Studies Towards a Fast and Efficient Total Synthesis of LL-Z1640-2

Submitted in fulfilment of the requirements for the Degree of Philosophy

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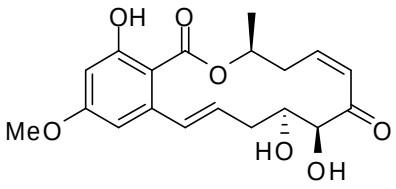
February 2009

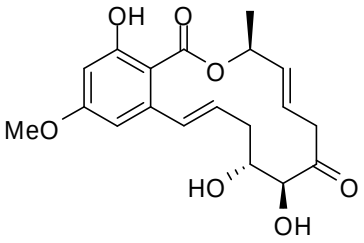
Abstract

LL-Z1640-2 (5Z-7-Oxo-zeaenol) was first isolated in 1978 from a culture broth. Although LL-Z1640-2 was initially classified as an anti-protazoan agent, it was not until 1999 that it's cytokine release inhibiting activity was discovered. More recently LL-Z1640-2 has been reported to selectively inhibit the kinase activity of TAK1.

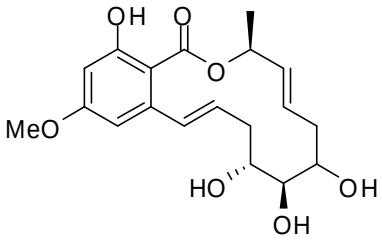
TAK1 (transforming growth factor ß-activated protein kinase 1) is a major member of the mitogen activated protein kinase kinase kinase (MAPKKK) family. TAK1 is responsible for the activation and control of at least three signalling pathways that play crucial roles in the inflammatory response. Hence, TAK1 has emerged as a prime target for the treatment and regulation of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.



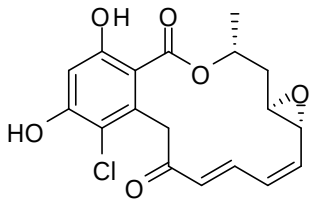
LL-Z1640-2



7-oxo-zeaenol



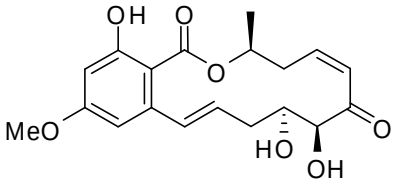
Zeaenol



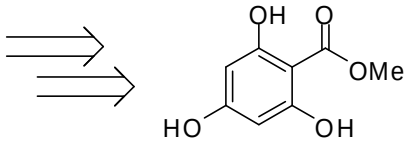
Radicicol

LL-Z1640-2 is structurally related to other 14 membered resorcylic lactones such as 7-oxo-zeaenol, zeaenol and radicicol. Although there has been a significant amount of work dedicated to the synthesis of radicicol, the efforts towards LL-Z1640-2 have been rather limited. At the outset of the research contained within this thesis, only two total syntheses of LL-Z1640-2 had been published. They were both lengthy (>20 steps) making them impractical for lead development.

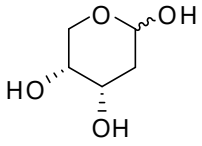
The work described in this thesis illustrates the attempted flexible and convergent synthesis of LL-Z1640-2 from the simple, commercially available, starting materials 2-deoxy-D-ribose and methyl 2,4,6-trihydroxybenzoate.



LL-Z1640-2



2-deoxy-D-ribose



Methyl 2,4,6-trihydroxybenzoate

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Acknowledgement

Financial support from the Biotechnology and Biological Science Research Council (BBSRC) is gratefully acknowledged.

I would like to express my sincere gratitude to my supervisor, Dr Rudi Marquez, for all his help, guidance, support and encouragement over the past few years.

I would also like to thank the staff at the Universities of Dundee and Glasgow who have provided technical support during my research: Dr Sandy Chudek (DU-NMR), Gina MacKay (DU-NMR, MS), Dr David Adams (GU-NMR) and Jim Tweedie (GU-MS). Also thanks to all the other researchers I've had the privilege and pleasure of working with during this time. A special mention has to go to the long list of Mike, Amit, Phil, Steve, Suzannah, Mark, Ian, Linsey, Mat, Neil, Stephanos, Belinda, Richard, Anna, Jennifer, and Sophia. Thank you to you all and to anyone I've missed out, you've all been great friends to me and have all helped to create a professional yet relaxed environment wherever we've been working together.

Ultimately, I would like to thank my family and friends for their encouragement and support throughout my entire time at university. I'd especially like to thank my parents for all their financial support over the years, without their help this would never have happened.

And finally I'd like to say a special thanks to Mary Margaret for her constant words of encouragement and putting up with me while I was writing up.

Thanks to you all

Murray

Author's Declaration

This thesis represents the original work of Murray Norman Robertson unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Dundee and University of Glasgow, under the supervision of Dr Rodolfo Marquez, during the period November 2004 to January 2008. Portions of the work described herein have been published elsewhere as listed below.

Henry, N.; Robertson, M. N.; Marquez, R. *Tetrahedron Letters* **2007**, *48*, 6088-6091.

Abbreviations

^{1}H	proton
22DMP	2,2-dimethoxypropane
2MP	2-methoxypropane
ACS	acute coronary syndrome
ADP	Adenosine diphosphate
app	apparent
ASK1	Apoptosis signal-regulating kinase 1
Asp	Aspartic acid
ATP	Adenosine-5'-triphosphate
br	broad
CAN	Ceric Ammonium Nitrate
Cat.	catalyst
CI	Chemical Ionisation
CSA	camphorsulfonic acid
Cys	Cysteine
d	doublet
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane

dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano benzoquinone
DHU	N,N'-dicyclohexylurea
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropanolamine
DIPEA	N,N'-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*'-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EI	Electron Impact
EtOAc	ethyl acetate
FTIR	Fourier Transform Infrared
g	gram(s)
H	Hour(s)
HRMS	High-Resolution Mass Spectrometry

HSP90	heat shock protein 90
IKK	IκB kinase
IL-1	Interleukin-1
JNK	c-Jun N-terminal kinase
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamine
LRMS	*low*-resolution mass spectrometry
M	Molar
m	multiplet
MAPK	Mitogen-activated protein kinase
MAPKK	Mitogen-activated protein kinase kinase
MAPKKK	Mitogen-activated protein kinase kinase kinase
Me	Methyl
MEKK1	Mitogen-activated protein kinase kinase 1,
mg	milligram(s)
MKK3	Mitogen-activated protein kinase kinase kinase
MKK4	Mitogen-activated protein kinase kinase 4
MKK6	Mitogen-activated protein kinase kinase 6
MKK7	Mitogen-activated protein kinase kinase 7

mL	millilitre(s)
mol	mole(s)
MOM	methoxymethyl
NMO	4-methylmorpholine-N-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
^{o}C	degrees centigrade
Pd/C	Palladium on carbon
PG	protecting group
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
*P*TSA	*p*-Toluene Sulfonic Acid
pTSA	*p*-Toluenesulfonic acid
Pyr	pyridine
q	quartet
quin	quintet
RA	Rheumatoid Arthritus

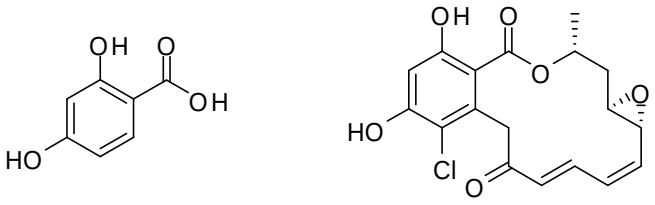
RCM	Ring Closing Metathesis
RNOS	reactive nitrogen oxide species
ROS	reactive oxygen species
RT	Room Temperature
s	singlet
SAPK2a	Stress Activated Protein Kinase 2a
sept	septet
sext	sextet
t	triplet
TAB1	TAK1 binding protein 1
TAB2	TAK1 binding protein 2
TAB3	TAK1 binding protein 3
TAK1	transforming growth factor-ß-activated kinase 1
TBAF	*tetra*-*n*-butylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	triisopropylsilyl

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Trt	trityl

1 Introduction

1.1 Resorcylic Acid Lactones

The resorcylic acid lactone (RAL) family are a group of compounds characterised by a macrcrocyclic lactone incorporating the acid functionality of a resorcylic acid **1**. The RAL family has grown significantly since the first isolation of radicicol **2** in 1953 (Figure 1.1).[1]



1
ß-Resocylic Acid

2
Radicicol

Figure 1.1 ß-Resocylic acid and Radicicol.

The original biological activities of most of the RALs did not attract much interest from organic chemistry community.[2] However in 1992 the inhibition of a specific protein kinase by radicicol was reported.[3] After this new discovery, radicicol became popular with biochemists and synthetic chemists alike. Multiple potential biological uses were reported with the most significant coming in 1998 when its ability to inhibit the APT binding of the 90 kDa heat shock protein (Hsp90) was reported.[4] The significance of this being that numerous mutated and overexpressed proteins rely upon the Hsp90 protein folding machinery for tumor progression. The mechanism of Hsp90 which mediates the protein folding process is dependent upon ATP. Therefore, when inhibitors of ATP are present, the Hsp90 machinery is unable to fold unwanted proteins into their biologically active form thus resulting in the degradation of protein substrates. Subsequently, Hsp90 has evolved into a promising anti-cancer target because multiple oncogenic proteins can be simultaneously degraded as a consequence of Hsp90 inhibition.[5] As a result of this, radicicol **2** has now been used as a lead compound and potent derivatives have been synthesised and are currently in clinical trials.[6]

The first total synthesis of radicicol was reported by Lett in 1992.[7, 8] Since this initial report several other total synthesis approaches have been reported including one from Danishefsky.[9-14]

1.2 LL-Z1640-2

The RAL LL-Z1640-2 (also known as 5Z-7-Oxo-zeaenol) **3** was first isolated in 1978 from an unidentified fungus[15] and then later from the fungal strain f6024.[16] Although it was originally classified as an anti-protozoan agent,[15] it was not until 1999 that the potential for LL-Z1640-2 **3** to be therapeutically useful for treating inflammatory and immunological diseases was discovered.[17]

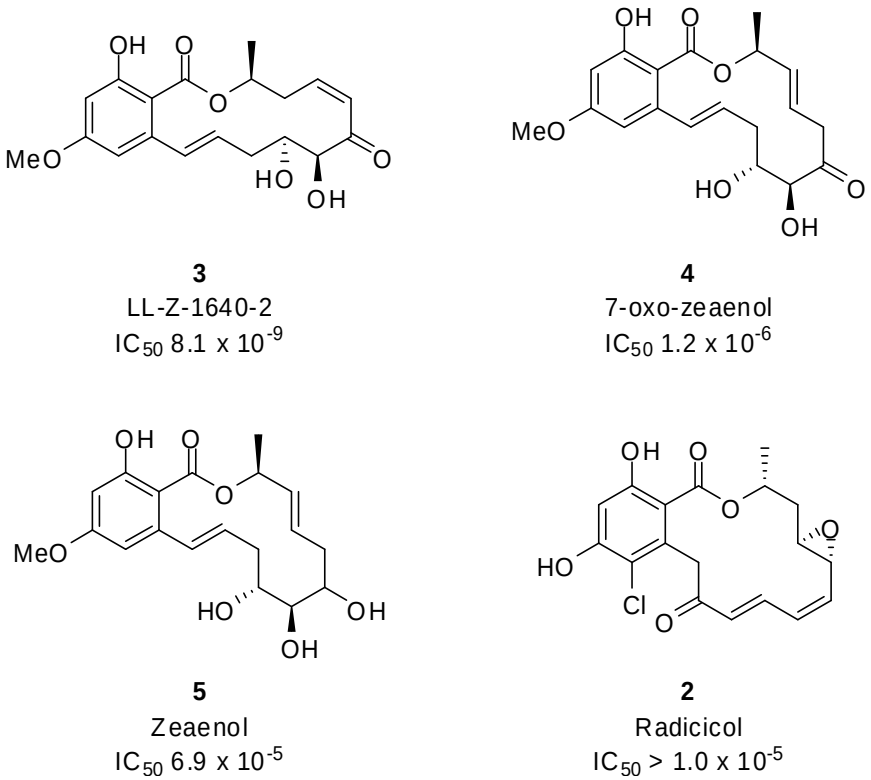


Figure 1.2 LL-Z1640-2 and a selection of structurally related RAL's

Ninomiya-Tsuji[16] identified LL-Z1640-2 **3** activity during a screen of 90 compounds as inhibitors of the MAPKKK (Mitogen-activated protein kinase kinase kinase) TAK1 (transforming growth factor-β-activated kinase-1). LL-Z1640-2 **3** was found to be a very potent inhibitor of TAK1, with an IC_{50} of 8 nM (Figure 1.2). The other structurally related RALs **2, 4** and **5** had little inhibitory activity.

It was also shown that LL-Z1640-2 **3** had no significant effect on the kinase activities of other members of the MAPKKK family such as MEKK1 (MAP extracellular signal-regulated KKK 1) and ASK1 (Apoptosis signal-regulating kinase 1).[16]

1.3 IC_{50}

In order to appreciate the biological significance of LL-Z1640-2 **3**, a number of terms and concepts have to be defined and explained. The IC_{50} of a compound is the concentration required to provide 50 % inhibition. This is most commonly used to represent the inhibitory effect of compounds on competition binding assays and functional antagonist assays.

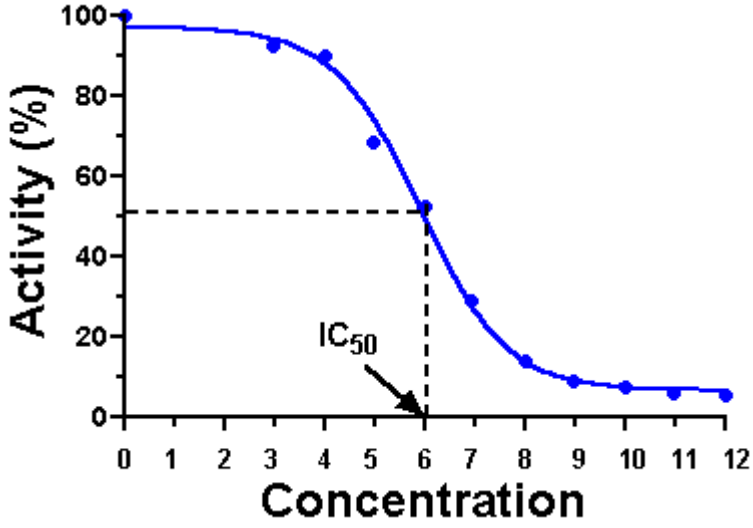


Figure 1.3 Dose response curve

The IC_{50} is a quantitative measure that is used to indicate the concentration of that needed to inhibit a given biological process by half. 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 above (Figure 1.3).[18]

1.4 Protein Kinases

A protein kinase is an enzyme that can modify other proteins by chemically adding phosphate groups to them, otherwise known as phosphorylation.[19] Phosphorylation usually results in a functional change of the target protein by changing an enzymes activity, cellular location, or association with other proteins. Kinases transmit signals and control complex processes in cells. Up to 518 different kinases have been identified in humans.[20]

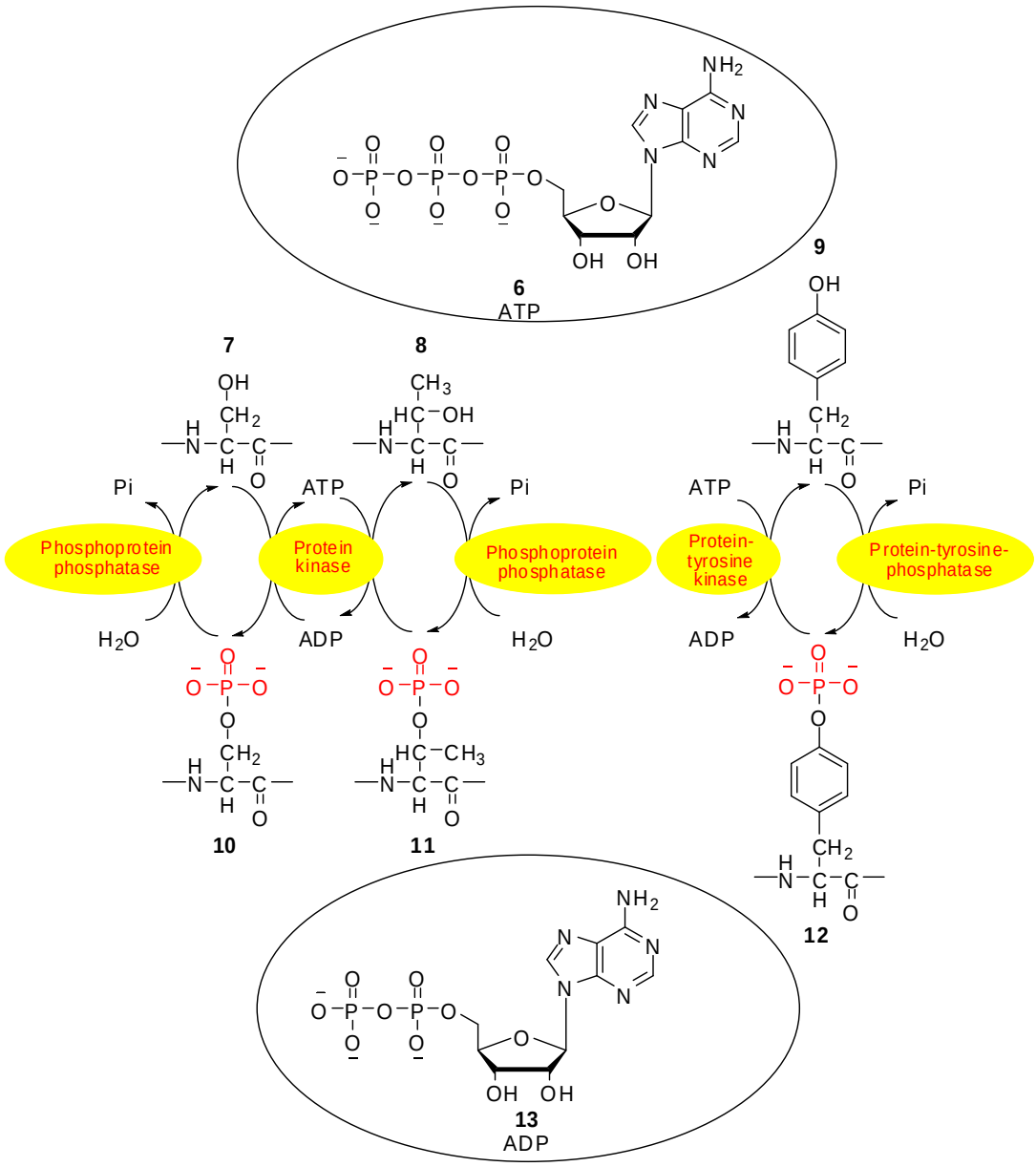


Figure 1.4 Schematic representation of protein phosphorylation

The chemical activity of a kinase involves removing a phosphate group from ATP **6** (adenosine triphosphate) and covalently attaching it to one of three amino acids that have a free hydroxyl group (serine **7**, threonine **8** or tyrosine **9**)(Figure 1.4). Most kinases act on both serine **7** and threonine **8**. Others act on tyrosine **9**, and a number, referred to as dual specificity kinases, act on all three residues. There are also some protein kinases that phosphorylate basic amino acid residues. For example histidine kinases phosphorylate histidine residues. Effectively, many enzymes, receptors and other proteins can be turned on or off by phosphorylation (Figure 1.5).

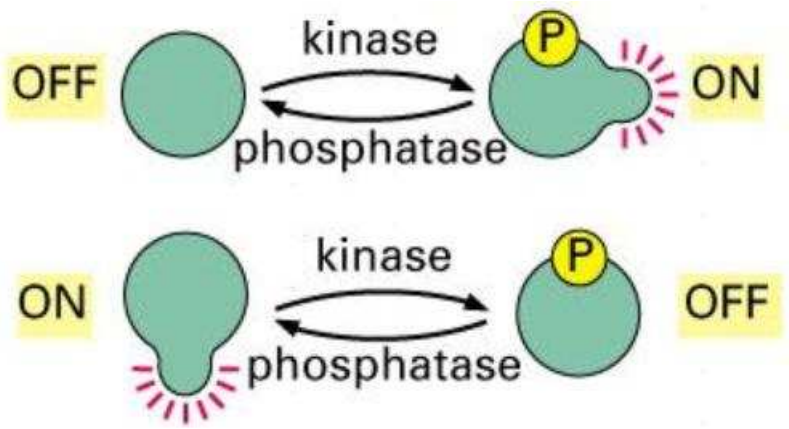


Figure 1.5 Phosphorylation turning enzymes and receptors "on" and "off".

Kinases have been defined as a significant drug target of the 21st century as abnormal or deregulated kinase activity is a common cause of disease and disorders such as cancer, inflammation and diabetes.[21] Furthermore their wide diversity makes them attractive drug targets for modern day drug design.

1.5 Inflammation

Inflammation is a highly ordered process and plays a major role in the host defence system. It is a protective attempt by the organism to remove harmful stimuli and to start the healing process of the tissue.

Without inflammation, wounds and infections would never heal which could lead tissue destruction and death of the organism. However, uncontrolled over-stimulation can lead to unwanted cell responses and to the development of inflammatory diseases.[22]

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial reaction of the host to harmful stimuli. A cascade of biochemical events propagates and matures the inflammatory response. The term chronic inflammation is used when the immune response persists for a prolonged period of time. Chronic inflammation leads to a progressive shift in the type of cells present at the site of inflammation and is characterised by simultaneous destruction and healing of tissue.

1.6 Inflammatory Disorders

Conditions connected with inflammation include a large, unrelated group of disorders which cause a variety of human diseases. The immune system is often

involved with inflammatory disorders which are demonstrated in allergic reactions and in some myopathies.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder where the immune system attacks the body causing inflammation which results in pain, swelling, stiffness and bone and cartilage destruction.[23] RA is thought to affect about 1 % of the adult population worldwide.[24] RA affects women three times more often as men and can also develop at any age. However, the risk of first developing the disease is greatest in women between the ages of 40 and 50 years old and in later years with men.

Crohn's Disease

Crohn's disease (also known as regional enteritis) is an autoimmune disease which can affect any part of the gastrointestinal tract. The symptoms of Crohn's disease vary among afflicted individuals. The main symptoms are abdominal pain, diarrhoea, constipation, vomiting, weight loss or weight gain. The disease can also cause problems outside the gastrointestinal tract such as skin rashes, arthritis and inflammation of the eye. Crohn's disease can occur at any age although it tends to develop most in the teens and twenties, with another peak incidence in the fifties to seventies.[25]

Acute Coronary Syndrome

Acute coronary syndrome (ACS) greatly increase the risk of death and/or the recurrence of serious cardiovascular events. ACS is due to the disorder of atherosclerotic plaque of which inflammation is a component.

Antithrombotic therapy is presently the cornerstone of the treatment of ACS.[26] Findings indicate the importance of inflammation in atherothrombosis and support therapeutic use of anti-inflammatory treatment. As a result of these findings there is now evidence showing that blocking inflammation could lower thrombosis and therefore ACS.[27]

Cancer

It has been shown that up to 15 % of cancer cases worldwide can be linked to infections.[28] A possible pathway for these infections to progress to cancer is for

the infection to persist within the host and induce chronic inflammation.[29] This inflammation is often accompanied by the formation of reactive oxygen and nitrogen species (ROS and RNOS) at the site of inflammation. ROS and RNOS have the potential to damage DNA, proteins and cell membranes and therefore favour carcinogenesis. In addition to this, chronic inflammation often results in repeated cycles of damage and compensating cell proliferation. This in turn increases the number of cells that are dividing and therefore subject to DNA damage that promotes the growth of malignant cells.[30]

1.7 The Mitogen-activated Protein Kinase Pathway

Cell surface receptors of eukaryotes are used to sense and respond to extracellular stimuli. Commonly, signal transduction pathways in eukaryotes regulate protein kinases that phosphorylate and control the activity of proteins involved in metabolic and transcriptional events. Many signal transduction pathways regulated by different cell-surface receptors are highly conserved in evolutionarily distant organisms.

The mitogen-activated protein kinase (MAPK) pathway is a conserved eukaryotic signalling module that converts receptor signals into various outputs.[31] The pathway includes three protein kinases: MAPKKK, MAPKK and MAPK. MAPK is activated through phosphorylation by MAPKK, which is first activated by MAPKKK.

1.8 TAK1

TAK1 is a member of the mitogen-activated protein kinase kinase kinase (MAPKKK) family that phosphorylates and activates MKK3, MKK4, MKK6 and MKK7 MAPKKs, which in turn activate the c-Jun N-terminal kinase (JNK) and p38 MAPKs (Figure 1.6).[32, 33] TAK1 participates in proinflammatory cellular signaling pathways such as the interleukin-1 (IL-1) pathway by activating both JNK/p38 MAPKs and IKKs (I kappa B kinase).[16, 34] The MAPK cascades constitute functional units that couple upstream input signals to a variety of outputs. MAPK cascades have been identified and characterised in organisms as diverse as yeasts and mammals.[35]

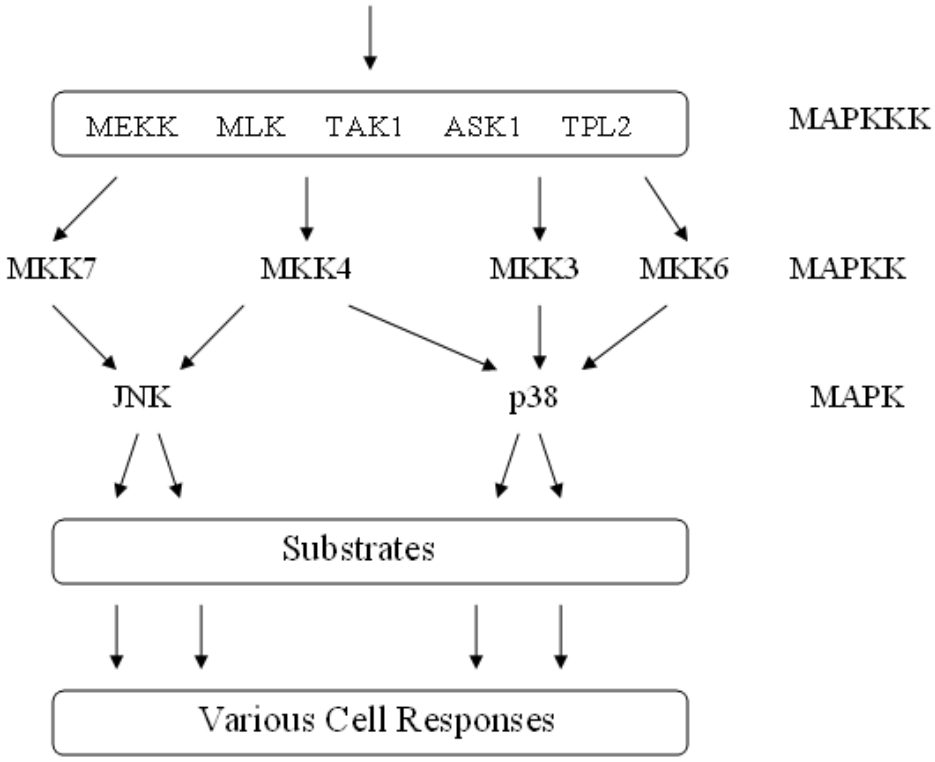


Figure 1.6 MAPK cascades

1.9 TAK1 as a Potential Drug Target

TAK1 along with it's regulatory subunits TAB1 (TAK1 binding protein 1) and TAB2 (TAK1 binding protein 2) or the structurally related TAB3 (TAK1 binding protein 3) lie at the head of three pro-inflammatory kinase cascades.[36, 37] The significance of TAK1 was reinforced by Cohen et al in 2003[36] when they showed that SAPK2a/p38α had feedback control on TAK1 via TAB1. They also found that the downregulation of TAK1 by SAPK2a/p38α was not just a feedback control device for limiting the activation of SAPK2a/p38α, but may also limit the activation of IKK and JNK and hence synchronise three signalling pathways that play key roles in the inflammatory response.

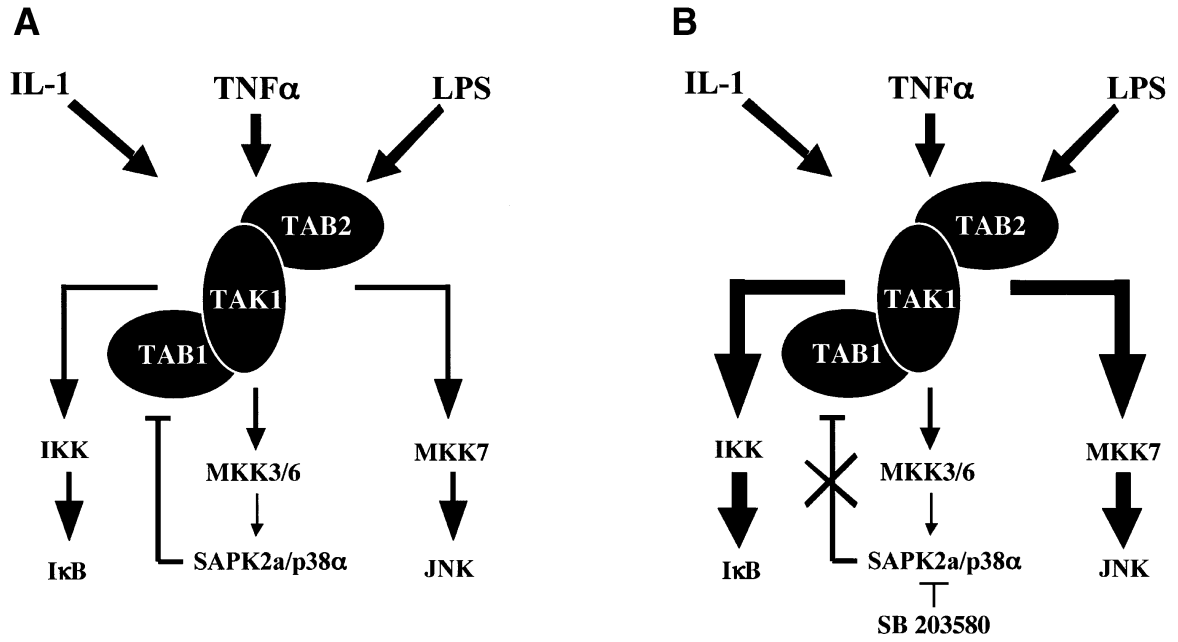


Figure 1.7 Schematic representation of the feedback control of TAK1 activity by SAPK2a/p38α.

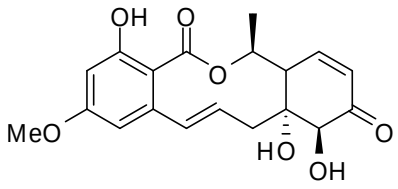
Figure 1.7 A shows the downregulation of TAK1 by SAPK2a/p38α, best thought to be via TAB1. In B, SAPK2a/p38α is inhibited and eliminates the feedback control of TAK1, causing upregulation of the JNK and IKK pathways. This discovery led to important implications in the development of anti-inflammatory drugs as previous studies had been focused on inhibiting SAPK2a/p38α. Potent, selective inhibitors of SAPK2a/p38α have in fact been studied for the treatment of rheumatoid arthritis and other chronic inflammatory diseases.[38-40]

Several lines of evidence suggest that TAK1 is a key molecule in proinflammatory signaling pathways. Various proinflammatory cytokines and endotoxins activate the kinase activity of endogenous TAK1.[41] Therefore, it can be expected that inhibition of TAK1 activity may be effective in preventing inflammation and tissue destruction promoted by proinflammatory cytokines.

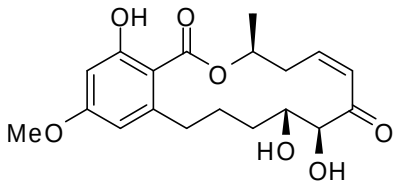
1.10 LL-Z1640-2 as a TAK1 Inhibitor

Ninomiya-Tsuji discovered that LL-Z1640-2 **3** inhibited the kinase activity of purified TAK1, whereas no significant inhibition of TAK1 activity was observed with structurally related compounds including radicicol **2**(Figure 1.2).[16] It was also discovered that LL-Z1640-2 **3** had no significant effect on the kinase activities of other members of the MAPKKK family, such as MEKK1 and ASK1. This was surprising as it had previously been shown that the two compounds, Ro

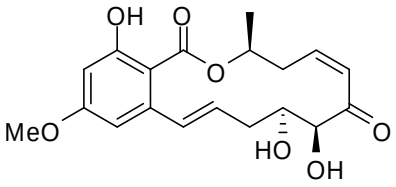
09-2210[42] **14** and L-783,277[43] **15**, with very similar structures to LL-Z1640-2 **3** inhibit MEK kinase activity (Figure 1.8).



14
Ro 09-2210
IC_{50} 59 x 10^{-9} M



15
L-783,277
IC_{50} 4 x 10^{-9} M

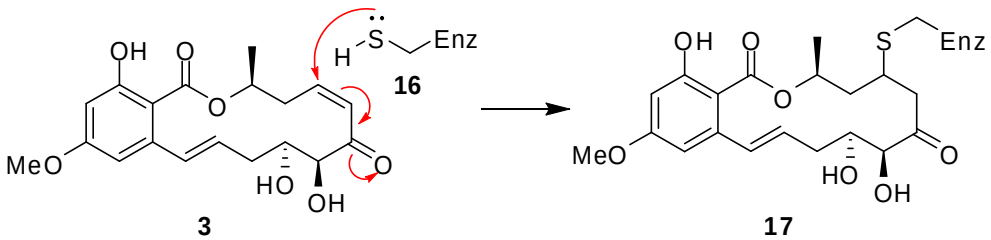


3
LL-Z1640-2
IC_{50} 411 x 10^{-9} M

Figure 1.8 Structurally related compounds and their MEK IC_{50}

LL-Z1640-2 **3** did inhibit MEK1 activity, however the concentration required was more than 50 fold higher than that required to inhibit TAK1. Therefore, LL-Z1640-2 **3** was shown as a selective inhibitor of TAK1.

Ninomiya-Tsuji also went on to show that binding of LL-Z1640-2 **3** to TAK1 was either irreversible or very slowly reversible and also a competitive inhibitor of ATP binding. They did not hypothesise any possible mechanisms for this inhibition, however Santi in 2006 published results showing that RALs containing a *cis*-enone are susceptible to Michael addition reactions with cysteine residues **16** within MAPK kinases (Figure 1.9).[44]

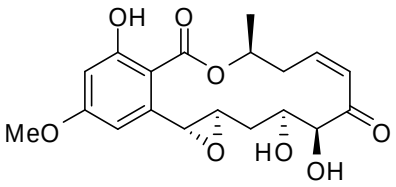


3 **16** **17**

Figure 1.9 Michael addition of the *cis*-enone function of RAL with a cysteine residue.

Santi's work discovered that the conserved Cys residue adjacent to the completely conserved Asp that is involved in the binding of Mg^{2+} complexed to

ATP in kinases inhibited by RALs. The work by Santi is further strengthened by the fact that kinases that are not inhibited by RALs have no Cys residue at that position. Upon screening the human kinome, 46 kinases were identified as having the essential Cys residue. During their initial screen of 124 kinases, 19 Cys containing kinases were evaluated using hypothemycin **18** (Figure 1.10) as the inhibitor. Hypothemycin **18** inhibited 18 of the 19 Cys containing kinases and only 3 of the other related kinases.



18
Hypothemycin

Figure 1.10 Hypothemycin

1.11 Irreversibility Issues

There is a common prejudice against irreversible inhibitors as drug discovery programmes almost never set out to make irreversible inhibitors. However, this assumption is contradicted by the fact that 19 of the 71 enzyme targets of marketed drugs are covalently modified by the drug.[45] Providing target selectivity can be achieved, there are a number of advantages of irreversible inhibitors over reversible binding agents. One of the main advantages includes the thermodynamic drive towards the formation of the covalent adduct. As such, high concentrations of the inhibitor are not required to obtain effective inhibition. Also, once covalently bound the inhibitor will not readily detach from the enzyme and as a result restoration of the enzyme function requires new synthesis. Work by Haber[46] has shown irreversible inhibition can avoid drug resistance thus potentially providing treatment for tumours that have become resistant to other forms of treatment.

1.12 Selectivity

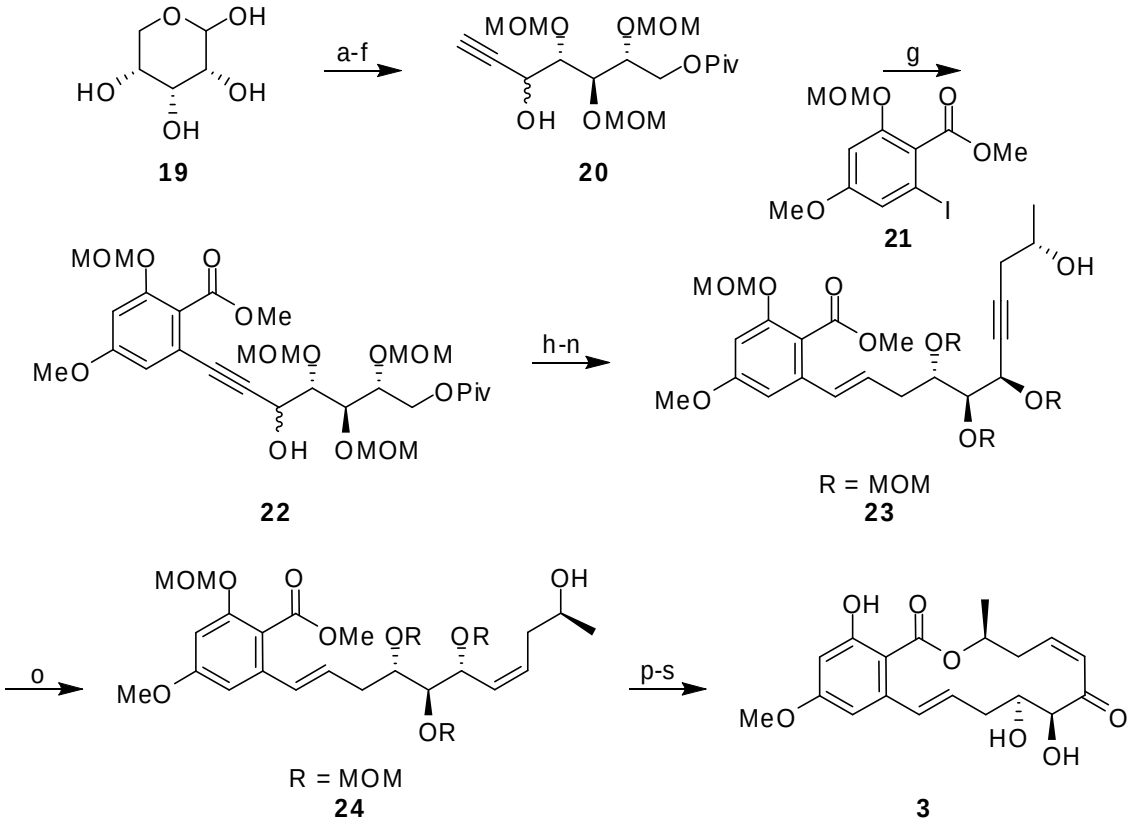
Inhibition caused by drugs may be either reversible or irreversible. A reversible situation occurs when an equilibrium is established between the enzyme and the inhibitory drug. Competitive inhibition occurs when the drug mimics the normal substrate and competes for the active site of the enzyme. Non-competitive inhibitors combine with the enzyme at a different site other than the active site.

This interaction causes the enzyme to change shape and disturbs the active site conformation.

Many of the first kinase inhibitors were ATP mimetics that bound to the active site and competed with cellular ATP. The ATP site is highly conserved across the kinome thus making it difficult to identify selective inhibitors that only target the therapeutically relevant kinase. Studies on isoforms of the p38 MAPK by Goldsmith[47, 48] showed that residues close to the ATP-binding site could be used to achieve selectivity. This was even demonstrated between the closely related kinases p38 and ERK2. Development of these strategies that exploit the amino acids in, or close to, the ATP-binding site of kinases continues. The ever increasing number of solved kinase structures also aids current and future development of these targets. A high degree of selectivity is on show in the majority of the kinase inhibitors that are currently in clinical trials. Most of these seem to be ATP mimics, however the discovery of alternative binding modes has been exploited.[49]

1.13 Total Synthesis of LL-Z1640-2

The first total synthesis of LL-Z1640-2 **3** was reported by Tatsuta 2001.[50] Tatsuta's approach was a mainly linear approach with longest linear sequence containing 19 steps with an overall yield of 2.3 % (Scheme 1.1).



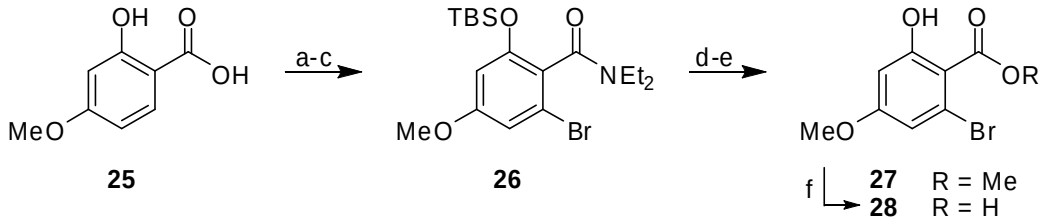
a) CSA, BnOH, 89 %. b) MOMCl, *i*-Pr_2NEt, MeCN, 85 %. c) H_2, $Pd(OH)_2$,EtOH, 100 %. d) TMS-acetylene, *n*-BuLi, $BF_3.Et_2O$, THF. e) PivCl, Py, 2 steps 48 %. f) TBAF, AcOH, THF, 100 %. g) **21**, $Pd(OAc)_2$, CuI, Ph_3P, Et_3N, 85 %. h) $ClCO_2Et$, Py, 98 %. i) H_2, $Pd/BaCO_3$, quinoline, EtOH. j)$Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, $HCOONH_4$, 1,4-dioxane, 2 steps 96 %. k) NaOMe, MeOH, 95 %. l) $(COCl)_2$, DMSO, Et_3N, DCM. m) Ph_3P, CBr, DCM, 2 steps 85 %. n) *n*-BuLi, $BF_3.Et_2O$, THF, 45 %. o) H_2, $Pd/BaCO_3$, quinoline, AcOEt. p) 2M NaOH, MeOH, 1,4-dioxane. q) Mukaiyama reagent, Et_3N, MeCN, 3 steps 47 %. r) 5 % HCl, MeOH, 76 %. s) Dess-Martin periodinane, DCM, 62 %.

Scheme 1.1 Tatsuta's overall scheme.

It was envisioned by Tatsuta that the two stereogenic alcohols present in the final product **3** could originate from a carbohydrate source. D-ribose **19** was used and compound **20** was derived in 6 steps in 36 % yield. Sonagashira coupling of **20** and the aromatic fragment **21** proceeded in 85 % to give compound **22**. Hydrogenolysis under Tsuji's conditions[51] gave the desired *E* olefin, which was converted to the carbonate ester. The allyl carbonate intermediate was then eliminated using palladium(0) ($Pd_2(dba)_3$) and ammonium formate as the hydride source. Selective deprotection and oxidation of the primary alcohol followed by a Corey-Fuchs reaction gave the alkyne unit which was used to open *S*-propylene oxide in the same pot to give alkyne **23**. Hydrogenation using Lindlar's catalyst afforded the desire *Z* olefin **24**. Saponification of the ester **24** and subsequent cyclisation using Mukaiyama conditions[52] afforded the lactone fragment. Final deprotection and selective oxidation of the allyl alcohol using Dess-Martin periodinane gave the α,ß-unsaturated ketone and completed the first total synthesis of LL-Z1640-2 **3**.

1.14 The Second Total Synthesis

The second synthesis of LL-Z1640-2 **3** was reported by Selles and Lett in 2002.[53, 54] They proposed a convergent and flexible approach and also showed conditions to selectively epoxidise **3** to hypothemycin **18**. However, their longest linear sequence contained 25 steps with an overall yield of 1.3 %.



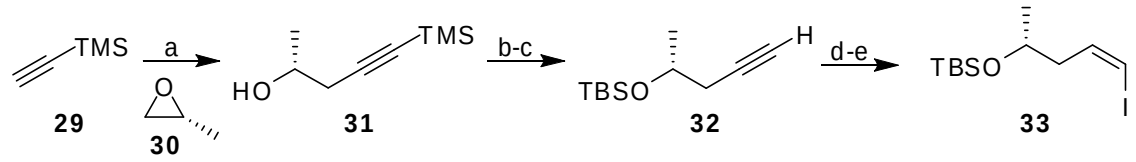
25 **26**

a) TBSCl, *i*Pr_2NEt, DMF. b) Et_2NAlMe_2, toluene, 2 steps 98 %. c) *t*-BuLi, Et_2O, Br_2, 75 %. d) Me_3O^+, BF_4-, DCM. e) Na_2CO_3, MeOH, 2 steps 76 %. f) NaOH, DME, 100 %.

Scheme 1.2 Lett's synthesis of aromatic fragment 27

In Lett's approach, LL-Z1640-2 **3** orginated from the key aromatic **27**, $C_{1'}$-C_6, and the $C_{7'}$-C_{10}, enantiopure subunits **33** and **38**. The aromatic unit **27** was synthesised from 4-methoxysalicylic acid **25** in 5 steps with an overall yield of 57 % (Scheme 1.2).

Synthesis of the $C_{7'}$-C_{10}, subunit began with (trimethylsilyl)acetylene **29**. (*R*) propylene oxide **30** was opened In the presence of the lithio derivative of **29** to give **31**. Silyl protection of the alcohol followed by specific deprotection of the TMS-alkyne gave **32** in 76 % over 3 steps. The iodoalkyne of **32** was produced then subjected to Corey's hydroboration procedure using Sia_2BH and acetic acid to form the enantiopure *Z* vinyl iodide **33** (Scheme 1.3).[55]



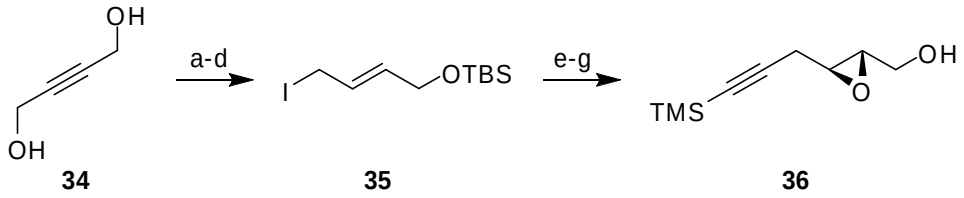
29 **30** **31** **32** **33**

a) *n*-BuLi, **30**, $BF_3.Et_2O$, Et_2O, 89 %. b) TBSCl, imidazole, DMF. c) K_2CO_3, MeOH, 2 steps 86 %. d) *n*-BuLi, I_2, THF, 86 %. e) Sia_2BH, THF, AcOH, 89 %.

Scheme 1.3 Lett's synthesis of the $C_{7'}$-C_{10}, subunit

The synthesis of the $C_{1'}$-C_6, sub unit began with 1,4-butynediol **34** which was converted to the silyl protected iodide **35** over 4 steps. The iodide was then coupled with (trimethylsilyl)acetylene **29** and then selective deprotected using

DDQ (5 mol %) to yield the free hydroxyl. Sharpless asymmetric epoxidation of the alkyneol afforded the desired epoxyalcohol **36** (Scheme 1.4).

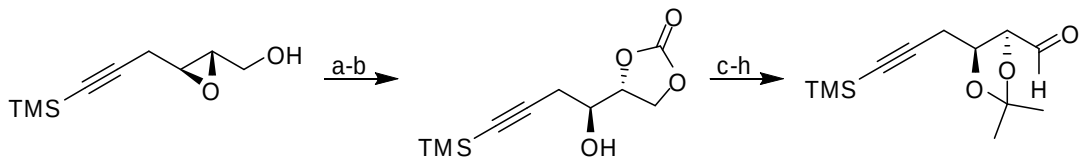


34 **35** **36**

a) Red-Al/ toluene, THF, 81 %. b) NaH, THF, then TBSCl, 76 %. c) MsCl, NEt_3, DCM. d) NaI, acetone. e) **29**, *n*-BuLi, THF, then **35** and HMPA. f) DDQ (5 mol%), $MeCN/H_2O$ (9/1). g) $Ti(OiPr)_4$, (+)-DET, DCM, *t*BuOOH.

Scheme 1.4 Lett's synthesis of the C_1'-C_6' subunit

Regio- and stereospecific epoxide opening gave the carbonate 37. Finally, protecting group manipulation and Swern oxidation gave aldehyde 38 in a total of 14 steps from 34 and in 13 % yield (Scheme 1.5)

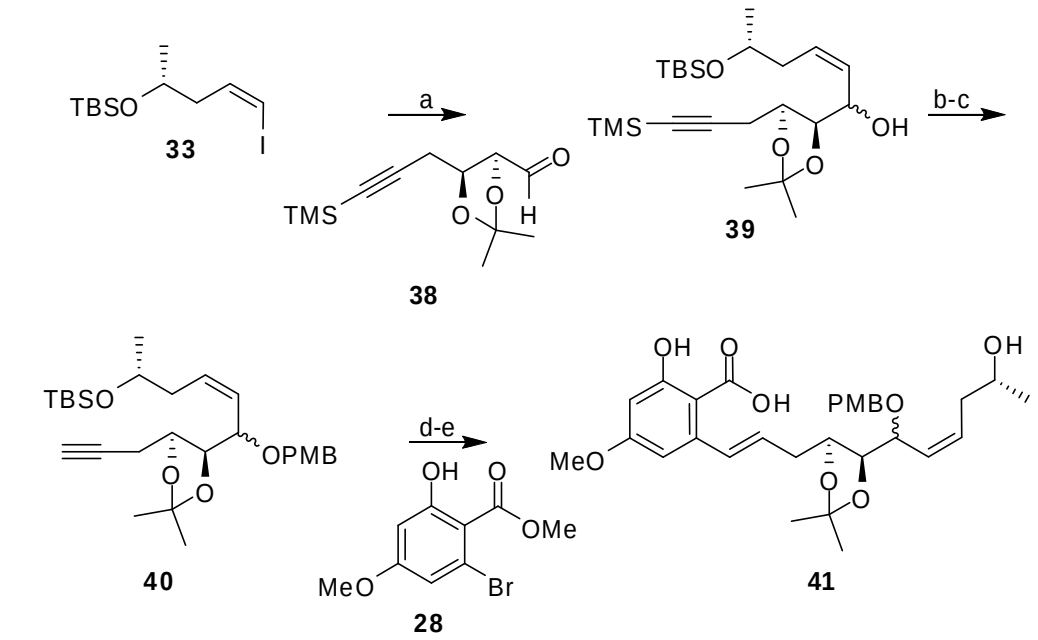


36 **37** **38**

a) PhNCO, DCM/pyridine. b) $BF_3.Et_2O$, Et_2O, then 1M H_2SO_4. c) MeONa, MeOH. d) TBSCl, imidazole, DMF. e) 2-methoxypropene, TsOH, DCM. f) *n*BuLi/hexane, Et_2O, then TBSCl, 98 %. g) DDQ, $MeCN/H_2O$ (9/1), 73 %. h) oxalyl chloride, DMSO, DCM, then Et_3N.

Scheme 1.5 Lett's regio- and stereospecific epoxide opening

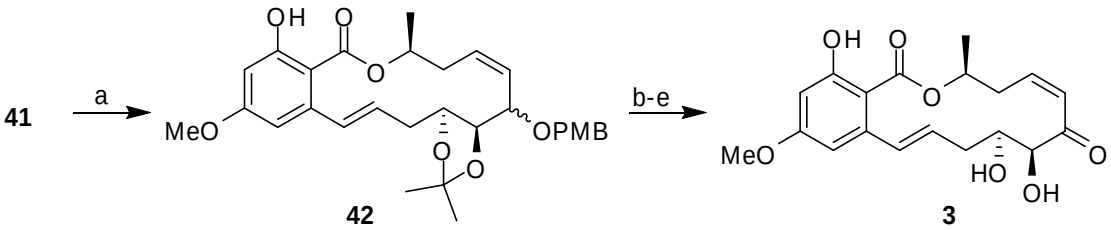
Condensation of units **38** and **33** gave two diastereoisomers **39**, epimeric at the C_6' position. Deprotection of the TMS-alkyne and protection of the free C_6'-OH gave **40** as a 60/40 inseparable mixture C_6'-OPMB ethers. Conversion of alkyne **40** to the corresponding vinyl borane followed by intermolecular Suzuki coupling with **28**, TBAF deprotection and methyl ester cleavage gave the cyclisation precursor **41** in 47 % yield.



a) **33**, Et_2O, then *t*-BuLi/pentane. b) K_2CO_3, MeOH. c) PMB-trichloroacetimidate, Et_2O, CF_3SO_3H. d) TBAF 1M/THF. e) **28**, DCC, DMAP, DCM

Scheme 1.6 Lett's synthesis of the complete scaffold.

It should be noted at this point that the diastereomeric mixture did not worry the authors. They had previously shown during their synthesis of radicicol **2** that the mixture of epimers could be carried forward in comparable yields throughout all the steps of their sequence.[56]



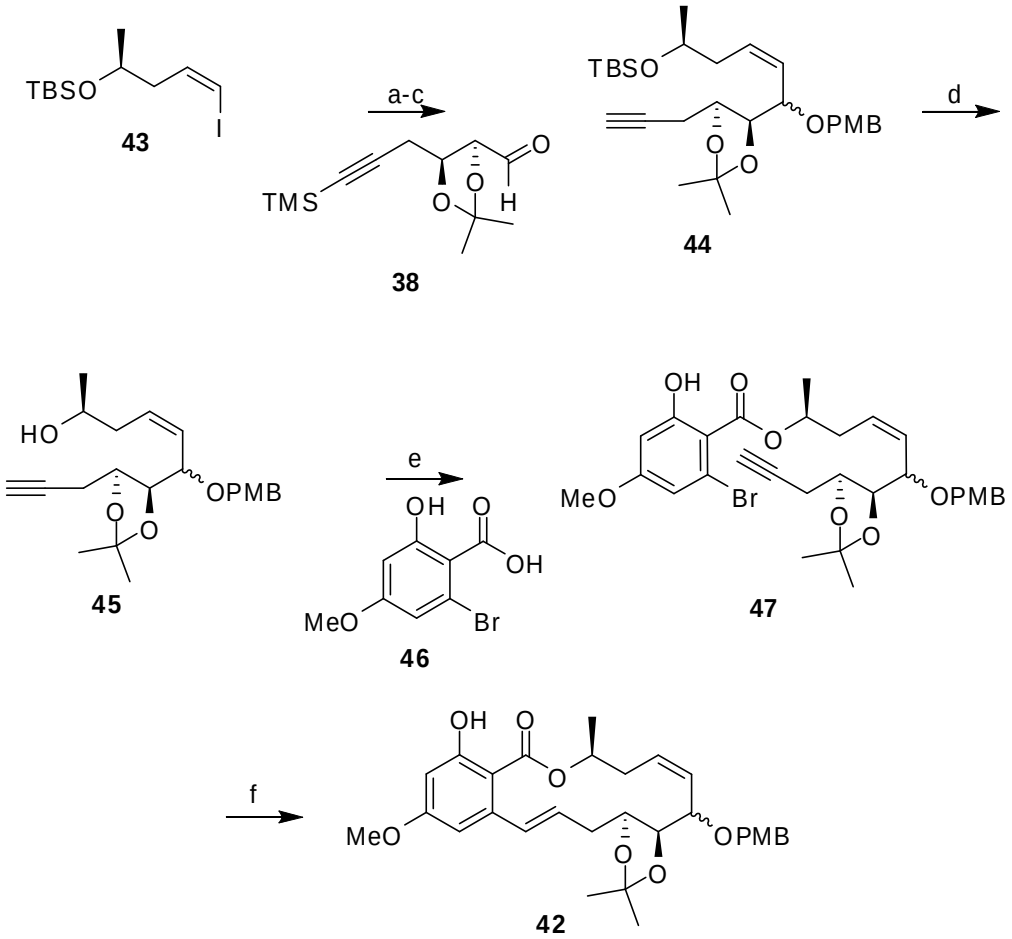
a) 0.007 M hydroxy-acid, PPh_3, DEAD, toluene, 67 % b) DDQ, DCM, 94 %. c) PCC, 2,5-DMP, DCM, 62 %. d) *p*TsOH, DCM/MeOH, 76 %. e) MCPBA/$NaHCO_3$ 17 %.

Scheme 1.7 Lett's macrolatonisation and completion of the synthesis.

Macrolatonisation of **41** via Mitsunobu conditions afforded the desired macrolide **42** with complete inversion of configuration at $C_{10'}$. Completion of the synthesis proved troublesome, but an effective route was found involving an interesting oxidation step that differentiated between the two diasteroisomers. Deprotection of the PMB group gave the free hydroxyl at the $C_{6'}$ position. Oxidation of this hydroxyl proved difficult and the authors decided to cleave the acetonide group to form the triol which was the precursor to Tatsutas[50] final compound. Tatsuta reported this final step to be tricky and reported that only

Dess-Martin reagent was effective. Lett also had problems at this stage and did not report any successful attempts at converting the triol into the desired final product **3**. Lett did have success however treating the epimeric mixture of free hydroxyls at the $C_{6'}$ position with PCC in the presence of 2,5-dimethylpyrazole. The major epimer was converted quantitatively into the *Z*-enone while the minor one was recovered unchanged. It was then found that fast Jones oxidation of the recovered minor epimer gave the desired *Z* enone in 35 %. Finally, acetonide cleavage, 76 %, gave the desired LL-Z1640-2 3 in a total of 26 linear steps and an overall yield of 1.2 % (Scheme 1.7).

As part of Lett's investigation into the flexible synthesis of LL-Z1640-2 **3**, he looked into intermolecular Suzuki couplings as another approach to building the 14 membered macrocycle (Scheme 1.8).



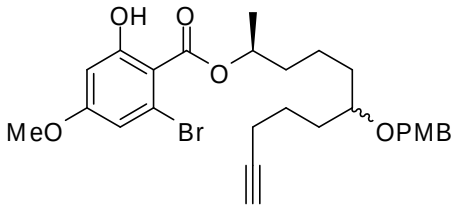
a) *t*-BuLi, Et_2O, **38**, pentane, b) K_2CO_3, MeOH, 56 %. c) PMB-trichloroacetimidate, Et_2O, CF_3SO_3H. d) TBAF 1M/THF. e) **46**, DCC, DMAP, DCM. f) Sia_2BH, THF, acetone, 2 M aq. K_3PO_4, 4 mol % $[Pd(OAc)_2{}^{+4}TFP]$, 15 %.

Scheme 1.8 Lett's Suzuki coupling approach.

The synthesis towards the Suzuki coupling precursor was very similar to his initial approach. Vinyl iodide **43** was obtained using the same procedure as to obtain

33 (Scheme 1.3) but (*S*) propylene oxide was opened to give the *S* derivative. The condensation of subunits **38** and **43** and further steps to **44** were also carried using the same procedures as before. The acid derivative **46** was obtained quantitatively from methyl ester **28** using sodium hydroxide. TBAF deprotection of **44** followed by DCC esterification of alcohol **45** and acid **46** gave the intramolecular Suzuki precursor **47** in 74 % over the two steps.

Optimised conditions for the intramolecular Suzuki coupling were found on model systems. These showed best results were obtained when excess Sia_2BH was destroyed by the addition of anhydrous acetone. After this addition of acetone, a successful Suzuki coupling was achieved. However, when applying these conditions to alkyne **47**, the desired macrolide **42** was isolated in 15 %. Interestingly, studies were also carried out on similar systems, compounds **48** and **49** (Figure 1.11) It was assumed that these systems should be energetically more favoured by less ring strain and steric interactions but these gave no trace of corresponding macrocycles.



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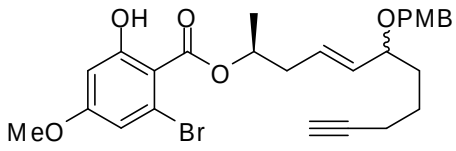
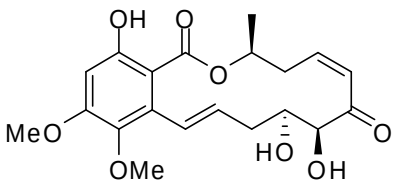


49

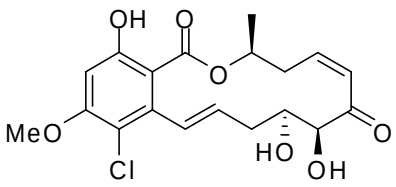
Figure 1.11 Energetically favoured compounds 48 and 49.

1.15 Modular Synthesis Approach

Most recently, a third total synthesis of LL-Z1640-2 **3** was published by Wissinger.[9] Their work took advantage of fluorous isolation technology which allowed the synthesis of LL-Z1640-2, radicicol A **50** and a radicicol A analogue **51** in the same mixture (Figure 1.12). This technique was also advantageous to future work as the system could be potentially automated opening up the possibilities of high-throughput synthesis.



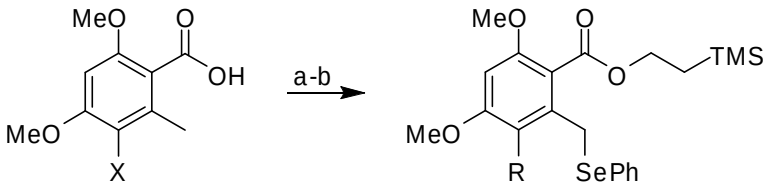
50



51

Figure 1.12 Radicicol A 50 and Radicicol A analogue 51

In Wissinger's approach the aromatic fragments **55-57** were synthesised in two steps from the acids **52-54** by esterification with 2-(trimethylsiyl)ethanol and successive formation of the selenide using LDA to deprotonate the benzylic position (Scheme 1.9).This two step stage was achieved in yields between 85-89 %.



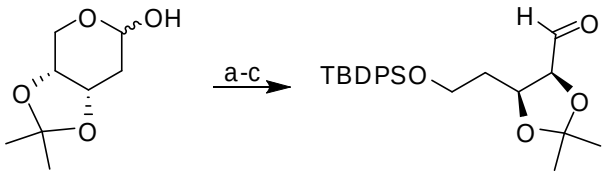
R = H (**52**)
R = OMe (**53**)
R = Cl (**54**)

R = H (**55**)
R = OMe (**56**)
R = Cl (**57**)

a) $(COCl)_2$, DMF (cat.), DCM, 2-(trimethylsilyl)ethanol, Et_3N, 4-DMAP (cat.), 96–98 %. b) LDA, $(PhSe)_2$, THF, 89–91 %.

Scheme 1.9 Wissinger's aromatic fragments 55-57.

Reduction of **58** with $LiAlH_4$ followed by selective silyl protection and oxidation using an immobilised version of IBX afforded the aldehyde **59** in 63 % over 3 steps (Scheme 1.10).

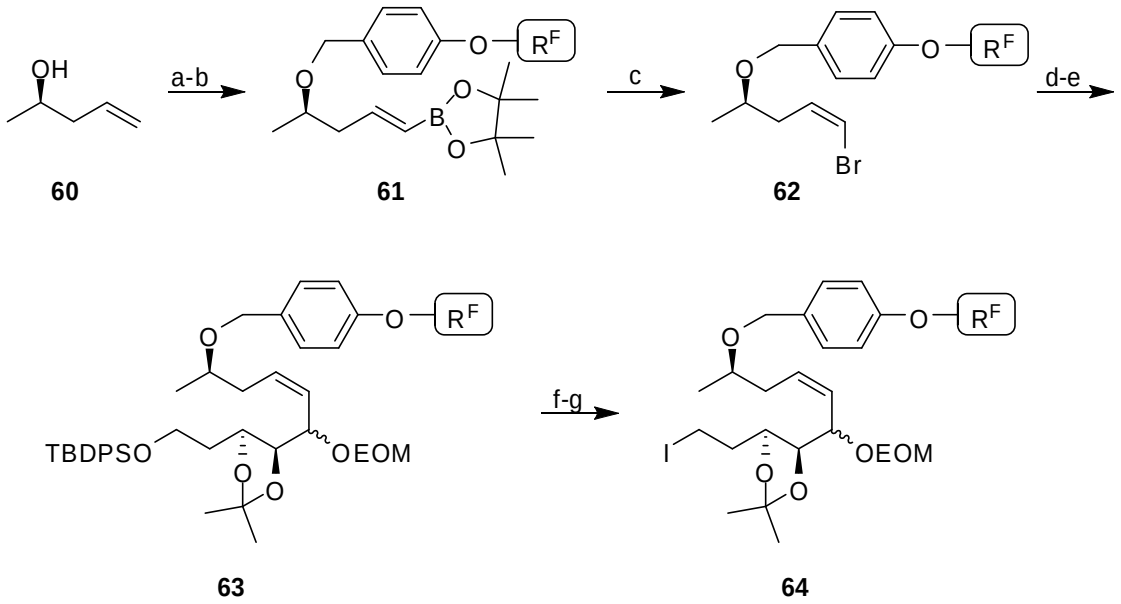


58 **59**

a) $LiAlH_4$, THF, 95 %. b) TBDPSCl, imidazole, DMF, 66 %. c) PS-IBX, DCM, 100 %.

Scheme 1.10 Wissinger's approach to intermediate 59.

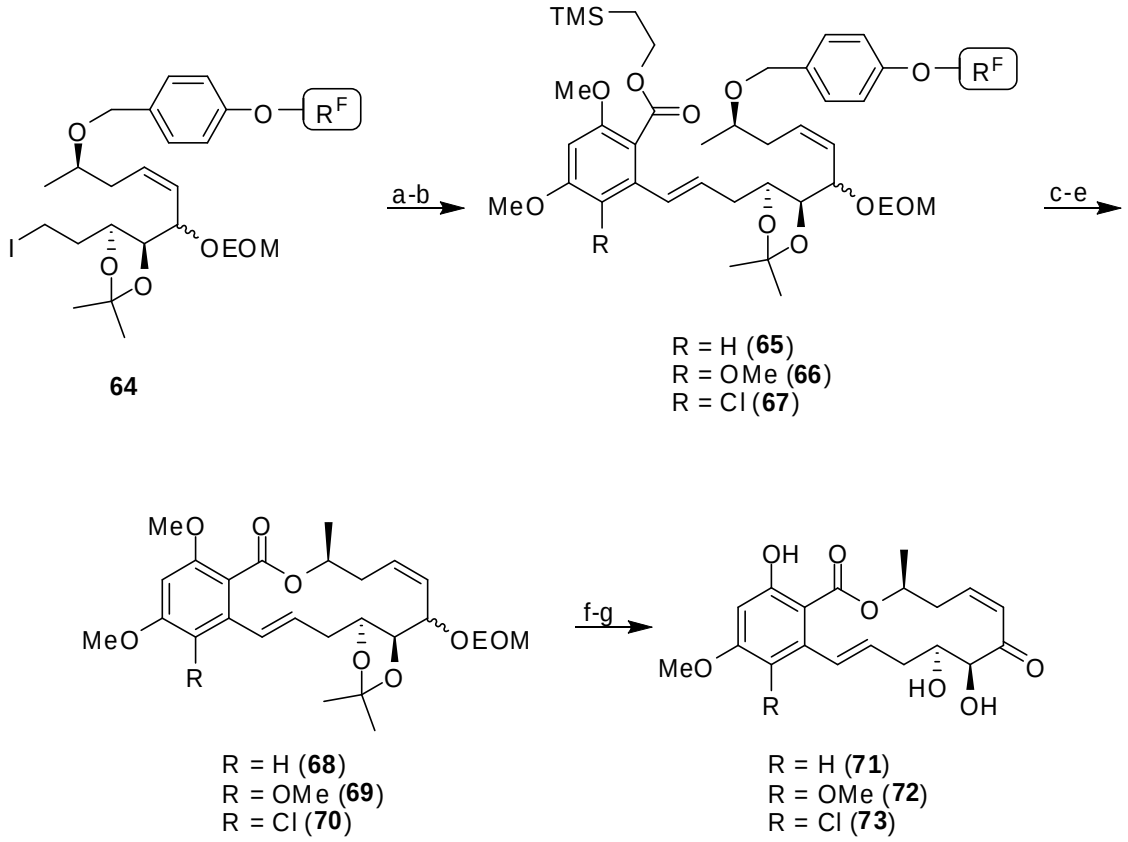
The longest linear sequence of the synthesis began with the protection of (*R*)-2-hydroxypentene **60** with the *fluorous* version of PMB trichloroacetimidate. Cross metathesis with vinyl borolane afforded the *trans*-vinyl borolane **61** with a stereoselectivity better than 20:1 *E*:*Z* and a yield of 85 % over the two steps. *Trans*-vinylborolane **61** was then stereospecifically converted to the *cis*-vinyl bromide **62** following a procedure by Brown et al.[57] Treatment of **62** with *t*BuLi and addition of aldehyde **59** followed by EOM protection afforded **63** as a mixture of diastereoisomers (3:1). The silyl-protected hydroxyl was converted to the iodide in two steps to give compound **64** (Scheme 1.11).



a) Fluorous PMB trichloracetimidate, CSA, DCM, 92 %. b) Vinylboronic acid pinacol ester, Grubbs II, toluene, 92 %. c) Br_2, Et_2O, NaOMe, 89 %. d) *t*-BuLi, THF/Et_2O, **59**, 88%. e) EOMCl, *i*Pr_2EtN, DMF, 96 %. f) TBAF, THF, 92 %. g) PPh_3, I_2, imidazole, THF, 91 %.

Scheme 1.11 Wissinger's approach to intermediate 64.

Iodide **64** was then alkylated with the three different aromatic fragments **55-57** and the selenide was oxidised and eliminated with hydrogen peroxide to give compounds **65-67**. The use of the fluorous tag enabled this work to be carried out without the need of traditional workups and purification. The crude reaction mixtures were simply loaded onto fluorous-silica and eluted with 75 % MeOH in water to remove all non-florous-tagged components. The tagged compounds were then recovered in the MeOH wash. The PMB group was removed with DDQ while the TMSE ester was cleaved using TBAF. Mitsunobu macrocylisation using fluorous-tagged triphenyl phosphine and diazo dicarboxylate gave the macrocycles **68-70** that were also recovered using the fluorous solid-phase extraction method. BCl_3 cleaved the EOM, acetonide group and selectively the ortho-phenol, in the presence of the other methyl ethers, in one step. The allylic alcohols were then oxidised with the polymer bound version of IBX to afford LL-Z1640-2 3, Radicicol A 50 and the radicicol analogue 51. In total the longest synthetic sequence contained 14 linear steps and the three macrocyles 3, 50 and 51 were obtained in an excellent 14.6-17.3 % yield (Scheme 1.12).

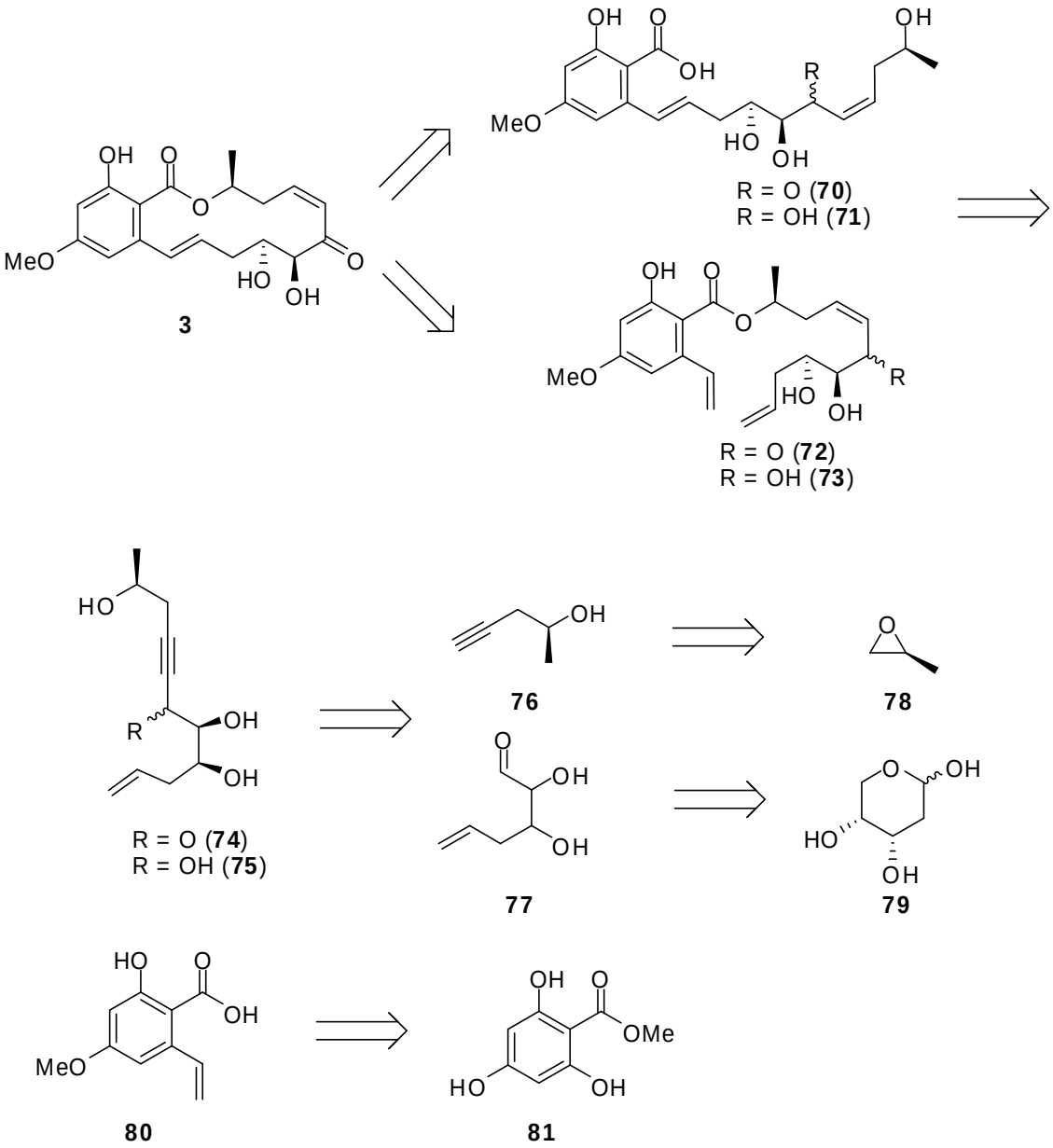


a) **55**-**57,** LDA, THF/HMPA 10:1, 88–91 %. b) H_2O_2, THF, 79–82 %. c) DDQ, DCM/H_2O 2:1, 70–80 %. d) TBAF, THF, 87%. e) R^FPh_3P, R^FDEAD, toluene, 81 %. f) BCl_3, DCM, 86%. g) PS-IBX, DCM, > 90 %. RF=$C_3H_6C_6F_{13}$,

Scheme 1.12 Wissinger's macrolactonisation and completion of the synthesis

1.16 Retrosynthetic Analysis

As part of our approach we envisioned a flexible and robust synthesis of LL-Z1640-2 **3** as originating from the macrolactonisation of acids **70/71** or from a Grubbs' catalyst mediated ring closing metathesis (RCM) of dienes **72/73**. The acids **70/71**, in turn could be the product of the cross methathesis of aryl alkene **80** and the complete straight chain fragments **74/75**. Alternatively, dienes **72, 73** could be the product of an esterification of acid **80** and complete straight chain fragments **74/75**. This flexibility in our approach was advantageous as we could foresee potential problems with the ring closing step due to the size and functionality of compounds **70-73** (Scheme 1.13).



Scheme 1.13 Retrosynthetic Analysis

The complete $C_{1'}$-$C_{10'}$ straight chain fragments **74/75** was thought to best originate from alkyne **76** and aldehyde **77**. Aldehyde **77** is the oxidised product of the Wittig olefination of 2-deoxy-D-ribose **79**. The aromatic fragment **80** was thought best to come from commercially available methyl 2,4,6-trihydroxybenzoate **81**.

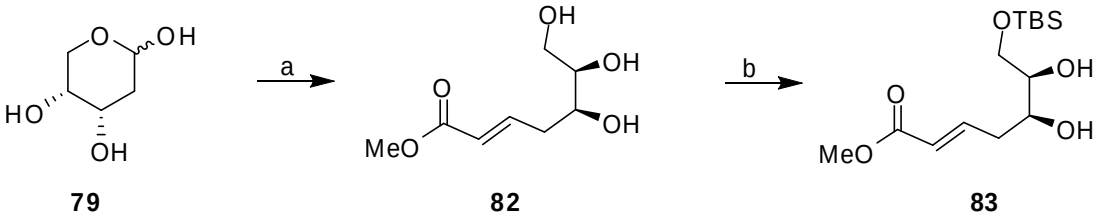
It should be noted that the timing of the oxidation of the alcohol at position $C_{6'}$ in the final ring and the selective reduction of the alkyne to the required *Z* alkene were both variable within our original plan. This again gave us more flexibility and thus, making our approach more desirable.

Allowing for the use of suitable orthogonal protecting groups it was proposed to make protected derivatives of **74/75** and **80** both in 5 steps respectively. Coupling of the two fragments and the remaining steps were also proposed to take 5 or 6 steps. This proposed route therefore formed the basis of a robust, cost and step efficient route which should allow the target compound **3** and it's related structures to be considered as realistic chemical biological leads for the first time.

2 Results and Discussion

2.1 Synthesis of the $C_{1'}$-$C_{10'}$ Unit

The synthesis of the $C_{1'}$-$C_{10'}$ unit began with the Wittig olefination of 2-deoxy-D-ribose **79** using the stabilised ylide, methyl(triphenylphosphoranylidene)-acetate, which afforded the desired triol **82** in 83 % and as a 9.5:1 *E*:*Z* ratio of diastereomers (Scheme 2.1).

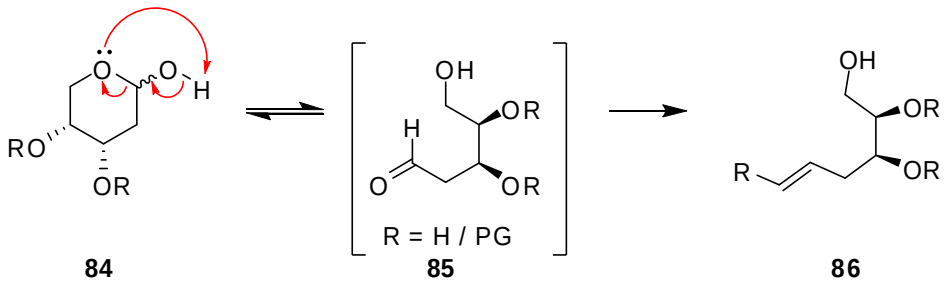


79 **82** **83**

a) $Ph_3P{=}CHCO_2Me$, THF, 75 %. b) TBSCl, Et_3N, DMAP, DCM, 83 %.

Scheme 2.1 Wittig olefination of 2-deoxy-D-ribose 79

The olefination proceeded due to the masked aldehyde character of C1 in the sugar. This was then exploited via Wittig conditions (Scheme 2.2).

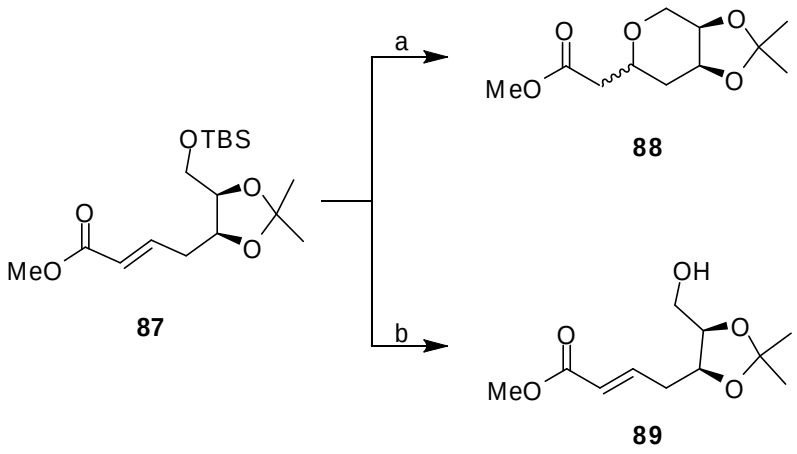


84 **85** **86**

Scheme 2.2 Wittig chemistry on sugars.

The primary alcohol was selectively protected as the TBS ether **83** and the remaining vicinal diol was then converted into the dimethyl ketal unit **87** in good overall yield (83 % and 86 % respectfully).

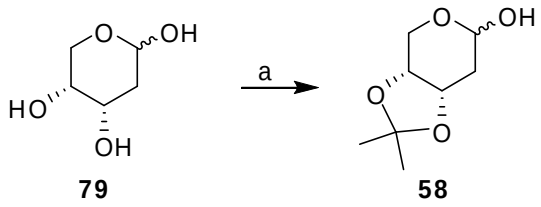
Initial attempts at the deprotection using TBAF resulted in the production of the pyran unit **88** with none of the desired free alcohol **89** being isolated. Although disappointing, this was not surprising considering the relative basic nature of TBAF and the presence of the dimethyl ketal unit, which might be facilitating the cyclisation via the Thorpe-Ingold Effect.[58] Deprotection using HF-pyr however yielded the required primary alcohol **89** in 98 % with no evidence of any cyclisation product **88** (Scheme 2.3).



a) TBAF, THF, 76 %. b) HF.Pyr, Pyr, THF, 98 %.

Scheme 2.3 TBS deprotection and formation of undesired pyran unit 88.

Faced with the competing cyclisation process during the deprotection step coupled with the need to protect and then de-protect the primary alcohol unit, it was decided that ketal protection of the carbohydrate starting material followed by olefination of the resulting lactol might prove a more efficient process (Scheme 2.4).



a) Various, see table 2.1

Scheme 2.4 Ketal protection of 2-deoxy-D-ribose

Our initial ketal introduction attempts were based on the procedure reported by Horton and co-workers.[59] Unfortunately, reproducible and acceptable yields were hard to maintain especially during scaling up. Conditions were then tested to optimise the step (Table 2.1).

Faced with an unreliable method for the scaling up of the first step of a total synthesis prompted us to develop an improved and optimised method, which could be readily and reproducibly scaled up. We were particularly concerned about the use of DMF in the initial procedure. DMF was used to deal with the poor solubility of the starting material **79** but, especially on larger scale reactions, the DMF caused issue during the reaction work up. Either large amounts of water had to be used to remove the DMF completely, or higher temperatures than normal had to be used during concentration under vacuum.

Unfortunately, it was found that the protected lactol **58** was very soluble in water and could only be extracted through the use of highly polar solvents like EtOAc. The use of EtOAc on the other hand, resulted in the DMF being extracted also from the aqueous phase. An alternative approach to the aqueous work-up was to simply concentrate the reaction. However, temperatures required to remove large amounts of DMF resulted in decomposition of any product formed.

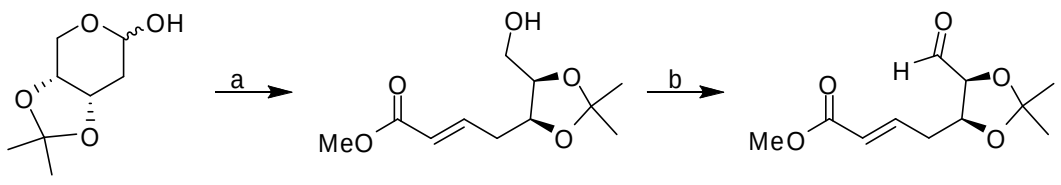
As part of our optimisation steps different combinations of solvents, catalyst and ketal generating reagents were explored. It was found that by switching from DMF to EtOAc as the solvent greatly improved yields. Furthermore, EtOAc could be easily removed under vacuum at lower temperature as to avoid decomposition of product. The best combination of conditions included using 2-methoxy-propene in EtOAc and using PPTS as a catalyst (86 % yield). These conditions were reproduced on a larger scale with only a small drop in yield.(75-80 %).

Table 2.1 Conditions for ketal protection

	Solvent	Reagent	Catalyst	Temperature (˚C)	Time (h)	Yield (%)
1	DMF	2MP	pTSA	0	1	33
2	DMF	2MP	pTSA	-10	1	40
3	DMF	2MP	CSA	-10	1	34
4	DMF	2MP	PPTS	-10	1	42
5	DMF	2,2DMP	pTSA	-10	1	38
6	DMF	2,2DMP	CSA	-10	1	67
7	DMF	2,2DMP	PPTS	-10	1	43
8	Toluene	2,2DMP	CSA	-10	1	0
9	Acetone	2,2DMP	CSA	-10	2	17
10	EtOAc	2,2DMP	CSA	-10	6	72
11	EtOAc	2,2DMP	PPTS	-10	6	78
12	EtOAc	2MP	PPTS	-10	6	86
13	EtOAc	2MP	pTSA	-10	6	43

2-methoxypropane (2MP), 2,2-dimethoxypropane (22DMP),

Wittig olefination of the protected sugar **58** with stabilised ylide, methyl(triphenylphosphoranylidene)-acetate gave the desired *E* alcohol **89** in 89 % yield. Traces of the *Z* olefin were also recovered but were impure and contained traces of the E product and further side products of the reaction. The alcohol **89** was then oxidised under Swern conditions to generate the desired aldehyde **90** in quantitative yield (Scheme 2.5).



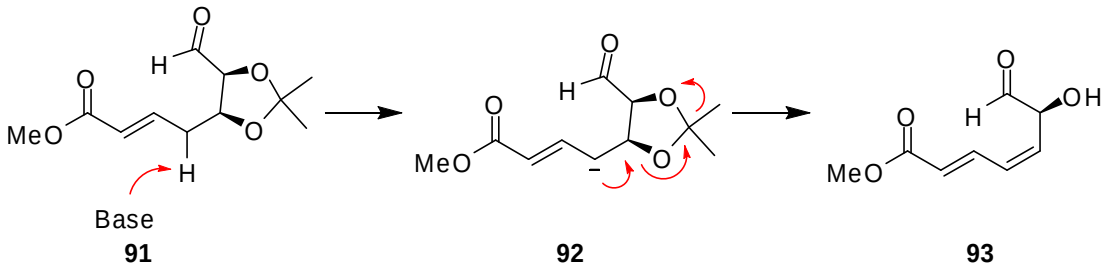
58 **89** **90**

a) $Ph_3P{=}CHCO_2Me$, THF, 89 %. b) $(COCl)_2$, DMSO, Et_3N, DCM, 100 %.

Scheme 2.5 Synthesis of aldehyde fragment 90.

Having successfully generated the desired aldehyde **90** the introduction of the remaining part of the C_1,-C_{10}, unit as an alkyne block was explored.

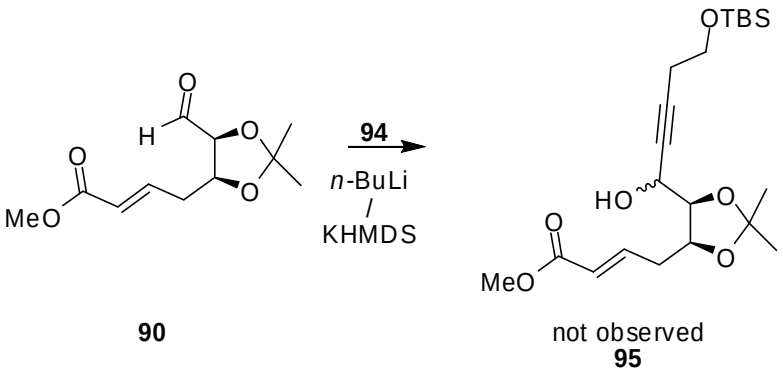
There were initial concerns that the presence of the ester unit would render the molecule too unstable to undergo a successful nucleophilic addition. It was quite feasible for the protons gamma to the ester unit could be removed under basic conditions employed, resulting with delta-elimination of the ketal unit through the expulsion of acetone (Scheme 2.6).



Scheme 2.6 Possible delta-elimination of the ketal unit mechanism.

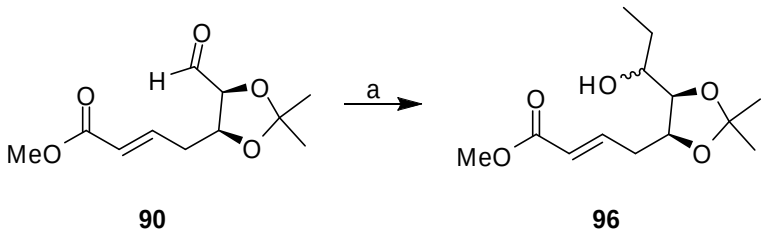
Another, relatively minor concern was the possibility that the alkoxy generated during the reaction could potentially perform a conjugated addition onto the conjugated ester unit similar to that observed during the deprotection of **87** (Scheme 2.3).

The required coupling was initially tested using aldehyde **90** and alkyne **94** (obtained in 88 % yield through the TBS protection of the commercially available 3-butynol). Initial attempts using *n*-BuLi and KHMDS as bases to generate the corresponding alkynyl anion failed to give any product and only yielded starting materials. Lewis acid catalysts (BF_3 etherate and zinc triflate additives) were also evaluated, but no desired product could be detected. Carreira's conditions[60] were also attempted, however, just as in the previous case, no alkyne addition was observed (Scheme 2.7).



Scheme 2.7 Attempted test coupling of aldehyde 90 and alkyne 94

The inability of the alkyne to add successfully under both lithium and zinc promoted conditions prompted us to consider the use of a different metal counter ion during the addition process. Treatment of alkyne **94** with ethylmagnesium bromide at a low temperature (-78 °C) failed to deprotonate the alkyne unit **94**, affording instead the ethyl addition product **96** when treated with aldehyde **90** (Scheme 2.8).

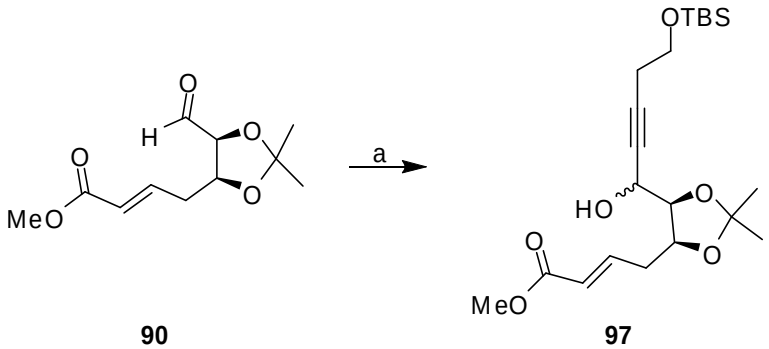


90 **96**

a) **94**, EtMgBr, THF, - 78 °C, 94 %

Scheme 2.8 Failed ethylmagnesium bromide deprotonation of of alkyne 94

Treatment of alkyne **94** with ethylmagnesium bromide at room temperature successfully generated the magnesium acetylide which upon trapping with the aldehyde **90** gave the desired alkyne product **97** as a 50:50 mixture of diastereomers in 88 % yield based on aldehyde recovered (Scheme 2.9). It should also be noted that no 1,4 addition side products was detected either.

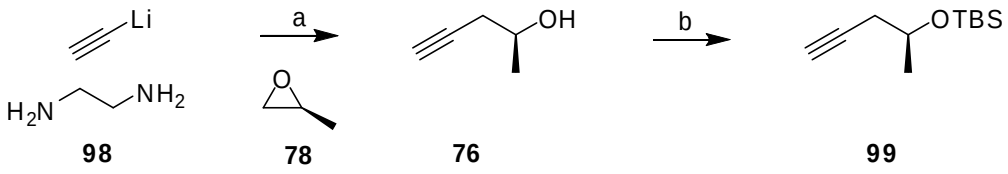


90 **97**

a) **94**, EtMgBr, THF, 94 %

Scheme 2.9 Successful coupling of units 90 and 94

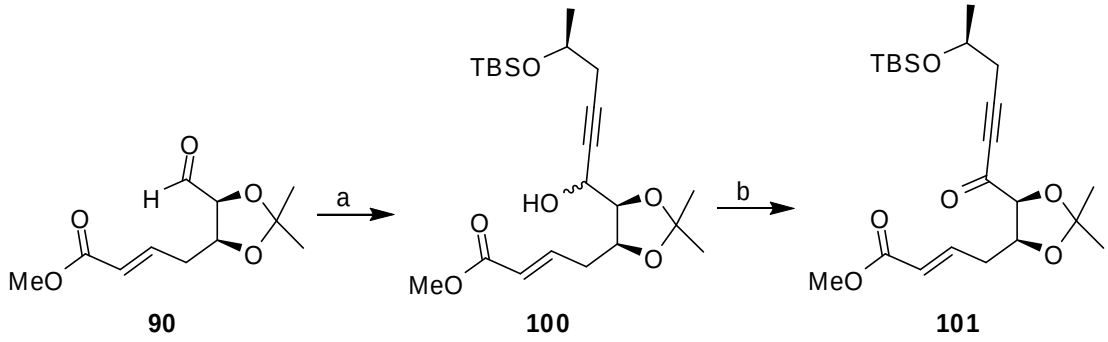
Having successfully achieved the addition of the alkyne model unit, we turned our attention to making the desired optically pure alkyne. Lithium acetylide ethylene diamine complex **98** was coupled with *S*-propylene oxide **78** to give the crude volatile alkynol **76** which was immediately protected to afford the required homo-propargylic silyl ether **99** in 71 % over 2 steps (Scheme 2.10)



a) **78**, DMSO. b) TBSCl, Imidazole, DMF, 71 %.

Scheme 2.10 Synthesis of fragment 99.

The TBS protected alkyne **99** was then treated with ethylmagnesium bromide under same conditions as those used in the model system and the resulting anion was added to aldehyde **90** to yield propargylic alcohol **100** as a 60:40 mixture of diastereomers in 69 % yield based on aldehyde recovered (Scheme 2.11). The propargylic alcohol diastereomeric mixture was then oxidised using TPAP/NMO conditions (59 %) and under Swern conditions (21 %) to give the spectroscopically simpler alkynone **101** that was used to corroborate the structure of the compound.



a) **99**, EtMgBr, THF, 69 %. b) TPAP, NMO, DCM, 59 %.

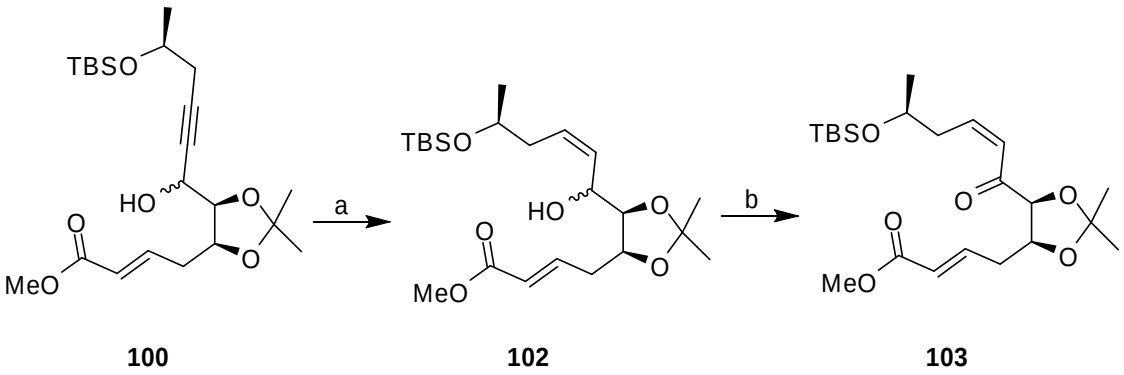
Scheme 2.11 Coupling of fragments 90 and 99 and oxidation.

Having successfully introduced the fully elaborated side chain with no apparent side products being formed, attempts were then made to selectively reduce alkynol **100** to the necessary *Z* alkene **102**. Despite the apparent simplicity of the step, this transformation proved to be extremely troublesome and resulted in a large amount of optimisation work before the reaction proceeded successfully (Table 2.2).

Table 2.2 Conditions for selective reduction of 100 to *Z* alkene 102

	Catalyst	Quinoline	Solvent	Product
1	Palladium 5 wt % on calcium carbonate unreduced	No	Toluene	SM
2			MeOH	SM
3	Palladium 5 wt % on calcium carbonate, poisonied with lead	No	Toluene	SM
4			MeOH	SM
5	Palladium 5 wt % on barium sulphate unreduced	No	Toluene	SM
6			MeOH	77 %
7	Palladium 5 wt % on calcium carbonate unreduced	Yes	Toluene	SM
8			MeOH	SM
9	Palladium 5 wt % on barium sulphate unreduced	Yes	Toluene	SM
10			MeOH	83 %

Surprisingly, most conditions were unsuccessful with the only reproducible results being obtained with Palladium on barium sulphate using MeOH as the solvent. The newly obtained alkenol diastereomeric mixture **102** was then oxidised under TPAP/NMO conditions (26 %) to generate the enone **103.** Also recoverd from the reaction was alkyneone **101** and alkyneol **100** as impure fractions. This was expected though as the hydrogenation was never recorded as quantitative. Enone **103** was used to corroborate the structure of alkene-ol **102** (Scheme 2.12).



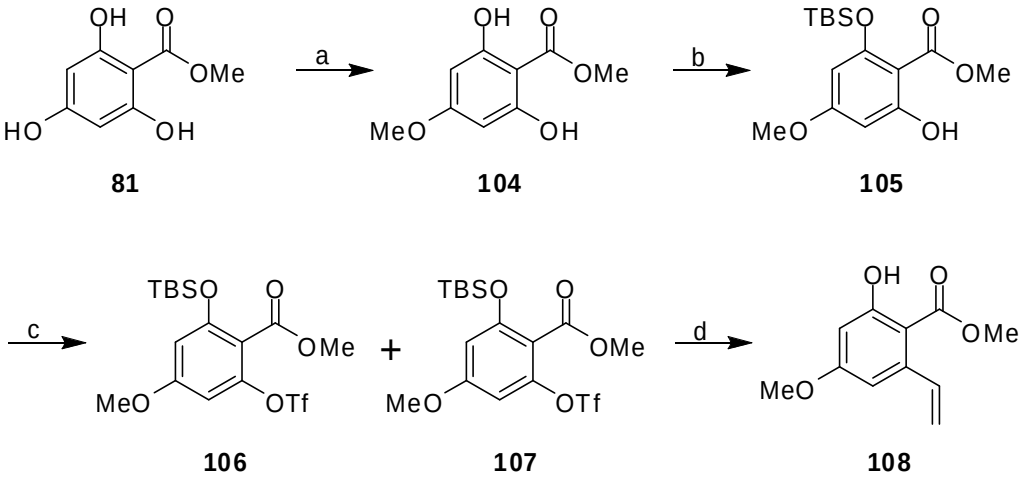
100 **102** **103**

a) H_2, Pd/BSO_4, MeOH, 77 %. b) TPAP, NMO, DCM, 26 %

Scheme 2.12 Alkyne reduction of 100 and oxidation.

2.2 Synthesis of the Aromatic Fragment

With the 10 carbon skeleton now in place, our attention was directed towards the synthesis of the aromatic fragment. Our synthesis began with commercially available methyl 2,4,6-trihydroxybenzoate **81** which was methylated selectively to afford the desired diphenol **104**. Mono-protection of diol **104** then proceeded in good yield to give the TBS silyl ether **105**. Initial attempts at converting the remaining hydroxyl group into the corresponding triflate **106** resulted in partial cleavage of the TBS group, yielding **107**. It was likely that this cleavage could be due to the acid (1 M HCl) workup. Subsequent attempts using citric acid during the workup gave the protected triflate **106** in quantitative yield. Stille coupling of the newly generated triflate **106** with vinyltributyl tin proceeded in excellent yield to afford the vinyl benzene unit **108**, interestingly, the TBS group was removed once again during the procedure (Scheme 2.13).



81 **104** **105**

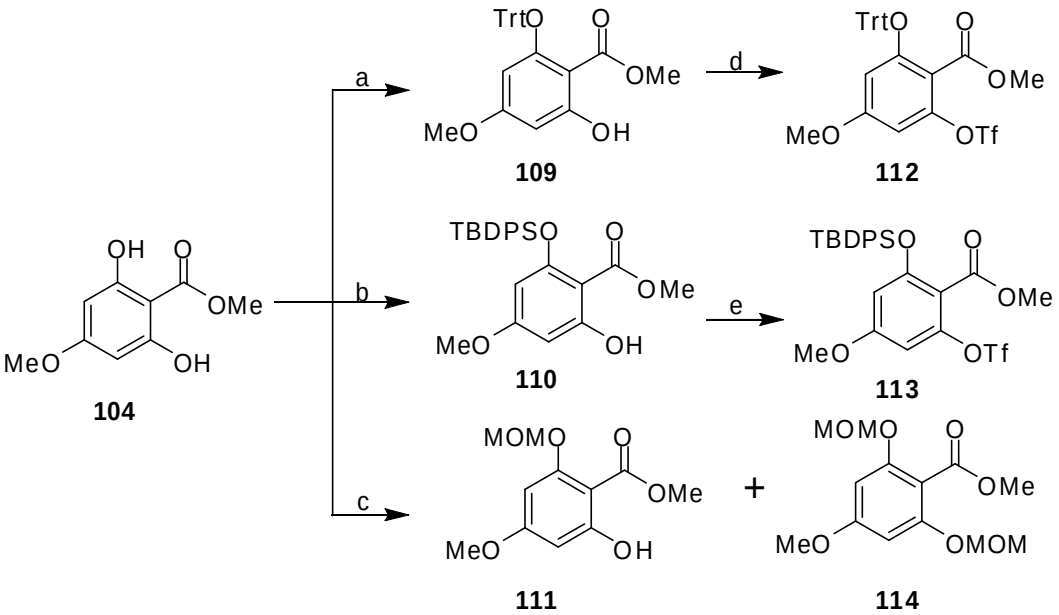
106 **107** **108**

a) TMS-CH_2N_2, $CHCl_3$, MeOH, 98 %. b) TBSCl, Et_3N, DCM, 100 %. c) Tf_2O, Pyr, 98 %. d) tributyl vinyl tin, $Pd(PPh_3)_4$, 97 %.

Scheme 2.13 Synthesis of vinyl aromatic unit 108

The difficulties that arose with the relative instability of the TBS group during the synthesis of the vinyl benzene unit **108** made us reconsider our choice of protecting group. A different protecting group also had the potential to ease possible conflicts and cross reactivity issues in future steps. As an alternative to the labile TBS group the introduction of the trityl, TBDPS and MOM groups was explored.

Treatment of diol **104** with either TrtCl or TBDPSCl afforded the desired trityl and TBDPS mono protected products **109** and **110** in 39 % and 99 % yields respectively, no bis-protected product was isolated. The MOM derivative proved to be more difficult. Initial attempts using MOMCl resulted in a mixture of mono **111** and bis-protected **114** products in 16 % and 83 % yields respectively (Scheme 2.14). Unfortunately, the lack of commercial availability of MOMCl meant that it was not possible to optimise the production of **111**. The same protection was attempted using MOMBr, however, this yielded none of the desired product **111** and resulted in complete decomposition of the starting material. No compound of any use was isolated from the reaction.



a) TrtCl, Et_3N, DCM, 39 %. b) TBDPSCl, Et_3N, DCM, 99 %. c) MOMCl, DIPEA, DCM, 16%. d) Tf_2O, Pyr, 99 %. e) Tf_2O, Pyr, 99 %

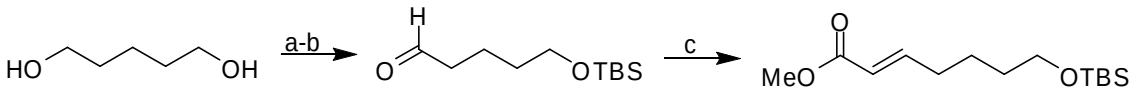
Scheme 2.14 Alternative protecting group strategies for aromatic unit 104.

The remaining hydroxyl group on **109** and **110** was converted to the corresponding triflates **112** and **113** using the citric acid workup as for **106**. Triflates **112** and **113** were both obtained in 99 % yield.

2.3 Cross Couplings

Having successfully completed the synthesis of the $C_{1'}$-$C_{10'}$ and aromatic fragments of LL-Z1640-2 **3**, the key cross metathesis couplings were attempted. Having a limited amount of the $C_{1'}$-$C_{10'}$ ester, cross metathesis was attempted between the aromatic alkene unit and a model conjugated ester unit **118**.

The test coupling partner **118** was synthesised quickly from pentane-1,5-diol **115** in 3 steps. Mono protection of diol **115** using stoichiometric NaH afforded the silyl ether **116** in 94 %.[61] The alcohol was then oxidised under Swern conditions to yield the aldehyde **117** in 77 % and finally Wittg olefination of aldehyde **117** using the stabilised ylide, methyl(triphenylphosphoranylidene)-acetate, afforded the desired conjugated ester **118** in 56 % (Scheme 2.15).



115 **117** **118**

a) NaH, TBSCl, THF, 94 %. b) $(COCl)_2$, DMSO, Et_3N, DCM, 77 %. c) $Ph_3P{=}CHCO_2Me$, THF, 56 %

Scheme 2.15 Synthesis of test coupling partner 117.

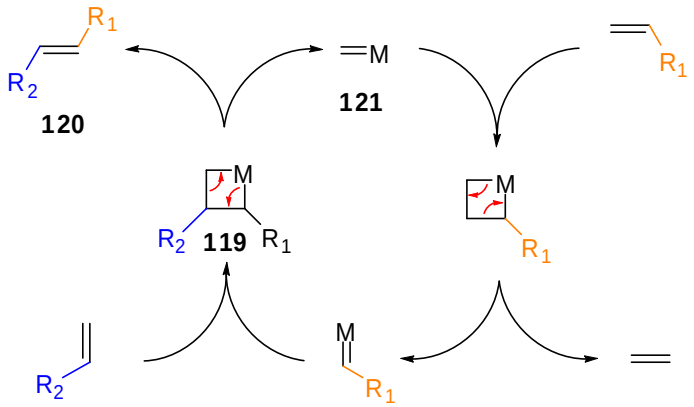
2.4 Olefin metathesis

Metathesis, with its numerous aspects, has become one of the most important chemical reactions and is now extremely useful.[62]

The name metathesis was given for the first time to this reaction by Calderon in 1967[63] but it was first observed 1931. Catalysed metathesis reactions were first reported in the 1950's by industrial chemists at Du Pont, Standard Oil and Phillips Petroleum when they reported that propene led to ethylene and 2-butenes when it was heated with molybdenum.[62]

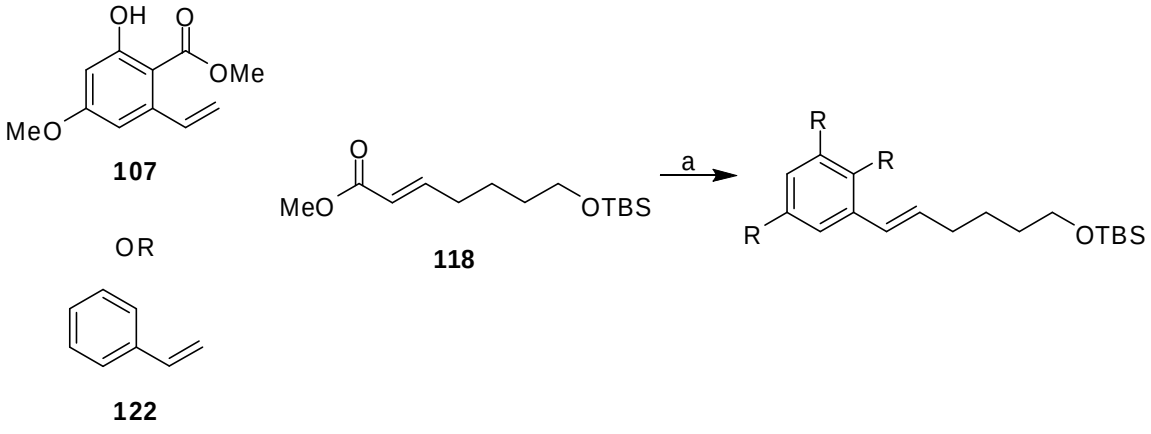
Classically cross metathesis is the coupling of two terminal alkenes under release of ethene, catalyzed by transition metal catalyst (ruthenium, molybdenum, tungsten). In theory, the reaction can lead to three possible pairs of geometric isomers, the *E*/*Z* pairs for two homocouplings and the cross-coupling products. However, there are various examples of two alkenes with different reactivity giving the cross-coupled product with excellent yields and excellent selectivity.[64]

Hérison and Chauvin first proposed the widely acknowledged mechanism of transition metal alkene metathesis in 1971.[65] The direct [2+2] cycloaddition of two alkenes is formally symmetry forbidden and thus has a very high activation energy. The Chauvin mechanism involves the [2+2] cycloaddition of an alkene double bond to a transition metal alkylidene to form a metallocyclobutane intermediate **119**. The metallocyclobutane **119** produced can then give the new alkene **120** and alkylidene **121**. Interaction with the *d*-orbitals on the metal catalyst lowers the activation energy enough that the reaction can proceed rapidly at modest temperatures (Scheme 2.16).



Scheme 2.16 Cross metathesis mechanism.

Conjugated ester **118** was then used to screen catalysts and conditions to find the most suitable for the actual coupling of **100** and **101**.



a) Various, see table 2.3.

Scheme 2.17 Cross metathesis model system.

The aromatic unit **107** was used in test couplings with the conjugated ester **118**. At the same time it was decided to screen commercially available styrene **122**. It was chosen due to it being readily available and it also had the advantage of

not having any electron withdrawing groups which could result in an electronic mismatch (Scheme 2.17)

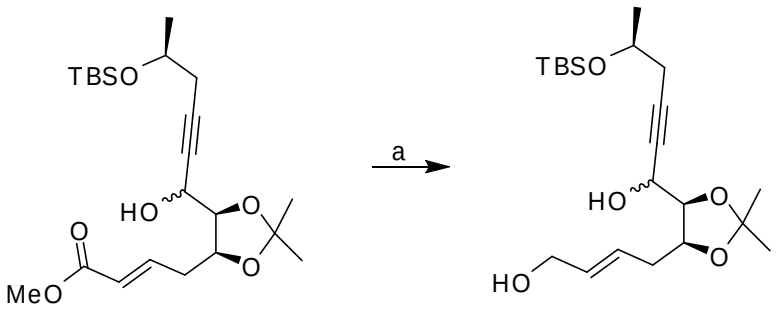
Unfortunately, no desired coupling was observed during our screen of Grubbs' First and Second generation catalyst. The ratios of the partners were varied from 1:1 to 2:1 in favour of both partners. Reaction time was also adjusted from 6 hours to 24 hours. Microwave assisted reactions were also investigated but none of the examples shown below (Table 2.3) yielded any desired product.

Table 2.3 Grubbs' cross coupling conditions.

	Partner			Temp. / Time			Partner			Temp. / Time	
	107	**117**	Cat	(˚C)	(h)		**121**	**117**	Cat	(˚C)	(h)
1	1 eq	1 eq	1st	45	6	11	1 eq	1 eq	1st	45	6
2	1 eq	1 eq	2nd	45	6	12	1 eq	1 eq	2nd	45	6
3	1 eq	2 eq	1st	45	6	13	1 eq	2 eq	1st	45	6
4	1 eq	2 eq	2nd	45	6	14	1 eq	2 eq	2nd	45	6
5	2 eq	1 eq	1st	45	6	15	2 eq	1 eq	1st	45	6
6	2 eq	1 eq	2nd	45	6	16	2 eq	1 eq	2nd	45	6
7	2 eq	1 eq	1st	45	24	17	2 eq	1 eq	1st	45	24
8	2 eq	1 eq	2nd	45	24	18	2 eq	1 eq	2nd	45	24
9	2 eq	1 eq	1st	110	0.5	19	2 eq	1 eq	1st	110	0.5
10	2 eq	1 eq	2nd	110	0.5	20	2 eq	1 eq	2nd	110	0.5

The only new compound to be isolated and characterised from any of the above reactions was dimerised styrene **123** from the reactions 11-20. With these disappointing results from the screen it was thought best to look into different coupling partners as the use of conjugated esters in cross metathesis did not look promising.

In an attempt to make another potential Grubbs coupling partner, alkyneol **100** was treated with DIBAL-H to give diol **124** in a quantitative yield (Scheme 2.18). Cross coupling of diol **124** and aromatic fragment **107** also failed.



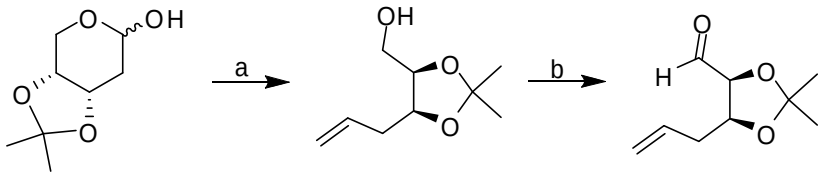
100 **124**

a) DIBAL-H, DCM, 100 %

Scheme 2.18 Reduction of 100 to form coupling partner 124.

2.5 A New Approach to the $C_{1'}$-$C_{10'}$ Unit

As part of our new approach, it was decided to remove the ester functionality from the alkene unit. Wittig olefination of the dimethyl ketal protected 2-deoxy-D-ridose **58** using methyltriphenyl-phosphonium iodide gave the desired terminal alkene **125** in reasonable yield.[66] Unfortunately, oxidation of the newly formed alcohol **125** generated a very unstable aldehyde **126** which decomposed within minutes of being formed. At the moment, we still cannot account for the reasons behind the aldehydes inherent instability (Scheme 2.19).

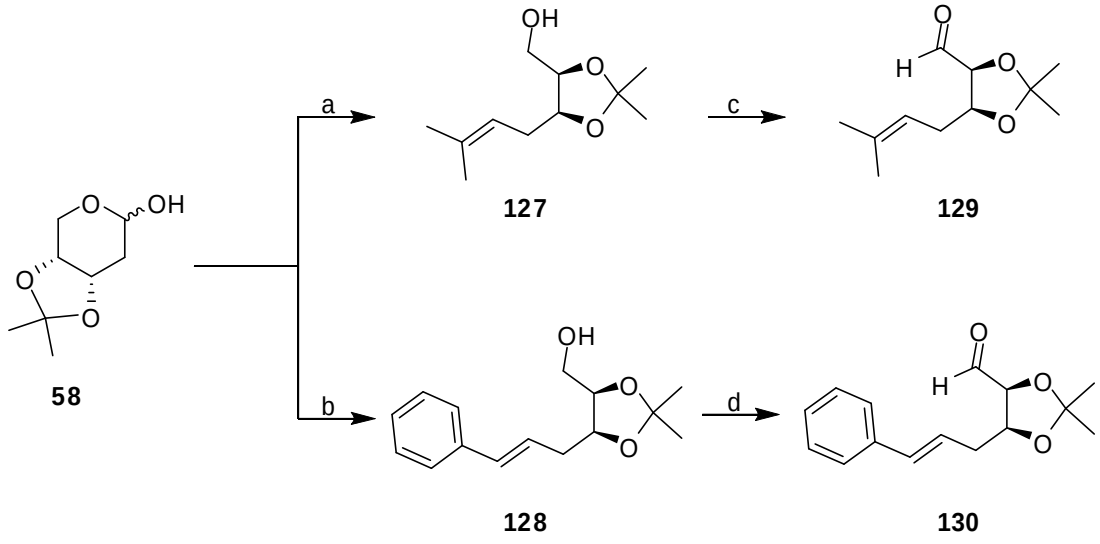


58 **125** **126**

a) $(Ph_3P\text{-}CH_3)I$, KHMDS, THF, 67 %. b) various conditions

Scheme 2.19 Synthesis of terminal olefin 125 and subsequent oxidation.

In an attempt to increase the stability of aldehyde **126** the olefins substitution was increased. As such, the *gem*-dimethyl **127** and the phenyl substituted **128** olefins were generated from the corresponding ylides in 56 % and 67 % yield respectively (Scheme 2.20). Olefin **128** was obtained as an inseparable mixture of *E*:*Z* diastereomers.

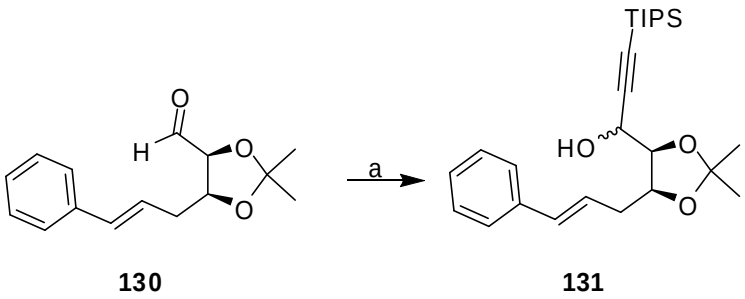


a) $(Ph_3P\text{-}i\text{Pr})I$, *n*-BuLi, THF, 56 %. b) $Ph_3P\text{-Bn})Cl$, KHMDS, THF, 67 %. c) $(COCl)_2$, DMSO, Et_3N, DCM, 92 %. d) $(COCl)_2$, DMSO, Et_3N, DCM, 97 %.

Scheme 2.20 Wittig derivatives of 125 and their corresponding aldehydes.

The newly obtained alcohols were then oxidised under Swern conditions to generate the desired aldehydes **129** and **130** in good yields. Significantly, in contrast to the terminal olefin **126**, these newly generated aldehydes were stable enough to be purified by flash column chromatography. A sample of aldehyde **130** was stable enough to be stored for months in the freezer without any noticeable decomposition.

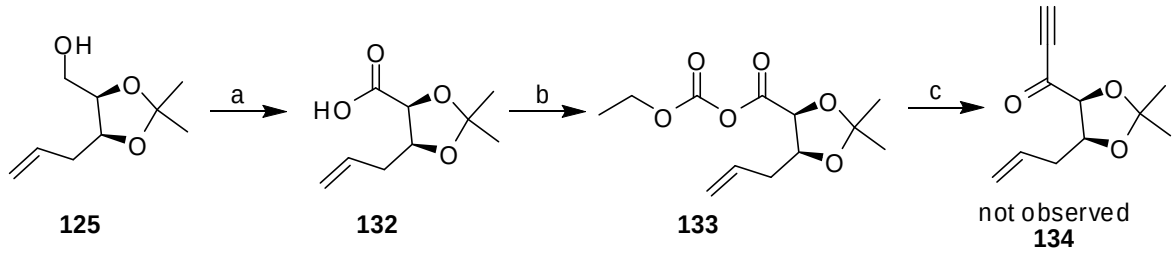
With stable aldehydes now being accessible, the next step was to introduce the required alkyne unit. A similar system using (triisopropylsilyl)acetylene was employed to test conditions. As in previous cases, deprotonation of the alkyne could not be effectively achieved when using either *n*-BuLi or KHMDS as bases. The best result obtained through this method was a non-reproducible 28 % yield for the generation of alkynol **131** from aldehyde **130** (Scheme 2.21)



a) TIPSCCH, KHMDS, THF, 28 %

Scheme 2.21 Alkynye coupling of aldhyde 130.

Despite having been able to successfully synthesise the desired aldehyde intermediates, the alkene substitution presented a potential problem which we felt could present an insurmountable obstacle later in the synthesis. Therefore alternative routes were investigated for the generation and manipulation of the terminal olefin, which would have a better chance of success in the cross-metathesis coupling. A possible route was found via the mixed anhydride **133.**[67] This could then be coupled with lithium acetylide to yield the acetylenic ketone **134** directly (Scheme 2.22).

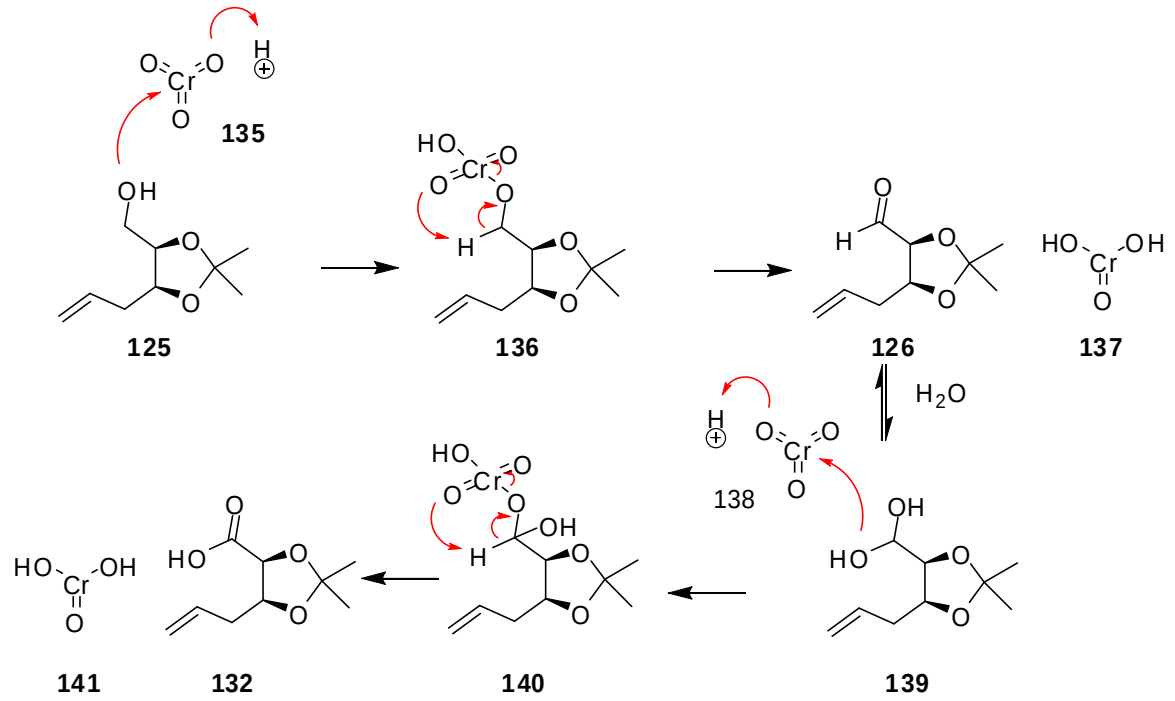


125 **132** **133** **134**

a) Jones, acetone, 42 %. b) ethyl chloroformate, Et_3N, 11 %. c) lithium acetylide, ethlenediamine complex.

Scheme 2.22 Jones Oxidation of 125 and alternative approach to alkyne addition.

Alcohol **125** was oxidised to carboxylic acid **132** using Jones reagent in an un-optimised 42 %. The low yield can be accounted for as the oxidation goes via the unstable aldehyde **126** (Scheme 2.23).



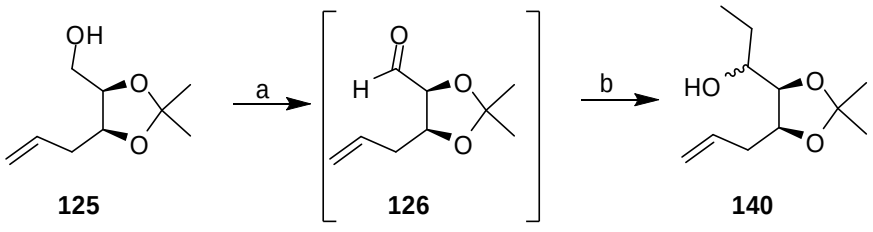
Scheme 2.23 Jones Oxidation Mechanism.

The resulting carboxylic acid **132** was treated with triethylamine and ethyl chloroformate to yield the mixed anhydride **133** in a poor 11 % yield with a further 15 % starting material recovered. Lithium acetylide, ethylenediamine complex was treated with the crude mixed anhydride **133**, but no desired acetylenic ketone **134** was isolated. With the two previous low yielding steps and a troublesome third step our attention focused on other routes towards the aliphatic chain.

2.6 One-Pot Oxidation Alkyne Coupling

Before looking to radically change our overall synthetic route towards LL-Z1640-2 **3**, it was decided to have one more look at the oxidation of compound **125**. In previous efforts, as part of the oxidation step consumption of starting material was observed. In some cases, traces of the aldehyde were detected in the crude ^{1}H NMRs. This led us to believe that the aldehyde was being produced, but was decomposing within minutes of being formed. This raised the possibility that a successful addition might be possible by trapping the crude aldehyde with the Grignard acetylide in a one pot process.

As part of our modified procedure, alcohol **125** was oxidised under standard Swern conditions and quenched with triethylamine. The reaction was then stirred at room temperature for 30 minutes and treated with ethyl magnesium bromide. After 2 hours the desired alcohol **140** was isolated as a mixture of diastereomers in a good yield of 66 % (Scheme 2.24).

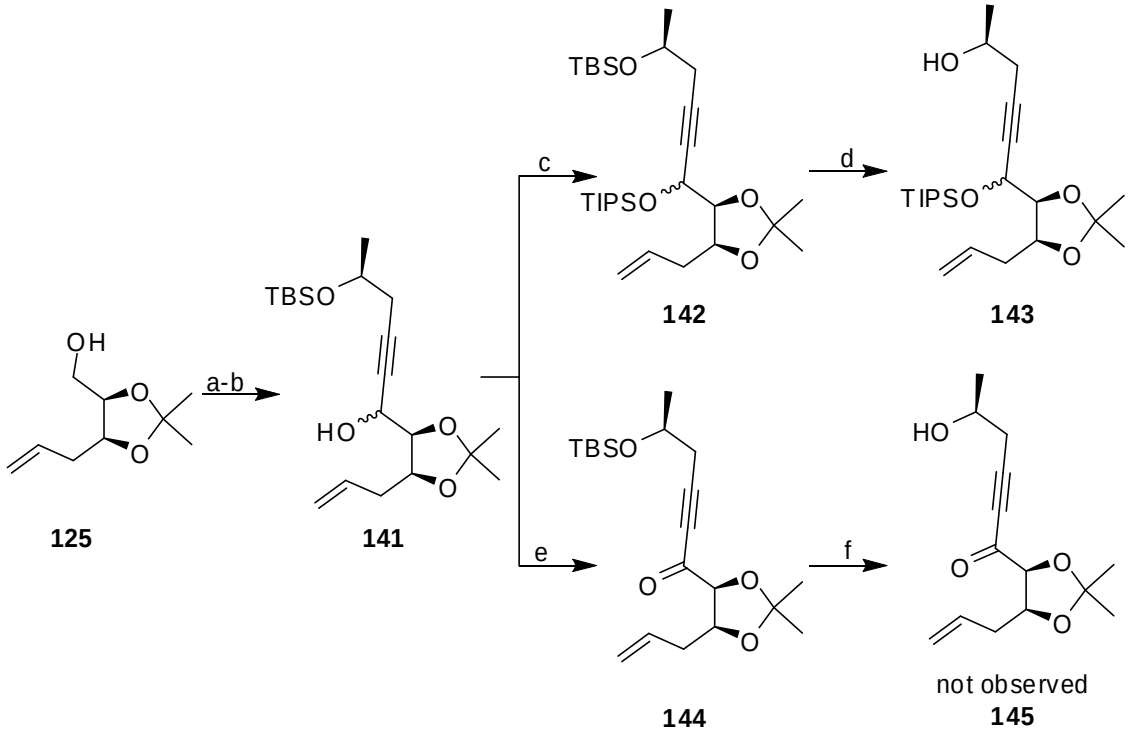


125 **126** **140**

a) $(COCl)_2$, DMSO, Et_3N, THF. b) EtMgBr, 66 %

Scheme 2.24 One-pot oxidation-alkyne coupling.

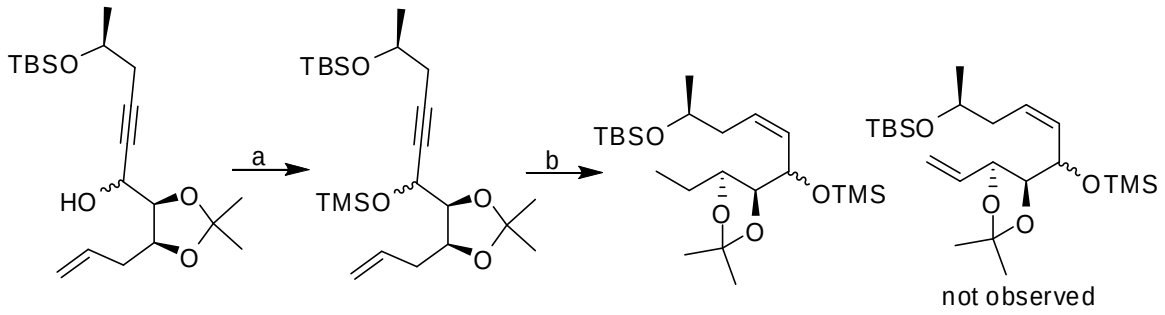
Based on this primary result, the same one-pot procedure was applied to the coupling of the crude aldehyde **126** with the Grignard acetylide to produce alkyneol **141** (Scheme 2.25). The Grignard acetylide was prepared using the same conditions as to make alkyne **100.**



a) $(COCl)_2$, DMSO, Et_3N, DCM. b) **99**, EtMgBr, THF, 54 %. c) TIPSCl, imidazole, DMF, 69 %. d) HF.Pyr, Pyr, THF, 60 %. e) $(COCl)_2$, DMSO, Et_3N, DCM, 94 %. f) various conditions.

Scheme 2.25 Coupling of desired fragments 99 and 125 and synthesis of coupling partners 143 and 145

Alkyneol **141** was produced and isolated in 54 % yield as a mixture of diastereomers. This was extremely encouraging considering the apparent instability of the aldehyde intermediate. The free alcohol was protected with the bulky TIPS group to give the disilyl compound **142**. The TBS group was then selectively removed using HF.Pyr to give the free secondary alcohol **143** in 60 % yield. An alternative route in which the alkynone unit was introduced earlier in the synthesis was pursued by oxidising **141** to the alkynone **144** under Swern conditions, 94 %. TPAP/NMO and manganese dioxide oxidations were also attempted, the yields were significantly lower (66 % and 12 % respectively). Attempts to remove the secondary TBS group of ketone **144** yielded none of the desired product **145**. Consumption of starting material was observed but no alcohol product **145** was observed (Scheme 2.25).



141 **146** **147** **148**

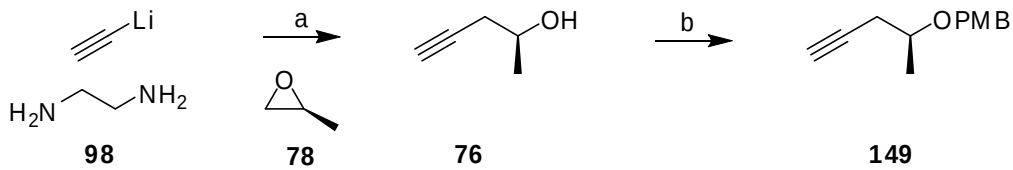
a) TMSCl, pyr., Et_2O, 93 %. b) H_2, Pd/BSO_4, toluene

Scheme 2.26 Hydrogenation of alkyne 146.

Once the alkyne unit was in place, the selective hydrogenation to generate the desired *Z* olefin was attempted. The secondary free hydroxyl group was first protected as a TMS ether using trimethylsilyl chloride in 93 %. Surprisingly, hydrogenation under the previously optimised conditions failed to generate any of the desired alkene **148,** affording instead the terminal alkane unit **147** in 12 %. Terminal alkene bond over reduction is unusual, as there are examples showing similar alkyne reductions in the presence of alkenes in the literature.[68] However, a similar example of over reduction has been shown within the Marquez group on a related framework (Scheme 2.26).[69]

2.7 Alkyne Protecting Group Optimisation

Based on the difficulties observed during the removal of the TBS group and with the aim of getting a higher yield between the protecting group manipulation steps (**141** to **143**), the protecting group was changed. The TBS silyl ether was exchanged for a PMB group which was introduced to the crude alkyne **76**, previously discussed, in excellent yield (Scheme 2.27).



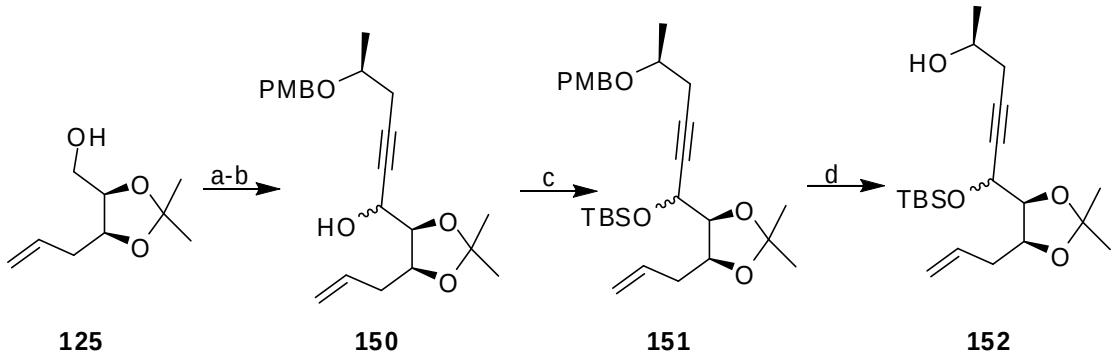
98 **78** **76** **149**

a) **78**, DMSO. b) PMBCl, NaH, DMF, 83 %.

Scheme 2.27 Alterative PMB protection of 76

The newly formed PMB protected alkyne **149** was converted to the Grignard acetylide and was coupled to the acetonide unit **125** via a similar one-pot Swern oxidation-Grignard addition coupling step in 54 % giving the desired product **150**

as a 55:45 mixture of diastereomers. Protection of the secondary alcohol as the TBS ether yielded the orthogonally protected unit **151** in 85 %. Treating ether **151** with DDQ selectively removed the PMB group and gave the desired secondary alcohol **152** in 81 % (Scheme 2.8).

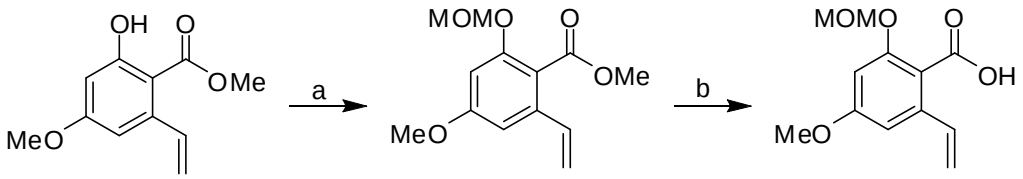


125 **150** **151** **152**

a) $(COCl)_2$, DMSO, Et_3N, DCM. b) **149**, EtMgBr, THF, 54 %. c) TBSCl, imidazole, DCM, 85 %. d) DDQ, DCM, 81 %.

Scheme 2.28 Coupling of 125 and 149 and protecting group manipulation

With both the PMB ether **150** and the free alcohol **152** efficiently synthesised they were now ready to be coupled to the aromatic fragment. However, due to previous difficulties encountered during the cross metathesis steps a modified strategy was pursued allowing the esterification step to take precedence. This would effectively change the cross metathesis into a ring closing metathesis (RCM) and as such increase the possibility of success. It must be noted that although there were some concerns about the geometrical arrangement of the reaction, the fact that a 14 membered macrocycle was being generated, gave us confidence that the *E* olefin could be easily accommodated. To minimise the chances of side reactions, it was decided to mask the free hydroxyl unit on the aromatic unit **108** using MOMCl to give the MOM ether **153** in 97 %. As stated previously, the commercial availability of MOMCl became a problem during the course of this research and further attempts to make **153** had to be approached using MOMBr. Similar to before, the MOMBr based reactions did not yield any product and results in degradation of the starting materials. Base hydrolysis of ester **153** using sodium hydroxide gave the desired carboxylic acid **154,** which was visible upon analysis of the crude reaction mixture but unstable to column chromatography (Scheme 2.29).

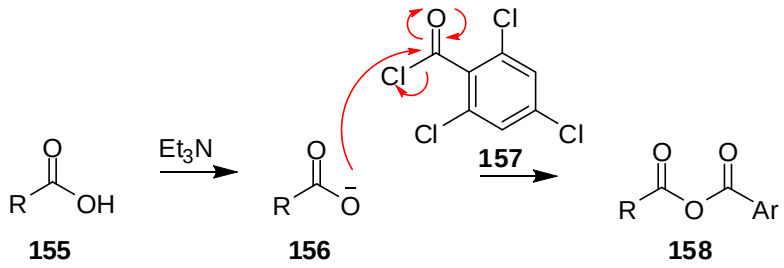


108 **153** **154**

a) MOMCl, K_2CO_3, Et_3N, acetone, 97 %. b) NaOH, dioxane, 81 %.

Scheme 2.29 Formation of acid 154

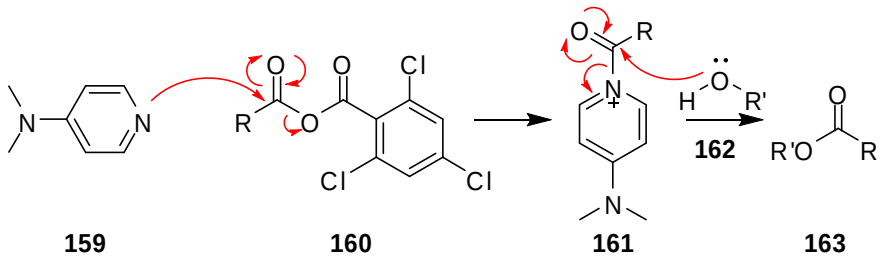
Coupling of the free acid **154** with the secondary alcohol **143** was first attempted under traditional Yamaguchi esterification conditions. The choice of Yamaguchi conditions was based on the ample literature precedence for the synthesis of highly functionalized esters under its mild conditions. The reaction is a two step process which starts with the formation of a mixed anhydride **158** between Yamaguchi's reagent (2,4,6-trichlorobenzoyl chloride) **157** and the carboxylic acid **155** coupling partner (Scheme 2.30).



155 **156** **158**

Scheme 2.30 Yamaguchi esterification

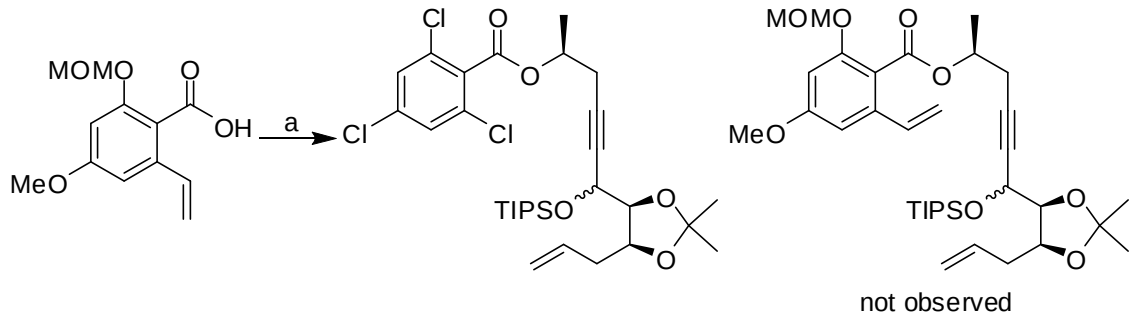
The mixed anhydride **158** then reacts with the alcohol in the presence of a stoichiometric amount of DMAP **159**, which acts as an acyl transfer reagent, to generate the desired ester **163** (Scheme 2.31).



159 **160** **161** **163**

Scheme 2.31 Yamaguchi esterification

Treatment of the carboxylic acid **154** with Yamaguchi's reagent **157** proceeded to form the mixed anhydride *in situ*, however, addition of alcohol **143** failed to generate the desired ester **165** (Scheme 2.32).

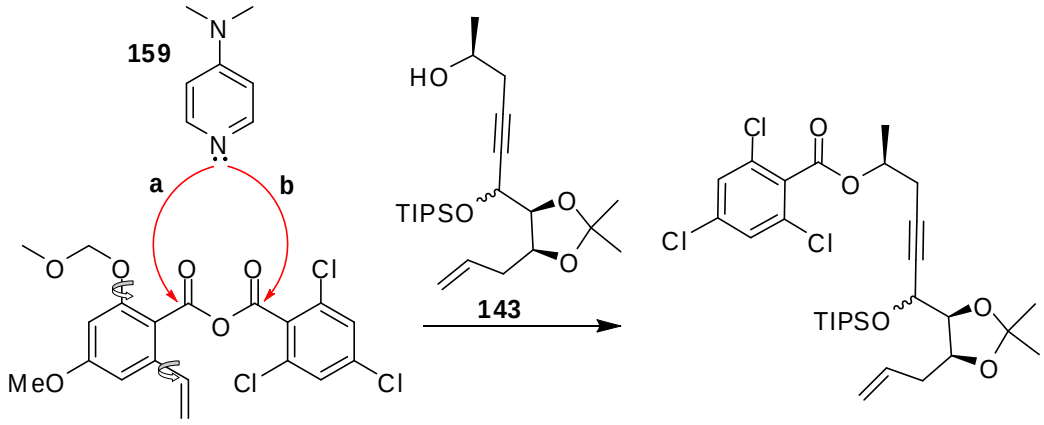


154 **164** **165**

a) Et_3N, **157**, **143**, THF.

Scheme 2.32 Yamaguchi esterification of 154 and 143

Interestingly, we were able to isolate and characterise the coupling product which was the product of Yamaguchi's reagent and the alcohol in 77 % yield, compound **164** (Scheme 2.32).



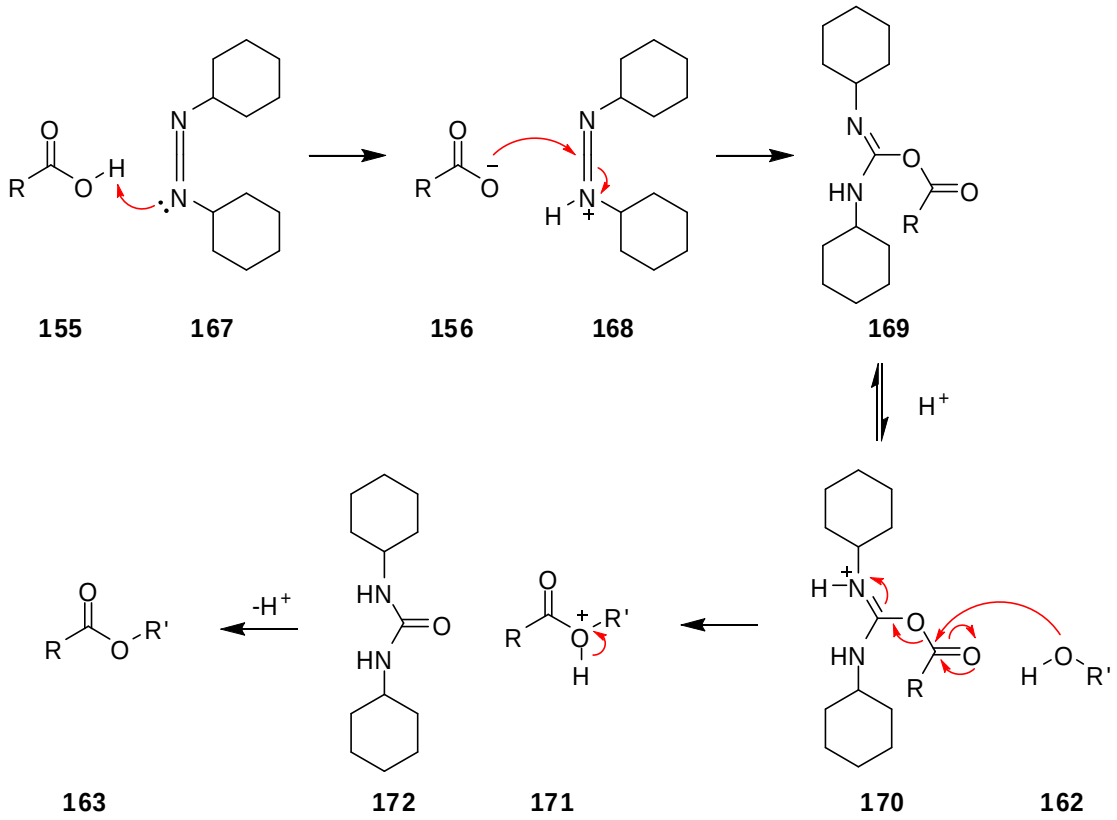
166 **164**

Scheme 2.33 Hindrance of path a by rotation of the MOM and vinyl groups of 166.

Although this was disappointing, the formation of ester **164** can be explained by considering the Yamaguchi mechanism. Once the mixed anhydride is formed, we believe that DMAP reacts regioselectively at the less hindered carbonyl site. In the above case, the desired route, a, is hindered by rotation of the MOM group and of the vinyl group. The combination of these two groups must be greater than that of the chlorines hindrance, route b (Scheme 2.33). Therefore, the DMAP **159** should attack the anhydride via route b and the resulting intermediate then reacts with alcohol **143** to give the coupling product **164**.

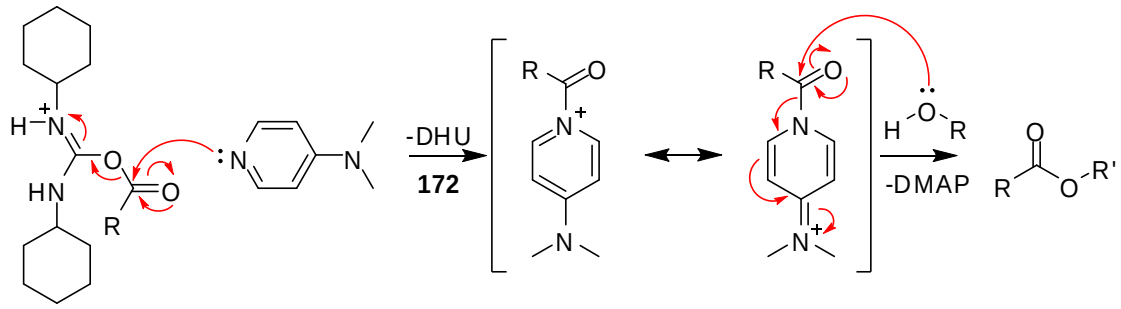
Faced with a disappointing Yamaguchi coupling, a Steglich esterification was then explored. The Steglich esterification was chosen, based on the same rationale as the Yamaguchi esterification, namely it uses mild conditions to esterify sterically demanding substructures.

Looking at the mechanism of the Steglich esterification it can be seen that the carboxylic acid is activated by the DCC. This allows the alcohol to attack at the desired carbonyl carbon. Unlike the Yamaguchi, where the sterics dictate the approach of the alcohol towards the mixed anhydride, the Steglich esterification only has one available carbonyl **170** and should therefore resolve the problems encountered during the Yamaguchi esterification attempts (Scheme 2.34).



Scheme 2.34 DCC coupling

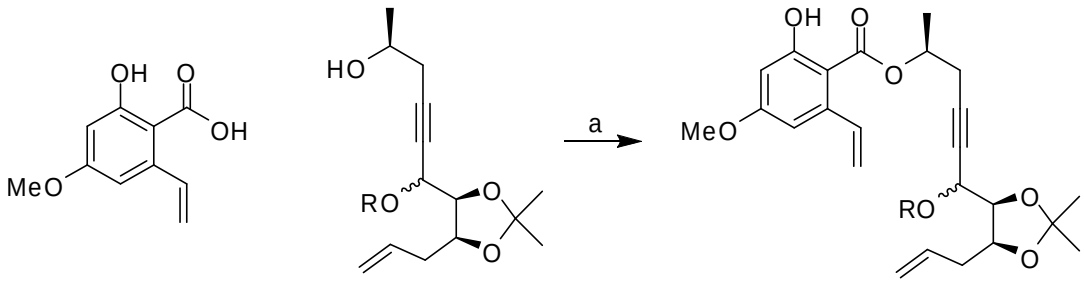
In addition, DMAP **159** can be added to the reaction as a catalyst. The DMAP **159** is a stronger nucleophile than the alcohol **162** therefore it reacts with the intermediate compound **170** leading to the reactive amide **174**. This intermediate cannot form intramolecular side products but reacts rapidly with alcohol **162** (Scheme 2.35).



170 **159** **173** **174** **163**

Scheme 2.35 DMAP catalysed DCC coupling

Carboxylic acid **175** was made using the same procedure that was used to form acid **154.** For the initial studies, it was decided to use acid **175** without protecting the free hydroxyl in the ortho position. Coupling of the acid **175** with the TIPS protected alkynol **143** proceeded in 32 % to afford the desired ester unit **176.** The same conditions using the TBS protected derivative **152** gave the esterified product **177** in 68 %.



175

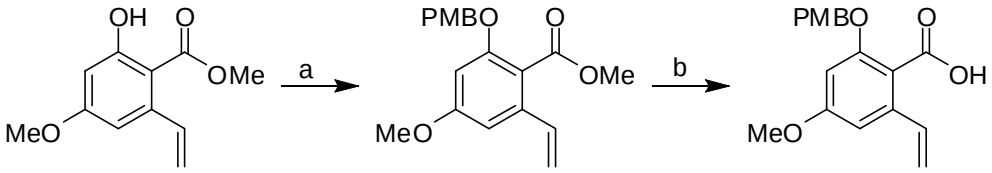
R = TIPS (**143**)
R = TBS (**152**)

R = TIPS (**176**)
R = TBS (**177**)

a) DMAP, DCC, DCM, 32-68 %

Scheme 2.36 DDC coupling of 175 with 143 and 152

With the successful coupling of the two partners in an acceptable yield, it was thought best to protect the free hydroxyl on the aromatic fragment in an attempt to minimise unwanted side reaction and perhaps improve the yield. A PMB group was introduced to **108** in 95 % yield and hydrolysed to the acid **179** (Scheme 2.37). The PMB protected acid **179**, similar to the MOM protected derivative **154**, was unstable to column purification and it was thought best to carry the acid on crude as it appeared relatively pure by ^{1}H and ^{13}C NMR spectra (Scheme 2.37).

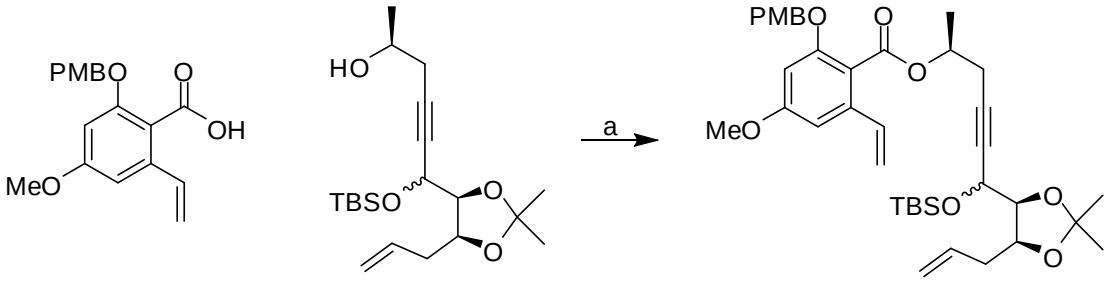


108 **178** **179**

a) K_2CO_3, TBAI, PMBCl, DMF, 95 %. b) NaOH, dioaxne.

Scheme 2.37 PMB protection of 108 and subsequent hydrolysis to acid 179

The coupling of acid **179** and alcohol **152** was carried out using the same conditions as to make **176** and **177**. This time however the esterified product **180** was only isolated in 17 % yield (Scheme 2.38).

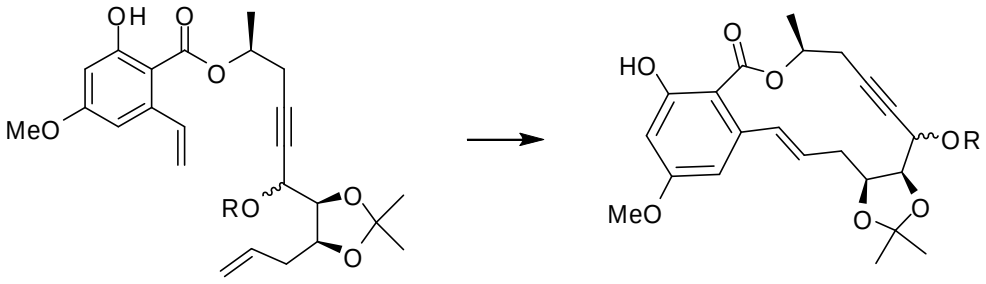


179 **152** **180**

a) DMAP, DCC, DCM, 31 %

Scheme 2.38 DDC coupling of 179 with 152

Having succeeded at the generation of the ester linkages, a revised end game strategy was considered. After some consideration, it was decided that the ring closing metathesis would take precedence over the alkyne hydrogenation step (Scheme 2.39).



R = TIPS (**176**)
R = TBS (**177**)

not observed
R = TIPS (**181**)
R = TBS (**182**)

Scheme 2.39 Proposed RCM of 176 and 177

This decision was largely based on the rationale that selective hydrogenation in the presence of terminal alkene had proved troublesome. There were still

concerns over the rigidity of the product and whether the presence of the alkyne would compete with the alkenes in the presence of Grubbs' catalyst.

The key cross coupling was attempted using Grubbs' First and Second generation catalysts. Unfortunately, despite repeated attempts, no desired products **181**/**182** could be isolated. TLC analysis of the crude reactions indicated that a number of side reactions were taking place and consuming all of the starting material.

2.8 Cobalt Complex Work

Faced with this complete lack of success from the RCM reactions it made us consider the real possibility that the alkyne unit might be actively involved in the cross metathesis process detrimentally affecting the reaction outcome.

A number of ways have been developed for the temporary masking of alkyne units, one of the most widely used is the use of cobalt hexacarbonyl complexes.[70, 71]

In our case, the use of a $Co(CO)_6$ complex was particularly attractive as it would not only protect the alkyne unit but it would also modify the molecules overall geometry and might improve the RCM's likelihood of working by reducing the strain to be introduced during cyclisation.

Complete and accurate characterisation of these cobalt complexes proved difficult as NMR analysis gave broad peaks and loss of resolution. This resulted in uncharacterisable spectra (Figure 2.1). Obtaining an accurate mass also proved difficult as the complex fragmented very easily under mass spectrometry conditions. It was found though that treating the deuterated solvent with sodium hydrogen carbonate and filtering the NMR sample through charcoal improved the quality of the spectra of the sample significantly (Figure 2.2).

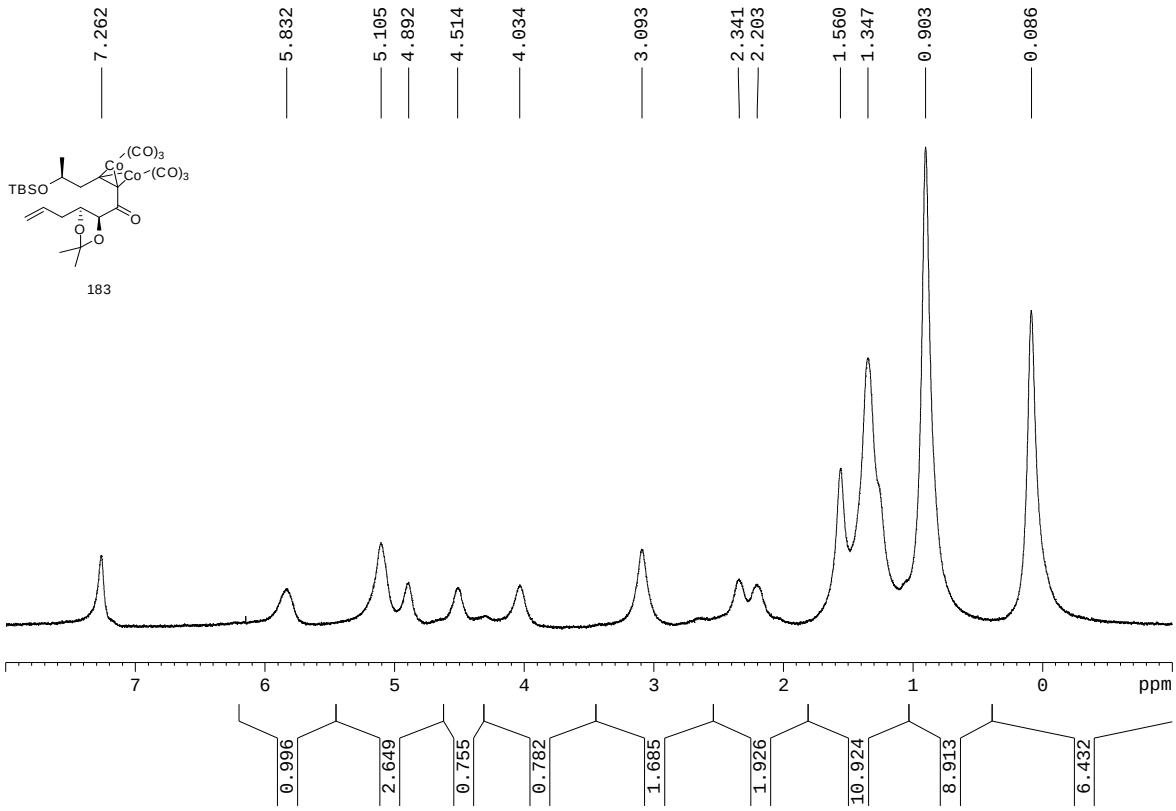


Figure 2.1 ^{1}H NMR of cobalt complex 183

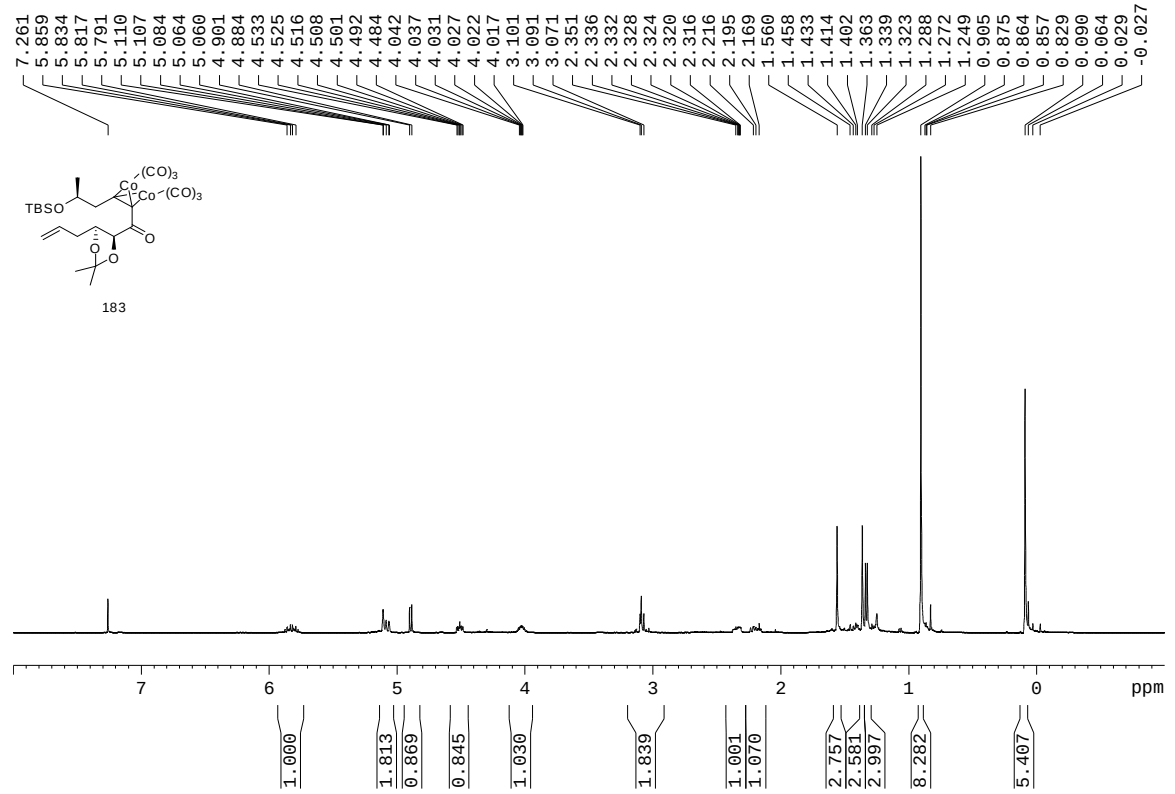
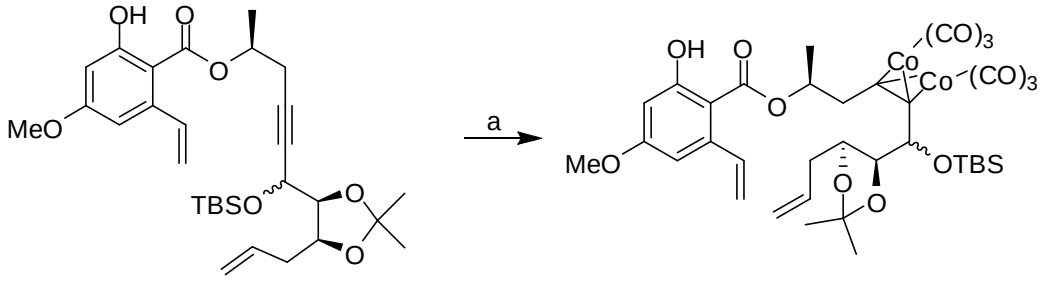


Figure 2.2 ^{1}H NMR of cobalt complex 183 after $CDCl_3$ treatment and filtering through charcoal.

Treatment of the RCM precursor **177** with dicobalt octacarbonyl proceeded to generate the desired cobalt complex **184** in quantative yield (Scheme 2.40).

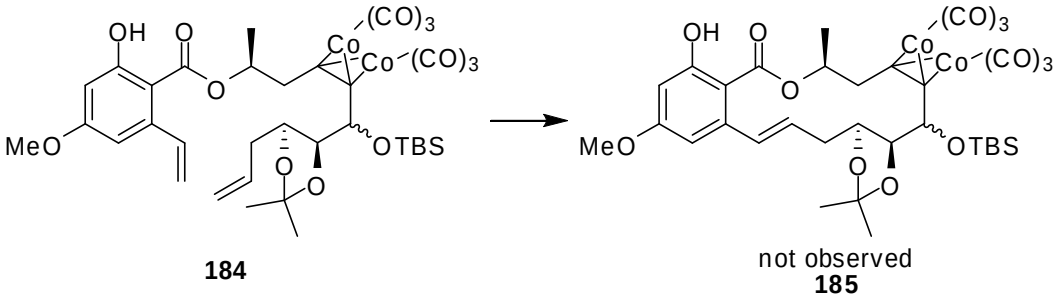


177 **184**

a) $Co_2(CO)_8$, toluene.

Scheme 2.40 Formation of cobalt complex 184

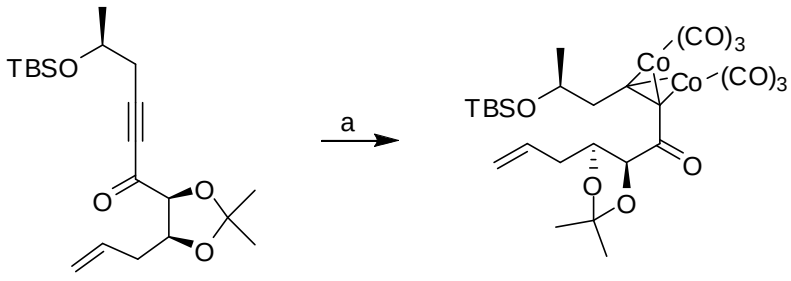
With the cobalt complex now in place, the diene unit **184** was treated with Grubbs' First and Second generation catalysts under varying conditions and with different ratios. Unfortunately, TLC analysis of the crude reactions mixtures indicated the formation of multiple products and no desired product **185** was ever isolated (Scheme 2.41).



184 not observed **185**

Scheme 2.41 Attempted RCM of cobalt complex 184 to macrocycle 185

Having failed to generate the desired macrocylce **185**, our last alternative was explored in our modified approach. The alkynone unit **144** was treated with dicobalt octacarbonyl and proceeded to generate the desired cobalt complex **186** in quantative yield (Scheme 2.42).

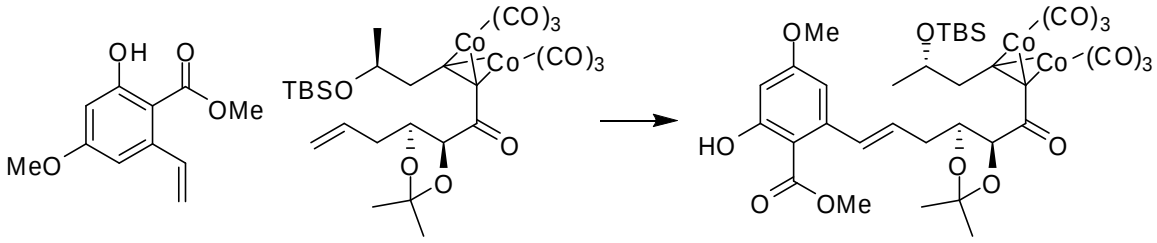


144 **186**

a) $Co_2(CO)_8$, toluene.

Scheme 2.42 Generation of cobalt complex 186

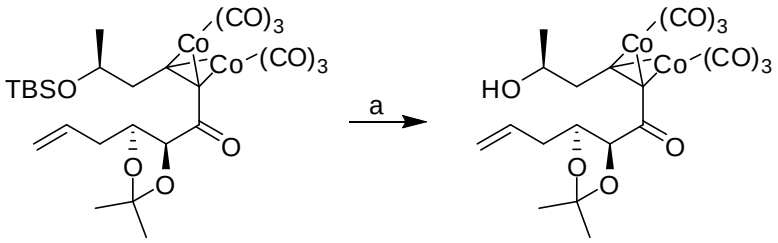
With the possibility of the above (Scheme 2.41) system still being too strained an effort at cross coupling fragment **108** with **186** was attempted (Scheme 2.43). Again, as above, many conditions and ratios of reagents were attempted but no desired product **187** was isolated.



108 **186** **187**

Scheme 2.43 Attempted cross coupling of 108 and 186

As shown in Scheme 2.25, the silyl deprotection of 144 resulted in decomposition of material and no free alcohol was isolated. Similar conditions were attempted with the cobalt complexed derivative 186 and this yielded the stable free alcohol 188 in 42 % (Scheme 2.44).

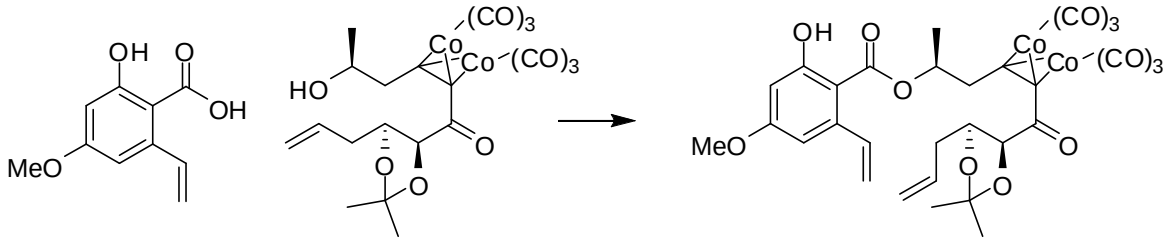


186 **188**

a) HF.Pyr, Pyr, THF, 42 %

Scheme 2.44 Deprotection of 186

This successful deprotection gave another possible coupling partner for the esterification step as in (Scheme 2.36). Under similar conditions however no esterified product was isolated from the complex reaction mixture (Scheme 2.45). This though was no great loss as alternative, more efficient routes to similar structures had already been found and further ring closing steps had proved to be troublesome.



175 **188** not observed **189**

Scheme 2.45 Attempted coupling of 175 and 188

2.9 Alternative Metal Couplings

Based on the difficulties encountered during the final RCM step of the synthesis and its continuous failure despite extensive experimentation, a new approach was developed.

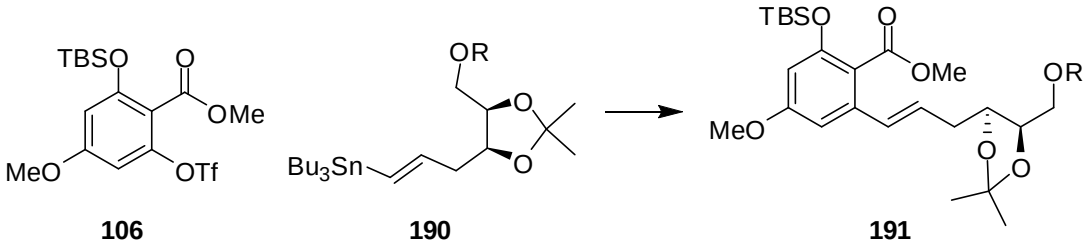
Our new approach was based on our previous results which showed that tributyl(vinyl)tin underwent an efficient Stille Coupling with the aromatic triflate **106**. Furthermore, results obtained previously in the group have showed that substituted vinyl stannanes can also couple efficiently with aromatic triflates.

Hence in our new approach we proposed to couple the aliphatic $C_{1'}$-$C_{10'}$ chain to the aromatic unit via an alternative metal mediated coupling.

2.10 Stille Coupling

The homologation of aldehydes to *E*-alkenylstannanes using $Bu_3SnCHBr_2$ has been reported by Hodgson.[72] Adapting these conditions, it was proposed that the synthesis of *E*-alkenylstannane derivatives of previously discussed terminal alkenes should be attempted.

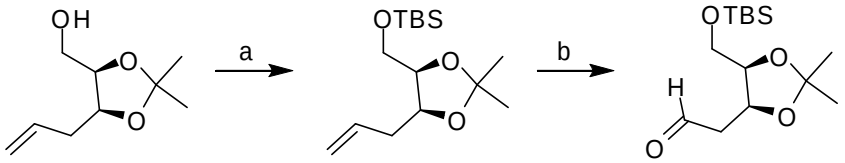
It was decided to initially look into making a unit such as **190** which could be coupled with an aromatic triflate **106** (Scheme 2.46). With unit **191** in place similar steps as shown before could be used to build up the molecule and the ring could be completed with a macrolactonisation step similar to the esterification previously used. Alternatively, the synthesis of the vinyl stannane derivative of the complete $C_{1'}$-$C_{10'}$ chain **190** could be attempted.



106 **190** **191**

Scheme 2.46 Proposed Stille coupling of 106 and 190

Our modified synthesis began with the attempted ozonolysis of silyl ether **192** which was obtained from previously described **125** in 95 % yield. Ozonolysis of the alkene gave a low conversion, 33 %, to the desired aldehyde **193** (Scheme 2.47). However, quantitative amounts of starting material were recovered from the reaction mixture. Faulty ozonolysis equipment prevented the optimisation of this procedure. Nevertheless, the approach was continued as enough aldehyde was obtained from the initial attempt.

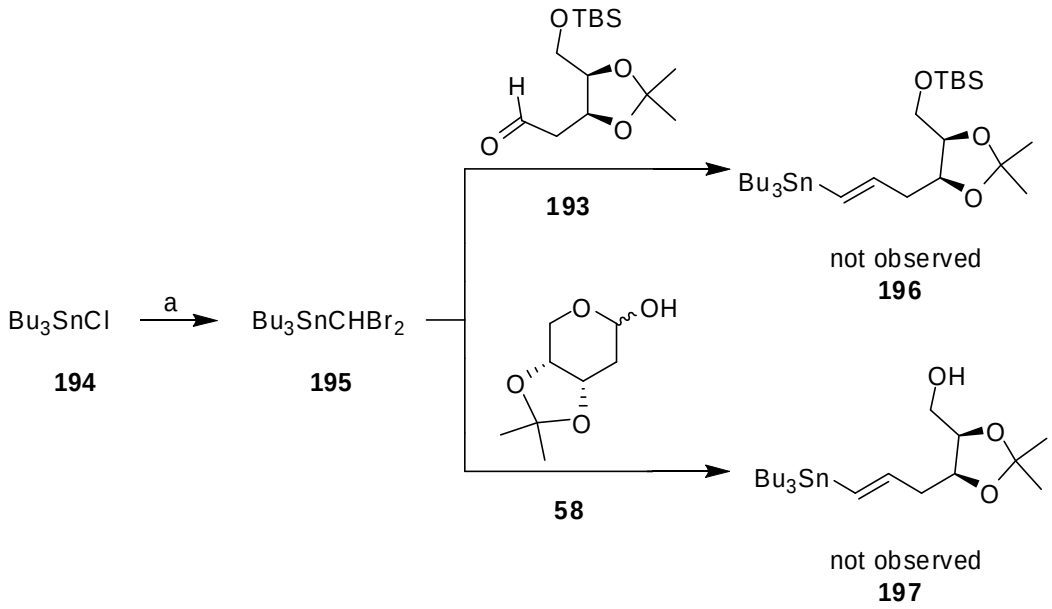


125 **192** **193**

a) TBSCl, Et_3N, DMAP, DCM, 95 %. b) O_3, DCM, 100 %

Scheme 2.47 Ozonolysis of the alkene 192

An alternative approach was also proposed to effectively liberate the aldehyde component of the lactol **58**, which could then potentially undergo the desired stannyl olefination to give **197**. However, it must be noted that the Hodgson olefination has never been reported on lactol systems to date.



a) DIPA, *n*-BuLi, CH_2Br_2, THF, Et_2O, 81 %.

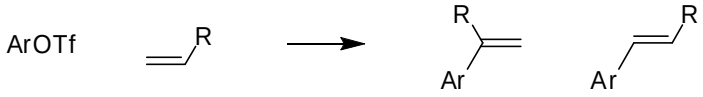
Scheme 2.48 Preparation of 195 and attempted Hodgson's olefination of 193 and 58.

Treatment of dibromomethane with freshly prepared LDA, followed by tributyltin chloride **194** yielded the stannane **195** in 81 %, which was stable to flash chromatography. Studies were then carried out to couple stannane **195** with aldehyde **193** and pyranose **58** using optimised conditions from the literature (Scheme 2.48). [72] Problems arose during the reaction, as the handling of the anhydrous chromium chloride proved extremely challenging and it was apparent that it was reacting in air before it could be introduced to the reaction. Unfortunately, no desired product could be detected from either reaction.

The reactivity of both the lactol and aldehyde towards the Hodgson olefination prompted us to consider other palladium catalysed couplings which would allow us to use the aryl triflate **106** to introduce the troublesome *E* double bond.

2.11 Heck Coupling

The classic Heck reaction involves the palladium catalysed coupling between an aryl or vinyl halide with an activated alkene in the presence of base with excellent *E* selectivity. However, there are examples of non-activated olefins coupling with aryl triflates.[73] Most of the examples however show that the competing reaction of the α-regioselective arylation **200** can be favoured over the desired ß product **201** (Scheme 2.49).

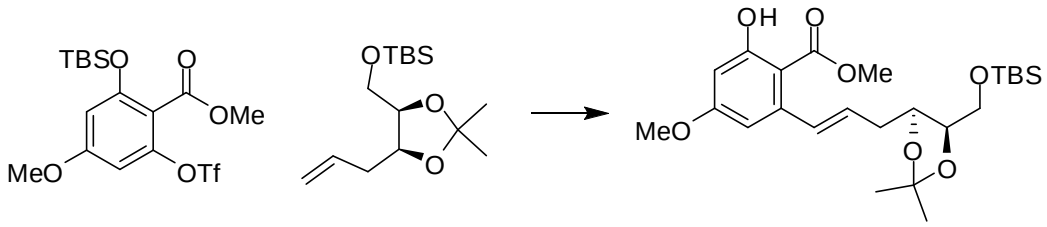


198 **199** **200** **201**

	Ar	Olefin	*E*/*Z*	Product (%) α	Product (%) ß
1	3-CH_3COPh	CH_2OH	>99/1	75	0
2	4-CH_3-OPh	$CH(OH)CH_3$	>99/1	83	2
3	Ph-	CH_2CH_2OH	>99/1	67	23
4	4-CH_3-OPh	$COOCH_3$	>99/1	0	84

Scheme 2.49 Literarature examples of Heck couplings of non-activated olefins

Following literature precedence the Heck coupling between triflate **106** and the terminal alkene **192** was attempted. Unfortunately, neither the desired product **202** nor the potential side product was observed in the crude reaction mixture. A number of further attempts were carried out altering conditions, including microwave assisted procedures, but no product could ever be detected (Scheme 2.50).

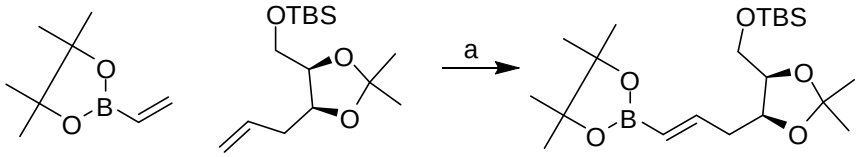


106 **192** not observed **202**

Scheme 2.50 Attempted Heck coupling of of fragments triflate 106 and alkene 192

2.12 Suzuki Coupling

Based on the disappointing Heck coupling results the Suzuki coupling of the aryl triflate with a suitable vinyl boronic acid was also considered. The only potential draw back to this approach was that the obvious route needed for the formation of the vinyl boronic acid would be via a cross metathesis of alkene **192** and commercially available vinylboronic acid pinacol ester **203** (Scheme 2.51). The lack of success with the cross metathesis reactions attempted up to this point made us apprehensive about it's likelihood to succeed but the study was carried out.

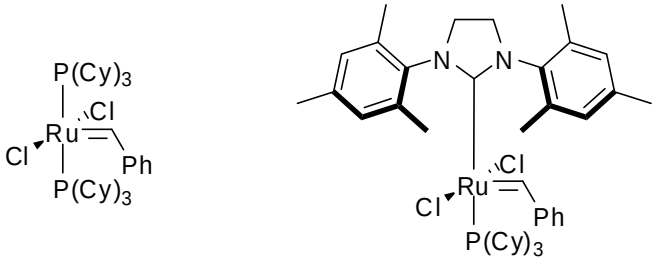


203 **192** **204**

a) Grubbs' second generation catalyst (5 mol %), DCM, 73 %

Scheme 2.51 Cross coupling of 203 and 192

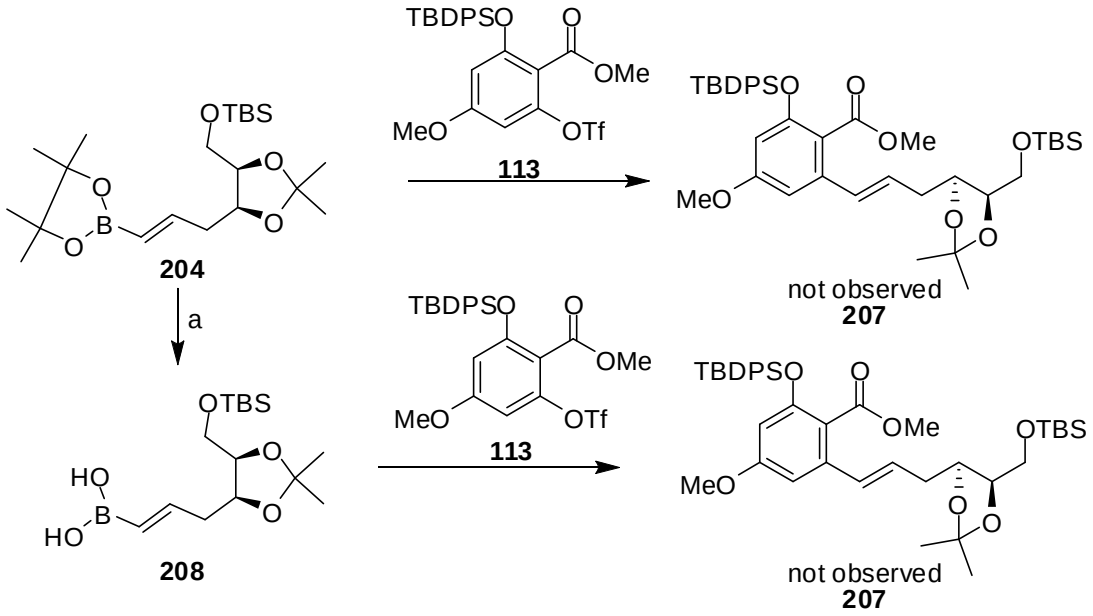
Using Grubbs' second generation catalyst **206** at 5 mol % and a 2:1 ratio of vinylboronic acid pinacol ester **203** and alkene **192** the desired vinyl boronic acid pinacol ester **204** was isolated in 73 % with a 4:1, separable, *E:Z* ratio. The use of Grubbs' first generation catalyst **205** under similar conditions, gave alkene **204** in 71 % in the same diastereomeric ratio.



205 **206**

Figure 2.3 Grubbs' first 205 and second 206 generation catalysts

This was very significant, as not only did it allow us to carry on with our Suzuki coupling based approach, but it also opened up the possibility of performing other cross coupling reactions using the same partner **192**.



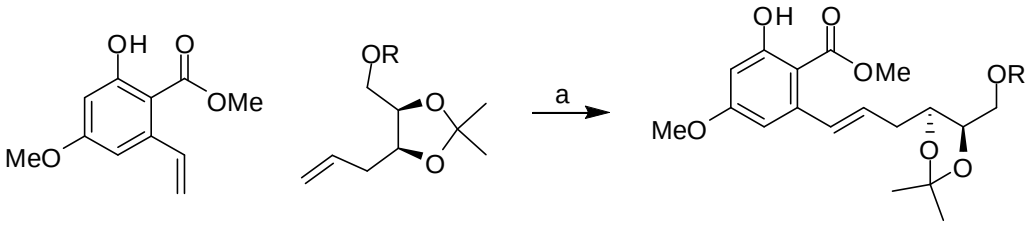
a) $NaIO_4$, NH_4Ac, acetone, H_2O.

Scheme 2.52 Proposed Suzuki couplings of 204 and 208 with 113.

The coupling of **204** with **113** was tested using $Pd(PPh)_4$ and $PdCl_2(dppf)$ as catalysts. None of these combinations lead to the formation of any of the desired product **207** and prompted us to wonder if the presence of the ester had made the triflate too unreactive. Ester **204** was converted to acid **208** using sodium metaperiodate and ammonium acetate. Due to concerns about the stability of acid **208**, no purification was carried out at this stage and was carried onto the next stage where it was subjected to the same conditions as the ester above. Once again, none of the desired product **207** could be isolated from any of the reactions.

2.13 Grubbs Mediated Cross Metathesis

Despite the lack of success in the Suzuki coupling reactions, the fact that alkene **192** was able to successfully undergo Grubbs-mediated cross metathesis opened a myriad of new possibilities. Hence, it was decided to screen conditions for the coupling of the vinyl aryl unit **108** and the terminal alkene **125** and **192** (Scheme 2.53).

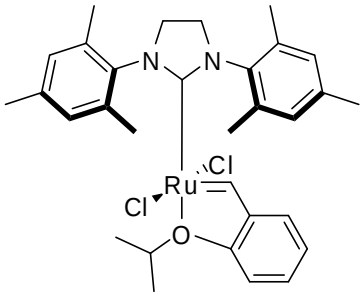


108 R = OH (**125**) R = TBS (**192**) R = OH (**210**) R = TBS (**182**)

a) various coditions, see table 2.4

Scheme 2.53 Grubbs mediated cross metathesis of 125 and 192 with 108.

The conditions tested are summarised below in Table 2.4. The successful cross metatheses were achieved using Hoveyda-Grubbs catalyst second generation (Figure 2.4). Grubbs' first and second generation catalyst either gave no desired product or reaction failed to proceed.



211

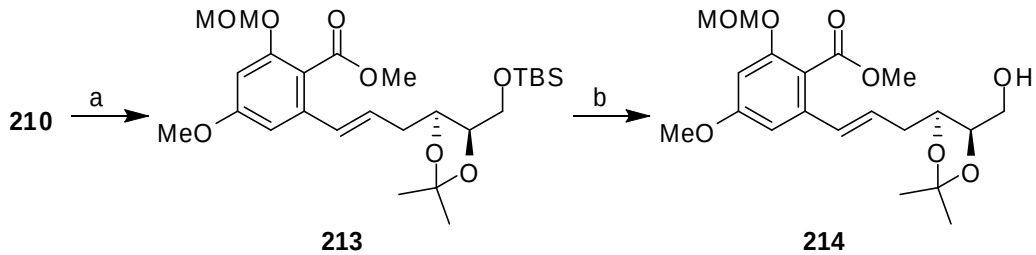
Figure 2.4 Hoveyda-Grubbs catalyst second generation.

Successful cross metathesis gave the desired hetrodimer as a consistent 9:1 *E*/*Z* mixture in all cases. The homodimer **212** amounts isolated were proportional to the success of the formation of hetrodimer **182** and could not be prevented. The optimised yield of 73 % for the cross metathesis was achieved using 30 mol % of catalyst (entry 10, Table 2.4).

Table 2.4 Conditions for Grubbs mediated cross metathesis

	108	**125/192**	R	Catalyst	Loading (%)	Time (h)	Product (%)	Homodimer (%)
1	2	1	H	1st	10	21	0	0
2	2	1	H	2nd	10	21	0	0
3	2	1	H	Hov	10	21	0	0
4	2	1	TBS	1st	10	21	0	0
5	2	1	TBS	2nd	10	21	0	0
6	2	1	TBS	Hov	10	21	32	15
7	1	1	TBS	Hov	20	21	35	16
8	1	2	TBS	Hov	20	21	65	22
9	1	2	TBS	Hov	20	48	71	25
10	1	2	TBS	Hov	30	48	73	27

The free hydroxyl of the coupled product **182** was then protected as the MOM ether. Despite the difficulties securing MOMCl and all the tendencies of MOMBr to destroy the aromatic substrates the MOM group was still the favoured protecting group. However, treatment of **182** with MOMBr and Hunig's base gave the desired MOM ether **213** in 90 % yield (Scheme 2.54). Although there is no clear explanation for this change in reactivity, it's possible that the extra functionality on the ring has stabilised the compound and prevented it from decomposing under identical conditions to those used before (Scheme 2.29). TBAF assisted removal of the TBS group proceeded in quantitative yield to give the free alcohol **214**.

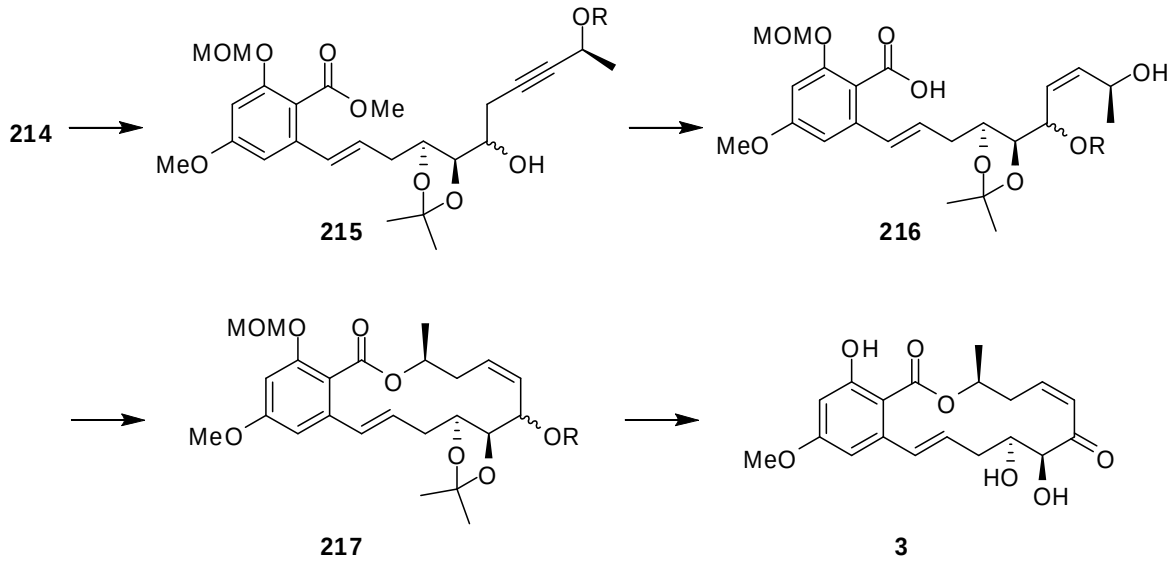


a) DIPEA, MOMBr, DCM, 90 %. b) TBAF, THF, 100 %

Scheme 2.54 Formation of free alcohol 214

Unfortunately by this stage, time constraints prevented me from taking the synthesis any further forward. Confidence was high though that the total

synthesis can be completed from this stage. However, synthetic organic chemistry is as much an art as it is a science and small substrate modification can drastically affect its reactivity and chemical behaviour. Yet, we were still positive about the synthesis with the only potential troublesome step being the macrolactonisation of **216** to **217** (Scheme 2.55).



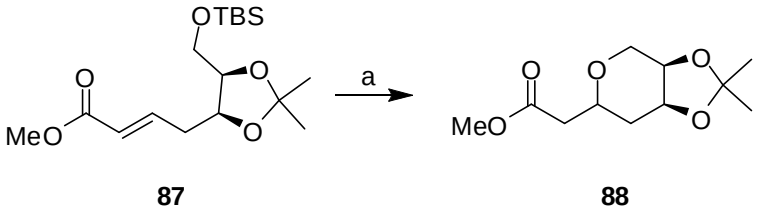
Scheme 2.55 Proposed future work

The completion of the synthesis from alcohol **214** was thought to follow the same one-pot Swern oxidation-Grignard acetylide coupling as before to produce alkyneol **215**. Selective hydrogenation to generate the desired *Z* olefin could then be attempted followed by selective deprotection of the secondary hydroxyl and base hydrolysis of the ester unit to give the desired carboxylic acid **216**. Macrolactonisation of carboxylic acid **216** should yield the macrocycle **217**. Global deprotection and oxidation of the allylic alcohol should then afford LL-Z1640-2 **3**.

2.14 Multi-substituted Pyrans from Carbohydrates

Pyrans are present in a large number of natural products and have been extensively used in biological and synthetic studies. Their significance as building blocks is reflected by the countless number of approaches employed for their synthesis. Unfortunately, most of the synthetic routes developed thus far tend to be either lengthy or of limited flexibility with regard to which products can be accessed.

During the undesired cyclisation of **87** shown previously (Scheme 2.56) led us to believe that our carbohydrate intermediates could be used as starting materials for the rapid formation of highly substituted pryan rings.



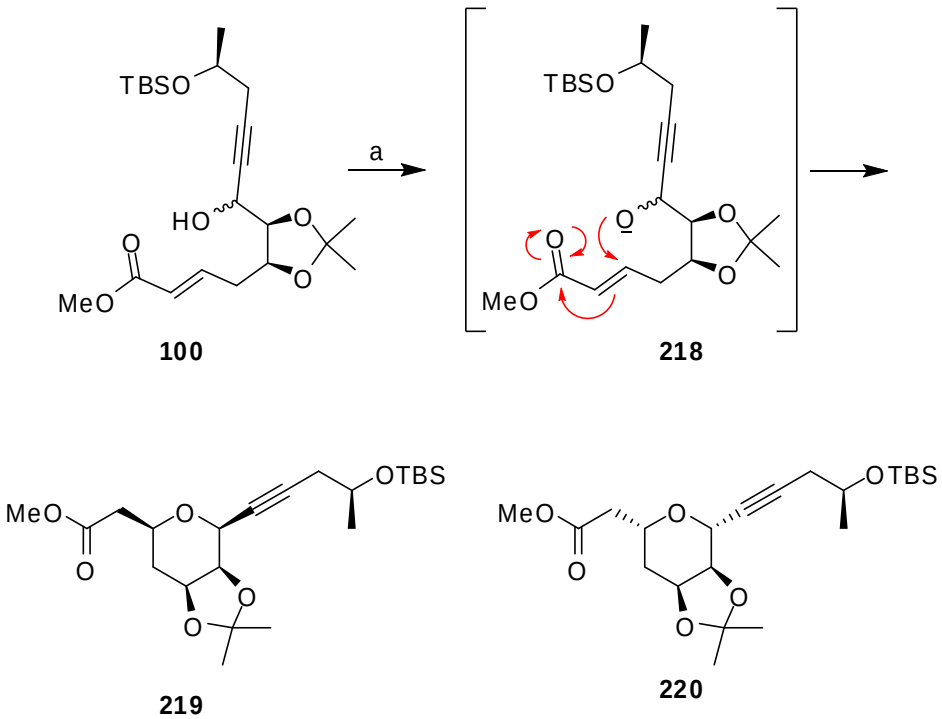
87 **88**

a) TBAF, THF, 76 %.

Scheme 2.56 Formation of pyran unit 88

Treatment of the propargylic alcohol **100** under basic conditions cleanly afforded the desired tetrasubstituted pyran rings **219** and **220** in good yield (Scheme 2.57). The relative stereochemistry of the pyran ring was determined through the use of coupling (*J*) values.

This approach has the advantage of offering the pyran ring in 3 steps from the protected carbohydrate starting material.



100 **218**

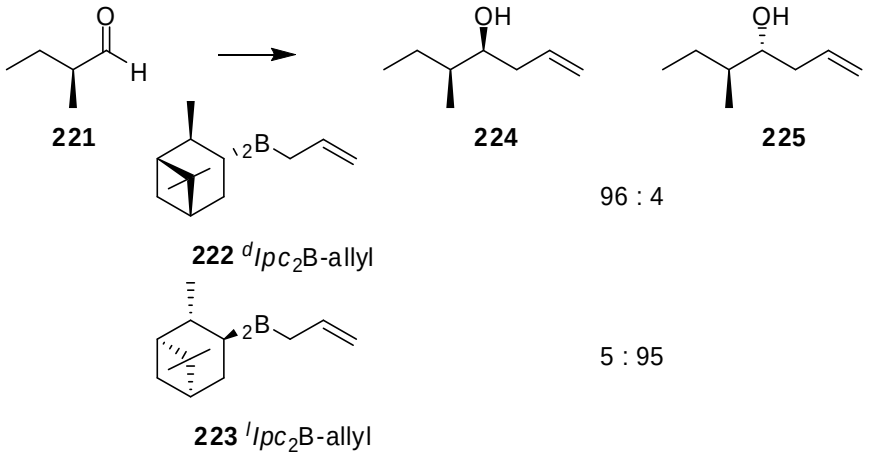
219 **220**

a) *t*BuOK, Et_2O, 74 %.

Scheme 2.57 Formation of tetrasubstituted pyran rings 219 and 220

Although time constraints prevented us from further investigating this methodology we believe that the stereochemistry of the nucleophilic addition onto the aldehyde unit could be controlled through the use of organoboranes

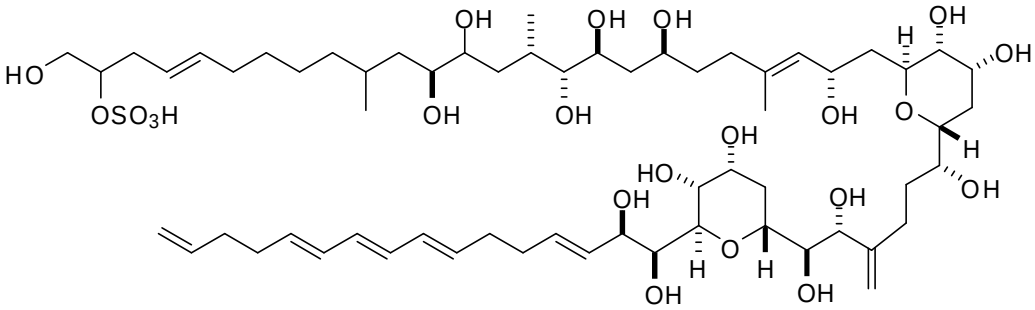
(Scheme 2.58).[74] The resulting alcohols could be used to generate diastereomerically pure polysubstituted pyrans in just 4 steps from readily available carbohydrates.



Scheme 2.58 Proposed control of nucleophilic addition to aldehydes using organoboranes

Furthermore, it is also possible that the corresponding *anti*-pyrans could be accessed through the cyclisation of the *Z*-conjugated esters. The *Z*-conjugated esters could potentially be accessed through the use of Taylors conditions.[75]

Eventually, it is proposed that this chemistry could be applied to the convergent, flexible and efficient synthesis of many natural products. Of specific interest to our group is the Amphidinols and particularly amphidinol 7 (AM7) **229** (Figure 2.5).[76]



229

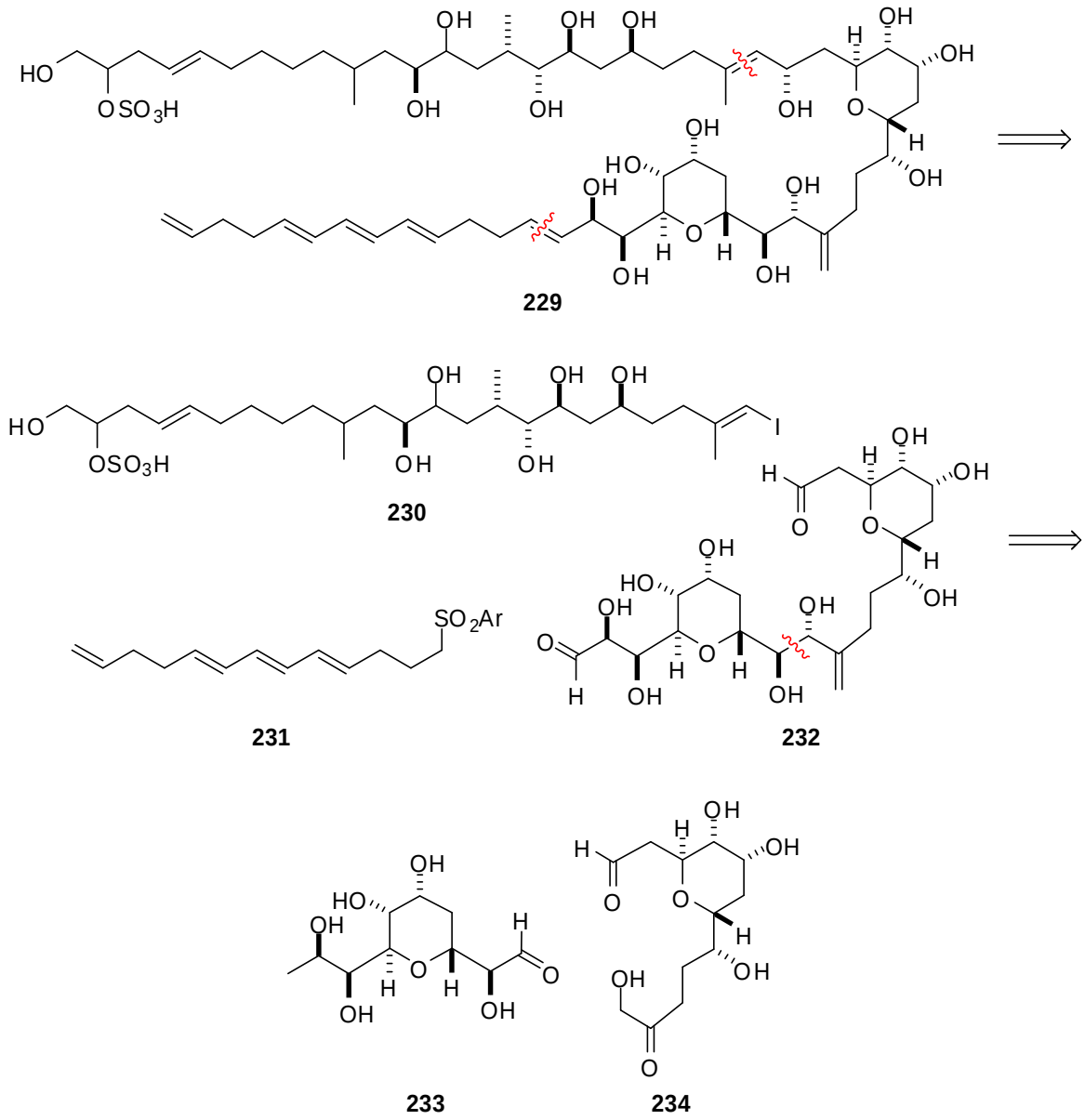
Figure 2.5 Amphidinol 7

AM7 **229** is a challenging synthetic target displaying two heavily hydroxylated side chains, an alternating polyene chain and two highly substituted tetrahydropyran units. AM7 **229** possess a 55 carbon backbone and 24 stereocentres.

A successful total synthesis of AM7 **229** or the structurally related AM3 has yet to be reported, although a number of lengthy approaches have been reported for the syntheses of the pyran and polyol sections.[77-80]

The work of significant interest to our research is the efficient synthesis and coupling of the pyran-bearing fragments **233** and **234** to generate the *bis*-pyran unit **232** (Scheme 2.59).

Unfortunately, this project was not taken beyond the early pyran ring formation due to time constraints and difficulties arising from my main project. This project has however been passed onto other members of the Marquez research group.



Scheme 2.59 Retrosynthetic analysis of AM7 and the interesting pyran fragments 233 and 234.

3 Experimental

3.1 General

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Anhydrous dimethylformamide (DMF) and triethylamine (TEA) was purchased from Aldrich Chemical Company. Tetrahydrofuran (THF), diethyl ether and dichloromethane (DCM) were distilled before use or were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). Anhydrous DCM was obtained by refluxing over calcium hydride for one hour, followed by distillation under argon. Anhydrous THF and diethyl ether were obtained by refluxing over sodium-benzophenone for one hour, followed by distillation under argon. All reagents were used as received, unless otherwise stated. Solvents were evaporated at reduced pressure at 35°C using a Buchi Rotavapor unless otherwise stated.

IR spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Spectrum BX Fourier Transform and JASCO FT/IR410 Fourier Transform spectrometers. Only significant absorptions (νmax) are reported in wavenumbers (cm^{-1}).

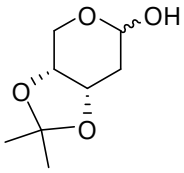
Proton magnetic resonance spectra (^{1}H-NMR) were recorded at 300, 400 or 500 MHz using Bruker DPX300, Bruker DPX Avance400 instrument and Bruker Avance500 instruments. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad), (2) coupling constant (J) quoted in Hertz to the nearest 0.1Hz and (3) number of equivalent nuclei (by integration). Carbon magnetic resonance spectra (^{13}C) were recorded at 75.1, 100 or 125.7MHz using Bruker DPX300, Bruker DPX Avance400 and Bruker Avance500 instruments. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate solvent peak.

High resolution mass spectra were recorded on a JEOL JMS-700 spectrometer by electrospray and chemical ionisation mass spectrometer operating at a resolution of 15000 full widths at half height.

Flash chromatography was performed using silica gel (Apollo Scientific Silica Gel 60, 40-63 micron) as the stationary phase. TLC was performed on aluminium sheets precoated with silica (Merck Silica Gel 60 F_{254}). The plates were visualised by the quenching of UV fluorescence (λmax254 nm) and/or by staining with anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

3.2 Experimental and Characterisation

2,2-Dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyran-6-ol, 58[59]



To a stirred solution of 2-deoxy-ribose (200 mg, 1.49 mmol) in EtOAc (7 mL) at -10 ˚C was added PPTS (15 mg) and 2-methoxypropene (0.19 mL, 1.98 mmol). The reaction mixture at -10 ˚C was then stirred for 6 hours. The reaction was then quenched with triethylamine (0.10 mL) and allowed to warm up to room temperature. The reaction was then concentrated at reduced pressure and purified by silica gel column chromatography using EtOAc (gradient 10-30 %) in 40-60 petroleum ether to afford **58** as an inseparable mixture of α and ß anomers (2.5:1) as a colourless oil (220 mg, 1.28 mmol, 86 %).

Major, α Anomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.48 (s, 3H), 1.77 (ddd, *J* = 14.8, 7.1, 4.2 Hz, 1H), 2.22 (dt, *J* = 14.8, 4.2 Hz, 1H), 3.68 (dd, *J* = 12.8, 3.6, 1H), 3.94 (dd, *J* = 12.8, 3.3 Hz, 1H), 4.12-4.19 (m, 1H), 4.46 (dt, *J* = 6.6, 4.3 Hz, 1H), 5.24 (dd, *J* = 7.1, 4.2 Hz, 1H)

^{13}C NMR (125MHz, $CDCl_3$) δ 25.4, 27.3, 32.2, 62.1, 70.7, 71.6, 90.9, 108.8.

ν_{max}(film)/cm^{-1} 2984, 2936, 1664, 1371.

Minor, ß Anomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.55 (s, 3H), 2.02-2.12 (m, 2H), 3.68-3.73 (m, 1H), 3.93-3.97 (m, 1H) 4.12-4.19 (m, 1H), 4.35-4.42 (m, 1H), 5.03-5.08 (m, 1H).

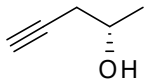
^{13}C NMR (125MHz, $CDCl_3$) δ 25.7, 28.1, 32.9, 60.8, 70.7, 71.3, 91.6, 109.5.

ν_{max}(film)/cm^{-1} 2984, 2936, 1664, 1371.

HRMS calcd for $C_8H_{14}NaO_4$ (M^++Na): 197.0784. Found 197.0772.

$[\alpha]^{20}_D$ –28.5 (c=1.0, CH_2Cl_2)

(*S*)-Pent-4-yn-2-ol, 76[81]



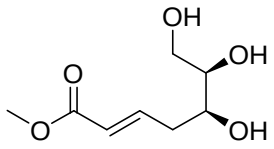
A stirred suspension of lithium acetylide, ethylenediamine complex (6.50 g, 70.6 mmol) in dry DMSO (125 mL) at 0 ˚C was treated with a solution of *S*-(-)-propyleneoxide (4.10 mL, 58.8 mmol) in DMSO (20 mL) dropwise. The reaction was then allowed to warm up to room temperature and it was stirred for a further 48 hours. The reaction was quenched with saturated NH_4Cl (150 mL) and extracted with Et_2O (200 mL x 3). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered and concentrated at atmospheric pressure to yield 6.09 g of the crude alcohol **76** as an orange oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.2 Hz, 3H), 2.00 (br, 1H), 2.06 (t, *J* = 2.6 Hz, 1H), 2.32 (ddd, *J* = 16.6, 6.6, 2.6 Hz, 1H), 2.40 (ddd, *J* = 16.6, 5.0, 2.6 Hz, 1H), 3.93-4.01 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 41.1, 66.3, 71.0, 81.0.

ν_{max} (film)/cm^{-1} 3397, 2972, 2914, 2116, 1436, 1119, 1025.

Methyl (2*E*, 5*S*, 6*R*)-5,6,7-trihydroxyhept-2-enoate, 82[82]



To a stirred solution of 2-deoxy-D-ribose **79** (2.0 g, 15.0 mmol) in THF (40 mL) was added methyl(triphenylphosphoranylidene)acetate (6.0 g, 18.0 mmol) and refluxed at 75 °C for 5 hours. Additional methyl(triphenylphosphoranylidene)-acetate (1.1 g, 3.3 mmol) was addedand refluxing was continued overnight. The reaction was then allowed to cool down to room temperature and was concentrated at reduced pressure. Purification by flash column chromatography (silica gel with MeOH (0-25 %) in $CHCl_3$ as the eluant) afforded the desired *E* conjugated ester **82** as a brown oil (2.15 g, 11.3 mmol, 75 %) plus the *Z* conjugated ester (240 mg, 1.26 mmol, 8 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34-2.41 (m, 1H), 2.48 (dddd, *J* = 14.8, 7.0, 3.6, 1.4 Hz, 1H), 3.55-3.58 (m, 1H), 3.61-3.74 (m, 2H), 3.79 (s, 3H), 3.75-3.78 (m, 1H), 3.86 (brs, 3H), 5.92 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.99 (dt, *J* = 15.7, 7.3 Hz, 1H).

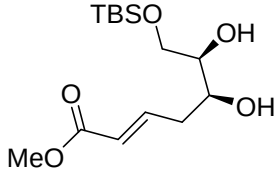
^{13}C NMR (125MHz, $CDCl_3$) δ 36.3, 51.0, 63.5, 72.0, 73.5, 123.8, 145.3, 167.0.

HRMS (CI^+) calcd for $C_8H_{15}O_5$ (M^++H): 191.0919. Found 191.0918.

ν_{max} (film)/cm^{-1} 3423, 2952, 1720, 1655, 1325, 1276, 1067.

$[\alpha]^{24}_D$ –1.2 (c=1, $CHCl_3$)

(5*S*,6*R*,*E*)-Methyl 7-(tert-butyldimethylsilyloxy)-5,6-dihydroxyhept-2-enoate, 83



To a stirred solution of alcohol **82** (1.52 g, 7.99 mmol) in DCM (10 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (1.44 g, 9.60 mmol),

triethylamine (1.67 mL, 12.00 mmol) and DMAP (0.20 g, 1.60 mmol) and stirred for 14 hours before being quenched with saturated aqueous ammonium chloride (20 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (20-40 %) in 40-60 petroleum ether as the eluant) afforded **83** as an orange oil (2.01 g, 6.60 mmol, 83 %).

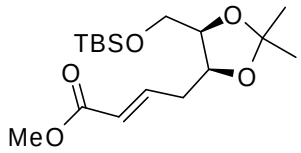
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.91 (s, 9H), 2.35 (d, *J* = 5.6 Hz, 1H), 2.37-2.46 (m, 1H), 2.55 (dddd, *J* = 14.9, 7.2, 4.0, 1.4 Hz, 1H), 2.61 (d, *J* = 5.6 Hz, 1H), 3.52-3.58 (m, 1H), 3.74 (s, 3H), 3.78 (d, *J* = 4.7 Hz, 2H), 3.80-3.85 (m, 1H), 5.95 (dt, *J* = 15.6, 1.4 Hz, 1H), 7.03 (dt, *J* = 15,6, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, -5.3, 18.3, 26.0, 36.3, 51.6, 64.1, 71.1, 73.1, 123.7, 145.5, 166.9.

HRMS (CI^+) calcd for $C_{14}H_{29}O_5Si$ (M^++H): 305.1784. Found 305.1781.

ν_{max} (film)/cm^{-1} 3460, 2929, 2361, 1731, 1462, 1254, 1162, 1076.

(*E*)-Methyl 4-((4*S*,5*R*)-5-((tert-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate, 87



A room temperature solution of diol **83** (2.22 g, 7.29 mmol) in acetone (15 mL) was treated with 2,2-dimethoxypropane (9.0 mL, 73.2 mmol) and PPTS (50 mg). The reaction mixture was then stirred for 14 hours before being diluted with EtOAc (20 mL), washed with saturated aqueous sodium bicarbonate (15 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **87** as a yellow oil (2.15 g, 6.23 mmol, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.33 (s, 3H), 1.42 (s, 3H), 2.42-2.52 (m, 1H), 2.53-2.62 (m, 1H), 3.63-3.68 (m, 2H), 3.73 (s, 3H), 4.13 (dd, *J* = 12.6, 6.1 Hz, 1H), 4.25 (ddd, *J* = 9.4, 5.6, 4.0 Hz, 1H), 5.92 (dt, *J* = 15.6, 1.5, 1H), 7.03 (dt, *J* = 15.6, 7.0 Hz, 1H).

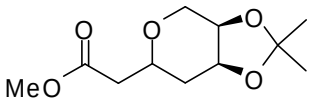
^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, -5.5, 18.2, 25.4, 25.8, 28.1, 32.4, 51.4, 61.6, 76.0, 78.0, 108.0, 122.8, 145.8, 166.7.

HRMS (CI^+) calcd for $C_{17}H_{33}O_5Si$ (M^++H): 345.2097. Found 345.2099.

ν_{max} (film)/cm^{-1} 2956, 2928, 2856, 1729, 1462, 1254, 1071.

$[\alpha]^{23}_D$ –33.2 (c=1, $CHCl_3$)

Methyl 2-((3*R*,7*S*)-2,2-dimethyltetrahydro-3H-[1,3]dioxolo[4,5-]pyran-6-yl)acetate, 88



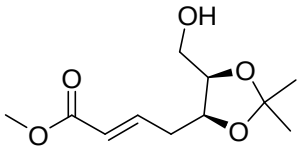
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.51 (s, 3H), 1.76 (ddd, *J* = 15.0, 11.6, 3.6 Hz, 1H), 2.12 (d, *J* = 14.8 Hz, 1H), 2.42 (dd, *J* = 15.2, 4.8 Hz, 1H), 2.50 (dd, 15.2, 8.0 Hz, 1H), 3.36 (dd, *J* = 11.5, 9.7 Hz, 1H), 3.70 (s, 3H), 3.88 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.92-4.06 (m, 1H), 4.06-4.14 (m, 1H), 4.34-4.39 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 28.3, 32.5, 40.7, 52.0, 67.9, 69.2, 70.0, 71.6, 109.2, 171.5.

ν_{max}(film)/cm^{-1} 1742, 1437, 1255, 1061

HRMS calcd for $C_{11}H_{19}O_5$ (M^++H); 231.1232. Found 231.1232

4-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester, 89



Method A

To a stirred solution of silyl ether **87** (72 mg, 0.21 mmol) in THF (2 mL) at 0 °C was added HF-Pyr:Pyr:THF solution (1:4:10, 3 mL) and the reaction mixture was stirred for 5 hours at 0 °C before being allowed to warm up to room temperature over night. Additional pyridine (1.0 mL) was added followed by HF-Pyr (0.5 mL) and stirring was continued for 3.5 hours. The reaction was slowly quenched with saturated aqueous sodium bicarbonate (20 mL) and extracted with DCM (40 mL x 3). The organic layers were combined, washed with citric acid (5 %, 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (30-60 %) in 40-60 petroleum ether as the eluant) afforded **89** as light orange oil (47 mg, 0.21 mmol, 98 %).

Method B

To a stirred solution of pyranol **58** (0.910 g, 5.22 mmol) in THF (15 mL) was added methyl(triphenylphosphoranylidene)acetate (1.92 g, 5.74 mmol) and refluxed at 75 °C for 5 hours. The reaction was then allowed to cool down to room temperature and was diluted with petroleum ether (30 mL). The reaction mixture was then filtered and concentrated at reduced pressure to give the crude product which was purified by flash column chromatography (silica gel with EtOAc (gradient 30-35 %) in 40-60 petroleum ether as the eluant) to afford the desired *E* conjugated ester **89** as a light orange oil (1.07 g, 4.66 mmol, 89 %) plus a fraction of partially separated *E*/*Z* diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.84 (brs, 1H), 2.44 (m, 1H), 2.54 (m, 1H), 3.66 (m, 2H) 3.73 (s, 3H), 4.22 (q *J* = 5.8 Hz, 1H) 4.29 (ddd, *J* = 8.8, 6.1, 4.6 Hz, 1H), 5.94 (m, 1H), 6.98 (dt, *J* =15.7, 6.9 Hz, 1H).

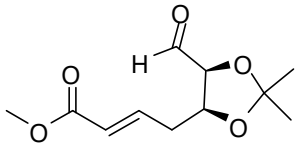
^{13}C NMR (125MHz, $CDCl_3$) δ 25.3, 28.0, 32.5, 51.6, 61.4, 75.4, 77.6, 108.6, 123.2, 145.0, 166.7

HRMS calcd for $C_{11}H_{18}NaO_5$ (M^++Na) 253.1052. Found 253.1055

ν_{max}(film)/cm^{-1} 2841, 2120, 1640, 1107.

$[\alpha]^{20}_D$ –31.9 (c=1.0, CH_2Cl_2)

Methyl (2*E*)-4-[(4*S*,5*S*)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl]but-2-enoate, 90



A -78 °C solution of oxalyl chloride (0.35 mL, 4.05 mmol) in DCM (10 mL) was treated with DMSO (0.57 mL, 8.10 mmol) and the reaction mixture was stirred at –78 °C for 40 minutes. A solution of alcohol **89** (0.62 g, 2.70 mmol) in DCM (3 mL) was added via canula and the reaction mixture was stirred for 1 hour at –78 °C before triethylamine (1.69 mL, 12.15 mmol) and DCM (5 mL) was added and the mixture allowed to warm up to room temperature over 1 hour. The reaction mixture was washed with brine (15 mL) and extracted with EtOAc (25 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (30 %) in 40-60 petroleum ether as the eluant) afforded **90** as a yellow oil (0.62 g, 2.70 mmol, 100 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.59 (s, 3H), 2.36 (m, 1H), 2.51 (m, 1H), 3.73 (s, 3H), 4.33 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.45 (ddd, *J* = 9.1, 7.2, 4.1 Hz, 1H), 5.92 (dt, *J* = 15.7, 1.4 Hz, 1H), 6.93 (dt, *J* = 15.7, 6.9 Hz, 1H), 9.68 (dd, *J* = 3.0, 0.4 Hz, 1H).

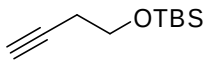
^{13}C NMR (125MHz, $CDCl_3$) δ 25.3, 27.7, 32.7, 51.7, 76.9, 81.7, 111.1, 124.0, 143.6, 166.6, 202.4.

HRMS calcd for $C_{11}H_{17}O_5$ (M^++H); 229.1075. Found 229.1071

ν_{max}(film)/cm^{-1} 2841, 1820, 1625, 1056.

$[\alpha]^{20}_{D}$ –59.4 (c=1.0, CH_2Cl_2)

(But-3-ynyloxy)(tert-butyl)dimethylsilane, 94[83]



To a stirred solution of 3-butyn-1-ol (2.00 g, 28.5 mmol) in DCM (70 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (5.16 g, 34.2 mmol), triethylamine (6.0 mL, 43.1 mmol) and DMAP (0.23 g, 1.8 mmol). The reaction was stirred for 4 hours before being quenched with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (60 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAC (30-50 %) in 40-60 petroleum ether as the eluant) afforded **94** as a colourless oil (4.63 g, 25.1 mmol, 88 %).

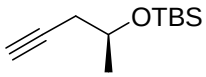
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.96 (t, *J* = 2.6 Hz, 1H), 2.40 (td, *J* = 7.1, 2.6 Hz, 2H), 3.77 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, 18.5, 23.0, 26.0, 61.9, 69.4, 81.7.

HRMS (CI^+) calcd for $C_{10}H_{21}OSi$ (M^++H): 185.1362. Found 185.1365

ν_{max}(film)/cm^{-1} 2960, 2927, 2118, 1480, 1255.

(*R*)-(+)-4-*tert*-Butyldimethylsiloxypent-1-yne, 99[84]



A solution of the freshly generated crude alcohol **76** (5.13 g) in DMF (40 mL) at room temperature was treated with imidazole (7.61 g, 111.74 mmol) and TBDMSCl (9.26 g, 61.46 mmol). The reaction was stirred for 20 hours before being quenched by the addition of water (20 mL) and extracted with a 50 % solution of EtO_2 / 40-60 petroleum ether (100 mL). The organic phase was then washed with brine (50 mL x 4) followed by water (50 mL x 2), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure at 20 ˚C. Purification by flash column chromatography (silica gel with EtO_2 (2 %) in 40-60 petroleum ether as the eluant) afforded **99** as a clear oil (3.51 g, 41.75 mmol, 71 % over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H). 0.06 (s, 3H), 0.87 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.97 (t, *J* = 2.7 Hz, 1H), 2.23 (ddd, *J* = 16.5, 7.1, 2.7 Hz, 1H), 2.34 (ddd, *J* = 16.5, 5.6, 2.6, 1H), 3.90-4.00 (m, 1H).

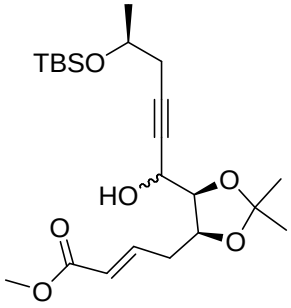
^{13}C NMR (125MHz, $CDCl_3$) δ -4.8, -4.7, 18.1, 23.2, 25.7, 29.3, 67.5, 69.6, 81.8.

HRMS (CI^+) calcd for $C_{11}H_{23}OSi$ (M^++H); 199.1518 Found 199.1521

ν_{max}(film)/cm^{-1} 2956, 2929, 2122, 1472, 1256.

$[\alpha]^{20}_D$ -1.8 (c=1.0, CH_2Cl_2)

(*E*)-4-((4*S*,5*R*)-5-[(*S*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-hex-2-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester, 100



A room temperature solution of alkyne **99** (480 mg, 2.43 mmol) in THF (9 mL was treated with ethylmagnesium bromide (3.0 M solution) (0.81 mL, 2.43 mmol) and the resulting mixture stirred for 2 hours at room temperature. The solution was then cooled down to -78 °C and treated with a solution of aldehyde **90** (0.62 g, 2.70 mmol) in THF (9 mL) and the stirring at -78 °C was continued for 2.5 hours. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel, with EtOAc (10 %) in 40-60 petroleum ether as the eluant) generated the desired propargylic alcohols **100** as an inseparable mixture of diastereoisomers (0.52 g, 1.21 mmol, 45 %) and a significant amount of unreacted starting aldehyde **99** which was cleanly recovered (154 mg, 0.67 mmol, 25 %). Yield based on starting material recovered 69 %.

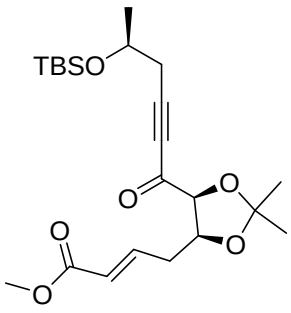
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H). 0.07 (s, 3H), 0.86 (s, 9H), 1.21 (d, *J* = 6.15 Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 3.94-2.25 (m, 4H), 3.92 (s, 3H) 3.93 (m, 1H), 4.29 (m, 1H), 4.43 (d, *J* = 5.5 Hz, 1H), 5.91 (d, *J* = 15.7, 1H), 6.99 (m, 1H),

^{13}C NMR (125MHz, $CDCl_3$) δ -4.5, 23.4, 25.4, 25.9, 29.7, 32.7, 51.5, 61.3, 62.1, 75.8, 80.3, 81.9, 85.2, 108.8, 122.9, 145.3, 166.9

HRMS calcd for $C_{22}H_{39}O_6Si_1$ (M^++H); 427.2510. Found 427.2492

ν_{max}(film)/cm^{-1} 2953, 2930, 2857, 2300, 1726, 1658, 1166.

(*E*)-4-[(4*S*,5*S*)-5-((*S*)-5-Methoxy-hex-2-ynoyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-2-enoic acid methyl ester, 101



Method A

A mixture of alcohol **100** (65 mg, 0.15 mmol), 4 Å molecular sieves (150 mg) and NMO (31 mg, 0.23 mmol) in DCM (1 mL) at room temperature was stirred for 30 minutes. TPAP (3 mg, 0.008 mmol) was added and the resulting dark green suspension was stirred at room temperature for 2 hours. The reaction was then filtered through silica and concentrated at reduced pressure. Purification by flash column chromatography (silica gel, with EtOAc (elution gradient 0-10 %) in 40-60 petroleum ether as the eluant) afforded the desired alkynone **101** (38 mg, 0.089 mmol, 59 %) as a clear oil.

Method B

A -78 °C solution of oxalyl chloride (0.02 mL, 0.20 mmol) in DCM (1 mL) was treated with DMSO (0.03 mL, 0.40 mmol) dropwise and the reaction mixture was stirred for 30 minutes. A solution of alcohol **100** (57 mg, 0.134 mmol) in DCM (1 mL) was added dropwise via canula followed by a DCM (1 mL) rinse and the reaction mixture was stirred for 1 hour at -78 °C before triethylamine (0.08 mL, 0.60 mmol) and DCM (1 mL) was added and the mixture allowed to warm up to room temperature over 45 minutes. DCM (1 mL) was added and the solution was washed with HCl (1 M) (2 mL) and saturated aqueous sodium bicarbonate (2 mL). The organic fraction was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **101** as a yellow oil (12 mg, 0.03 mmol, 21 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.25 (d, *J* = 6.1, 3H), 1.38 (s, 3H), 1.63 (s, 3H), 2.37 (m, 1H), 2.59-2.48 (m, 3H), 3.73 (s, 3H), 4.04 (m, 1H), 4.47 (m, 1H), 4.57 (d, *J* = 7.3 Hz, 1H), 5.92 (dt, *J* = 15.8, 1.5, 1H), 6.95 (dt, *J* = 6.93, 1.85, 1H).

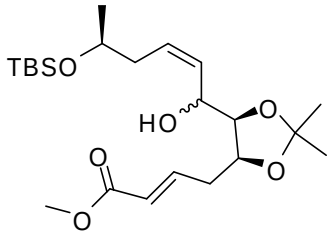
^{13}C NMR (125MHz, $CDCl_3$) δ -4.7, -4.6, 18.2, 23.7, 25.4, 25.9, 27.2, 30.2, 33.3, 51.7, 66.8, 76.7, 83.0, 97.3, 111.2, 123.7, 144.3, 166.7, 186.3.

HRMS calcd for $C_{22}H_{36}NaO_6Si$ (M^++Na); 447.2173. Found 447.2176

ν_{max}(film)/cm^{-1} 2929, 2211, 1825, 1725, 1256.

$[\alpha]^{20}_D$ -21.2 (c=1.0, CH_2Cl_2)

(E)-Methyl 4-((4S,5R)-5-((S,Z)-5-(tert-butyldimethylsilyloxy)-1-hydroxyhex-2-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate, 102



To a stirred solution of alkyne **100** (170 mg, 0.40 mmol) in MeOH (2 mL) was added palladium on barium sulphate (250 mg) and quinoline (0.5 mL) at room temperature. The flask was evacuated and purged with hydrogen 5 times and hydrogen was bubbled through the solution for 10 minutes. After 7 hours under hydrogen the reaction mixture was filtered through celite and concentrated at reduced pressure. Analysis of the crude showed **102** as a colourless oil and was taken onto the next step without an further purification.

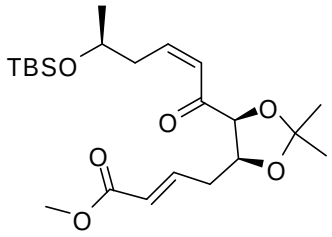
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03-0.08 (m, 12H), 0.88-0.90 (m, 18H), 1.13-1.17 (m, 6H), 1.33-1.37 (m, 6H), 1.41-1.44 (m, 6H), 2.23-2.59 (m, 8H), 3.64-3.66 (m, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 3.79-4.42 (m, 6H), 5.47-5.55 (m, 2H), 5.65-5.83 (m, 2H), 5.89-5.96 (m, 2H), 6.95-7.15 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ -4.4, -4.2, 18.3, 18.4, 23.8, 24.4, 25.4, 25.7, 26.0, 26.1, 27.9, 28.0, 28.2, 29.1, 33.2, 33.8, 38.1, 38.6, 51.6, 51.7, 65.2, 66.0, 75.7,

76.5, 77.0, 77.3, 77.4, 77.7, 80.5, 80.8, 108.6, 108.8, 122.9, 123.2, 129.5, 129.7, 131.9, 132.4, 145.5, 146.5.

HRMS (CI^+) calcd for $C_{22}H_{41}O_6Si$ (M^++H): 429.2672. Found 429.2675.

(*E*)-Methyl 4-((4*S*,5*S*)-5-((*S*,*Z*)-5-(*tert*-butyldimethylsilyloxy)hex-2-enoyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate, 103



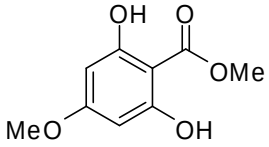
A mixture of alcohol **102** (157 mg, 0.37 mmol), 4 Å molecular sieves (400 mg) and NMO (75 mg, 0.56 mmol) in DCM (2 mL) at room temperature was stirred for 30 minutes. TPAP (7 mg, 0.02 mmol) was added and the resulting dark green suspension was stirred at room temperature for 4 hours. The reaction was then filtered through silica and concentrated at reduced pressure. Purification by flash column chromatography (silica gel, with EtOAc (elution gradient 0-10 %) in 40-60 petroleum ether as the eluant) afforded the desired alkynone **103** (41 mg, 0.10 mmol, 26 %) as a clear oil. Alkenol **100** and alkynone **101** were also recovered as impure fractions

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.37 (s, 3H), 1.59 (s, 3H), 2.29-2.46 (m, 4H), 2.73-2.82 (m, 1H), 3.65 (s, 3H), 3.93-4.00 (m, 1H), 4.47 (d, *J* = 7.6 Hz, 1H), 5.61-5.80 (m, 1H), 5.92-5.92 (m, 1H), 6.17-6.35 (m, 1H), 6.97-7.14 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ -4.4, , 18.3, 23.8, 24.4, 25.7, 29.7, 33.2, 38.4, 50.7, 65.1, 66.5, 75.1, 76.6, 77.0, 109.3, 122.9, 129.5, 140.5 145.5, 199.6.

HRMS (CI^+) calcd for $C_{22}H_{39}O_6Si$ (M^++H): 427.2516. Found 427.2517.

Methyl 2,6-dihydroxy-4-methoxybenzoate, 104



To a solution of methyl 2,4,6-trihydroxybenzoate **81** (19.2 g, 0.10 mol) in $CHCl_3$:MeOH (3:1, 1.0 L) at 0 ˚C was added trimethylsilyl-diazomethane (2.0 M, 65 mL, 0.13 mol) and stirred for 15 hours. A second aliquot of trimethylsilyl-diazomethane (2.0 M, 35 mL, 0.70 mol) was added and the reaction stirred for a further 10 hours before being diluted with MeOH (150 mL) and quenched with acetic acid (30 mL). The reaction was concentrated at reduced pressure to afford a crude solid which upon washing with 40-60 petroleum ether resulted in **104** as white crystals (20.21 g, 0.10 mol, 98 %).

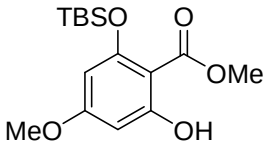
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.04 (s, 3H), 6.04 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 55.6, 91.6, 93.5, 160.1, 166.5, 171.8.

HRMS (CI^+) calcd for $C_9H_{11}O_5$ (M^++H): 199.0606. Found 199.0609.

ν_{max} (film)/cm^{-1} 3413, 1647, 1430, 1314, 1203, 1153.

Methyl 2-(*tert*-butyldimethylsilyloxy)-6-hydroxy-4-methoxybenzoate, 105



To a stirred solution of alcohol **104** (13.10 g, 66.10 mmol) in DCM (330 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (8.47 g, 56.19 mmol) and triethylamine (20.3 mL, 145.64 mmol) and stirred for 20 hours before quenched with saturated aqueous ammonium chloride (200 mL) and extracted with DCM (250 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (5 %) in 40-60 petroleum ether as the eluant) afforded **105** as a white solid (16.39 g, 52.29 mmol, 93 %) plus

unreacted starting material (2.73 g, 13.76 mmol, 21 %). Yield based on starting material recovered, 100 %.

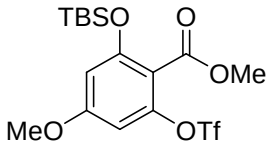
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (s, 6H), 1.00 (s, 9H), 3.77 (s, 3H), 3.88 (s, 3H), 5.89 (d, *J* = 2.5 Hz, 1H), 6.12 (d, *J* = 2.5 Hz, 1H), 11.84 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3, 18.3, 25.6, 51.6, 55.3, 94.5, 99.4, 99.4, 158.3, 164.8, 165.8, 171.6.

HRMS (CI^+) calcd for $C_{15}H_{25}O_5Si$ (M^++H): 313.1471. Found 313.1473.

ν_{max} (film)/cm^{-1} 3429, 3103, 3009, 2955, 2850, 1648, 1260, 1073.

Methyl 2-(tert-butyldimethylsilyloxy)-4-methoxy-6-(trifluoromethylsulfonyloxy)benzoate, 106



A 0 ˚C solution of alcohol **105** (9.16 g, 29.33 mmol) in DCM (50 mL) was treated with pyridine (8.54 mL, 105.6 mmol) and trifluoromethanesulfonic anhydride (10.0 g, 35.18 mmol) and the reaction mixture was stirred for 3 hours. The reaction was quenched with water (25 mL), citric acid (1 M, 25 mL) and extracted with Et_2O (75 mL x 3). The organic layers were combined, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (25 %) in 40-60 petroleum ether as the eluant) afforded **106** as an orange oil (12.81 g, 28.82 mmol, 98 %)

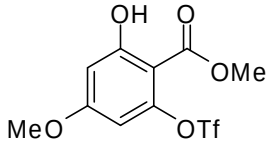
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 6H), 0.97 (s, 9H), 3.80 (s, 3H), 3.87 (s, 3H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H)

^{13}C NMR (125MHz, $CDCl_3$) δ -4.3, 18.2, 25.5, 52.5, 60.6, 107.1, 111.4, 113.5, 120.0, 148.0, 155.9, 158.5, 163.9.

HRMS (CI^+) calcd for $C_{16}H_{24}O_7F_3SiS$ (M^++H): 445.0964. Found 445.0963.

ν_{max} (film)/cm^{-1} 2955, 2860, 1740, 1619, 1570, 1427.

Methyl 2-hydroxy-4-methoxy-6-(trifluoromethylsulfonyloxy)benzoate, 107



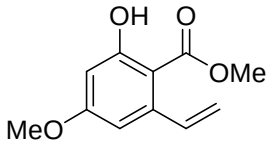
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.98 (s, 3H), 6.34 (d, *J* = 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 11.71 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 56.1, 100.4, 101.0, 103.4, 118.8 (q, *J* = 320.7 Hz), 149.6, 164.6, 165.5, 168.9.

HRMS (EI$^+$) calcd for $C_{10}H_9F_3O_7S$ (M^++H): 330.0021. Found 330.0019.

ν_{max} (film)/cm^{-1} 2960, 1680, 1577, 1205.

Methyl 2-hydroxy-4-methoxy-6-vinylbenzoate, 108[85]



A suspension of lithium chloride (3.63 g, 85.6 mmol) in DMF (200 mL) was heated to 60 °C. A solution of triflate **107** (12.68 g, 28.5 mmol) in DMF (80 mL) was then added followed by tri-2-furylphosphine (1.06 g, 4.6 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.52 g, 0.57 mmol). The reaction mixture was stirred at room temperature for 30 minutes, then tributyl vinyl tin (10.0 mL, 34.2 mmol) was added and the reaction was heated to 60 °C for 5 hours. The reaction was then quenched with saturated aqueous potassium fluoride solution (200 mL) and extracted with EtOAc (250 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with Et_2O (10 %) in 40-60 petroleum ether as the eluant) afforded **108** as white crystals (5.76 g, 27.7 mmol, 97 %).

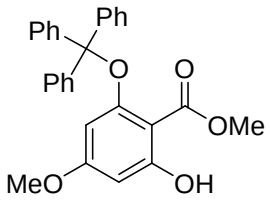
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.92 (s, 3H), 5.24 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.46 (dd, *J* = 17.2, 1.5 Hz, 1H), 6.42 (d, *J* = 2.6 Hz, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 7.23-7.30 (m, 1H), 11.66 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 55.5, 100.3, 103.9, 108.3, 115.8, 138.4, 143.6, 164.3, 165.1, 171.7.

HRMS (EI^+) calcd for $C_{11}H_{12}O_4$ (M^+): 208.0736. Found 208.0733.

ν_{max} (film)/cm^{-1} 2925, 2854, 1733, 1648, 1437, 1328, 1257, 1159.

Methyl 2-hydroxy-4-methoxy-6-(trityloxy)benzoate, 109



To a stirred solution of alcohol **104** (0.73 g, 3.68 mmol) in DCM (15 mL) at room temperature was added triphenylmethyl chloride (0.98 g, 3.50 mmol) and triethylamine (1.13 mL, 8.10 mmol) and the reaction mixture was stirred for 48 hours. The reaction was quenched with saturated aqueous ammonium chloride (15 mL) and extracted with DCM (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **109** as a white solid (0.64 g, 1.45 mmol, 39 %)

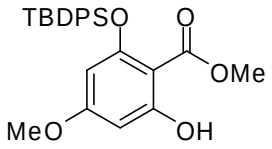
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (s, 3H), 3.74 (s, 3H), 5.61 (d, *J* = 2.4 Hz, 1H), 5.95 (d, *J* = 2.4 Hz, 1H), 7.20-7.24 (m, 3H), 7.27-7.32 (m, 6H), 7.43-7.46 (m, 6H), 11.69 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 51.8, 55.0, 92.2, 94.8, 99.7, 100.9, 127.3, 127.7, 128.8, 143.7, 158.6, 163.5, 164.7, 171.6.

HRMS (CI^+) calcd for $C_9H_{11}O_5$ (M^+-$C_{19}H_{15}$): 199.0606. Found 199.0610.

ν_{max} (film)/cm^{-1} 1648, 1577, 1491, 1435, 1264.

Methyl 2-(*tert*-butyldiphenylsilyloxy)-6-hydroxy-4-methoxybenzoate, 110



To a stirred solution of alcohol **104** (0.70 g, 3.56 mmol) in DCM (15 mL) at room temperature was added *tert*-butyldiphenylsilyl chloride (0.88 mL, 3.38 mmol) and triethylamine (1.09 mL, 7.83 mmol) and the reaction mixture was stirred for 48 hours. The reaction was quenched with saturated aqueous ammonium chloride (15 mL), extracted with DCM (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **110** as a white solid (1.47 g, 3.37 mmol, 99 %) plus recovered starting material (37 mg, 0.19 mmol).

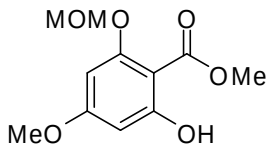
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.36 (s, 3H), 3.89 (s, 3H), 5.54 (d, *J* = 2.5 Hz, 1H), 6.03 (d, *J* = 2.5 Hz, 1H), 7.36-7.44 (m, 6H), 7.71-7.73 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 26.2, 51.8, 54.8, 95.1, 98.7, 99.1, 127.6, 127.9, 130.1, 132.1, 135.5, 158.2, 164.4, 165.2.

HRMS (CI^+) calcd for $C_{25}H_{29}O_5Si$ (M^++H): 437.1784. Found 437.1786.

ν_{max} (film)/cm^{-1} 2857, 1652, 1615, 1575, 1427, 1210, 1100.

Methyl 2-hydroxy-4-methoxy-6-(methoxymethoxy)benzoate, 111



A stirred solution of diol **104** (130 mg, 0.63 mmol) in DCM (2 mL) at room temperature was treated with DIPEA (0.26 mL, 1.51 mmol) and chloromethyl methyl ether (0.07 mL, 0.95 mmol) and the reaction mixture was stirred for 18 hours . The reaction was quenched with water (3 mL) and the resulting mixture was extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column

chromatography (silica gel with EtOAc (20 %) in 40-60 petroleum ether as the eluant) afforded **111** as a colourless oil (20 g, 0.10 mmol, 16 %) and **114** as a colourless oil (150 g, 0.53 mmol, 83 %)

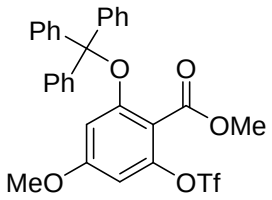
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.77 (s, 3H), 5.18 (s, 2H), 6.16 (s, 2H), 11.90 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 55.6, 56.6, 94.9, 95.2, 95.2, 159.7, 165.3, 165.6, 171.6.

HRMS (EI^+) calcd for $C_{11}H_{15}O_6$ (M^+): 242.0790. Found 242.0792.

ν_{max} (film)/cm^{-1} 2955, 1732, 1579, 1436, 1218.

Methyl 4-methoxy-2-(trifluoromethylsulfonyloxy)-6-(trityloxy)benzoate, 112



A 0 ˚C solution of alcohol **109** (0.67 g, 1.52 mmol) in pyridine (4 mL) was treated with trifluoromethanesulfonic anhydride (0.27 ml, 1.67 mmol) and the reaction mixture was stirred for 4 hours. The reaction was quenched with water (5 mL), citric acid (1 M, 5 mL) and extracted with Et_2O (15 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (20 %) in 40-60 petroleum ether as the eluant) afforded **112** as an orange oil (0.86 g, 1.50 mmol, 99 %).

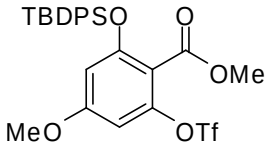
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.93 (s, 3H), 6.87 (s, 2H), 7.25-7.26 (m, 15H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 53.1, 56.6, 82.1, 108.8, 113.5, 113.8, 117.0, 127.2, 127.3, 128.0, 147.0, 148.9, 149.0, 161.0, 162.6.

HRMS (CI^+) calcd for $C_{10}H_{10}F_3O_7S$ (M^+-$C_{19}H_{15}$): 331.0099. Found 331.0101.

ν_{max} (film)/cm^{-1} 3061, 1737, 1562, 1490, 1433, 1322, 1211, 1144.

Methyl 2-(*tert*-butyldiphenylsilyloxy)-4-methoxy-6-(trifluoromethylsulfonyloxy)benzoate, 113



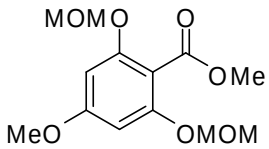
A 0 ˚C solution of alcohol **110** (1.52 g, 2.29 mmol) in pyridine (6 mL) was treated with trifluoromethanesulfonic anhydride (0.41 ml, 2.52 mmol) and the reaction mixture was stirred for 4 hours. The reaction was quenched with water (10 mL), citric acid (1 M, 10 mL) and extracted with Et_2O (20 mL x 3). The organic layers were combined, washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (20 %) in 40-60 petroleum ether as the eluant) afforded **113** as an orange oil (1.29 g, 2.27 mmol, 99 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.29 (s, 3H), 3.94 (s, 3H), 5.92 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 7.32-7.50 (m, 6H), 7.7-7.76 (m, 4).

^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 24.9, 53.4, 56.7, 82.4, 108.8, 113.2, 117.0, 129.2, 130.4, 137.0, 153.9, 157.0, 161.5, 162.2.

HRMS (EI$^+$) calcd for $C_{26}H_{28}F_3O_7SSi$ (M^++H): 569.1277. Found 569.1281.

Methyl 4-methoxy-2,6-bis(methoxymethoxy)benzoate, 114



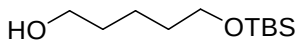
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 6H), 3.78 (s, 3H), 3.80 (s, 3H), 5.15 (s, 4H), 6.39 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 55.7, 56.4, 94.9, 95.2, 156.1, 162.3, 166.9.

HRMS (EI$^+$) calcd for $C_{13}H_{18}O_7$ (M^+): 286.1053. Found 286.1049.

ν_{max} (film)/cm^{-1} 2920, 2852, 1732, 1433, 1268.

5-(*tert*-Butyldimethylsilyloxy)pentan-1-ol, 116[86]



To a suspension of NaH (60 % in mineral oil, 1.53 g, 38.25 mmol) in THF (90 mL) at 0 °C was added a solution of 1,5-pentanediol **115** (4.1 mL, 39.0 mmol) in THF (90 mL). The mixture was stirred for 45 minutes, a solution of *tert*-butyldimethylsilyl chloride (5.50 g, 36.5 mmol) in THF (60 mL). The reaction was allowed to reach room temperature and stirred for 2 hours. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (250 mL x 3). The organic fractions were combined, concentrated at reduced pressure, washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (30 %) in 40-60 petroleum ether as the eluant) afforded **116** as a colourless oil (7.47 g, 34.20 mmol, 94 %).

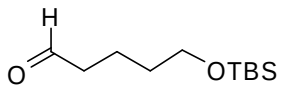
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.38-1.44 (m, 2H), 1.48 (br, 1H), 1.51-1.62 (m, 4H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, 18.1, 22.5, 25.7, 31.9, 34.3, 62.2, 62.9.

HRMS (CI$^+$) calcd for $C_{11}H_{27}O_2Si$ (M^++H): 219.1780. Found 219.1779.

ν_{max} (film)/cm^{-1} 2936, 2858, 1254, 1101.

5-(*tert*-Butyldimethylsilyloxy)pentanal, 117[86]



A -78 °C solution of oxalyl chloride (2.8 mL, 32.25 mmol) in DCM (100 mL) was treated with DMSO (4.58 mL, 64.50 mmol) and the reaction mixture was stirred for 30 minutes. A solution of alcohol **116** (4.70 g, 21.50 mmol) in DCM (30 mL) was added via canula and the reaction mixture was stirred for 1 hour at -78 °C before triethylamine (13.5 mL, 96.8 mmol) and DCM (50 mL) was added and the mixture allowed to warm up to room temperature over 1 hour. The reaction

mixture was washed with brine (150 mL) and extracted with EtOAc (250 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with Et_2O (10 %) in 40-60 petroleum ether as the eluant) afforded **117** as a colourless oil (3.58 g, 16.56 mmol, 77 %).

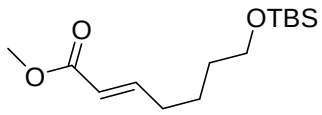
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.51-1.58 (m, 2H), 1.66-1.73 (m, 2H), 2.46 (dt, *J* = 7.3, 1.8 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 9.77 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, 18.1, 25.7, 29.9, 44.3, 63.2, 199.7.

HRMS (CI^+) calcd for $C_{11}H_{25}O_2Si$ (M^++H); 217.1624. Found 217.1621.

ν_{max} (film)/cm^{-1} 2941, 1727, 1453, 1123, 1035.

(*E*)-Methyl 7-(*tert*-butyldimethylsilyloxy)hept-2-enoate, 118[87]



To a stirred solution of freshly prepared aldehyde **117** (4.65 g, 21.50 mmol) in THF (100 mL) was added methyl(triphenylphosphoranylidene)acetate (13.0 g, 56.48 mmol) and refluxed at 75 °C for 5 hours. The reaction was then allowed to cool down to room temperature and was diluted with petroleum ether (100 mL). The reaction mixture was then filtered and concentrated at reduced pressure to give the crude product which was purified by flash column chromatography (silica gel with EtOAc (0-5 %) in 40-60 petroleum ether as the eluant) afforded **118** as a colourless oil (3.25 g, 11.94 mmol, 56 %).

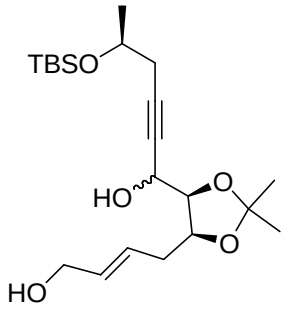
^{1}H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 6H), 0.83 (s, 9H), 1.43-1.50 (m, 4H), 2.14-2.19 (m, 2H), 3.55 (t, *J* = 5.5 Hz, 2H), 3.65 (s, 3H), 5.76 (d, *J* = 15.1 Hz, 1H), 6.91 (dt, *J* = 15.1, 7.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.3, 24.4, 26.0, 32.0, 32.2, 51.3, 62.7, 121.0, 149.5, 167.1.

HRMS (CI^+) calcd for $C_{14}H_{29}O_3Si$ (M^++H): 273.1886. Found 273.1887.

ν_{max} (film)/cm^{-1} 2934, 2857, 1726, 1461, 1317.

(*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-((4*R*,5*S*)-5-((*E*)-4-hydroxybut-2-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-yn-1-ol, 124



A 0 °C solution of ester **100** (40 mg, 0.10 mmol) in DCM (1 mL) was treated with dibal-H (1 M, 0.3 mL, 0.30 mmol) and the reaction mixture was stirred for 2 hours. DCM (3 mL) was added and the reaction was quenched with water (0.01 mL) followed by aqueous sodium hydroxide (15 %, 0.01 mL) and finally water (0.01 mL). The mixture was allowed to warm up to room temperature and stirred for a further 15 minutes. Anhydrous $MgSO_4$ was added and the reaction mixture was filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (15-50 %) in 40-60 petroleum ether as the eluant) afforded **124** as a yellow oil in a 60:40 mixture of diastereomers (40 mg, 0.10 mmol, 100 %).

Major product

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.22 (d, *J* =6.1 Hz, 3H), 1.35 (s, 3H), 1.48 (s, 3H), 1.73 (br, 2H), 2.30-2.55 (m, 4H), 3.92-4.00 (m, 1H), 4.08-4.11 (m, 3H), 4.22-4.24 (m,1H), 4.40-4.42 (m, 1H), 5.73-5.75 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 4.6, 4.6, 18.3, 23.5, 25.5, 26.0, 27.7, 29.5, 29.9, 32.5, 62.4, 63.7, 67.6, 70.8, 85.1, 79.8, 107.7, 129.1, 131.7.

Minor product

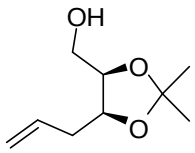
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.21 (d, *J* =6.2 Hz, 3H), 1.36 (s, 3H), 1.50 (s, 3H), 1.73 (br, 2H), 2.30-2.55 (m, 4H), 3.92-4.00 (m, 1H), 4.08-4.11 (m, 3H), 4.22-4.24 (m,1H), 4.40-4.42 (m, 1H), 5.73-5.75 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 4.6, 4.6, 19.3, 23.5, 25.5, 26.0, 27.7, 29.8, 31.1, 35.0, 62.4, 63.8, 67.5, 77.0, 72.5, 77.4, 99.5, 128.4, 131.6.

HRMS (EI^+) calcd for $C_{21}H_{39}O_5Si(M^+)$: 399.2567. Found 399.2569.

ν_{max} (film)/cm^{-1} 3411, 2930, 2857, 2233, 1462, 1257, 1065.

[(4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl]methanol, 125[66]



To a stirred suspension of methyltriphenyl-phosphonium iodide (6.80 g, 16.8 mmol) in THF (35 mL) was added KHMDS (0.5 M in toluene, 25.3 mL, 12.6 mmol) at -78 ˚C. The solution was warmed to 0 ˚C and stirred for 30 minutes before being cooled down once again to -78 ˚C. Acetonide **58** (0.73 g, 4.2 mmol) in THF (5 mL) was then added via cannula and the solution was warmed up to room temperature overnight (12 hours). The reaction was then quenched with saturated aqueous ammonium chloride (40 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. The crude was dissolved in EtOAc (10 %) in 40-60 petroleum ether to crash out most of the triphenylphosphine oxide. The mixture was filtered and concentrated at reduced pressure. Purification of the crude residue by flash column chromatography (silica gel with EtOAc (0-20 %) in 40-60 petroleum ether as the eluant) afforded **125** as a colourless oil (490 mg, 2.8 mmol, 67 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.48 (s, 3H), 2.25-2.32 (m, 1H), 2.37-2.44 (m, 1H), 3.65 (t, *J* = 5.7 Hz, 2H), 5.10-5.17 (m, 2H), 5.78-5.89 (m, 1H).

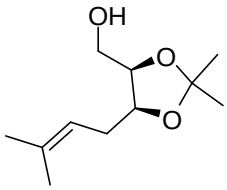
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 28.0, 33.6, 61.3, 76.2, 77.8, 108.1, 117.2, 134.2.

HRMS (CI^+) calcd for $C_9H_{17}O_3$ (M^++H): 173.1178. Found 173.1175.

ν_{max} (film)/cm^{-1} 3450, 3077, 2987, 2929, 2853, 1643, 1457, 1379, 1235, 1217, 1045.

$[\alpha]^{19}_D$ –15.6 (c=1, $CHCl_3$)

[(4*R*,5*S*)-2,2-Dimethyl-5-(3-methylbut-2-en-1-yl)-1,3-dioxolan-4-yl]methanol, 127



To a suspension of isopropyltriphenylphosphonium iodide (1.40 g, 3.31 mmol) in THF (3 mL) at -78 °C was added *n*-BuLi (1.6 M, 2.0 mL, 3.2 mmol) drop wise over 10 minutes and allowed to reach 0 °C. After 20 minutes the mixture was cooled to -78 °C and a solution of acetonide **58** (232 mg, 1.33 mmol) in THF (1 mL) was added. The reaction was allowed to reach room temperature and stirring continued for 10 hours. The reaction was quenched with water (1 mL) and was diluted with Et_2O (10 mL). The resulting mixture was filtered through a pad a celite and the filtrate washed with water (10 mL). The organic fraction was dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (silica gel with EtOAc (25-40 %) in 40-60 petroleum ether as the eluant) afforded **127** as a yellow oil (150 mg, 0.75 mmol, 56 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.48 (s, 3H), 1.63 (s, 3H), 1.71 (s, 3H), 1.83-1.90 (m, 1H), 2.18-2.27 (m, 1H), 2.29-2.39 (m, 1H), 3.57-3.68 (m, 2H), 4.13-4.24 (m, 2H), 5.12 (t, *J* = 6.9 Hz, 1H).

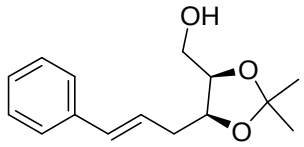
^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 25.6, 25.9, 28.2, 28.7, 61.8, 77.0, 78.0, 108.2, 119.4, 134.5.

HRMS (CI^+) calcd for $C_{11}H_{21}O_3$ (M^++H): 201.1491. Found 201.1487.

ν_{max} (film)/cm^{-1} 3449, 2984, 2931, 1378, 1216, 1044.

$[\alpha]^{20}_D$ 20.8 (c=1, $CHCl_3$)

((4*R*,5*S*)-5-cinnamyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol, 128[88]



A -78 ˚C suspension of benzyltriphenylphosphonium chloride (2.75 g, 7.08 mmol) in THF (10 mL) was treated with KHMDS (0.5 M in toluene, 12.4 mL, 6.20 mmol) and allowed to reach 0 ˚C for 30 minutes. The reaction mixture was then cooled down to -78 ˚C and acetonide **58** (0.616 g, 3.54 mmol) in THF (2 mL) was added via cannula and the solution was warmed up to room temperature overnight (13 hours). The reaction was quenched with saturated aqueous ammonium chloride (40 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. The crude was dissolved in EtOAc (10 %) in 40-60 petroleum ether to crash out most of the triphenylphosphine oxide which was filtered off and the crude was concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (30 %) in 40-60 petroleum ether as the eluant) afforded the desired *E* conjugated ester **128** as a colourless oil (590 mg, 2.37 mmol, 67 %) and the Z conjugated ester (100 mg, 0.40 mmol, 11 %).

***E* product**

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.51 (s, 3H), 1.86 (t, *J* = 6.0 Hz, 1H), 2.40-2.49 (m, 1H), 2.53-2.62 (m, 1H), 3.70 (t, *J* = 5.8 Hz, 2H), 4.22 (dd, *J* = 11.6, 5.8 Hz, 1H), 4.27-4.35 (m, 1H), 6.23 (ddd, *J* = 15.9, 7.6, 6.4 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 7.17-7.25 (m, 1H), 7.26-7.39 (m, 4H).

^{13}C NMR (75 MHz, CD_3OD) δ 25.8, 28.5, 34.3, 61.9, 78.2, 79.4, 109.3, 127.1, 128.1, 129.2, 129.5, 133.3, 138.9.

***Z* product**

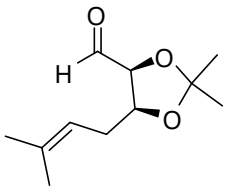
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.46 (s, 3H), 1.79 (t, *J* = 5.4 Hz, 1H), 2.53-2.62 (m, 1H), 2.64-2.73 (m, 1H), 3.55-3.58 (m, 1H), 4.22 (dd, *J* = 11.6, 5.8 Hz, 1H), 4.27-4.35 (m, 1H), 5.71 (dt, *J* = 11.7, 7.0 Hz, 1H), 6.57 (d, *J* = 11.7 Hz, 1H), 7.17-7.25 (m, 1H), 7.26-7.39 (m, 4H).

^{13}C NMR (75 MHz, CD_3OD) δ 28.4, 29.9, 34.3, 61.9, 78.2, 79.3, 109.3, 127.5, 127.8, 129.3, 129.8, 131.8, 138.6.

HRMS (CI^+) calcd for $C_{15}H_{21}O_3$ (M^++H): 249.1491. Found 249.1489.

ν_{max} (film)/cm^{-1} 3456, 2986, 2935, 1598, 1494, 1449, 1163, 1043.

(4*S*,5*S*)-2,2-Dimethyl-5-(3-methylbut-2-en-1-yl)-1,3-dioxolane-4-carbaldehyde, 129



A -78 ˚C solution of oxalyl chloride (0.10 mL, 1.20 mmol) in DCM (5 mL) was treated with DMSO (0.16 mL, 2.40 mmol) and the reaction mixture was stirred for 30 minutes. A solution of alcohol **127** (120 g, 0.60 mmol) in DCM (5 mL) was added dropwise and the reaction mixture was stirred for 1 hour at -78 ˚C before triethylamine (0.63 mL, 4.80 mmol) was added and the mixture allowed to warm up to room temperature over 1 hour. The reaction mixture was washed with HCl (1 M, 5 mL), saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (25 %) in 40-60 petroleum ether as the eluant) to afford **129** as a yellow oil (110 mg, 0.55 mmol, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.59 (s, 3H), 1.60 (s, 3H), 1.71 (s, 3H), 2.28 (dd, *J* = 6.7, 6.7 Hz, 2H), 4.31 (dd, *J* = 7.1, 3.1 Hz, 1H), 4.39 (dt, *J* = 6.9, 6.7, Hz, 1H), 5.15 (dt, *J* = 6.9, 1.4 Hz, 1H), 9.64 (d, *J* = 3.1 Hz, 1H).

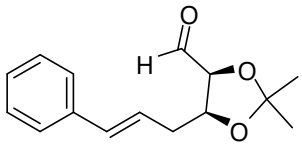
^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 25.3, 25.9, 27.5, 28.7, 78.8, 82.0, 110.6, 118.6, 135.3, 201.6.

HRMS (CI^+) calcd for $C_{11}H_{19}O_3$ (M^++H): 199.1334. Found 199.1331.

ν_{max} (film)/cm^{-1} 2986, 2932, 1734, 1457, 1067.

$[\alpha]^{23}_D$ –7.6 (c=1, $CHCl_3$)

(4*S*,5*S*)-2,2-Dimethyl-5-[(2*E*)-3-phenylprop-2-en-1-yl]-1,3-dioxolane-4-carbaldehyde, 130[88]



A -78 ˚C solution of oxalyl chloride (0.21 mL, 2.38 mmol) in DCM (10 mL) was treated with DMSO (0.32 mL, 4.76 mmol) and the reaction was stirred at –78 ˚C for 30 minutes. A solution of alcohol **128** (290 mg, 1.19 mmol) in DCM (5 mL) was added via canula and the reaction mixture was stirred for 45 minutes at –78 ˚C before triethylamine (1.25 mL, 9.52 mmol) was added and the mixture allowed to warm up to room temperature over 1 hour. The reaction mixture was washed with HCl (1 M, 10 mL), saturated aqueous sodium bicarbonate (10 mL) and brine (15 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (30 %) in 40-60 petroleum ether as the eluant) to afford the desired *E* conjugated ester **130** as a yellow oil (0.223 g, 0.91 mmol, 77 %) plus a fraction of partially separated *E*/*Z* diastereomers.

***E* product**

^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.61 (s, 3H), 2.38-2.57 (m, 1H), 3.05-3.14 (m, 1H), 4.34 (dd, *J* = 7.3, 3.1 Hz, 1H), 4.42-4.50 (m, 1H), 6.19 (dt, *J* = 15.9, 7.0 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 7.24-7.18 (m, 1H), 7.28-7.36 (m, 4H), 9.70 (d, *J* = 3.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 27.5, 33.5, 78.4, 81.9, 110.8, 124.8, 126.3, 127.5, 128.6, 128.7, 133.3, 202.1.

***Z* product**

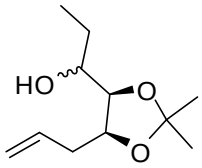
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.57 (s, 3H), 2.38-2.57 (m, 1H), 3.05-3.14 (m, 1H), 4.32 (dd, *J* = 7.3, 3.1 Hz, 1H), 4.42-4.50 (m, 1H), 5.69 (dt, *J* = 11.7, 7.0 Hz, 1H), 6.57 (d, *J* = 11.7 Hz, 1H), 7.24-7.18 (m, 1H), 7.28-7.36 (m, 4H), 9.60 (d, *J* = 3.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 29.1, 33.6, 78.2, 81.8, 108.7, 126.2, 126.4, 127.1, 128.4, 128.5, 137.0, 201.7.

HRMS (CI^+) calcd for $C_{15}H_{19}O_3$ (M^++H): 247.1334. Found 247.1337.

ν_{max} (film)/cm^{-1} 2988, 1732, 1494, 1381, 1070.

1-((4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol, 140



A -78 ˚C solution of oxalyl chloride (0.10 mL, 1.14 mmol) in THF (5 mL) in a flask wrapped in tin foil to eliminate light was treated with DMSO (0.15 mL, 2.26 mmol) and the reaction mixture was stirred for 30 minutes. A solution of alcohol **125** (100 mg, 0.58 mmol) in THF (5 mL) was added dropwise and the reaction mixture was stirred for 30 minutes at -78 ˚C before a triethylamine (0.60 mL, 4.28 mmol) was added and the mixture was allowed to warm up to room temperature over 30 minutes. The reaction mixture was cooled to –78 ˚C and ethylmagnesium bromide solution (3.0 M, 0.29 mL, 0.87 mmol) was added dropwise. The reaction was allowed to reach room temperature and stirred for 2 hours. The reaction was then quenched with saturated aqueous ammonium chloride (15 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (20 %) in 40-60 petroleum ether as the eluant) afforded **140** as a colourless oil (77 mg, 0.38 mmol, 66 %).

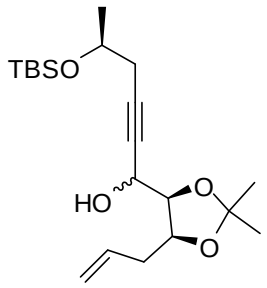
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.41 (s, 3H), 1.49 (s, 3H), 1.80 (ddd, *J* = 14.2, 7.6, 2.9 Hz, 2H), 1.91-2.11 (m, 2H), 2.28-2.36 (m, 2H), 2.43-2.51 (m, 2H), 3.25-3.32 (m, 1H), 3.63 (dt, *J* = 8.5, 2.9 Hz, 1H), 3.88 (dd, *J* = 8.5, 5.6 Hz, 1H), 3.95 (dd, *J* = 6.2, 4.6 Hz, 1H), 4.12-4.28 (m, 2H), 5.06-5.14 (m, 4H), 5.79-5.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 9.4, 10.3, 25.2, 25.9, 27.7, 27.7, 27.5, 28.3, 34.6, 35.0, 71.0, 71.1, 79.6, 80.0, 108.1, 108.2, 117.3, 134.9, 135.6.

LRMS calcd for $C_{11}H_{21}O_3$ (M^++H): 201.1491. Found 201.2.

ν_{max} (film)/cm^{-1} 3488, 2983, 2921, 1460, 1379, 1218, 1061.

(*S*)-1-((4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(*tert*-butyldimethylsilyloxy)hex-2-yn-1-ol, 141



A -78 ˚C solution of oxalyl chloride (0.08 mL, 0.96 mmol) in THF (3 mL), in a flask wrapped in tin foil to eliminate light, was treated with DMSO (0.14 mL, 1.97 mmol) dropwise and the reaction mixture was stirred for 30 minutes. A solution of alcohol **125** (110 g, 0.64 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 1 hour at -78 ˚C before triethylamine (0.40 mL, 2.86 mmol) and THF (5 mL) was added and the mixture was allowed to warm up to room temperature over 30 minutes. The reaction mixture was cooled to –78 ˚C and the solution of deprotonated alkyne was added and the reaction mixture was allowed to warm up to room temperature and stirred for 2 0.5 hours . The reaction was quenched with saturated aqueous ammonium chloride (15 mL), extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (0-10 %) in 40-60 petroleum ether as the eluant) afforded **141** as a mixture of diastereomers (128 mg, 0.35 mmol, 54 %).

Deprotonation of alkyne **99**

To a solution of alkyne **99** (250 mg, 1.28 mmol) in THF (5 mL) at room temperature was added ethylmagnesium bromide solution (3.0 M, 0.32 mL, 0.96 mmol) and stirring was continued for 2 hours.

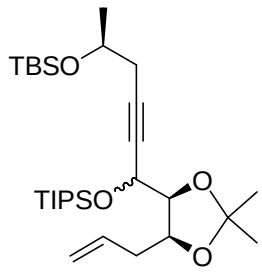
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10-0.18 (m, 6H), 0.88-0.90 (m, 9H), 1.22-1.25 (m, 3H), 1.33-1.35 (m, 3H), 1.47-1.52 (m, 3H), 2.24-2.74 (m, 5H), 3.90-3.99 (m, 1H), 4.02-4.09 (m, 1H), 4.18-4.28 (m, 1H), 4.39-4.47 (m, 2H), 5.06-5.16 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, -4.5, 18.3, 23.4, 23.5, 25.5, 25.5, 25.9, 27.6, 28.1, 29.8, 29.9, 33.9, 34.1, 61.4, 62.4, 67.5, 67.6, 76.8, 77.4, 79.8, 80.4, 84.9, 85.1, 108.7, 108.9, 117.2, 117.3, 134.8, 135.1.

HRMS (FAB^+) calcd for $C_{20}H_{37}O_4Si$ (M^++H): 369.2461. Found 369.2462.

ν_{max} (film)/cm^{-1} 3448, 2955, 2930, 2857, 2345, 1638, 1218, 1098.

(*S*)-5-((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-diisopropyl-2,9,11,11,12,12-hexamethyl-4,10-dioxa-3,11-disilatridec-6-yne, 142



To a stirred solution of alcohol **141** (70 mg, 0.18 mmol) in DMF (3 mL) at room temperature was added imidazole (50 mg, 0.72 mmol) and triisopropylsilyl chloride (0.08 mL, 0.37 mmol) and stirred for 19 hours. Imidazole (30 mg, 0.37 mmol) and triisopropylsilyl chloride (0.04 mL, 0.19 mmol) were added and stirring continued for a further 5 hours before the addition of saturated aqueous sodium bicarbonate (30 mL) and extraction with 50 % EtOAC, 40-60 petroleum ether (30 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (1 %) in 40-60 petroleum ether as

the eluant) afforded **142** as an inseparable mixture of diastereoisomers (55:45) (60 mg, 0.12 mmol, 69 %).

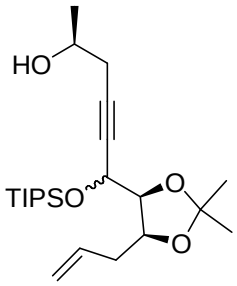
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04-0.07 (m, 12H), 0.87 (s, 9H), 0.88 (s, 9H), 1.09 (d, *J* = 5.6 Hz, 36H), 1.11-1.21 (m, 6H), 1.24 (d, *J* = 6.0 Hz, 6H), 1.34 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 2.24 (dt, *J* = 8.2, 1.9 Hz, 1H), 2.28 (dt, *J* = 8.2, 1.9 Hz, 1H), 2.37-2.60 (m, 6H), 3.89-3.97 (m, 2H), 4.08 (t, *J* = 6.2 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 1H), 4.19-4.24 (m, 2H), 4.53 (dt, *J* = 6.6, 2.0 Hz, 1H), 4.61 4.53 (dt, *J* = 6.4, 2.0 Hz, 1H), 5.07-5.13 (m, 4H), 5.84-5.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.6, 12.3, 12.8, 18.1, 18.3, 18.3, 23.3, 25.7, 25.8, 26.0, 27.9, 28.1, 29.9, 30.0, 34.3, 34.7, 62.8, 62.9, 63.2, 67.6, 67.7, 77.3, 77.4, 80.6, 80.6, 83.8, 85.0, 108.5, 108.8, 116.7, 116.8, 135.8, 135.8.

HRMS (CI^+) calcd for $C_{29}H_{58}O_4Si_2$ (M^++H): 525.3795. Found 525.3793.

ν_{max} (film)/cm^{-1} 3076, 2931, 2866, 2238, 1642, 1463, 1378, 1255, 1217, 1125.

((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(triisopropylsilyloxy)hex-4-yn-2-ol, 143



To a stirred solution of silyl ether **142** (110 mg, 0.21 mmol) in THF (3 mL) at 0 °C was added HF-Pyr:Pyr:THF solution (1:4:10, 2.4 mL) and stirred for 44 hours. The reaction was slowly quenched with saturated aqueous sodium bicarbonate (20 mL) and extracted with EtOAc (25 mL x 3). The organic layers were combined and washed with citric acid (5 %, 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (5 %) in 40-60 petroleum ether as the eluant) afforded **143** as a yellow oil in a 60:40 mixture of diastereomers (50 mg, 0.13 mmol, 60 %).

Major product

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 5.6 Hz, 18H), 1.12-1.18 (m, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 3H), 1.54 (s, 3H), 2.20-2.41 (m, 2H), 2.67-2.85 (m, 2H), 3.90-4.01 (m, 1H), 4.06-4.15 (m, 1H), 4.20-4.33 (m, 1H), 4.52 (dt, *J* = 5.1, 1.7 Hz, 1H), 5.06-5.13 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.0, 25.4, 27.3, 29.7, 32.0, 33.5, 63.4, 66.5, 77.5, 79.9, 80.3, 83.8, 108.7, 116.7, 135.5.

Minor product

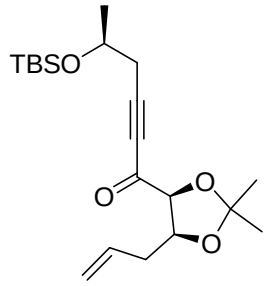
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 5.6 Hz, 18H), 1.12-1.18 (m, 3H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.36 (s, 3H), 1.48 (s, 3H), 2.20-2.41 (m, 2H), 2.67-2.85 (m, 2H), 3.90-4.01 (m, 1H), 4.06-4.15 (m, 1H), 4.20-4.33 (m, 1H), 4.59 (dt, *J* = 7.1, 2.2 Hz, 1H), 5.06-5.13 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 18.0, 25.6, 27.9, 29.5, 31.7, 34.3, 62.6, 63.3, 77.5, 80.7, 82.7, 83.6, 108.5, 116.9,135.2.

HRMS (FAB$^+$) calcd for $C_{23}H_{43}O_4Si$ (M^++H): 411.2931. Found 411.2928.

ν_{max} (film)/cm^{-1} 3442, 3076, 2943, 2866, 2234, 1642, 1379, 1216, 1063.

(*S*)-1-((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(*tert*-butyldimethylsilyloxy)hex-2-yn-1-one, 144



Method A

A mixture of alcohol **141** (60 mg, 0.15 mmol), 4 Å molecular sieves (150 mg) and NMO (30 mg, 0.22 mmol) in DCM (1 mL) was stirred at room temperature for 30

minutes. TPAP (3 mg, 0.007 mmol) was added and the reaction mixture was stirred for 14 hours before being filtered through a pad of silica and concentrated. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **101** as a yellow oil (36 mg, 0.098 mmol, 66 %).

Method B

A -78 °C solution of oxalyl chloride (0.03 mL, 0.34 mmol) in DCM (2 mL) was treated with DMSO (0.05 mL, 0.67 mmol) dropwise and the reaction mixture was stirred for 30 minutes. A solution of alcohol **141** (60 mg, 0.17 mmol) in DCM (1 mL) was added dropwise via canula followed by a DCM (1 mL) rinse and the reaction mixture was stirred for 1 hour at -78 °C before triethylamine (0.19 mL, 1.34 mmol) and DCM (2 mL) was added and the mixture allowed to warm up to room temperature over 45 minutes. DCM (5 mL) was added and the solution was washed with HCl (1 M) (5 mL) and saturated aqueous sodium bicarbonate (5 mL). The organic fraction was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (20 %) in 40-60 petroleum ether as the eluant) afforded **144** as a yellow oil (58 mg, 0.16 mmol, 94 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 3H), 1.62 (s, 3H), 2.21-2.30 (m, 1H), 2.36-2.42 (m, 1H), 2.48 (dd, *J* = 17.0, 6.6 Hz, 1H), 2.56 (dd, *J* = 17.0, 5.5 Hz, 1H), 4.03 (sext, *J* = 6.1 Hz, 1H), 4.41 (ddd, *J* = 9.5, 7.3, 3.9, Hz, 1H), 4.52 (d, *J* = 7.3 Hz, 1H), 5.08-5.14 (m, 2H), 5.77-5.87 (m, 1H).

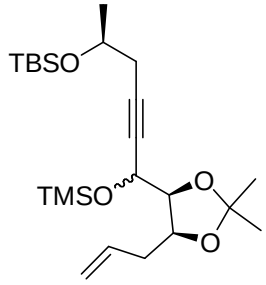
^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.6, 18.1, 23.7, 25.4, 25.9, 27.2, 30.2, 34.8, 66.9, 78.0, 81.7, 83.3, 96.5, 110.8, 117.8, 134.1, 186.5.

HRMS (FAB$^+$) calcd for $C_{20}H_{35}O_4Si$ (M^++H): 367.2305. Found 367.2307.

$[\alpha]^{26}_D$ –20.4 (c=1.0, $CHCl_3$)

ν_{max} (film)/cm^{-1} 3077, 2982, 2930, 2857, 2232, 1642, 1462, 1216.

(*S*)-4-((4S,5S)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,8,10,10,11,11-heptamethyl-3,9-dioxa-2,10-disiladodec-5-yne, 146



To a solution of alcohol **141** (120 mg, 0.32 mmol) in Et_2O (1 mL) at 0 °C was added trimethylsilyl chloride (0.06 mL, 0.49 mmol) and pyridine (0.05 mL, 0.58 mmol). The resulting white slurry was stirred at room temperature for 20 hours, diluted with 40-60 petroleum ether (2 mL), filtered through alumina and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with Et_2O (10-50 %) in 40-60 petroleum ether as the eluant) afforded **146** as an inseparable mixture of diastereoisomers (55:45) (120 mg, 0.27 mmol, 84 %) plus unreacted starting material (10 mg, 0.03 mmol, 9 %). Yield based on starting material recovered, 93 %.

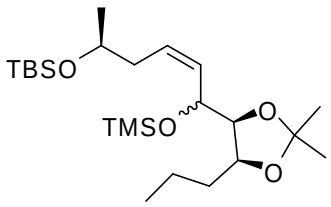
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05-0.06 (m, 12H), 0.18 (s, 18H), 0.88,(s, 18H), 1.20-1.26 (m, 6H), 1.34 (s, 6H), 1.47 (s, 3H), 1.48 (s, 3H), 2.25-2.33 (m, 4H), 2.35-2.59 (m, 4H), 3.91-3.98 (m, 2H), 4.08-4.13 (m, 2H), 4.23-4.30 (m, 2H), 4.30-4.42 (m, 2H), 5.08-5.18 (m, 4H), 5.82-5.92 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.6, -4.6, 0.5, 0.5, 18.2, 25.7, 26.0, 28.0, 29.5, 29.9, 30.0, 32.0, 34.1, 34.4, 62.6, 62.6, 67.5, 67.7, 77.3, 77.3, 80.2, 80.7, 81.1, 84.0, 108.4, 108.8, 116.8, 116.8, 135.5, 135.6.

HRMS (CI^+) calcd for $C_{23}H_{45}O_4Si_2$ (M^++H): 441.2856. Found 441.2853.

ν_{max} (film)/cm^{-1} 2965, 2921, 2856, 2222, 1250, 1083.

(8*S*,*Z*)-4-((4*S*,5*S*)-2,2-Dimethyl-5-propyl-1,3-dioxolan-4-yl)-2,2,8,10,10,11,11-heptamethyl-3,9-dioxa-2,10-disiladodec-5-ene, 147



To a stirred solution of alkyne **146** (110 mg, 0.26 mmol) in toluene (2 mL) was added palladium on barium sulphate (5 %) (90 mg) and quinoline (0.5 mL) at room temperature. The flask was evacuated and purged with hydrogen 5 times and hydrogen was bubbled through the solution for 10 minutes. After 5 hours under hydrogen the reaction mixture was filtered through celite and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (0-1 %) in 40-60 petroleum ether as the eluant) afforded **147** as a colourless oil and only as one diastereomer (13 mg, 0.03 mmol, 12 %).

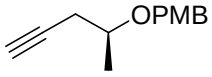
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.09 (s, 9H), 0.88 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.50-1.66 (m, 4H), 2.22-2.30 (m, 2H), 3.84-3.89 (m, 2H), 4.15-4.19 (m, 1H), 4.43 (dt, *J* = 8.9, 0.8 Hz, 1H), 5.41 (ddt, *J* = 11.1, 9.2, 1.8 Hz, 1H), 5.61 (ddt, *J* = 11.1, 7.1, 0.8 Hz, 1H).

^{13}C NMR (125MHz, $CDCl_3$) δ -4.5, -4.3, 0.9, 14.3, 19.9, 24.0, 25.5, 26.0, 28.3, 29.9, 32.1, 38.4, 67.4, 68.6, 77.8, 80.00, 107.5, 129.2, 132.1.

HRMS (EI^+) calcd for $C_{23}H_{48}O_4Si_2$ (M^++H): 444.3091. Found 444.3090.

ν_{max} (film)/cm^{-1} 2960, 2928, 2856, 1458, 1252, 1079.

1-(((*S*)-Pent-4-yn-2-yloxy)methyl)-4-methoxybenzene, 149[89]



To a suspension of sodium hydride (60 % in mineral oil, 490 mg, 12.35 mmol) in DMF (50 mL) at 0 °C was added a solution of the freshly generated crude alcohol **76** (0.81 g) in DMF (50 mL). The mixture was stirred for 15 minutes and the

para-methoxybenzyl chloride (1.9 mL, 14.3 mmol) was added. The reaction was allowed to reach room temperature and stirred for 18 hours. The reaction mixture was then poured onto brine (250 mL) and extracted with Et_2O (250 mL x 3). The organic fractions were concentrated at reduced pressure and washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with Et_2O (30 %) in 40-60 petroleum ether as the eluant) afforded **149** as a cloudy white oil (1.61 g, 7.88 mmol, 83 % over 2 steps).

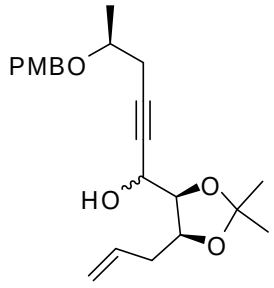
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, *J* = 6.1 Hz, 3H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.35 (ddd, *J* = 16.6, 7.1, 2.7 Hz, 1H), 2.49 (ddd, *J* = 16.6, 4.9, 2.7 Hz, 1H), 3.65-3.70 (m, 1H), 3.80 (s, 3H), 4.50 (s, 2H), 6.86-6.89 (m, 2H), 7.26-7.30 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 26.0, 55.1, 70.0, 72.8, 73.0, 81.2, 113.7, 129.1, 130.6, 159.1.

HRMS (EI^+) calcd for $C_{13}H_{16}O_2$ (M^+): 204.1150. Found 204.1152.

ν_{max} (film)/cm^{-1} 2972, 2933, 2836, 2119, 1612, 1586, 1513, 1247, 1034.

(S)-1-((4R,5S)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxybenzyloxy)hex-2-yn-1-ol, 150



A -78 °C solution of oxalyl chloride (0.25 mL, 2.90 mmol) in THF (10 mL), in a flask wrapped in tin foil to eliminate light was treated with DMSO (0.38 mL, 5.79 mmol) dropwise and the reaction mixture was stirred for 30 minutes. A solution of alcohol **125** (330 mg, 1.93 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred for 1 hour at -78 °C before triethylamine (1.2 mL, 8.61 mmol) and THF (5 mL) was added and the mixture allowed to warm up to room temperature over 30 minutes. The reaction mixture was cooled to –78 °C and the solution of deprotonated alkyne was added the reaction mixture was

allowed to warm up to room temperature and stirred for 2.5 hours. The reaction was quenched with saturated aqueous ammonium chloride (25 mL) and extracted with EtOAc (35 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10-20 %) in 40-60 petroleum ether as the eluant) afforded **150** as a 55:45 mixture of diastereomers and as a yellow oil (128 mg, 0.35 mmol, 54 %).

Deprotonation of alkyne **149**

To a solution of alkyne **149** (0.60 g, 2.92 mmol) in THF (15 mL) at room temperature was added ethylmagnesium bromide solution (3.0 M, 0.77 mL, 2.31 mmol) and stirring was continued for 2 hours.

Major product

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.1 Hz, 3H), 1.36 (s, 3H), 1.51 (s, 3H), 2.37-2.58 (m, 4H), 3.65-3.69 (m, 1H), 3.80 (s, 3H), 4.10-4.13 (m, 1H), 4.24-4.29 (m, 1H), 4.41-4.44 (m, 1H), 4.48 (s, 2H), 5.08-5.17 (m, 2H), 5.82-5.92 (m, 1H), 6.86-6.91 (m, 2H), 7.25-7.29 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 25.5, 26.6, 27.6, 33.9, 55.4, 62.4, 70.5, 73.1, 77.4, 79.8, 80.4, 84.5, 108.6, 113.9, 117.2, 129.4, 130.7, 135.1, 159.3.

Minor product

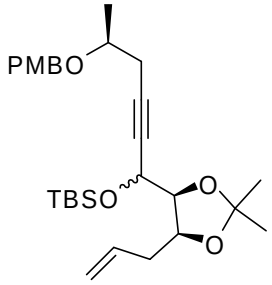
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 4.9 Hz, 3H), 1.38 (s, 3H), 1.49 (s, 3H), 2.37-2.58 (m, 4H), 3.65-3.69 (m, 1H), 3.81 (s, 3H), 4.10-4.13 (m, 1H), 4.24-4.29 (m, 1H), 4.41-4.44 (m, 1H), 4.47 (s, 2H), 5.08-5.17 (m, 2H), 5.82-5.92 (m, 1H), 6.86-6.91 (m, 2H), 7.25-7.29 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 25.5, 26.5, 28.1, 34.2, 55.4, 61.4, 70.5, 73.1, 77.4, 79.8, 80.4, 84.5, 108.6, 113.9, 117.2, 129.4, 130.7, 135.1, 159.3.

HRMS (CI^+) calcd for $C_{22}H_{31}O_5$ (M^++H): 375.2171. Found 375.2173.

ν_{max} (film)/cm^{-1} 3447, 3074, 2983, 2868, 2835, 1612, 1586, 1513, 1248, 1172.

((*S*)-1-((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxybenzyloxy)hex-2-ynyloxy)(*tert*-butyl)dimethylsilane, 151



To a solution of the alcohol **150** (370 mg, 1.0 mmol) in DCM (12 mL) at room temperature was added imidazole (200 mg, 3.0 mmol) and *tert*-butyldimethylsilyl chloride (190 mg, 1.25 mmol) and stirred for 20 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (10 mL) and extracted with DCM (15 mL x 3). The organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (15 %) in 40-60 petroleum ether as the eluant) afforded **151** as an inseparable mixture of diastereoisomers (55:45) yellow oil (420 mg, 0.09 mmol, 85 %).

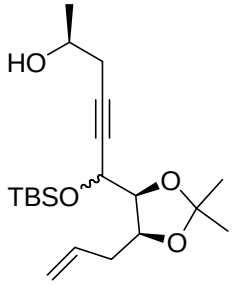
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10-0.18 (m, 16H), 0.89 (s, 9H), 0.91(s, 9H), 1.28 (d, *J* = 6.1 Hz, 3H), 1.29 (d, *J* = 6.1 Hz, 3H), 1.34 (s, 3H), 1.34 (s, 3H), 1.47 (s, 3H), 1.29 (s, 3H), 2.31-2.61 (m, 8H), 3.60-3.70 (m, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 4.02-4.12 (m, 2H), 4.16-4.23 (m, 2H), 4.42 (dt, *J* = 6.8, 2.0 Hz, 1), 4.47 (s, 2H), 4.49 (s, 2H), 5.00-5.10 (m, 3H), 5.11-5.14 (m, 1H), 5.83-5.94 (m, 2H), 6.85-6.88 (m, 4H), 7.24-7.28 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.4, -4.3, 18.2, 18.5, 19.8, 19.9, 25.7, 25.8, 25.9, 26.0, 26.4, 26.6, 27.9, 28.1, 34.3, 34.5, 55.4, 62.6, 63.1, 70.5, 70.5, 73.3, 73.4, 76.3, 76.4, 77.4, 80.3, 80.5, 108.5, 108.7, 113.9, 113.9, 118.2, 118.4, 129.3, 129.3, 130.7, 130.8, 134.9, 134.9, 159.2, 159.3.

ν_{max} (film)/cm^{-1} 3074, 2983, 2930, 2857, 1613, 1513, 1378, 1249, 1076.

HRMS (CI$^+$) calcd for $C_{28}H_{45}O_5Si$ (M^++H): 489.3036. Found 489.3040.

((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(*tert*-butyldimethylsilyloxy)hex-4-yn-2-ol, 152



To a stirred solution of PMB-ether **152** (230 mg, 0.47 mmol) in DCM (15 mL) at 0 °C was added pH 7 buffer (15 mL) and DDQ (140 mg, 0.61 mmol) and stirred for 2 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (20 mL) and extracted with DCM (40 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (0-10 %) in 40-60 petroleum ether as the eluant) afforded **152** as an inseparable mixture of diastereoisomers (55:45) yellow oil (140 g, 0.38 mmol, 81 %).

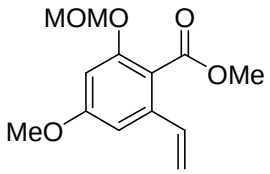
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.18 (s, 3H), 0.89 (s, 9H), 0.9, (s, 9H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.47 (s, 3H), 1.52 (s, 3H), 2.22-2.77 (m, 8H), 3.89-4.01 (m, 2H), 4.01-4.08 (m, 2H), 4.17-4.29 (m, 2H), 4.40 (dt, 5.4, *J* = 1.7 Hz, 1H), 4.46 (dt, J = 7.3, 2.1, 1H), 5.06-5.17 (m, 4H), 5.82-5.97 (m, 2 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, -4.5, 18.4, 23.8, 23.5, 25.3, 25.5, 25.9, 27.6, 28.1, 30.4, 31.4, 33.9, 34.1, 61.7, 62.1, 67.7, 67.1, 76.8, 77.8, 79.7, 80.4, 85.6, 85.7, 108.8, 109.0, 117.0, 117.2, 135.0, 135.4

HRMS (FAB^+) calcd for $C_{20}H_{37}O_4Si$ (M^++H): 369.2461. Found 369.2460.

ν_{max} (film)/cm^{-1} 3650, 2931, 2857, 2345, 1640, 1379, 1069.

Methyl 4-methoxy-2-(methoxymethoxy)-6-vinylbenzoate, 153



A 0 °C solution of phenol **108** (123 mg, 0.59 mmol) in acetone (2 mL) was treated with potassium carbonate (490 mg, 3.54 mmol), triethlyamine (0.45 mL, 3.25 mmol) and chloromethyl methyl ether (0.22 mL, 2.95 mmol) and was allowed to warm up to room temperature. Additional acetone (2 mL) was added to dilute the reaction mixture and stirring was continued for 17 hours. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous sodium hydroxide (5 mL) and HCl (1 M, 5 mL). The organic fraction was dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (5 %) in 40-60 petroleum ether as the eluant) to afford the desired product **153** as a colourless oil (81 mg, 0.32 mmol, 54 %) plus a unreacted starting material **108** (54 mg, 0.259 mmol, 44 %). Yield based on starting material recovered 97 %.

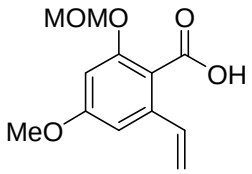
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 5.16 (s, 2H), 5.32 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.70 (dd, *J* = 17.3, 0.7 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (100MHz, $CDCl_3$) δ 52.3, 55.4, 94.9, 101.0, 103.7, 109.5, 116.5, 130.9, 137.4, 159.0, 161.1, 168.4.

HRMS (EI^+) calcd for $C_{13}H_{16}O_5$ (M^+): 252.0998. Found 252.0997.

ν_{max} (film)/cm^{-1} 3092, 3001, 2952, 2836, 1729, 1655, 1599, 1434, 1321, 1152, 1021.

4-Methoxy-2-(methoxymethoxy)-6-vinylbenzoic acid, 154



A solution of ester **153** (80 mg, 0.32 mmol) in dioxane (3 mL) was treated with aqueous sodium hydroxide (2 M, 2.4 mL, 4.76 mmol) and refluxed for 3 days. The reaction was allowed to cool down to room temperature, diluted with water (2 mL), acidified with HCl (1 M, 6 mL) and extracted with $CHCl_3$ (10 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc as the eluant) afforded **154** as an off white solid (61 mg, 0.26 mmol, 81 %).

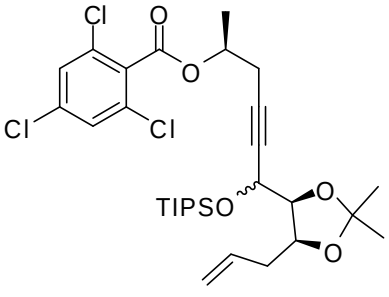
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.84 (s, 3H), 5.24 (s, 2H), 5.36 (d, *J* = 11.0 Hz, 1H), 5.70 (d, *J* = 17.3 Hz, 1H), 6.7 (d, *J* = 2.2 Hz, 1H), 6.8 (d, *J* = 2.2 Hz, 1H), 7.10 (dd, *J* = 17.3, 11.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 55.1, 56.6, 95.4, 100.8, 103.8, 114.1, 133.0, 139.7, 165.4, 165.9, 171.2.

HRMS (EI^+) calcd for $C_{12}H_{14}O_5$ (M^+): 238.0841. Found 238.0845.

ν_{max} (film)/cm^{-1} 2922, 1629, 1464, 1424, 1263.

((4S,5S)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(triisopropylsilyloxy)hex-4-yn-2-yl 2,4,6-trichlorobenzoate, 164



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.01 (s, 18H), 1.16-1.32 (m, 12H), 1.39-1.44 (m, 6H), 1.89-2.69 (m, 8H), 3.99-4.19 (m, 6H), 4.48 (d, *J* = 6.4 Hz, 1H),

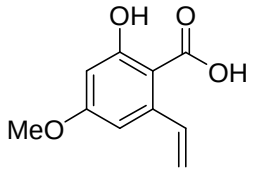
4.55 (d, *J* = 6.3 Hz, 1H), 4.93-5.07 (m, 2H), 5.17-5.26 (m, 2H), 5.72-5.82 (m, 2H), 7,28 (s, 2H), 7.30 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 12.4, 19.1, 19.2, 25.7, 25.9, 27.1, 28.0, 29.6, 34.1, 34.3, 35.2, 62.6, 63.0, 69.7, 69.9, 70.5, 80.0, 80.7, 82.2, 82.5, 84.0, 108.4, 108.7, 116.1, 117.0, 128.6, 132.6, 132.9, 135.1, 135.1, 138.8, 138.9, 142.3, 142.6, 161.1, 165.2.

HRMS (CI$^+$) calcd for $C_{30}H_{44}Cl_3O_5Si$ (M^++H): 617.2024. Found 617.2025

ν_{max} (film)/cm^{-1} 3079, 2941, 2864, 2347, 1743, 1579, 1548, 1460, 1271, 1118.

2-Hydroxy-4-methoxy-6-vinylbenzoic acid, 175



To a stirred solution of ester **108** (2.50g, 12.0 mmol) in dioxane (80 mL) was added aqueous NaOH (2.0 M, 90 mL, 180.2 mmol) and the resulting mixture was refluxed for 19 hours. The reaction was allowed to cool to room temperature and acidified with HCl (1 M, 250 mL) and extracted with $CHCl_3$ (350 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure to afford the crude residue. Washing the crude with 40-60 petroleum ether allowed the isolation of acid **175** as off white crystals (2.22 g, 11.43 mmol, 95 %).

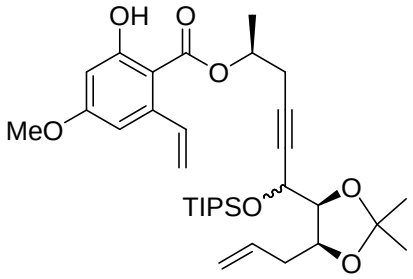
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.30 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.51 (dd, *J* = 17.1, 1.5 Hz, 1H), 6.44 (d, *J* = 2.6 Hz, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 7.38 (dd, *J* = 17.1, 10.8 Hz, 1H), 11.38 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 100.4, 102.4, 109.1, 116.7, 138.2, 145.0, 165.3, 166.1, 175.4.

HRMS (EI$^+$) calcd for $C_{10}H_{10}O_4$ (M^+): 194.0579. Found 194.0581.

ν_{max} (film)/cm^{-1} 2978, 1636, 1465, 1262, 1005.

((4S,5S)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(triisopropylsilyloxy)hex-4-yn-2-yl 2-hydroxy-4-methoxy-6-vinylbenzoate, 176



To a stirred solution of alcohol **143** (90 mg, 0.22 mmol) in DCM (3 mL) at room temperature was added DMAP (30 mg, 0.26 mmol), DCC (0.10 g, 0.49 mmol) and acid **175** (4 mg, 0.21 mmol) and stirred for 24 hours before being diluted with water (2 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (3 %) in 40-60 petroleum ether as the eluant) afforded **176** as an inseparable mixture of diastereoisomers (55:45) (4 mg, 0.07 mmol, 32 %).

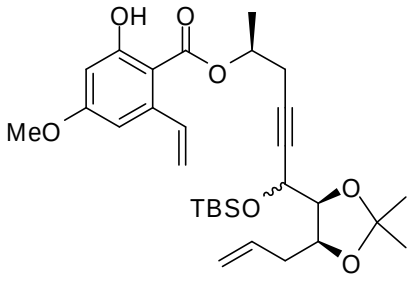
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03-1.08 (m, 12H), 1.10-1.20 (m, 12H), 1.23-1.29 (m, 12H), 1.31 (s, 6H), 1.33 (s, 6H), 1.45 (s, 6H), 2.49-2.71 (m, 8H), 3.82 (s, 6H), 4.10-4.16 (m, 2H), 4.16-4.22 (m, 2H), 4.51-4.56 (m, 1H), 4.58-4.62 (m, 1H), 5.05-5.07 (m, 2H), 5.16-5.27 (m, 4H), 5.41 (dd, *J* = 17.3, 1.1 Hz, 2H), 5.82-5.92 (m, 2H), 6.41 (d, *J* = 2.4 Hz, 2H), 6.50 (d, *J* = 2.4 Hz, 2H), 7.29-7.41 (m, 2H), 11.65 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 12.8, 18.1, 18.3, 19.6, 19.6, 26.1, 26.2, 27.8, 28.0, 29.9, 34.3, 34.6, 55.6, 62.8, 63.2, 70.7, 70.9, 77.3, 77.4, 80.5, 80.5, 81.7, 81.9, 82.0, 82.2, 100.3, 100.3, 103.8, 103.9, 108.5, 108.6, 108.6, 108.8, 115.6, 115.7, 116.8, 116.9, 135.6, 135.6, 138.7, 138.8, 144.0, 144.1, 164.3, 165.2, 165.2, 170.6.

HRMS (FAB^+) calcd for $C_{33}H_{50}O_7SiNa$ (M^++Na): 609.3224. Found 609.3220.

ν_{max} (film)/cm^{-1} 2935, 2865, 2345, 1653, 1608, 1255, 1063.

((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(*tert*-butyldimethylsilyloxy)hex-4-yn-2-yl 2-hydroxy-4-methoxy-6-vinylbenzoate, 177



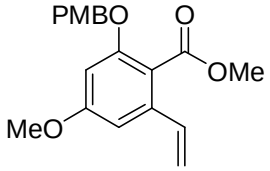
To a stirred solution of alcohol **152** (80 mg, 0.21 mmol) in DCM (3 mL) at room temperature was added DMAP (30 mg, 0.25 mmol), DCC (100 mg, 0.46 mmol) and acid **175** (40 mg, 0.21 mmol) and stirred for 40 hours before being diluted with water (2 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (75 %) in 40-60 petroleum ether as the eluant) afforded **177** as an inseparable mixture of diastereoisomers (55:45) (80 mg, 0.14 mmol, 68 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05-0.09 (m, 12H), 0.86-0.87 (m, 18H), 1.28-1.32 (m, 6H), 1.44-1.46 (m, 6H), 1.52-1.56 (m, 6H), 2.21-2.64 (m, 8H), 3.80 (s, 6H), 3.99-4.18 (m, 6H), 4.40 (dt, *J* = 6.6, 1.9 Hz, 2H), 4.45 (dt, *J* = 7.0, 1.9 Hz, 2H), 5.02-5.09 (m, 4H), 5.17-5.26 (m, 4H), 5.79-5.88 (m, 2H), 6.39 (d, *J* = 2.6 Hz, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 7.24-7.36 (m, 2H), 11.60 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.7, -4.6, 18.1, 18.3, 26.2, 26.1, 27.7, 28.5, 29.9, 34.3, 34.6, 55.6, 62.8, 63.2, 70.7, 70.9, 77.3, 77.4, 80.4, 80.5, 81.9, 82.0, 82.3, 82.2, 100.5, 100.6, 103.8, 104.0, 108.5, 108.6, 108.7, 108.8, 115.6, 115.8, 116.8, 117.0, 135.6, 135.9, 138.7, 140.0, 144.1, 144.6, 165.0, 165.2, 165.3, 170.6.

HRMS (CI^+) calcd for $C_{30}H_{45}O_7Si$ (M^++H): 545.2935. Found 545.2933.

Methyl 4-methoxy-2-[(4-methoxybenzyl)oxy]-6-vinylbenzoate, 178



A stirred solution of alcohol **108** (1.50 g, 7.20 mmol) in DMF (75 mL), potassium carbonate (1.49 g, 10.79 mmol), tetrabutylammonium iodide (270 mg, 0.73 mmol) and 4-methoxybenzyl chloride (1.46 mL, 10.79 mmol) was heated at 80 °C for 15 hours. The reaction was then allowed to cool down to room temperature, diluted with DCM (75 mL), washed with water (100 mL) and extracted with DCM (100 mL x 3). The organic fractions were concentrated at reduced pressure to reduce the volume and were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (20 %) in 40-60 petroleum ether as the eluant) afforded **178** as a colourless oil (2.25 g, 6.85 mmol, 95 %).

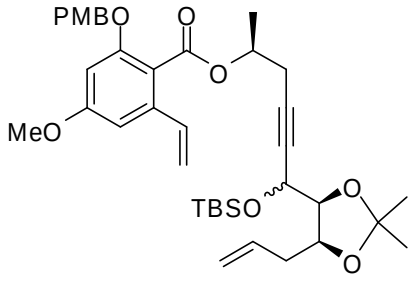
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 5.01 (s, 2H), 5.33 (dd, *J* = 10.9, 0.8 Hz, 1H), 5.71 (dd, *J* = 17.3, 0.8 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 6.66 (d, *J* = 2.2 Hz,1H), 6.73 (dd, *J* = 17.3, 10.9 Hz, 1H), 6.85-6.91 (m, 2H), 7.27-7.34 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 55.4, 55.6, 70.5, 100.0, 102.0, 114.0, 117.2, 128.7, 130.4, 133.9, 137.9, 157.4, 159.4, 161.5, 168.5.

HRMS (EI^+) calcd for $C_{19}H_{20}O_5$ (M^+): 328.1311. Found 328.1309.

ν_{max} (film)/cm^{-1} 2950, 1726, 1514, 1247, 1159, 1031.

((4*S*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(*tert*-butyldimethylsilyloxy)hex-4-yn-2-yl 4-methoxy-2-(4-methoxybenzyloxy)-6-vinylbenzoate, 180



To a stirred solution of alcohol **152** (80 mg, 0.21 mmol) in DCM (3 mL) at room temperature was added DMAP (30 mg, 0.25 mmol), DCC (100 mg, 0.46 mmol) and crude acid **179** (89 mg) and stirred for 16 hours before being diluted with water (2 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (0-20 %) in 40-60 petroleum ether as the eluant) afforded **180** as an inseparable mixture of diastereoisomers (55:45) (40 mg, 0.06 mmol, 31 %).

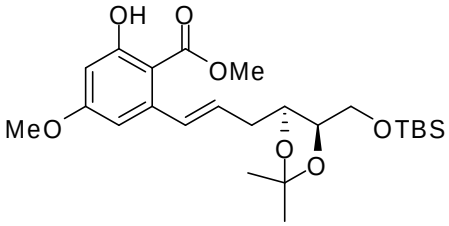
^{1}H NMR (400 MHz, $CDCl_3$) 0.06-0.13 (m, 12H), 0.87-0.89 (m, 18H), 1.25-1.26 (m, 6H), 1.32-1.35 (m, 6H), 1.45-1.47 (m, 6H), 2.35-2.69 (m, 8H), 3.78-3.80 (m, 12H), 4.01-4.20 (m, 6H), 4.39 (dt, *J* = 6.8, 1.9 Hz, 1H), 4.46 (dt, *J* = 6.9, 1.8 Hz, 1H), 4.97 (s, 4H), 5.04-5.12 (m, 4H), 5.13-5.30 (m, 2H), 5.31-5.36 (m, 2H), 5.68 (d, *J* = 0.8 Hz, 1H), 5.73 (d, *J* = 0.8 Hz, 1H), 5.79-5.91 (m, 2H), 6.43 (d, *J* = 2.1 Hz, 2H), 6.64 (d, *J* = 2.1 Hz, 2H), 6.87-6.89 (m, 2H), 7.27-7.31 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, -4.5, -3.8, 18.2, 18.4, 19.1, 19.2, 25.1, 25.7, 25.9, 25.9, 27.9, 28.1, 29.8, 34.0, 34.3, 34.5, 49.4, 55.4, 55.6, 62.6, 63.0, 69.7, 69.9, 70.5, 80.2, 80.5, 81.4, 81.9, 82.0, 82.2, 99.6, 101.8, 108.5, 108.7, 114.0, 116.8, 117.2, 117.2, 129.1, 128.5, 133.9, 135.6, 135.6, 137.8, 157.3, 159.6, 161.4, 167.2.

HRMS (FAB$^+$) calcd for $C_{38}H_{52}O_8SiNa$ (M^++Na): 687.3329. Found 687.3328.

ν_{max} (film)/cm^{-1} 3076, 2984, 2930, 2855, 1725, 1601, 1514, 1253, 1056.

Methyl 2-((*E*)-3-((4*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-enyl)-6-hydroxy-4-methoxybenzoate, 182



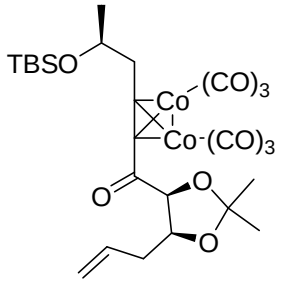
To a stirred solution of styrene **108** (0.05 g, 0.24 mmol) and alkene **192** (0.14 g, 0.48 mmol) in DCM (4 mL) was added Hoveyda-Grubbs Catalyst second Generation (0.05 g) and refluxed in the dark for 48 hours. The reaction mixture was allowed to cool down to room temperature and was filtered through silica and concentrated at reduced pressure. Purification by flash column chromatography (silica gel Et_2O (5 %) in 40-60 petroleum ether as the eluant) afforded **182** as a colourless oil (80 mg, 0.17 mmol, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.35 (s, 3H), 1.45 (s, 3H), 2.44-2.60 (m, 2H), 3.64-3.75 (m, 2H), 3.81 (s, 3H), 3.90 (s, 3H), 4.19-4.07 (m, 2H), 6.01 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.38 (d, *J* = 2.6 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H). 7.02 (d, *J* = 15.6 Hz, 1H), 11.65 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, -5.2, 18.4, 25.7, 26.0, 28.4, 33.2, 52.1, 55.5, 62.0, 77.3, 77.8, 99.9, 103.8, 108.1, 129.2, 133.0, 143.2, 164.1, 165.1, 171.9.

HRMS (CI^+) calcd for $C_{24}H_{39}O_7Si$ (M^++H): 467.2465. Found 467.2464

Cobalt Complex, 186



To a solution of alkyne **144** (80 mg, 0.22 mmol) in toluene (15 mL) at room temperature was added dicobalt octacarbonyl (150 mg, 0.44 mmol) and stirred for 16 hours. The reaction mixture was then filtered through celite and

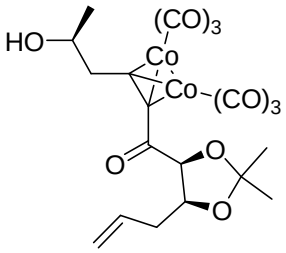
concentrated at reduced pressure to give the crude product. No further purification was carried out.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.33 (d, *J* = 6.0 Hz, 3H), 1.36 (s, 3H), 1.56 (s, 3H), 2.15-2.25 (m, 1H), 2.32-2.38 (m, 1H), 3.02-3.15 (m, 2H), 3.99-4.08 (m, 1H), 4.48-4.54 (m, 1H), 4.89 (d, *J* = 6.8 Hz, 1H), 5.05-5.12 (m, 2H), 5.76-5.89 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.7, 18.1, 24.7, 25.9, 27.7, 28.4, 33.7, 36.4, 69.8, 71.3, 74.9, 80.5, 109.1, 116.2, 135.4, 206.7.

ν_{max} (film)/cm^{-1} 2919, 1649, 1359, 1065.

Cobalt Complex, 188



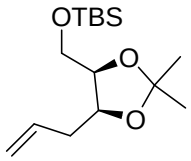
To a stirred solution of silyl ether **186** (140 mg, 0.22 mmol) in THF (4 mL) at 0 ˚C was added HF-Pyr:Pyr:THF solution (1:4:10, 6 mL) and stirred for 18 hours before being slowly quenched with saturated aqueous sodium bicarbonate (30 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined and washed with citric acid (5 %, 100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (10 %) in 40-60 petroleum ether as the eluant) afforded **188** as a dark red oil (50 mg, 0.09 mmol, 42 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.9 Hz, 3H), 1.36 (s, 3H), 1.57 (s, 3H), 2.17-2.29 (m, 1H), 2.64-2.39 (m, 1H), 2.64 (d, *J* = 4.4 Hz, 1H), 3.01 (dd, *J* = 15.8, 9.2 Hz, 1H), 3.12 (dd, *J* = 15.8, 2.7 Hz, 1H), 3.94-4.02 (m, 1H), 4.46-4.57 (m, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 5.06-5.14 (m, 2H), 5.78-5.89 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 25.3, 27.5, 35.7, 44.2, 68.5, 77.7, 82.3, 84.2, 97.44, 110.1, 118.1, 134.0, 198.4, 198.5, 198.5, 198.6, 198.6, 198.6, 204.5.

ν_{max} (film)/cm^{-1} 3567, 2920, 1654, 1457, 1060.

(((4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(tert-butyl)dimethylsilane, 192



To a stirred solution of alcohol **125** (1.87 g, 10.8 mmol) in DCM (50 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (2.17 g, 14.0 mmol), triethylamine (2.71 mL, 19.44 mmol) and DMAP (0.13 g, 1.1 mmol). The reaction mixture was stirred for 14 hours before being quenched with saturated aqueous ammonium chloride (50 mL) and extracted with DCM (50 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (30-50 %) in 40-60 petroleum ether as the eluant) afforded **192** as a colourless oil (2.94 g, 10.3 mmol, 95 %).

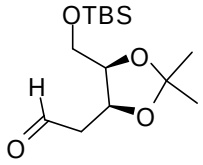
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.34 (s, 3H), 1.43 (s, 3H), 2.29-2.45 (m, 2H), 3.61-3.71 (m, 2H), 4.09-4.13 (m, 1H), 4.19-4.23 (m, 1H), 5.08-5.15 (m, 2H), 5.84-5.94 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, -5.4, 18.3, 25.2, 25.9, 28.2, 33.9, 61.9, 77.1, 77.8, 107.9, 116.8, 135.3.

HRMS (CI^+) calcd for $C_{15}H_{31}O_3Si$ (M^++H): 287.2042. Found 287.2046.

ν_{max} (film)/cm^{-1} 2954, 2931, 1643, 1472, 1257, 1100.

2-((4*S*,5*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde, 193[90]



A solution of alkene **192** (0.62 g, 2.2 mmol) in DCM (20 mL) was cooled to -78 ˚C. O_3 was then bubbled through the solution for 1 hour before being purged with oxygen and allowed to warm up to room temperature. The reaction mixture was treated with triphenylphosphine (0.75 g, 2.86 mmol), stirred vigorously overnight and concentrated at reduced pressure. The crude was dissolved in Et_2O (15 %) in 40-60 petroleum ether, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with DCM (15-100 %) in 40-60 petroleum ether as the eluant) afforded **193** as a colourless oil (210 mg, 0.73 mmol, 34 %) plus unreacted starting material **192** (430 mg, 1.43 mmol, 66 %). Yield based on starting material 100 %.

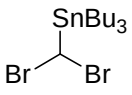
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.05 (s, 3H), 0.87 (s, 9H), 1.35 (s, 3H), 1.41 (s, 3H), 2.76 (ddd, *J* = 17.1, 7.9, 1.8 Hz, 1H), 2.87 (ddd, *J* = 17.1, 5.9, 1.3 Hz, 1H), 3.60-3.63 (m, 2H), 4.14-4.19 (m, 1H), 4.79 ((dd, *J* = 7.9, 5.9 Hz, 1H), 9.79 (t, *J* = 1.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, -5.3, 18.3, 25.1, 25.9, 27.5, 39.9, 61.8, 76.8, 78.0, 108.7, 197.4.

HRMS (CI^+) calcd for $C_{14}H_{29}O_4Si$ (M^++H): 289.1835. Found 289.1839

ν_{max} (film)/cm^{-1} 2989, 2957, 2930, 2857, 1716, 1255, 1078.

(Dibromomethyl)tributylstannane, 195[72]



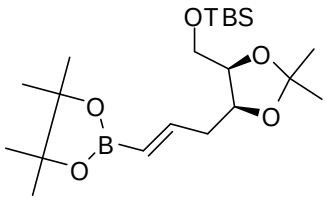
A 0 ˚C stirred solution of diisopropylamine (0.58 mL, 4.2 mmol) in THF (4 mL) and Et_2O (6 mL) was treated with n-butyllithium (2.5 M in hexanes, 1.45 mL, 3.6 mmol) and stirred for 15 minutes at 0 ˚C before being cooled to –95 ˚C. A

solution of dibromomethane (0.27 mL, 3.9 mmol) in THF (3 mL) was added slowly to the reaction mixture and stirring continued for 15 minutes at –90 °C. A solution of tributyltin chloride **194** (1.17 mL, 3.0 mmol) in THF (3 mL) was added slowly and the reaction was allowed to warm to –63 °C for 1 hour. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and allowed to rapidly warm to room temperature before removal of most of the solvents at reduced pressure. The concentrated reaction mixture was diluted with water (9 mL) and 40-60 petroleum ether (15 mL) and filtered through celite then finally extracted with 40-60 petroleum ether (15 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with in 40-60 petroleum ether as the eluant) afforded **195** as a colourless oil (1.13 g, 2.44 mmol, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.3 Hz, 9H), 1.11-1.16 (m, 6H), 1.30-1.39 (m, 6H), 1.57-1.62 (m, 6H), 5.32 (t, *J* = 10.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 13.8, 27.4, 28.6, 28.7.

tert-Butyl(((4*R*,5*S*)-2,2-dimethyl-5-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane, 204



To a solution of alkene **192** (200 mg, 0.69 mmol) in DCM (2 mL) was added vinylboronic acid pinicol ester (0.08 mL, 0.48 mmol) and Grubbs first generation catalyst (2.5 %, 0.015 g) and refluxed in the dark for 13 hours. The reaction mixture was allowed to cool down to room temperature, filtered through celite and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with Et_2O (5 %) in 40-60 petroleum ether as the eluant) afforded **204** as a yellow oil as a 4:1 mixture of E:Z isomers (203 mg, 0.49 mmol, 73 %).

_E_ product

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.26 (s, 12H), 1.37 (s, 3H), 1.42 (s, 3H), 2.25-2.61 (m, 2H), 3.57-3.77 (m, 2H), 4.06-4.30 (m, 2H), 5.55 (dt, *J* = 18.0, 1.5 Hz, 1H), 6.68 (dt, *J* = 18.0, 6.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 5.3, 18.3, 24.9, 25.7, 26.0, 28.3, 35.9, 62.0, 76.5, 77.8, 83.2, 108.1, 150.5.

HRMS (CI^+) calcd for $C_{21}H_{42}BO_5Si$ (M^++H): 413.2895. Found 413.2890.

ν_{max} (film)/cm^{-1} 2956, 2856, 1655, 1437, 1068.

_Z_ product

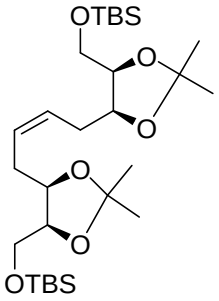
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 1.26 (s, 12H), 1.42 (s, 3H), 1.44 (s, 3H), 2.25-2.61 (m, 2H), 3.57-3.77 (m, 2H), 4.06-4.30 (m, 2H), 5.48 (dt, *J* = 13.6, 1.5 Hz, 1H), 6.54 (dt, *J* = 13.6, 7.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 5.4, 18.4, 25.0, 25.7, 26.0, 27.8, 32.3, 62.0, 77.6, 78.0, 83.0, 108.0, 151.6.

HRMS (CI^+) calcd for $C_{21}H_{42}BO_5Si$ (M^++H): 413.2895. Found 413.2890.

ν_{max} (film)/cm^{-1} 2929, 2856, 1631, 1424, 1259, 1076

(*Z*)-1-((4*R*,5*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((4*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ene, 212



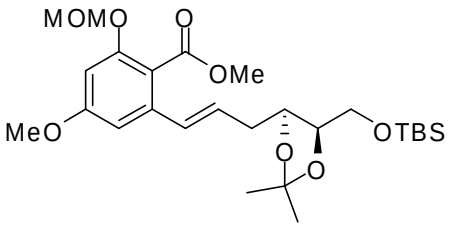
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 12H), 0.88 (s, 18H), 1.33 (s, 3H), 1.42 (s, 3H), 2.32-2.38 (m, 4H), 3.54-3.71 (m, 4H), 4.07-4.20 (m, 4H), 5.61 (d, *J* = 3.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, -5.2, 18.4, 25.7, 26.1, 28.3, 32.8, 62.1, 77.7, 78.0, 108.0, 129.1.

HRMS (CI^+) calcd for $C_{28}H_{57}O_6Si_2$ (M^++H): 545.3694. Found 545.3689

ν_{max} (film)/cm^{-1} 2956, 2930, 2857, 1655, 1472, 1378, 1255, 1100.

Methyl 2-((*E*)-3-((4*S*,5*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-enyl)-4-methoxy-6-(methoxymethoxy)benzoate, 213



To a stirred solution of alcohol **210** (1.29 g, 2.77 mmol) in DCM (30 mL) at room temperature was added *N*,*N*-diisopropylethylamine (1.45 mL, 8.32 mmol). The reaction mixture was cooled down to 0 °C and bromomethyl methyl ether (0.45 mL, 5.51 mmol) was added and the solution was allowed to warm up to room temperature and stirred for 19 hours. The reaction was quenched with saturated aqueous sodium bicarbonate (25 mL), extracted with Et_2O (35 mL x 3),

dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (15 %) in 40-60 petroleum ether as the eluant) afforded **213** as a colourless oil (1.27 g, 2.48 mmol, 90 %).

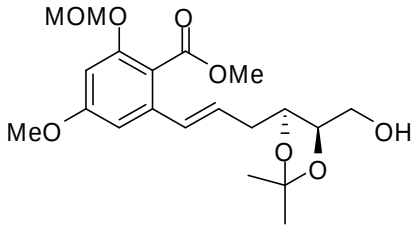
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.34 (s, 3H), 1.43 (s, 3H), 2.46-2.53 (m, 2H), 3.45 (s, 3H), 3.65-3.70 (m, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 4.11-4.15 (m, 1H), 4.20-4.25 (m, 1H), 5.15 (s, 2H), 6.23-6.31(m, 1H), 6.43 (d, *J* = 15.7 Hz, 1H), 6,59 (d, *J* = 2.2 Hz, 1H), 6.70 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, -5.2, 18.4, 25.7, 26.0, 28.3, 33.4, 52.3, 55.6, 56.3, 62.0, 77.2, 77.9, 95.0, 100.9, 103.7, 108.2, 116.6, 128.6, 130.6, 137.7, 155.7, 161.4, 168.5.

HRMS (CI^+) calcd for $C_{26}H_{43}O_8Si$ (M^++H): 511.2727. Found 511.2721

ν_{max} (film)/cm^{-1} 2955, 2929, 2856, 1654, 1610, 1327, 1159, 1097.

(S)-1-((4R,5S)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(4-Methyl 2-((*E*)-3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-1-enyl)-4-methoxy-6-(methoxymethoxy)benzoate, 214



A solution of silyl ether **213** (60 mg, 0.12 mmol) in THF (2 mL) at room temperature was treated with TBAF (1 M, 0.23 mL, 0.23 mmol) and stirred for 30 minutes. The reaction was quenched with saturated aqueous ammonium chloride (2 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated at reduced pressure. Purification by flash column chromatography (silica gel with EtOAc (50-75 %) in 40-60 petroleum ether as the eluant) afforded **214** as an off white oil (50 mg, 0.12 mmol, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.50 (s, 3H), 1.86 (t, *J* = 6.1 Hz, 1H), 2.39-2.48 (m, 1H), 2.50-2.59 (m, 1H), 3.46 (s, 3H), 3.68 (t, *J* = 5.8 Hz, 2H), 3.82 (s, 3H), 3.90 (s, 3H), 4.21 (q, *J* = 5.8 Hz, 1H), 4.29 (dt, *J* = 8.0, 5.8 Hz, 1H), 5.16 (s, 2H), 6.19 (ddd, *J* = 15.6, 7.8, 6.1 Hz, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H).

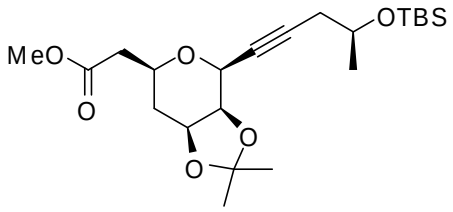
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 28.0, 33.2, 52.2, 55.4, 56.1, 61.3, 76.3, 77.8, 94.7, 100.6, 103.6, 108.2, 116.2, 128.8, 129.6, 137.3, 155.5, 161.2, 168.4.

HRMS (EI^+) calcd for $C_{20}H_{28}O_8$ (M^+): 396.1784. Found 396.1788

ν_{max} (film)/cm^{-1} 3503, 2988, 2937, 1727, 1601, 1576, 1433, 1267, 1154, 1047.

$[\alpha]^{25}_D$ -5.6 (c=1.0, CH_2Cl_2)

Methyl 2-((3S,4S,6R,7S)-4-((S)-4-(tert-butyldimethylsilyloxy)pent-1-ynyl)-2,2-dimethyltetrahydro-3αH-[1,3]dioxolo[4,5-]pyran-6-yl)acetate, 219



219

A stirred solution of alcohol **100** (292 mg, 0.68 mmol) in diethyl ether (20 ml) at -78 °C was treated with potassium tert butoxide (0.083 g , 0.68 mmol) and stirred for 3 hours at -78 °C. The reaction was quenched with a saturated ammonium chloride solution (15 ml) and extracted with EtOAc (30 ml). The organic layers were combined, dried over $NaSO_4$, filtered and concentrated under vaccum. Purification by flash column chromatography (silica gel, with EtOAc (2.5 %) in 40-60 petroleum ether as the eluant) generated the desired pyran rings **219** (32 mg, 0.08 mmol, 12 %) and **220** (145 mg, 0.34 mmol, 50 %). Unreacted starting alcohol **100** (46 mg, 0.11 mmol, 16 %) was also cleanly recovered.

^{1}H NMR (500MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.23-1.26 (m, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 2.30 (ddd, *J* = 16,5, 7.0,

2.2 Hz, 1H), 2.36-2.42 (m, 2H), 2.43-2.51 (m, 2H), 2.67 (dd, *J* = 15.6, 7.2 Hz, 1H), 3.97 (dd, *J* = 12.6, 5.9 Hz, 1H), 4.08 (dd, *J* = 5.2, 1.7 Hz, 1H), 4.27-4.33 (m, 1H), 4.08 (dt, *J* = 4.1, 1.7 Hz, 1H), 4.87-4.89 (m, 1H)

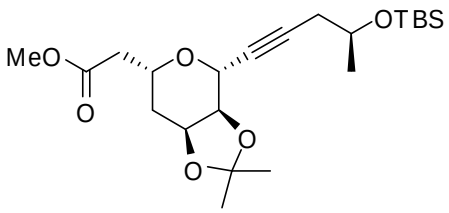
^{13}C NMR (125MHz, $CDCl_3$) δ-4.7, -4.5, 18.2, 23.5, 25.9, 26.5, 29.8, 31.1, 34.0, 40.0, 51.9, 60.6, 65.9, 67.9, 70.6, 74.9, 77.7, 109.4, 171.3

ν_{max}(film)/cm^{-1} 2253 (m), 1726 (w), 1215 (s)1096 (m)

HRMS calcd for $C_{22}H_{39}O_6Si_1$ (M^++H); 427.2510. Found 427.2492

$[\alpha]^{20}_D$ -4.3 (c=0.5, $CHCl_3$)

Methyl 2-((3S,4R,6R,7S)-4-((S)-4-(tert-butyldimethylsilyloxy)pent-1-ynyl)-2,2-dimethyltetrahydro-3αH-[1,3]dioxolo[4,5-]pyran-6-yl)acetate, 220



^{1}H NMR (500MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.37 (s, 3H), 1.51 (s, 3H), 1.72 (ddd, *J*= 14.8, 11.8, 4.0 Hz, 1H), 2.14 (dt, *J* = 14.9, 2.2 Hz, 1H), 2.27 (ddd, *J* = 16.5, 7.3, 2.0 Hz, 1H), 2.42 (m, 1H), 2.40 (m, 1H), 2.64 (dd, *J* = 15.6, 7.4 Hz, 1H), 3.69 (s, 3H), 3.96 (m, 2H), 4.06 (m, 2H), .4.37 (m, 1H)

^{13}C NMR (125MHz, $CDCl_3$) δ -4.6, -4.6, 18.2, 23.6, 26.0, 26.2, 28.4, 30.0, 32.4, 40.5, 51.9, 60.4, 67.8, 69.5, 72.0, 75.4, 84.1, 109.6, 171.1.

ν_{max}(film)/cm^{-1} 2251, 1745, 1351, 1050.

HRMS calcd for $C_{22}H_{39}O_6Si_1$ (M^++H); 427.2510. Found 427.2492

$[\alpha]^{20}_D$ +32.9 (c=1.5, $CHCl_3$)

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5 Appendix

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Fast and efficient synthesis of the complete LL-Z1640-2 framework

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Received 30 April 2007; revised 18 June 2007; accepted 27 June 2007
Available online 4 July 2007

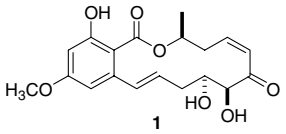
Abstract—The convergent synthesis of the complete LL-Z1640-2 framework has been completed. This fast and efficient approach provides flexible access into the resorcyclic lactones.

TAK1 is a member of the mitogen-activated protein kinase kinase kinase (MAPKKK) family that phosphorylate and activate MKK3, MKK4, MKK6 and MKK7 MAPKKs, which in turn activate the c-Jun N-terminal kinase (JNK) and p38 MAPKs.[1] It has also been recently demonstrated that TAK1 activates IkB kinases (IKKs), ultimately leading to activation of the transcription factor NF-κB.[2]

A significant amount of work has been devoted in trying to understand TAK1 and its role in the areas of cell apoptosis, and tumour necrosis, as well as on proinflammatory diseases. Several lines of evidence tend to suggest that TAK1 is a key participant in proinflammatory signalling pathways, i.e., by activating both JNK/p38 MAPKs and IKKs in the interleukin 1 (IL-1) signalling pathway.[3] The mechanism by which the IL-TAK1 signalling pathway is positively and negatively regulated remains poorly understood, and their physiological functions remain to be clarified. However, it is believed that selective inhibition of TAK1 might be effective in preventing inflammation and tissue destruction promoted by proinflammatory cytokines.[4]

As a part of our biological chemistry programme in understanding inflammatory responses, we were interested in the development of a potent and selective set of chemical genetic probes that would allow us to understand better the role of TAK1.

LL-Z1640-2 (also known as 5*Z*-7-oxo-zeaenol and C292) (**1**) was isolated in 1978 from the culture broth of fungal strain f6024.[5] Although it was originally classified as an anti-protozoan agent, it was not until 1999 that its cytokine release inhibiting activity was discovered.[6] LL-Z1640-2 (**1**) has been shown to be a selective protein tyrosine kinase inhibitor, not inhibiting either protein kinase A (PKA) or protein kinase C (PKC).[7]



1

Significantly, preliminary data suggest that LL-Z1640-2 (**1**), can selectively and irreversibly inhibit the kinase activity of purified TAK1 at very low concentrations (IC_{50} 8.1 nM). Furthermore, **1** had no effect on the kinase activity of other members of the MAPKKK family (MEKK1 and ASK1).[7] In addition LL-Z1640-2 (**1**) has also been reported as having significant activity versus tumour necrosis factor-alpha (TNF-α) production in cells with an IC_{50} of 6 nM.[6]

LL-Z1640-2 (**1**) is structurally related to the 14-membered macrocyclic lactones hypothemycin (**2**), 87-250904-F1 (**3**), zeaenol (**4**), 7-oxo-zeaenol (**5**), radicicol (**6**), and various simpler zearalanone and zearalanols (Fig. 1). However, **1** is unique amongst the resorcyclic lactones in its potency in targeting TAK1, raising the prospect of becoming a truly selective starting point in chemical genetics research.[8]

Keywords: LL-Z1640-2; Resorcyclic lactones; Anti-inflammatory.
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doi:10.1016/j.tetlet.2007.06.151

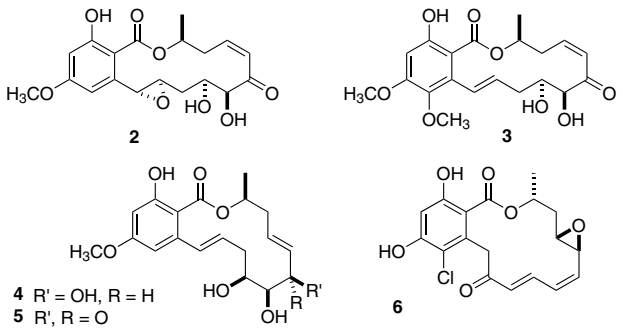


Figure 1.

Although there has been a significant amount of work dedicated to the synthesis of radicicol **6** by Danishefsky and co-workers, efforts towards LL-Z1640-2 (**1**), have been rather limited. This lack of synthetic interest has translated into a lack of chemical genetic probes through which the active site of TAK1 could be explored and understood.[9,10]

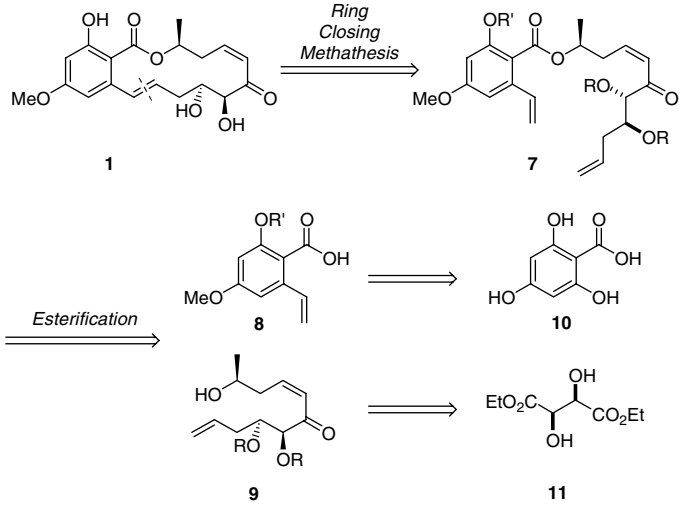
Herein, we report a flexible and efficient approach to the synthesis of the complete LL-Z1640-2 (**1**) framework and its C9 epimer, which molecular modelling should be useful in helping elucidate the conformation of LL-Z1640-2 (**1**) within the TAK1 active site. We believe that our robust and cost effective approach provides the foundations which will allow these compounds to be considered as realistic chemical biological leads for the first time.

Our convergent retrosynthetic analysis called for the cleavage of the macrocyclic ring at the ester functionality and the benzylic double bond, generating the vinyl benzoic acid **8** and C1–C10 alcohol **9** (Scheme 1).

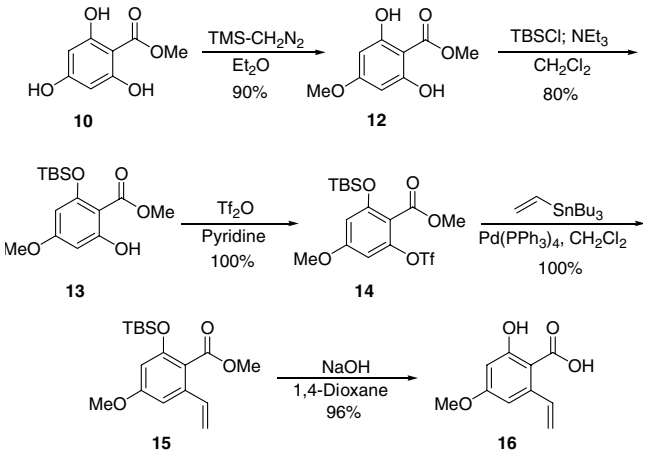
The synthesis of the vinyl benzoic acid unit **8** began with commercially available methyl 2,4,6-trihydroxybenzoate **10** which was methylated selectively at the C4 position to afford the desired diol **12** in excellent yield.[11] Monosilylation of diol **12** proceeded in good yield to produce the TBS silyl ether **13**, which was then converted to the corresponding triflate **14** in quantitative yield (Scheme 2).

A Stille coupling of the newly generated aryl triflate with vinyltributyl tin proceeded in excellent yield to afford the desired vinyl benzene **15**. Finally, saponification of the methyl ester proceeded with concomitant desilylation to generate the free benzoic acid **16** in near quantitative yield.

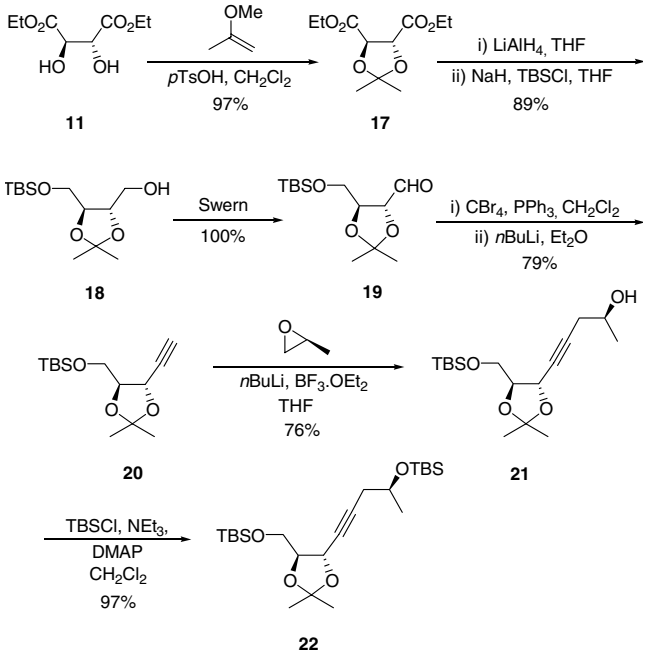
Our synthesis of the aliphatic C1–C10 unit began with readily available (L)-(+)-diethyl tartrate **11** which was protected as the dimethyl ketal **17**. Reduction of the diester functionality generated the corresponding diol unit, which upon selective hydroxyl group silylation provided TBS ether **18** in excellent yield.[12] Swern oxidation of alcohol **18** proceeded in quantitative yield to generate the expected aldehyde **19**, which upon treatment under Corey–Fuchs olefination conditions gave the desired alkyne **20** in high yield. The newly generated alkyne **20** was then alkylated with (*S*)-propylene oxide under



Scheme 1.



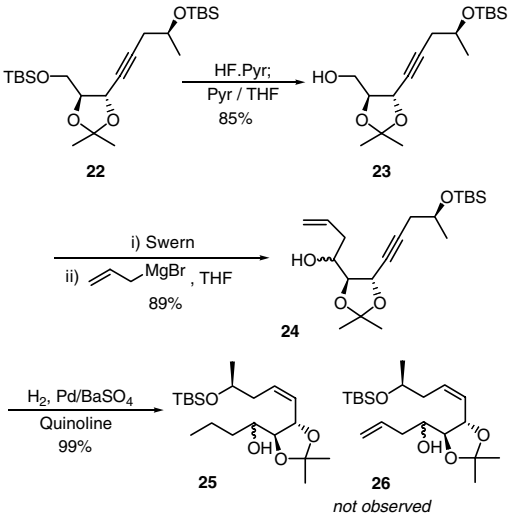
Scheme 2.



Scheme 3.

highly activated conditions to afford the desired internal alkynol **21** as a single diastereomer in good yield. Silylation proceeded efficiently to generate the bis-TBS silyl ether **22** in very high yield (Scheme 3).

The last steps of the synthesis of the C1–C10 unit began with selective deprotection of the primary TBS silyl ether of alkyne **22** under carefully monitored conditions to afford the desired primary alcohol **23** in good yield. Rewardingly, a one-pot oxidation–allylation sequence proceeded to generate homoallylic alcohol **24** as a mixture of diastereomers (1:1) in excellent yield over the two steps (Scheme 4). No attempt was made to control the stereochemistry of allylation as we wanted to access both LL-Z1640-2 and its C9 anomer for biological evaluation.



Scheme 4.

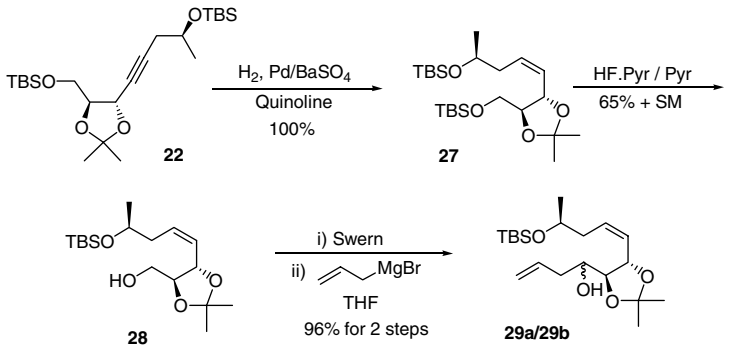
Having successfully completed the synthesis of the C1–C10 unit, we focused our attention on the conversion of the alkyne unit into the *Z*-alkene functionality present in LL-Z1640-2 (**1**). Unfortunately, despite repeated experimentation, all hydrogenation attempts failed to provide us with the desired diene unit **26**, affording instead the over-reduced alkane **25**. We believe that this over-reduction could be attributed to the presence of the free homoallylic alcohol unit.

The loss of the key terminal alkene functionality during the introduction of the internal alkene moiety prompted us to re-evaluate the synthetic route. Our modified approach to the synthesis of the C1–C10 unit of LL-Z1640-2 began with the previously obtained bis-TBS ether **22**, which was selectively reduced to generate the *Z*-olefin **27** in quantitative yield and with complete stereocontrol. Selective TBS group removal then provided primary alcohol **28** in good yield. A similar one-pot Swern oxidation–allylation procedure to that used previously proceeded cleanly and in excellent yield to complete the syntheses of the C1–C10 fragments of LL-Z1640-2 and 9-*epi*-LL-Z1640-2, **29a** and **29b**, respectively (Scheme 5).

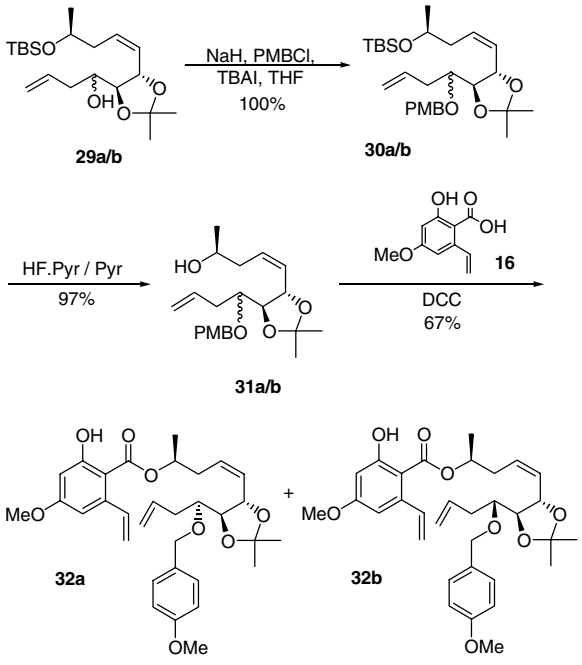
Having successfully introduced both alkene units with complete stereocontrol, we decided to introduce the remaining units of the LL-Z1640-2 framework. Hence, alkenes **29a/29b** were protected to give the corresponding PMB ethers **30a/b** in quantitative yield. Careful removal of the secondary TBS silyl ether afforded secondary alcohols **31a/b** required for the esterification (Scheme 6).

Gratifyingly, reaction of alcohols **31a/b** with the previously described vinyl benzoic acid **16** proceeded cleanly to generate esters **32a** and **32b** incorporating the entire LL-Z1640-2 (**1**) and the 9-*epi*-LL-Z1640-2 frameworks in good overall yields.

In conclusion, we have demonstrated a fast, high yielding and flexible approach to the synthesis of LL-Z1640-2



Scheme 5.



Scheme 6.

(**1**) and its C9-epimer taking advantage of two-directional chain functionalisation and of an efficient synthetic pathway. The completion of the synthesis as well as the results of our biological assessment of all the intermediates will be reported in due course.

Acknowledgements

We thank the Cunningham Trust, and the EPSRC for supporting this work. M.N.R. thanks the BBSRC for a postgraduate studentship. R.M. thanks Dr. Ian Sword and the University of Glasgow, for financial support.

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