1-(5-(4-(trimethylsilyl)but-2-enyl)furan-2-yl)propan-1-ol 561



Anhydrous dichloromethane (5 cm^3) was added to a mixture of alkene **558** (107 mg, 0.764 mmol) and allyltrimethylsilane (0.36 cm^3, 2.29 mmol). The reaction mixture was heated to reflux under an argon atmosphere after which Grubbs second generation catalyst (32 mg, 0.0382 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled to room temperature and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded allylsilane **561** (72 mg, 36%) as a yellow oil and as an inseparable *E*:*Z*-mixture (7:2); R_f 0.61; ν_{max}(film)/cm^{-1} 3433 (OH), 2962, 1681 (C=C), 1249 and 1018 (O-Si); δ_H (400 MHz; $CDCl_3$) (*E* isomer) 0.01 (9 H, s, Si(CCH_3)$_3$), 0.86 (3 H, d, *J* 6.8, CHCH_3), 1.03 (3 H, d, *J* 6.8, CHCH_3), 1.46 (2 H, dd, *J* 1.2 and 8.0, CH_2TMS), 1.78 (1 H, d, *J* 5.2, OH), 2.05-2.15 (1 H, m, C*H*(CH_3)$_2$), 3.32 (2 H, dd, *J* 6.8 and 11.8, CH_2), 4.30 (1 H, dd, *J* 5.2 and 7.2, C*H*OH), 5.30-5.60 (2 H, m, J_{trans} 15.1, C*H*=C*H*), 5.99 (1 H, d, *J* 3.3, C*H*=CO) and 6.12 (1 H, d, *J* 3.3, C*H*CO); δ_C(100 MHz; $CDCl_3$) -1.5 (3×*C*H_3), 15.5 (2×*C*H_3), 24.3 (TMS*C*H_2), 31.8 (*C*H_2), 35.0 (H*C*(CH_3)$_2$), 74.5 (H*C*OH), 106.8 (*C*H), 109.1 (*C*H), 127.8 (*C*H=*C*H), 144.5 (CH_2*C*) and 151.1 (*C*HCOH); MS (FAB) *m*/*z* 249 $[M\text{-}OH]^+$; HRMS *m*/*z* 249.1670 (249.1675 calcd for $C_{15}H_{25}OSi$, $M\text{-}OH^+$).

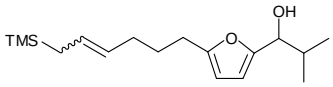
2-Methyl-1-[5-((*E*/*Z*)-5-trimethylsilanyl-pent-3-enyl)-furan-2-yl]-propan-1-ol 449



Anhydrous dichloromethane (5 cm^3) was added to a mixture of alkene **450** (123 mg, 0.632 mmol) and allyltrimethylsilane (0.30 cm^3, 1.89 mmol) and the reaction heated to reflux after which Grubbs second generation catalyst (27 mg, 0.0316 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded allylsilane **449** (92 mg, 52%) as a yellow oil and as an inseparable mixture *E*:*Z*-mixture

(6.15:1); ν_{max}(film)/cm^{-1} 3441 (OH), 2955, 1689 (C=C), 1250 and 1041 (O-Si); δ_H(400 MHz; $CDCl_3$) 0.04 (9 H, s, (Si(C*H*$_3$)$_3$), 0.88 (3 H, d, *J* 6.8, CHC*H*$_3$), 1.07 (3 H, d, *J* 6.8, CHC*H*$_3$), 1.42 (2 H, d, *J* 7.9, C*H*$_2$TMS), 2.12 (1 H, sext., *J* 6.8, C*H*(CH$_3$)$_2$), 2.34 (2 H, q, *J* 7.0, C*H*$_2$CH$_2$), 2.67 (2 H, t, *J* 7.0, CH$_2$C*H*$_2$), 4.32-4.34 (1 H, m, C*H*OH), 5.24-5.50 (2 H, m, J_{trans} 15.0, C*H*=C*H*), 5.94 (1 H, d, *J* 3.1, C*H*=CO) and 6.13 (1 H, d, *J* 3.1, C*H*CO); δ_C(100 MHz; $CDCl_3$) -1.7 (3×*C*H$_3$), 15.8 (2×*C*H$_3$), 24.3 (TMS*C*H$_2$), 28.5 (CH$_2$*C*H$_2$), 31.9 (*C*H$_2$CH$_2$), 35.0 (H*C*(CH$_3$)$_2$), 74.5 (H*C*OH), 106.8 (*C*H), 109.1 (*C*H), 127.8 (*C*H=*C*H), 149.5 (CH$_2$*C*) and 151.6 (*C*HCOH); MS (CI) *m*/*z* 263.3 [M-OH]$^+$, 279.3 [M-H]$^+$; HRMS *m*/*z* 280.1763 (280.1859 calcd for $C_{16}H_{28}O_2Si$, M^+).

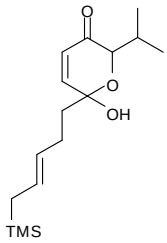
2-Methyl-1-[5-((*E*/*Z*)-6-trimethylsilanyl-hex-4-enyl)-furan-2-yl]-propan-1-ol **562**



Anhydrous dichloromethane (5 cm^3) was added to **559** (200 mg, 0.960 mmol) and allyltrimethylsilane (0.53 cm^3, 3.36 mmol) and the reaction heated to reflux after which Grubbs second generation catalyst (41 mg, 0.048 mmol) was added. The reaction mixture was heated under reflux in the dark for 48 h, cooled and the solvent concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (90:10)] of the crude residue afforded **562** (127 mg, 45%) as a yellow oil and as an inseparable *E*:*Z*-mixture (2:1); R_f 0.52 (Solvent *A*); ν_{max}(film)/cm^{-1} 3394 (OH), 2955, 1249, 1010 (O-Si) and 964; δ_H(400 MHz; $CDCl_3$) 0.00 (9 H, s, (Si(C*H*$_3$)$_3$), 0.86 (3 H, d, *J* 6.8, CH(C*H*$_3$)), 1.03 (3 H, d, *J* 6.8, C*H*(CH$_3$)), 1.42 (2 H, t, *J* 7.0, CH$_2$), 1.62-1.79 and 2.00-2.20 (6 H, 2×m, 3×CH$_2$), 2.59-2.65 (1 H, m, C*H*(CH$_3$)$_2$), 4.27-4.32 (1 H, m, C*H*OH), 5.20-5.29 (1 H, m, CH=C*H*), 5.38-5.44 (1 H, m, C*H*=CH), 5.91 (1 H, d, *J* 3.0, C*H*=CO) and 6.10 (1 H, d, *J* 3.0, C*H*CO); δ_C(100 MHz; $CDCl_3$) -1.7 (3×*C*H$_3$), 16.0 (2×*C*H$_3$), 24.4 (TMS*C*H$_2$), 28.6 (CH$_2$*C*H$_2$CH$_2$), 29.4 (*C*H$_2$CH$_2$CH$_2$), 34.8 (H*C*(CH$_3$)$_2$), 38.6 (CH$_2$CH$_2$*C*H$_2$), 74.8 (H*C*OH), 106.6 (*C*H), 109.0 (*C*H), 127.8 (*C*H=*C*H), 149.4 (CH$_2$*C*) and 151.6 (*C*HCOH); MS (CI) *m*/*z* 207 [M-CH$_2$TMS]$^+$, 277 [M-OH]$^+$; HRMS *m*/*z* 277.1984 (277.1988 calcd for $C_{17}H_{29}OSi$, M-OH$^+$).

6-Hydroxy-2-isopropyl-6-((*E*)-5-trimethylsilanyl-pent-3-enyl)-6*H*-pyran-3-one

448



Procedure A

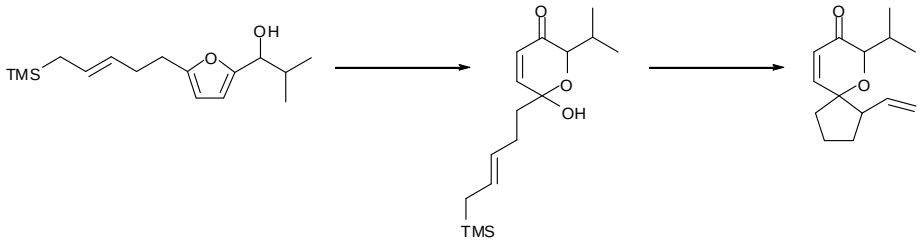
To a solution of alcohol **449** (64 mg, 0.228 mmol) in anhydrous dichloromethane (5 cm^3) was added *meta*-chloroperoxybenzoic acid (*m*CPBA) (56 mg, 0.251 mmol) at 0 °C. The reaction was allowed to warm up to room temperature and left to stir overnight. An extra portion of *meta*-chloroperoxybenzoic acid (*m*CPBA) (28 mg, 0.125 mmol) was added and the solution was stirred overnight. The reaction mixture was diluted with dichloromethane (5 cm^3) and saturated aqueous sodium hydrogen carbonate (5 cm^3). The organic layer was separated and washed with water (5 cm^3), brine (5 cm^3) and dried over anhydrous sodium sulfate. The solution was then filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (80:20)] of the crude residue caused product degradation. Product **448** seen at R_f 0.34 (Solvent *B*).

Procedure B

To a solution of alcohol **449** (44.4 mg, 0.158 mmol) in dry dichloromethane (1.5 cm^3) at 0 °C, was added vanadyl acetylacetonate ($VO(acac)_2$) (4.2 mg, 0.0158 mmol). The solution turned instantly green and *tert*-butyl hydroperoxide (TBHP) (40 µL, 0.237 mmol) was then added dropwise. The now dark red reaction mixture was stirred for 2 h at 0 °C, then filtered through a pad of Celite® and the filtrate concentrated *in vacuo*. Purification of the crude residue by FCC [petroleum ether-ethyl acetate (80:20)] afforded pyrone **448** (4.1 mg, 8.7%); R_f 0.42 (Solvent *A*); ν_{max}(film)/cm^{-1} 3423, 2960, 1686, 1248 and 841; δ_H (400 MHz, $CDCl_3$) 0.00 (9 H, s, $Si(CH_3)_3$), 0.82 (3 H, d, *J* 6.7, $CH(CH_3)$), 1.05 (3 H, d, *J* 6.7, $CH(CH_3)$), 1.42-1.44 (2 H, m, CH_2), 1.90 (2 H, t, *J* 2.8, $CH{=}CHCH_2CH_2$), 2.42-2.50 (2 H, m, $CH{=}CHCH_2CH_2$), 4.33-4.38 (1 H, m, (CO)C*H*), 5.32-5.40 (1 H, m, CH=C*H*), 5.49-5.53 (1 H, m, C*H*=CH), 6.03-6.08 (1 H, m, C*H*=CH(CO)) and 6.74-6.80 (1 H, m, CH=C*H*(CO)); δ_C(100 MHz; $CDCl_3$) -1.5 ($3\times CH_3$), 18.5 ($2\times CH_3$), 21.6

(HC=CH*C*H$_2$CH$_2$), 25.2 (*C*H$_2$), 28.6 (*C*(CH$_3$)$_2$), 45.0 (HC=CHCH$_2$*C*H$_2$), 90.5 (H*C*O), 93.4 (*C*OH), 126.0 (H*C*=*C*H and HC=*C*HCO), 144.3 (H*C*=CHCO) and 196.9 (*C*=O); MS (CI) *m*/*z* 297.3 [M+H]$^+$; HRMS *m*/*z* 297.1888 (297.1886 calcd for $C_{16}H_{29}O_3Si$, M+H$^+$).

7-Isopropyl-1-vinyl-6-oxa-spiro[4.5]dec-9-en-8-one <u>447</u>



To a stirred solution of allylsilane **449** (90 mg, 0.321 mmol) in dry dichloromethane (3 cm^3) was added vanadyl acetylacetonate (VO(acac)$_2$) (8.5 mg, 0.0321 mmol) at 0 °C. The solution turned instantly green and *tert*-butyl hydroperoxide (TBHP) (0.08 cm^3, 0.481 mmol) was added dropwise. The dark red solution was stirred for 1.5 h at 0 °C then allowed to warm up to room temperature and filtered through Celite®. The solvent was concentrated *in vacuo* to ~1 cm^3 and then dry dichloromethane (2 cm^3) was added and the solution cooled down to −78 °C. Boron trifluorodiethyletherate ($BF_3{\cdot}OEt_2$) (0.12 cm^3, 0.962 mmol) was added slowly and stirring continued for 30 min at −78 °C. The reaction mixture was allowed to warm up to room temperature and was then quenched with saturated aqueous ammonium chloride (5 cm^3) and extracted with dichloromethane (2×7 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), water (10 cm^3) and saturated aqueous ammonium chloride (10 cm^3), then dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Purification by FCC [petroleum ether-ethyl acetate (95:5) *then* (50:50)] of the crude residue afforded bicyclic pyran **447** (5.4 mg, ~1%); ν_{max}(film)/cm^{-1} 2973, 2253, 1737, 1265 and 1095; δ_H(400 MHz; $CDCl_3$) 0.76 (3 H, d, *J* 6.8, CH_3), 1.10 (3 H, d, *J* 6.8, CH_3), 0.80-1.04 and 1.16-1.76 (6 H, 2×m, 3×CH_2), 2.12-2.64 (2 H, m, C*H*(CH$_3$)$_2$ and *H*CCH=CH$_2$), 4.05 (1 H, dd, *J* 2.8 and 4.4, (OC*H*), 5.04 (2 H, dd, *J* 7.7 and 13.5, CH=C*H*$_2$), 5.60-5.68 (1 H, m, C*H*=CH$_2$), 5.91 (1 H, d, *J* 10.0, C*H*=CH(CO)) and 6.70 (1 H, d, *J* 10.0, CH=C*H*(CO)); δ_C(100 MHz; $CDCl_3$) 18.4 ((*C*H$_3$)$_2$), 23.6 (CH$_2$*C*H$_2$CH$_2$), 28.4 (CH$_2$CH$_2$*C*H$_2$), 28.9 (*C*(CH$_3$)$_2$), 39.2 (*C*H$_2$CH$_2$CH$_2$), 51.5 (*C*CH=CH), 80.9 (*C*), 94.1 (*C*C(CH$_3$)$_2$), 116.9 (CH=*C*H), 132.6 (HC=*C*HCO), 138.0 (*C*H=CH), 147.1 (H*C*=CHCO) and 196.1 (*C*=O).

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