STUDIES TOWARDS THE SYNTHESIS OF PELORUSIDE A

by

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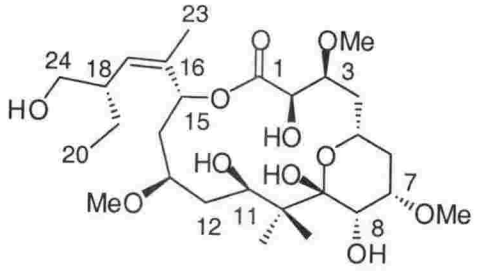
Abstract

In the search for new treatments for cancer, advances in biology have provided targets for the destruction of cancer cells. One such structure the microtubule, a protein required for cell division, has been the target of many successful anticancer agents including the multi-million dollar earning Taxol® (paclitaxel) and the epothilones, currently in late-stage clinical trials. More recently it has been shown that peloruside A **1**, a secondary metabolite isolated from the New Zealand marine sponge *Mycale hentscheli*, prevents cell division by stabilising microtubules, and thus offers promise as a novel anticancer agent. However, due to its limited natural abundance, significant quantities of peloruside A can only be obtained through chemical synthesis.



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A retrosynthetic analysis of peloruside A divided the molecule into four key fragments:

a) the commercially available C-1 to C-2 benzyloxy acetic acid fragment;
b) the C-3 to C-7 fragment;
c) the C-8 to C-11 fragment and
d) the remaining C-12 to C-24 portion of the macrocycle and side chain.

The C-3 to C-7 and C-8 to C-11 fragments combine to form a key intermediate pyranose ring. This thesis however, addresses the synthesis of two of these key fragments, namely the C-8 to C-11 and C-12 to C-24 fragments.

An efficient synthesis of the C-8 to C-11 fragment of peloruside A, starting from commercially available pantolactone, has been developed. This synthesis proceeds in good overall yield, and has been successfully reproduced on the multigram scale. The significant portion of this thesis, however, is dedicated to the synthesis of the C-12 to C-24 fragment. After our initial strategy proved unviable, a short, facile method for the synthesis of the C-12 to C-24 fragment, involving the formation of a *bis*-silyl ether, was developed. The protocol for its desired coupling, via a boron-mediated, remote 1,5-*anti*-induction aldol reaction has also been established. These and subsequent studies provided valuable insight into the origin of 1,5-*anti* induction in boron-mediated aldol reactions.

For those departed, and for those who remain. And in particular, for Darren.

Take off my shield
And take my hand
And with arms outstretched
Expose my body and mind
I give these to you freely

Then set me free
Take away my tears
And dance through my soul
Until only the dreams remain
And I can believe

My angel

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A PhD is a journey. Not only of scientific discovery, but more importantly, of personal growth. It is interesting to look back and think about where I have come from, and where I am going, and to think about all of the people that have shaped my experience. If there is one thing that I am certain about, it's that I've certainly changed a lot over the last few years, and for this I thank the following people.

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have another friend quite like you! And Anna. Thank you for being my social organising committee and for never failing to encourage me to have a life. Even though you are the youngest, thank you for being the mother hen to all of us.

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"When the rain washes you clean ... you'll know"

S. Nicks, CA 2003

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Glossary

AcOH	acetic acid
BINOL	1,1'-Bi(2-naphthol)
bs	broad singlet
$CDCl_3$	deuterated chloroform
CDI	carbonyldiimidazole
CH_2Cl_2	dichloromethane
COD	cyclooctadienyl
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DIBAL-H	diisobutylaluminium hydride
DCC	dicyclohexylcarbodiimide
DEPT	Distortionless Enhancement by Polarisation Transfer
DKR	Dynamic Kinetic Resolution
DMAP	dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ds	diastereoselectivity
ee	enantiomeric excess
Et_2O	diethylether
EtOAc	ethyl acetate
$E1_{cb}$	Elimination unimolecular conjugate base
EDCI	1-[3-(Dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride
FID	Flame Ionisation Detector
G1	gap 1
G2	gap 2
G2/M	gap 2/mitosis

GC	gas chromatograpy
GDP	guanosine 5'-diphosphate
GTP	guanosine 5'-triphosphate
HMPA	hexamethylphosphoramide
HP-20S	Poly(styrene-divinylbenzene) stationary support (Supelco)
HPLC	high pressure liquid chromatography
HRESIMS	High Resolution Electro-spray Ionisation Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
IC_{50}	50% Inhibitory Concentration
Ipc	isopentylcamphenyl
IR	Infrared
J	scalar coupling constant
$LiAlH_4$	lithium aluminium hydride
$LiBH_4$	lithium borohydride
Lipase *PS*	Lipase *Pseudomonas cepacia*
LDA	lithium diisopropylamide
LTMP	lithium tetramethylpiperidide
m	multiplet
M phase	mitosis phase
MAPs	microtubule associated proteins
mes	mesitylene (1,3,5-trimethylbenzene)
MDR	multiple drug resistant
MOM	methoxymethyl ether
MTOC	microtubule organising centre
$NaBH_4$	sodium borohydride
nOe	nuclear Overhauser effect
NMR	nuclear magnetic resonance
P_i	orthophosphate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pel A	peloruside A

P-gp	P-glycoprotein
PMB	*para*-methoxy benzyl
Py	pyridine
RCM	ring closing metathesis
R_f	retention factor
rt	room temperature
t	triplet
TES	triethylsilyl
TEM	Transmission Electron Micrograph
TEMPO	4-methoxy-2,2,6,6-tetramethyl-piperidine-1-oxyl
Tf	triflate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl
UV	ultra violet
WST1	water soluble tetrazolium
$ZnBH_4$	zinc borohydride
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
δ	chemical shift (ppm)

Preface

Cancer is a group of diseases characterised by the uncontrolled growth and spread of abnormal cells that invade and disrupt other tissues and spread to other areas of the body. If the spread is not controlled, it can result in death. Cancer is a growing public health problem whose estimated worldwide new incidences are over six million cases per year.[1] In New Zealand in 1999, approximately 16,700 people were diagnosed with cancer, and about 7,600 died as a result of this invasive disease. This makes cancer the leading cause of death in New Zealand, accounting for over 27% of deaths from all causes.[2]

This thesis represents part of a collaborative effort towards the total synthesis of the novel anti-cancer agent, peloruside A, with the overall view to providing a practical and efficient synthesis of this compound. Studies towards the determination of the absolute stereochemistry of peloruside A will also be discussed. However, as with many scientific journeys, results can lead in unexpected directions. During the synthesis of a key fragment of peloruside A, the opportunity arose to investigate the origin of the selectivity in boron mediated 1,5-*anti* aldol reactions. These results are reported accordingly.

Chapter One

Introduction

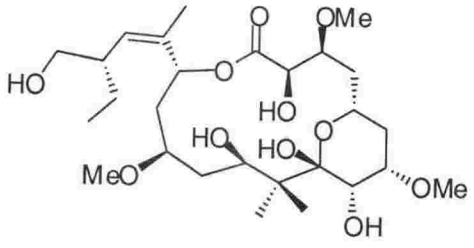
1.1: Tubulin stabilising antimitotic compounds – an overview

In the search for anticancer drugs, compounds from natural sources, such as paclitaxel, extracted in 1971 from the bark of the Pacific Yew tree[3] and bryostatin, isolated from a marine bryozan,[4] have displayed useful anticancer activity and proven successful in clinical trials. In fact, paclitaxel, known clinically as Taxol, is one of the most successful cancer drugs ever produced. Since 1992 it has added months to the lives of over 800,000 patients with cancers of the breast, ovary or lung - in the process accumulating over $1.5 billion a year in revenue for Bristol-Myers Squibb. Eight years after the initial discovery of paclitaxel, it was determined that its unique anti-cancer activity can be attributed to its tubulin-binding mechanism of action.[5] Taxol functions by crippling a cell's ability to divide, or undergo mitosis. The drug binds to and stabilises the rod-like structures inside the cell called microtubules that, like moving train tracks, help chromosomes arrange and split in two during cell division.

However, Taxol and its late-stage semisynthetic derivative Docetaxel (taxotere) are not miracle drugs. Clinical trials with Taxol on metastasising renal[6] and colon[7] carcinomas have been disappointing. Furthermore, some cancers mutate and become resistant to Taxol.[8,9] Thus even when a tumour is all but eliminated by Taxol, a few cells possessing mutant phenotypes may remain, growing into more deadly tumours. Additionally, the therapeutic index of Taxol is narrow due to mechanism-based side effects of neutropenia, peripheral neuropathy, alopecia and hypersensitivity reactions.[10] Taxol is also highly hydrophobic, necessitating delivery in Cremophor, which in itself can induce cardiac arrhythmias and extensive hypersensitivity reactions.[11]

Nevertheless, the phenomenal clinical success of Taxol promoted the search for new drugs with similar mechanisms of action. Once again, mother nature offered a solution in the form of the epothilones A and B, whose isolation in the late 1980's from culture extracts of the cellulose-degrading mycobacterium *Sorangium cellulosum* (first found in soil collected from the banks of the Zambesi River)[12] provided an additional class of tubulin stabilising anti-cancer drugs. The epothilones exhibit superiority over paclitaxel as a killer of tumour cells, particularly with cell lines exhibiting multiple drug resistance (MDR).[13,14] In some of the cytotoxicity experiments, epothilone B demonstrated a 2000-5000 fold higher potency than paclitaxel, a striking enough observation to awaken and stimulate the interest of many in both the academic community and the pharmaceutical industry. Consequently, the epothilones and analogues thereof, are currently undergoing advanced clinical trials.

Even though paclitaxel and the epothilones are the most well known tubulin-stabilising antimitotic drugs, a small number of other tubulin-stabilising compounds exist. Of particular interest to us is the discovery that peloruside A (pel A) **(1)**, a novel secondary metabolite isolated from a New Zealand marine sponge, *Mycale hentscheli*,[15] exhibits potent paclitaxel-like microtubule-stabilising activity.[16,17]



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Pel A belongs to one of three classes of tubulin-stabilising compounds – namely the macrolide class which includes the epothilones (to which peloruside is structurally related) and the laulimalides,[18] isolated from the marine sponge *Cacospongia mycofijiensis*. Other classes are a) the terpenoids, including the taxanes,

eleutherobin/sarcodictyin[19] (isolated from marine corals), and the bacterial metabolite WS9885B;[20] and b) the polyhydroxylated alkatetraene lactones, including discodermolide, isolated from a Carribean sponge.[21,22] Reported IC_{50} values for the cytotoxicity of these drugs are generally in the low nM range.

Although it is possible that pel A may not introduce anything substantially new to the antimitotic group of drugs, it is anticipated that its unique structure, and hence differing bioactivity, will offer distinct advantages when compared to the other known microtubule-stabilizing compounds. Furthermore, therapeutic anti-cancer drug cocktails comprise a mixture of drugs having unique and complementary properties,[23,24] to which pel A may be a valuable constituent. Multi-drug treatment regimes applied either as a single cocktail or in a rotating sequence, may help to prevent the development of resistant subclones that arise in long-term chemotherapy.

As is the case with many natural products, obtaining a sufficient quantity of the desired compound from its natural source can be a serious limitation in drug development. Although *Mycale hentscheli* is endemic to New Zealand, occurring in scattered populations in calm coastal water around both the North and South Islands, pel A levels in these populations are not large, with less than one third of the individuals in a population containing detectable levels of the metabolite.[25] It has been estimated that to obtain 30 mg of peloruside, 30 kg of sponge will have to be collected. To date, the scarcity of pel A has prevented in-depth biological studies from being conducted. However, before an overview of our strategy for the synthesis of pel A is discussed, it will be instructive to first examine further the molecular and cellular biology of tubulin binding agents, and how pel A relates to them.

1.2: Tubulin, microtubules and the cytoskeleton

Tubulin is a heterodimeric protein primarily composed of α- and β-tubulin subunits and represents the monomeric building blocks of microtubules. Microtubules, in turn, are one of the fundamental structural components of the cytoskeleton in all eukaryotic cells. Operating either alone, or in conjunction with other proteins to form more complex structures, microtubules serve as structural beams and conveyer belts within cells. They rigidify the cell and translocate vesicles, granules, organelles and chromosomes. Although these filamentous protein networks are usually transparent and hence often neglected in cell drawings, this "nanolevel web" plays a crucial role in the dynamic organization of the interior of living cells and its existence should not be over looked.

Structually, microtubules are regular internetworked linear polymers (protofilaments) of highly dynamic assemblies of heterodimers of α- and ß-tubulin. When thirteen of these protofilaments are arranged parallel to a cylindrical axis they self-assemble to form microtububes of approximately 24 nm in diameter and up to several μm in length. The α,ß heterodimer is itself very compact but can be divided into three functional domains: the amino-terminal domain containing the nucleotide-binding region, the intermediate domain containing the paclitaxel-binding site, and the carboxy-terminal domain, which probably constitutes the binding surface for motor proteins.[26]

Formation of microtubules proceeds by a nucleation-elongation mechanism and occurs within an area of the cell called the "aster".[27] Nucleation is the initial phase of the process in which preformed heterodimers of α- and β-tubulin assemble in the presence of Mg^{2+}, guanosine 5´-triphosphate (GTP) and microtubule-associated proteins (MAPs). This process is relatively slow until a short microtubule is formed, triggering the much faster elongation process. The elongation phase involves the extension of the microtubule nucleus at both ends by a reversible, non-covalent addition of tubulin heterodimers to form growing oligomers that become linear rows of tubulin beads. Although both ends can either grow or dissociate, the (+)-end, which is kinetically more

dynamic, usually grows faster than the (-)-end, (which is less dynamic). Conversely, net shortening takes place at the (-)-end, figure 1. "Treadmilling" or "flux" occurs when both of these dynamic processes occur at once, resulting in a net flow of subunits from the plus to the minus end without a significant change in microtubule length.[27] Figure 2 depicts the assembly of tubulin into microtubules and the influence that paclitaxel and the epothilones have on tubulin polymerisation.

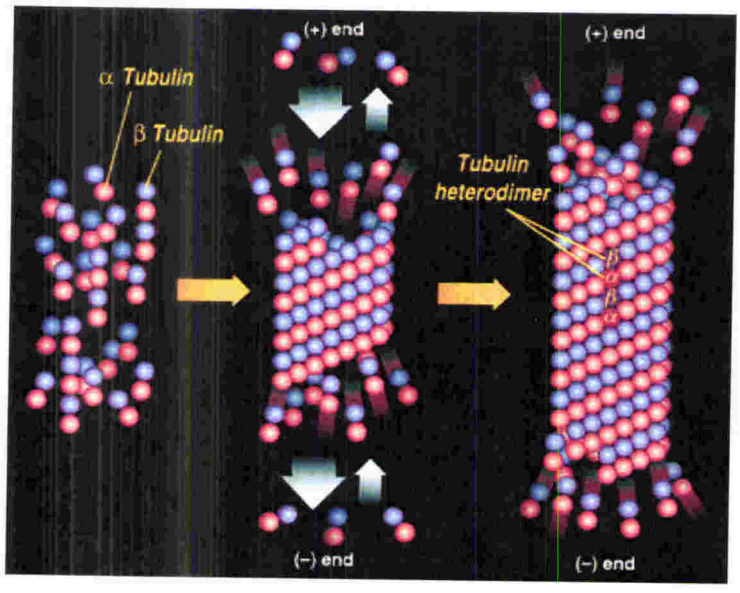


Figure 1: Polymerisation of tubulin to microtubules[1]

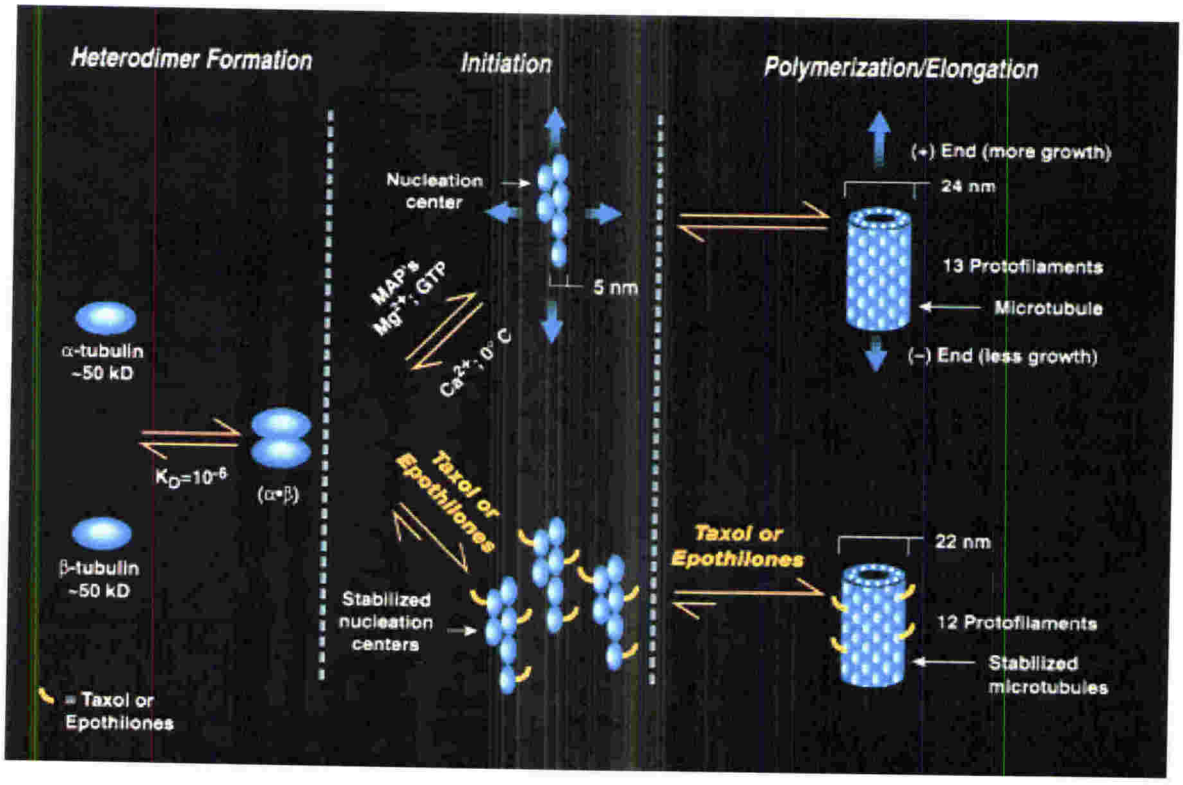


Figure 2: Dynamic equilibria of tubulin-microtubule[1]

Bound GTP molecules regulate the growth and dissolution of microtubules. Each tubulin dimer carries two GTP molecules, one on the α-subunit or N site and one in the β-subunit. However only the exchangable ß subunit appears to function as a GTPase.[28] During polymerisation, the GTP molecule hydrolyses to guanosine diphosphate (GDP) and orthophosphate (P_i). GTP, GDP, and P_i form a "cap" on the ends of the microtubules that facilitates further growth due to their high affinity for additional tubulin subunits.[29] Conversely, hydrolysis of the GTP subunit on the end of the microtubule causes shortening of the microtubule.[30] While the half-life of tubulin at 37 °C is nearly a full day, that of a given microtubule may be only about 10 minutes. Accordingly, microtubules are in a constant state of flux responding to the needs of the cell. This state of stochastic switching between shortening and growing phases at the ends of the individual microtubule is called "dynamic instability" and is controlled by regulatory processes within the cell.[29,31]

Tubulin is a major component of the cellular apparatus known as the mitotic spindle, and hence plays a crucial role throughout mitosis – the process during cell replication in which the duplicated genetic material, in the form of chromatids, is partitioned equally between the two daughter cells. Mitotic spindle microtubules are especially dynamic, and exchange their tubulin with tubulin in the cytoplasmic pool with half-lives of less than a minute.[32] A cell enters mitosis after transcending through the Gap 1 (G1), chromosome replication (S phase) and Gap 2 (G2) phases of the cell cycle (collectively known as interphase), figure 3. During prophase, the first division of mitosis, the homologous sister chromatids contract and pair within the nucleus. Outside the nucleus, two dipolar spindle-shaped arrays of microtubules are formed outward from organising centres known as centrioles.[I] The centrioles, or microtubule-organising centres (MTOC), act as the major site of microtubule nucleation by lowering the critical concentration of tubulin required for polymerisation and anchoring the (-)-ends of the resulting microtubules.[33] Near the end of prophase the nuclear envelope breaks down, allowing the spindle microtubules to enter the nuclear area. Kinetochores (mirotubule

[I] Centrioles consist of a ring of nine groups of three fused microtubules

binding proteins) then form on either face of the centromere[II] and become attached to special microtubules called kinetochore microtubules. These microtubules radiate in opposite directions from each side of every chromosome and interact with the (+)-end of the spindle microtubules. Once the spindle microtubule/kinetochore/chromosome complex is formed, metaphase commences.

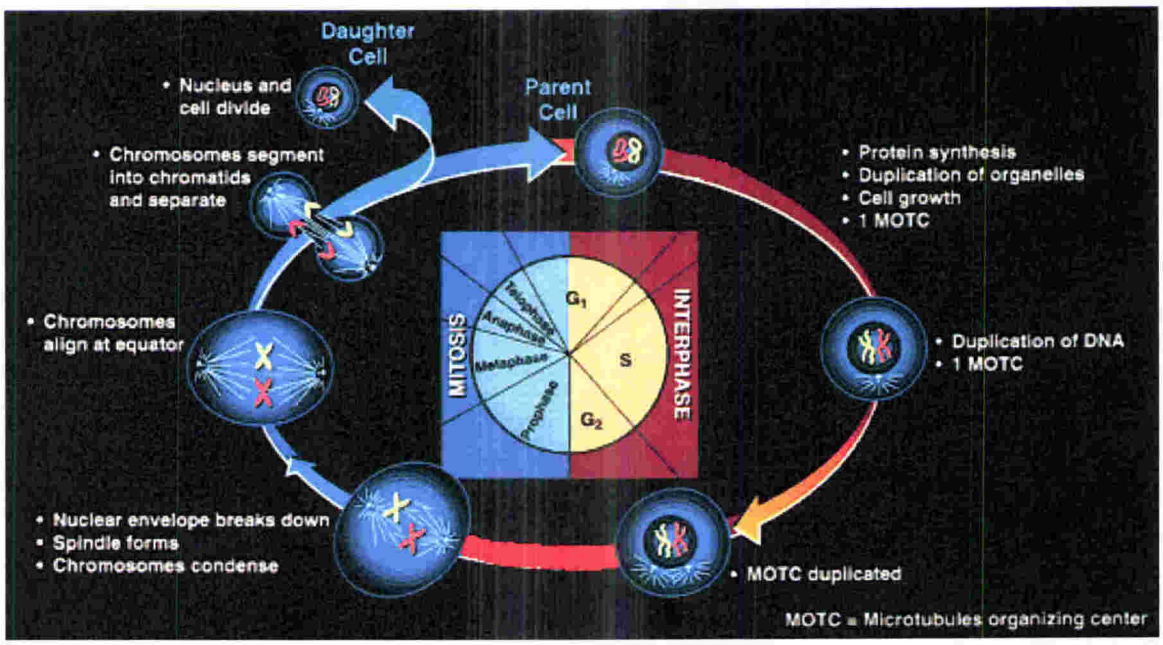


Figure 3: Schematic diagram of the cell cycle[1]

At metaphase, the sister chromatids are assembled to an equatorial position on the mitotic spindle by the dynamic action of the microtubules and associated motor enzymes. This eventual congression at the cellular equator is the net result of both P-motion (towards the pole) and AP-motion (away from the pole) and can be thought of as a gentle jostling motion to align the chromatids along the equator. The P movement is driven by a (-)-end directed motor protein in the kinetochore, while the AP movement is driven by a (+)-end motor protein. The kinetochores also contain motor enzymes that destabilise the microtubules, leading to a loss of tubulin heterodimers from the (+) end,

[II] The centromere is the region on the chromomsome where the individual sister chromatids meet

or net microtubule shrinkage.[32,34] Movement of the microtubules is also dependent upon the inherent microtubule dynamics.[30,32,33,34a]

The next stage of cell division is anaphase during which the microtubule dynamics change and the chromatids partition and move to the new spindle poles on the dynamic microtubules, where new cells are being formed. Anaphase microtubule dynamics are particularly rapid, with motor proteins at the poles effectively reeling in the chromosomes by shortening the microtubules.[34] In this process, duplicate chromosomes are provided to each of the two daughter cells.

1.3: Tubulin binding agents and cell death

1.3.1: The two divisions of antimitotic compounds

Interruption of microtubule dynamics has proven to be an effective target for cancer chemotherapy. These rapid dynamics are extremely sensitive to tubulin-interactive agents that exert their antimitotic action at the metaphase to anaphase transition, possibly by mimicking the actions of naturally occurring regulatory proteins,[35] figure 4. Ultimately, this results in arrest at the G2/M transition. Many antimitotic compounds, including the well established chemotherapeutic agents colchicine, the *Vinca* alkaloids, (including vincristine and vinblastine) and podophylotoxin, operate by interfering with the formation and growth of microtubules during mitosis.[36] At appropriate concentrations, these drugs inhibit the formation of spindle microtubules or

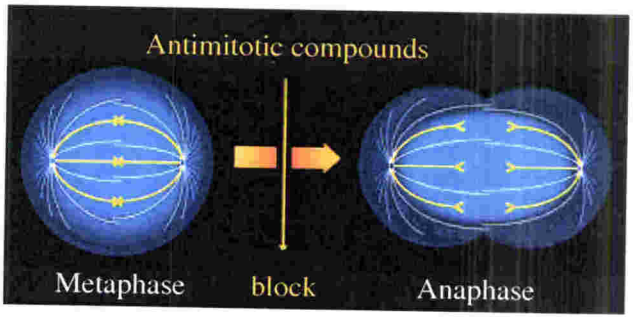


Figure 4: Blocking of mitotic spindle division by antimitotic compounds[1]

depolymerise existing ones. Tubulin is instead diverted into other types of aggregates. This class of antimitotic compounds further includes combretastatin,[37] maytansine,[38] rhizoxin,[38] phomopsin,[38] the dolastatins,[38,39,40] cryptonphycins,[41] benzimidazoles (such as nocadazol),[29,31a,42] the curacins[43] and the baceterial metabolite RPR112378.[20] Selected natural products promoting the depolymerisation of tubulin are shown in figure 5.

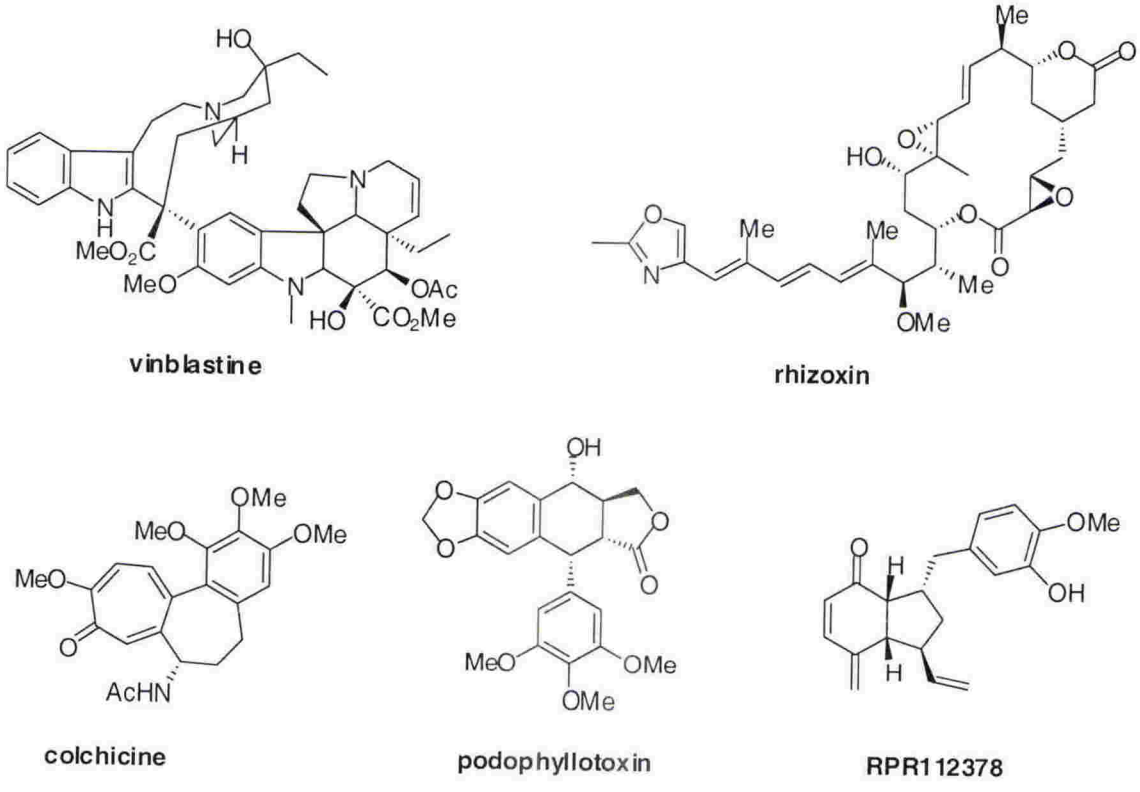


Figure 5: Selected natural products promoting tubulin depolymerisation

Paclitaxel however, has a mechanism of action unlike any of the tubulin-targeting agents that preceded it to the clinic. In contrast to the antimitotic drugs described above, paclitaxel promotes tubulin-polymerisation, stabilises microtubules and thereby alters normal microtubule dynamics. This results in the formation of abnormal mitotic spindles, mitotic arrest, and the initiation of apoptosis (programmed cell death).[44,45] At concentrations that are stoichiometric or near-stoichiometric with respect to the

concentration of tubulin present in solution, paclitaxel causes thick microtubule bundles to form in cultured cells, even in the absence of GTP or MAPs. Once formed, the microtubules are resistant to cold or calcium induced depolymerisation.[5] Data supports the hypothesis that binding of a molecule of paclitaxel to a tubulin subunit in microtubules induces a conformational change in that subunit that strongly reduces its ability to dissociate when the subunit becomes exposed at the microtubule end.[46]

For more than 15 years paclitaxel, and the structurally related taxanes, were the only compounds known to have this mechanism of action. However, over time, additional drug classes have been shown to act by a similar mechanism. In particular the recently discovered epothilones, identified after screening tens of thousands of compounds for their ability to polymerise tubulin, have been shown to induce tubulin polymerisation in a manner similar to that of pacliltaxel.[14,47] In fact, when compared to paclitaxel, both epothilones A and B have reported higher potencies as tubulin polymerisation agents, although *in vivo* studies identified epothilone B as being too toxic for use as an anticancer drug. The lactam analogue of epothilone B however, referred to as aza-epothilone B, has shown considerable potential in oncology, and has recently entered phase II clinical trials.[48]

A computer-assisted search for novel compounds with structural analogy to colchicine site inhibitors, also identified the marine natural product (+)-discodermolide, isolated from the sponge *Discodermia dissolute*, as an antimitotic agent.[21,49] Indeed, discodermolide-treated breast carcinoma cells displayed spectacular rearrangement of the microtubule cytoskeleton, including extensive microtubule bundling at concentrations one tenth of those required by paclitaxel.[21] The enhanced bundling observed with both discodermolide and the epothilones when compared with paclitaxel is readily understood in terms of the apparent increased affinity of these compounds for tubulin relative to paclitaxel.

However, paclitaxel, the epothilones and discodermolide are not the only antimitotic agents that stimulate tubulin polymerisation. Gradually other natural products have been added to this class of compounds. These include laulimalide,[18] eleutherobin,[50] sarcodictyin and more, recently peloruside A, figure 6.

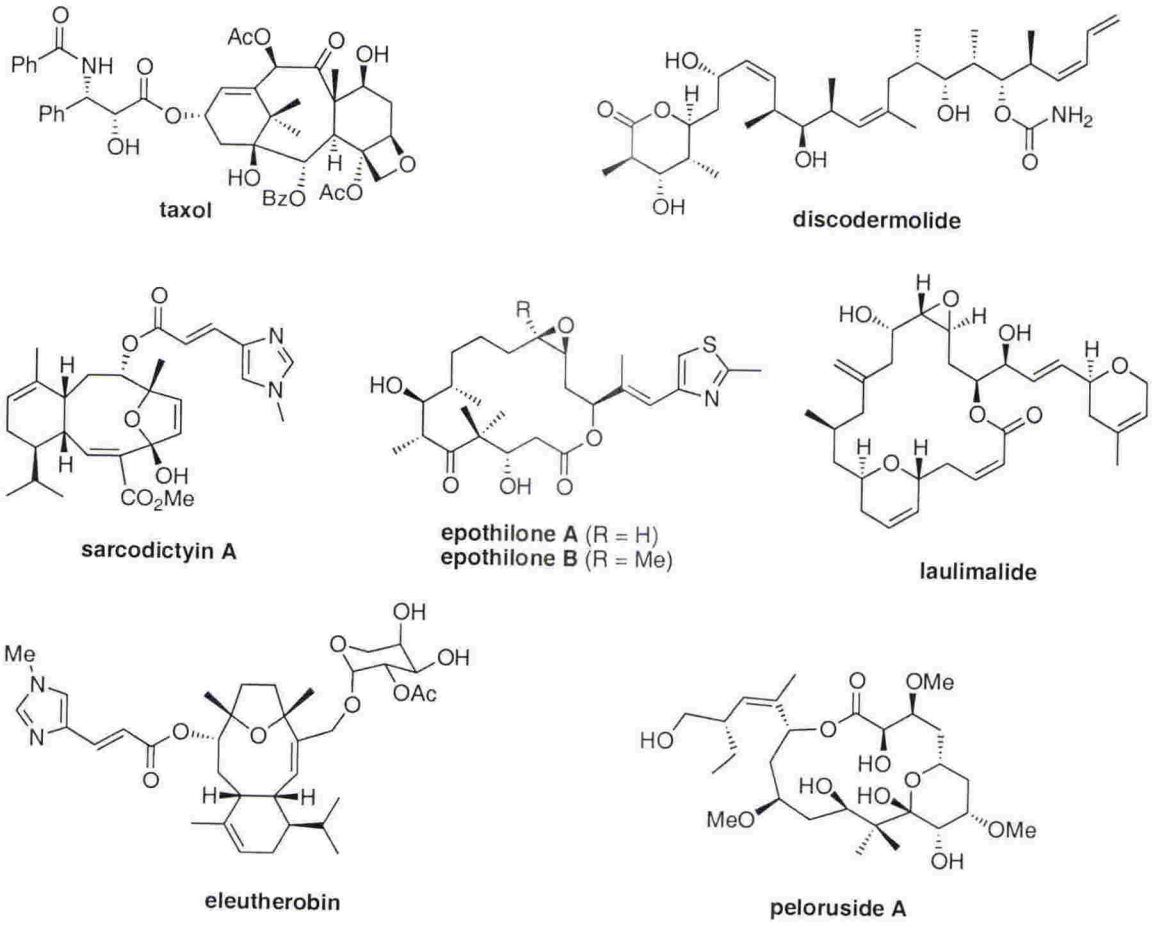


Figure 6: Selected natural products with tubulin polymerisation and microtubule stabilisation properties.

1.3.2: Mode of action of the antimitotic agents

It had long been thought that the mechanisms of action of the two classes of compounds were fundamentally different due to the easily recognisable visible effects of either microtuble polymerisation or depolymerisation. However, this concept was

recently revisited because at low concentrations both classes of compounds appear to inhibit cell proliferation by kinetically stabilising the dynamics of spindle microtubules and not by changing the mass of polymerised material.[51] This is best illustrated by paclitaxel, which is perhaps the most widely studied antimitotic agent. Numerous studies have shown that in addition to stimulating microtubule polymerisation, paclitaxel also inhibits tubulin exchange at microtubule ends and treadmilling at polymer mass steady state.[52,53] Such observations however, depend greatly upon the stoichiometry of binding of paclitaxel to the microtubule.[46] Comparisons between paclitaxel and vinblastine yielded similar results and lead to the hypothesis that differences in the actions of antimitotic drugs may result from the relationship between the stoichiometry of binding of the drug to the microtubules and the degree to which the specific dynamic parameters, such as the extent of growing or shortening, are suppressed.

In the case of paclitaxel, induction of apoptosis has generally been directly associated with G2/M arrest and occurs as a direct consequence of centrosomal impairment, induction of abnormal spindles and suppression of microtubule dynamics.[54] However, in some instances, the cell may pass through the M phase of the cell cycle yet arrest at the G1 stage.[55] Significant debate exists concerning the mechanism by which paclitaxel induces a stable late-G1 block. One scenario involves a critical element of G1 control being sequestered on microtubules, and that the activation of the element requires its release. The release and activation of this element can occur either in a dynamic microtubule system or can be triggered in the absence of microtubules, but would not occur when microtubules are stabilised by paclitaxel. Alternatively, by inducing hyper-assembly of microtubules, paclitaxel might impose a checkpoint control upon the cells. Checkpoint controls, which normally function to assure the integrity of the genome, arrest the cell cycle at a discrete point until all prerequisite events have been completed.[56] However, the triggering of apoptosis by aberrant mitosis or by subsequent multinucleated G1-like state related to mitotic slippage, largely depends on cell type and drug schedule.[54] Other antimitotic agents, including the epothilones[1] have also been reported to arrest cells at the G1 phase of the cell cycle.

Although numerous studies and their insights have identified a myriad of cellular and molecular effects of antimitotic agents that may offer promise in cancer therapy, these results have often generated contradictory observations.[57] What is known though is that the cytotoxicity of these antimitotic compounds involves signalling distinct from DNA damaging drugs but common to all microtubule-active drugs with the specific hallmark of Bcl-2 hyperphosphorylation.[58,59] Bcl-2 is a receptor found on the mitochondrial membrane that plays a regulatory role in apoptosis. The serine/threonine kinase(s) responsible for Bcl-2 phosphorylation, however, have not been conclusively identified.

The controversial role of p53[III] in paclitaxel-induced apoptosis is still under debate. Although it was initially thought that paclitaxel-induced apoptosis is p53-independent[60,61] again, this depends on cell type and drug concentration. At concentrations too low to inhibit mitotic progression (3 – 6 nM) paclitaxel can completely inhibit cell proliferation in cells producing higher than normal amounts of p53. Hence, paclitaxel has been shown to compliment the effects of p53 sufficiently to cause arrest at G1 and G2.[62]

1.4: Biochemistry of peloruside A

1.4.1: Cell cycle arrest and effects on the cytoskeleton

Like its famous predecessor paclitaxel, peloruside A also causes cells to accumulate at the G2/M phase of the cell cycle, as evidenced by an increase in the number of cells in metaphase during flow cytometry studies.[17] Such observations support the hypothesis that pel A is interacting with the cytoskeleton of cells, in particular, with the microtubules involved in the formation of the spindle. In a manner analogous to the other microtubule stabilisers, pel A causes the formation of microtubules in the absence of microtubule-associated proteins (MAPs) and GTP. Once

[III] p53 is a tumour suppressor gene that often plays a crucial role in apoptosis

formed, the microtubules are resistant to cold or calcium induced depolymerisation.[17] Figure 7 is a Transmission Electron Micrograph of pel A induced polymerised microtubules, (*in vivo* preparation).[17]

Figure 7: TEM of PelA induced polymerised tubulin

Although studies comparing pel A with paclitaxel indicated that the arrest in G2/M was more complete for paclitaxel, Western blot results indicate that pel A appears to be more potent than paclitaxel in inducing microtubule polymerisation.[17] A simple cellular assay was used in which the shift in tubulin from depolymerised (soluble) to polymerised (particulate) forms was followed by electrophoresis and Western blotting of centrifuged soluble (**S**) and polymerised (**P**) fractions, figure 8. At 100 nM concentrations, complete tubulin polymerisation was observed for both pel A and paclitaxel. Colchicine, on the other hand, drove the process toward the depolymerised form as expected, figure 8A. The shift in tubulin dynamics was rapid for both pel A and paclitaxel, being complete for 100 nM pel A at or before '0 min' (about 30 min after addition of compund to intact cells) and complete for 100 nM paclitaxel at '5 min' (35 min after compound addition), figure 8B.

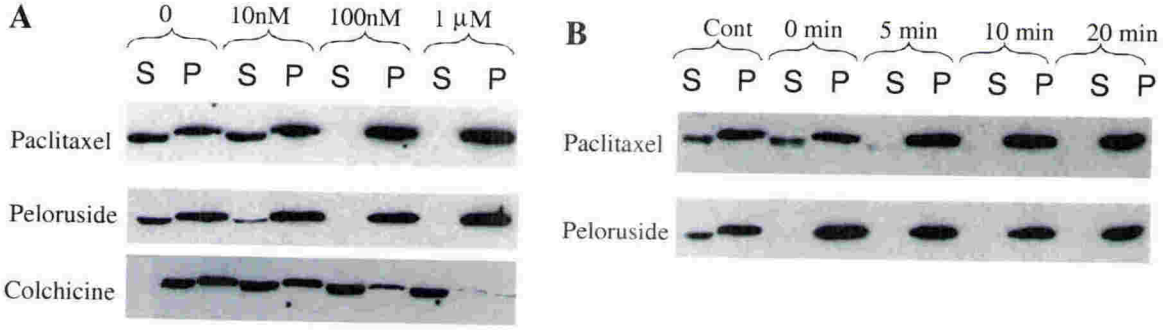


Figure 8: Western blotting showing the effects of paclitaxel, peloruside A and colchicine on tubulin polymerisation

Upon the treatment of human lung carcinoma (H441) cells with pel A, abnormal cytoskeletal rod-like fibres were also observed. Figure 9 shows cells treated for 48 hours with 100 nM peloruside (B) or 100 nM paclitaxel (C). Control cells (A) were left untreated. The fibres did not stain with anti-tubulin or anti-actin[IV] antibodies, and thus appear not to be microtubular bundles or actin fibres. Other abnormal cytoskeletal elements, including multiple asters were also observed.[17] These observations are consistent with studies of this nature on other known tubulin-binders including discodermolide and the epothilones A and B.

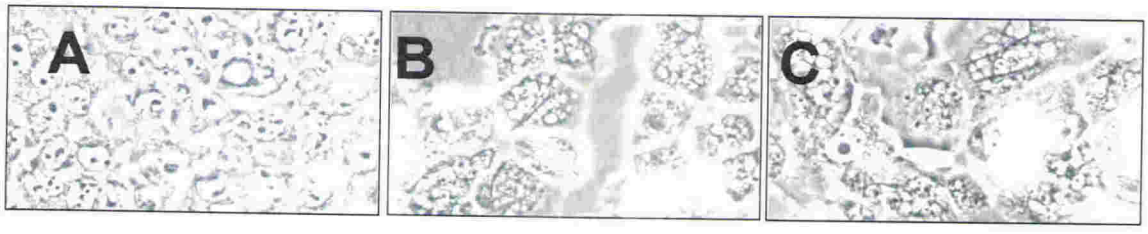


Figure 9: H441 Human lung carcinoma cells showing cytoskeletal bundles. **A**: Control. **B** Treated for 48 hours with100 nM peloruside A. **C**: Treated for 48 hours with 100 nM paclitaxel

1.4.2: Cytotoxicity and the identification of apoptotic pathways

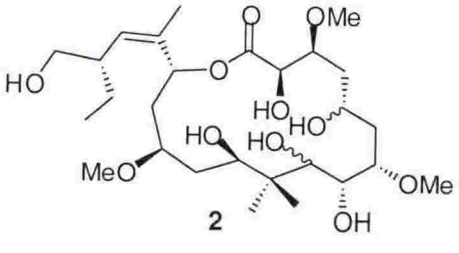
The cytotoxic activity of pel A has been determined in a number of cell lines including the human myeloid leukaemic cell line HL-60, the nontransformed murine myeloid cell line 32D, the human lung adenocarcinoma cell line H441 and 32D cells transformed with *ras* and *bcr/abl* oncogenes. IC_{50} values for pel A ranged from 4 nM to 15 nM in the different cell lines.[17] These values are comparable to those of other antimitotic drugs.

[IV] Actin is a filamentateous protein found in muscle tissue and in the cytoskeleton of cells

However, considerable work is still required to determine the exact mode of action of pel A. Although the microtubule is presumably the major site of action of pel A, it is not necessarily this particular interaction that kills the cells. A proteomics approach has been used to decipher some of the downstream changes due to the action of pel A, with tryptic digest finger printing identifying a 37 kDa protein altered by both pel A and pacitaxel, as an isoform of α-tubulin.[63] Further proteomics analysis has revealed points of difference between paclitaxel and pel A, however this work is on-going and awaits further confirmation. Preliminary *in vitro* studies examining the effects of paclitaxel and pel A on neutrophil superoxide production also revealed differences in the immunosuppressive action of both compounds.[64] Neutrophils are cells involved with the immune system's response that, among other functions, destroy foreign bodies by producing superoxide radicals. Again, these observations point to differences in the secondary targets of paclitaxel and pel A.

What is perhaps more striking though, are the differing effects of paclitaxel and pel A on the metabolic activity of cells as measured by WST-1 (water soluble tetrazolium) dye reduction. Only metabolically active cells achieve reduction as this requires functional mitochondrial dehydrogenases. Pel A (180 μM) stimulated WST-1 dye reduction by 20±12%, rather than inhibiting it, as might be expected for a potent cytotoxic agent. By contrast, Taxol inhibited WST-1 reduction by 70 ± 2% at 120 μM but has little effect at 15-30 μM.[63] Such results point to key differences in the initial cellular responses to the two compounds and suggest unique mechanisms of action, depending on concentration and time of exposure.

It is also interesting to note that the sodium borohydride reduction product of pel A, **2**,[65] does not stabilise microtubules, figure 10,[17] yet is only 30-fold less cytotoxic than pel A, figure 11.[16] The observation that **2** causes cell death at nanomolar concentrations without polymerising microtubules



2

further illustrates the importance of cytotoxic pathways independent of tubulin polymerisation.

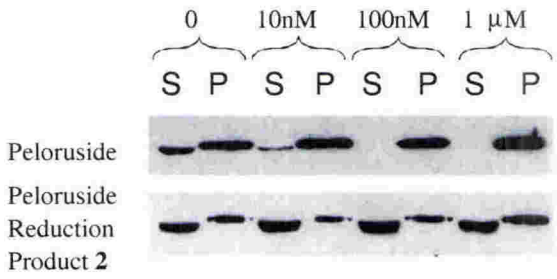


Figure 10: Western blot of pel A and the reduction product **2**

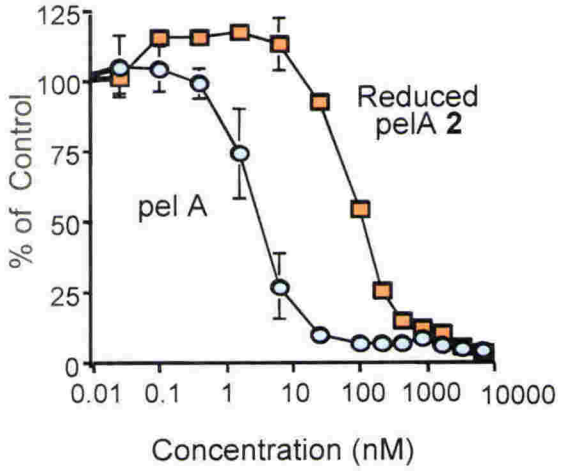


Figure 11: Cytotoxicity of pel A and the reduction product **2**

1.5: Tubulin binding sites

The diverse, seemingly unrelated structures of antimitotic anticancer agents raises the question of whether they bind to the same or different sites on tubulin. Primarily, two very distinct binding sites have been identified, corresponding to the primary mode of action of the antimitotic agent. The first site, found only on unpolymerised tubulin dimer but not the intact microtubule, is the colchicine site.[66] Many other natural products such as cornigerine, podophyllotoxin, and combretastatin A also bind to the colchicine site, thus preventing tubulin polymeristation. It is also believed that the recently discovered antimitotic agent, RPR112378 binds to, or near, the colchicine-binding site.[20] The other predominant binding site is the paclitaxel-binding site.[28, 67]

Each α/ß-tubulin heterodimer contains one paclitaxel-binding site located between the protofilaments formed from α and ß tubulin association. Paclitaxel does not bind to free tubulin.[68] The epothilones,[13] discodermolide[13,69] and eleutherobin all inhibit the binding of [^{3}H] paclitaxel to tubulin polymers, while laulimalide has been shown to bind to a unique site on ß-tubulin.[70] To date, it is not known if pel A binds directly to microtubules, and if so, whether it binds to the same site as paclitaxel.

1.6: Multiple Drug Resistance

Resistance to paclitaxel has generally been associated with either over-expression of the P-glycoprotein efflux pump,[71] decreased intracellular levels of polymerised tubulin,[71] or as a result of a mutation of the paclitaxel-binding site on tubulin.[72] Phosphoglycoprotein is a membrane glycoprotein that functions as a drug efflux pump, thereby reducing the effective intracellular concentration of anticancer drugs. Overexpression of P-gp leads to the multiple drug resistant (MDR) phenotype, wherein tumour cells become simultaneously resistant to a multitude of drugs.[13,73] Eleutherobin shows similar MDR sensitivity to paclitaxel, however, epothilones, discodermolide,[22] sarcodictyins and laulimalide look promising in this regard, being only transported to a limited extent by P-gp.[13] Studies comparing the cytotoxicity of pel A with paclitaxel in cell lines that either overexpress or do not express P-gp are under investigation.

Mutations in the ß-tubulin structural gene results in the resistance of some cell lines to both paclitaxel and the epothilones.[69b,74] Such cell lines include the ovarian carcinoma 1A9/A8 and 1A9/B10 cell lines, with mutations at amino acids ß274$^{Thr\rightarrow Ile}$ and ß282$^{Arg\rightarrow Gln}$, respectively. Other selected mutations in similar cell lines affecting paclitaxel cytotoxicity but not discodermolide toxicity have also been reported.[72] Laulimalide was also active in epothilone-[74a] and paclitaxel-resistant[74b] cell lines bearing paclitaxel site mutations in the M40 ß-tubulin gene.[70] These studies suggest that even those tubulin-binding drugs that compete with radiolabeled paclitaxel for what appears to be the same binding site, display subtle differences in their interaction with the specific amino acid

residues of the β-tubulin binding site. Hence each antimitotic drug offers distinctive advantages over one another with respect to resistant cell lines. It is thus anticipated that pel A will exhibit its own unique cytotoxity with respect to various resistant cancer cell lines.

1.7: The development of peloruside A as a viable drug candidate

Although the strategy of using tubulin as a target for cancer chemotherapy has been well established,[75] different microtubule inhibitors vary in their ability to selectively destroy tumour cells in a clinical setting. While the chemotherapeutic effect of microtubule inhibitors would seem in some way linked to the most evident effect of the drugs, mitotic arrest, there is no direct evidence in support of this assumption - the difference in chemotherapeutic efficacy may lie in more subtle effects. For example both paclitaxel and nocodazole impose mitotic arrest on mammalian cells,[55] yet paclitaxel has shown promise in chemotherapy, particularly in the treatment of ovarian and breast cancers, while nocadazole has not.

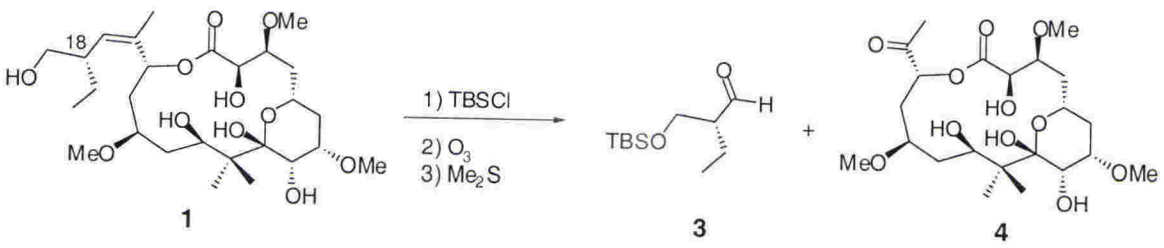
Fortunately though, recent *in vivo* tests have shown pel A to be efficacious in tumour regression.[76] A sample of pel A (5mg) was tested on mice bearing the colon 38 tumour using a single intraperitoneal dose of 40mg/kg. At this dose, pel A was found to be toxic in four of the five mice, however the remaining mouse showed no toxicity and survived for the duration of the experiment with no evidence of tumour. A further sample of drug (3 mg) was then tested on mice bearing the colon 38 tumour using a lower single intraperitoneal dose of 25 mg/kg. It was again toxic in four of the five mice. The surviving mouse however, showed complete tumour regression with further tumour regression being observed in all the dead mice. Although further studies are required in order to determine the effective dosage *in vivo*, these results are particularly encouraging because they involved a single bolus dose of pel A, yet anti-cancer treatments normally require multiple doses or intravenous infusion to be effective.

Whether pel A will equal the utility of Taxol in treating cancer however, can only be answered after significant investment in the drug development and clinical trial process, which ultimately requires an abundant supply of pel A. Due to its scarce natural abundance, it is anticipated that significant quantities of pel A can only be obtained through chemical synthesis. However, at the time of commencing this project, the absolute stereochemistry of pel A was unknown. Ideally, it would be desirable to know the absolute stereochemistry of pel A at the beginning, if not during the early stages of the synthesis, to avoid any possible repetition of work. Thus, methods for determining the absolute stereochemistry of pel A will be discussed before an overview of our synthetic strategies for the synthesis of pel A is provided.

1.8: Determination of the absolute stereochemistry of peloruside A

Possible methods of determining the absolute stereochemistry of pel A include: a) the synthesis of one enantiomer of pel A followed by comparison of the optical rotation of this enantiomer with that of natural pel A; b) ring opening the macrolide under mild, aqueous conditions, followed by esterification of the resulting carboxylic acid moiety with a chiral reagent and comparison of the absolute stereochemistry at C-2 by ^{1}H NMR spectroscopy in a manner similar to Mosher's method;[77,78] and c) comparing a synthesised fragment of pel A of known stereochemistry with a similar fragment cleaved from the natural product.

The last strategy initially appeared to be the most viable, with the details of this chosen fragmentation given in scheme 1. This approach involves selectively protecting the primary hydroxyl group of pel A with the *tert*-butyldimethylsilyl (TBS) moiety, followed by ozonolysis and work-up to produce the side chain fragment **3**. The synthesis of an identical fragment of known chirality at C-18 has been reported.[79] Chiral gas chromatography would then be used to compare the retention times of the cleaved side chain **3** and both the synthetically derived racemic, and enantiomerically pure, versions of **3**. The attraction of this strategy is that it not only enables the absolute stereochemistry of C-18 to be determined, and hence the absolute stereochemistry of the entire molecule, but also results in the formation of the macrolide segment **4** which may have its own unique biological properties.

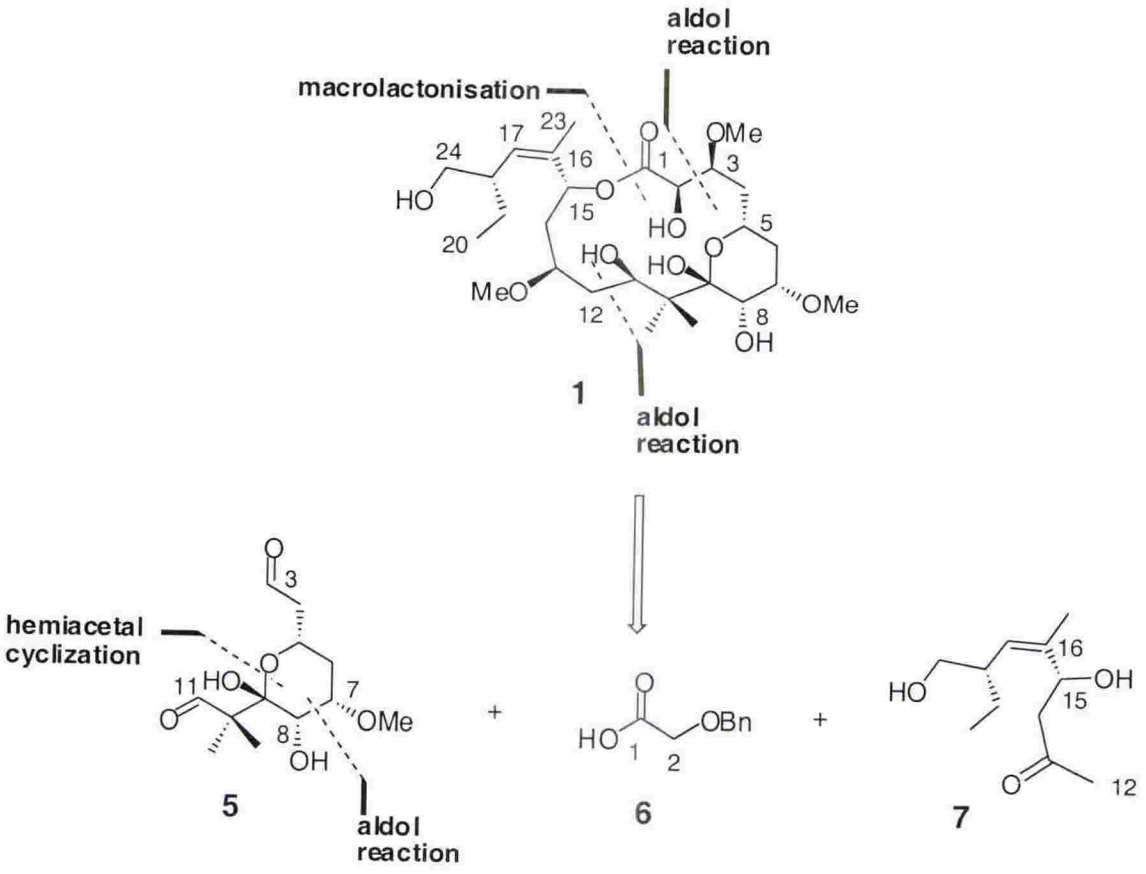


Scheme 1: Methodology for the determination of the absolute stereochemistry of pel A

1.9: Synthetic strategies towards the synthesis of peloruside A

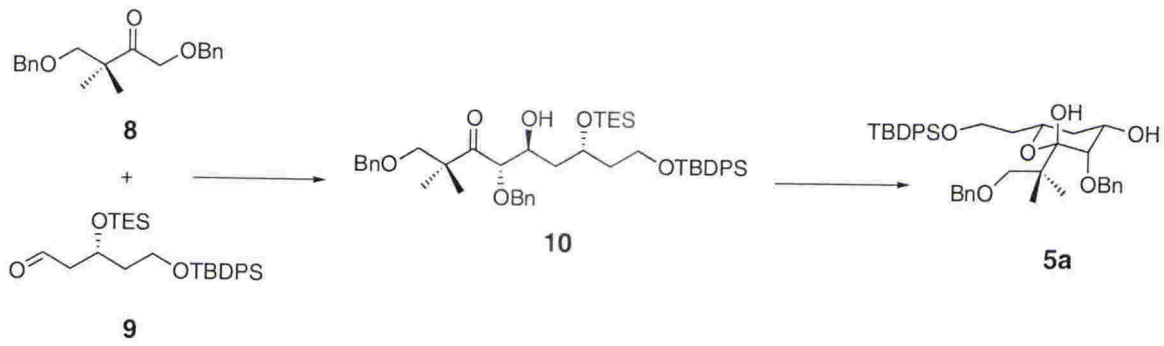
1.9.1: Retrosynthetic Analysis

Although the structure of pel A is considerably less complex than that of paclitaxel, it nevertheless poses some considerable synthetic challenges, particularly in the formation of the pyranose ring and control of the 10 stereogenic centres. Moreover, pel A provides many opportunities for the discovery and development of new synthetic technologies and strategies. Scheme 2 illustrates the fragmentation of the synthetic target to three main building blocks: the pyranose ring **5**, commercially available benzyloxyacetic acid **6**, and the remaining side chain and macrocycle fragment **7**. The two bond disconnections depicted on pyranose ring **5** facilitate the synthesis of this core.



Scheme 2: Retrosynthetic analysis of peloruside A

Formation of pyranose **5a**, a synthon for the C-3 to C-11 fragment, would commence with a diastereoselective aldol reaction between the enolate of *gem*-dimethyl ketone **8** and aldehyde **9** to give ß-hydroxy ketone **10**, scheme 3. *In situ* deprotection of the triethylsilyl (TES) moiety under mildly acidic conditions, with subsequent cyclisation,[80] was envisioned to afford **5a**.



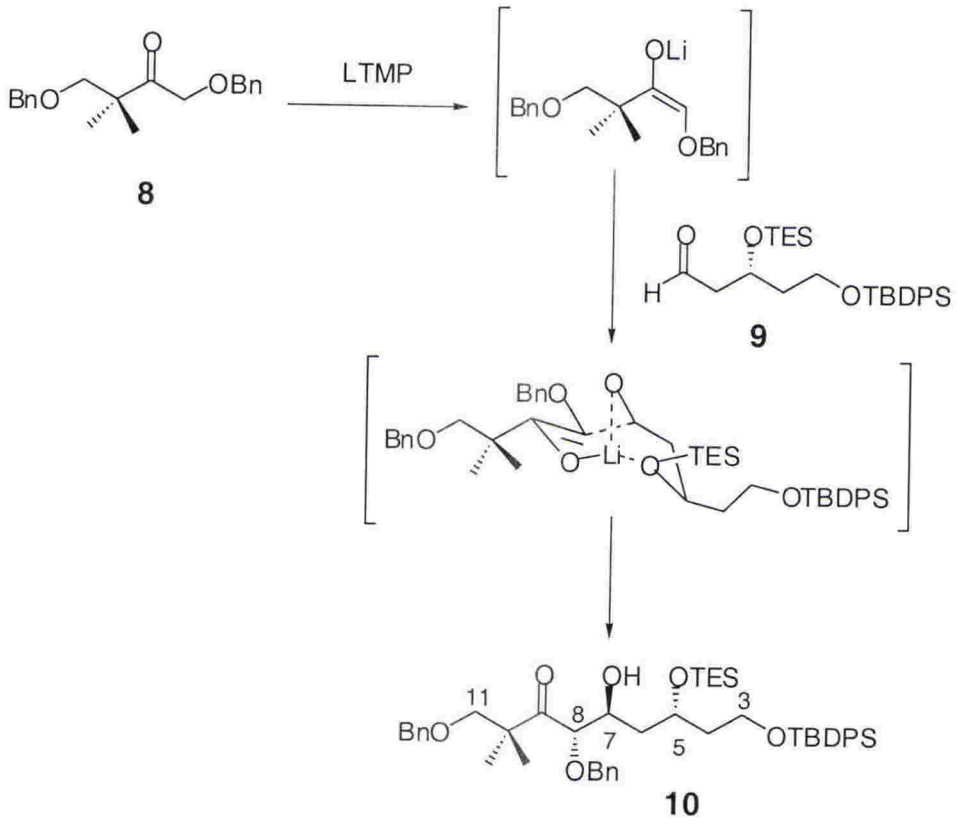
Scheme 3: Formation of pyranose **5a**

Although the total synthesis of pel A is outlined in this thesis, the research contains in this thesis involvedd developing a plausible strategy for the synthesis of the C-8 to C-24 carbon backbone of pel A. Accordingly, this required synthesising the two key retrosynthetic fragments, the C-12 to C-24 fragment **7** and the *gem*-dimethyl ketone fragment **8**. Progress towards the incorporation of ketone **8** into pyranose **5a** is outside the scope of this thesis, however for completeness, strategies for the synthesis and assembly of all the key fragments of pel A will be outlined in the subsequent pages of this chapter.

1.9.2: Synthesis of the C-3 to C-11 fragment of peloruside A

Controlling the stereochemical outcome during the formation of the pyranose ring of pel A will be one of the more challenging aspects of the synthesis. First, the desired axial orientation of the C-8 benzyloxy substituent in **5a** requires formation of the *E* enolate of *gem*-dimethyl ketone **8**. Although the close proximity of the *gem*-dimethyl substituents to the carbonyl group will favour formation of the *Z* enolate, it is anticipated that the use of lithium tetramethylpiperidide (LTMP), a sterically hindered base, will give the desired *E* geometry,[81] scheme 4.

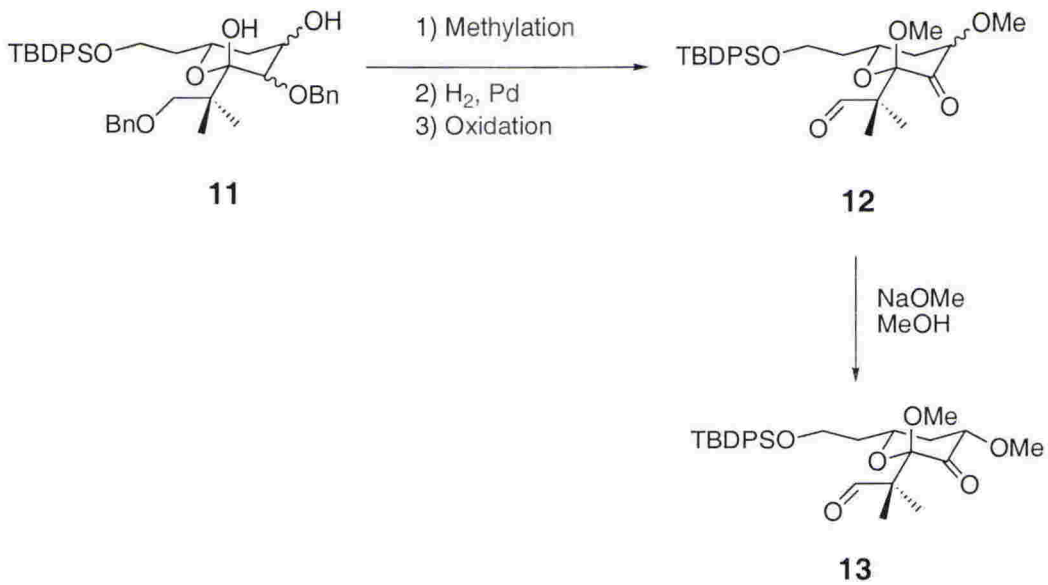
Controlling the facial selectivity of the subsequent aldol reaction necessitates a transition state involving chelation control of the ß-hydroxy substituent. Lithium[v] has been reported to display useful levels of chelation control,[82] as depicted in scheme 4. Here lithium chelates to the enolate anion and to both the aldehyde carbonyl oxygen and the ß-alkoxy oxygen of the approaching aldehyde. Chelation of the lithium enolate to the approaching aldehyde moiety occurs via a six-membered twist-boat Zimmerman-Traxler transition state,[83] with coordination of lithium to the OTES substituent resulting in the chair conformation of the aldehyde partner. Chelation occurs with both the *gem*-dimethyl side chain and the alkyl chain of the ß-hydroxy aldehyde adopting an equatorial orientation. Thus, the anticipated net outcome of this reaction is the desired *anti*- relationship between the C-5 and C-7 and C-7 and C-8 substituents.



Scheme 4: Proposed control of the stereochemistry of the pyranose ring by ß-alkoxy lithium chelation

[v] Magnesium has also been shown to have similar levels of chelation control

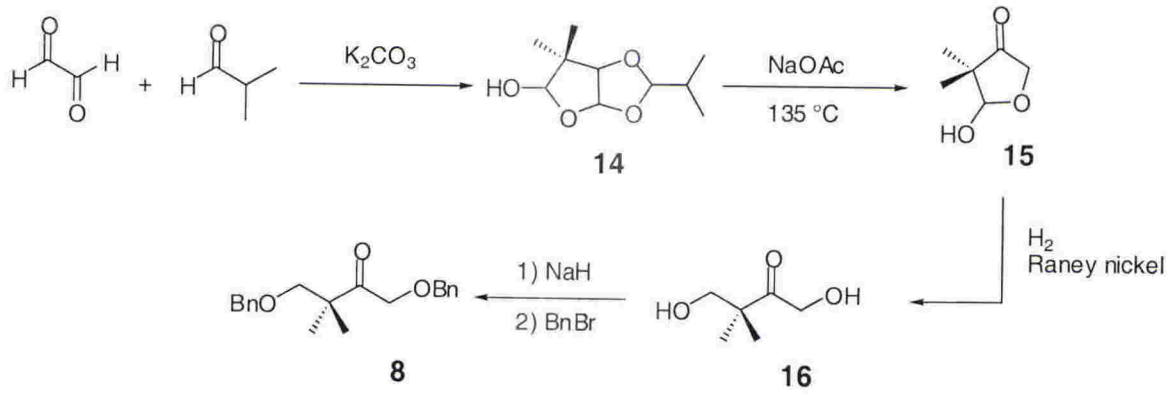
If a stereoselective aldol reaction proved unviable, an alternative, although slightly more involved approach for the formation of the pyranose ring has been proposed. An unselective aldol reaction between the enolate of ketone **8** and aldehyde **9** would give, after *in situ* deprotection of the TES substituent, pyranose **11** as a mixture of diastereomers with the two alkyl chains adopting the equatorial orientation, scheme 5. Upon methylation, hydrogenation and oxidation, cyclic intermediate **12** would be formed. The C-7 methoxy could then be epimerised to the equatorial position to give **13** by treatment of **12** in a basic medium.[84] At a later stage in the synthesis, the cyclic ketone could be asymmetrically reduced with $NaBH_4$, or other suitable reducing agent, to give the axial conformation of the C-8 ring hydroxyl.



11 **12** **13**

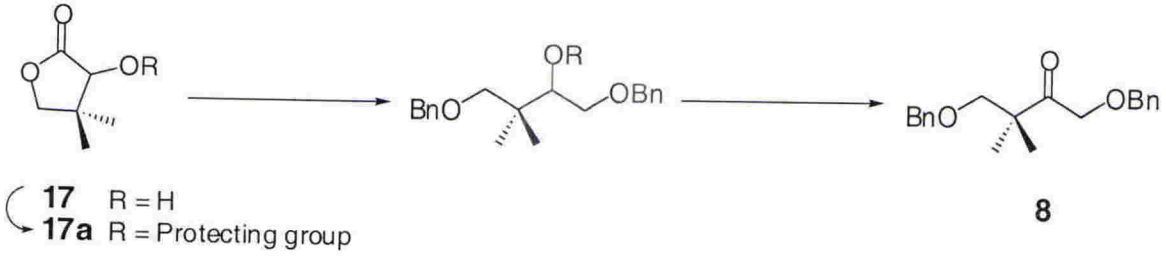
Scheme 5: Alternative strategy for the synthesis of the pyranose ring

Two strategies have been proposed for the synthesis of ketone **8**. The first of these commences with an aldol reaction between glyoxal and isobutyraldehyde, forming the intermediate acetal **14**, scheme 6. The base catalysed thermal rearrangement of **14** gives hydroxy furanone **15**, which is subsequently reduced to diol **16**, then benzylated to afford **8**. Although it is conceivable that difficulties may be encountered in preventing self-condensation during the first aldol reaction, a patented procedure for this synthesis has been reported.[85]



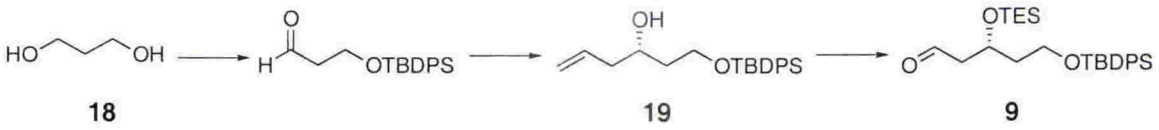
Scheme 6: Synthesis of ketone **38** starting with glyoxal and isobutyraldehyde

Alternatively, reduction of commercially available pantolactone **17**, followed by selective benzylation of the primary hydroxy groups and oxidation of the remaining secondary alcohol yields ketone **8**, scheme 7. Although this three-step synthesis appears to be ideal, difficulties could be encountered in selectively benzylating the primary hydroxyl groups in the presence of the secondary alcohol. Thus the alternative five-step strategy commencing with the protection of pantolactone to give **17a** may be required, scheme 7. The subsequent reduction of **17a**, followed by benzylation, deprotection and oxidation yields ketone **8**. Even though the primary hydroxyls could be selectively protected with alternative protecting groups, such as silylanes,[86] due to literature precedent for the formation of benzloxy enolates[87] and its overall fit within the synthetic strategy, synthesis of the ketone derivative in its benzylated form was preferred.



Scheme 7: Synthesis of ketone **8** starting with pantolactone

It was proposed that the synthesis of the final fragment of the pyranose ring, aldehyde **9**, would commence with the mono silylation of commercially available propane-1,3-diol. Oxidation, followed by asymmetric allyl boration using ally diisopinocampheyl-borane,[88] yields the intermediate alcohol **19**, which is further silylated and ozonolysed, to give aldehyde **9**,[80] scheme 8.

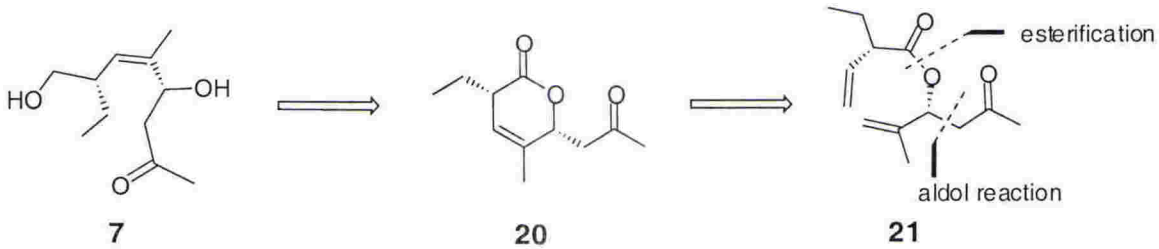


18 **19** **9**

Scheme 8: Synthesis of aldehyde **9**

1.9.3: Sythesis of the C-12 to C-24 fragment of peloruside A

Two strategies were considered for the synthesis of the C-12 to C-24 fragment of pel A. The key intermediate in the first of these strategies is the keto-lactone **20**, which when reduced, gives the C-12 to C-24 fragment 7, scheme 9. Lactone **20** results from the ring closing metathesis (RCM) of ester **21**, itself formed from an esterification and aldol condensation reaction, as depicted. For clarity, it should be noted that a regio- and stereoselective aldol reaction between keto-lactone **20** and the pyranose fragment of pel A would first be conducted before lactone **20** is reductively opened.

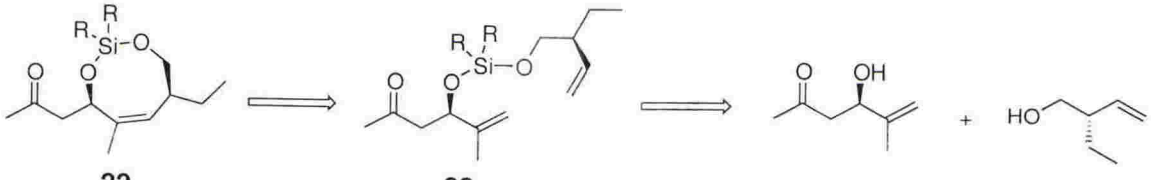


7 **20** **21**

Scheme 9: Initial retrosynthetic analysis for the formation of the C-12 to C-24 fragment

Amongst the strategies considered for the synthesis of the C-12 to C-24 fragment, the aldol reaction with keto-lactone **20** was perhaps the most intriguing. Despite a multitude of precedent for the formation of kinetic verses thermodynamic enolates, as the α - lactone proton in **20** is also susceptible to deprotonation, this may result in double bond isomerization and in difficulties with controlling the regiochemistry of the aldol reaction. However, as it was believed that the synthesis of **20** would be relatively straightforward, this strategy warranted investigation.

In the eventuality of encountering difficulties in controlling the regiochemistry of the aforementioned aldol reaction, the alternative synthesis of the *bis*-alkoxysilyl ether **22** was considered for the formation of the C-12 to C-24 fragment, scheme 10. *Bis*-alkoxy ether **22** is essentially the "tethered" analogue of **7**. Initial concerns about the synthesis of this eight membered *bis*-alkoxysilyl ether by the RCM of the corresponding acyclic precursor **23** were subsequently alleviated by recent publications reporting the synthesis of similar molecules by RCM.[89,90] Diene **23** could in turn be synthesised by the silylation of ß-hydroxyketone **24** and (*S*)-3-hydroxymethylpent-1-ene **25**.

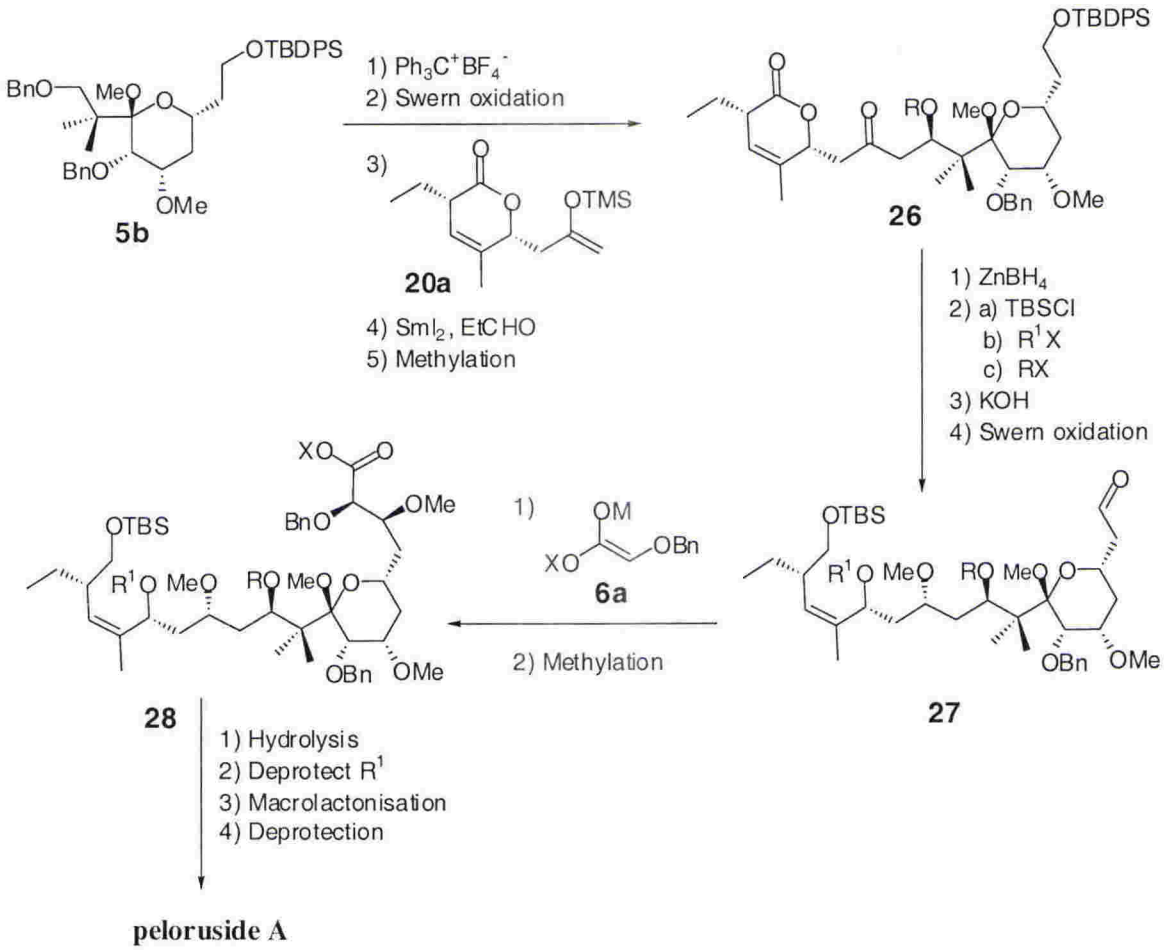


22 **23** **24** **25**

Scheme 10: Alternative retrosynthesis of the C-12 to C-24 fragment

1.9.4: The assembly of peloruside A

To accommodate for the variability in the synthesis of the key fragments of pel A, different methodologies for the assembly of these fragments have been developed. In particular, two key strategies have been proposed reflecting the inclusion of the different C-12 to C-24 fragments into the total synthesis. The first of these strategies involves the incorporation of lactone **20** into the overall synthetic plan, as outlined in scheme 11.

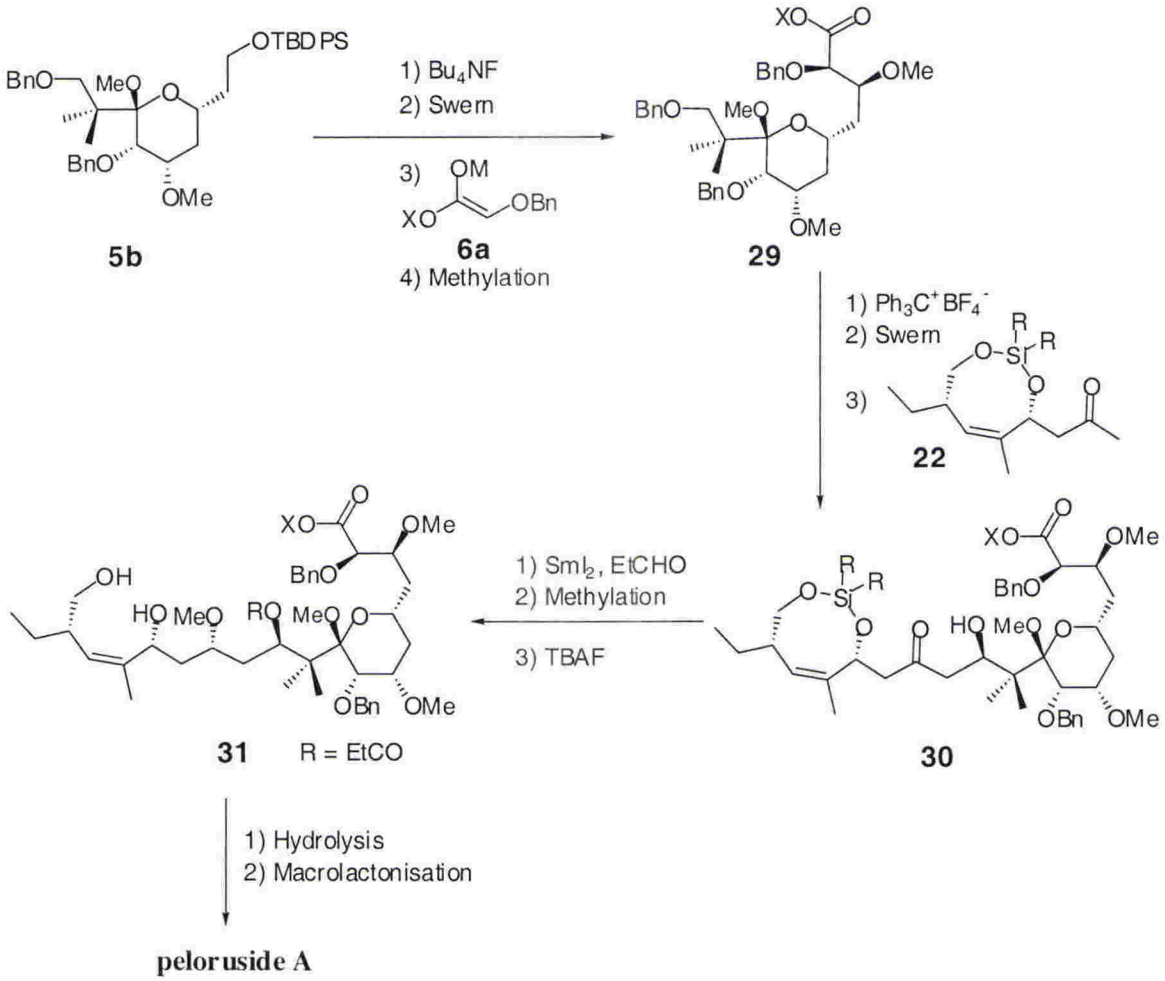


Scheme 11: Synthesis of peloruside A: Strategy 1

To facilitate the coupling of fragment **20a** (the TMS enol ether of **20**), pyranose **5a** would be first methylated to give **5b**, selectively debenzylated, using triphenylmethyltetrafluoroborate,[91] the ensuing hydroxyl oxidised to an aldehyde under Swern conditions,[92] and an asymmetric aldol reaction with **20a** conducted. It was envisioned that a Lewis acid catalysed Mukaiyama aldol reaction would be used to control the stereochemistry of this reaction.[93] A Evans-Tischenko reduction[97] when then be employed to give the desired C-11 to C-13 *anti* relatioship and the resulting hydroxyl methylated to give **26**, (where R = $EtCO_2$). The lactone would then be reductively opened using $ZnBH_4$, which would also result in the deprotection of the propanyl ester. Thus, this overall transformation would result in three hydroxyl moieties, a primary, allylic and secondary which can be

selectively protected, before the primary *tert*-butyldiphenylsilyl protecting group is deprotected[94] and the resulting hydroxyl oxidised to give aldehyde **27**. An asymmetric aldol reaction between **27** and the enolate of the benzyloxy acid derivative **6a**, followed by methylation of the resulting alcohol will follow to yield **21**. It is proposed that a chiral auxiliary (X), such as Evans' oxazolidinone[95] will exert the necessary π-facial selectivity required for this aldol reaction. Finally, hydrolysis of the auxiliary, followed by deprotection of the allylic hydroxy substituent, Yamaguchi macrolactonisation,[96] and deprotection of the remaining protecting groups, including the methoxy acetal, gives peloruside A.

Alternatively, if the C-12 to C-22 *bis*-alkoxysilyl ether fragment **22** is incorporated into the synthesis, the order of assembly of the key fragments varies slightly, as depicted in scheme 12 overleaf. First, the *tert*-butyldiphenylsilyl group on pyranose **5b** will be removed and the resulting hydroxyl oxidised to the aldehyde. An aldol reaction with the benzyloxy derivative **6a**, followed by methylation of the newly formed hydroxyl, then gives intermediate **29**. Selective clevage of the primary benzyl ether, followed by Swern oxidation, and an asymmetric aldol reaction with *bis*-alkoxysilyl ether **22** would then give the complete carbon skeleton **30**. An Evans-Tishchenko reduction of **30** with samarium iodide and propanal, then establishes the correct stereochemistry for the 1,3,5–triol sequence and protects the C-11 hydroxyl as the propanoyl ester.[97] Methylation of the resulting hydroxyl, followed by desilylation of the *bis*-silyl ether gives intermediate **31**. Following the hydrolysis of the chiral auxiliary, and propanoyl ester (R), a Yamaguchi macrolactonisation will then be attempted directly with **31** to give peloruside A. If a mixture containing the 16, 21 or the 11 membered lactones is formed, a series of protection and deprotection strategies will be required to selectively protect the C-11 and C-24 hydroxyl groups before the macrolactonisation.



Scheme 12: Synthesis of peloruside A: Strategy 2

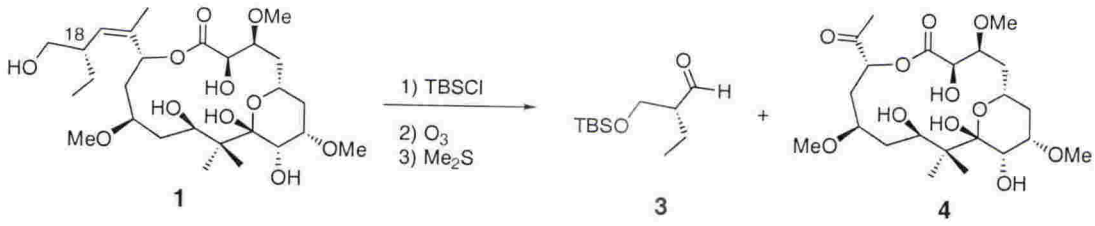
Although not without its own unique challenges, the above synthesis appears flexible and convergent enough to enable modifications to be made as required, and at a later date, to facilitate the synthesis of analogues of peloruside A. More recently, several papers concerning the synthesis or partial synthesis or peloruside A have appeared in the literature. These publications are reviewd in the appendix (page 178).

Chapter Two

Determination of the absolute stereochemistry of peloruside A

2.1: Review

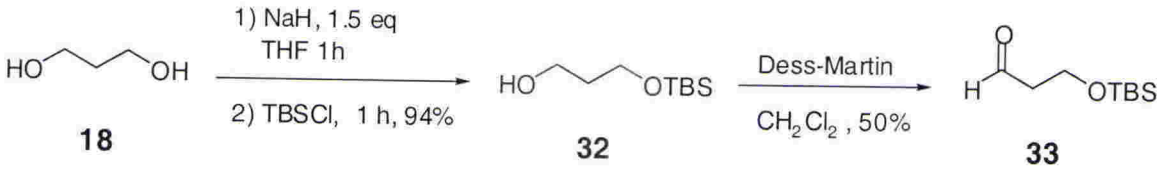
As previously discussed, determination of the absolute stereochemistry of pel A was to be achieved by determining the stereochemistry at C-18 of the side chain, scheme 13. One possible approach to this requires silylation of the primary hydroxyl of pel A, followed by ozonolysis to produce 2-((*tert*-butyldimethyl)-siloxymethyl)butanal **3**. After synthesising both the racemic and enantiomerically pure versions of **3**, chiral gas chromatography would first be used to compare the retention times of these derivatives, thus enabling the order of elution of the (*R*)- and (*S*)- enantiomers to be determined. By co-injecting a synthetic racemic mixture of **3** with the cleaved fragment of pel A, the relative retention time of the cleaved fragment, and hence the chirality at C-18, could then be deduced. Due to the limited abundance of pel A, investigations into this strategy began with the synthesis of the racemic alkyl side chain. This would provide valuable insight into any potential problems that may arise with handling a substrate such as **3**, and enable the optimum conditions for the separation of the two enantiomers by chiral gas chromatography to be determined.



Scheme 13: Strategy for the determination of the absolute stereochemistry of peloruside A

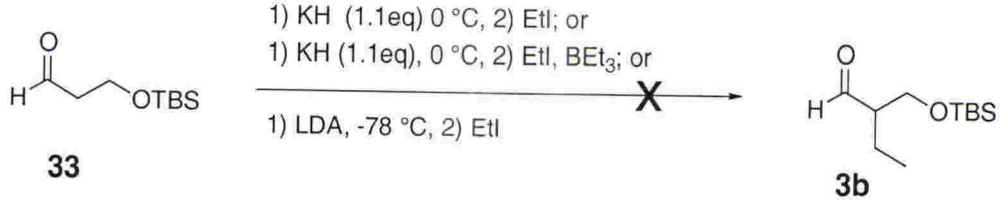
2.2: Strategy One

The availability of propan-1,3-diol **18** provided a convenient starting point for the synthesis of the racemic alkyl fragment. Monosilylation of diol **18**,[98] followed by a Dess-Martin oxidation[99] resulted in the formation of 3-(*tert*-butyldimethyl-siloxy)propanal **32**, scheme 14. However, due to its apparent volatility, propensity to decompose, and difficulties in finding an adequate stain for thin layer chromatography (t.l.c) analysis, purification of aldehyde **33** proved to be somewhat troublesome. Nevertheless, eventually gram quantities of **33** were produced in an overall modest yield.



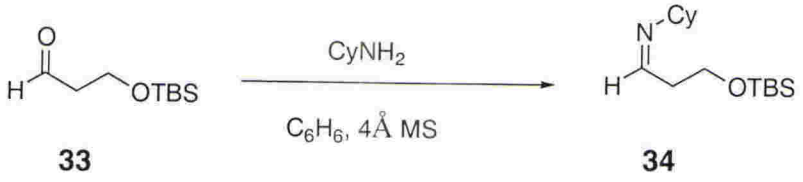
Scheme 14: Formation of *tert*-butyldimethylsiloxypropanal

To complete the racemic synthesis of the side chain, an α-alkylation reaction of **33** with ethyl iodide was required. Although the alkylation of aldehydes is problematic, with dialkylation and self-condensation frequently being observed, during the attempted alkylation of **33** it was nonetheless disappointing to observe none of the desired alkylated adduct **3b**. A variety of conditions were investigated, as detailed in scheme 15, however in all instances, the starting material simply decomposed.



Scheme 15: Attempted α-alkylation reactions

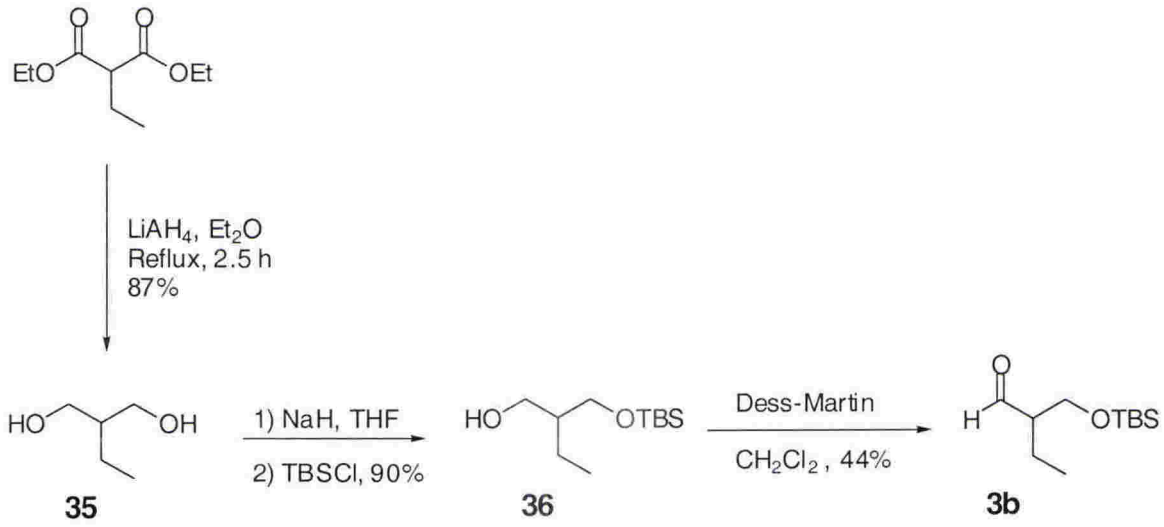
In an endeavour to synthesise a substrate more amenable to α-alkylation, attempts were made to convert **33** into the potentially more robust *N*-cyclohexyl-3-(*tert*-butyldimethylsiloxy)imine **34**, scheme 16. Although ^{1}H NMR spectroscopic analysis indicated that imine **34** had indeed been synthesised, on the sub-gram scale, attempts at separating the excess cyclohexylamine from the desired immine proved futile. Consequently, this procedure was abandoned.



33 **34**

Scheme 16: Attempted synthesis of *N*-cyclohexyl-3-(*tert*-butyldimethylsiloxy)imine

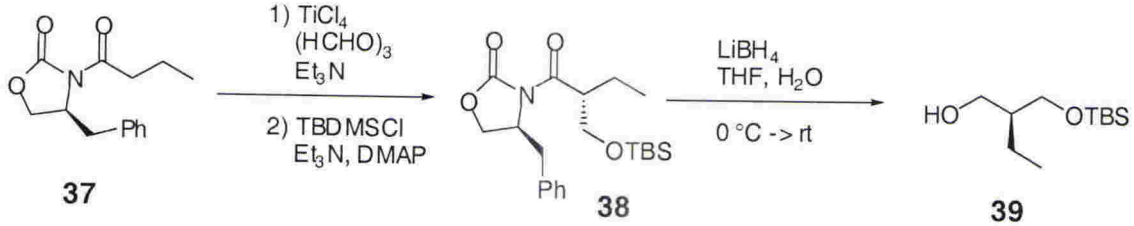
In view of these findings an alternative, and indeed more elegant, strategy for the synthesis of **3b** was devised, scheme 17. This involved the reduction of diethylethylmalonate,[100] monosilylation of the ensuing diol and a Dess-Martin oxidation to form the racemic fragment **3b**. Fortunately, these transformations proceeded relatively smoothly. Although literature precedent called for the reduction of the malonate in diethylether at room temperatrure, to ensure complete conversion of the starting substrate to the requisite diol, the reaction mixture was heated at reflux. Yields were comparable to those previously reported.[100] Unfortunately, yields for the oxidation were once again modest as difficulties were encountered in encouraging this reaction to go to completion whilst preventing the decomposition of starting material. Similar difficulties were encountered with the attempted oxidation of **36** using pyridium chlorochromate (PCC) as the oxidant.



Scheme 17: Alternative strategy for the racemic synthesis of fragment **3b**

Having synthesised racemic **3b**, investigations into determining the optimum conditions required for the separation of the enantiomers using a 30m x 0.25mm Cyclodex-B™ chiral gas chromatography column were conducted. As the retention times for the enantiomers were very similar, some problems were encountered when attempting to separate the enantiomers. The apparent instability of aldehyde **3b**, which rapidly oxidises to the corresponding acid within a few days (even with storage under argon at <4°C), also provided an additional hurdle. Numerous changes to the run conditions were required before distinguishable, yet overlapping peaks, for the enantiomers were observed.

Thus with a suitable synthetic strategy for the racemic synthesis of the alkyl side chain in place, work began on the synthesis of the enantiomerically pure alkyl side-chain. Literature precedent[79] for the synthesis of (-)-(2*S*)-2-((*tert*-butyldimethyl-siloxy)methyl)butan-1-ol initially involved an enantioselective alkylation reaction using Evan's chiral oxazolidinone **37**, titanium(IV) chloride, triethylamine, and trioxane, scheme 18. Subsequent *in situ* protection of the hydroxyl group using *tert*-butyldimethylsilylchloride gives **38**. The enantiomeric excess of the alkylation reaction was reported to be greater than 99%, yet the reported overall yield for the two transformations was a mere 48%.

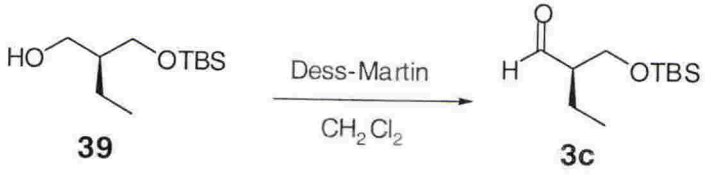


Scheme 18: Literature precedent for the synthesis of (-)-(2S)-2-((*tert*-butyldimethyl-siloxy)methyl) butan-1-ol **39**

Reproduction of the literature methodology for the titanium tetrachloride mediated α-alkylation reaction gave astonishingly poor yields. Grams of substrate **37** would yield only milligram quantities of the requisite product. In total, only 10 mg of **38** was ever isolated.

Thus with only a 10 mg sample of **38**, the auxiliary was apprehensively cleaved using a solution of $LiBH_4$ in wet THF. Fortunately this proceeded smoothly. Due to the small sample of the desired alcohol **39**, purification of the crude material by flash chromatography was particularly challenging. Nevertheless, 5 mg of pure (-)-(2*S*)-2-((*tert*-butyldimethylsiloxy)methyl)butan-1-ol **39** was isolated.

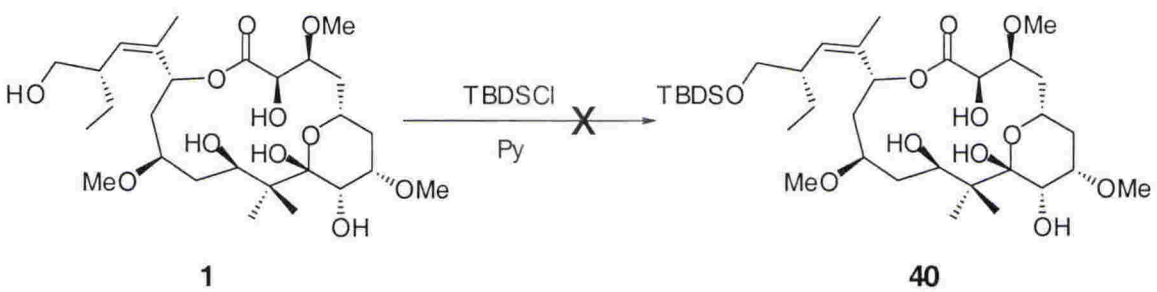
Once again, the Dess-Martin oxidation protocol was followed for the oxidation of **39**. This protocol is particularly facile for the oxidation of milligram quantities of substrate. After a simple filtration of the crude reaction mixture through a Pasteur pipette sized silica gel plug, a sufficient quantity of the enantiomerically pure aldehyde **3c** was obtained for analysis by gas chromatography; scheme 19. Thus, with great anticipation, enantiomerically pure **3c** and a freshly prepared sample of the racemic aldehyde **3b** were co-injected into the gas chromatogram.



Scheme 19: Final oxidation of the enantiomerically pure alcohol

Although separation of the enantiomers by gas chromatography was not ideal, it was nevertheless possible to conclude that the (*S*)-enantiomer was the first enantiomer eluted, as evidenced by an increase in the peak height of the first of the two eluted peaks. Thus all that remained in this strategy was to silylate pel A with the *tert*-butyldimethylsilyl group then cleave the olefinic bond, via ozonolysis, to form the corresponding aldehyde.

Unfortunately this was where considerable difficulties arose. Due to the 1 mg sample size of pel A that was available, silylation proved unviable, scheme 20. Presumably this was due to the dilution at which the reaction was conducted – effective silylation requires concentrated conditions.[101] Although we acknowledged that small-scale reactions are often troublesome and present their own unique practical difficulties, this was nevertheless an exceptionally disappointing result. An alternative approach was required.

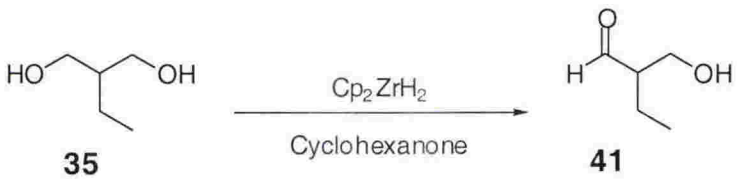


1 **40**

Scheme 20: The attempted silylation of peloruside A

2.3: Strategy Two

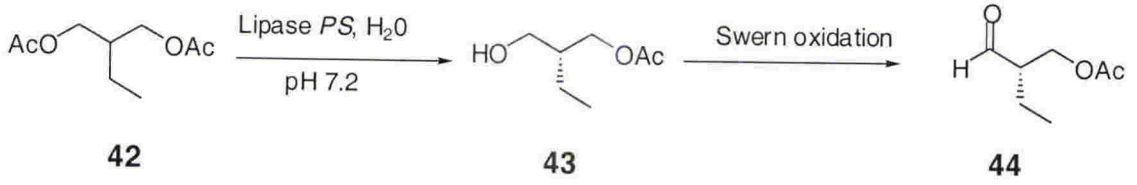
Two factors were of utmost concern when redefining the target molecule. First, a protecting group had to be chosen that had a much greater likelihood of being incorporated onto a natural product on such a small scale, and second, there had to be a facile synthesis for the corresponding enantiomerically pure side chain. Although one could contemplate simply performing ozonlysis on unprotected pel A, there were some concerns with this strategy. While an Oppenauer-type oxidation of diol **35** using Cp_2ZrH_2 could be conducted, scheme 21,[102] formation of the required enantiomer would be difficult and would ultimately require the manipulation of (-)-(2*S*)-2-((tert-butyldimethylsiloxy)-methyl)butan-1-ol **39**, or similarly protected alcohol. Given the difficulties in synthesising the siloxy alcohol, further chemical manipulations on this segment were unpractical. It was also conceivable that **41** would be a difficult molecule to work with due to its low molecular mass and highly polar nature. Consequently, this strategy was discarded.



Scheme 21: Possible Oppenauer-type oxidation of **35**

Literature precedent for the acetylation of many natural products[103] prompted us to believe that the primary hydroxyl group of the side chain of pel A would also be amenable to acetylation. However unlike the previous silylation strategy, in which only the primary hydroxyl terminus was expected to be protected, acetylation of pel A would ultimately result in the acetylation of many, if not all, of the free hydroxyls in pel A. Although it was initially desirable to retain the remaining portion of pel A in its unprotected form after oxidative cleavage (for potential biological testing), this was not of fundamental importance to the strategy. Thus, a review of the literature was conducted to determine if there was synthetic methodology for the synthesis of the enantiomerically pure acetylated

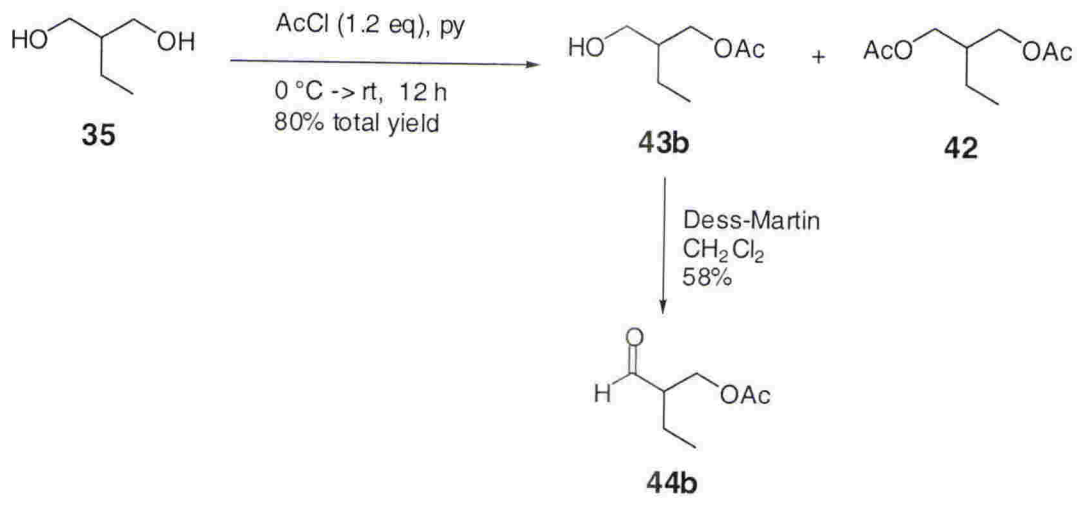
alkyl side chain. Fortuitously, such methodology had been reported,[100] as outlined in scheme 22. Here the lipase, extracted from the microorganism *Pseudomonas cepacia*, kinetically deacetylates, and hence resolves, the diacetylated precursor, **42**. Alcohol **43** is subsequently oxidised under Swern conditions to give enantiomerically pure **44**.



42 **43** **44**

Scheme 22: Alternative strategy for the synthesis of an enantiomerically pure side chain **44**

Thus with a plausible strategy for the synthesis of the enantiomerically pure acetylated side chain in place, all that remained was a methodology for the synthesis of the racemic acetylated side chain. Needing both the monoacetylated alcohol **43b**, (for the racemic synthesis) and the diacetylated alcohol **42** (for the enzymatic resolution), a solution of diol **35** was acetylated under standard conditions but with only 1.2 equivalents of acetyl chloride, scheme 23. This produced an easily separable mixture of the monoacetylated and diacetylated alcohols, **43b** and **42** respectively, in a 1:1 ratio. Although there was literature precedent for the oxidation of **43b** under Swern conditions, the Dess-Martin oxidation protocol had been effectively adapted to meet our requirements for small-scale sample sizes and therefore this later oxidation protocol was followed. However like its silylated counterpart, **44b** was also prone to decomposition and was difficult to detect via t.l.c. Numerous stains were screened[104] before a combination of reagents, saturated σ-dianisidine in glacial acetic acid, was found to be suitable.



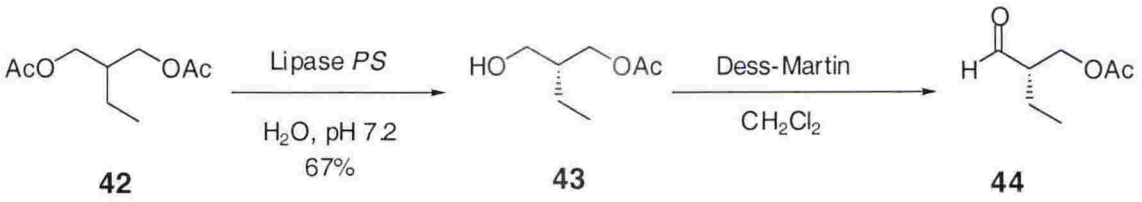
Scheme 23: Formation of the acetylated racemic fragment **44b**

Thus with the racemic aldehyde in hand, attempts were then made at separating the two acetylated enantiomers using the 30m x 0.25mm Cyclodex-B™ column. Although numerous changes were made to the operating conditions during the GC studies, regrettably, these enantiomers were practically inseparable with this particular column. After some consideration, a decision was made to invest in a 60 m x 0.25 mm Cyclodex-B™ column as it was anticipated that the increased length of the column would result in a greater separation of the two peaks for the eluted enantiomers. Thankfully this assumption came to fruition. The acetylated enantiomers could indeed be separated when using the 60 m x 0.25 mm Cyclodex-B™ column, albeit after an extended two hour run time! The optimum run conditions were as follows: Inlet: Split 275°C; Detector: FID 320°C; Carrier gas: hydrogen; Flow: 35.8 cm^3s^{-1}; Temperature programme: Isothermal at 60°C.

Having established the conditions required for the adequate separation of the two acetylated enantiomers, our focus then shifted towards the enzymatic resolution of the diacetylated precursor **42**. As surmised in the literature,[100] diacetate **42** readily undergoes hydrolysis into the racemic monoacetate in the absence of lipase *PS*, (thus **42** must be added to an aqueous solution of lipase *PS* buffered at pH 7.2). Although the literature reported enantiomeric excesses of greater than 88% at 69% hydrolysis, the cost of the

enzyme meant that this reaction could only be conducted at 5% of the scale reported. Consequently, it was a little more difficult to monitor the hydrolysis rate and the ee value,[VI] using only 100 mg of the lipase, was only 72%. This result however, was still adequate.

Thus with only 40 mg of enantiomer **43** available, and with the knowledge that the corresponding aldehyde **44** has limited stability, a small (8 mg) sample of purified **43** was subjected to a Dess-Martin oxidation. Once again, this methodology proved to be successful with milligram quantities of aldehyde **44** being produced after purification though a small (pasteur pipette sized) silica gel plug, scheme 24.



Scheme 24: Synthesis of the acetylated, enantiomerically enriched side chain.

Concurrently, racemic 2-(acetoxymethyl)butanal was synthesised and the racemic and enantiomerically pure fragments co-injected into the gas chromotograph. As anticipated, the two samples co-eluted. The (*R*) enantiomer elutes first from the column with a retention time of 116.5 minutes, while the (*S*)-enantiomer has a longer retention time of 119.5 minutes. The gas chromatograph trace of racemic aldehyde **44b** coinjected with the (*S*) enantiomer **44** is given in figure 12.

[VI] The enantiomeric excess was determined by g.c analysis of the corresponding aldehyde

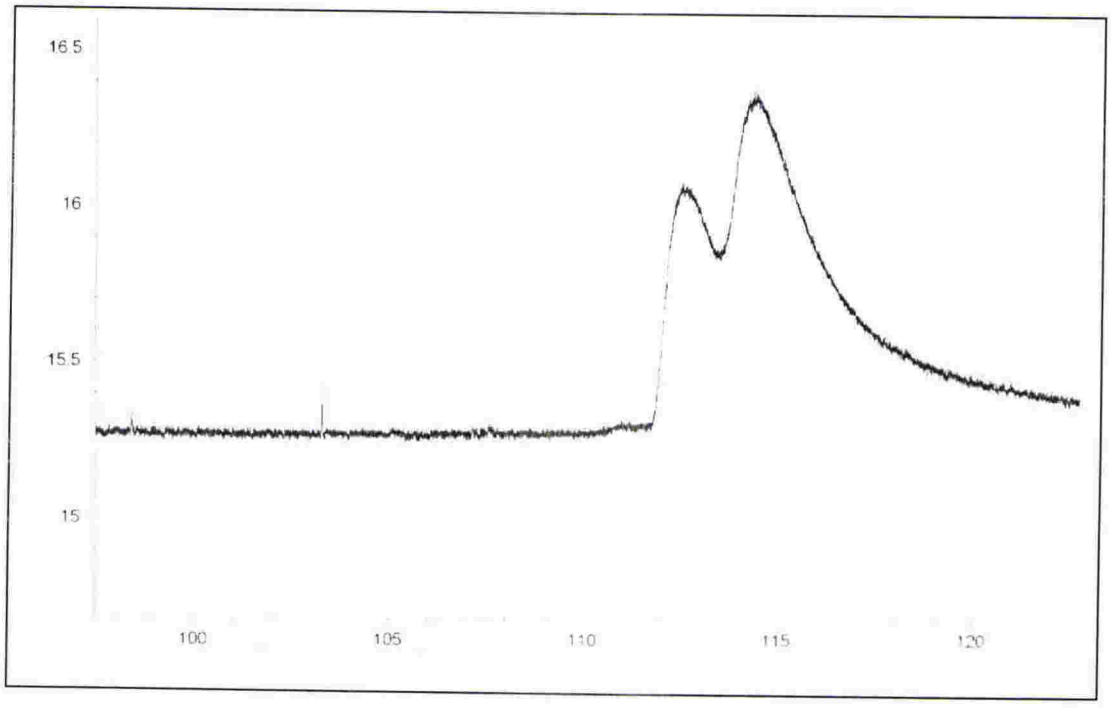
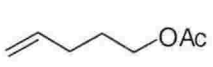


Figure 12: Gas chromatograph trace of the racemic aldehyde **44b** co-injected with the (*S*)-enantiomer **44**

Once again, the point in the strategy had now been reached where pel A had to be manipulated. But this time only 0.5 mg of pel A was available. However, even before any attempts at acetylating pel A were made, two important questions needed to be answered. First at this scale, would the final enantiomer even be detectable by the gas chromatograph, and second, how feasible were small-scale ozonolysis reactions?

To determine the sensitivity of the gas chromatograph, some approximate concentration studies were conducted. Due to the instability of **40b** and the 2 hour run times required for good peak resolution, pinene was instead chosen as a standard. Fortunately, 3 μL aliquots taken at dilutions as low as 0.01 mg of pinene per 1 mL of dichloromethane could be detected by the GC. This equated to 2.2×10^{-10} moles of substrate and indicated that, when starting with a 0.5 mg sample of pel A (9.11×10^{-7} moles), the cleaved acetylated side chain should be detected, even if the acetylation and ozonolysis reactions went to only 10% completion.

The easily prepared model compounds **45** and **46**, figure 13, were then synthesised in order to investigate small-scale ozonolysis reactions. What became apparent in these studies was that the length of time that the substrate was exposed to ozone was crucial - between two and three seconds was ideal for samples sizes of less than 1 mg. Furthermore, triphenylphosphine, as compared to dimethylsulphide, appeared to be a better reagent by which to reductively work-up the reaction. Nevertheless, these were difficult reactions. Undesired side products were always formed, and there was a fine balance between the complete conversion of the alkenes to the corresponding aldehydes with additional side products, or incomplete reactions and fewer side products. Isoprene was added to the reaction mixture in an attempt to "mop-up" the excess ozone, although this proved futile. All the same, as much experimenting as was practical had been conducted and the acetylation of pel A was attempted.



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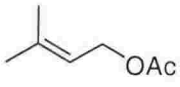
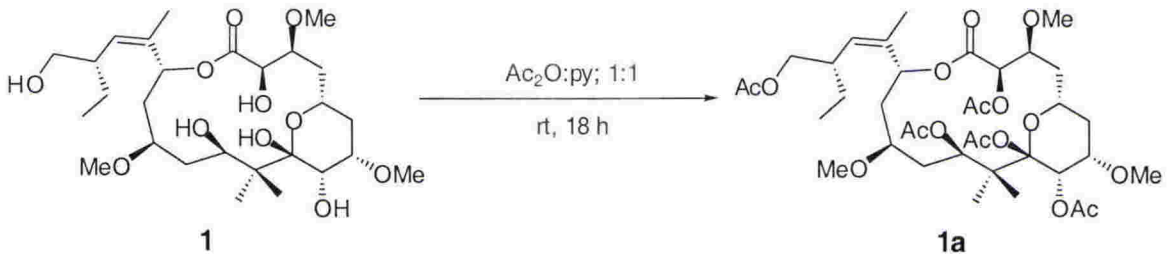


46

Figure 13: Model substrates for small-scale ozonolysis reactions

A 0.5 mg sample of pel A was thus dissolved in 1 ml of a 1:1 mixture of acetic anhydride:pyridine, then left to stir for 18 hours at room temperature in the dark, scheme 25. The solution was then passed through a small glass column packed with HP-20S (polystyrene divinylbenzene) beads and the eluent combined with 3 mL of distilled water and passed through the same column. The resulting eluent was diluted with a further 3 mL of water and passed through the column. The column was then washed with approximately 25 mL of water to remove most of the remaining pyridine and acetic anhydride, then 10 mL of 20:1 water:acetone, and 2.5 mL of 1:1 water:acetone to remove any unacetylated pel A. The reaction product was then eluted with 6 mL of acetone and the solvent removed under reduced pressure. Silica gel t.l.c analysis of the crude material revealed the presence of two major spots with R_f values of approximately 0.50 to 0.55 in

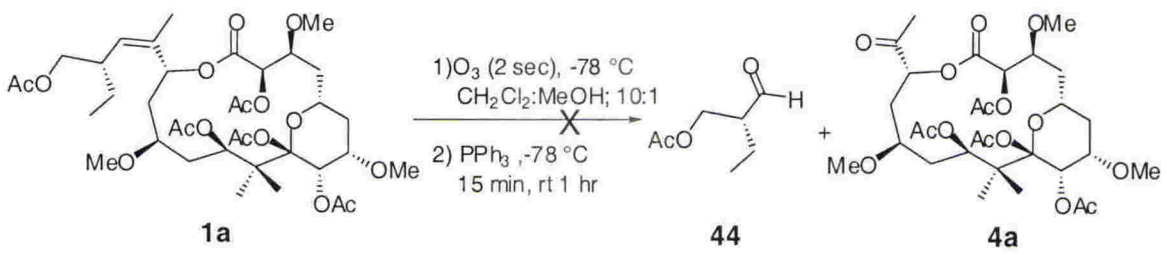
5% MeOH:CH_2Cl_2. It was believed that these two products were the tetra and penta acetylated adducts. The crude material was then purified further by silica gel chromatography using a solvent gradient from pure CH_2Cl_2 to 10% MeOH:CH_2Cl_2. Due to the exceptionally small sample size, the two major products were collected as one fraction.



Scheme 25: Acetylation of peloruside A

Spectral analysis of the combined products by ^1H NMR revealed the presence of two major acetyl methyl peaks at δ 2.24 and δ 2.07, three peaks of slightly lower intensity at δ 2.19, δ 2.14 and δ 2.22, and several other minor acetyl peaks in the same region of the spectrum. Characteristic peaks of pel A, such as the methoxy peaks between δ 3.3 and δ 3.5 ppm were also present in spectrum. This suggested that although we had not cleanly acetylated every free hydroxyl of pel A, we speculated that the least sterically encumbered primary hydroxyl was definitely acetlyated. Due to the small sample size, we were unable to obtain any other conclusive evidence that we had acetylated pelA, however chromatographic analysis most definitely suggested that pel A had been acetylated. For example, native pel A elutes from HP-20S beads with a 3.3:1 solution of acetone:water.[65] Our sample however, was washed with a 1:1 solution of acetone:water, which would most certainly remove any unacetylated pel A. The less polar acetylated adduct however, would remain on the column. Furthermore, pel A cannot be eluted from a silica gel column when using a solvent gradient from pure CH_2Cl_2 to 10% MeOH.

0.25 mg of the purified acetylated pelA was then subjected to ozonolysis, scheme 26, with a sample from the crude reaction mixture being subsequently injected into the gas chromatograph. The initial GC trace looked encouraging – an exceptionally small peak with a retention time of approximately 116 min was observed. Although this differed slightly from the retention times of 116.5 and 119.5 minutes previously reported, we postulated that this was within experimental error and subjected a second sample, spiked with a freshly prepared sample of the racemic aldehyde, to GC analysis. Unfortunately, in this and subsequent runs, three peaks were observed. Unbelievably, an impurity present had a retention time within 20 seconds of the desired enantiomers.



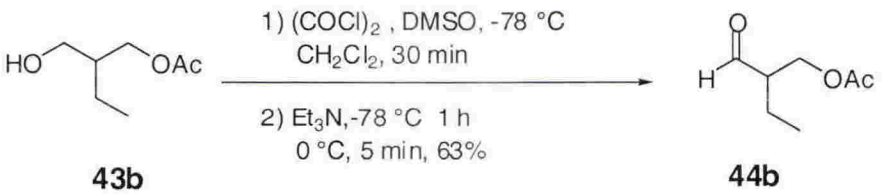
1a **44** **4a**

Scheme 26: Attempted ozonolysis of acetylated peloruside A

To say the least, these results were tremendously disappointing. In an attempt to determine why the desired compound was not detected, a small sample of the racemic aldehyde was subjected to our ozonolysis conditions. Although in theory it is the intermediate ozonolide, and not the subsequent aldehyde, that will be exposed to ozone, it was important to determine how stable the resulting aldehyde is in the presence of excess ozone. Indeed, the ^{1}H NMR of our crude product told an interesting story – there was no sign of the aldehyde substrate. Obviously, on such a small scale, even the smallest trace of excess ozone would destroy our desired compound. It became apparent that on this scale, and with our particular substrate, this was not a plausible strategy.

Although this strategy was beginning to look particularly dubious, after investing so much time into this project it seemed careless to not to at least consider one last option - namely that of a dihydroxylation of the olefinic double bond using osmium tetroxide followed by a periodate oxidative cleavage.[105] As I was unwilling to take any uncalculated risks, model studies on a trisubstitued alkene closing resembling that of the side chain of pel A first needed to be conducted. Indeed, such a substrate could be synthesised by performing a Wittig[106] reaction on aldehyde **44b** using triphenylphosphoranylidene isopropane. However, to add to the frustration, this meant returning to the starting point of the synthesis as all of the precursors had been consumed.

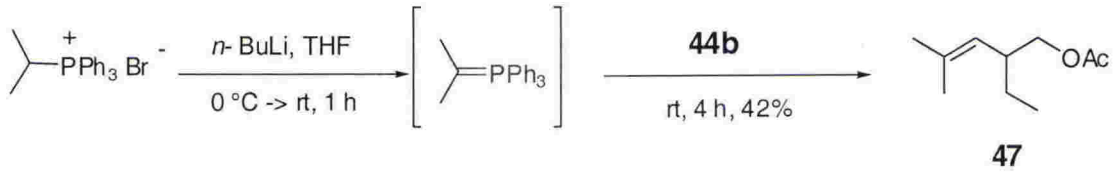
Thus aldehyde **44b** was synthesised in a manner similar to that previously discussed, although, due to the larger scale, the Swern oxidation procedure was used, scheme 27. Although there was literature precedent for this synthesis,[100] it was found that a slight modification of the literature procedure was required to give yields similar to those previously reported. It is interesting to note that the yields for both the Dess-Martin and Swern oxidations of alcohol **43b** are comparable.



43b **44b**

Scheme 27: Swern oxidation of alcohol **39b**

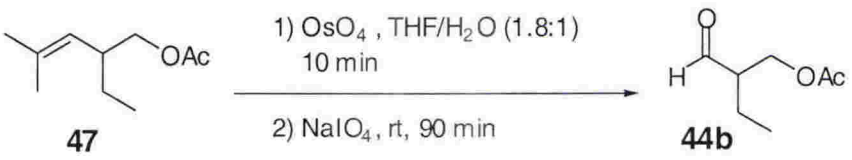
Isopropyltriphenylphosphonium bromide, synthesised according to literature procedure,[107] was then used as the precursor for the *in situ* formation of triphenyl-phosphoranylidene isopropane, scheme 28 overleaf. Aldehyde **44b** was subsequently added to the ylide, with the model alkene **47** being synthesised in modest yield.



47

Scheme 28: Synthesise of the model alkene substrate **47**

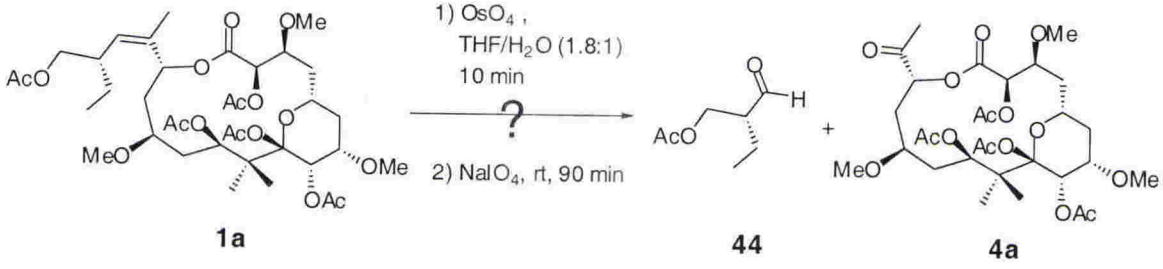
Alkene **47** was then subjected to oxidative cleavage using 10 mol % OsO_4 and sodium periodate, scheme 29. Fortunately, on the 15 mg scale, the required aldehyde **44b** was isolated and characterised. This reaction was then scaled down to the 0.5 mg scale and analysed via gas chromatography. Again results looked promising, with two peaks eluting with the same retention times as those for the racemic aldehyde.



47 44b

Scheme 29: Model studies for the oxidative cleavage of pel A

After preparing a second sample of acetylated pel A, all that remained was the oxidative cleavage of the double bond of pel A. Thus, a 0.5 mg sample of acetylated pel A was subjected to the dihydroxylation conditions previously devised for the model studies, scheme 30. The crude sample was subsequently injected into the gas chromatograph. Upon observing a single peak near those of our desired enantiomers, a second sample, spiked with the racemic aldehyde was injected.



Scheme 30: Attempted osmium/periodate olefinic cleavage of peloruside A

Disappointingly, the peaks did not co-elute. There was no evidence of the desired cleaved side chain fragment from pel A, only an impurity that again had a retention time within 20 seconds of the desired enantiomers. The source of this impurity remained a mystery. It was not observed in the previous model studies.

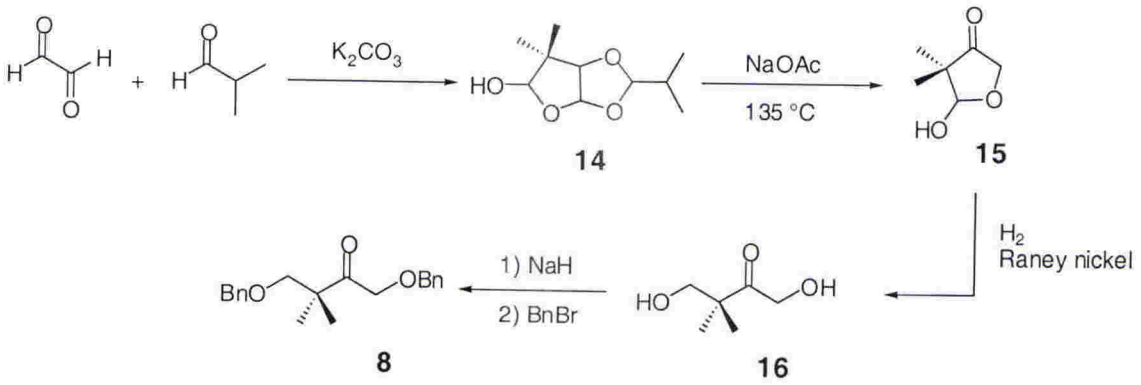
We could only speculate as to why this strategy failed. Perhaps the reaction conditions weren't specific enough for the cleavage of the olefinic bond in pel A and alternative reactions, that ultimately destroyed the desired fragment, occurred. In any case, with a limited natural abundance of pel A, it was not feasible to repeat these experiments. From the observed results it appeared that a larger sample size of pel A was required if this strategy was to succeed. Consequently, the project was discontinued.[VII]

[VII] The total synthesis, and hence determination of the absolute stereochemistry, of pel A was subsequently published by Xibin Liao, Yusheng Wu and Jef K. De Brabander; see *Angewante Chemie, Int. Ed. Engl.* **2003**, 42, 1648. The absolute configuration of pel A was reported to be opposite to the one shown throughout this thesis

Synthesis of the C-8 to C-11 fragment of Peloruside A

3.1: Strategy One

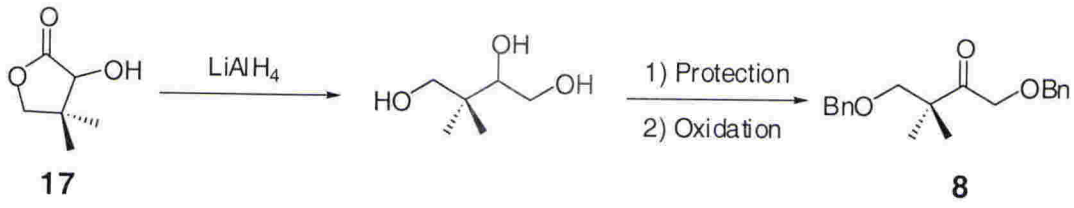
Amongst the strategies considered for the synthesis of the gem-dimethyl ketone **8**, the aldol reaction between glyoxal and isobutyraldehyde appeared to offer the most potential as the starting point in our synthesis, scheme 31. Although this strategy has the advantage in that it does not require the regioselective protection of primary alcohols in the presence of a secondary alcohol, it was quickly established that the formation of **14** was more difficult than originally envisioned. The large-scale patent procedure[85] that was followed for the formation of **14** appeared to be unsuitable on the multigram scale. Rather than cleanly producing **14**, a menagerie of aldol condensation and self-condensation was observed. The methodology required for the successful implementation of this protocol appeared to require very precise conditions. Determining these exact conditions would be a particularly laborious process and hence, an avenue we were not prepared to explore at this stage.



Scheme 31: Synthesis of the *gem*-dimethylketone **8**: Strategy One

3.2: Strategy Two

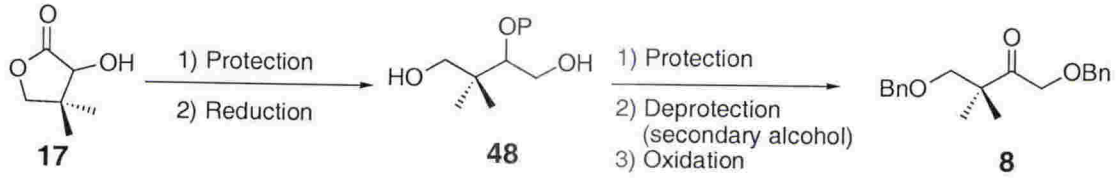
Consequently, we focussed our attention on the formation of *gem*-dimethylketone **8** from pantolactone **17**, scheme 32. Literature precedent indicated that the reductive ring opening of **17** could be achieved using a solution of lithium aluminium hydride ($LiAlH_4$) in THF.[108] However in our hands, the yields for this procedure were disappointingly low even though several attempts were made at this strategy. Consequently attempts were made at reducing the lactone using a solution of $NaBH_4$ in ethanol, but again, the yield of the desired triol was exceptionally low.



17 **8**

Scheme 32: Proposed route for formation of *gem*-dimethyl ketone **8**

Our limited success in reducing unprotected pantolactone **17** prompted us to investigate the reductive ring opening of a suitably protected species, scheme 33. We felt that the highly polar nature of the triol and the workup conditions, which requires filtration through a small silica gel plug, may have lowered the yields. Although the protection of pantolactone would add additional steps to the synthesis, the protected diol **48** has the advantage in that regioselective protection strategies are no longer required when protecting the primary alcohols.

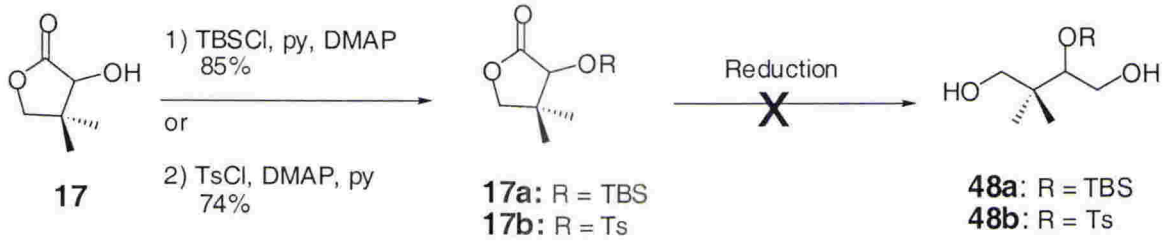


17 **48** **8**

Scheme 33: Modified strategy for the formation of *gem*-dimethylketone **8**

The ability to perform a one-pot desilylation-oxidation[109] of aliphatic *tert*-butyldimethylsilyl ethers using catalytic quantities of $PdCl_2(MeCN)_2$ prompted us to first investigate the protection, and subsequent reduction of the silyl protected lactone **17a**, scheme 34. Although protection of lactone **17** as the silyl ether proceeded smoothly, initial investigations within our laboratory into the reduction of this lactone were disappointing. Upon reduction of the lactone the silyl group preferentially migrated to the primary terminus.[110] In many respects this was not an entirely unexpected observation as the ability of a silyl group to migrate from one hydroxyl to another is not uncommon and frequently causes problems in organic synthesis.[111] In fact, the TBS group is particularly renowned for its migratory ability.[112] Thus, an alternative protecting group was sought.

Accordingly, it was proposed that a tosyl group would suffice as a protecting group. Even though one may question the wisdom of reducing the lactone in the presence of the tosyl functionality, literature precedent existed for the tosylation of pentalactone **17**, followed by reductive ring opening using diisobutylaluminium hydride (DIBAL-H).[113] Thus this strategy warranted investigation, scheme 34. Although synthesis of protected lactone **17b** proceeded smoothly in yields comparable to those reported in the literature, in our hands, the subsequent reductive ring opening using DIBAL-H was unsuccessful. Diol **48b** was only ever formed in abysmal yields, even after the addition of excess DIBAL-H and the implementation of longer reaction times.



Scheme 34: Protection of pantolactone **17** and attempted reduction

Consequently, alternative reduction protocols were investigated. The portion-wise addition of $NaBH_4$ to a solution of the tosyl protected lactone **17b** in THF at 0 °C produced a myriad of undesired side products, with no trace of the desired diol **48b**. ^1H

NMR of the crude product suggested that the lactone had not undergone ring opening. Similar results were observed when lithium borohydride ($LiBH_4$) was added in portions at 0 °C to a solution of **17b** in THF. Although a solution of lactone **17b** and $LiAlH_4$ in refluxing THF primarily resulted in the decomposition of the lactone, there was some evidence by ^1H NMR that the lactone had undergone reductive ring opening.

Even though these results were less than desirable, they suggested that if a more stable protecting group was used, the lactone might be successively reduced using a solution of $LiAlH_4$ in refluxing THF. Being rather chemically inert, it was therefore postulated that an ether-protecting group would be suitable. In particular, an allyl ether was chosen for this purpose as there was some evidence for dual deprotection/oxidation at a later stage in the synthesis.[114]

A standard Williamsons ether synthesis protocol,[115] using allyl bromide as the alkyl halide, was followed to synthesise the allyl protected lactone. The use of the more polar DMF, rather than THF, as a solvent produced optimal results. However, due to an untimely quench of the NMR magnet, we were unable to conclusively prove that the desired allyl protected lactone had been synthesised. Conclusive mass spectral data on the compound was also unattainable. Nevertheless, due to the interests of time, and from IR and t.l.c analysis, it was concluded that the hydroxyl functionality had been protected with an allyl group, and we decided to continue on with the synthesis.

Thus, the next step in this strategy was the reduction of the allyl protected lactone. Based on our previous observations, $LiAlH_4$ was initially chosen as a reducing agent. Fortunately, after a little experimentation with the reaction conditions, the lactone was successfully reduced in a modest 57% yield. The workup procedure in this synthesis was important, requiring the quenching of the reaction with hydrated sodium sulfate followed by filtration though a small silica gel plug for optimum yields.

Having successively reduced the lactone, the next functional group transformation involved the protection of the two primary hydroxyl groups. As there is literature

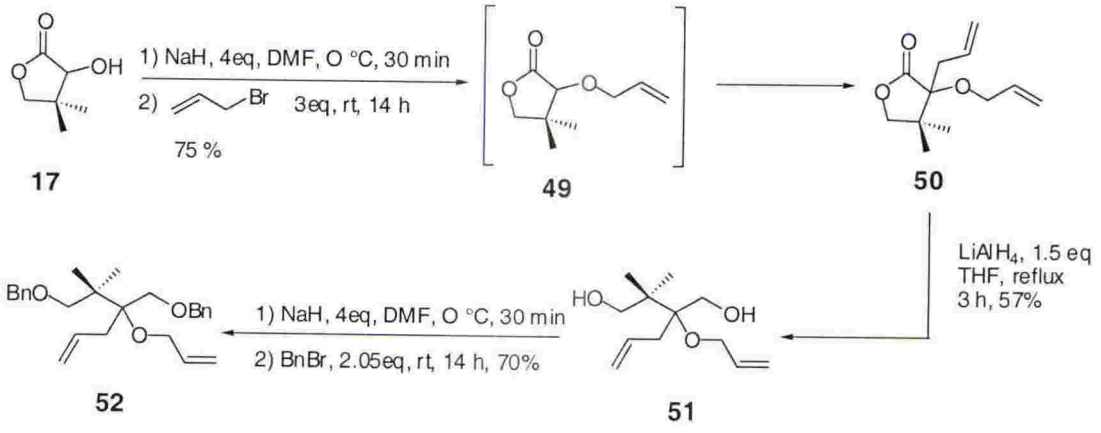
precedent for the formation of β-benzyloxy enolates,[87] and the commercially available benzyloxyacetic acid is also a key fragment in our retrosynthetic analysis, it was decided that the protection of the hydroxyl groups as benzyl ethers was most appropriate. This would allow for a global deprotection of the benzyl groups upon the completion of our synthesis. Consequently our proposed diol was benzylated, again following Williamson's ether synthesis protocol, in 77% yield.

Thus at this stage of the synthesis, strategies for the deprotection of the allyl group were investigated. Ideally, removal of the allyl group can be effected by metal catalysed isomerization of the allyl ether to the corresponding propenyl ether, with subsequent H^+ or Hg^{2+} hydrolysis[116] or oxidative cleavage.[117] Appropriate metal catalysts include palladium on carbon,[118] palladium *tetrakis*-triphenylphosphine,[119] and *tris*-triphenylphosphine rhodium(I) chloride (Wilkinson's catalyst). [120] The aforementioned strategies were thus attempted on our allyl-protected substrate, but with little success. Consequently alternative strategies, including the use of sodium borohydride and iodine (it is believed that $NaBH_4/I_2$ in THF is a source of diborane which initially coordinates to the ethereal oxygen),[121] oxidative cleavage using selenium dioxide and acetic acid[122] or titanium trichloride and magnesium,[123,VIII] were investigated. Allyl transfer reactions, involving palladium chloride and acetic acid[124] or palladium chloride, copper chloride and O_2[125] were also attempted. Unfortunately, none of these were successful.

Not surprisingly, these results were particularly puzzling. However just as frustration set in, we obtained access to another NMR instrument and were able to fully analyse the synthetic precursors. This provided us with some valuable information. Both ^1H and ^{13}C NMR analysis revealed that even though we had protected the hydroxyl group of the starting lactone **17**, the initial allyl protected lactone underwent a subsequent α-substitution reaction, forming the di-substituted species **50**, scheme 35. Thus, our previous reduction and benzylation strategies, as discussed above, had actually been

[VIII] Although $TiCl_3$ and Mg is also known to cleave benzyl ethers, the cleavage of allyl ethers is more facile as the η3-allyl complexes formed in the reaction are more stable than the corresponding η3-benzyl complexes; see reference 123

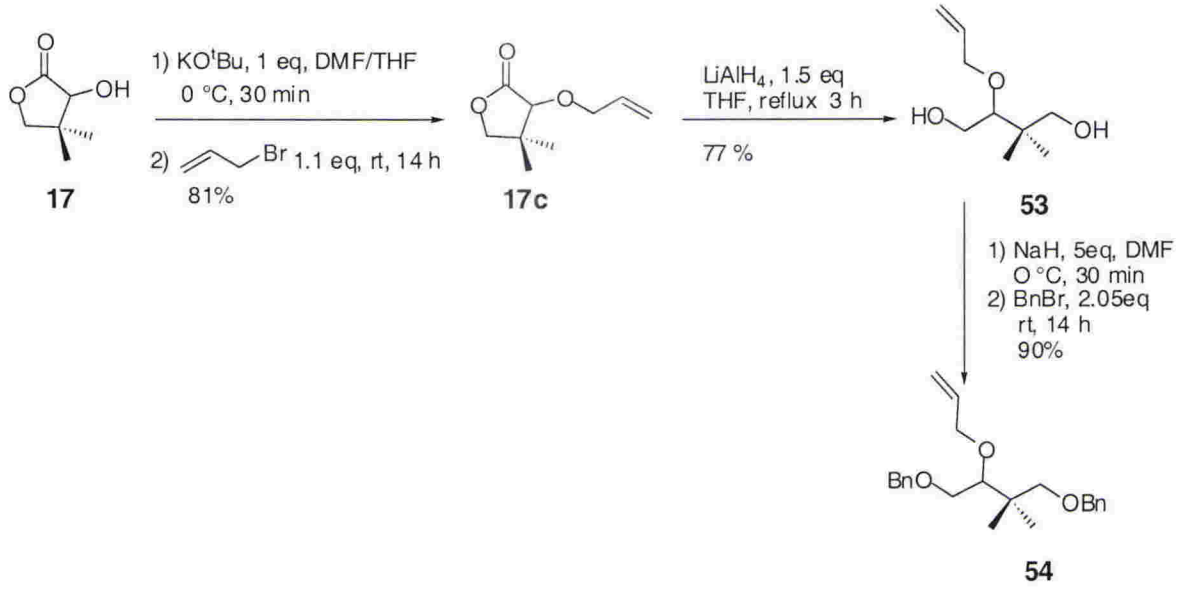
conducted on the disubstituted species **50**. Suddenly the discrepancies in our data and the potential problems with our methodology became glaringly obvious.



Scheme 35: Formation of the dialkylated species

In an attempt to prevent disubstitution from occurring, for every mole of lactone used the number of moles of NaH and allyl bromide were limited to 1.1 and 1.05, respectively. Previously four moles of NaH and three moles of allyl bromide had been used. For the most part, these conditions prevented disubstitution from occurring, however they also resulted in incomplete reactions. These problems were circumvented by the use of 1 equivalent of potassium-*tert*-butoxide in a 1:1 solution of THF/DMF, followed by the addition of 1.1 equivalents of allyl bromide. The desired allyl protected lactone **17c** was cleanly produced in 82% yield, scheme 36. Initially we proposed that the steric bulk of the base may favour mono-substitution, although it was later found that an excess of the base would also result in the disubstituted adduct.[126] Thus, simply the ability to accurately measure one equivalent of potassium-*tert*-butoxide, when compared to NaH, resulted in the clean formation of the desired mono alkylated adduct **17c**.

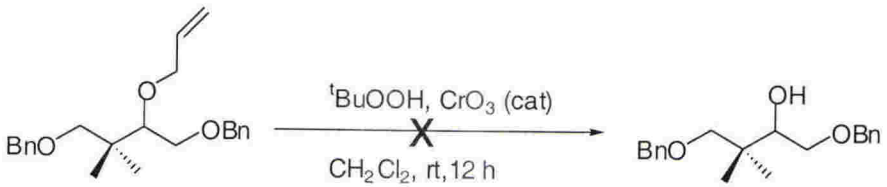
Fortunately the techniques developed for the reduction of the lactone **50** were also applicable for the reduction of the allyl protected lactone **17c**. In fact, when compared to the reduction of **50**, the yield for the reduction of **17c** improved dramatically with the desired diol **53** being synthesised in a respectable 77% yield. Subsequent benzylation of **53** again proceeded smoothly with the dibenzylated species **54** being synthesised in 90% yield, scheme 36.



Scheme 36: Synthesis of the benzyl protected allyl ether **54**

With the allyl ether **54** successfully synthesised, the next major challenge was removing the allyl group. As alluded to earlier, it was proposed that a two-step, one pot, dual deprotection/oxidation of the allyl ether **54** was plausible. Although such methodology is sparse, there is literature precedent indicating that the combination of *tert*-butyl hydroperoxide (TBHP) and CrO_3 initially deprotects an allyl group, then oxidises the resulting alcohol.[114] One can infer from the literature that this deprotection arises from the allylic hydroxylation of the allyl substituent to from a hemiacetal, which decomposes to an unsaturated aldehyde and an alcohol. Upon the addition of a second equivalent of TBHP (to reoxidise the chromium catalyst), the resultant alcohol is then oxidised to the ketone.[127] However when these conditions were applied to allyl ether **54**, starting material was predominately isolated, scheme 37. ^{1}H NMR analysis of the crude

material however, indicated the presence of trace amounts of an aldehyde moiety, suggesting that these reagents preferentially deprotected and oxidised the benzyl groups.



54 **55**

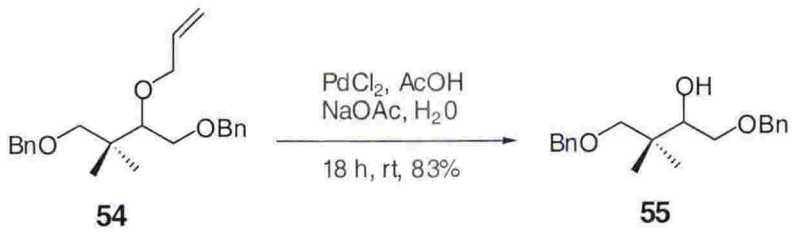
Scheme 37: Attempted dual deprotection/oxidation of allyl ether **54**

Allyl groups can also be oxidatively deprotected with chromia-pilliared montmorillonite clay and *tert*-butyl hydroperoxide.[127,128] However due to mechanistic similarities between this system and the previous example, and the observation by Choudary *et. al.* that such systems can be extended successfully to oxidative debenzylation reactions, we opted against exploring this strategy and focussed on simply deprotecting the allyl group. Even though a dual deprotection/oxidation strategy may still be applicable for our system, this would involve a significant investment of time, and was not of utmost importance to our synthesis.

Ideally, a catalytic methodology was sought for the deprotection of the allyl group so the previous experimental conditions, using palladium on carbon to isomerise the double bond,[118] were repeated on the correct substrate. Although this methodology looked somewhat promising, the reaction would not go to completion with extended reaction times resulting in the decomposition of the starting substrate. Consequently, the $PdCl_2$, CuCl, O_2 system was investigated. Again initial results looked promising, but unfortunately similar difficulties to those observed with the Pd/C system were encountered.

Although only a small proportion of the thirty or so methods for the deprotection of allyl groups[129] had been surveyed, an intuitive hunch prompted us to investigate the milder

reaction conditions of palladium chloride, acetic acid, sodium acetate and water.[124] Gratifyingly, the allyl ether was cleanly deprotected, forming the corresponding secondary alcohol **55** in a respectable 83% yield, scheme 38.



54 **55**

Scheme 38: Deprotection of the allyl group

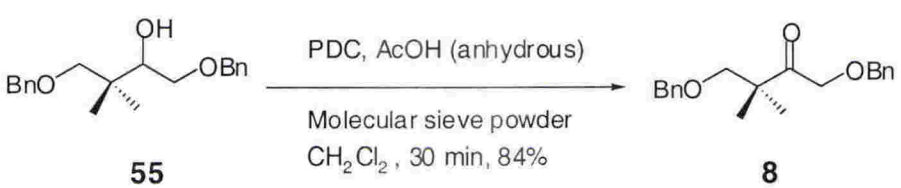
This deprotection strategy however, is not without its pitfalls. Stoichiometric amounts of palladium chloride are required, which due to its expense, does not facilitate a particularly economic synthesis upon scale-up. Nevertheless, we decided to continue on with our strategy and experiment further with allyl deprotection methodologies at a later stage. Thus the final obstacle to overcome in this synthesis was the oxidation of the secondary alcohol.

Ideally, a fairly benign oxidation procedure was desirable, so investigations into the oxidation of alcohol **55** using an aqueous solution of sodium hypochlorite and acetic acid[130] were conducted. Unfortunately, these conditions were not particularly effective for our system, with the desired ketone being formed in a mere 10% yield. The starting material predominantly decomposed, presumably as a consequence of over oxidation. Next, a TEMPO oxidation was investigated. This is also a fairly benign oxidation procedure, requiring only catalytic amounts of 4-methoxy-2,2,6,6,-tetramethylpiperidine-1-oxyl with continuous generation of the oxoammonium salt by NaOCl under aqueous organic two-phase conditions.[131] However, in contrast to the previous oxidation strategy, starting material was only ever isolated using this protocol.

Although not an ideal choice of reagent, we nevertheless turned towards the use of chromium derivatives as oxidising agents. Initially a solution of chromium trioxide in

acetic acid looked promising,[132] though the ketone was only ever obtained in a mere 30% yield. A solution of PCC and $CaCO_3$ in dichloromethane, however, held more potential. Although the desired ketone **8** was synthesised in approximately 50% yield, the reaction would not go to completion, even if excess PCC and longer reaction times were used. Substitution of $CaCO_3$ for NaOAc as the base offered some improvement, enabling ketone **8** to be synthesised in a 60% yield. Nevertheless, we were still plagued by incomplete reactions, with approximately 10% of the preceding alcohol still remaining.

A subsequent review of the literature however, indicated that such practical difficulties were frequently encountered. Unduly long reaction times and the requirement of a large excess of pyridinium chromate oxidising agents, leading to unsatisfactory yields, are common problems.[133] Czernecki *et al*[133a] however, determined that the use of anhydrous acetic acid and freshly activated molecular sieve powder in combination with pyridinum dichromate (PDC) were the decisive factors for achieving reproducible and successful oxidations. Such adaptations enabled the amount of toxic PDC to be limited to 1.5 mole equivalents. Fortunately this methodology was also applicable for alcohol **55**, with complete oxidation to the desired ketone **8** occurring in a respectable 84% yield, scheme 39.



55 **8**

Scheme 39: Synthesis of ketone **8**

The ^{1}H NMR spectrum of ketone **8** is shown in figure 14 overleaf. The C-1 and C-4 protons, previously reported as doublet of doublets at δ 3.64 and 3.49, and as doublets at δ 3.38 and 3.27 ppm, respectively, in alcohol **55** are now reduced to two singlets at δ 4.38 and δ 3.44 ppm in ketone **8**. Similarly, the previously diastereotopic methyl substituents at δ 0.97 and 0.96 ppm in alcohol **55**, are now homotopic with a chemical shift of 1.17 ppm in ketone **8**.

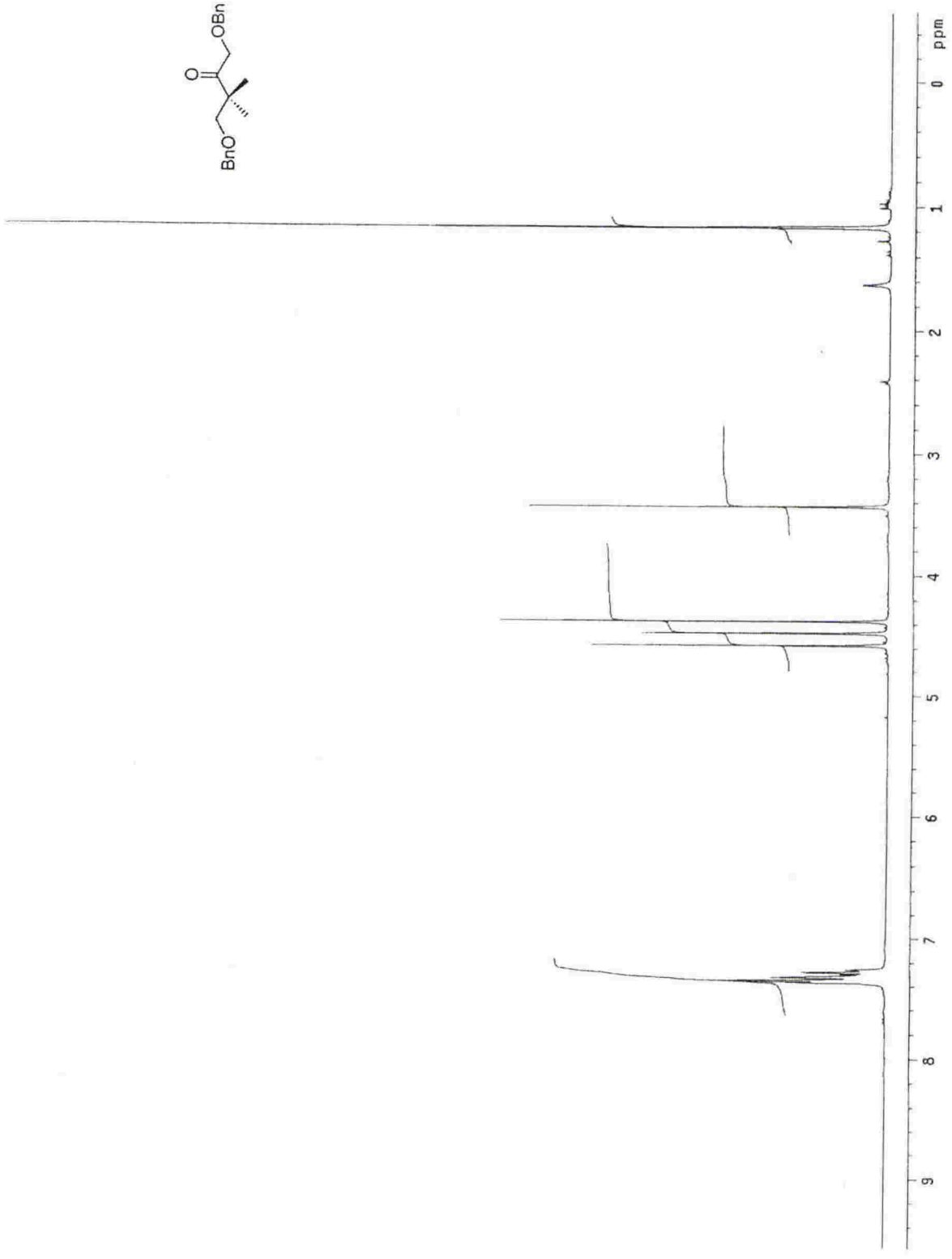


Figure 14: ^{1}H NMR of *gem*-dimethyl ketone **8**

Although it is highly plausible that another oxidation strategy may improve the yield or eliminate the need for a chromium reagent during the oxidation of **55**, we were nevertheless satisfied with our methodology and the knowledge that the synthesis of the final *gem*-dimethyl ketone is plausible. All that remained was to reinvestigate alternative methods for the deprotection of the allyl group.

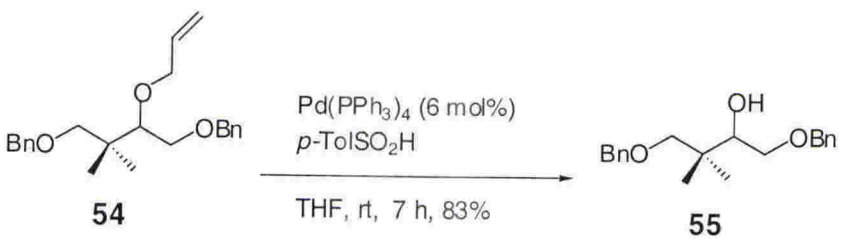
Unfortunately studies into the use of the $NaBH_4/I_2$ system[121] and the SeO_2 system[122] for the deprotection of allyl ether **54** were disappointing. Both resulted in the decomposition of the starting substrate. The use of Wilkinson's catalyst and DABCO (1,4-diazabicyclo[2.2.2]octane) in 10% aq ethanol initially looked more promising.[120] Surprisingly though, analysis of the crude substrate by ^{1}H NMR indicated that there was a small amount of the debenzylated adduct along with the requisite deprotected allyl ether. This was unexpected as literature precedent indicated that benzyl groups are stable to these reaction conditions but the unwanted reaction may have occurred as a result of unduly long reaction times.[IX] An additional problem with this rhodium catalysed deprotection was the cleavage of the intermediate isomerised ether. We wished to avoid the Hg^{2+} promoted cleavage of the propenyl ether, and opted instead for an acidic work-up, but this resulted in the incomplete cleavage of the isomerised ether. Although it appeared highly likely that these difficulties might be surpassed by careful manipulation of the reaction conditions, a fortuitous sequence of events prompted us to disregard this strategy.

A further review of the literature drew our attention to work published by Nagakura *et. al.* in 1997, whereby allyl ethers could be cleaved using *p*-toluenesulfinic acid as both an allyl acceptor and proton source in combination with catalytic amounts of Pd(0) in CH_2Cl_2.[134] As the sulfinic acid was not readily available, this methodology was not initially attempted. Simultaneously, a guest lecturer revealed that they had been

[IX] Significantly longer times than those reported in the literature were used as GC analysis indicated that the reaction was not complete

having similar difficulties with the deprotection of allyl groups and found that with a slight modification of Nagakura's procedures, they were able to reproducibly deprotect allyl groups in good yields. A communication by Kunz and Opatz[135] thus indicated that the choice of solvent played a critical role in this reaction with the use of 1,2-dimethoxyethane or dioxane, as compared to dichloromethane, produced more reproducible results.

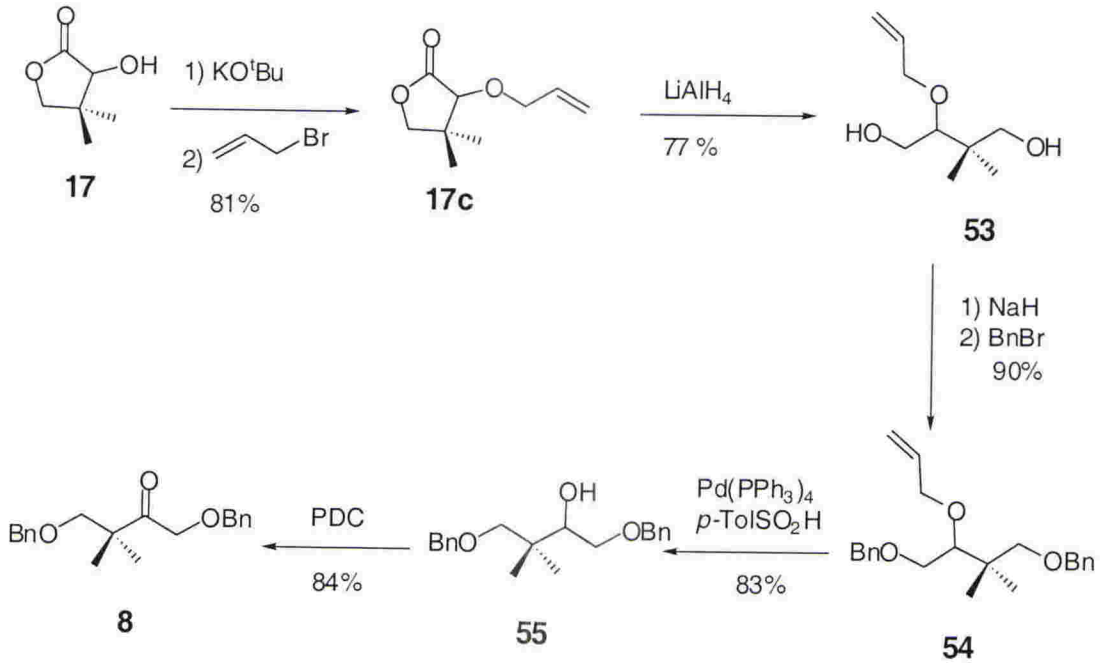
Thus the precedent of Kunz and Opatz was followed and attempts were made at deprotecting allyl ether **54** in dioxane with *p*-toluenesulfinic acid and catalytic (6 mol%) $Pd(PPh_3)_4$; a slightly lower loading than that reported. Gratifyingly, a clean conversion of allyl ether **54** to alcohol **55** was observed. This initial result prompted further experimentations with catalytic loadings and solvents. Although additional reductions in the catalytic loading resulted in incomplete reactions, dioxane could be successfully substituted with the more environmentally benign and less hazardous THF, scheme 40. Thus allyl ether **54** could be reproducibly deprotected with THF as the solvent.



54 **55**

Scheme 40: Catalytic deprotection of the allyl ether **54** with $Pd(PPh_3)_4$

The catalytic deprotection of the allyl ether **54** thus represents the last synthetic challenge in the synthesis of *gem*-dimethylketone **8**. For clarity, the overall synthetic scheme is shown in scheme 41 overleaf, with the overall yield for this synthesis being a respectable 35% over the five steps. Furthermore, additional work in our laboratory has demonstrated that this strategy can be performed on the multi-gram scale.[136]



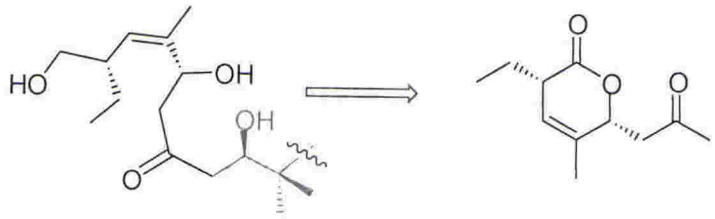
Scheme 41: Overall synthesis of *gem*-dimethyl ketone **8**

Chapter Four

Synthesis of the C-12 to C-24 fragment of Peloruside A: Strategy 1

4:1: The lactone approach

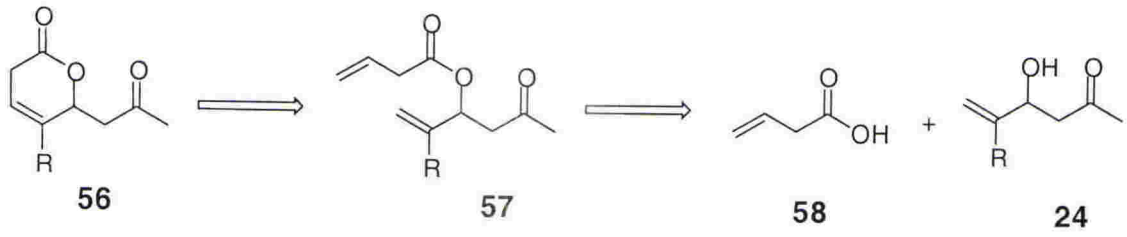
The first strategy investigated for the synthesis of the C-12 to C-22 fragment of pel A involved formation of lactone **20**, scheme 42. Lactone **20** is reductively opened, following a regio-and stereoselective aldol reaction with the pyranose fragment of pel A (depicted in red) to give the carbon skeleton below.



20

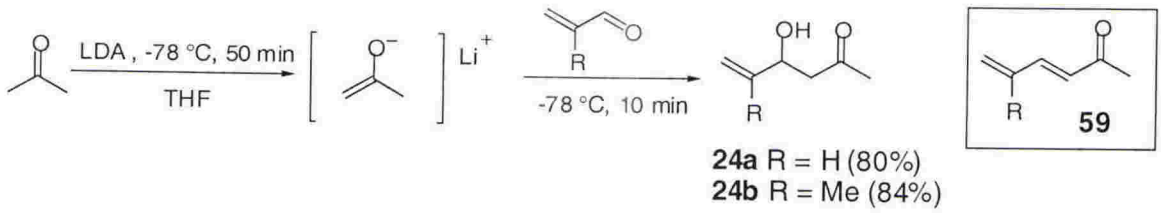
Scheme 42: Retrosynthetic analysis for the synthesis of the C-12 to C-24 fragment

To initially test the viability of this strategy, a racemic synthesis of the target lactone was investigated, with the ethyl substituent from the side chain also being omitted, scheme 43. Modified lactone **56** results from the RCM of diene **57**, itself formed from the esterification reaction of vinyl acetic acid **58** with the aldol adduct **24**. With a view to investigating the bioactivity of analogues of pel A, synthesis of the non-methylated (R = H) analogue of pel A was also explored



Scheme 43: Retrosynthetic analysis for the synthesis of the model C-12 to C-24 fragment

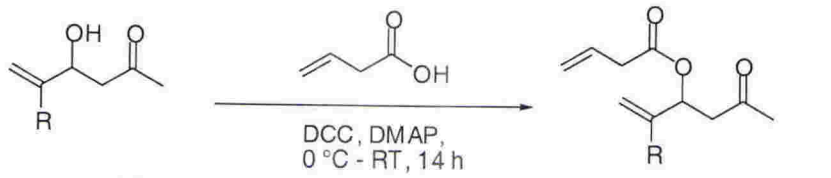
The starting point in this synthesis involved formation of the β-hydroxyketones, **24a** and **24b**, using standard, low temperature aldol reactions, scheme 44. Literature precedent was followed for the synthesis of (±)-4-hydroxy-5-hexene-2-one **24a**, whereby the lithium enolate of acetone was captured by acrolein.[137] A slight adaptation of this protocol, with methacrolein being substituted for acrolein, enabled us to synthesise the methylated derivative **24b**, in 84%. The successful reproduction of these results however depended greatly upon the purity and dryness of the solvents and reagents, particularly that of the THF. Inadequately dry THF often resulted in lower yields and a propensity of the resulting β-hydroxy ketone to undergo elimination, forming the highly unsaturated dienone **59**.



Scheme 44: Formation of ß-hydroxyketones **24a** and **24b**

The β-hydroxyketone was then coupled to vinyl acetic acid following a standard dicyclohexylcarbodiimide (DCC), dimethylaminopyridine (DMAP) esterification protocol. Although this reaction successfully produced the corresponding esters, **57a** and **57b**, scheme 45, purification proved to be somewhat tedious. Flash chromatography would not adequately remove all of the dicyclohexyl urea by-product formed during this

reaction without severely jeopardising the yield, yet bulb-to-bulb distillation alone would not separate the small portion of the α,β unsaturated dienone **59** also formed during the reaction. Consequently the most successful purification strategy involved a combination of flash chromatography, followed by bulb-to-bulb distillation. Although this was not ideal methodology, yields of 80% or greater were nevertheless obtained for the synthesis of esters **57a** and **57b**.



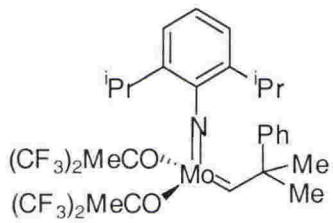
24a R = H
24b R = Me

57a R = H, 84%
57b R = Me, 80%

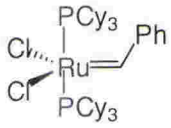
Scheme 45: Synthesis of esters **57a** and **57b**

Due to these difficulties, alternative coupling reagents were investigated. Although the use of 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) resulted in the formation of the desired ester, a significant portion of the conjugated enone **59** resulted, even after formation of a pre-mixed solution of vinyl acetic acid and EDCI at 0 °C. The alternative choice of carbonyldiimidazole (CDI) as a coupling reagent resulted in an uncharacterisable mixture of products.

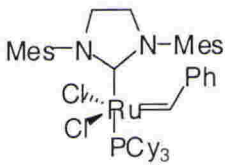
Nevertheless, with the esters **57a** and **57b** in hand, the next stage in the strategy involved the synthesis of the corresponding lactones via RCM. Some of the more common alkylidene-metal complexes widely used for RCM include the alkoxy-imido molybdenum complex (the Schrock/Hoyveda catalyst) **60**,[138] the benzylidene ruthenium complex (Grubbs' Catalyst) **61**[139] and the modified benzylidene ruthenium complexes coordinated to 1,3-dimesitylimidazol-2-ylidene ligands (Grubbs' second generation catalyst)[140] **62**, figure 15. The crucial factors we considered when choosing the appropriate catalyst for our substrate were reactivity, stability and availability/cost.



60



61



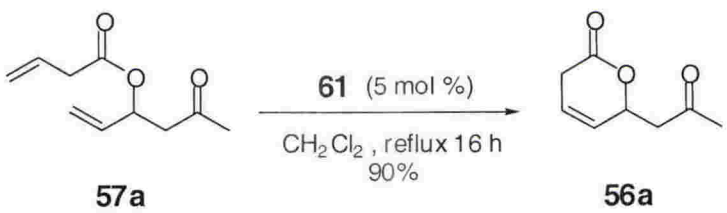
62

Figure 15: Examples of common metal-alkylidene metathesis catalysts

Compared to Grubbs' catalyst **61**, the molybdenum complex **60** exhibits high reactivity towards a broad range of substrates containing numerous steric and electronic variations.[140] Unfortunately though, it also suffers from extreme sensitivity to air and moisture as well as decomposition upon storage. Grubbs' second-generation catalyst **62** however, exhibits activity similar to that of the molybdenum complex **60** yet has also retained remarkable air and moisture stability characteristic of the parent benzylidene ruthenium complex **61**.[141] The enhanced reactivity of Grubb's second-generation ruthenium catalyst over its first generation counterpart is believed to arise as a result of the greater basicity of the imidazole ligands, when compared to their unsaturated analogues, which in turn translates into increased activity.[142] This enhanced basicity is due to the lack of carbene stabilisation provided by the absence of π-interactions.

Although one would thus expect the second-generation ruthenium catalyst **62** to be the catalyst of choice, due to its expense (or the additional steps required for its synthesis)[141] we opted to first explore the viability of the commercially available Grubbs' first generation ruthenium catalyst **61**. This catalyst generally exhibits excellent activity for ring closing metathesis resulting in the formation of five or six-membered rings, although its activity drops dramatically for the synthesis of larger cyclic compounds.[140] Difficulties in the RCM of substituted olefins using Grubbs' first generation catalyst have also been reported.[140,141]

As the synthesis of lactone **56a** required RCM involving an unsubstitued olefin, we were fairly confident that Grubbs' first generation catalyst would be adequate for this purpose. Accordingly, we were justly rewarded when lactone **56a** was synthesised in a 90% yield, scheme 46. One disadvantage of this strategy however, was that 5 mol percent of the catalyst was required for complete cyclisation. Several attempts were made at decreasing the catalytic loading, but without success. As a consequence, purification of the lactone proved to be somewhat difficult and tedious.[X] Separation of the residual ruthenium from the desired product by flash chromatography was problematic, and bulb-to-bulb distillation simply resulted in decomposition of lactone.



Scheme 46: Synthesis of lactone **56a**

An interesting observation however was made upon the attempted cyclisation of ester **57b**, scheme 47. The ^{1}H NMR of the product, after a solution of ester **57b** was refluxed with five mol % of **61** in CH_2Cl_2 for 24 hours, revealed some anomalous peaks, particularly in the olefinic region of the spectrum. Two singlets were observed at δ 4.98 and δ 4.90 ppm, integrating for two protons each, along with two multiplets at δ 5.76 and δ 5.68 ppm. Additionally, the ^{13}C NMR of this sample revealed thirteen ^{13}C resonances, four more than that of the anticipated lactone **56b**.

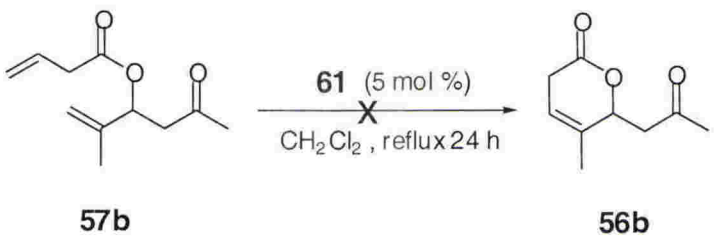


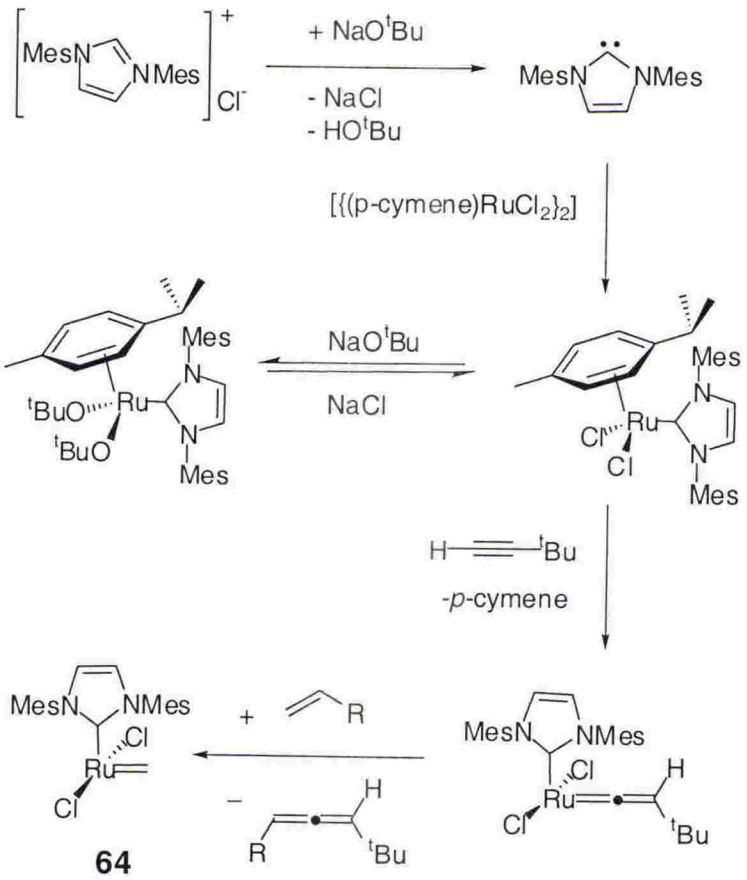
Figure 47: Attempted RCM of ester **57b** using Grubbs' catalyst **61**

[X] 5 mol% of the catalyst equates to approximately 25 wt%

After consideration of these facts, it was apparent that ester **57b** had undergone an intermolecular dimerisation to form the *E* and *Z* isomers **63**, scheme 48. High resolution electrospray ionisation mass spectroscopy (HRESIMS) gave an ion with mass of 365.20 corresponding to that of the proposed dimer in protonated form ($M+H^+$). With this

product still prevailed. Clearly the methyl substituent on the olefin was hindering intramolecular cyclization.

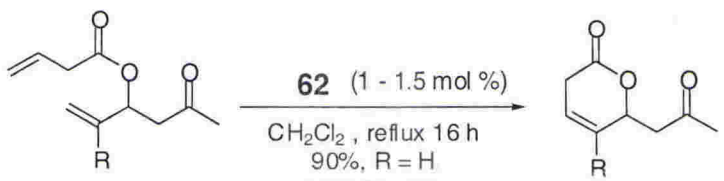
Given this observation, it was concluded that a more active metathesis catalyst was required for the RCM of the methylated substrate. Due to the availability of materials, studies into the applicability of the ruthenium vinylidene metathesis catalyst **64** generated *in situ* (scheme 49),[143] were initially explored. Although reaction rates are slightly slower for this vinylidene catalyst, its general reactivity profile towards a variety of substrates is similar to the analogous, highly active, second generation ruthenium alkylidene compounds.



Scheme 49: Proposed pathways for catalyst generation and decomposition[143]

As depicted in scheme 49, the formation of the ruthenium vinylidene catalyst requires the use of one equivalent of sodium *tert*-butoxide. Unfortunately the presence of this base during the attempted RCM of **57** resulted in alkene isomerization. The analogous α,β unsaturated ester was the only product isolated. Initially it was proposed that an increase in the length of time between the addition of sodium *tert*-butoxide and diene **57** may ensure complete deprotonation of the imidazolinylidene ligand, and hence, prevent the excess NaO^{t}Bu from causing the unwanted isomerization. However, during these studies we were able to obtain Grubbs' second-generation ruthenium benzylidene catalyst **62**. Thus we opted to investigate the potential of **62** in the RCM of diene **57b** and discontinued the studies involving the *in situ* formation of the vinylidene catalyst.

Fortunately the greater reactivity of second-generation ruthenium benzylidene catalyst **62** enabled the desired lactone **56b** to be synthesised in an 85% yield, scheme 50. The ^{13}C NMR spectrum of lactone **56b** is shown in figure 16 overleaf; with the signals for the C-8 and C-9 methyl carbons at δ 30.2 and δ 18.8 ppm, signals for the C-2 and C-6 methylene carbons at δ 46.8 and δ 31.3 ppm, the signal for the C-5 methine carbon at δ 78.9 ppm, the signal for the C-3 olefinic methylene carbon at δ 117.6 ppm, with the remaining quarternary olefinic, ester and ketone carbons signals at δ 131.9, δ 169.0 and δ 204.8 ppm, respectively. Moreover, the RCM of diene **57b** was conducted with only a 1.5% catalytic loading. Given these positive results, the ruthenium benzylidene catalyst **62** was used for the RCM of the unsubstituted diene **57a**. The lower catalytic loading would alleviate some of the problems with the purification of the resulting lactone. Indeed, lactone **56a** was once again synthesised in a 90% yield, but this time only a 1% catalytic loading was required.

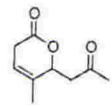


57a R = H
57b R = Me

56a R = H
56b R = Me

Scheme 50: RCM using second-generation Grubbs' catalyst **62**

INDEX	FREQUENCY	PPM	HEIGHT
1	15450.741	204.821	37.5
2	12747.758	166.989	91.0
3	9945.864	131.895	36.3
4	8875.629	117.859	102.7
5	5952.611	78.910	88.2
6	5864.719	77.745	44.1
7	5832.675	77.320	48.5
8	5800.631	76.895	45.4
9	3533.140	46.837	123.8
10	2358.185	31.261	58.8
11	2278.154	30.213	104.2
12	1420.986	18.837	103.8



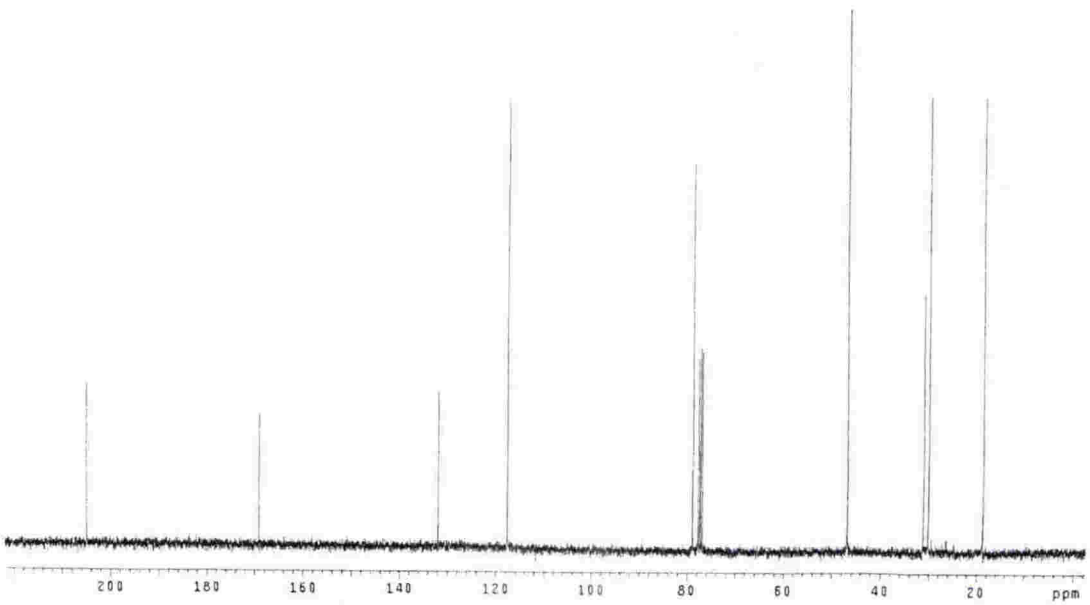
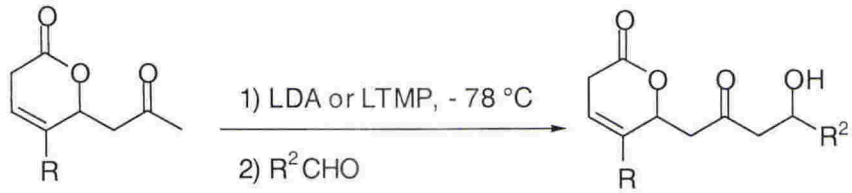


Figure 16: ^{13}C NMR of lactone **56b**

With the key intermediate lactones synthesised, all that remained in this strategy was a regioselective aldol reaction between the lactone and the pyranose ring of peloruside. Even though there is a multitude of precedent for the selective formation of kinetic verses thermodynamic enolates, our system presented additional difficulties with the possibility of both double bond isomerization and a second aldol reaction occurring α or γ to the lactone carbonyl. Thus, to investigate this system, aldol reactions were conducted with butyraldehyde or benzaldehyde being used as model substrates for the pyranose ring, scheme 51.



56a R = H
56b R = Me

R = H, Me
R^2 = Ph, C_3H_7

Scheme 51: Model aldol studies with lactones **56a** and **56b**

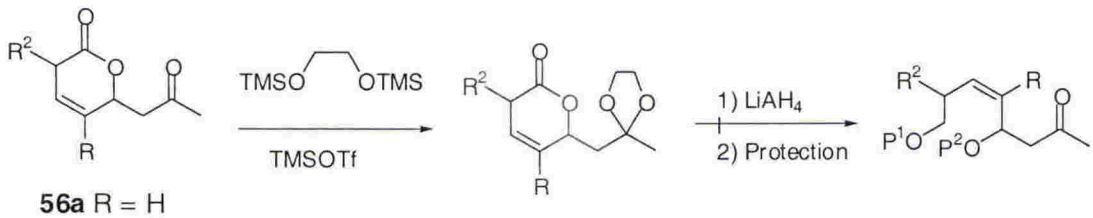
Initial studies involved enolate formation at –78 °C using LDA as the base. Unfortunately, these reactions were problematic. The desired aldol product was formed along with a multitude of other products; as indicated by ^{1}H NMR and HRESIMS analysis. Furthermore there was evidence for an aldol reaction occurring α to the lactone. Consequently it was postulated that a more sterically hindered base, such as LTMP, would favour the formation of the kinetic enolate at –78 °C. Again, numerous aldol reaction studies were conducted with LTMP as the base, but once again, mixtures of products resulted. Although disappointing, these results were not entirely unexpected.

The pKa values of ester and ketone α protons are approximately 25 and 20, respectively. Thus one would expect the more acidic ketone α-proton (C-8) of **56** to deprotonate preferentially. Incorporation of the adjacent olefin moiety in lactone **56** however, would result in a decrease in the pKa value of the lactone α-proton (C-2) in **56**. At the time of commencing the synthesis, we were unsure about the influence that the olefinic moiety would have on the pKa of the lactone α-proton. However from the above experimental results, the pKa at C-2 appears to be equivalent to, or perhaps even lower, than that at C-8, as a mixture of aldol products were obtained.

Subsequently, a pKa prediction server called SPARC[XI] was used to predict the pKa values of the α protons at the methylene C-2 and methyl C-8 positions of **56**. Remarkably, a pKa of 11.5 was reported for the C-2 position, with a value of 17.3 being

given for C-8. The dramatic decrease in the pKa of the lactone α-proton was somewhat unexpected.

Potentially the problems in controlling the regiochemisty of the aldol reactions could be circumvented by protecting the ketone under neutral conditions using 1,2–di(trimethyl-silyoxy)ethane, scheme 52. Reduction of the lactone, followed by protection of the resulting diol, would then enable a regioselective, kintetically controlled, aldol reaction to be preformed at the desired α-methyl position. However, this modification adds several steps to our synthesis and is, for the most part, undesirable.



56a R = H
56b R = Me

Scheme 52: Alternative strategy for the synthesis of the C-12 to C-24 fragment of peloruside A

Alternatively, one may speculate that the combination of the ethyl substituent, where R^2 = Et, and a sterically hindered base such as LTMP, may prevent the lactone α-proton from being deprotonated. Although a plausible suggestion, we believed that enough time had been spent on this strategy and an alternative, less problematic, methodology should be investigated. Consequently we discontinued these studies and turned our attention towards the synthesis of the C-12 to C-24 fragment using the cyclic *bis* silyl ether tether.

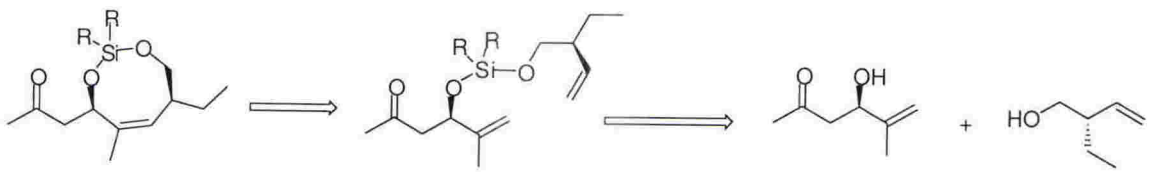
[XI] See, http://ibmlc2.chem.uga.edu/sparc/index.cfm

Chapter Five

Synthesis of the C-12 to C-24 fragment of peloruside A: Strategy Two

5.1: Initial aldol studies with the cyclic *bis*-silyl ethers

As the previously described strategy for the synthesis of the C-12 to C-24 fragment of pel A was problematic, an alternative strategy involving the synthesis of the *bis*-alkoxysilyl ether **22** was investigated, scheme 53. It was anticipated that RCM of the appropriate acyclic precursor **23** would form the desired *bis*-silyl ether **22**. Diene **23** could in turn, be synthesised by the addition of β-hydroxyketone **24** and *(S)*-2-ethyl-but-3-ene-1-ol **25** to the appropriate dichlorosilane. In this way, the silane acts as both a tether for the RCM and a protecting group for both alcohols.



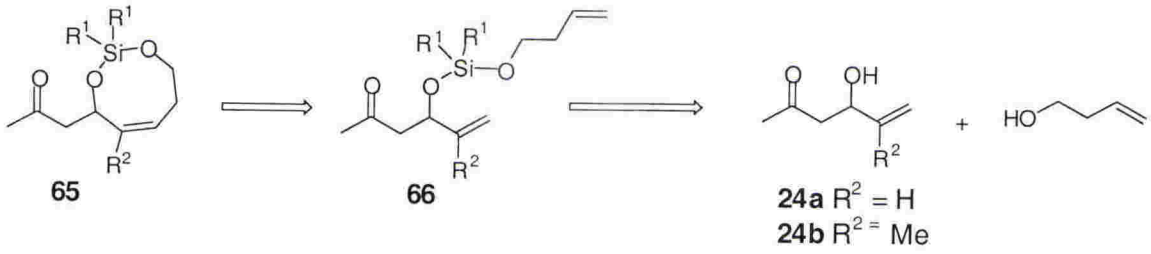
22 **23** **24** **25**

Scheme 53: Retrosynthetic stragety (II) for synthesis of the C-12 to C-24 fragment of peloruside A

There were many factors that needed to be considered when choosing the appropriate dichlorodialkylsilyl substrate as a tether for this reaction. First, the *bis*-silyl ether **22** needed to be robust enough to withstand the aldol reaction and subsequent chemical transformations. Second, the intermediate acyclic silyl tethered ether **23** needed to be amenable to RCM and finally, the impact of the silyl substituents (R) in the subsequent asymmetric aldol reactions needed to be addressed. Although it was anticipated that the

larger phenyl substituents would form a more robust cyclic ether and may offer advantages in controlling the subsequent asymmetric aldol reaction (see chapter 6), many of the reported RCM studies forming similar silyl tethered ethers had been conducted with the smaller methyl substituents.[89,90,144] Even though many disubstituted isopropyl and phenyl derivatives had been synthesised for other purposes,[145] it was unknown if the steric, or electronic constraints of these larger substituents would impede the RCM reaction of our substrate.[146] In view of these considerations, all three alkyl groups were initially investigated in order to find the combination of reagents that would best suit our purposes.

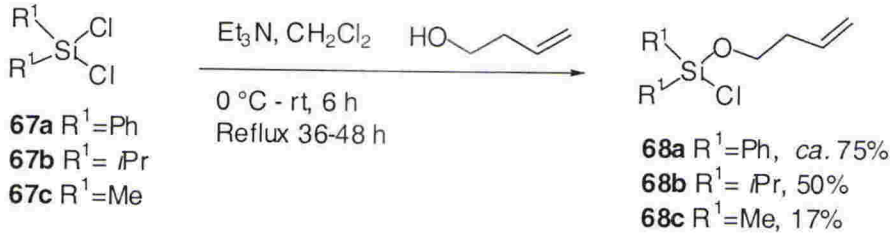
The above retrosynthetic strategy was further modified in that although both *(R)*- and *(S)*-2-ethylbut-3-en-1-ol are available in one step using a Zr-catalysed ethylmagnesation of 2,5-dihydrofuran,[147] for simplicity but-3-en-1-ol was coupled to the appropriate silyl derivative, scheme 54. Our emphasis was initially on establishing a racemic synthesis for the C-12 to C-24 fragment of pel A. Once a plausible racemic strategy had been devised, this would then be adapted for the asymmetric synthesis of peloruside A.



Scheme 54: Simplified retrosynthetic analysis for synthesis of the C-12 to C-24 fragment

Thus, the first step in this strategy was the formation of the mono silyl ethers **68**, scheme 55. During these syntheses, problems were encountered in preventing disubstitution from occurring. Even though numerous changes were made to the reaction conditions in an attempt to improve the ratio of mono- to disubstitution adducts, the controlling factor in determining whether mono- or disubstitution occurred appeared to be the size of the substituents on the silyl tether. Disubstitution predominates with small

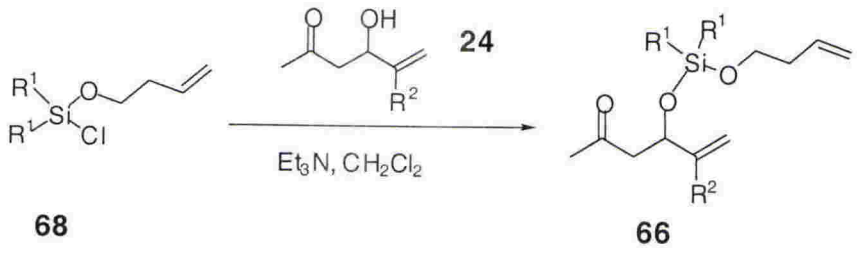
substituents when the solution of but-3-en-1-ol in dichloromethane was slowly added, at 0 °C, to a solution of the dichlorosilane in dichloromethane. For example, with dimethyldichlorosilane as a starting substrate, the desired monosilyl ether, but-3-en-1-oxydimethylsilyl chloride **68c**, was formed in a mere 17% yield. The undesired diether was formed in 50% yield. These results progressively improved as the size of the alkyl group increased, with isopropyl **68b** giving the desired monosilyl ether in 50% yield, and the diphenyl substrate **68a** giving the analogous diphenyl monosilyl ether in approximately[XII] 75% yield. No improvement could be made with these yields, even when the temperature of the initial reaction mixture was lowered to –40 °C. Additionally, the reaction would not go to completion unless the solution was refluxed.



Scheme 55: Synthesis of the but-3-en-1-oxydialkylsilyl chlorides

The ß-hydroxy ketone **24** was then coupled to the silyl tethers **68** to form the corresponding *bis*-silyl ether adducts **66**, scheme 56. As but-3-en-1-oxydiphenylsilyl chloride **68a** could not be isolated by fractional distillation due to its high boiling point, this substrate was made *in situ* and the corresponding ß-hydroxy ketone added to the reaction vessel. Yields for the synthesis of the but-3-en-1-oxydialkylsilyl chloride derivatives are summarised in Table 1.

[XII] But-3-en-1-oxydiphenylsilyl chloride could not be purified by fractional distillation. The percentage of mono-to di- substituted adduct was based upon ^{1}H NMR analysis of the crude substrate.



68 66

Scheme 56: Synthesis of the but-3-en-1-oxydialkylsilyl chloride derivatives **66**

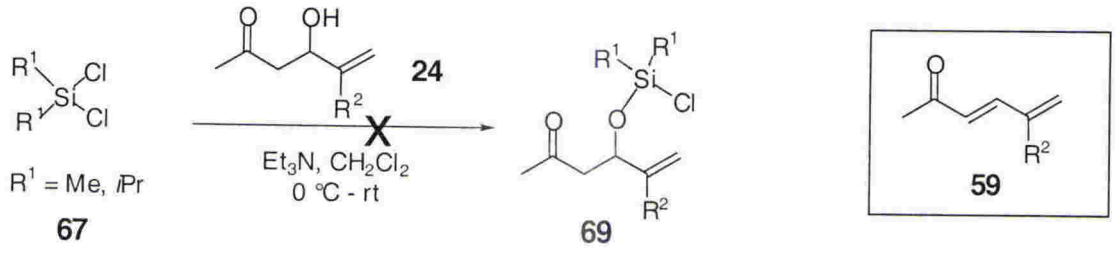
Table 1. Yields for the formation of the but-3-en-1-oxydialkylsilyl chloride derivatives

Entry	Compound	Substituents	Isolated yield
1	**66a**	R^1 = Ph, R^2 = Me	61%[a]
2	**66b**	R^1 = Ph, R^2 = H	65%[a]
3	**66c**	R^1 = ^{i}Pr, R^2 = Me	86%[b]
4	**66d**	R^1 = ^{i}Pr, R^2 = H	82%[b]
5	**66e**	R^1 = Me, R^2 = H	77%

[a]Overall yield from Ph_2SiCl_2;[b]Catalytic DMAP required

Although formation of these silyl adducts occurred relatively smoothly and in good yields, it was interesting to note that formation of the butenoxydiisopropylsilyl chloride derivatives, **66c** and **66d**, required the addition of catalytic amounts of DMAP. DMAP displaces the chloride ion, forming the silyl pyridinium ion, which is more amenable to nucleophilic displacement by the approaching alcohol.[148] DMAP however, is not required for the analogous but-3-en-1-oxydimethylsilyl chloride derivative **66e**. Because of the smaller size of the methyl substituents, the approaching alcohol can more readily approach the silicon atom and hence displace the chloride ion in the dimethyl tethered adducts. Even though the diphenyl substituents of the analogous but-3-en-1-oxydiphenylsilyl chloride derivatives, **66a** and **66b**, are similar in size to the isopropyl substituents, presumably the electron donating properties of the phenyl substituents favour the displacement of the chloride ion, making it act as a better leaving group. Thus, this facilitates the nucleophilic displacement by the approaching alcohol.

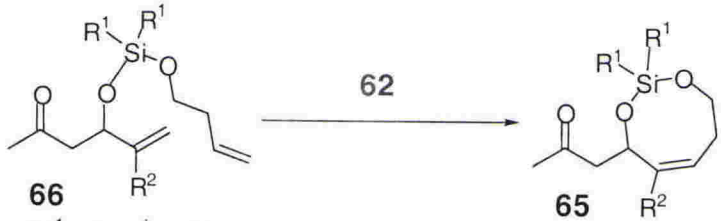
In an attempt improve the initial selectivity of the first mono etherification reaction the order of addition of the two alcohols was reversed. By adding the more sterically encumbered β-hydroxyketone **24** first we anticipated that this would limit the amount of the disubstituted adduct formed, scheme 57. However, changing the order of addition simply resulted in elimination of a hydroxide ion from the β-hydroxyketone to form the unsaturated ketone **59**. Presumably this elimination occurs via an $E1_{cb}$ mechanism involving deprotonation of **24** to form the thermodynamically stable, highly conjugated enone **59**. The electron withdrawing chlorides on the dichlorosilane derivatives **67** undoubtedly make these substrates less amenable to alkoxy substitution reactions with the competing $E1_{cb}$ elimination being favoured. A variety of conditions were trialed, however in all instances, the unsaturated ketone **59** predominated.



Scheme 57: Attempted reversal of the order of addition of the hydroxy substrates

Nevertheless, with the required *bis* silyl ethers **66a-e** in hand, investigations into the corresponding RCM reactions were conducted, scheme 58. As Boiteau *et. al.*,[149] had used Grubbs' second generation ruthenium catalyst **62** in refluxing benzene for the RCM of similar silyl tethered substrates, these conditions were initally used for the RCM of **66e**. Although the desired cyclic ether was formed, an unknown, and inseparable by-product was also formed in almost equivalent yield. The solvent was then changed to dichloromethane and the solution was heated to reflux with five mole percent of **62**. T.l.c analysis of the reaction solution after 30 minutes however, indicated that at least three compounds were now present. Clearly an impurity was forming at a rate similar to that of the desired cyclic ether. The reaction was then conducted in CH_2Cl_2 at room temperature, again with 5 mol % of the catalyst. Although the side product was once again formed,

this time it was far less prevalent. However 5 mol % of **62** was evidently not sufficient for this reaction as the starting acyclic silyl ether was still present.



66
R^1 = Me, ^{i}Pr, Ph
R^2 = H, Me

65

Scheme 58: Desired RCM of the but-3-en-1-oxydialkylsilyl chloride derivatives

The instability of the dimethyl silyl tether was potentially the cause of the impurity, therefore the RCM of the diphenyl tethered substrate **66b**, was attempted. It was also unknown if this diphenyl tethered substrate would even be amenable to RCM. Seven mole % of catalyst **62** was thus added to a solution of **66b** in CH_2Cl_2 and the reaction stirred at room temperature for 10 hours. Fortunately, the desired cyclic adduct was formed, but again a small amount of an impurity was present. These results however did indicate that the RCM of the *bis*-silyl ether is a finely tuned process depending on both the reaction temperature and catalytic loading and not on the alkyl or aryl substituents on the silyl tethers. Thus, by carefully deducing the optimum amount of catalyst required for each system, one should be able to preferentially form the desired cyclic adduct and control undesirable competing reactions.

This assumption was investigated by repeating the RCM of **66b** in CH_2Cl_2 at room temperature with a 10% catalytic loading of **62**. Fortunately, the desired cyclic silyl ether was formed almost exclusively. The optimum conditions for the RCM of the isopropyl tethered silyl ether **66d**, where R^2 = H, also required the addition of at least 10 mole percent of **62**, with the desired 4,8-*O*-diphenylsilanediyloct-5-en-2-one being formed in a respectable 81%. Due to the very poor yield (17%) when forming the initial dimethylsilyl chloride adduct, it was decided that the dimethylsilyl tether was an inappropriate reagent to use synthetically and the synthesis 4,8-di-*O*-dimethylsilanediyl-5-octen-2-one was never optimised.

The RCM of the acyclic ethers where R^2 = Me however, proved to be a little more problematic. Due to the increased steric requirement of the methyl substituented olefin, and hence slower reaction rates, a minimum of 12 mole percent of the catalyst was required for these RCM reactions. Yields for these cyclisations were also slightly lower at 54% for the phenyl derivative and 60% for the isopropyl derivative. A summary of the RCM of the *bis*-silyl ether precursors is given in table 2.

Table 2. Synthesis of *bis*-silyl cyclic ethers **65** by RCM

Entry	Compound	Substituents	Isolated yield
6	**65a**	R^1 = Ph, R^2 = Me	54%
7	**65b**	R^1 = Ph, R^2 = H	81%
8	**65c**	R^1 = *i*Pr, R^2 = Me	60%
9	**65d**	R^1 = *i*Pr, R^2 = H	74%
10	**65e**	R^1 = Me, R^2 = H	42%[a]

[a]Due to the low yields of the proceeding monosilyation reaction, RCM was not optimised

The ^{1}H NMR spectrum of 4,8-*O*-diphenylsilanediyl-5-methyloct-5-en-2-one **65a** is given in figure 17 overleaf. The three dimensional representation of **65a** is shown as one enantiomer in figure 18 for ease of discussion. Noteworthy features in the ^{1}H spectrum include the differentiation of the diastereotopic protons on C-3 with signals at δ 2.94 (dd, J = 9.9, 15.3 Hz) and δ 2.62 (dd, J = 3.6, 15.3 Hz). The large *trans* coupling of 9.9 Hz between H-4 and H-3b enables us to assign the signal for H-3b at δ 2.94, and 3a therefore at δ 2.62. Ring protons H-7a and H-7b are also in quite distinct chemical environments with signals at δ 2.93 and δ 2.26, respectively. As illustrated in figure 18, the shielding effect of the ring oxygens on H-7b accounts for its high field shift. A summary of the ^{1}H and ^{13}C NMR spectral assignments for **65a** is given in table 3.

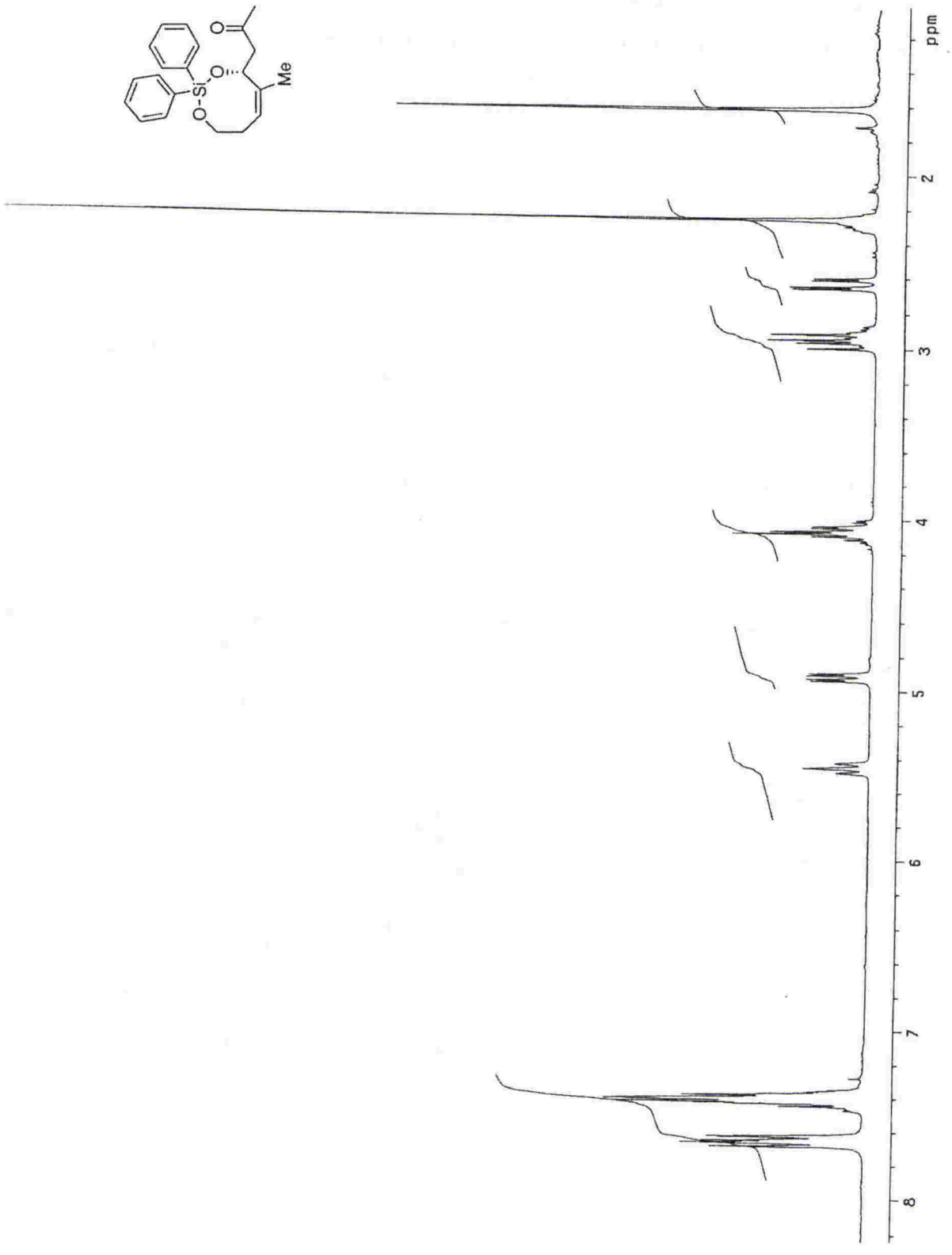


Figure 17: ^{1}H NMR spectrum of 4,8-*O*-diphenylsilanediyl-5-methyloct-5-en-2-one **65a**

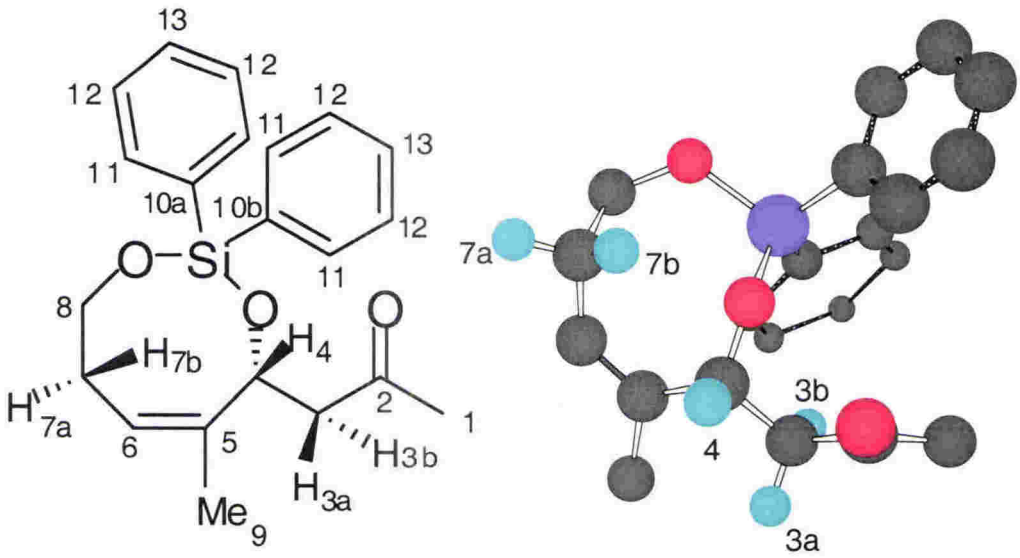
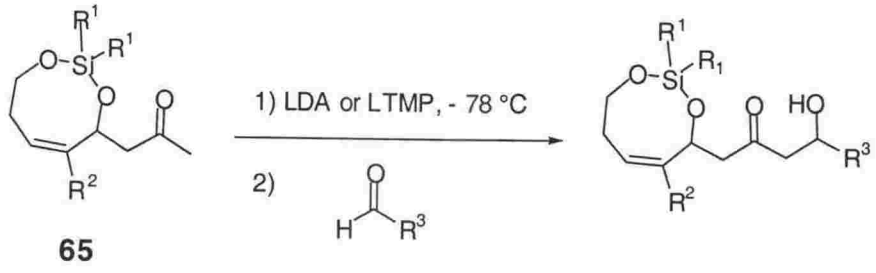


Figure 18: 4,8-*O*-diphenylsilanediyl-5-methyloct-5-en-2-one **65a**

Table 3: ^{1}H and ^{13}C NMR data for **65a**

Position	**δ ^{13}C**	**δ ^{1}H**
1	30.9	2.25 (s, 3 H)
2	207.6	-
3a	49.6	2.62 (dd, *J* = 3.6, 15.3 Hz, 1 H)
3b	-	2.94 (dd, *J* = 9.9, 15.3 Hz, 1 H)
4	71.7	4.90 (dd, *J* = 3.6, 9.9 Hz, 1H)
5	140.8	-
6	125.1	5.44 (t, *J* = 8.1 Hz, 1 H)
7a	31.2	2.93 (m, 1 H)
7b	-	2.26 (m, 1 H)
8	64.4	4.05 (m, 2 H)
9 (Me)	21.5	1.60 (s, 3 H)
10a	133.7	-
10b	133.4	-
11	134.8	7.64 (m, 4H)
12	128.1	7.39 (m, 6H)
13	130.4	7.39 (m, 6H)

With a plausible strategy for the synthesis of the requisite cyclic ethers in place, model aldol studies were conducted, scheme 59. Initially diphenylsilane **65b** was chosen as the starting ketone, and was subjected to a LDA mediated aldol reaction, using butyraldehyde as the aldehyde acceptor. Although the absence of the methyl singlet (formerly at δ 2.22) in the ^{1}H NMR of the crude reaction product indicated that an aldol reaction had occurred, the reaction had not proceeded in the desired manner. Not only had a menagerie of products been formed but it also appeared that the silyl tether had been partially cleaved. TLC analysis of the crude product mixture indicated that many polar products had been formed. Similar results were observed for the 4,8-*O*-diphenylsilanediyl-5-methyloct-5-en-2-one **65a** and 4,8-*O*-dimethylsilanediyloct-5-en-2-one **65e** derivatives. Unfortunately, attempts made at deciphering the products were unsuccessful due to the vast assortment of products formed.



Scheme 59: Model aldol reactions with the *bis*-silyl ethers

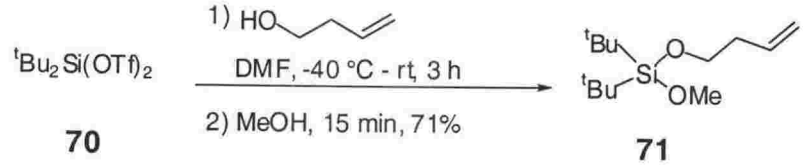
Even though the aforementioned reactions were conducted under kinetic conditions (-78 °C), it was postulated that potentially excess base had deprotonated an α-methylene proton resulting in elimination of the siloxy group via an $E1_{cb}$ type mechanism. A series of singlet peaks at approximately δ 7.3, 7.2, 6.3 and 6.2 ppm were observed in the ^{1}H NMR spectra for the partically purified products, providing some evidence for the formation of an unsaturated dienone analogous to **59**. Thus, the above aldol reaction was repeated, this time using LTMP, a more sterically hindered base. Extreme care was also taken to ensure that no excess base was present. However, similar results were observed. A change in aldehyde acceptor from butylaldehyde to pivaldehyde did not improve the outcome. Again the aldol reaction was repeated, but this time the aprotic solvent

hexamethylphosphoramide (HMPA) was added in an attempt to solvate the lithium ion, and hence, assist in the formation of the enolate. Unfortunately, once again similar results were observed. It appeared as if an aldol reaction had occurred, yet the silyl tether was simultaneously being cleaved. Due to the vast assortment of products, it was never possible to isolate any single adduct to confirm these propositions.

These results were very frustrating as the silyl tether appeared to simply be not robust enough for these particular aldol reactions. This was a particularly puzzling observation. Although we were unaware of any literature procedures for the aldol reactions of similar cyclic silyl tethered substrates, analogous substrates had been subjected to demanding reaction conditions. For example, a seven membered *bis* cyclic ether had been synthesised by the $Fe(CO)_5$-promoted cyclocarbonylation of a diyne in toluene at 120 °C for 24 hours.[150] However, based upon the above observations, one could only conclude that a more robust tether was required.

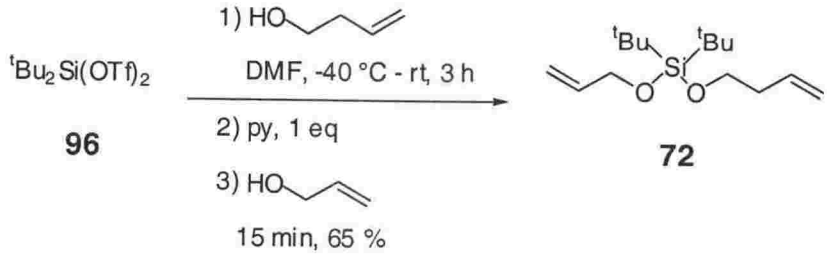
An alternative silyl tether that may be a slightly more robust was the di-*tert*-butyl silyl derivative. Without any ready access to di-*tert*-butyldichlorosilane, in a somewhat unprecedented manner, attempts were made at forming the acyclic *bis*-ethers using di-*tert*-butylsilylbis(trifluoromethanesulfonate) **70** as a starting substrate.[XIII] To ascertain if this methodology was feasible, a two-step, one-pot reaction was conducted whereby a solution of **70** in DMF at –40 °C was first exposed to but-3-en-1-ol then quenched with an excess of methanol, scheme 60. Indeed the desired *bis*-ether **71** was formed in a respectable 71% yield after purification by flash chromatography.

[XIII] Although this is a commonly used reagent for the intramolecular silylation of diols, at the time of these studies, the author was unaware of any reports of the intermolecular disilylation of alcohols.



Scheme 60: Initial study on the dietherification of **70**

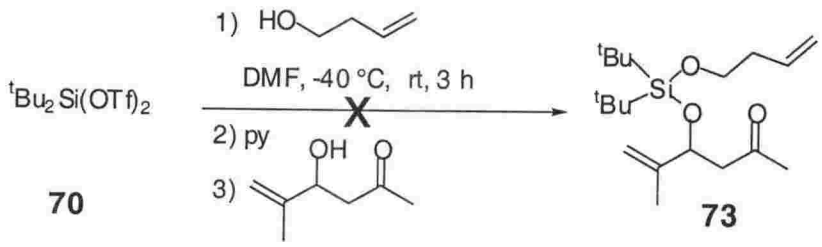
To further confirm the viability of this tethering strategy, a second model study was conducted. A solution of **70** in DMF at –40 °C was exposed to one equivalent of but-3-en-1-ol, followed by one equivalent of pyridine, then 1.1 equivalents of allyl alcohol, scheme 61. Pyridine was added to neutralise the liberated triflic acid. (As this method was to be adapted for the coupling of the ß-hydroxy ketone to the mono substituted silyl tether, it was proposed that the liberated triflic acid could cause the acid catalysed dehydration of the ß-hydroxy ketone). Again this modified strategy was successful with the desired *bis*-ether being **72** obtained in 65% after purification by flash chromatography.



Scheme 61: Second exploratory study into the dietherification of **70**

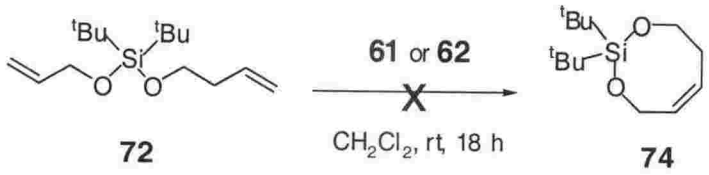
Numerous attempts were then made at coupling the desired ß-hydroxy ketone to the *tert*-butylsilyl tether, scheme 62. After the addition of one equivalent of but-3-en-1-ol, different ratios of pyridine, ranging from none to two equivalents were added before the addition of the ß-hydroxy ketone. In some instances DMAP was added, either in catalytic or stoichiometric quantities, and the reaction temperature varied from – 40 °C to 80 °C

after the initial addition of but-3-en-1-ol. However in the best scenario, with two equivalents of pyridine and catalytic DMAP, ^{1}H NMR analysis of the crude reaction mixture indicated that the desired *bis*-silylether **73** had been formed in only approximately 10% yield. Under most conditions, starting material and a small fraction of the unsaturated dienone **59** were isolated. Reversal of the addition of the alkoxy substrates, with the ß-hydroxy ketone being added before but-3-en-1-ol, once again resulted in the formation of the unsaturated compound **59** (refer to page 79).



Scheme 62: Attempted formation of the *tert*-butyl tethered ether

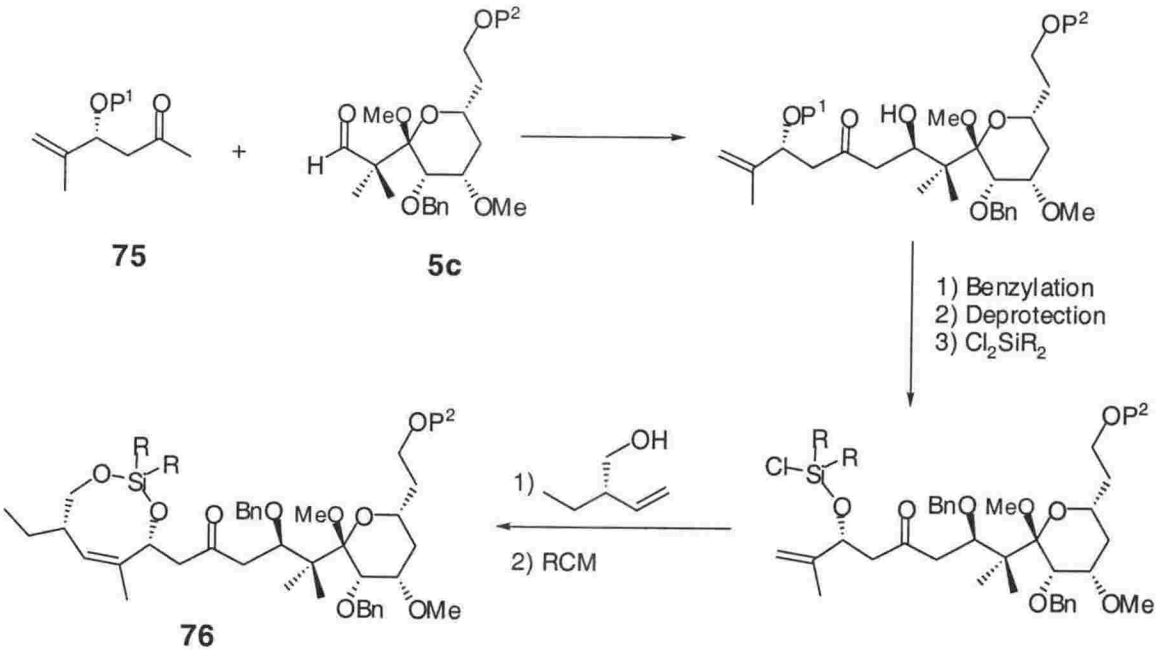
Furthermore, the attempted RCM of the previously synthesised 4-(3-butenoxy)-3-(allyloxy)-di-*tert*-butylsilane **72**, using either Grubbs' first or second-generation ruthenium catalyst, proved troublesome, scheme 63. Starting material was predominantly isolated, even after the addition of six mol % of the second-generation catalyst **62**. Thus, even in the eventuality of synthesising the desired ß-keto substituted derivative **73**, it seemed likely that this substrate would not be particularly amenable to RCM. Evidently, a di-*tert*-butyl silyl tether was not a viable option.



Scheme 63: Attempted RCM of the dialkylated di-*tert*-butyl silyl derivative **72**

5.2: Adaptation to a more linear approach for the synthesis of the C-12 to C-24 fragment of peloruside A

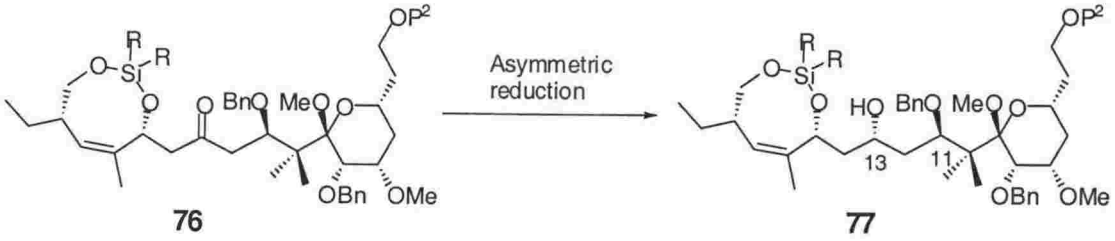
In view of the previous results it appeared that a less than ideal linear synthesis, involving the incorporation of the silyl tether at a later stage in the synthesis, was required for the formation of pel A, scheme 64. This strategy commences with an aldol reaction between the suitably protected ß-hydroxyketone **75** and pyranose **5c**.[XIV] The resulting hydroxyl substituent would then be benzylated, to facilitate a global debenzylation at a later stage of the synthesis, and the protecting group (P^1) removed to allow for attachment of the silyl tether. *(S)*-2-ethyl-but-3-en-1-ol is then added to the silyl tether, followed by RCM, to give key intermediate **76**.



Scheme 64: A more linear approach for the synthesis of peloruside A.

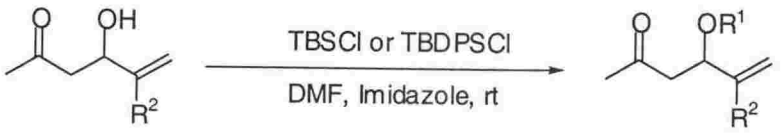
[XIV] It was anticipated that an asymmetric Mukiyama aldol reaction (using *(R)* or *(S)* BINOL as a ligand, or a boron mediated 1,5-*anti* aldol reaction (using PMB as a protecting group) would eventually be used to control the stereochemistry of this aldol reaction.

The asymmetric reduction of **76** would be the challenging part in this synthesis. A series of reducing agents would need to be investigated to ascertain which choice of reagent would give the highest yield of the desired 1,3-*anti* product **77**. If formation of the desired *anti* adduct proves elusive, it is anticipated that the ketone could be selectively reduced with $ZnBH_4$ to give the *syn* product, which could be subsequently inverted by a Mitsunobu reaction.[151] Similar chemical transformations to those previously discussed in the introduction, including the attachment of the C-1 to C-2 carbon framework, and a Yamaguchi macrolactonisation, are then required to complete the synthesis of pel A.



Scheme 65: Asymmetric reduction of key intermediate **77**

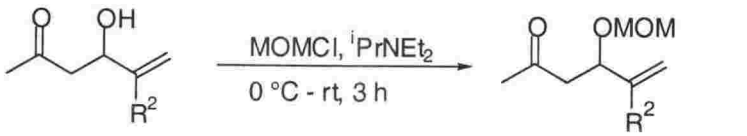
In order to test the feasibility of this new synthetic strategy, and in particular the plausibility of the asymmetric reduction, model studies were conducted with pivaldehyde as a substrate for the pyranose ring. Thus, the ß-hydroxyketones **24** were first protected, as either silyl derivatives, or the methoxymethylether (MOM) derivatives, schemes 66 and 67, respectively. Protection of the hydroxyl group as the methoxymethylether proceeded in noticeably lower yields than formation of the silyl derivatives.



24a R^2 = Me
24b R^2 = H

75a R^1 = TBS, R^2 = Me, 73%
75b R^1 = TBS, R^2 = H, 74%
75c R^1 = TBDPS, R^2 = Me, 75%

Scheme 66: Silylation of the ß-hydroxy ketones

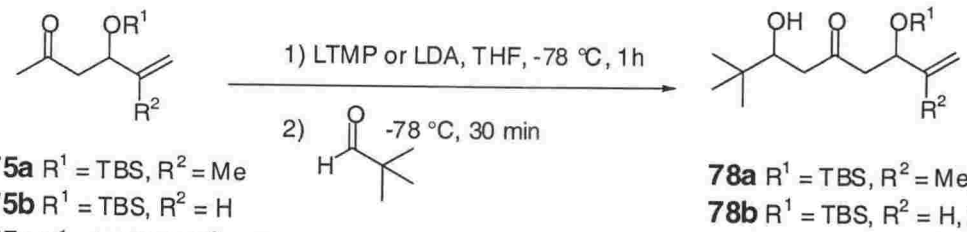


24a R^2 = Me
24b R^2 = H

75d R^2 = Me, 32%*
75e R^2 = H, 48%
*unoptimised

Scheme 67: Etherification of the ß-hydroxy ketones

The subsequent aldol reactions of the protected ß-hydroxy ketones with pivaldehyde as the aldehyde acceptor proceeded smoothly and provided some much needed reassurance that successful aldol reactions were indeed possible! Once again, yields for the reactions with the silyl protecting groups were higher than those with the MOM protecting group, suggesting that protection of the ß-hydroxyketone as the methoxymethyl ether was not an optimum strategy, scheme 68. Consequently, further studies with the MOM derivatives were discontinued.



75a R^1 = TBS, R^2 = Me
75b R^1 = TBS, R^2 = H
75c R^1 = TBDPS, R^2 = Me
75d R^1 = MOM, R^2 = Me

78a R^1 = TBS, R^2 = Me, 65%
78b R^1 = TBS, R^2 = H, 68%
78c R^1 = TBDPS, R^2 = Me, 67%
78d R^1 = MOM, R^2 = Me, 56%

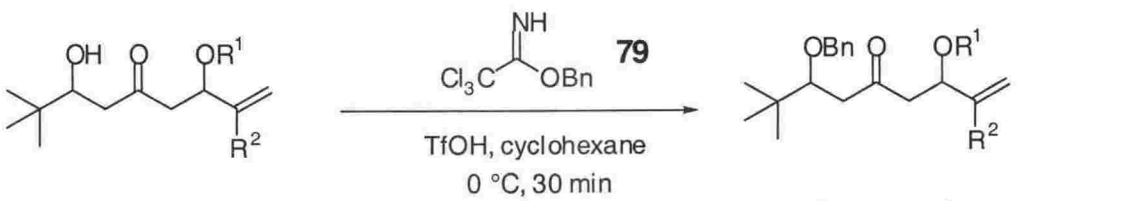
Scheme 68: Model aldol studies with pivaldehyde

Benzylation of the aldol adducts however, proved to be more challenging than expected due to the presence of additional acidic protons α to the ketone. First aldol adduct **78a** was exposed to one equivalent of NaH followed by benzyl bromide. However these conditions resulted in the decomposition of the starting material. In the event that excess NaH was causing the unwanted decomposition of the substrate, a 1 M solution of

potassium *tert*-butoxide in THF was used as the base as this can be more accurately measured than a 60% dispersion of NaH in mineral oil. However once again, the starting substrate decomposed. Obviously, a milder method of benzylating the hydroxyl substituent was required.

Attempts were then made at benzylating **78a** by using a suspension of freshly prepared silver oxide and benzyl bromide in DMF.[151] Yet again, these conditions resulted in the decomposition of the starting substrate. Analysis of the crude material by ^{1}H NMR indicated that the silyl group had been removed under these conditions. Reactions involving a change of solvent from DMF to CH_2Cl_2, or the addition of catalytic KI in an attempt to activate the alkyl halide, fared no better. In all instances, the substrate decomposed.

It was thus decided that the hydroxy group could be more satisfactory benzylated under mildly acidic conditions using benzyl trichloroacetimidate **79** as a benzyl donor.[152] Benzyl trichloroacetimidate can be readily synthesised by the NaH catalysed addition of benzyl alcohol to trichloroacetonitrile.[153] Fortunately, this protocol worked well with the benzyl adducts **80b** and **80c** being synthesised in 72% and 71% respectively, scheme 69.



78b R^1 = TBS, R^2 = H
78c R^1 = TBDPS, R^2 = Me

80b R^1 = TBS, R^2 = H, 72%
80c R^1 = TBDPS, R^2 = Me, 71%

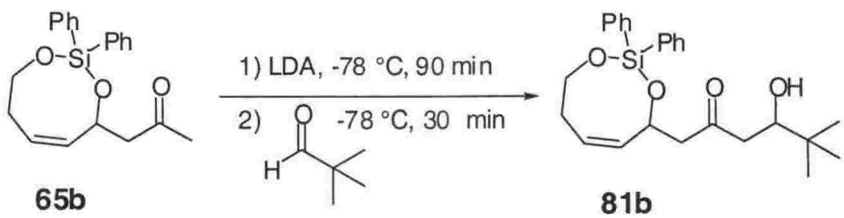
Scheme 69: Benzylation of the aldol adducts with benzyl trichloroacetimidate

5.3: Revisiting the original cyclic *bis*-silyl ether strategy

Although the above linear strategy was progressing at a satisfactory rate, ultimately this was not the most desirable approach. Since these aldol reactions could be successfully performed on the milligram scale and in respectable yields, it was apparent that there was nothing technically wrong with the manner in which the previous aldol reactions, involving the *bis*-silyl ethers, were being conducted. Some underlying phenomenon was preventing these cyclic *bis*-silyl ethers from successfully participating in aldol reactions.

After much consideration, it was proposed that a potential cause of our problems was the *bis*-silyl cyclic ethers containing sub-milligram quantities of ruthenium by-products. Indeed Maynard and Grubbs[154] surmised in a recent article that the highly-coloured ruthenium complexes and the residual ruthenium that forms as a by-product during ruthenium alkylidene catalysed RCM reactions often cause problems such as olefin isomerization during product distillation and the decomposition of substrates over time. Thus it seemed only logical that the residual ruthenium was responsible for the problems encountered during the aforementioned aldol reactions.

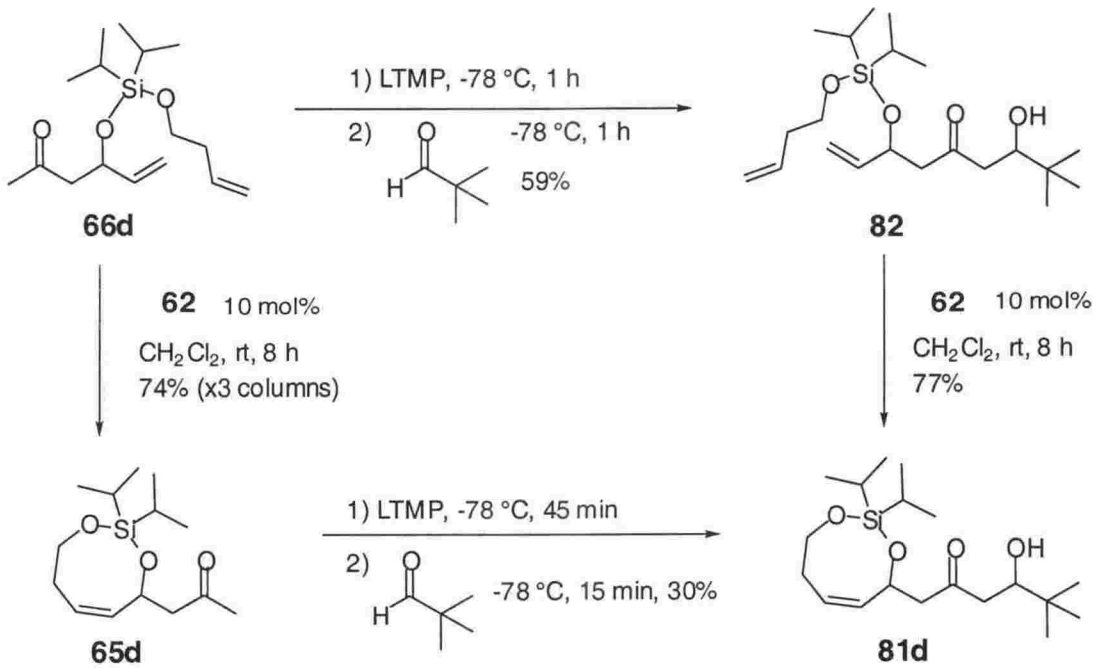
To investigate this supposition, **65b** was subjected to rigorous purification by preparative HPLC with detection by mass-spectromentry, before an aldol reaction between itself and pivaldehyde was conducted, scheme 70. Gratifyingly, ^{1}H NMR analysis of the crude reaction mixture indicated that the desired aldol adduct **81b** had been formed.



65b **81b**

Scheme 70: Aldol reaction of **65b** purified by preparative HPLC

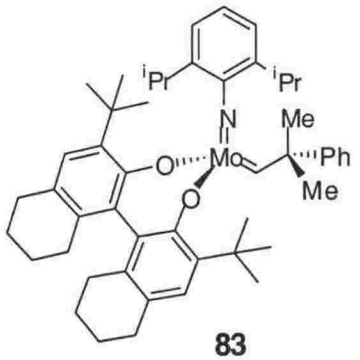
Diisopropylsilyl ether **66d** was then subjected to an aldol reaction with pivaldehyde, scheme 71. Again this aldol reaction was a success, with the aldol adduct **82** being produced in a respectable 59% yield. Diene **82** was then subjected to RCM with catalyst **62** to give the *bis*-silyl cyclic **81d** in a 77% yield. Alternatively **65d** was synthesised by the RCM of the acyclic adduct **66d** and the residual oil rigorously purified three times by flash chromatography, before being subjected to an aldol reaction with pivaldehyde, figure 71. Fortunately, this aldol reaction was moderately successful with the desired aldol adduct **81d** being formed in 30%. Presumably this low yield was due to the purity of the starting material. However, more importantly, these studies indicated that aldol reactions of the cyclic *bis*-ethers are indeed viable, provided the cyclic ether is of adequate quality.



Scheme 71: Racemic aldol studies

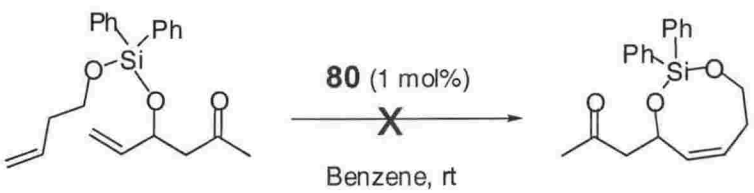
5.4: Removing the residual ruthenium

Ideally, the problems encountered with the removal of the residual ruthenium could be largely alleviated if a more active, or polymer bound, RCM catalyst was used. Recently Hoyveda and Schrock reported the use of the chiral Mo-based catalysts, such as **83**, to synthesise six and seven membered siloxanes bearing tertiary ether centres.[155] Although such molybdenum catalysts are extremely air and water sensitive, necessitating glove box conditions, the synthesis of the aforementioned siloxanes could be achieved using 1 to 5 mol% of the molybdenum catalyst. Thus, it was anticipated that the RCM of our silyl-tethered ethers could also be achieved with low catalytic loadings (1-2 mol %) of **83**.



83

In preparation for the Mo-catalysed RCM, benzene was added to precursor **66b** and the solvent removed under reduced pressure to allow for the azeotropic distillation of any residual water. This process was repeated three times. The attempted Mo-catalysed RCM of **66b** was then conducted in a glove box, with the solution of the diene in benzene being stirred for 24 h at room temperature in a manner analogous to that reported in the literature,[156] scheme 72. Although this procedure was attempted on several occasions, with the catalytic loading being increased to 5 mol%, unfortunately only the acyclic ether was ever isolated. Obviously this was not a suitable catalyst for our substrate.



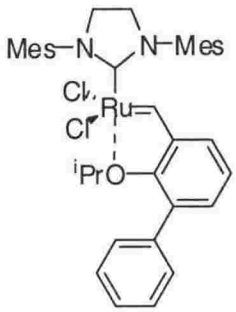
66b **65b**

Scheme 72: Attempted synthesis of **65b** by Mo-catalysed RCM

Even though more time could be invested in finding an alternative RCM catalyst, in the interim, a method for removing the residual ruthenium from the RCM of the *bis*-siloxy ethers using Grubbs' second-generation catalyst was required. Purification by preparative HPLC was too onerous to be synthetically useful. Reports of the purification of RCM adducts by the addition of water soluble tris(hydroxymethyl)phosphine, as a ligand to capture any unwanted ruthenium, indicated that this might a viable option.[155] However, although readily available, $P(CH_2OH)_3$ is still a somewhat expensive reagent. Other procedures for the removal of ruthenium by-products formed from the Grubbs reagent include the use of the somewhat toxic $Pb(OAc)_4$ to oxidise the ruthenium metal,[156] or treatment with Ph_3PO or DMSO.[157] These methods allowed for the reduction of the ruthenium levels down to approximately 1-2 μg per 5 mg of product(s).

More recently though, a superior methodology for the removal of residual ruthenium from RCM reaction products was reported. This involves the sequential treatment of the RCM adduct with silica gel, activated carbon (50 weight equivalent relative to the crude products), and column chromatography on silica gel, to give compounds with residual ruthenium levels of 0.06-0.53 μg per 5 mg of product.[158] Requiring both inexpensive and non-toxic reagents, this methodology was successively applied for the purification of our RCM adducts. Thus, the yields previously reported in Table 2 are those after purification by this methodology.

A future objective of this research however, is to find a more suitable RCM catalyst for this transformation. Either a more active RCM catalyst that can be used in lower catalytic loadings, or a polymer bound catalyst that can be recycled and hence removed from the reaction mixture by simple filtration, is required. Two recent advancements in this area, both by Blechert *et. al.*, include the highly active ruthenium metathesis catalyst **84**[159] or the polymer bound derivative **85**,[160] figure 19. It is anticipated that the applicability of these, or similar alternatives, will be explored at a later date.



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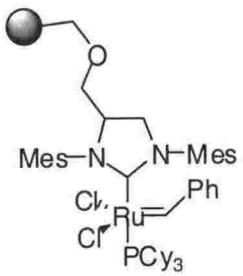

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Figure 19: Alternative RCM catalysts

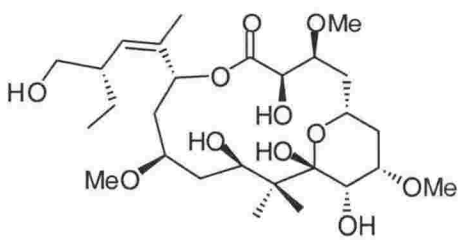
Nevertheless, for the time being, a suitable strategy for the racemic synthesis, and subsequent aldol reaction, of the C-12 to C-24 fragment of pel A had been developed. It was now time to extend these basic principles and apply them to the asymmetric synthesis of this fragment.

Chapter 6

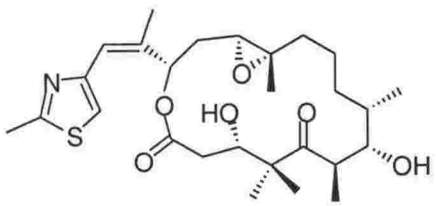
Asymmetric synthesis of the C-12 to C-24 fragment of pelourside A

6.1: Key stereochemical features

With guidelines in place for the synthesis of the C-12 to C-24 fragment of pel A, the next challenge was to synthesise this fragment asymmetrically and develop a methodology for its stereoselective coupling to the pyranose ring. Due to the apparent structural similarity between pel A and the 16 membered macrolide, epothilone B, figure 20, it was initially thought that pel A may act as an epothilone surrogate by binding to a common site on ß-tubulin.[xv] Initially our focus was on the synthesis of the enantiomer shown below, however a flexible strategy was planned which would allow for the synthesis of either enantiomer of pel A.



peloruside A

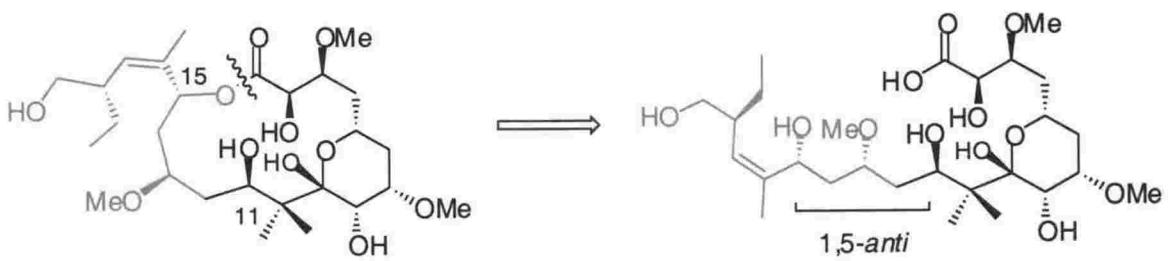


epothilone B

Figure 20: Structural similarities between peloruside A and epothilone B

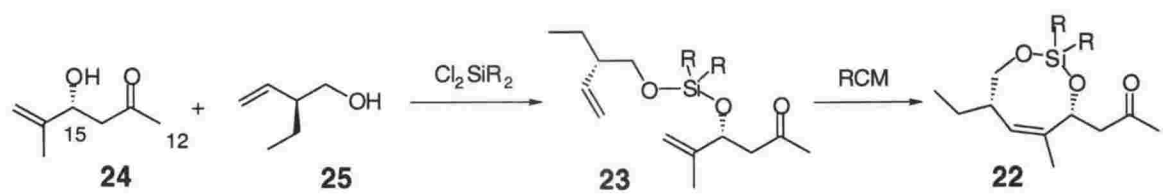
[xv] This appeared to be a common misconception by many in the academic community. Until its absolute stereochemistry was determined, all publications concerning the synthesis of pel A focussed on synthesising the enantiomer shown.

A review of the retrosynthetic analysis for pel A highlights the required 1,5-*anti* relationship between the C-11 and C-15 stereocentres, scheme 73. To achieve this 1,5-*anti* relationship, a boron-mediated aldol reaction between the C-12 to C-24 fragment of pel A and the aldehyde acceptor of the pyranose ring will be performed. Although Evans[161] and Paterson[162] pioneered this area of remote 1,5-induction in boron-mediated aldol reactions, to-date only limited explanations have been given for this surprising phenomenon. Thus, in achieving the 1,5-*anti* relationship required for the synthesis of pel A, it is anticipated that further insight into the origin of these boron-mediated reactions will be gained.



Scheme 73: Retrosynthesis of peloruside A showing the required 1,5-*anti* relationship between the C-11 and C-15 stereocentres with the C-12 to C-24 framework in red

A review of the synthesis of the C-12 to C-24 fragment of pel A is given in scheme 74. The cyclic *bis*-silyl ether **22** is the tethered version of the side chain shown in red above. However, for simplicity, the ethyl side chain will be once again omitted. The focus of this chapter is thus on asymmetrically synthesising the ß-hydroxyketone **24** and developing an appropriate protocol for the boron-mediated 1,5-*anti* aldol reaction of the *bis*-silyl ether. These two concepts will be discussed in turn.



Scheme 74: Retrosynthesis for the formation of the C-12 to C-24 fragment of pel A

6.2. Synthesis of (*R*)-4-hydroxy-5-methylhex-5-en-2-one

From the outset, we were aware of a published procedure for the synthesis of the desired (*R*)-4-hydroxy-5-methylhex-5-en-2-one **24**. This required a diisopinocamphyl-borane mediated enantioselective aldol reaction between acetone and methacrolein.[163] However, as the enantiomeric excess for this reaction was 73% with a yield of 68%, we optimistically proposed that an alternative, and indeed better, synthesis of this target compound could be developed. Upon reviewing the literature, two general strategies for the enantioselective synthesis of this ß-hydroxy ketone emerged: a) the kinetic resolution of the racemic alcohol and b) an alternative enantioselective aldol reaction.

6.2.1: The kinetic resolution of (±)-4-hydroxy-5-methylhex-5-en-2-one

The kinetic resolution of racemic substrates can be performed using one of two approaches, figure 21.[164] The first, and more established approach is a classic kinetic resolution. Here resolution of the enantiomers (R + S) occurs when $k_R \neq k_S$ and when the reaction is stopped at some stage at or near 50% conversion. The enantiomers are then separated by obtaining the product (P), formed from R, and the non-converted starting substrate (S). A difference in the specific rate constants (k_R, k_S) is obtained by using a chiral catalyst, which may be either chemical or biological nature. Dynamic resolution however, encompasses both classic resolution and an additional racemising process, k_{rac}. Again substrate racemisation may be achieved either by chemical or biological catalysis and, provided that $k_{rac} > k_S$, all of the substrate is transformed into a single product enantiomer in 100% theoretical yield. Due to the enhanced yields of dynamic kinetic resolution, this is clearly the more desirable strategy for the resolution of racemic substrates.

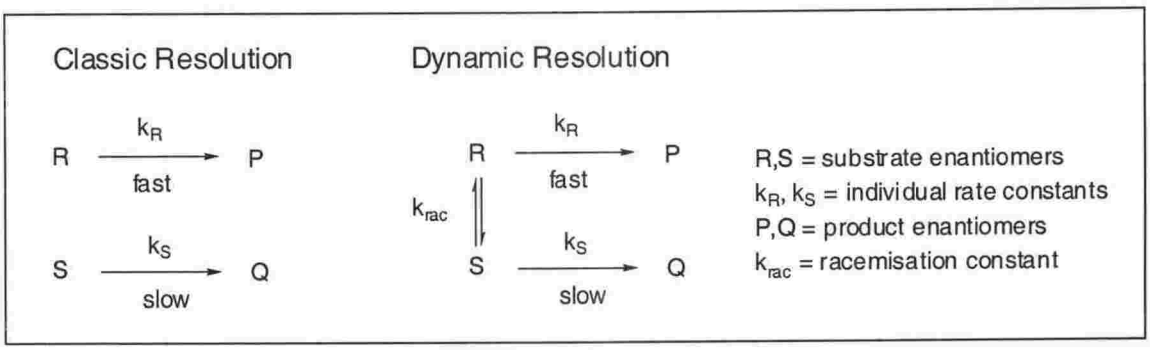
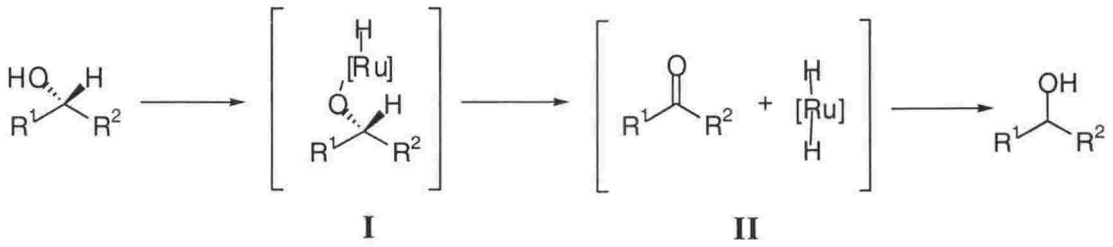


Figure 21: Classic versus Dynamic Kinetic Resolution

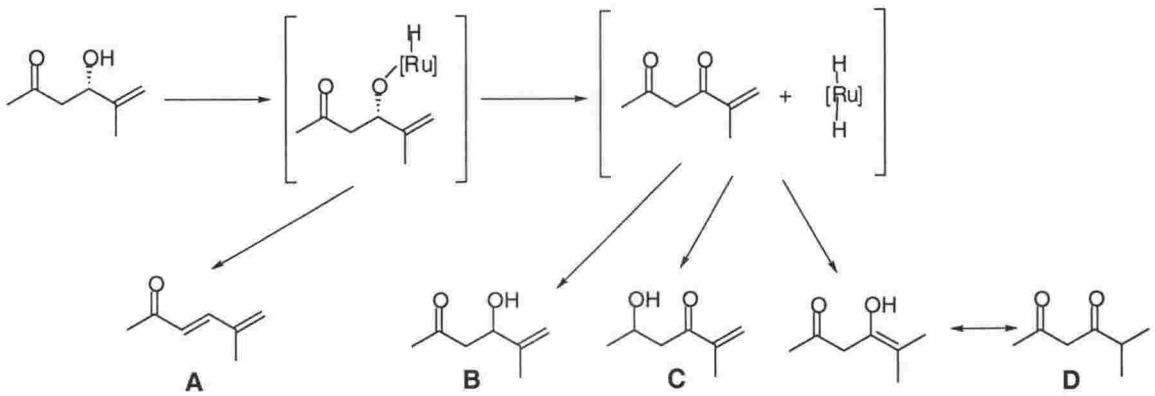
However, upon reviewing the procedures required for dynamic kinetic resolutions, it appeared that our ß-hydroxy ketone would not be particularly amenable to such methodology. Typically the dynamic kinetic resolution (DKR) of secondary alcohols involves the transition metal-catalysed racemisation of the alcohol coupled with enzymatic resolution.[165] Ruthenium is frequently the transition metal of choice, with the racemisation of the substrate commencing with a base-mediated hydrogen abstraction from a hydrogen donor to form the intermediate ruthenium alkoxy species **I**, scheme 75.[166a] Abstraction of the α-proton then gives the intermediate ketone and a ruthenium hydride complex **II**. Finally, the subsequent readdition of the hydrogens to the ketone completes the catalytic cycle to give the racemised substrate.



Scheme 75: Mechanism of the ruthenium-catalysed hydrogen transfer reaction

Due to the presence of a ketone moiety in our starting substrate, it is unlikely that such a DKR is feasible for the following reasons, scheme 76. First, the α-ketone proton could be

preferentially abstracted leading to the α,ß-unsaturated adduct **A**, second, the original ketone moiety itself could be reduced to give **C**, and third, readdition of the hydrogens in a 1,4-fashion would give the diketone **D**. A biocatalytic DKR of our ß-hydroxy ketone, where dehydrogenases are required for the oxidative process and redox-enzymes are required for the reductive process,[165] could also suffer a similar fate.



Scheme 76: Proposed products from the *in situ* racemisation of the starting substrate during the attempted DKR of the ß-hydroxy ketone

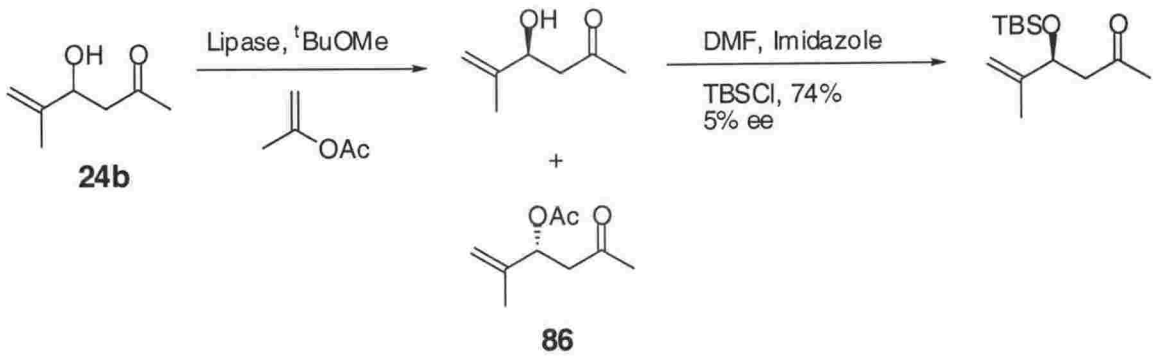
Thus, in light of the potential pitfalls of the DKR of the ß-hydroxy ketone, investigations into classical kinetic resolution techniques were made. Traditionally this requires the use of an esterase to resolve the secondary alcohol, however more recently, non-enzymatic strategies[166] such as palladium catalysed sparteine oxidative kinetic resolutions,[167] the Sharpless resolution of allylic alcohols,[168] or Fu's azaferrocene catalysed enatioselective acylation,[169] have been developed.

Unfortunately, upon closer examination of the non-enzymatic strategies, some potential problems were highlighted. For example, the palladium catalysed oxidative kinetic resolution requires the use of the naturally occurring chiral base, (-)-sparteine, which unfortunately can only be obtained in one enantiomeric form. Unlike traditional esterase resolutions, where either enantiomer can be obtained either directly, or by the deacetylation of acetylated alcohol, if the undesired enantiomer is formed during this

oxidative strategy, there are no easy methods of obtaining the correct enantiomer. The strategy by Fu also presented some practical difficulties as the synthesis of the azaferrocene catalyst required the use of preparative chiral HPLC, which was not readily available. Although the Sharpless methodology appeared to offer some promise as either enantiomer can be synthesised, due the extremely stringent conditions required for effective epoxidation strategies and the potentially explosive nature of the requisite *tert*-butyl hydroperoxide solution, we initially opted to explore alternative strategies.

Thus, the more traditional approach of resolving secondary alcohols using esterases was investigated. Enantioselective esterases are particularly useful enzymes for the kinetic resolution of secondary alcohols due to their efficiency, their applicability to a wide range of substrates and the ease at which the reactions can be performed on a large scale. Unfortunately though, there is little X-ray structural information available about these esterases and the appropriate enzyme is usually chosen by screening. Hence two candidates, lipases from *Candia antartica*[170] and *Pseudomonus cepia*,[171] were investigated for their ability to enantioselectively esterify, and hence kinetically resolve our ß-hydroxy ketone.

The racemic ß-hydroxyketone **24b** was dissolved in *tert*-butylmethyl ether with the appropriate esterase and isopropenyl acetate as the acyl donor, scheme 77. The heterogenous slurry was then stirred rapidly at room temperature with progress of these reactions being monitored by ^{1}H NMR. After seven days for the *Candida antartica* lipase, and five days for the *Pseudomonus cepia* lipase, the reactions reached 50% completion and the lipase was removed by filtration. To determine the enantiomeric excess of these esterification reactions, the ß-hydroxy ketone was separated from the acetylated compound by flash chromatography and a portion converted into the TBS silyl ether. This silylation was necessary in order to make a less polar and bulkier derivative that was more amenable to analysis by chiral gas chromatography. Unfortunately though, chiral gas chromatography revealed that the enantiomeric excess for both esterases was extremely low at approximately 5%.



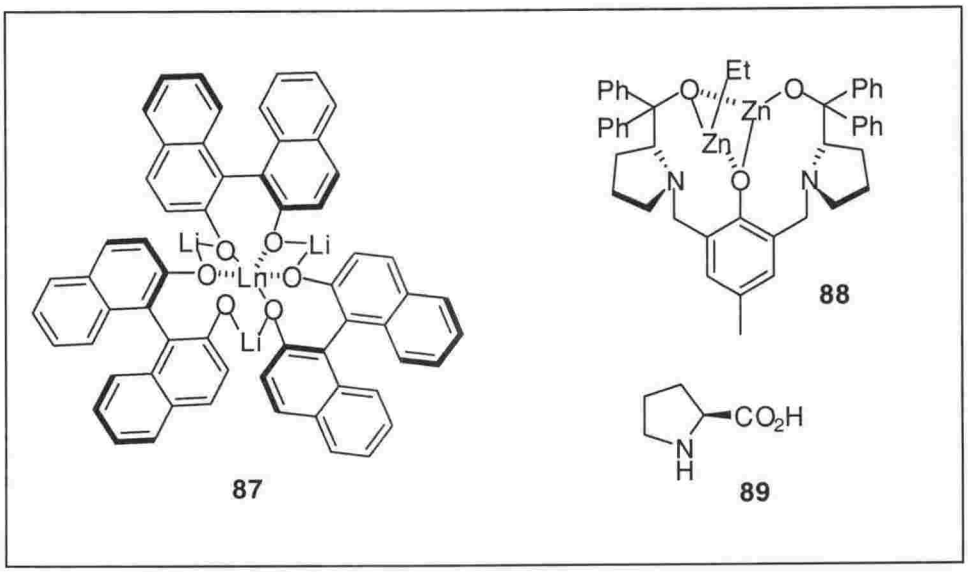
Scheme 77: Attempted kinetic resolution of (±)-4-hydroxy-5-methylhex-5-en-2-one using lipase from either *Candida antartica* or *Pseudomonus Cepia*

In many respects these results were not surprising. According to the empirical rules of Kazlauskas,[172] lipase stereoselectivity is set mainly by steric interactions between the enzyme and substrate, with the enantioselectivity of the esterification of secondary alcohols depending upon the relative size of the two neighbouring groups. Thus, if the groups are similar, as with our ß-hydroxyketone, poor resolution is obtained. Although non-steric interactions between the enzyme and the substrate can provide for enantioselective differentiation, the electron density of both the carbonyl and olefinic functional groups of the ß-hydroxy ketone provided for little electronic differentiation. Thus, the enzymatic kinetic resolution of ß-hydroxy ketone **24b** did not appear to be particularly viable and investigations into alternative enantioselective aldol reactions were conducted.

6.2.2: Asymmetric aldol reaction

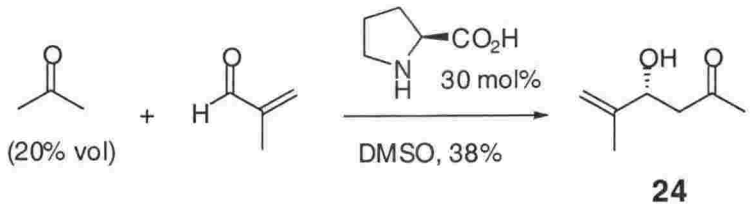
The search for catalysts that mimic the selectivity of biological aldolases has been the subject of intense efforts in recent years. Many catalysts, including the (*R*)-$LnLi_3$tris(binapthoxide) catalyst **87** developed by Shibasaki *et. al.* [173] and the dinuclear Zn catalyst **88** developed by Trost *et. al.*[174] offered potential for the synthesis of our desired ß-hydroxy ketone, however the recently developed procedure by List for the (*L*)-proline

(89) catalysed asymmetric aldol reaction between acetone and a variety of aldehydes,[175] appeared to be the more straightforward strategy. Although the reaction between methacrolein and acetone was not reported, we proposed that List's methodology could be adapted for the synthesis (*R*)-4-hydroxy-5-methyl-5-hexen-2-one.



87 88 89

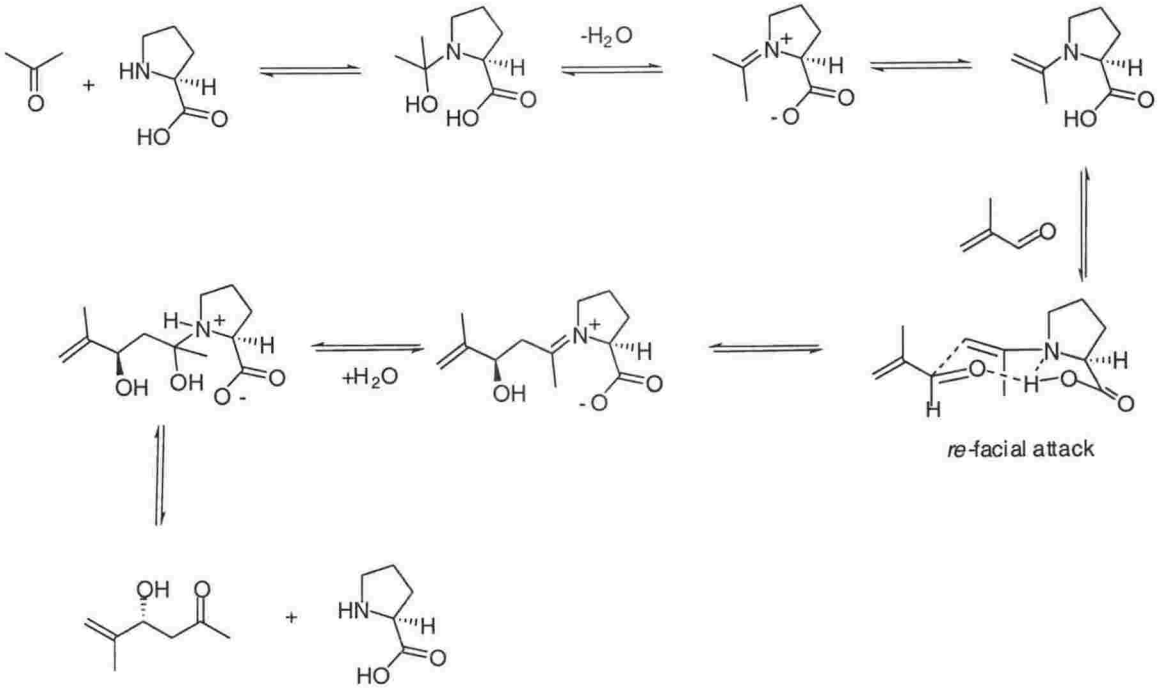
Thus, 30 mol % of (*L*)-proline was added to a solution of methacrolein in 4:1 v/v DMSO:acetone in a procedure analogous to that reported by List, scheme 78. Initially we had concerns that the α,ß-unsaturated ketone would be preferentially formed, via a proline catalysed elimination reaction, but with relief, the desired ß-hydroxyketone **24** was formed in a modest 38% yield. The replacement of DMSO by acetone, which has been reported to improve the yields of some proline catalysed reactions,[176b] was unfruitful in our particular studies.



24

Scheme 78: (*L*)-proline catalysed asymmetric aldol reaction for the synthesis of (*R*)-4-hydroxy-5-methylhex-5-en-2-one

At present it is assumed that this asymmetric aldol reaction occurs via an enamine mechanism with proline acting as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base co-catalyst in the form of the carboxylate, scheme 79.[176a] The enantioselectivity can be explained with a metal-free version of a Zimmerman-Traxler type transition state,[83] with the tricyclic hydrogen bonded framework accounting for the enantiofacial selectivity. To determine the enantiomeric excess of this reaction, the ß-hydroxy ketone was again protected as the *tert*-butyldimethylsilyl ether. The GC trace of the silylated reaction product is shown in figure 22 overleaf, with the (*R*)-enantiomer, being formed in a respectable 74% ee.[XVI]



Scheme 79: Proposed mechanism the (*L*)-proline catalysed aldol reaction

[XVI] Precedent from List's work enables use to assign this as the major enantiomer

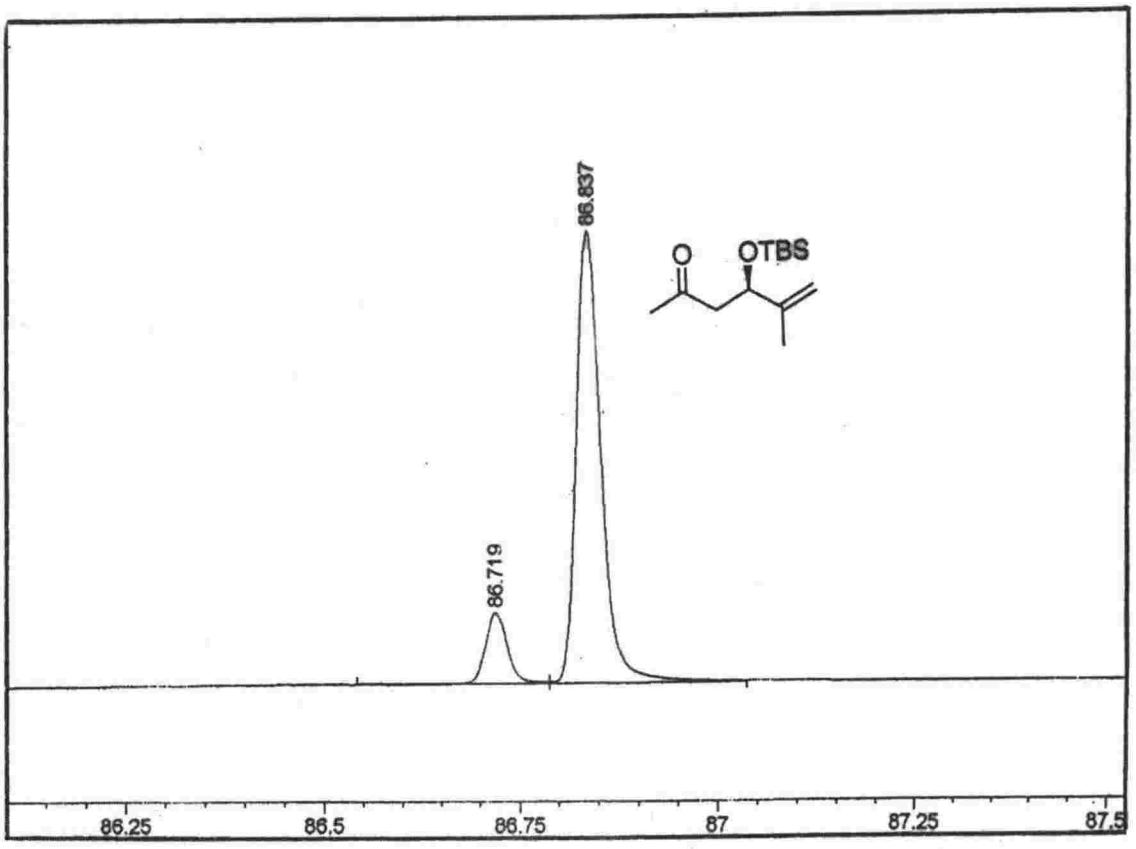


Figure 21: GC trace of the silylated enantiomers.

Unfortunately, when this methodology was repeated with acrolein as the aldehyde substrate, none of the desired aldol product was observed. This result, was however, in accordance with observations made by List, whereby significant proportions of α,ß-unsaturated ketones were formed during the proline catalysed aldol reactions of α-unsubstituted aldehydes.[176b] It is believed that this unsaturation occurs as a result of a Mannich-type condensation reaction, and not by the proline catalysed dehydration of the ß-hydroxy ketone.

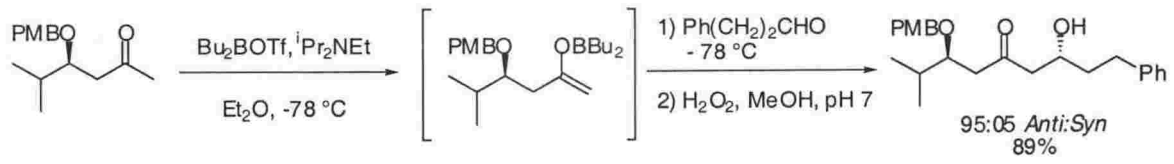
Nevertheless in the interim, a suitable strategy for the synthesis of (*R*)-4-hydroxy-5-methylhex-5-en-2-one had been developed. Although the yields for this proline catalysed asymmetric aldol reaction are modest, due to the inexpensive, non-toxic and

straightforward nature of this reaction, it was concluded that, for the synthesis of the (*R*)-4-hydroxy-5-methyl-hex-5-en-2-one, this was the best strategy.[XVII] Thus, our next major challenge was to develop methodology suitable for obtaining the desired 1,5-*anti* aldol product. However before our proposed methodology for achieving this transformation is discussed, it is instructive to first highlight what is already known about boron mediated 1,5-*anti* aldol reactions.

6.3. Boron mediated 1,5-*anti* aldol reactions

6.3.1: A Brief Overview

The boron mediated 1,5-*anti* aldol reaction commences with the enolisation of a ketone, using a base (either triethylamine or diispropylethylamine) and the appropriate boron reagent, L_2BX, (where L = alkyl ligand and X = Cl or OTf). The enol boronate then nucleophilically attacks an aldehyde moiety, forming a boryl ether. Oxidative workup (MeOH, H_2O_2, pH 7 buffer solution) liberates the ß-hydroxyketone. The notable feature of these reactions, such as the one illustrated in scheme 80, is the often remarkable diastereoselectivity observed in the product ß-hydroxy ketone. More often than not, the 1,5-*anti* adduct is favoured.[176]



Scheme 80: The basic boron mediated 1,5-*anti* aldol reaction

[XVII] Although (D) Proline is commercially available, it is more expensive than its (L) counterpart and hence an alternative procedure for the synthesis of the (*S*)-ß-hydroxy ketone will be sought. In the future, investigations will be made into the BINOL-Ti catalysed Mukaiyama aldol reactions between the silyl enol ether of acetone and methacrolein. Refer to reference 93.

Although the diastereoselectivities of these reactions are enhanced by a variety of factors, including the choice of boron reagent and the local asymmetric environment, the primary influence in these reactions has long been speculated to be an electrostatic effect exerted by the ß-alkoxy substituent.[162a,177] Consequently, the nature of the ß-oxygen protecting group is critical in determining the level of asymmetric induction.[163] In general, high 1,5-*anti* selectivities are almost always obtained when the ß-hydroxy protecting group is a *para*-methoxybenzyl ether or a benzylidine acetal[162a,163] and as a result these protecting groups are used almost exclusively, figure 23. To date, no studies or models have been reported for this surprising process. However, the preference for aromatic substituents at the ß position initially suggested to us that a favourable π-stacking interactions may, at least, be partially responsible for the observed stereochemical outcome.

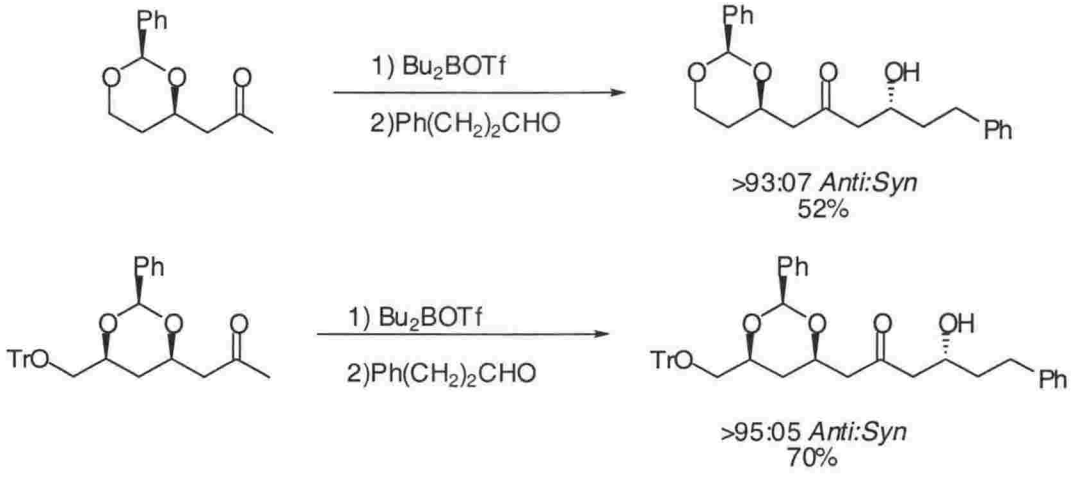


Figure 23: Examples of boron mediated 1,5-*anti* aldol reactions

The phrase 'π-stacking' signifies, in its simplest form, the positioning of a multiple bond (typically either C-O or C-C) parallel to and at approximately 3.5 Å over an aromatic ring.[178] Compelling evidence suggests that an attractive interaction is involved in these π-π interactions, yet the exact nature of the π-stacking effect (either charge transfer or simple Van der Waals forces) is still a subject of some debate in the synthetic and computational arenas.[179] Nevertheless, since the first synthetic application of π stacking interactions by Corey *et. al.* in 1972 for the synthesis of the

prostaglandins,[179] designed π-stacking effects have been encouraged for the control of asymmetric bond forming reactions, under both stoichiometric (chiral auxiliaries) and catalytic conditions, and more recently, for the purpose of assisting in molecular recognition.[179]

Some examples where π stacking effects have been applied in a stoichiometric manner are given in figure 24. These include the use of (–)-8-phenylmenthol derivatives in both asymmetric [3+2] cycloadditions catalysed by $Ni(COD)_2$, equation (1),[180] and in nucleophilic additions with Grignard reagents, equation (2).[181] Perhaps the most focussed study to date in this area however, was reported by Evans *et. al.* in 1987.[182] By changing the substituents on a oxazolidinone dieneophile, it was unambiguously established that appropriately orientated aromatic rings, such as that shown in equation (3), contribute to the enhanced diastereoselectivity of the Diels-Alder reactions of α,ß-unsaturated *N*-acyloxazolidinones.

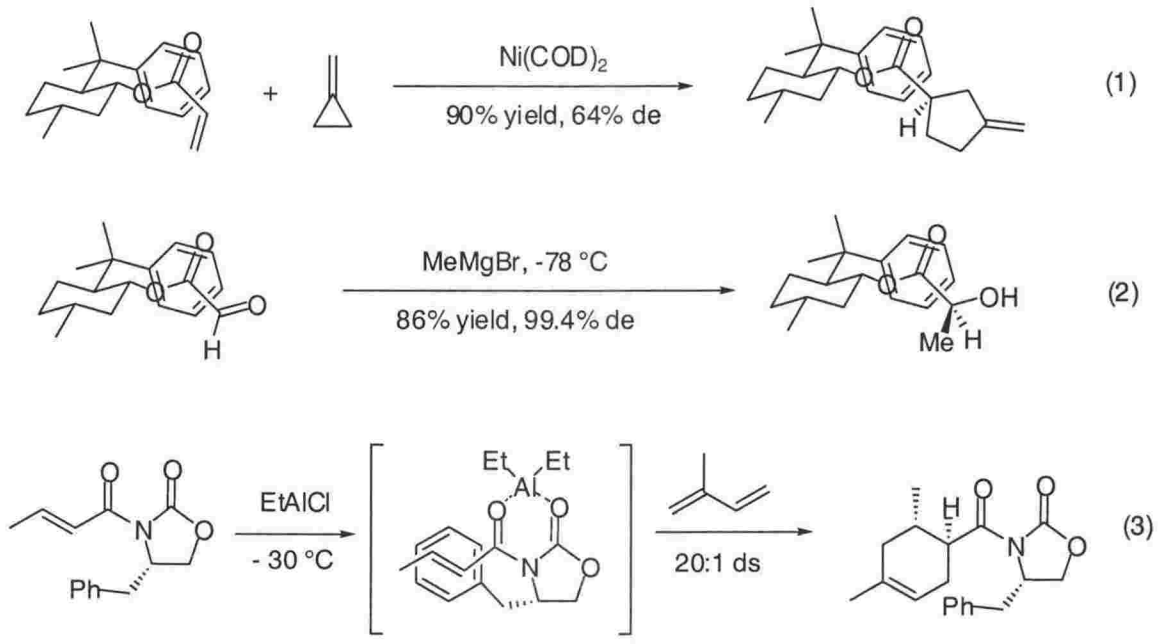
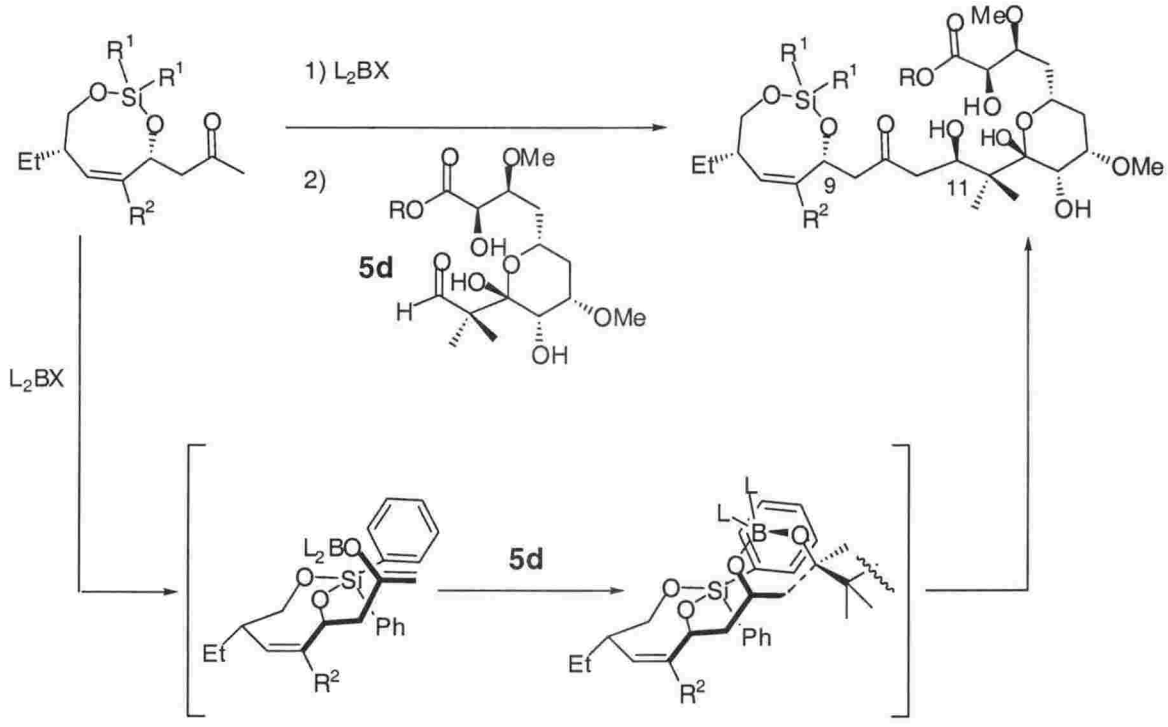


Figure 24: π stacking effects in asymmetric synthesis.

6.3.2: The proposed transition state for the boron mediated 1,5-*anti* induction in the synthesis of peloruside A

Coupling the C-12 to C-24 fragment of pel A to the pyranose requires efficient *anti*-induction between C-11 and C-15 in which the stereochemical controlling element is the silyl protected ß-hydroxy substituent, scheme 81. Consequently, it was postulated that the proximity of the initially formed boron enolate to the phenyl substituents on the silyl tether, where R^1 = Ph, would result in favourable π-stacking interactions and hence a transition state geometry leading to efficient 1,5-*anti* induction.



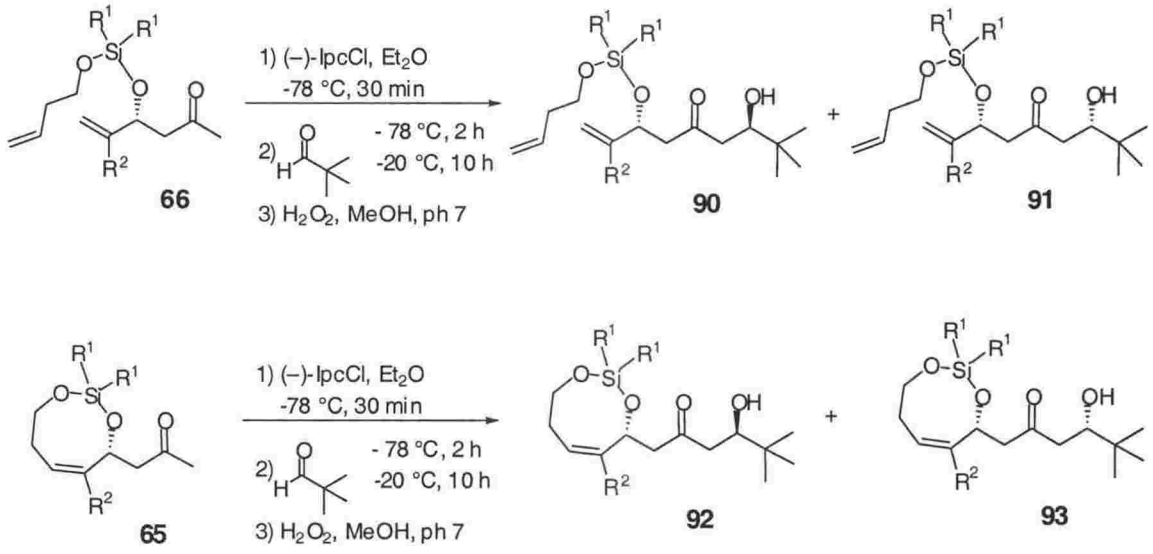
Scheme 81: Proposed transition state for asymmetric control

The enolate would adopt the geometry, as depicted in scheme 81, to minimise the steric interactions between the cyclohexyl boron substituents and the phenyl substituents. The aldehyde **5d** thus approaches the enolate from the opposite face to the phenyl substituent

and chelates to the boron enolate though a twist boat transition state with the large alkyl group on the aldehyde adopting a geometry away from the phenyl ring and the aldehyde proton orientated towards the phenyl ring. Although one normally expects chelation to occur via a chair transition state, molecular calculations indicate that the twist-boat transition state for analogous boron mediated aldol reaction is energetically more favourable, by 1 to 4 kcal/mol.[183] In sum, this sequence of events leads to the desired 1,5-*anti* product.

6.3.3: Studies into the synthesis of peloruside A

To investigate this hypothesis, both the acyclic **66** and cyclic **65** ketone derivatives were subjected to boron mediated aldol reactions, with pivaldehyde being used as a model for the pyranose ring, scheme 82. The enantiomerically pure derivatives, where R^2 = Me, were synthesised from (*R*)-4-hydroxy-5-methylhex-5-en-2-one using the procedures detailed in chapter 5. By comparing both the acyclic and cyclic derivatives, insight into the supposed 'electrostatic effect' exerted by the ß-alkoxy substituent could be gained. Similarly, being comparable in size, the effects of both the isopropyl and phenyl silyl tethers (R^1) were investigated as this enabled distinctions to be made between the electrostatic and steric effects of these tethers. The effects of the boron ligands, where L = cyclohexyl or (-)-diisopinocampheyl were also investigated. Generally these boron mediated reactions proceeded smoothly and in good yields. The diastereoselectivity of these reactions was determined by ^{13}C NMR analysis of the crude substrate, *vide infra,* and results of these studies are summarised in Table 4 overleaf.



Scheme 82: Boron mediated 1,5-*anti*-aldol studies

Table 4: Boron mediated 1,5-*anti* aldol studies

Entry	Substrate	R^1	R^2	Boron Reagent	Yield	Diastereoselectivity	
1	**66a**	*i*Pr	Me	(–)-Ipc_2BCl	93%	2.2:1	(**90a**:**91a**)
2	**66a**	*i*Pr	Me	Cy_2BOTf	97%	1.2:1	(**90a**:**91a**)
3[a]	**66b**	Ph	H	(–)-Ipc_2BCl	98%	2:1	(**90b**:**91b**)
4[a]	**65a**	*i*Pr	H	Cy_2BOTf	85%	1.2:1	(**92a**:**93a**)
5	**65b**	*i*Pr	Me	(–)-Ipc_2BCl	88%	1.5:1	(**92b**:**93b**)
6	**65b**	*i*Pr	Me	Cy_2BOTf	95%	1.2:1	(**92b**:**93b**)
7	**65c**	Ph	Me	(–)-Ipc_2BCl	94%	>99:1	(**92c**:**93c**)
8	**65c**	Ph	Me	Cy_2BOTf	68%[b]	>99:1	(**92c**:**93c**)
9[a]	**65d**	Ph	H	(–)-Ipc_2BCl	60%[b]	>99:1	(**92d**:**93d**)

[a]performed using the racemic substrate; [b]unoptimised.

The most striking observation from the above studies is the poor diastereoselectivities observed for all the acyclic derivatives, entries 1,2 and 3. Although moderate improvements in the diastereoselectivities are observed with the use of (–)-Ipc_2BCl (compare entries 1 and 2), the differences in the ratio of *anti* to *syn* products are

negligible. (–)-Ipc_2BCl is reported to improve the π-facial selectivity for the *anti*-adducts.[184] Thus, from this result alone, one can conclude that it is not the electrostatic effect of the ß-siloxy substituent that is predominantly influencing π-facial discrimination in these boron mediated aldol reactions.

When comparing the aldol reactions of the cyclic derivatives (entries 4 to 9) some striking observations are made. With the isopropyl silyl tether (entries 4, 5 and 6), once again poor diastereoselectivities are observed. This is particularly evident in the ^{13}C NMR spectra with the two diastereomers producing different chemical shifts as expected. For example the spectrum of 7,11-*O*-diisopropylsilanediyl-2,2-dimethyl-3-hydroxyundec-8-en-5-one (entry 4) is shown in figure 25 (page 114) with an enlargement of the spectral window from δ 45 to 76 ppm. The most notable change in the chemical environment of the two diastereomers is reflected by the chemical shifts of the newly formed methine (C-3) carbons, at δ 75.0 and δ74.7 ppm, and the neighbouring methylene (C-4) carbons, at δ 46.5 and δ 46.2 ppm. However, when synthesising 7,11-*O*-diphenylsilanediyl-2,2-dimethyl3-hydroxyundec-8-en-5-one **65d** (entry 9), only one diastereomer was observed by ^{13}C NMR. The spectrum of **65d** is shown in figure 26 (page 115) with an expansion of the spectral window from δ 45 to δ 76 ppm clearly indicating that only one diastereomer is present. The analogous chemical shifts of the C-3 and C-4 carbons of **65d** are at δ 74.8 and δ 46.1 ppm respectively.

Given that the isopropyl and phenyl substituents on the silyl tether are of comparable size, it was apparent that the size of the phenyl substituents was not primarily responsible for the high levels of asymmetric induction. Furthermore, by comparing entries 7 and 8, it was evident that the chiral ligand was not responsible for the observed asymmetric induction. Thus, one could conclude that the orbital interactions between the phenyl group and the enolate were responsible for the observed stereochemical induction. However, before this statement could be made, we first needed to determine that the *anti* adduct had indeed been synthesised. [XVIII]

[XVIII] One could speculate that the *anti* product predominates as the use of the (–)-Ipc_2 enhances the proportion of the *anti* product

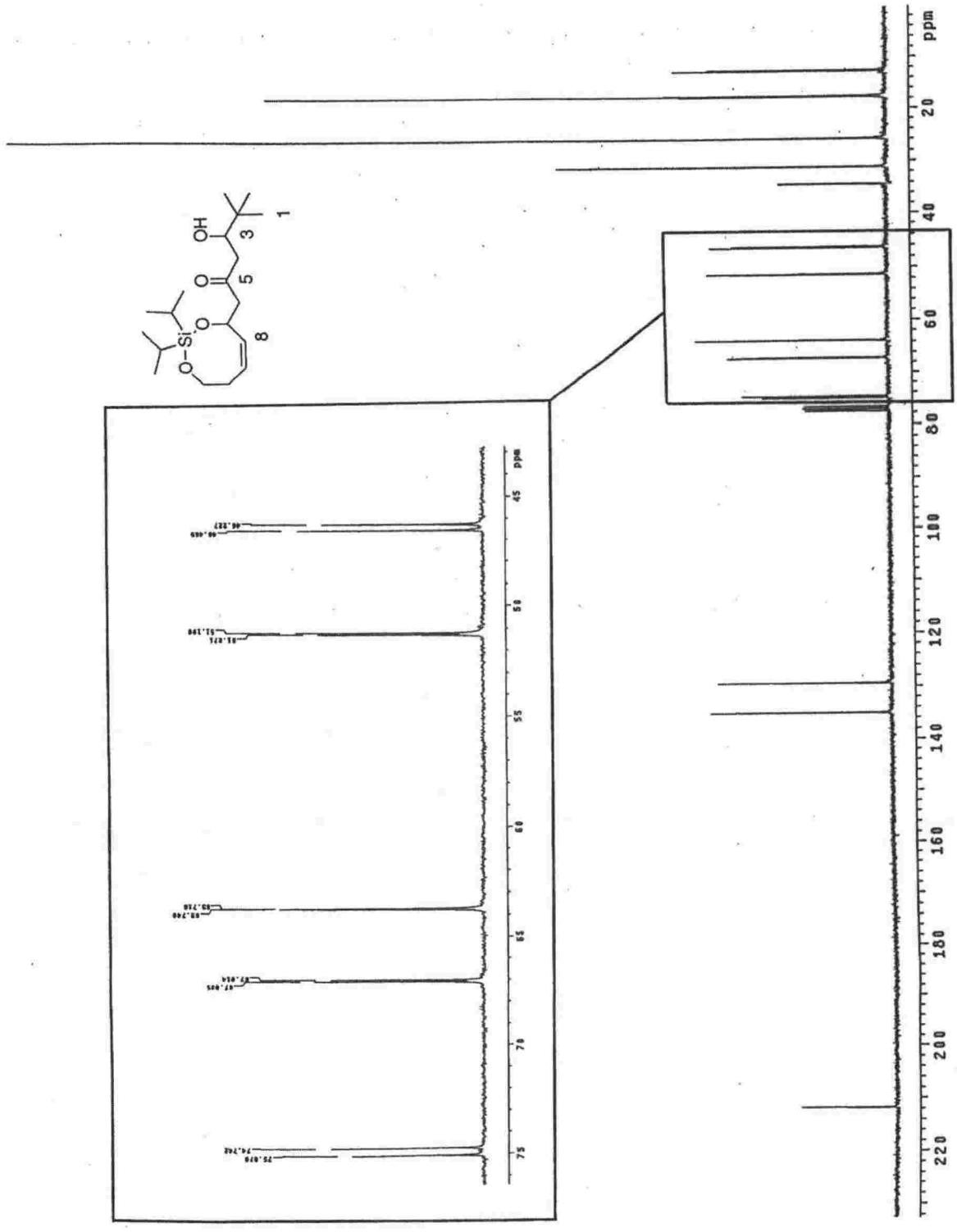


Figure 25: ^{13}C NMR of racemic 7,11-*O*-diisopropylsilanediyl-2,2-dimethyl-3-hydroxy-undec-8-en-5-one

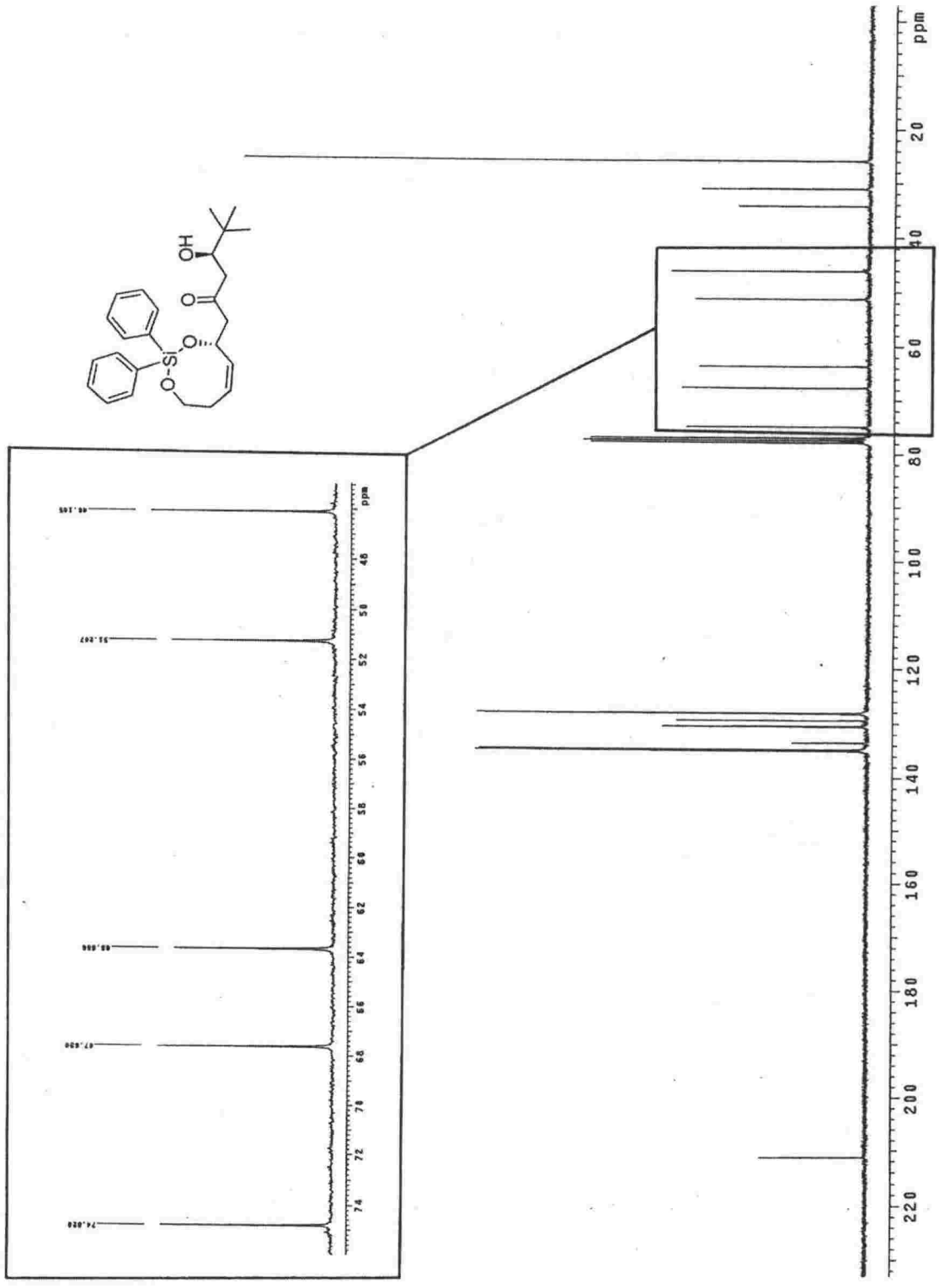
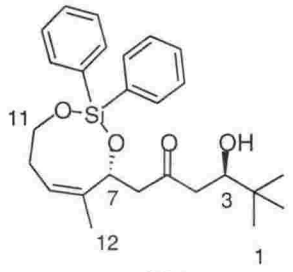


Figure 25: ^{13}C NMR of 7,11-*O*-diphenylsilanediyl-2,2-dimethyl-3-hydroxyundec-8-en-5-one

6.3.4: Determination of the *anti* stereochemistry

To determine the relative stereochemistry at C-3 of the aldol adduct, **92c** was subjected to rigorous NMR analysis. A summary of the ^{1}H, ^{13}C, COSY and nOe NMR spectral data for this substrate (recorded in $CDCl_3$) is provided in table 5, with the ^{1}H and ^{13}C spectra given in figures 27 and 28, respectively.



92c

Table 5: NMR data for **92c**

Position	$\delta^{13}C^{a}$		$\delta^{1}H$	COSY	nOe
^{t}Bu (1)	25.9		0.89 (s, 3H)	-	4a, 4b
^{t}Bu (2)	34.3	C	-	-	-
3	74.8	CH	3.78 (dd, J = 10.5, 1.8 Hz, 1H)	4a, 4b	-
4a	46.1	CH_2	2.58 (dd, J = 17.7, 10.2 Hz, 1H)	3, 4b	1, 6a
4b	-	CH_2	2.76 (dd, J = 17.8, 2.0 Hz, 1H)	3, 4a	1, 6b
5	211.5	C	-	-	-
6a	49.5	CH_2	2.99 (dd, J= 14.9, 9.8 Hz, 1H)	7	4a
6b	-	CH_2	2.62 (dd, J = 14.9, 3.7 Hz, 1H)	7	12
7	71.9	CH	4.90 (dd, J = 9.8, 3.3 Hz, 1H)	6a, 6b	-
8	125.1	C	-	-	-
9	140.7	CH	5.42 (t, J = 9.6 Hz, 1H)	10a, 10b	-
10a	30.9	CH_2	2.28 (m, 1H)	10b, 11	-
10b	-	CH_2	2.91 (m, 1H)	10a, 11	-
11	64.3	CH_2	4.05 (m, 2H)	10a, 10b	-
12 (Me)	21.5	CH_3	1.60 (s, 3H, 1H)	-	3

[a]Multiplicity determined by HSQC Dept

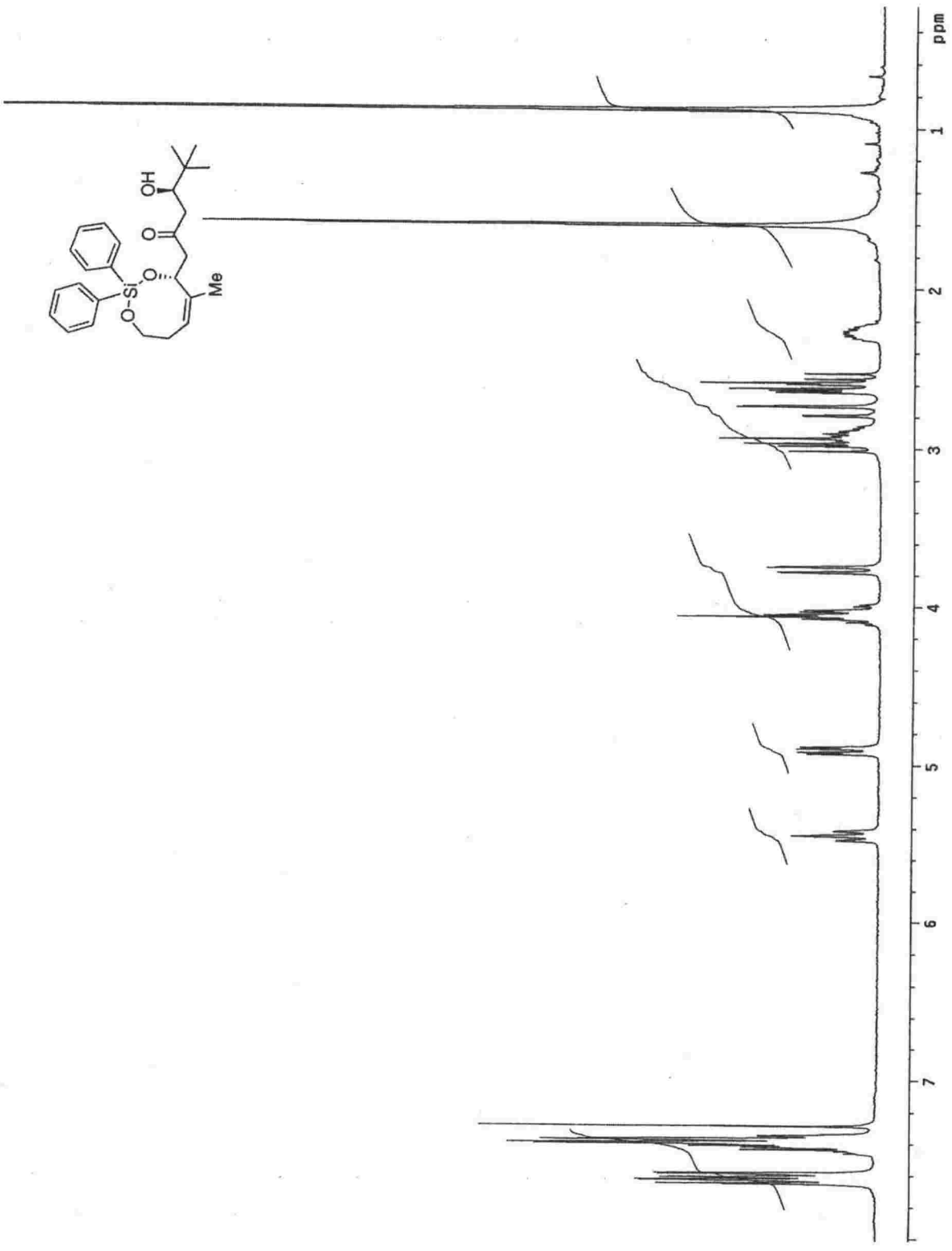


Figure 27: ^{1}H NMR spectrum of (3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-2,2,8-trimethylundec-8-en-5-one

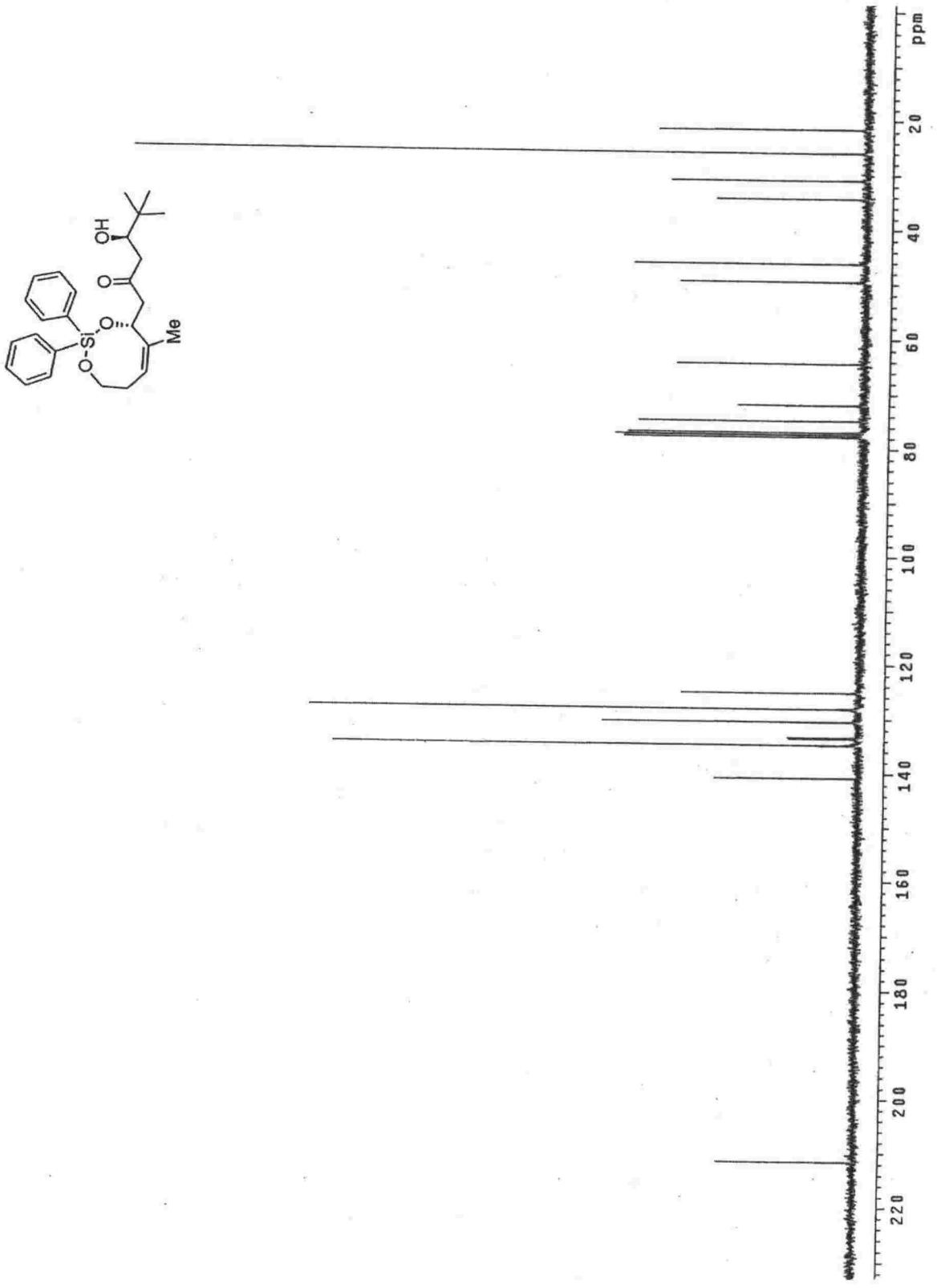


Figure 27: ^{13}C NMR spectrum of (3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-2,2,8-trimethylundec-8-en-5-one

The starting point for determining the stereochemistry at C-3, was determining the relative orientations of H-6a and H-6b, figure 28. The large *trans* coupling of 9.8 Hz between H-7 and H-6a enabled H-6b to be differentiated, with H-6b being on the front face of the molecule as shown. The difference in the chemical environment of H-6a and H-6b also indicated that there was restricted movement of the C-6 to C-8 carbon framework. Similarly, the *trans* coupling of 10.2 Hz between H-3 and H-4a enables H-4a and H-4b to be differentiated.

The crucial part in this analysis, however, was determining the conformation of the C-1 to C-5 carbon framework. NOe's between H-1 (^{t}Bu) and both H-4a and H-4b indicated that the ^{t}Bu group bissects both H-4a and H-4b, yet did not distinguish between the geometry shown below or a more linear conformation with the side chain extended in a zig-zag fashion from C-5. This information was obtained from the nOe correlations between H-12 (Me) and H-6a and 3. NOes between H-12 and H-3 indicated that the C-1 to C-5 framework adopts the conformation shown below - these nOes would not be observed if a more linear conformation was favoured. NOes between C-12 and H-6b enabled us to determine that the methyl group (H-12) was sitting on the front face of the compound, as depicted. Thus, if the methyl substituent is on the front face of the molecule and nOes are observed between C-12 and H-3, then H-3 must be on the front face of the molecule, with the hydroxyl behind. This corresponds to the anticipated 1,5–*anti* relationship. This analysis is further supported by the nOe between H-6a and H-4a.

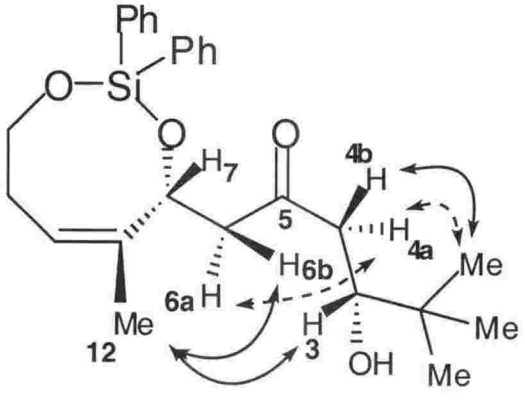


Figure 29: NOe correlations of (3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-3-hydroxy-2,2,8-trimethylundec-8-en-5-one

Although it was impossible to perform the same spectral analysis of 4,8-*O*-diphenylsilanediyl-5-octen-2-one **92d** due to the absence of the methyl substituent, by analogy we assumed that the 1,5-*anti* diastereomer was preferentially formed. In any case, a satisfactory strategy for the synthesis of the C-12 to C-24 fragment of pel A and its asymmetric coupling to the pyranose ring had been developed. Gratifyingly, this boron mediated 1,5-*anti* aldol reaction proceeded in both excellent yield and with excellent diastereomeric selectivity.

To provide further evidence for the involvement of π stacking in the observed 1,5-*anti* induction, modelling studies on the cyclic substrates were performed.[XIX] The methyl enol of ethers of the cyclic isopropyl derivative **I** and phenyl derivative **II** were modelled, figure 30. As seen, excellent overlap between the enol ether and a phenyl ring is occurring **II**, while with the isopropyl silanes **I** no interaction is available and the enol ether adopts an open geometry. Consequently, this results in π-facial discrimination for the phenyl substituents, while the open geometry of the isopropyl silyl derivatives is conducive to the approach of the aldehyde from either face.

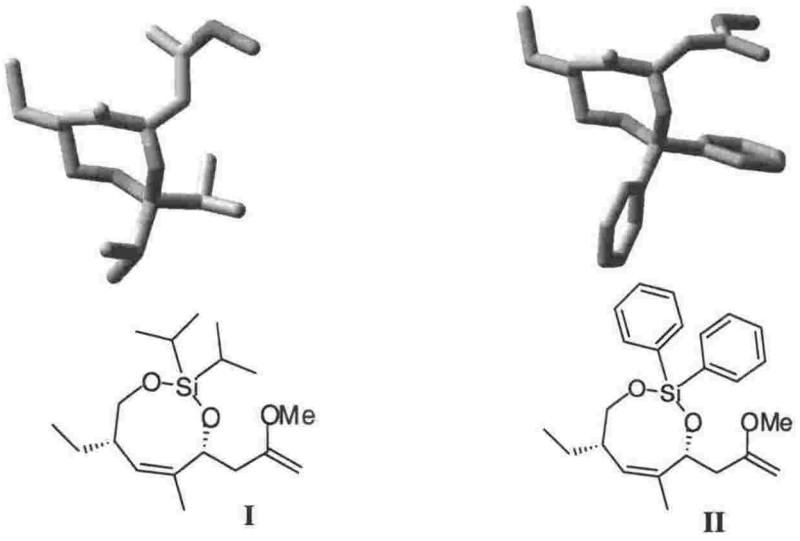
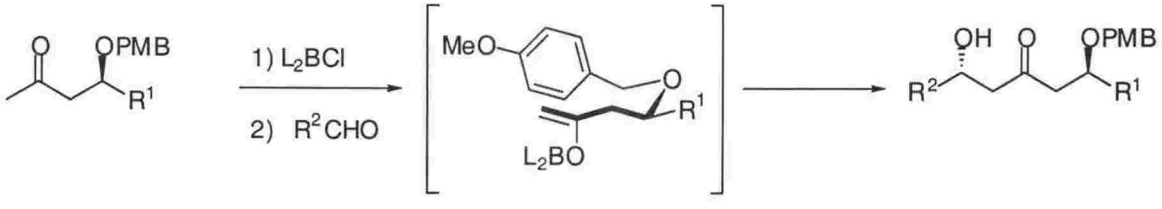


Figure 29: Molecular modelling of $^{i}Pr_2Si$ and Ph_2Si enol ethers

[XIX] Courtesy of Dr Paul Teesdale-Spittle, SBS, Victoria University of Wellington. Molecular models were energy minimized using the OPLSAA forcefield as implemented in Macromodel v7.2 using the Maestro v4.1 interface, and the lowest energy structures retained.

6.3.5: Putting the pieces of the puzzle together

The high diastereoselectivity observed in the above experiments certainly justifies our hypothesis about the importance of π-stacking in certain boron-mediated 1,5-*anti* aldol reactions. The selectivities observed with entries 7-9 in table 7 are not due to electronic properties but are a result of the enolate being fixed in a conformation conducive to interaction with a single phenyl ring. These observations, however, raised some puzzling issues. If π-stacking interactions are responsible for the aforementioned 1,5-*anti* induction, could similar interactions be responsible for the previously reported 1,5-*anti* induction observed in acyclic systems where a *para*-methoxy benzyl substituent is placed at the ß-position? Theoretically, a transition state, such as that depicted in scheme 83, would account for the high 1,5-*anti* stereoselectivity observed. Similarly, if the transition state depicted below is responsible for the high degree of asymmetric induction for the PMB derivatives, a similar transition state could be proposed for the acyclic phenyl derivatives **66**. Theoretically, these transition states could also involve aromatic-enolate interactions. Yet, referring back to table 4, entry 3 (pg 112) it is apparent that only nominal 1,5 asymmetric induction is observed in these cases.

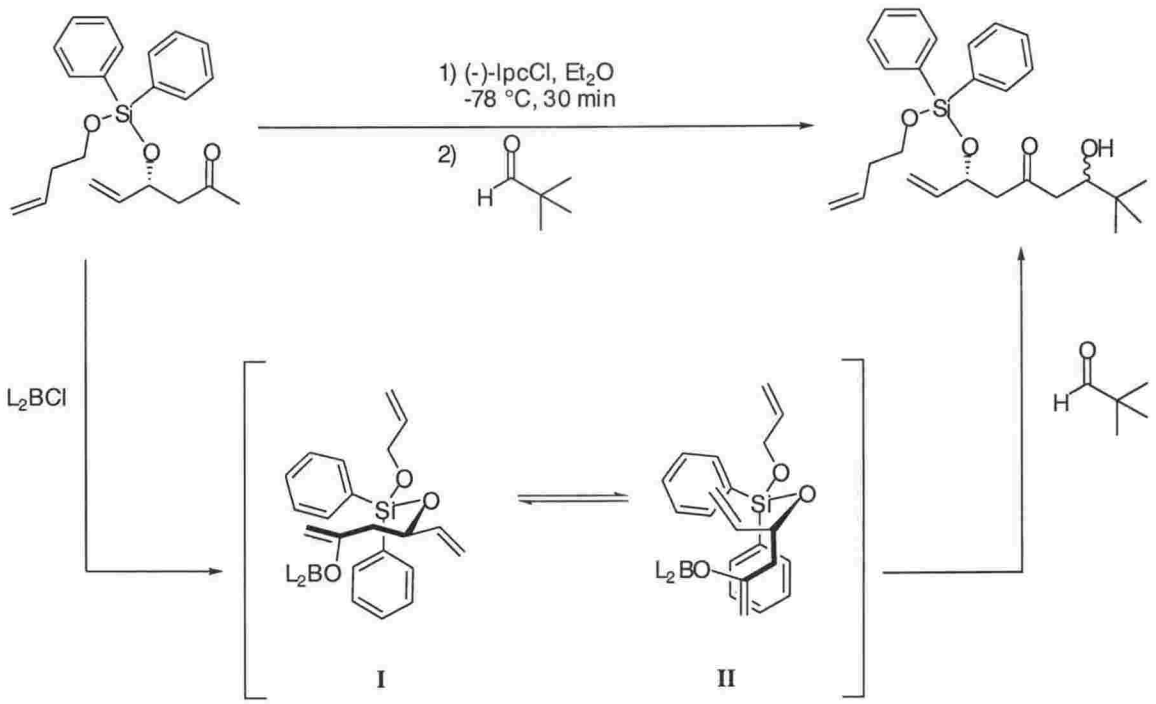


Scheme 83: Proposed conformation for the boron mediated 1,5-*anti* aldol reaction with substrates containing the PMB protecting group

After some consideration, it was proposed that the key difference between the above PMB mediated inductive asymmetric aldol reaction and the non-inductive reactions with the acyclic diphenyl sustituents **66** was the possibility of different transition states for the two aforementioned derivatives. By incorporating two phenyl moieties on a flexible

acyclic tether, two transition state conformations are favourable for the acyclic phenyl derivative, scheme 84.

The equatorial orientation of the olefinic side chain in conformation **I**, would initially appear to favour conformation **I** over **II**. However, there may be some π-stacking interactions between this olefinic side chain and an aromatic ring, as depicted in **II**. In any case, having two phenyl substituents on the acyclic tether results in the possibility of at least two seemingly favourable conformers, resulting in negligible π-facial discrimination.



Scheme 84: Proposed conformations for the acyclic phenyl derivatives

Although some answers to the origin of 1,5-*anti* asymmetric induction had been gained, much still remained to adequately explain the inductive effects in other systems. We could confidently state that it is not the frequently reported electrostatic effects of the ß-oxygen that is responsible for these observations, however the exact influence of many

of the ß-hydroxy protecting groups was still unexplained. With the view that aromatic π interactions must be at least partially responsible for the asymmetric 1,5-*anti* induction in acyclic systems further studies into the origin of the selectivity in boron mediated1,5-*anti* aldol reactions were conducted. These studies are discussed in the subsequent chapter.

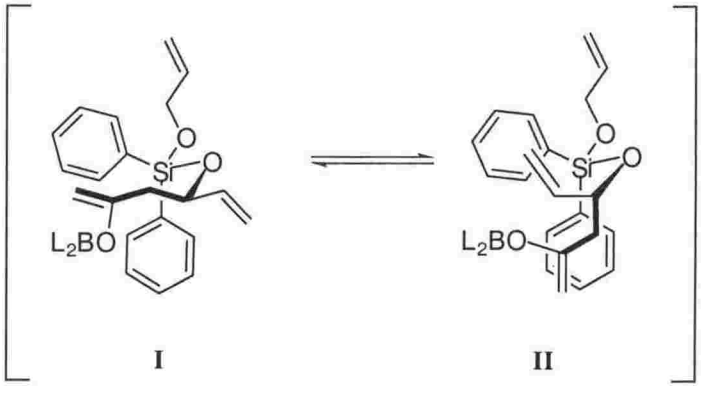
Chapter 7

Studies into the origin of 1,5-*anti* induction in boron-mediated aldol reactions

7.1: Acyclic systems

7.1.1: The *tert*-butyl diphenyl silyl derivative

As discussed in chapter 6, it was postulated that the reason for the poor diastereoselectivities observed with the diphenysilyl acyclic adduct (**66b**, pg 112) could be accounted for by the propensity of the substrate to exist in two conformers, as reviewed below. Although one would normally expect conformer **I** to be more favourable due to the equatorial orientation of the vinyl substituent, conformer **II** is simply a chain flip that may also result in additional π-stacking interactions.



I **II**

To clarify these results it was proposed that some additional aldol studies without the olefinic substituents were required. This would enable us to determine the influence, if any, of these substituents on the proposed conformations. The simplest way of conducting these reactions was to synthesise ß-hydroxyketones and subsequently protect

them with a *tert*-butyldiphenylsilyl substituent. Although the boron-enolates could again adopt the conformations as shown in figure 31, the influence of the alkyl substituent, R^1, may favour one conformer over the other and lead to differences in the diastereoselectivities. It was hoped that the larger, R^1 substituents, such as the isopropyl or *tert*-butyl derivative would favour conformation **I**, leading to enhanced diastereoselectivies.

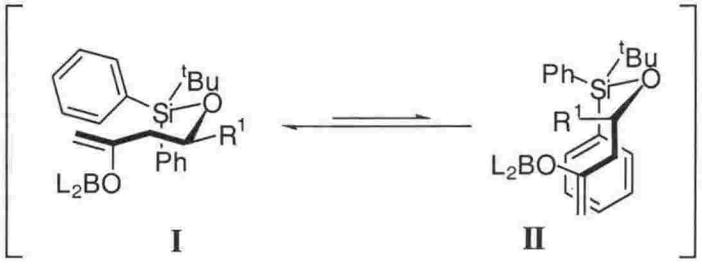
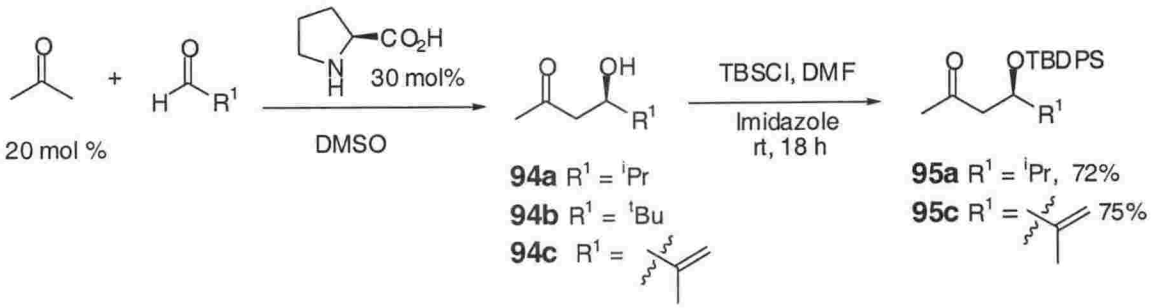


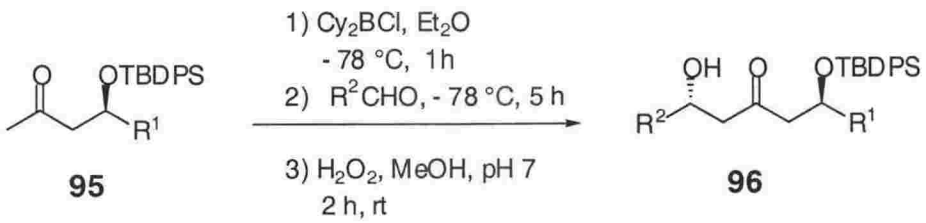
Figure 31: Possible conformations for the *tert*-butyldiphenylsilyl boron-enol ether

Thus List's[176a,b] procedure was once again used for the synthesis of the requisite ß-hydroxy ketones **94**, which were subsequently protected as the *tert*-butyldiphenylsilyl derivatives **95** using standard silylation techniques, scheme 85. Unfortunately, the most desirable adduct, where R^1 = *tert*-butyl, could not be synthesised. Numerous attempts were made at protecting the *tert*-butyl ß-hydroxy precursor, **94b**, but with little avail. Standard silylation techniques, as highlighted below, resulted in the isolation of starting materials, even after extended reaction periods. Even the combination of pyridine, $AgNO_3$ and *tert*-butyldiphenylsilylchloride,[185] which is believed to enhance silylation reactions via the formation of the intermediate silyl nitrate,[186] primarily resulted in the reisolation of the starting ß-hydroxy ketone. As anticipated, the use of one equivalent of potassium hydride as a base, along with catalytic amounts of the chelating macrocycle 18-Crown-6, and one equivalent of *tert*-butyldiphenylsilyl chloride resulted in decomposition of the starting material.[186]



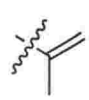
Scheme 85: Synthesis of the *tert*-butyldiphenyl silyl protected ß-hydroxyl ketones

Nevertheless, with the suitable silylated derivatives **95a** and **95c** in hand, a selection of Cy_2BCl mediated aldol studies were conducted, scheme 86. Unfortunately, the alkyl substituent (R^1) appeared to have little influence on the diastereoselectivites of these reactions with ratios from 2:1 to 2.5:1 being observed, table 6. By using both isopropylaldehyde and pivaldehyde as the aldehyde acceptor, we were able to establish that the aldehyde had only a limited effect on the observed diastereoselectivities.[187]



Scheme 86: Aldol studies with the *tert*-butyldiphenylsilyl derivatives

Table 6: Boron mediated aldol studies with the *tert*-butyldiphenylsilyl derivatives

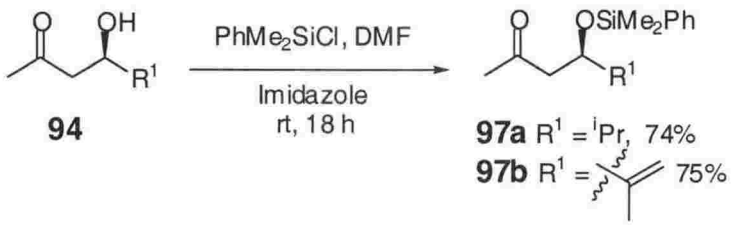
Product	R^1	R^2	Yield	Diastereoselectivity[a]
96a	*i*Pr	*i*Pr	88%	2:1
96b	*i*Pr	*t*Bu	86%	2.5:1
96c			89%	2:1

[a]Diastereoselectivities determined by ^{13}C NMR analysis of the crude substrate

Thus it was apparent that the interconversion of the two proposed conformations was a facile process. Consequently, a substituent with only one aromatic ring was required as the ß-hydroxy protecting group.

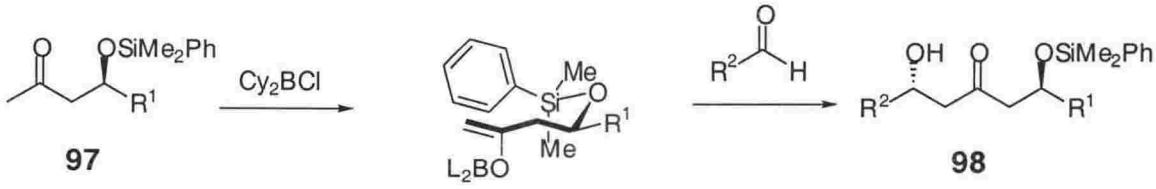
7.1.2: The dimethylphenyl silyl derivative

To eliminate the possibility of having two favourable conformations, it was proposed that the analogous dimethylphenylsilyl derivative would more suitable at the ß-position. Thus, the ß-hydroxy ketones **94** were protected as the dimethylphenyl silyl derivatives, scheme 87.



Scheme 87: Synthesis of the dimethylphenylsilyl derivatives

A selection of Cy_2BCl mediated aldol reactions were then conducted with the dimethylphenyl silyl derivatives **97**, scheme 88. It was proposed that these silyl derivatives would participate in the boron mediated aldol reactions by adopting the conformation shown below to maximise π-π interactions. Such interactions would result in the desired 1,5-*anti* adducts **98**.



Scheme 88: Aldol studies with the dimethylphenylsilyl derivatives

Although the yields for these reactions were good, exceptionally poor diastereoselectivities were observed, table 7. Obviously π-stacking interactions were not involved in these particular transition states.

Table 7: Boron mediated aldol studies with the dimethylphenylsilyl derivatives

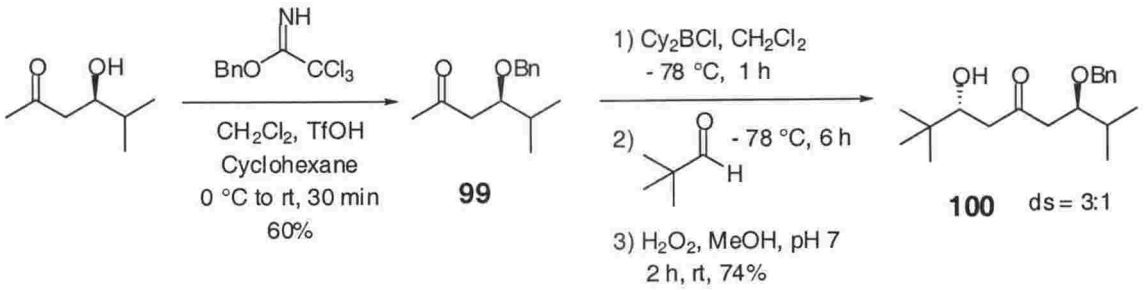
Product	R^1	R^2	Yield	Diastereoselectivity[a]
98a	^{i}Pr	^{t}Bu	80%	1.1:1
98b			82%	1.1:1

[a]Diastereoselectivities determined by ^{13}C NMR analysis of the crude product

The lack of asymmetric induction in these aldol studies was initially particularly puzzling. However upon closely reviewing the literature, it became apparent that the PMB ether was used exclusively for good 1,5-*anti* induction in acyclic systems, suggesting that an electron-donating group is required for effective asymmetric induction and that a benzyl ether would be less effective. To investigate this supposition, the appropriately protected benzyl derivative was synthesised.

7.1.3: The benzyl ether as a protecting group

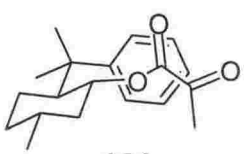
Synthesis of the requisite benzyl derivative began with the benzylation of (*R*)-5-methyl-4-hydroxylhexan-2-one using the previously described benzyl imidate methodology.[153] This reaction proceeded smoothly, giving the desired benzylated adduct **99** in a modest 60% yield, scheme 89. A boron-mediated aldol reaction with pivaldehyde was then conducted and, as anticipated, only moderate diastereoselectivity was observed. The ratio of diastereomers, determined to be 3:1 by ^{13}C NMR analysis, was significantly inferior to the almost exclusive ratios observed for the *para*-methoxy benzyl derivatives.



Scheme 89: Aldol study with the benzyl protected derivative

As the steric size of the paramethoxy benzyl and the benzyl derivatives are comparable, this suggests that it is not a steric factor that is responsible for the differing levels of asymmetric induction observed for both derivatives. Rather, these results suggest that it is the electron donating ability of the OMe substituent that is crucial for efficient interaction between the enolate and aromatic substituent. It is a well renowned phenomenon that methoxy substituents donate electron density to an aromatic ring, and by doing so, presumably increase the capacity of the aromatic ring to participate in π stacking interactions. For example, the ^{1}H chemical shifts of the ring protons in anisole are 6.65, 7.14 and 6.74 ppm respectively, for the *ortho*, *meta* and *para* postitions, compared to the ^{1}H chemical shift of 7.37 for benzene,[188] showing that these protons are shielded by an increase in electron density.

An example of a subtle change to an electronic environment and its effect on π stacking interactions is the fluorescent quenching abilities of the glyoxylates **101** and **102**.[189] By removing the cyclohexyl moiety to give derivative **102**, intramolecular quenching for this derivative proved to be even more efficient. Less rigidly defined conformations, such as that of glyoxylate **102**, are particularly sensitive to subtle changes in their electronic environment.[179] We observed a similar phenomenon for the flexible, acyclic benzyl **99** and the PMB derivatives (scheme 80, pg 107), as evidenced by a difference in the diastereoselectivities of the analogous aldol reactions.



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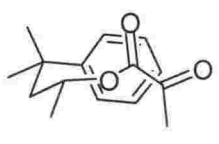
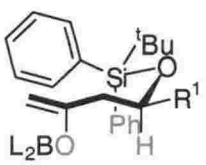


102

7.1.5: Conclusions

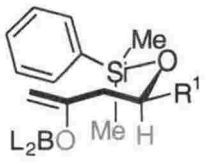
The above results suggest that these boron mediated 1,5-*anti* aldol reactions are particularly sensitive to slight changes in the substituent at the ß-position. If subtle π-stacking interactions are responsible for the differences between the benzyl and PMB derivatives, then the proposed transition state will also be influenced by other subtle changes to the ß-substituent. Indeed, by considering the conformers **A** and **B** for the previously discussed silyl derivatives, one can see how the phenyl, or methyl, substituents on the silyl tethers affect the diastereoselectivities. In both **A** and **B**, unfavourable 1,3-diaxial interactions between the methyl, or phenyl, substituent on the silyl tether, the axial H (as depicted) and the boron enolate oxygen results in a less favourable, higher energy, conformation. Consequently, low diastereoselectivities are observed for the subsequent aldol reactions.

This proposition is further verified by an additional study whereby the analogous paramethoxyphenyldimethylsilyl substituted substrate **C** was synthesised and subjected to boron mediated aldol reactions, using Cy_2BCl as the boron reagent. [xx] Again, poor diastereoselectivities, ranging from 1.2:1 to 2:1 were observed. From this observation, two important conclusions can be made. First, it is not the steric influence of the OMe substituent that is somehow enhancing the diastereoselectivity for the previously reported PMB mediated 1,5-*anti* aldol reactions. Second, the presence of the methyl substituents significantly disfavours the proposed conformation **C**. Apparently these unfavourable 1,3-diaxial interactions cannot be overcome by an increase in the electron density of the aromatic ring.



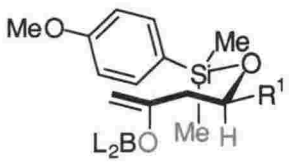
A

ds: 2 :1 to 2.5:1



B

ds: 1.1:1

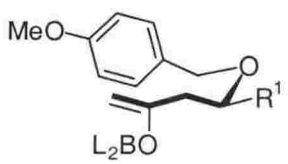


C

ds:1.2:1 to 2:1

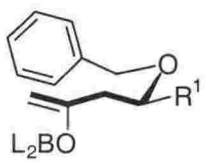
[xx] Results courtesy of Dr Y. Dong, Victoria University of Wellington

Thus, in summarising the above information, a few general statements concerning boron mediated acyclic 1,5-*anti* aldol reactions can be made. An electron rich aromatic system is required at the ß-position of the parent ß-hydroxy ketone, conformation **D**. Although moderate selectivity is observed with a benzyloxy substituent at the ß-postion **E**, diastereoselectivities are greatly enhanced by the electron rich, paramethoxybenzyl derivative. The steric effect of the paramethoxybenzyl substituent is not responsible for the high levels of 1,5-*anti* induction, as observed with the poor diastereoselectives obtained with the paramethoxydimethylsilyl derivative **C**. Although the electron donating abilities of the paramethoxy substituent greatly enhance the diastereoselectivities for the PMB derivatives, the additional methyl substituents in **C**, disfavour the formation of the π-stacked transition state and outweigh any additional positive influence of the methoxy substituent. However it is not solely these methyl substituents that result in decreased levels of 1,5-asymmetric induction, again compare aldol reactions with the OBn (**E**) and PMB (**D**) derivatives. Unfavourable 1,3-diaxial interactions and a relatively electron poor aromatic ring explains the poor diastereosectivites observed with the dimethylphenylsilyl **B** and *tert*-butyldiphenylsilyl **A** derivatives. The presence of two phenyl substituents in **A** also leads to two possible transition state conformations.



D

ds: >95:5



E

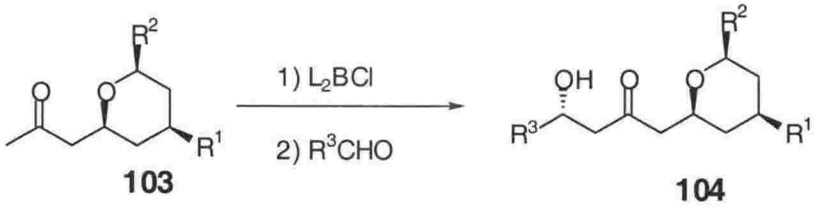
ds: 3:1

Thus to date, all of these observations are consistent with a model in which π-stacking interactions are responsible for the high degree of boron mediated 1,5-*anti* induction observed with the PMB derivatives. For effective π-stacking interactions, and hence efficient boron mediated 1,5-*anti*-induction, an electron rich aromatic system, attached to the ß-oxygen via a methylene linkage, is required.

7.2: Cyclic systems

7.2.1: The pyranose system

Next, we turned our attention to other cyclic systems, such as **103**, in which excellent 1,5-*anti* induction has been observed, scheme 90. Kozmin reported selectivities of over 99:1 with pyrans of the type **103** where R^1 = benzyl, and R^2 = allyl.[178] Kozmin rationalized the high stereoselectivity to be a consequence of the ß-alkoxy group and cited the studies conducted by Evans[162] on alternative cyclic systems as precedence for this observation.

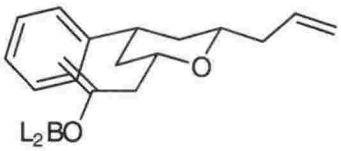


103 **104**

Scheme 90: Boron mediated1,5-*anti* aldol studies in cyclic systems

However, due to the presence of benzyl substituent R^1, we proposed that a conformation such as **I**, where R^1 = allyl, R^2 = OBn, in figure 32, was responsible for the high diastereoselectivity. Our initial impression was that π-stacking interactions were responsible for this preferred conformation, however upon closer examination, the intramolecular distance of approximately 7.5 Å between the benzyl substituent and the boron enolate was not amenable to π stacking. Thus, it appeared that with these systems, aldehyde facial discrimination was achieved by simple steric hinderance from the C-4 (R^1) substituent. This was confirmed by the molecular modelling of the methyl enol ether of **103** (where R^1 = allyl, R^2 = OBn), figure 32.[XXI]

[XXI] Courtesy of Dr Paul Teesdale Spittle, SBS, Victoria University of Wellington



I

Figure 32: Proposed conformation for the boron enolate of **103**

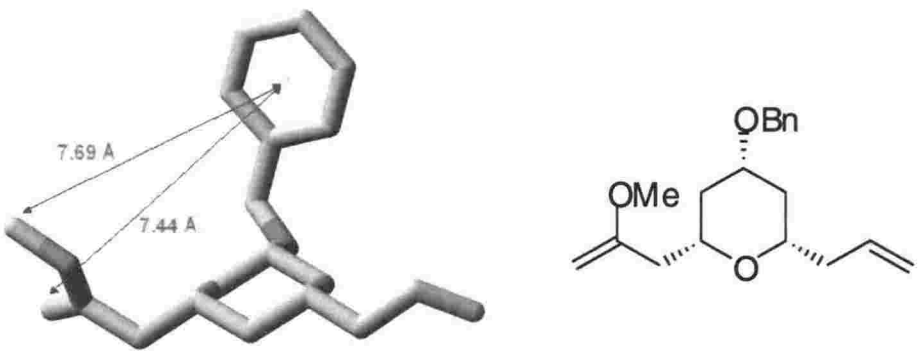
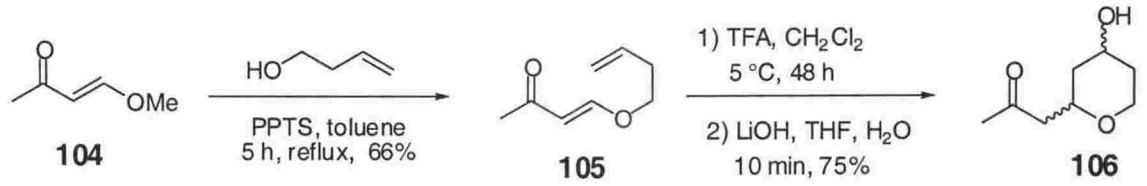


Figure 33: Molecular modelling of the methoxy enol ether of pyranose **103**

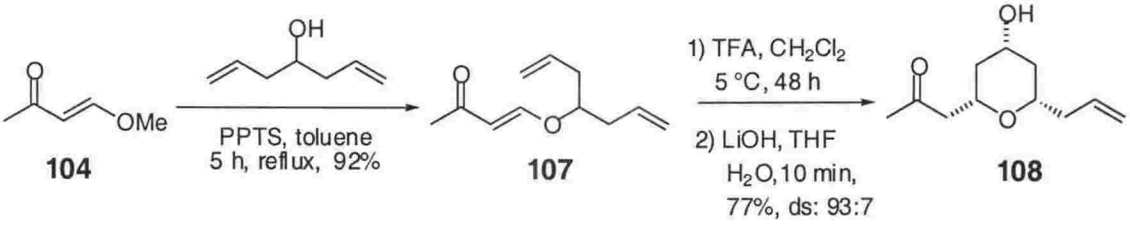
To further verify this hypothesis, a similar cyclic derivative with a different substituent at C-4 was synthesised. In an attempt to simplify the system, a derivative where R^2 = H, was made by the addition of the readily available but-3-en-1-ol to 4-methoxybut-3-en-2-one, as depicted in scheme 91. Unfortunately the subsequent Prins rearrangement[190] resulted in a 4:1 mixture of diastereomers. Presumably this diasteromeric mixture was a consequence of the absence of a R^2 substituent (scheme 90), which would normally adopt an equatorial position to favour the intermediate chair transition state during the Prins rearrangement.



104 **105** **106**

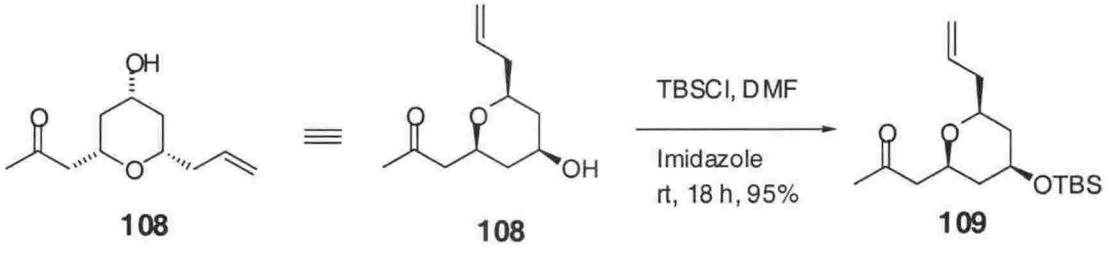
Scheme 91: Attempted synthesis of aldol precursor **106**

To avoid the added complications of accounting for the effects of the diastereomers during the subsequent aldol studies, the original synthesis, as reported by Kozmin was repeated, to give the intermediate pyranose adduct **108** in good diastereoselectivity, scheme 92. The free hydroxyl group was then protected, in excellent yield, with a TBS group to form the aldol precursor **109**, scheme 93.



104 **107** **108**

Scheme 92: Synthesis of the intermediate pyranose adduct **108**[178]

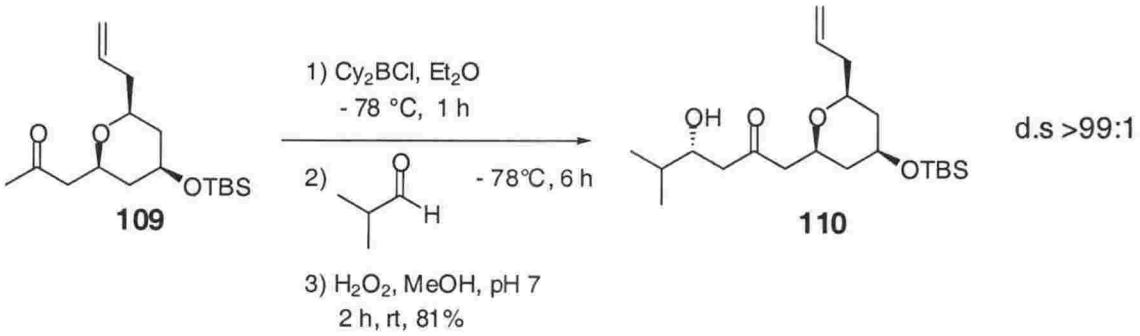


108 **108** **109**

Scheme 93: Synthesis of novel aldol precursor **109**

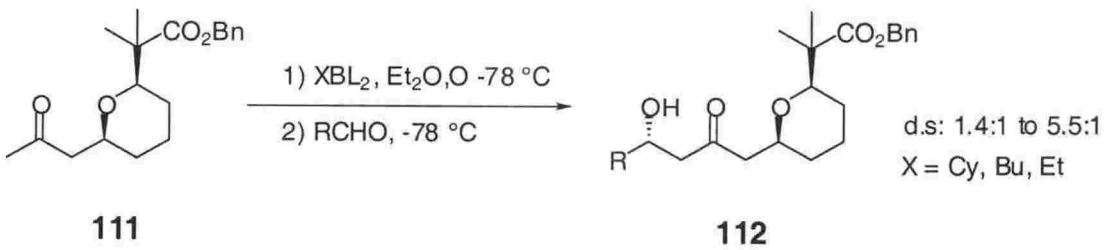
A boron mediated aldol reaction between **109** and isobutyraldehyde was then conducted, scheme 94, and as anticipated, excellent levels of diastereoselective induction were

observed.[XXII] From these results, it can be verified that π-stacking interactions were not responsible for the observed high levels of diastereoselectivity in these cyclic systems, and it appeared that it was the steric influence of the substituent at C-4 that predominantly influenced the stereochemical outcome of these reactions. However, based on these studies alone, there was still not sufficient evidence to confidently make this proposition. An aldol study on a similar substrate without a C-4 substituent would be required to produce low levels of selectivity.



Scheme 94: Boron mediated 1,5-*anti* aldol reaction with pyranose **109**

Fortunately, a review of the literature revealed that such studies had already been conducted. During the synthesis of the C-1 to C-21 fragment of the dimeric polyketide natural product SCH 351448, De Brabander *et. al.* conducted a boron mediated aldol reaction using **111**, scheme 95.[191] Again, De Brabander cited studies by the Evans[162a] and Paterson[163a] groups as precedent for this 1,5-*anti* induction. However, in De Brabander's subsequent studies, only low to modest levels of diastereodifferentation were observed.



Scheme 95: Boron mediated 1,5-*anti* aldol studies conducted by De Brabander *et. al.*

[XXII] Determined by ^{13}C NMR analysis of the crude product

Although the intrinsic facial bias of the enolborinate partner was reported to be responsible for some of the more subtle differences in the levels of stereochemical induction for the different aldehyde partners, no explanation was given for the overall decreased levels of stereochemical induction when compared to the examples reported by Evans, Paterson, or Kozmin. Enhanced stereoselectivities in De Brabander's studies were only obtained after screening a variety of boron reagents with different ligands. However, after comparing our studies with those by Kozmin and De Brabander, it seemed apparent that the steric nature of the C-4 substituent greatly influences the degree of stereochemical induction. Where there is no appendage at C-4, as in De Brabander's case, poor diastereoselectives are observed.

This concept is illustrated by considering the conformation of the pyran ring and the proposed transition state shown in figure 34. Here the enolate side chain adopts an equatorial orientation, with the larger boron substituent positioning itself furthest away from the cyclohexyl ring to minimise the electrostatic repulsive effects of the ring oxygen and the steric effects of the boron ligands. Where R^1 is large, such as OTBS or OBn, the aldehyde preferentially approaches the enolate from the front face with the larger R^3 substituent on the aldehyde adopting an equatorial position in the intermediate transition state.[xxiii] Such a transition state gives the desired *anti-* diastereoselectivity. A summary of the diastereoselectivities for the various R^1, R^2 and boron ligands (L) is provided in Table 8 overleaf.

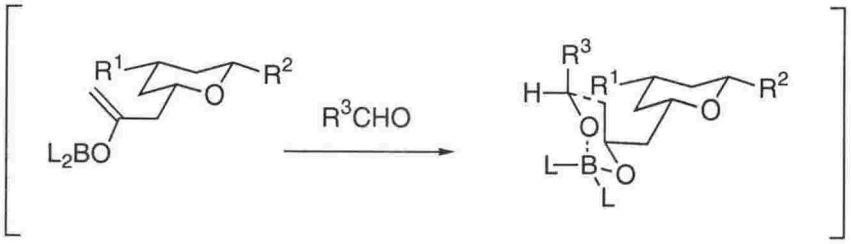
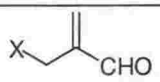
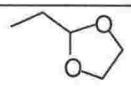


Figure 34: Proposed transition state for the boron-mediated aldol reaction

[xxiii] Due to the minimal energy difference between the chair and twist boat transition state, this transition state has been shown in the chair conformation as this is easier to depict pictorially and does not alter the stereochemical outcome

Table 8: Boron mediated aldol studies with derivatives of pyranose **103**

R^1	R^2	L	RCHO	Diastereoselectivity *(anti:syn)*	Ref
OBn	allyl	Cy		> 99:1	178
OTBS	allyl	Cy	^{t}BuCHO	> 99:1	192
H	CMe_2CO_2Bn	Cy	EtCHO	1.8:1	192
H	CMe_2CO_2Bn	Et	EtCHO	5.5:1	192

X = 

From this analysis, a lack of a substituent at C-4 clearly results in inherently lower diastereoselectivities as there is no R^1 substituent to hinder the approach of the aldehyde from the back face. Thus, the analysis becomes a little more complicated. With no substituents to obstruct the approach of the aldehyde from the back face, it becomes more difficult to determine the relative energies of the both the *anti* and *syn* transition states.[193] In these cases, the choice of ligands on the boron enolate will have a much greater influence on the preferred transition state, but without an in depth knowledge of the preferred transition state conformation, it is difficult to predict the stereochemical outcome of these aldol reactions.

7.3: Boron mediated 1,5-*anti* induction – a summary

From the studies discussed in this and the preceding chapter, some general observations concerning the origin of diastereoselectivity in boron mediated 1,5-*anti* aldol reactions can be made. Although the statement that these reactions are 'influenced by the ß-hydroxy substituent' has not been disputed, it needs to be addressed with caution. A more in depth analysis of each system is required. Thus in general, we have identified and proposed transition states for three different systems that arise when conducting boron-mediated aldol reactions. These are summarised below:

i) Acyclic 1,5-anti boron mediated aldol reactions

The judicious use of electron rich π systems at the ß-hydroxy protecting group is required for favourable π interactions and hence selectivities in acyclic boron mediated 1,5-*anti* induction. Unfavourable 1,3-diaxial interactions are observed if there are substituents on the carbon, or silicon, linkage to these electron rich aromatic groups. These interactions greatly disfavour the formation of the proposed π-stacked transition state, resulting in negligible selectivities.

ii) Rigid cyclic systems with favourable π-stacking interactions

In some cyclic systems, such as that developed for the synthesis of pel A, the cyclic system is rigid enough to hold the aromatic ring in close proximity to the enolate. This leads to favourable π stacking interactions, and hence selectivities.

iii) Cyclic systems where steric hinderance directs the approach of the aldehyde

The carbon framework of the cyclic system dictates the stereochemical outcome of the reaction. Such systems are more difficult to analyse and require careful consideration of the proposed transition states.

Chapter8:

Concluding Remarks

Although we were unsuccessful in determining the absolute stereochemistry of peloruside A, presumably due to the small sample size or complex nature of this molecule, significant advancements have been made towards its synthesis. To-date, a successful strategy for the synthesis of the C-8 to C-24 framework has been developed. This carbon framework is depicted in figure 35.

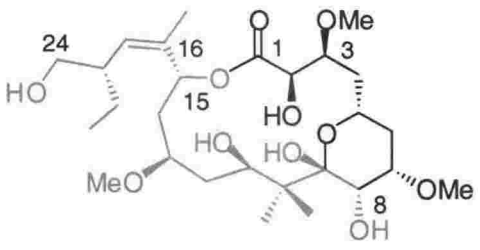


Figure 35: Peloruside A with the C-8 to C-24 framework highlighted

The synthesis of the C-8 to C-11 fragment proceeds smoothly and needs no further investigation. This five-step synthesis proceeds in good overall yield and has been successfully performed on the multigram scale.

A short, facile synthesis of the C-12 to C-24 fragment has also been developed. To date, the ethyl side chain has not been incorporated into the synthesis, however precedent by Hoyveda[147] indicates that this should be a relatively uncomplicated adaptation. Nevertheless, we are equally interested in the analogue without the ethyl substituent as this may provide valuable insight into the biological activity of pel A and potentially lead to the development of simplified analogues. Similarly, our strategy facilitates the synthesis of both the C-16 methylated, and unmethylated, analogues which again will be of interest during biological testing.

There are however, a few improvements and changes that need be made to our strategy. Since the determination of pel A's absolute stereochemistry by De Brabander,[204] the most pressing adaptation required is the synthesis of the correct enantiomer of the C-12 to C-24 fragment. In particular, this requires the synthesis of the (*S*)-enantiomer of the key intermediate ß-hydroxyketone **24**. Although precedent by Paterson[164] could be followed for the synthesis of **24**, it would be valuable to first investigate some alternative strategies including the BINOL-Ti catalysed Mukaiyama aldol reaction between the silyl enol ether of acetone and methacrolein, or acrolein.[93]

A future objective of this research is also to find a more active RCM catalyst for the synthesis of the *bis*-silyl ether **65**. Not only would this reduce the amount of catalyst required but would greatly facilitate the purification process.

However, more importantly, during the synthesis of the C-12 to C-24 fragment of pel A and subsequent aldol studies, valuable insight into the origin of 1,5-*anti* induction in boron-mediated aldol reactions has been gained.[194] Our studies point to three modes of operation in effect during boron-mediated aldol reactions. First, in acyclic systems, the judicious use of electron-rich π-systems as ß-hydroxy protecting groups must be used to provide for favourable π stacking and hence high selectivities. Second, in some cyclic systems containing aromatic moieties, such as those studied during the synthesis of pel A, the rigidity of the system facilitates favourable π-stacking interactions, and hence, diastereoselectivies. And finally, in other cyclic systems, simple steric hindrance is responsible for the observed selectivities. These insights will undoubtedly aid in the planning of synthetic routes during the synthesis of further natural products.

Chapter9:

Experimental Section

9.1. General:

Unless otherwise stated, the following conditions apply. All reactions were performed under argon in oven-dried glassware using dry solvents and standard syringe techniques. Diethyl ether and THF were distilled from sodium benzophenone ketyl radical ion. Dichloromethane, triethylamine and methanol were distilled from calcium hydride. Diisopropylamine and pyridine were distilled from sodium hydroxide. Benzene was successively shaken with concentrated sulfuric acid, water, dilute sodium hydroxide and water, before being dried with calcium hydride and distilled. Acetone was distilled from potassium carbonate. Anhydrous dimethylformamide was purchased from Aldrich Chemical Company and used without further purification. All other reagents were of commercial quality and distilled prior to use if necessary.

Reaction progress was monitored using aluminium backed TLC plates pre-coated with silica UV254 and visualised by either UV radiation (254 nm), ceric ammonium molybdate dip or using an iodine tank unless otherwise stated. Purification of products via flash chromatography was conducted using a column filled with silica gel 60 (220-240 mesh) with the solvent systems as indicted. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Inova at 300 and 75 MHz respectively; and are referenced to solvent peaks (^{1}H – residual $CHCl_3$ (7.26 ppm), ^{13}C – $CDCl_3$,(77.0 ppm)). Infrared spectra were obtained on a Biorad FTS-7 spectrometer or a Bruker Tensor 27 FTIR spectrometer. Electrospray High-resolution mass spectroscopy was recorded on a Mariner time of flight spectrometer. Diastereoselectivities were determined by averaging the ^{13}C NMR peak heights for the diastereotopic signals of the crude product.

Experimental data is reported in chronological order. The following compounds were synthesised according to literature precedent: 3-(*tert*-butyldimethylsiloxy)propanol **(32)**,[98] Des Martin Periodinane,[99] (*S*)-4-benzyl-3-butyryl-2-oxazolidinone **(37)**[195], (+)-(4*S*)-3-[(2'R)-2'-((*tert*-butyldimethylsiloxy)-methyl)-butanoyl]-4-benzyl-2-oxazolidinone **(38)**,[79](-)-(2S)-2-((*tert*-butyldimethyl-siloxy)methyl)butanol **(39)**,[79] (-)-(2*S*)-2-((*tert*-butyldimethylsiloxy)methyl)-butanal **(3c)**,[79] isopropyltriphenylphosphonium bromide,[108] dihydro-2-(tosyloxy)-3,3-dimethyl-(2H)-furanone **(17b)**,[113] 4-hydroxy-5-hexene-2-one **(24a)**,[137] Grubbs second generation ruthenium catalyst **(62)**,[141] benzyltrichloroacetimidate **(79)**[134,XXIV,] dicyclohexylboron hydride (Cy_2BH),[196] dicyclohexylborontriflate (Cy_2BOTf)[197], dicyclohexylboronchloride (Cy_2BCl),[197] diisopinocampheylboron hydride (Ipc_2BH)[198], diisopinocamphenylboron chloride (Ipc_2BCl)[199], (*R*)-4-hydroxyl-5-methyl-hexan-2-one **(94a)**,[176a,176b] (*R*)-4-hydroxy-5,5-dimethyl-hexan-2-one **(94b)**,[176a,176b] 4-methoxy-3-butene-2-one **(104)**,[200] 3-butene-4-(hepta–1,6-diene-4-oxy)-2-one **(107)**[178] and 1-(6-allyl-4-hydroxy)tetrahydropyran-2-yl)-propan-2-one **(108)**.[178]

[XXIV] The purification procedure reported in the literature for the synthesis of benzyl trichloroacetimidate, involving the washing the initially formed filtrate with pentane, proved to be unsuitable as two immiscible layers were formed. Consequently, the residual oil was purified by rapid distillation at 0.1 mm/Hg. It is imperative that this distillation is performed rapidly as the intramolecular thermal rearrangement of benzyl trichloroacetimidate to the *N*-benzyl amide is frequently observed after prolonged heating of the substrate.

9.2. Experimental for Chapter 2:

3-(*tert*-Butyldimethylsiloxy)propanal (33). To a stirred solution of 3-(*tert*-butyldimethylsiloxy)propanol **(32)** (2.20 g, 11.55 mmol) in CH_2Cl_2 (80 mL)was added water (200 μL) followed Dess-Martin periodinane (6.30 g, 13.86 mmol). After 4 h at room temperature additional Dess-Martin periodinane (6.30 g, 13.86 mmol) was added and the reaction stirred at room temperature overnight. The solution was then diluted with 100 mL of Et_2O and treated with a 1:1 mixture of saturated $NaHCO_3$:NaS_2O_3 (100 mL) for 15 minutes. The ether layer was collected and the aqueous phase extracted once with ether. The combined organic layers were then washed with brine, dried over $MgSO_4$ and the solvent carefully removed under reduced pressure. The residual oil was then purified by flash chromatography (10:1 pentane:Et_2O) to give 3-(*tert*-butyldimethylsiloxy)-propanal **(33)** (1.09 g, 50%). NMR spectral data matched that previously reported.[201]

2-(Hydroxymethyl)butan-1-ol (35). This was synthesised in the manner previously reported[100] with the exception that the solution was refluxed in Et_2O for 2.5 h and the product purified by bulb-to-bulb distillation.

2-((*tert*-Butyldimethyl-siloxy)methyl)butanol (36). To solid NaH (204 mg, 8.49 mmol), washed three times with hexanes, was added dropwise a solution of 2-ethyl-1,3-propanediol **(35)** (590 mg, 5.66 mmol) in THF (13 mL). The reaction was stirred vigorously for 45 min at room temperature. *Tert*-butyldimethylsilylchloride (854 mg, 5.66 mmol) in THF (4 mL) was then added in one portion and the reaction stirred vigorously for 45 minutes before being quenched cautiously with water. The resulting solution was extracted with Et_2O, washed with 10% K_2CO_3, brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residual oil was purified by flash chromatography (10:1 hexanes:EtOAc), to give **36** (1.11 g, 90%) as a colourless oil. NMR spectral data matched that previously reported.[100]

2-(*tert*-Butyldimethylsiloxymethyl)butanal (3b). To a stirred solution of 2-(*tert*-butyldimethyl-siloxymethyl) butanol **(37)** (395 mg, 1.81 mmol) in CH_2Cl_2 (12.4 mL) was added Dess-Martin periodinane (1.15 g, 2.71 mmol) and the reaction stirred for 6 h at room temperature. ^1H NMR analysis of a small portion of the reaction product indicated that some of the starting substrate **37** was still present and a further 1.15 g of the periodinane was added and the reaction stirred at room temperature overnight. The solution was diluted further with CH_2Cl_2 (50 mL) and filtered through a small, 0.5 cm thick, plug of silica gel. The residual oil was purified by flash chromatography (10:1 pentane:Et_2O) to give **3b** (170 mg, 44%). NMR spectral data matched that previously reported.[79]

2-(Acetoxymethyl)butanol (43b) and 2-(Acetoxymethyl)but-1-ylacetate (42). To a rapidly stirred solution of 2-(hydroxymethyl)butan-1-ol **(35)** in pyridine (20 mL) at 0 °C was added dropwise acetyl chloride (942 μL, 13.25 mmol). The reaction was allowed to warm to room temperature overnight before being quenched with water and extracted twice with EtOAc. The organic extracts were washed once with satd. aq. $NaHCO_3$ solution, brine and dried over Na_2SO_4. The residual pyridine was removed by co-distillation with toluene and the crude material purified by gradient flash chromatography (5:1 to 3:1 hexanes:EtOAc) to give **43b** (637 mg, 40%) and **42** (821 mg, 40%). NMR spectral data matched those previously reported.[100]

2-(Acetoxymethyl)butanal (44b). This compound was synthesised using a variety of conditions, as indicated below. In all instances, the NMR spectral data matched that previously reported. [100]

a) *Small scale Des-Martin oxidation of 2-(acetoxymethyl)butanol* **(43b).** To a stirred solution of **43b** (8 mg, 0.055 mmol) in CH_2Cl_2 (500 μL) was added Dess-Martin periodinane (35 mg, 0.082 mmol). The solution was stirred for 2.5 h at room temperature then an additional 35 mg of Dess-Martin periodinane was added. After an additional 3 h the resulting solution was loaded onto a Pasteur pipette sized silica gel column and eluted with CH_2Cl_2 (2 mL) to give **44b** as a colourless oil.

b) *Modified Swern oxidation of* **43b**. To a solution of oxalyl chloride (773 μL, 8.87 mmol) in CH_2Cl_2 (72 mL) at –78 °C, was added dropwise DMSO (1.26 μL, 17.73 mmol). The solution was stirred for 15 minutes before a solution of **43b** (1.08 g, 7.39 mmol) in CH_2Cl_2 (21 mL) was added dropwise. The resulting solution was stirred at –78 °C for 30 minutes, Et_3N (4.02 mL, 28.8 mmol) was slowly added, at which point the cloudy solution turned clear. The solution was stirred for an additional 1.25 h at –78 °C then at 0 °C for 5 minutes before being diluted with sat. aq. $NaHCO_3$. The resulting solution was then extracted twice with CH_2Cl_2, and the organic extracts washed twice with a 1M sodium bisulfite solution, once with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residual oil diluted with CH_2Cl_2 (20 mL) and purified immediately by passage through a small, 1.5 cm thick, 3 cm diameter, silica gel plug. The silica plug was then washed with a further CH_2Cl_2, (20 mL) and the solvent removed under reduced pressure to give **44b** (672 mg, 63%) that was used without further purification.

c) *From the periodate oxidative cleavage of 4-(acetoxymethyl)-2-methyl-hex-2-ene* **(46)**. 4-(acetoxymethyl)-2-methyl-hex-2-ene **(46)** (6 mg) was dissolved in THF (540 μL) H_2O (300 μL). A 70 μL aliquot of this solution, which equates to 0.5 mg or 2.94 μmol of **9**, was then transferred to a second flask and 3 μL (0.3 μmol) of a 2.5 wt % solution of osmium tetraoxide in *tert*-butanol added. The solution was stirred at room temperature for 10 minutes before $NaIO_4$ (2.5 mg, 11.5 μmol) was added. The solution was stirred vigorously at room temperature, and the progress of the reaction monitored by GC using a 60 m x 0.25 mm Cyclodex-B™ column and the following conditions: Inlet: Split 275°C; Detector: FID 320°C; Carrier gas: hydrogen; Flow: 35.8 cm^3s^{-1}; Temperature programme: Isothermal at 60°C. The GC conditions were as follows. After 2 h no starting material was present and two peaks with retention times of 116.5 and 119.5 minutes were observed on the GC trace.

This experiment was previously conducted using 15 mg of **46**. After 3 hours the solution was diluted with Et_2O, (20mL), washed with brine, dried over $MgSO_4$ and filtered. The

solvent was then removed under reduced pressure to give **44b** as a colourless oil. NMR spectral data matched that previously reported.[100]

4-(Acetoxymethyl)-2-methyl-hex-2-ene (47). To a mixture of isopropyltriphenylphosphonium bromide (720 mg, 1.87 mmol) in THF (20 mL) at 0 °C was added a 1.6 M solution of *n*-BuLi in hexanes (1.17 mL, 1.87 mmol). A red solution was observed due to the formation of triphenylphosphoranylidene isopropane. After the mixture was stirred for 1 h at room temperature, a solution of **44b** (245 mg, 1.70 mmol) in dry THF (1.5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 4 h then poured into 50 mL of hexanes. The precipitated triphenylphosphine oxide was removed by filtration and the resulting solution concentrated *in vacuo*. The residue was purified by gradient flash chromatography (hexane, 50:1 hexanes:EtOAc) to give **47** (120 mg, 42%) as a colourless oil. ^{1}H NMR: δ 4.85 (d, J = 9.9 Hz, 1H), 3.92 (d, J = 6.9 Hz, 2H), 2.51 (m, 1H), 2.06 (s, 3H), 1.74 (s, 3H), 1.65 (s, 3H), 1.51 (m, 1H), 1.21 (m, 1H), 0.87 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR: δ 171.5, 134.4, 125.3, 68.0, 39.3, 26.1, 25.2, 21.3, 18.5, 11.7 ppm. IR (neat): 2966, 1739, 1230, 1035, 733 cm^{-1}.

9.3: Experimental for Chapter 3:

Dihydro-2-(allyloxy)-4,4-dimethyl-(2H)-furanone (17c). To a solution of pantolactone **(17)** (10.0 g, 76.8 mmol) in DMF (80 mL) at 0 °C was added a 1M solution of potassium *tert*-butoxide in THF (76.8 mL, 76.8 mmol). The cooling bath was then removed and the solution stirred at room temperature for 30 minutes. A solution of allyl bromide (6.99 mL, 80.6 mmol) in THF (7 mL) was then added dropwise and the resulting mixture stirred at room temperature overnight before being quenched with water and extracted twice with Et_2O. The combined organic extracts were washed twice with sat. aq. $NaHCO_3$, once with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography of the crude product (5:1 hexanes:EtOAc) gave **17c** (10.6 g, 81%) as a colourless oil. ^{1}H NMR: δ 5.90 (m, 1H), 5.32 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.24 (d, *J* = 10.2 Hz, 1 H), 4.46 (dd, *J* = 12.9, 5.1 Hz, 1 H), 4.20 (dd, *J* = 12.9, 6.3 Hz, 1 H), 3.99 (d, *J* = 8.7 Hz, 1 H), 3.89 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 1H), 1.17 (s, 3H), 1.10 (s, 3H) ppm. ^{13}C NMR: δ 175.3, 133.8, 118.0, 80.7, 76.3, 71.6, 40.3, 23.3, 19.2 ppm. IR (neat): 2971, 1788, 1124 cm^{-1}. HRMS: Calcd for $C_9H_{14}O_3$ ($M+H^+$): 171.1016. Found: 171.1020.

2,2-Dimethyl-3-(3-propeneoxy)butane-1-4-diol (53). A 25 mL flask equipped with side arm and reflux condensor was charged with $LiAlH_4$ (305 mg, 7.85 mmol) and THF (10 mL). A solution of **17c** (891 mg, 5.23 mmol) in THF (5 mL) was then added cautiously dropwise over 15 minutes. The resulting solution was refluxed for 3 h before being cooled to 0 °C and quenched by the portion-wise addition of hydrated sodium sulfate. The residue was diluted with ethanol (50 mL), filtered though a 0.5 cm x 3 cm diameter silica gel plug, dried with anhydrous Na_2SO_4, and the solvents removed under reduced pressure. Flash chromatography of the crude product (1:1 hexanes:EtOAc) gave **53** (690 mg, 76%) as a colourless oil. ^{1}H NMR: δ 5.95 (m, 1H), 5.29 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.19 (dd, *J* = 10.5, 1.2 Hz, 1 H), 4.19 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1H), 4.07 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1H), 3.80 (dd, *J* = 12.0, 3.90 Hz, 1H), 3.70 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.20 (dd, *J* = 4.2, 3.9 Hz, 1H), 2.36 (bs, 2H), 0.96 (s, 3H), 0.94 (s, 3H) ppm. ^{13}C NMR: δ

134.7, 117.1, 85.7, 72.6, 69.1, 60.6, 39.1, 23.0, 21.3 ppm. IR (neat): 3345, 2967, 2876, 1048 cm^{-1}. HRMS: Calcd for $C_9H_{18}O_3$ 175.1334 ($M+H^+$). Found 175.1329.

1,4-Dibenzyloxy-2,2-dimethyl-3-(3-propeneoxy)-butane (54). To a 25 mL flask containing NaH (491 mg, 20.5 mmol) (washed three times with hexanes) in DMF (6.5 mL) at 0 °C was added a solution of **53** (713 mg, 4.09 mmol) in DMF (5 mL) over five minutes. When gas evolution had ceased, benzyl bromide (998 μl, 8.39 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature overnight. The solution was then cautiously quenched with water, extracted twice with Et_2O and the combined organic extracts washed twice with sat. aq. $NaCO_3$ solution, once with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Flash chromatography of the crude product (hexanes) gave the benzylated ether **54** (1.30 g, 90%) as a colourless oil. ^{1}H NMR: δ 7.32 (m, 10H), 5.93 (m, 1H), 5.24 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.52 (s, 2H), 4.46 (s, 2H), 4.34 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1H), 4.03 (ddt, *J* = 12.6, 5.4, 1.5 Hz, 1H), 3.58 (m, 2H), 3.38 (d, *J* = 8.7 Hz, 1H), 3.15 (d, *J* = 8.7 Hz, 1H), 0.95 (s, 3H) 0.92, (s, 3H) ppm. ^{13}C NMR: δ 138.9, 138.6, 135.8, 128.3, 127.8, 127.7, 127.4, 115.7, 82.5, 77.2, 73.2, 72.0, 38.7, 20.9, 22.2 ppm. IR (neat): 3028, 2906, 2859, 1092 cm^{-1}.

1,4-Dibenzyloxy-2,2-dimethyl-3-hydroxy-butane (55). *p*-Toluenesulfinic acid (82 mg, 0.52 mmol) was added at room temperature to a solution of **54** (167 mg, 0.47 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol) in THF (4.7 mL). The reaction mixture was stirred at room temperature for 7 h before Et_3N (13 μl) was added. The solvent was then removed under reduced pressure and the residue purified immediately by gradient flash chromatography (50:1 to 20:1 hexanes:EtOAc) to give **5** (122 mg, 83%) as a colourless oil. ^{1}H NMR: δ 7.37 (m, 10H), 4.57 (s, 2H), 4.50 (s, 2H), 3.78 (ddd, *J* = 8.4, 3.3, 3.0 Hz, 1H), 3.64 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.49 (dd, *J* = 9.6, 8.4 Hz, 1H), 3.38 (d, *J* = 8.7 Hz, 1H), 3.27 (d, *J* = 8.7 Hz, 1H), 3.03 (d, *J* = 3.3 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H) ppm. ^{13}C NMR:δ 138.4, 129.5, 128.2, 127.8, 127.6, 127.5, 78.2, 75.7, 73.4, 73.3, 71.7, 37.4, 21.6, 20.3 ppm. IR

(neat): 3498, 2987, 2848, 1105 cm^{-1}. HRMS: Calcd for $C_{20}H_{26}O_3$ 315.1950 ($M+H^+$). Found 315.1955.

1,4-Dibenzyloxy-3,3-dimethyl-2-butanone (8). To a solution of **54** (100 mg, 0.32 mmol) in CH_2Cl_2 (1.6 mL) was added pyridinium dichromate (181 mg, 0.48 mmol), freshly activated 3Å molecular sieve powder (260 mg) then anhydrous AcOH (32 μl, 0.55 mmol). The reaction was stirred at room temperature for 15 minutes before being diluted with CH_2Cl_2 and filtered though a small (0.5 cm) bilayer Celite™/silica gel plug. The filtrate was washed with water then brine and the organic phase dried over $MgSO_4$. The solvent was removed under reduced pressure and residue purified via flash chromatography (50:1 hexanes:EtOAc) to give **8** (81 mg, 82 %) as a colourless oil. ^1H NMR: δ7.35 (m, 10H), 4.58 (s, 2H), 4.48 (s, 2H), 4.38 (s, 2H), 3.44 (s, 2H),1.17 (s, 6H) ppm. ^{13}C NMR: δ 210.8, 138.2, 137.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 77.3, 73.6, 73.3, 72.4, 47.6, 22.1 ppm. IR (neat): 3031, 2967, 2932, 2869, 1723, 1100 cm^{-1}. HRMS: Calcd for $C_{20}H_{24}O_3$ 313.1805 ($M+H^+$). Found 313.1798.

9.4. Experimental for Chapter 4:

4-Hydroxy-5-methylhex-5-en-2-one (24b). To a solution of diisopropylamine (1.37 mL, 9.81 mmol) in dry THF (40 mL) cooled to –78 °C was added a 2M solution of *n*-BuLi in hexanes (4.90 mL, 9.81 mmol). After stirring at –78 °C for 10 min, a solution of acetone (600 μl, 8.17 mmol) in THF (4 mL) was added slowly over 5 min. Stirring at –78 °C was continued for 50 min and then a solution of methacrolein (811 μl, 9.81 mmol) in THF (4 mL) added. The mixture was stirred at –78 °C for a further 10 min, followed by the addition of sat. aq. NH_4Cl. The mixture was then extracted twice with Et_2O and the organic extracts washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Bulb-to-bulb distillation (58-60 °C, 0.4 mm/Hg) gave **24b** (882 mg, 84%) as a colourless oil. NMR spectral data matched that previously reported.[202]

4-(3-Butenoyl)hex-5-en-2-one (57a). To a solution of the ß-hydroxy-ketone **24a** (1.00 g, 9.64 mmol) in CH_2Cl_2 (45 mL) was added vinylacetic acid (819 μL, 9.64 mmol), dicyclohexylcarbodiimide (1.99 g, 9.64 mmol) and DMAP (54 mg, 0.45 mmol) and the reaction stirred at room temperature overnight. The precipitated dicyclohexyl urea was removed by filtration and the precipitate washed with 60 mL of ice-cold CH_2Cl_2. The combined organic extracts were then washed once with water, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was initially purified by flash chromatography (5:1 hexanes:EtOAc) to give **57a** containing small amounts of dicyclohexyl urea. This was further purified by bulb-to-bulb distillation (90-100 °C, 0.4 mm/Hg) to give pure **57a** (1.28 g, 80%) as a colourless oil. ^{1}H NMR: δ 5.89 (m, 2H) 5.70 (m, 1H), 5.26 (m, 4H), 3.12 (dd, J = 1.4 Hz, 1H), 3.10 (dd, J = 1.4 Hz, 1H), 2.88 (dd, J = 16.5, 7.7 Hz, 1H), 2.71 (dd, J = 16.5, 5.5 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR: δ 204.5, 170.3, 135.2, 130.0, 118.6, 117.1, 70.5, 47.7, 39.1, 30.4 ppm. IR (neat): 3087, 2934, 1738, 1723, 1167 cm^{-1}. HRMS: Calcd for $C_{10}H_{18}NO_3$ 200.1291 ($M+NH_4^+$). Found 200.1281.

4-(3-Butenoyl)-5-methylhex-5-en-2-one (57b). To a solution of 4-hydroxy-5-methyl-5-hexen-2-one **(24b)** (824 mg, 6.43 mmol) in CH_2Cl_2 (30 mL) was added vinylacetic acid (601 μL, 7.07 mmol), dicyclohexylcarbodiimide (1.46 g, 7.07 mmol) and DMAP (40 mg, 0.32 mmol) and the reaction stirred at room temperature overnight. The precipitated dicyclohexyl urea was then removed by filtration, and the precipitate washed with 50 mL of ice-cold CH_2Cl_2. The combined organic extracts were then washed once with water, dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was initially purified by flash chromatography (5:1 hexanes:EtOAc) to give **57b** containing small amounts of dicyclohexyl urea. Further purification by bulb-to-bulb distillation (85-95°C, 0.4 mm/Hg) gave pure **57b** (1.06 g, 84 %) as a colourless oil. ^{1}H NMR: δ 5.92 (m, 1H), 5.64 (dd, J = 8.8, 4.5 Hz, 1H), 5.21 (m, 1H), 5.17 (m, 1H), 5.02 (d, J = 0.85 Hz, 1H), 4.94 (t, J = 1.4 Hz, 1H), 3.12 (t, J = 1.4 Hz, 1H), 3.10 (t, J = 1.4 Hz, 1H), 2.88 (dd, J = 16.3, 8.8 Hz, 1H), 2.70 (dd, J = 16.3, 4.5 Hz, 1H), 2.21 (s, 3H), 1.77 (s, 3H) ppm. ^{13}C NMR: δ 204.8, 170.2, 142.2, 130.0, 118.6, 113.0, 72.9, 46.5, 39.1, 30.3, 18.3 ppm. IR (neat): 1736, 1719, 1360, 1158, 1057 cm^{-1}. HRMS: Calcd for $C_{11}H_{20}NO_3$ 214.1441 ($M+NH_4^+$). Found 214.1438.

5-Acetonyl-δ-lact-3-en-1-one (56a). To a side-armed flask equipped with a reflux condenser containing **57a** (56 mg, 0.31 mmol) was added CH_2Cl_2 (20 mL) and tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium (IV) dichloride **(62)** (3 mg, 3.4 μmol). The resulting maroon solution was refluxed for 2.5 h then the solvent was removed under reduced pressure. Gradient flash chromatography (5:1 to 2:1 hexanes:EtOAc) of the brown residue gave **56a** (43 mg, 90%) a colourless oil. ^{1}H NMR: δ 5.85 (s, 2H), 5.43 (m, 1H), 3.09 (m, 2H), 3.01 (dd, J = 17.2, 6.4 Hz, 1H), 2.81 (dd, J = 17.2, 6.5 Hz, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR: δ 204.3, 168.2, 125.6, 122.5, 75.4, 48.4, 30.7, 29.8 ppm. IR (neat):1732, 1713, 1362, 1272, 1220, 1072 cm^{-1}. HRMS: Calcd for $C_8H_{14}NO_3$ 172.0973 ($M+NH_4^+$). Found 172.0968.

5-Acetonyl-4-methyl-δ-lact-3-en-1-one (56b). To a side-armed flask equipped with a reflux condensor containing **57b** (250 mg, 1.27 mmol) was added CH_2Cl_2 (100 mL) and tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium (IV) dichloride **(62)** (11 mg, 0.013 mmol). The resulting maroon solution was refluxed for 2.5 h then the solvent was removed under reduced pressure. Gradient flash chromatography (5:1 to 2:1 hexanes:EtOAc) of the brown residue gave **57b** (182 mg, 85%) as a colourless oil. ^{1}H NMR: δ 5.54 (m, 1H), 5.22 (m, 1H), 3.06 (m, 2H), 2.83 (m, 2H), 2.22 (s, 3H), 1.74 (s, 3H) ppm. ^{13}C NMR: δ 204.8, 169.0, 131.9, 117.6, 78.9, 46.8, 31.3, 30.2, 18.8 ppm. IR (neat): 1730, 1715, 1355, 1214, 1154, 1063 cm^{-1}. HRMS: Calcd for $C_9H_{16}NO_3$ 186.1134 ($M+NH_4^+$). Found 186.1125.

9.5. Experimental for Chapter 5:

But-3-en-1-oxydiphenylsilyl chloride (68a). To a stirred mixture of diphenylsilyl-dichloride (330 μl, 1.57 mmol) and Et_3N (241 μl, 1.73 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added a solution of 3-buten-1-ol (135 μl, 1.57 mmol) in CH_2Cl_2 (2 mL) dropwise. The reaction mixture was stirred at room temperature before being heated at reflux for 36 h. The solution was then cooled to room temperature and concentrated under reduced pressure. The resultant oil was dissolved in a 1:1 vol:vol ether:pentane mixture (15 mL), suction filtered, and reconcentrated to afford an oil, which was used without further purification.

But-3-en-1-oxydiisopropylsilyl chloride (68b). To a stirred mixture of diisopropylsilyl-dichloride (4 mL, 22.2 mmol) and Et_3N (3.4 mL, 24.4 mmol) in CH_2Cl_2 85 mL at 0 °C was added a solution of 3-buten-1-ol (1.91 mL, 22.2 mmol) in CH_2Cl_2 (20 mL) over 30 min. The reaction mixture was stirred at room temperature for 6 h before being heated at reflux for 48 h. After cooling to room temperature and concentrating under reduced pressure, the resultant oil was dissolved in a 1:1 vol:vol ether:pentane mixture (100 mL), suction filtered and reconcentrated to afford an oil. Fractional distillation of the crude material gave **68b** as a colourless oil (bp 58 – 60°C, 1 mm/Hg, 2.64g, 54%). ^{1}H NMR: δ 5.82 (m, 1H), 5.06 (m, 2H), 3.83 (t, J = 6.6 Hz, 2H), 2.32 (dt, J = 13.5, 6.9 Hz, 2H) 1.07 (m, 14H) ppm. ^{13}C NMR: δ 135.1, 117.0, 63.6, 37.0, 17.0, 16.9, 15.2 ppm. IR (neat): 2954, 2876, 1109, 994, 922, 886 cm^{-1}.

But-3-en-1-oxydimethylsilyl chloride (68c). To a stirred mixture of dimethylsilyldichloride (4.54 mL, 37.5 mmol) and Et_3N (5.75 mL, 41.25 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of 3-buten-1-ol (3.23 mL, 37.5 mmol) in CH_2Cl_2 (45 mL) ropwise over 45 min. The reaction mixture was then stirred at room temperature for 16 h before being heated at reflux for 12 h. After cooling to room

temperature and concentrating under reduced pressure, the resultant oil was dissolved in a 1:1 vol:vol ether:pentane mixture (120 mL), suction filtered and reconcentrated to afford an oil. Fractional distillation of the crude material gave 1.06 g (17 %) of **68c** as a colourless oil (bp 63 – 65°C, 7 mm/Hg).^{1}H NMR: δ 5.82 (m, 1H), 5.10 (m,1H), 3.81 (t, *J* = 6.9 Hz, 2H), 2.36 (dt, *J* = 13.5, 6.9 Hz, 2H), 0.49 (s, 6H) ppm.[xxv]

General procedure for the formation of Diphenylsilyl derivatives (66a) and (66b)

To a 0 °C stirred solution of the crude but-3-enoxydiphenylsilylchloride **(68a)** (2.5 mmol) and the appropriate β-hydroxyketone (1.57 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (218 μl, 1.57 mmol) dropwise. The ice bath was then removed and the solution stirred at room temparature for 2.5 h before being quenched with satd. aq. $NaHCO_3$. The solution was then extracted twice with Et_2O and the organic extracts washed with water, brine, and dried over $MgSO_4$. Filtration and concentration gave a residual oil, which was purified by flash chromatography on silica gel (20:1 hexanes:EtOAc) to give the diphenyl *bis*-silylether as a colourless oil. Yields are reported for the total conversion from dichlorodiphenylsilylchloride **(68a)**.

4-(But-3-en-1-oxydiphenylsilyloxy)-5-methylhex-5-en-2-one (66a).

Dichlorodiphenylsilane **(68a)** (330 μl, 1.57 mmol) gave **66a** (335 mg, 0.95 mmol) in an overall yield of 61%. ^{1}H NMR: δ 7.65 (m, 4H), 7.41 (m, 6H), 5.84 (m, 1H), 5.07 (m, 2H), 4.93 (s, 1H), 4.80 (m, 2H), 3.80 (t, *J* = 6.9 Hz, 2H), 2.82 (dd, *J* = 15, 7.5 Hz, 1H), 2.58 (dd, *J* = 15, 5.4 Hz, 1H), 2.35 (dt, *J* = 13.2, 6.6 Hz, 2H), 2.10 (s, 3H), 1.73 (s, 3H) ppm. ^{13}C NMR: δ 206.9, 145.7, 135.4, 135.3, 132.9, 130.6, 130.5, 128.0, 116.8, 112.5, 73.5, 62.9, 50.5, 37.1, 31.2, 17.6 ppm. IR (neat): 3079, 2924, 2878, 1714, 1087, 719 cm^{-1}. HRMS: Calcd. for $C_{23}H_{28}O_3SiNa$ 403.1680 ($M + Na^+$). Found: 403.1699.

[xxv] Unfortunately only ^{1}H NMR spectral data is available. Due to the compounds unsuitability in the synthetic strategy it was deemed of little value to resynthesise this derivative for characterisation purposes only.

4-(But-3-en-1-oxydiphenylsilyloxy)hex-5-en-2-one (66b). Dichlorodiphenylsilane (330 μl, 1.57 mmol) produced **66b** (374 mg, 1.02 mmol) in an overall yield of 65%. ^{1}H NMR: δ 7.65 (m, 4 H), 7.41 (m, 6 H), 5.50 (m, 2 H), 5.09 (m, 4 H), 4.84 (dt, *J* = 12.9, 6.0 Hz, 1H), 3.81 (t, *J* = 6.9 Hz, 2H), 2.79 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.61 (dd, *J* = 15.4, 5.7 Hz, 1H), 2.35, (dt, *J* = 13.8, 6.9 Hz, 2H), 2.11 (s, 3H) ppm. ^{13}C NMR: δ 206.7, 139.5, 135.4, 135.3, 130.6, 128.1, 128.0, 116.8, 115.5, 70.8, 63.0, 51.8, 37.1, 31.3 ppm. IR (neat): 3071, 3003, 2874, 1715, 1115, 1079, 914, 717 cm^{-1}. HRMS: Calcd. for $C_{22}H_{26}O_3SiNa$: 389.1542 (M + Na$^+$). Found: 389.1543.

General procedure for the formation of diisopropylsilylethers (66c) and (66d)

To a stirred solution of but-3-en-1-oxydiisopropylsilylchloride **(68b)** (1.2 mmol), the appropriate β-hydroxyketone (1 mmol), and DMAP (0.05 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (1.2 mmol) dropwise. The resulting solution was stirred at room temperature for 18 h then quenched with satd. aq. $NaHCO_3$ and extracted twice with Et_2O. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography (20:1 hexanes:EtOAc) to give the requisite diisopropylsilylethers.

4-(But-3-en-1-oxydiisopropylsilyloxy)-5-methylhex-5-en-2-one (66c). β-Hydroxyketone **24a** (329 mg, 2.57 mmol) gave **66c** (687 mg, 86%) as a colourless oil. ^{1}H NMR: δ 5.84 (m, 1H), 5.04 (m, 2H), 4.81 (s, 1H), 4.76 (t, *J* = 6.3 Hz, 1H), 3.74 (t, *J* = 6.9 Hz, 2H), 2.74 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.57 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.30, (dt, *J* = 13.8, 6.6 Hz, 2H), 2.17 (s, 3H), 1.73 (s, 3H), 1.02 (m, 14H) ppm. ^{13}C NMR: δ 207.4, 146.5, 135.6, 116.6, 111.8, 73.0, 62.8, 50.9, 37.5, 31.7, 17.6, 17.5, 12.5, 12.4 ppm. IR (neat): 2945, 2867, 1716, 1085, 1060, 999, 883, 688 cm^{-1}. HRMS: Calcd. for $C_{17}H_{32}O_3SiNa$ 335.2012 (M + Na$^+$). Found: 335.2013.

4-(But-3-en-1-oxydiisopropylsilyloxy)hex-5-en-2-one (66d). β-Hydroxyketone **24b** (243 mg, 2.13 mmol) gave **66d** (521 mg, 82%) as a colourless oil. ^{1}H NMR: δ 5.84 (m, 2H), 5.20 (m, 4H), 4.78 (dt, *J*= 12.3, 6.3 Hz, 1H), 3.75 (t, *J* = 6.9 Hz, 2H), 2.74 (dd, *J* = 15.3, 6.6 Hz, 1H), 2.57 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.29 (dt, *J* = 13.5, 6.6 Hz, 2H), 2.16 (s, 3H), 1.01 (m, 14H) ppm. ^{13}C NMR: δ 207.2, 140.3, 135.6, 116.6, 114.8, 70.2, 62.8, 52.2, 37.5, 31.7, 17.6, 17.5, 12.5, 12.4 ppm. IR (neat): 2944, 2867, 1717, 1087, 990, 883, 689 cm^{-1}. HRMS: Calcd. for $C_{16}H_{30}O_3SiNa$ 321.1847 (M + Na$^+$). Found: 321.1856.

4-(But-3-en-1-oxydimethylsilyloxy)hex-5-en-2-one (66e). To a stirred solution of 3-buteneoxydimethylsilylchloride **(68c)** (386 mg, 2.34 mmol) and β-hydroxyketone **24a** (243 mg, 2.13 mmol) in CH_2Cl_2 (10.5 mL) was added Et_3N (386 μl, 2.77 mmol) dropwise. The solution was then stirred at room temperature for 3 h before being quenched with satd. aq. $NaHCO_3$, extracted twice with Et_2O, and the organic extracts washed with water, brine, and dried over $MgSO_4$. Filtration and concentration gave a residual oil, which was purified by gradient flash chromatography (10:1 to 5:1 hexanes:EtOAc) to give **68e** (396 mg, 77%) as a colourless oil. ^{1}H NMR: δ 5.85 (m, 2H), 5.26 (m, 4H), 4.75 (m, 1H), 3.70 (t, *J* = 6.9 Hz, 2H), 2.76 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.53 (dd, *J* = 15.3, 5.1 Hz, 1H), 2.31 (dt, *J* = 13.8, 6.9 Hz, 2H), 2.19 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H) ppm. ^{13}C NMR: δ 206.9, 139.7, 135.1, 116.5, 114.6, 69.9, 62.0, 51.3, 36.9, 31.4, -2.7, -2.8 ppm. IR (neat): 2962, 2873, 1718, 1257, 1072, 1034, 796 cm^{-1}.

General procedure for RCM reactions

To a solution of the diene (1 mmol) in CH_2Cl_2 (100 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium (IV) dichloride **(62)** (0.09 mmol for R^2 = H, 0.12 mmol for R^2 = Me). The reaction mixture was stirred for 8-12 h at room temperature, the solvent was removed under reduced pressure and the dark residue filtered through a short pad of silica gel (10:1 hexanes:EtOAc). The filtered solution was then stirred with activated charcoal

(8.5 g) for 24 h. The mixture was filtered, concentrated *in vacuo* and purified by careful gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc) to provide the cyclic olefin as a colourless oil.

(4*R*, 5*Z*)-4,8-*O*-diphenylsilanediyl-5-methyloct-5-en-2-one (65a). Diene **66a** (270 mg, 0.71 mmol) gave **65a** in 54 % yield (135 mg). ^{1}H NMR: δ 7.64 (m, 4H), 7.39 (m, 6H), 5.44 (t, *J* = 8.1 Hz, 1H), 4.90 (dd, *J* = 9.6. 3.9 Hz, 1H), 4.05 (m, 2H), 2.94 (dd, *J* = 15.3, 9.9 Hz, 1H), 2.93 (m, 1H), 2.62 (dd, *J* = 15.3, 3.6 Hz, 1H), 2.26 (m, 1H), 2.25 (s, 3H), 1.60 (s, 3H) ppm. ^{13}C NMR: δ 207.6, 140.8, 134.8, 133.8, 133.5, 130.5, 130.4, 128.1, 125.1, 71.7, 64.4, 49.6, 31.2, 30.9, 21.5 ppm. IR (neat): 3070, 2919, 2876, 1713, 1115, 1083, 716, 699 cm^{-1}. HRMS: Cald for $C_{21}H_{25}O_3Si$ 353.1568 (M + H$^+$). Found: 353.1565.

(5*Z*)-4,8-*O*-diphenylsilanediyloct-5-en-2-one (65b). Diene **66b** (80 mg, 0.22 mmol) gave **65b** in 81 % yield (60 mg). ^{1}H NMR: δ 7.65 (m, 4H), 7.39 (m, 6H), 5.73 (m, 2H), 5.13 (m, 1H), 4.09 (m, 1H), 3.94 (m, 1H), 2.96 (dd, *J* = 15.0, 8.1 Hz, 1H), 2.64 (dd, *J*= 15.0, 4.5 Hz, 1H), 2.63 (m, 1H), 2.42 (m, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR: δ 207.3, 135.2, 135.0, 134.8, 133.7, 130.5, 130.4, 129.3, 128.2, 128.1, 67.4, 63.7, 51.5, 31.3, 31.1 ppm. IR (neat): 3067, 3013, 2955, 2926, 2878, 1715, 1128, 1082, 720, 700 cm^{-1}. HRMS: Calcd. for $C_{20}H_{23}O_3Si$ 339.1408 (M + H$^+$). Found: 339.1411.

(4*R*, 5*Z*)-4,8-*O*-di-(isopropyl)silanediyl-5-methyloct-5-en-2-one (65c). Diene **66c** (110 mg, 0.35 mmol) gave **65c** in 60 % yield (60 mg). ^{1}H NMR: δ 5.42 (m, 1 H), 4.89 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.9 (m, 2 H), 2.82 (dd, *J* = 14.4, 9.6 Hz, 1 H), 2.72 (m, 1 H), 2.50 (dd, *J* = 14.7, 3.6 Hz, 1 H), 2.25 (s, 3 H), 2.24 (m. 1 H), 1.74 (s, 3 H), 1.00 (m, 14 H) ppm. ^{13}C NMR: δ 208.1, 140.6, 125.0, 71.0, 64.3, 49.6, 31.6, 30.8, 21.1, 17.6, 17.5, 12.8, 12.5 ppm. IR (neat): 2943, 2866, 1715, 1112, 1036, 883, 693 cm^{-1}. HRMS: Calcd for $C_{15}H_{29}O_3Si$ (M + H$^+$) 285.1891. Found: 285.1881.

(5*Z*)-4,8-*O*-di-(isopropyl)silanediyloct-5-en-2-one (65d). Diene **66d** (340 mg, 1.14 mmol) gave **65d** in 74% yield (229 mg). ^{1}H NMR: δ 5.72 (m, 2H), 4.93 (m, 1H), 3.91 (m, 2H), 2.80 (dd, *J* = 14.7, 8.4 Hz, 1H), 2.56 (m, 1H), 2.54 (dd, *J* = 14.7, 4.8 Hz, 1H), 2.40 (m, 1H), 2.23 (s, 3H), 1.02 (m, 14H) ppm. ^{13}C NMR: δ 207.9, 135.3, 129.4, 66.9, 63.8, 51.5, 31.7, 31.1, 17.7, 17.6, 17.5, 12.8, 12.5 ppm. IR (neat): 2944, 2867, 1715, 1120, 1011, 732 cm^{-1}. HRMS: Calcd. for $C_{14}H_{27}O_3Si$ 271.1717 (M + H$^+$). Found: 271.1724.

(5*Z*)-4,8-*O*-di-methylsilanediyloct-5-en-2-one (65e). (Unoptimised). To a solution of diene **66e** (60 mg, 0.25 mmol) in CH_2Cl_2 (18 mL) was added tricyclohexylkphosphine-[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium (IV) dichloride **(62)** (10 mg, 0.12 mmol) and the solution stirred at room temperature for 16 h. The solvent was removed under reduced pressure, and the dark brown residue purified by gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc) to give **65e** (90 mg, 42%). (Substrate characterised by ^{1}H NMR only). ^{1}H NMR: δ 5.78 (m, 2H), 4.94 (m, 1H), 3.94 (m, 1H), 3.78 (m, 1H), 2.81 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.56 (dd, *J* = 15.3, 4.5 Hz, 1H), 2.20 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H) ppm.

But-3-ene-1-oxymethoxydi-*tert*-butylsilane (71). To a solution of di-*tert*-butylsilyl-*bis*-(trifluoromethanesulfonate) (500 μL, 1.39 mmol) in DMF (5 mL) at – 40 °C was added dropwise a solution of but-3-en-1-ol (120 μL, 1.39 mmol) in DMF (5 mL). The cooling bath was removed and the reaction stirred for 2 h before being quenched with methanol then extracted twice with Et_2O. The combined organic fractions were washed three times with satd. aq. $NaHCO_3$, once with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave a residual oil which was purified by flash chromatography (50:1 hexanes:EtOAc) to give **71** (240 mg, 71%) as a colourless oil. ^{1}H NMR: δ 5.88 (m, 1H), 5.08 (m, 2H), 3.91 (t, *J* = 6.6 Hz, 2H), 3.66 (s, 3H), 2.36 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.04 (s, 18H) ppm. ^{13}C NMR: δ 135.7, 116.6, 63.7, 52.3, 37.7, 28.1, 21.4 ppm.

But-3-ene-1-oxyallyloxy-di-*tert*-butylsilane (72). To a solution of di-*tert*-butylsilyl-*bis*-(trifluoromethanesulfonate) (300 μL, 0.82 mmol) in DMF (3 mL) at – 40 °C was added dropwise a solution of but-3-en-1-ol (71 μL, 0.82 mmol) in DMF (1.5 mL). The cooling bath was removed and the reaction allowed to gradually warm to room temperature. After 1 h, pyridine (67 μL, 0.82 mmol) then allyl alcohol (112 μL, 1.65 mmol) were added and the reaction stirred for a further 30 min before being quenched by pyridine (67 μL, 0.82 mmol). The solution was diluted with water, extracted twice with Et_2O, and the combined organic fractions washed three times with satd. aq. $NaHCO_3$, once with brine and dried over $MgSO_4$ before being filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography (hexanes) to give **72** (145 mg, 65%) as a colourless oil. ^{1}H NMR: δ 5.92 (m, 2H), 5.35 (m, 1H), 5.10 (m, 3H), 4.40 (dd, J = 3.9, 1.8 Hz, 2H), 3.88 (t, J = 6.9 Hz, 2H), 2.34 (d,t, J = 13.2, 6.6 Hz, 2H), 1.04 (s, 18H) ppm. ^{13}C NMR:137.6, 135.8, 116.6, 113.7, 64.6, 63.6, 37.7, 28.1, 21.4 δ ppm. IR (neat): 2968, 2933, 2858, 1093,913, 825 cm^{-1}.

4-*tert*-Butyldimethylsiloxy-5-methyl-5-hexen-2-one (75a). To a solution of 4-hydroxyl-5-methy-hex-5-ene-2-one **(24a)** (300 mg, 2.34 mmol) in DMF (2.5 mL) was added *tert*-butyldimethylsilylchloride (388 mg, 2.58 mmol) and imidazole (351 mg, 5.15 mmol). After stirring at room temperature for 24 h, the solution was quenched with water and extracted twice with Et_2O. The organic extracts were washed twice with satd. aq. $NaHCO_3$, once with brine and dried over $MgSO_4$ before being filtered and the solvent removed under reduced pressure. The residual oil was purified by gradient flash chromatography (hexanes to 50:1: hexanes:EtOAc) to give **75a** (413 mg, 73%) as a colourless oil. ^{1}H NMR:δ 4.95 (s, 1H), 4.78 (s, 1H), 4.54 (dd, J = 8.4, 3.9 Hz, 1H), 2.74 (dd, J = 14.7, 8.7 Hz, 1H), 2.39 (dd, J = 18.3, 3.9 Hz, 1H), 2.16 (s, 3H), 1.69, (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00, (s, 3H) ppm. ^{13}C NMR: δ 207.8, 147.0, 111.5, 73.7, 50.6, 32.0, 26.0, 18.3, 17.46, -4.6, -5.1 ppm. IR (neat): 2930, 2857, 1360, 1718, 1251, 1074, 835, 776 cm^{-1}. HRMS: Calcd. for $C_{13}H_{27}O_2Si$ 243.1774 (M + H$^+$): Found. 243.1780.

4-*tert*-Butyldimethylsiloxyhex-5-en-2-one (75b). To a solution of 4-hydroxy-5-hexen-2-one **(24b)** (300 mg, 2.63 mmol) in DMF (2 mL) was added *tert*-butyldimethylsilyl-chloride (436 mg, 2.89 mmol) and imidazole (394 mg, 5.78 mmol). After stirring at room temperature for 24 h, the solution was quenched with satd. aq. NH_4Cl and extracted twice with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography (50:1 hexanes:EtOAc) to give **75b** (446 mg, 74%) as a colourless oil. ^1H NMR: δ 5.78 (dd, J = 12.0, 6.0 Hz, 1H), 5.15 (m, 1H), 5.01 (m, 1H), 4.55 (m, 1H), 2.43 (dd, J = 15.0, 9.0 Hz, 1H), 2.43 (dd, J = 15.0, 3.0 Hz, 1H), 1.90 (s, 3H), 0.83 (s, 9H), - 0.2 (s, 6H) ppm. ^{13}C NMR: δ 207.4, 140.6, 114.5, 70.7, 51.9, 32.0, 26.0, 18.3, -4.2, -4.9 ppm. IR (neat): 2956, 2930, 2858, 1718, 1078, 834, 776 cm^{-1}. HRMS: Calcd. for $C_{12}H_{25}O_2SiNa$ 229.1624 ($M + Na^+$). Found: 229.1618.

4-*tert*-Butyldiphenylsiloxy-5-methylhex-5-en-2-one (75c). To a solution of 4-hydroxy-5-methylhex-5-en-2-one **(24a)** (437 mg, 3.4 mmol) in DMF (4.5 mL) was added *tert*-butyldiphenylsilylchloride (976 μL, 3.75 mmol) and imidazole (464 mg, 6.82 mmol). After stirring at room temperature for 36 h, the solution was quenched with water and extracted twice with Et_2O. The organic extracts were then washed twice with satd. aq. $NaHCO_3$, once with brine and dried over $MgSO_4$ before being filtered and the solvent removed under reduced pressure. The residual oil was purified by gradient flash chromatography (hexanes to 50:1: hexanes:EtOAc) to give **75c** (920 mg, 75%) as a colourless oil. ^1H NMR: δ 7.65 (m, 4H), 7.38 (m, 6H), 4.78 (s, 1H), 4.72 (s, 1H), 4.59 (t, J = 6 Hz, 1H), 2.61 (dd, J = 14.7, 6.0 Hz,1H), 2.52 (dd, J = 14.7, 6.6 Hz, 1H), 2.10 (s, 3H), 1.68 (s, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR: δ 206.8, 145.8, 136.2, 134.1, 133.7, 130.0, 128.0, 127.8, 127.7, 112.6, 74.1, 50.8, 31.1, 27.2, 19.6, 17.4 ppm. IR (neat): 3072, 2931, 2857, 1713, 1427, 1360, 1162, 1106, 1063, 739, 700 cm^{-1}. HRMS: Calcd. for $C_{23}H_{30}O_2SiNa$ 389.1922 ($M + Na^+$). Found: 389.1907.

4-*O*-(Methoxymethyloxy)-5-methylhex-5-en-2-one (75d). To a solution of 4-hydroxy-5-methylhex-5-ene-2-one **(24a)** (1.0g, 7.80 mmol), in *N*,*N*-diisopropylethylamine (2.72 mL) at 0 °C was added methoxymethylchloride (593 μL, 7.80 mmol) dropwise. The reaction was stirred for 3 h, gradually warming to room temperature, before being quenched with water and extracted twice with Et_2O. The organic extracts were washed with satd. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residual oil was purified by flash chromatography (5:1 hexanes:EtOAc) to give **75d** (430 mg, 32%, unoptimised) as a colourless oil. ^{1}H NMR: δ 5.01 (s, 1H), 4.94 (t, *J* = 0.6 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.53 (dd, *J* = 9.3, 3.9 Hz, 1H), 4.48 (d, *J* = 6.6 Hz, 1H), 3.34 (s, 3H), 2.82 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.46 (dd, *J* = 15.9, 3.9 Hz, 1H), 2.20 (s, 3H), 1.68 (s, 3H) ppm. ^{13}C NMR: δ 206.8, 143.2, 114.7, 94.0, 76.0, 56.0, 48.2, 31.2, 17.3 ppm. IR (neat): 2947, 2824, 1715, 1096, 1026, 914 cm^{-1}.

4-*O*-(Methoxymethyloxy)hex-5-en-2-one (75e). To a solution of 4-hydroxy-5-hexene-2-one **(24b)** (350 mg, 3.07 mmol), in *N*,*N*-diisopropylethylamine (1.06 mL, 6.13 mmol) at 0 °C was added methoxymethylchloride (221 μL, 2.91 mmol) dropwise. The reaction was stirred for 3 h, gradually warming to room temperature, before being quenched with water and extracted twice with Et_2O. The organic extracts were washed with satd. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residual oil was purified by flash chromatography (5:1 hexanes:EtOAc) to give **75e** (221mg, 48 %) as a colourless oil. ^{1}H NMR: δ 5.71 (dd, *J* = 10.5, 7.8 Hz, 1H), 5.22 (m, 2H), 4.67 (d, *J* = 6.9 Hz, 1H), 4.52 (d, *J* = 6.9 Hz, 1H), 3.34 (s, 3H), 2.80 (dd, *J* = 15.9, 8.7 Hz, 1H), 2.53 (dd, *J* = 15.6, 4.8 1H), 2.19 (s, 3H) ppm. ^{13}C NMR: δ 206.3, 136.9, 117.8, 94.1, 73.4, 55.6, 49.2, 31.1 ppm. IR (neat): 2935, 2894, 1716, 1027, 919 cm^{-1}.

Representative procedure for aldol reactions

To a solution of diisopropylamine or tetramethylpiperidine (1.05 mmol) in dry THF (3 mL) cooled to –78 °C was added butyllithium (1.00 mmol, 1.6 M solution in hexanes) dropwise. After stirring at –78 °C for 10 min, a solution of the ketone (1.00 mmol) in THF (3 mL) was added dropwise. Stirring was continued for 50 min before a solution of pivaldehyde (1.20 mmol) in THF (2 mL) was added. The resultant solution was then stirred at –78 °C for a further 15 minutes, before being quenched by the addition of satd

0.92 (s, 18H), 0.90 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H) ppm. ^{13}C NMR: δ 211.5, 140.5, 114.8, 74.9, 74.6, 70.9, 70.8, 52.0, 51.8, 46.7, 46.4, 26.1, 34.1, 25.9, 18.4, -4.2, -4.8 ppm. IR (neat): 3500, 2956, 2858, 1707, 1076, 835, 776 cm^{-1}.

7-*tert*-Butyldiphenylsiloxy-3-hydroxy-2,2,8-trimethylnon-8-ene-5-one (78c). Ketone **75c** (755 mg, 3.11 mmol) gave **78c** (681 mg, 67%) as a colourless oil after purification by gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc). Spectral data reported for the racemic product. ^{1}H NMR: δ 4.99 (s, 1H), 4.82 (s, 1H), 4.56 (dd, J = 8.7, 3.9 Hz, 1H), 3.71 (m, 1H), 3.05 (d, J = 2.7 Hz, 1H), 2.84 – 2.43 (m, 4H), 1.73 (s, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H) ppm. ^{13}C NMR: δ 211.8, 211.5, 146.8, 111.7, 75.0, 74.6, 73.7, 73.6, 50.5, 46.7, 46.5, 34.3, 34.2, 26.0, 25.9, 18.7, 17.6, -4.6, -5.1 ppm. IR (neat): 3507, 2955, 2858, 1709, 1072, 835, 776 cm^{-1}.

7-*O*-(Methoxymethyloxy)-3-hydroxy-2,2,8-trimethylnon-8-ene-5-one (78d). Ketone **75d** (390 mg, 2.26 mmol) gave **78d** (325 mg, 56%) as a colourless oil after purification by gradient flash chromatography (5:1 to 3:1 hexanes:EtOAc) on a silica gel column neutralised with 0.01% Et_3N in 5:1 hexane:EtOAc. Spectral data reported for the racemic product. ^{1}H NMR: δ 5.05 (s, 1H), 4.98 (s,1H), 4.62 (d, J = 6.6 Hz, 1H), 4.60 (m, 1H), 4.50 (d, J = 6.6 Hz, 1H), 3.76 (m, 1H), 3.36 (d, J = 2.4 Hz, 1H), 2.89 (m, 1H), 2.74 – 2.46 (m, 3H), 1.71 (s, 3H), 0.93 (s, 9H) ppm. ^{13}C NMR: δ 206.2, 114.8, 94.0, 76.0, 75.8, 75.1, 74.8, 56.1, 48.1, 48.0, 45.8, 32.4, 25.9, 17.4 ppm. (The compound decomposed before further spectral data could be obtained).

3-Benzyloxy-7-*tert*-butyldimethylsiloxy-2,2,8-trimethylnon-8-ene-5-one (80b). To a solution of aldol adduct **78b** (662mg, 2.0 mmol) in cyclohexane (20 mL) cooled to 0 °C was added benzyltrichloroacetimidate (**79**) (385 μl, 2.12 mmol) followed by freshly

distilled trifluoromethanesulfonic acid (8.8 μl, 0.10 mmol) dropwise. A cream precipitate was immediately observed. The resulting mixture was stirred at room temperature for 30 min before being quenched with water then extracted twice with hexanes. The organic extracts were washed with satd. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by gradient flash chromatography (hexanes to 50:1; hexanes:EtOAc) gave **80b** (601 mg, 72%) as a colourless oil. Spectral data reported for the racemic product. ^{1}H NMR: δ 7.33 (m, 5H), 4.97 (s, 1H), 4.79 (s, 1H), 4.55 (m, 3H), 3.76 (m, 1H), 2.84 – 2.37 (m, 4H), 1.74 (s, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ppm. ^{13}C NMR: δ 208.9, 208.6, 147.1, 147.0, 139.4, 139.3, 128.5, 128.1, 127.7, 127.5, 127.2, 111.6, 111.5, 82.9, 82.8, 74.4, 74.0, 73.4, 73.1, 51.0, 47.1, 46.3, 35.9, 35.8, 26.4, 26.3, 26.0, 17.6, 17.5, -4.6, -5.0 ppm. IR (neat): 2955, 2859, 1717, 1073, 835 cm^{-1}.

3-Benzyloxy-7-*tert*-butyldiphenylsiloxy-2,2,8-trimethylnon-8-ene-5-one (80c). To a solution of aldol adduct **78c** (172 mg, 0.48 mmol) in cyclohexane (5 mL) cooled to 0 °C was added benzyltrichloroacetimidate (92 μl, 0.51 mmol) followed by freshly distilled trifluoromethanesulfonic acid (5 μl, 0.06 mmol) dropwise. A cream precipitate was immediately observed and the resulting mixture was stirred at room temperature for 30 min before being quenched with water. The solution was then extracted with hexanes and the organic extracts washed with satd. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by gradient flash chromatography (hexanes to 50:1; hexanes:EtOAc) gave **80c** (143 mg, 71 %) as a colourless oil. Spectral data is reported for the racemic product. ^{1}H NMR: δ 7.69 (m, 4H), 7.34 (m, 11H), 4.80 (m, 1H), 4.74 (m, 1H), 4.62 (m, 1H), 4.46 (m, 2H), 3.62 (dd, J = 7.8, 3.9 Hz, 1H), 2.71 – 2.25 (m, 4H), 1.71 (s, 3H), 1.08 (s, 9H), 0.89 (s, 3H), 0.88 (s, 3H) ppm. ^{13}C NMR: δ 208.0, 207.8, 145.8, 145.6, 139.4, 136.3, 136.2, 134.1, 133.6, 130.0, 129.9, 128.4, 127.9, 127.8, 127.7, 127.5, 112.7, 82.8, 82.6, 74.1, 74.0, 73.9, 51.1, 50.9, 46.0, 45.8, 35.8, 27.2, 26.4, 26.3, 19.6, 17.5, 17.4 ppm. IR (neat): 3070, 2956, 2859, 1714, 1106, 1067, 736, 700cm^{-1}.

4-(But-3-en-1-oxydiisopropylsilyloxy)-7-hydroxy-8,8-dimethyl-non-8-ene-5-one (82). To a solution tetramethylpiperidine (60 μL, 0.36 mmol) in dry THF (1.5 mL) cooled to –78 °C was added *n*-BuLi (222 μL, 0.36 mmol, 1.6 M solution in hexanes). After stirring at –78 °C for 10 min a solution of the ketone **66d** (106 mg, 0.36 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 90 min before pivaldehyde (58 μL, 0.53 mmol) was added dropwise, and the solution was stirred at –78 °C for a further 30 min before being quenched with water. The solution was then extracted twice with Et_2O and the organic extracts washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residual oil was purified by gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc) to give **82** (80 mg, 59%) as a colourless oil. Spectral data reported for the racemic product. ^{1}H NMR: δ 5.84 (m, 2H), 5.12 (m, 4H), 4.83 (m, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 2.93 (d, *J* = 3Hz, 1H), 2.78 – 2.52 (m, 4H), 2.33 (dt, *J* = 13.5, 6.6 Hz, 2H), 1.04 (s, 6H), 1.03 (s, 6H), 1.00 (m, 2H), 0.92 (s, 9H) ppm. ^{13}C NMR: δ 210.8, 139.9, 135.3, 116.5, 114.8, 114.7, 74.6, 70.0, 69.9, 62.6, 52.0, 51.8, 46.0, 45.8, 37.2, 34.1, 34.0, 25.6, 17.4, 17.3, 17.1, 17.0, 12.2 ppm. IR (neat): 3500, 2946, 2868, 1707, 1092, 1094, 885, 691cm-^{1}.

(8*Z*)-7,11-*O*-diisopropylsilanediyl-3-hydroxy-2,2-dimethyl-undec-8-ene-5-one (81d). **Strategy A.** To a solution of diene **82d** (60 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[benzylidine]ruthenium (IV) dichloride **(62)** (13 mg, 0.016 mmol) and the reaction stirred for 8 h at room temperature. The solvent was then removed under reduced pressure and the resultant brown oil purified rigorously three times by flash chromatography (10:1 hexanes:EtOAc) to give **81d** (43 mg, 77%) as a colourless oil. Spectral data is reported for the racemic product. ^{1}H NMR: δ 5.71 (m, 2H), 4.93 (m, 1H), 3.88 (m, 2H) 3.71 (m, 1H), 3.05 (d, *J* = 3.3 Hz, 1H), 3.00 (d, *J* = 3.0 Hz, 1H), 2.87 – 2.32 (m, 6H), 1.00 (m, 14H), 0.91 (s, 3H) ppm. ^{13}C NMR: δ 211.8, 211.7, 135.1, 135.0, 129.5, 129.4, 75.1, 74.7, 67.1, 67.0, 63.7, 51.3, 51.2, 46.5, 46.2, 34.3, 31.1, 25.0, 17.7, 17.6, 17.5, 12.7, 12.5 ppm. IR (neat): 3502, 2945, 2869, 1706, 1112, 1064, 1004, 695 cm-^{1}.

(8*Z*)-7,11-*O*-diisopropylsilanediyl-3-hydroxy-2,2-dimethyl-undec-8-ene-5-one (81d). Strategy B. To a solution of tetramethylpiperidine (143 μL, 0.85 mmol) in dry THF (3 mL) cooled to –78°C was added *n*-BuLi (529 μL, 0.86 mmol, 1.6M solution in hexanes). After stirring at –78 °C for 10 min a solution of *bis*-silyl ether **65d** (229 mg, 0.86 mmol) in THF (3 mL) was added dropwise. Stirring was continued for 45 min before pivaldehyde (110 μL, 1.02 mmol) was added dropwise and the resultant solution stirred for a further 15 min before being quenched by the addition of water. The solution was then extracted twice with Et_2O and the organic extracts washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The residual product was purified by flash chromatography (10:1 hexanes:EtOAc) to give **81d** (90 mg, 30%, unoptimised) as a colourless oil. Spectral data matched that reported above.

9.6: Experimental for Chapter 6:

(*R*)-4-Hydroxy-5-methyl-5-hexen-2-one (24). L-proline (438 mg, 3.76 mmol) was added to a solution of DMSO:acetone (4:1) (125 mL) and the resulting suspension stirred for 15 min at room temperature. Freshly distilled methacrolein (1.04 mL, 12.5 mmol) was then added. After being stirred at room temperature overnight, the resulting yellow solution was quenched with satd. aq. NH_4Cl, extracted twice with Et_2O and the organic extracts washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residual oil purified by flash chromatography on a silica gel column neutralised with 0.01% Et_3N (3:1 hexanes:EtOAc) to give **24** (611 mg, 38%) which was used immediately.[203] The enantiomeric excess of this reaction was determined by silylation followed by chiral GC analysis, as detailed below.

(*R*)-4-*tert*-Butyldimethylsilyl-5-methyl-hex-5-en-2-one. To a solution of the β-hydroxy ketone **24** (200 mg, 1.56 mmol) in DMF (3 mL) was added *tert*-butyldimethylsilyl-chloride (259 mg, 1.72 mmol) and imidazole (212 mg, 3.12 mmol). After stirring at room temperature for 24 h, the solution was quenched with water, extracted twice with Et_2O, and the organic extracts washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography (50:1 hexanes: EtOAc) to give (*R*)-4-*tert*butyldimethylsilyl-5-methyl-hex-5-en-2-one (202 mg); 74% ee determined using a 60 m x 0.25 mm Cyclodex-B™ column and the following conditions: Inlet: Split 275°C; Detector: FID 320°C; Carrier gas: hydrogen; Flow: 35.8 cm^3s^{-1}; Temperature programme: Isothermal at 75°C. ^1H NMR:δ 4.95 (s, 1H), 4.78 (s, 1H), 4.54 (dd, J = 8.4, 3.9 Hz, 1H), 2.74 (dd, J = 14.7, 8.7 Hz, 1H), 2.39 (dd, J = 18.3, 3.9, Hz, 1H), 2.16 (s, 3H), 1.69, (s, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00, (s, 3H) ppm. ^{13}C NMR: δ 207.8, 147.0, 111.5, 73.7, 50.6, 32.0, 26.0, 18.3, 17.46, -4.6, -5.1 ppm. IR (neat): 2930, 2857, 1360, 1718, 1251, 1074, 835, 776 cm^{-1}. HRMS: Calcd for $C_{13}H_{27}O_2Si$ 243.1774 ($M + H^+$). Found. 243.1780.

Representative procedure for aldol reactions

To a stirred solution of Cy_2OBTf or (—)-Ipc_2BCl (1.5 mmol) in 4 mL of anhydrous Et_2O at –78 °C or 0 °C respectively, was slowly added Et_3N (1.7 mmol). A solution of the ketone (1 mmol) in Et_2O (4 mL) was then added via cannula. The reaction mixture was stirred for 30 minutes, before being cooled to –78 °C (if necessary) at which point pivaldehyde (2 mmol) was added slowly dropwise. The solution was stirred at –78 °C for 2 h then for 10 h at –20 °C before being quenched at –20 °C by the addition of pH 7 buffer solution, methanol and hydrogen peroxide (30% solution). The solution was then stirred at room temperature for 3 h before being extracted twice with Et_2O. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc) gave the aldol adducts as colourless oils.

3-(3-Butenoxydiisopropylsilyloxy)-7-hydroxy-2,8,8-trimethyl-non-1-ene-5-one (90a/91a). (Entry 1, table 4): Reaction of **66a** (50 mg, 0.16 mmol) with (–)-Ipc_2BCl gave **90a/91a** in 93% (59 mg), ds = 2.2:1. Spectral data is reported for the combined diastereomers. ^{1}H NMR: δ 5.86 (m, 1 H), 5.06 (m, 2H), 5.00 (s, 1H), 4.84 (s, 1H), 4.78 (t, J = 6.3 Hz, 1H), 3.74 (m, 2H), 2.79 – 2.44 (m, 4H), 2.31 (dt, J = 13.5, 6.9 Hz, 2H), 1.75 (s, 3H), 1.03 (m, 14H), 0.92 (s, 9H) ppm. ^{13}C NMR: δ 211.2, 211.1, 146.4, 135.5, 116.6, 112.0, 111.9, 74.9, 74.8, 72.9, 62.9, 50.8, 50.7, 46.2, 46.1, 37.5, 34.3, 26.0, 25.9, 17.6, 17.5, 17.3, 12.5, 12.4 ppm. IR (neat): 3530, 2948, 2868, 1709, 1101, 909 cm^{-1}. HRMS: Calcd. for $C_{22}H_{42}O_4SiNa$ 421.2734 ($M + Na^+$). Found: 421.2744.

3-(3-Butenoxydiisopropylsilyloxy)-7-hydroxy-2,8,8-trimethyl-non-1-ene-5-one (90a/91a). (Entry 2, table 4). Reaction of **(66a)** (50 mg, 0.16 mmol) with Cy_2BOTf gave **90a/91a** in 97% (61 mg), ds = 1.2:1.

3-(3-Butenoxydiphenylsilyloxy)-7-hydroxy-8,8-dimethylnon-1-ene-5-one (90b/91b). (Entry 3, table 4). Reaction of **66b** (62 mg, 0.17 mmol) with (–)-Ipc_2BCl gave **90b/91b** in 98% (75 mg), ds = 2:1. Spectral data is reported for the combined diastereomers. ^1H NMR: δ 7.65 (m, 2H), 7.43 (m, 3H), 5.89 (m, 2H), 5.25 (m, 4H), 4.84 (dd J = 12.0, 6.0 Hz, 1H), 3.81 (t, J = 12 Hz, 1H), 3.69 (m, 1H), 2.9 – 2.4 (m, 4H), 2.35 (dt, J = 15.0, 6.9 Hz, 2H), 0.88 (s, 9H) ppm. ^{13}C NMR: δ 210.6, 210.5, 139.3, 135.3, 135.2, 132.8, 132.7, 130.7, 130.6, 128.1, 128.0, 116.9, 115.6, 75.0, 70.7, 63.0, 51.8, 51.6, 45.9, 45.7, 37.1, 34.4, 34.3, 25.9. IR (neat): 3517, 3073, 2954, 2875, 1707, 1125, 1115, 1086, 741, 720, 698 cm^{-1}. HRMS: Calcd for $C_{27}H_{36}O_4SiNa$ 475.2267 ($M + Na^+$). Found: 475.2275.

4-(3-Butenoxydiisopropylsilyloxy)-7-hydroxy-8,8-dimethyl-non-8-ene-5-one (92a/93a). (Entry 4, table 4). Reaction of **65a** (71 mg, 0.26 mmol) with Cy_2BOTf gave **192a/93a** in 85% (79 mg), ds = 2:1. Spectral data reported for the racemic product. ^1H NMR: δ 5.84 (m, 2H), 5.12 (m, 4H), 4.83 (m, 1H), 3.78 (t, J = 6.6 Hz, 2H), 2.93 (d, J = 3Hz, 1H), 2.78 – 2.52 (m, 4H), 2.33 (dt, J = 13.5, 6.6 Hz, 2H), 1.04 (s, 6H), 1.03 (s, 6H), 1.00 (m, 2H), 0.92 (s, 9H) ppm. ^{13}C NMR: δ 210.8, 139.9, 135.3, 116.5, 114.8, 114.7, 74.6, 70.0, 69.9, 62.6, 52.0, 51.8, 46.0, 45.8, 37.2, 34.1, 34.0, 25.6, 17.4, 17.3, 17.1, 17.0, 12.2 ppm. IR (neat): 3500, 2946, 2868, 1707, 1092, 1094, 885, 691cm-^{1}.

(3*RS*,7*R*,8*Z*)-7,11-*O*-diisopropylsilanediyl-3-hydroxy-2,2,8-trimethyl-undec-8-ene-5-one (92b/93b). (Entry 5, table 4) Reaction of **65b** (106 mg, 0.37 mmol) with (–)-Ipc_2BCl gave **92b/93b** in 88% (120 mg), ds = 1.5:1. Spectral data reported for one diastereomer, separated by flash chromatography. ^1H NMR: δ 5.43 (t, J = 8.7 Hz, 1H), 4.89 (dd, J = 9.6, 3.3, Hz, 1H), 3.85 (m, 2H), 3.00 – 2.48 (m, 5H), 2.22 (m, 1H), 1.75 (s, 3H), 1.02 (m, 14H), 0.93 (s, 9H) ppm. ^{13}C NMR: δ 211.9, 140.5, 125.0, 74.7, 71.2, 64.3, 49.5, 46.4, 34.3, 30.8, 25.9, 21.2, 17.7, 17.6, 17.5, 17.4, 12.8, 12.5 ppm. IR (neat): 3479, 2954, 2868, 1709, 1114, 1006, 940, 733, 696 cm^{-1}. HRMS: Calcd for $C_{20}H_{39}O_4Si$ 371.2602 ($M + H^+$). Found: 371.2612.

(3*RS*,7*R*,8*Z*)-7,11-*O*-diisopropylsilanediyl-3-hydroxy-2,2,8-trimethylundec-8-ene-5-one (92b/93b). (Entry 6, table 4) Reaction of **65b** (30 mg, 0.11 mmol) with Cy_2BOTf gave **92b/93b** in 95% (37 mg), ds = 1.2:1. Spectral data matched that reported above.

(3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-3-hydroxy-2,2,8-trimethylundec-8-ene-5-one (92c). (Entry 7, table 4) Reaction of **65c** (100 mg, 0.28 mmol) with (–)-Ipc_2BCl gave **92c** in 94% (115 mg), ds = 99>1. ^{1}H NMR: δ 7.61 (m, 4H), 7.38 (m, 6H), 5.44 (t, *J* = 9.6 Hz, 1H), 4.90 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.06 (m, 2H), 3.76 (dd, *J* = 10.5, 1.8 Hz, 1H), 2.99 (dd, *J* =14.9, 9.8 Hz, 1H), 2.91 (m, 1H), 2.76 (dd, *J* = 17.8, 1.8 Hz, 1H), 2.62 (dd, *J* = 14.7, 3.6 Hz, 1H), 2.58 (dd, *J* = 17.7, 10.2 Hz, 1H), 2.28 (m, 1H), 1.61 (s, 3H), 0.89 (s, 9H) ppm. ^{13}C NMR: δ 211.5, 140.7, 134.8, 134.7, 133.6, 133.3, 130.5, 130.4, 128.1, 74.8, 71.9, 64.3, 49.5, 46.1, 34.3, 30.9, 25.9, 21.5 ppm. IR (neat): 3480, 3070, 2955, 2873, 2247, 1706, 1116, 1073, 909, 730, 716, 699 cm^{-1}. HRMS: Calcd for $C_{26}H_{34}O_4SiNa$ 461.2120 (M + Na$^+$). Found: 461.2119.

(3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-3-hydroxy-2,2,8-trimethylundec-8-ene-5-one (92c). (Entry 8, table 4). (Unoptimised). Reaction of **65c** (127 mg, 0.36 mmol) with Cy_2BOTf gave **92c** in 68% (108 mg), ds = 99>1. Spectral data matched that reported above.

(3*R*,7*R*,8*Z*)-7,11-*O*-diphenylsilanediyl-3-hydroxy-2,2-dimethylundec-8ene-5-one (92d). (Entry 9, table 4). (Unoptimised). Reaction of **92d** (114 mg, 0.34 mmol) with (–)-Ipc_2BCl gave **19d** in 60% (86 mg), ds = 99>1. ^{1}H NMR: δ 7.64 (m, 4H), 7.40 (m, 6H), 5.74 (m, 2H), 5.14 (m, 1H), 4.09 (m, 1H), 3.94 (m, 1H), 3.74 (d, *J* = 10.2, Hz, 1H), 3.03 – 2.39 (m, 6H), 0.88 (s, 9H) ppm. ^{13}C NMR: δ 211.2, 135.0, 134.7, 133.5, 133.4, 130.6, 130.4, 129.4, 128.2, 128.1, 74.8, 67.6, 63.7, 51.3, 46.1, 34.3, 31.0, 25.9 ppm. IR (neat): 3509, 3019, 2959, 2873, 1709, 1125, 1070, 723 cm^{-1}. HRMS: Calcd. for $C_{25}H_{32}O_4SiNa$ 447.1961 (M + Na$^+$). Found: 447.1962.

9.7. Experimental for chapter 7:

Representative procedure for the synthesis of the tert-butyldiphenylsiloxy ketones

To a solution of the β-hydroxyketone (1 mmol) in DMF (1.5 mL) was added *tert*-butyldiphenylsilylchloride (1.1 mmol) and imidazole (2 mmol). After stirring at room temperature for 24 h the solution was quenched with water then extracted twice with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography, (50:1 hexanes:EtOAc) to give the silylated adducts as colourless oils.

(4*R*)-4-*tert*-Butyldiphenylsiloxy-5-methylhexan-2-one (95a). 4-hydroxy-5-methyl-hexane-2-one **(94a)** (646 mg, 5.0 mmol) gave **95a** (1.32 g, 72% yield). ^{1}H NMR: δ 7.70 (m, 4H), 7.42 (m, 6H), 4.18 (m,1H), 2.56 (dd, *J* = 15.9, 6.6 Hz, 1H), 2.42 (dd, *J* = 15.9, 5.4 Hz, 1H), 1.88 (s, 3H), 1.72 (m, 1H), 1.06 (s, 9H), 0.94 (d, *J* = 6.6 Hz), 0.81 (d, J = 6.9 Hz) ppm. ^{13}C NMR: δ 207.6, 136.3, 1362, 134.5, 134.3, 129.9, 127.8, 127.7, 73.9, 47.8, 33.7, 30.8, 27.3, 19.8, 18.0, 17.5 ppm. IR (neat): 3072, 2960, 2932, 2857, 1715, 1660, 1110, 1068, 740, 703cm^{-1}. HRMS: Calcd for $C_{23}H_{33}O_2Si$ 369.2305 (M + H$^+$). Found: 369.2245.

(*R*)-4-*tert*-Butyldiphenylsiloxy-5-methylhex-5-en-2-one (95c). 4-hydroxy-5-methylhex-5-ene-2-one **(94c)** (546 mg, 4.2 mmol) gave 1.15 g (75%) of **95c**. ^{1}H NMR: δ 7.65 (m, 4H), 7.38 (m, 6H), 4.78 (s, 1H), 4.72 (s, 1H), 4.59 (t, *J* = 6 Hz, 1H), 2.61 (dd, *J* = 14.7, 6.0 Hz,1H), 2.52 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.10 (s, 3H), 1.68 (s, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR: δ 206.8, 145.8, 136.2, 134.1, 133.7, 130.0, 128.0, 127.8, 127.7, 112.6, 74.1, 50.8, 31.1, 27.2, 19.6, 17.4 ppm. IR (neat): 3072, 2931, 2857, 1713, 1427, 1360, 1162, 1106, 1063, 739, 700 cm^{-1}. HRMS: Calcd. for $C_{23}H_{30}O_2SiNa$ 389.1922 (M + Na$^+$). Found: 389.1907.

Representative procedure for aldol reactions

All aldol reactions reported in this section were conducted in the following manner: To a stirred solution of Cy_2BCl (1.5 mmol) in anhydrous Et_2O (4 mL) at 0 °C was slowly added Et_3N (1.7 mmol). A solution of the ketone (1 mmol) in Et_2O (2 mL) was then added via cannula. The reaction mixture was stirred at 0 °C for 30 min before being cooled to –78 °C at which point the aldehyde (1.5 mmol) was slowly added dropwise. The solution was then stirred at –78 °C for 5-6 h, before being quenched at –78 °C by the addition of pH 7 buffer solution, methanol and hydrogen peroxide (30% solution). The solution was stirred at room temperature for 2.5 h then extracted twice with Et_2O. The organic extracts were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by gradient flash chromatography (50:1 to 10:1 hexanes:EtOAc) gave the aldol adducts as colourless oils.

(3*RS*,7*R*)-7-*tert*-Butyldiphenylsiloxy-3-hydroxy-2,2,8-trimethylnonan-5-one (96a). The aldol reaction of **95a** (201 mg, 0.52 mmol) with pivaldehyde gave **96a** (201 mg, 88% yield), ds = 2:1. Spectral data reported for one diastereomer, separated by flash chromatography. ^{1}H NMR: δ 7.74 (dd, *J* = 7.2,1.2 Hz, 2H), 7.68 (dd, *J* = 7.5,1.2 Hz, 2H), 7.42 (m, 6H), 4.20 (m, 1H), 3.52 (dd, *J* = 9.0, 2.1 Hz, 1H), 2.61 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.43 (dd, *J* = 16.2, 4.8 Hz, 1H), 2.28 (m, 2H), 1.73 (m, 1H), 1.06 (s, 9H), 0.95 (d, *J* = 6.3 Hz, 3H), 0.86 (bs, 6H), 0.81 (d, J = 6.6 Hz) ppm. ^{13}C NMR: δ 211.3, 136.3, 136.2, 134.6, 134.1, 129.9, 127.8, 74.7, 73.6, 47.7, 45.2, 34.2, 33.7, 27.3, 25.9, 19.7, 17.9, 17.6 ppm. IR (neat): 3502, 3072, 2957, 2858, 1709, 1110, 1057, 823, 702 cm^{-1}. HRMS: Calcd for $C_{28}H_{42}O_3SiNa$ 477.2854 (M + Na^+). Found: 477.2796.

(3*RS*,7*R*)-7-*tert*-Butyldiphenylsiloxy-3-hydroxy-2,8-dimethylnonan-5-one (96b). The aldol reaction of **95a** (119 mg, 0.32 mmol) and isobutylaldehyde gave **96b** (125 mg, 86% yield), ds = 2.5:1. Spectral data reported for one diastereomer (separated by flash chromatography). ^{1}H NMR: δ 7.69 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.63 (dd, *J* = 7.8,1.5 Hz,

2H), 7.37 (m, 6H), 4.16 (m, 1H), 3.55 (dt, J = 11.7, 6.0 Hz, 1H), 2.79 (bs, 1H), 2.55 - 2.24 (m, 4H), 1.68 (m, 1H), 1.54 (m, 1H), 1.02 (s, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz) ppm. ^{13}C NMR: δ 211.2, 136.3, 136.2, 134.6, 134.1, 130.0, 129.8, 127.8, 127.7, 73.6, 72.0, 47.6, 47.1, 33.7, 33.0, 27.3, 19.7, 18.6, 18.0, 17.9, 17.6 ppm. IR (neat): 3478, 3072, 2929, 2932, 2859, 1707, 1109, 1006, 760, 701cm^{-1}. HRMS: Calcd for $C_{27}H_{40}O_3SiNa$ 463.2653 (M + Na^+). Found: 463.2638.

(3*RS*,7*R*)-7-*tert*-Butyldiphenylsiloxy-2,8-dimethyl-3-hydroxynona-1-8-diene-5-one (96c). The aldol reaction of **95c** (453 mg, 1.23 mmol) with methacrolein gave **96c** (505 mg, 89% yield), ds = 1.2:1. Spectral data reported for the combined diastereomers. ^{1}H NMR: δ 7.67 (m, 4H), 7.40 (m, 6H), 4.95 (s, 1H), 4.83 (bs, 2H), 4.77 (s, 1H), 4.61 (m, 1H), 4.32 (m, 1H), 3.90 (bs, 1H), 2.73 – 2.2.40 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.07 (s, 9H). ^{13}C NMR: δ 209.5, 145.7, 136.2, 136.1, 134.1, 133.5, 130.1, 130.0, 127.9, 127.8, 112.7, 111.4, 73.8, 73.7, 70.9, 50.5, 49.0, 48.8, 27.2, 19.6, 18.6, 18.5, 17.5 ppm. IR (neat): 3450, 3073, 2932, 2858, 1709, 1111, 1072, 822, 702, 612 cm^{-1}. HRMS: Calcd for $C_{27}H_{37}O_3Si$: 437.2528 (M + H^+). Found: 437.2507.

Representative procedure for the synthesis of the dimethylphenylsiloxy ketones

To a solution of the β-hydroxyketone (1 mmol) in DMF (1.5 mL) was added dimethylphenylsilylchloride (1.1 mmol) and imidazole (2.2 mmol). After stirring at room temperature for 24 h, the solution was quenched with water then extracted twice with Et_2O. The organic extracts were washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by flash chromatography (20:1 hexanes:EtOAc) to give the silylated adducts as colourless oils.

(*R*)-4-Dimethylphenylsiloxy-5-methyl-hexan-2-one (97a). Silylation of (*R*)-4-hydroxy-5-methyl-hexan-2-one **(94a)** (450 mg, 3.48 mmol) gave **97a** (682 mg, 74% yield) after purification by flash chromatography. ^{1}H NMR: δ 7.57 (m, 2H), 7.34 (m, 3H), 4.06 (ddd, *J* = 12.3, 8.1, 3.9 Hz, 1H), 2.60 (d, *J* = 15.6, 8.1 Hz, 1H), 2.36 (dd, *J* = 15.6, 3.9 Hz, 1 H), 2.14, s (3H), 1.66 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.37 (s, 3H), 0.36 (s, 3H) ppm. ^{13}C NMR: δ 207.9, 138.2, 133.3, 129.3, 127.6, 73.5, 47.3, 33.6, 31.2, 17.7, 17.5, -1.3, -1.4 ppm. IR (neat): 3071, 2960, 1717, 1357, 1250, 1117, 1079, 1051, 829, 782, 699 cm^{-1}.

(4*R*)-4-Dimethylphenylsiloxy-5-methylhex-5-en-2-one (97b). Silylation of (4*R*)-4-hydroxy-5-methylhex-5-en-2-one **(94a)** (250 mg, 1.95 mmol) gave **97b** (404 mg, 72% yield) as a colourless oil after purification by flash chromatography. ^{1}H NMR: δ 7.55 (m, 2H), 7.36 (m, 3H), 4.90 (s, 1H), 4.77 (s, 1H), 4.57 (dd, *J* = 8.7, 3.9 Hz, 1H), 2.75 (dd, *J* = 14.7, 8.7 Hz, 1H), 2.42 (dd, *J* = 14.7, 3.9 Hz, 1H), 2.10 (s, 3H), 1.67 (s, 1H), 0.36 (s, 3H), 0.35 (s, 3H) ppm. ^{13}C NMR: δ 206.9, 146.1, 137.5, 133.3, 129.4, 127.5, 111.4, 73.2, 50.0, 31.1, 17.2, -1.5, -1.8 ppm; IR (neat): 3072, 2958, 1714, 1251, 1162, 1070, 830, 814, 783, 699 cm^{-1}. HRMS: Cald for $C_{15}H_{22}O_2NSi$ 280.1719 (M + NH_4^+). Found: 280.1727.

(3*RS*,7*R*)-3-Hydroxy-2,2,8-trimethyl-7-dimethylphenylsiloxy-nonane-5-one (98a). The aldol reaction of ketone **97a** (100 mg, 0.38 mmol) with pivaldehyde gave the corresponding aldol adduct **98a** (106 mg, 80% yield), ds: 1:1.1. Spectral data reported for one diastereomer (separated by flash chromatography). ^{1}H NMR: δ 7.58 (m, 2H), 7.38 (m, 3H), 4.10 (ddd, *J* = 9.0, 8.4, 3.6 Hz, 1H), 3.63 (dd, *J* = 10.4, 1.9 Hz, 1H), 2.71 – 2.31 (m, 4H), 1.68 (m, 1H), 0.88 (s, 9H), 0.84 (m, 6H), 0.39 (s, 6H) ppm. ^{13}C NMR: δ 212.3, 138.2, 133.5, 130.0, 127.7, 74.9, 73.7, 47.1, 45.8, 34.1, 33.6, 25.6, 17.9, 17.5, -1.2, -1.4 ppm. IR (neat): 3500, 2959, 2905, 2873, 1709, 1252, 1117, 1056, 829, 785, 744, 700 cm^{-1}.

(3*RS*,7*R*)-3-Hydroxy-2,8-dimethyl-7-dimethylphenylsiloxynona-1,8-dien-5-one (98b). The aldol reaction of ketone **97b** (100 mg, 0.38 mmol) with methacrolein gave the corresponding aldol adduct **98b** (104 mg, 82% yield), ds: 1:1.1. Spectral data reported for the combined diastereomers. ^{1}H NMR: δ 7.59 (m, 2H), 7.40 (m, 3H), 5.00 (d, *J* = 0.6Hz, 1H), 4.94 (s, 1H), 4.86 (s, 1H), 4.81 (t, *J* = 1.2 Hz, 1H), 4.61 (m, 1H), 4.45 (t, *J* = 6.3 Hz, 1H), 2.85 – 2.41 (m, 4H), 1.72 (d, *J* = 3.6 Hz, 3H), 1.69 (s, 3H), 0.40 (s, 6H), 0.39 (s, 3H), 0.38 (s, 3H) ppm; ^{13}C NMR: δ 210.4, 210.3, 146.4, 146.3, 145.8, 133.8, 133.3, 130.0, 129.9, 128.1, 128.0, 112.2, 112.1, 111.4, 73.7, 71.3, 71.0, 50.3, 50.2, 49.7, 49.6, 18.6, 18.5, -1.0, - 1.1, -1.5 ppm. IR (neat): 3420, 3072, 2958, 1708, 1251, 1117, 1071, 829, 784, 700 cm^{-1}. HRMS: Cald for $C_{19}H_{32}NO_3Si$ 350.2135 (M + NH_4^+). Found: 350.2146.

(*R*)-4-Benzyloxy-5-methyl-hexan-2-one (99). To a solution of *(R)*-4-hydroxy-5-methyl-hexane-2-one (240 mg, 1.86 mmol) in 6 mL of CH_2Cl_2:cyclohexane (2:1) cooled to 0 °C was added benzyl trichloroacetimidate **(79)** (345 μl, 1.86 mmol) followed by freshly distilled trifluoromethanesulfonic acid (33 μl, 0.37 mmol) dropwise. The appearance of a cream precipitate was immediately observed and the resulting mixture stirred at room temperature for 30 min before being quenched with water (5 mL). The solution was then extracted twice with hexanes and the organic extracts washed with satd. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography (20:1 hexanes:EtOAc) gave **99** (216 mg, 60%) as a colourless oil. ^{1}H NMR: δ 7.33 (m, 5H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J*= 11.4 Hz, 1H), 3.83 (m, 1H), 2.71 (d, *J* = 15.9, 8.4 Hz, 1 H), 4.46 (d, *J* = 15.9, 3.6 Hz, 1H), 2.16 (s, 3H), 1.98 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 6H) ppm. ^{13}C NMR: δ 207.8, 138.4, 128.5, 128.0, 127.4, 127.3, 127.2, 79.9, 71.8, 44.6, 30.9, 30.6, 17.9, 17.2 ppm. IR (neat): 3032, 2960, 2874, 1712, 1355, 1070, 733, 697 cm^{-1}. HRMS: Cald for $C_{14}H_{21}O_2$ 221.1548 (M + H^+). Found: 221.1536.

(3*RS*,7*R*)-7-Benzyloxy-3-hydroxy-2,2,8-trimethylnonan-5-one (100). The aldol reaction of ketone **99** (240 mg, 1.09 mmol) with pivaldehyde gave the corresponding aldol adduct **100** (246 mg, 74% yield), ds: 3:1. Spectral data reported for the combined diastereomers). ^{1}H NMR: δ 7.33 (m, 5H), 4.53 (m, 2H), 3.85 (m, 1H), 3.73 (dd, *J* = 10.2, 1.8 Hz, 1H), 2.79 – 2.42 (m, 4H), 1.98 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 6H), 0.89 (s, 9H) ppm. ^{13}C NMR: δ 212.3, 138.8, 129.2, 128.6, 128.3, 128.2, 128.0, 127.9, 127.8, 80.7, 80.5, 74.9, 72.5, 72.4, 46.2, 45.5, 45.2, 45.1, 34.4, 31.1, 25.9, 18.6, 18.5, 17.7, 17.6 ppm. IR (neat): 3500, 3032, 2959, 2871, 1706, 1067, 734, 697 cm^{-1}. HRMS: Cald for $C_{19}H_{34}NO_3$ 324.2529 (M + NH_4^+) Found:324.2533.

4-(But-1-ene-4-yloxy)-but-3-ene-2-one (105). A 50 mL round bottom flask equipped with stir bar, 8 cm Vigreux column and distillation head was charged with but-3-enol (1.07 mL, 12.49 mmol), 4-methoxybut-3-en-2-one (1.53 mL, 14.98 mmol), pyridinium *p*-toluenesulfonate (31 mg, 0.12 mmol) and toluene (25 mL). The reaction mixture was heated for 4 h at a gentle reflux, allowing for a slow distillation of the methanol-toluene mixture. After cooling the solution to room temperature, the solvent was removed under reduced pressure to give a red/brown oil. The crude material was purified by flash chromatography (10:1 hexanes:EtOAc) to give **105** (1.15 g, 66%) as an orange oil. ^{1}H NMR: δ 7.50 (d, *J* = 12.6 Hz, 1H), 5.76 (m, 1H), 5.55 (d, *J* = 12.6 Hz, 1H), 5.09 (m, 2H), 3.88 (t, *J* = 6.6 Hz, 1H), 2.43 (dt, *J* = 13.2, 6.6, Hz, 2H), 2.14 (s, 3H) ppm. ^{13}C NMR: δ 197.2, 162.3, 133.2, 117.6, 107.1, 70.0, 33.0, 27.6 ppm. IR (neat): 3079, 2947, 1618, 1591, 1202, 1147, 957, 920 cm^{-1}.

1-[(2*S*,4*R*,6*S*)-(6-Allyl-4-(*tert*-butyldimethylsiloxy)tetrahydro-pyran-2-yl]-propan-2-one (109). To a solution of alcohol **108** (200mg, 1.01 mmol) in DMF (3 mL)was added *tert*-butyldimethylsilylchloride (167 mg, 1.11 mmol) and imidazole (137 mg, 2.02 mmol). After stirring at room temperature for 24 h, the solution was quenched with water and

extracted twice with Et_2O. The organic extracts were then washed with brine, dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The residual oil was purified by gradient flash chromatography (hexanes:20:1; hexanxes:EtOAc) to give **109** (300 mg, 95%) as a colourless oil. ^1H NMR: δ 5.07 (m, 1H), 5.03 (m, 2H), 3.75 (m, 2H), 3.35 (m, 1H), 2.71 (dd, *J*= 15.6, 7.8 Hz, 1H), 2.41 (dd, *J* = 15.6, 4.8 Hz, 1 H), 2.26 (m, 1H), 2.17 (s, 3H), 2.16 (m, 1H), 1.80 (m, 2H), 1.20 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H) ppm. ^{13}C NMR: δ 207.7, 134.9, 117.0,75.4, 72.3, 68.6, 49.9, 41.6, 41.1, 40.6, 31.4, 26.0, 18.3, -4.4 ppm. IR (neat): 2929, 2856, 1716, 1251, 1124, 1068, 835, 774 cm^{-1}. HRMS: Cald for $C_{17}H_{33}O_3Si$ 313.2205 ($M + H^+$). Found: 313.2194.

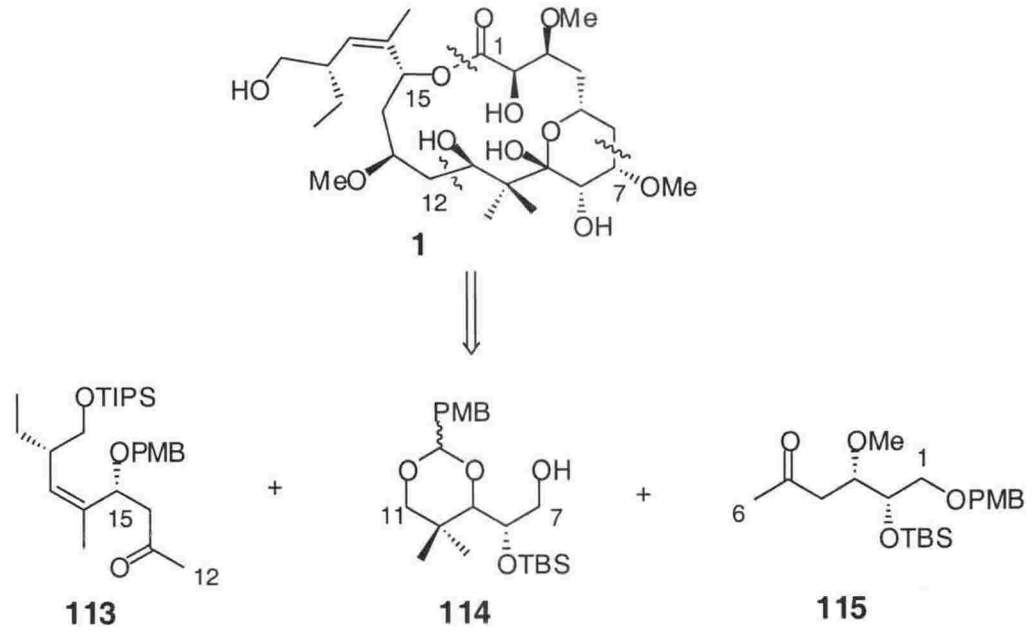
(4*R*)-1-[(2*S*,4*R*,6*S*)-(6-Allyl-4-(tert-butyldimethylsilyloxy)tetrahydro-pyran-2-yl]-4-hydroxy-5,5-dimethylhexan-2-one (110). Reaction of ketone **109** (287 mg, 0.92 mmol) with pivaldehyde gave the corresponding aldol adduct **110** (296 mg, 81%) as a colourless oil; d.s: >95:5. ^1H NMR: δ5.74 (m, 1H), 5.02 (m, 2H), 3.37 (m, 3H), 3.32 (m, 1H), 2.95 (d, *J* = 3Hz, 1H), 2.73 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.65 (m, 1H), 2.46 (dd, *J* = 17.1, 10.5, Hz, 1H), 2.36 (dd, *J* = 15.0, 3.9 1H), 2.22 (m, 1H), 2.14 (m, 1H), 1.77 (m, 2H), 1.19 (m, 2H), 0.88 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H) ppm. ^{13}C NMR: δ 211.2, 134.4, 116.9, 75.1, 74.5, 72.3, 68.3, 49.2, 46.1, 41.3, 40.7, 40.1, 34.1, 25.7, 25.6, 18.0, -4.7 ppm. IR (neat): 3478, 2952, 2857, 1708, 1643, 1071, 835, 774 cm^{-1}. HRMS: Cald for $C_{22}H_{43}O_4Si$ 399.2928 ($M + H^+$) Found: 399.2925.

Appendix

Progress towards the synthesis of peloruside A

The unique biological activity of peloruside A has resulted in this compound being a particularly attractive target for many synthetic chemists. Accordingly, in the past few years, several publications regarding the total or partial synthesis of peloruside A have appeared in the literature. Provided below is a review of those publications that appeared prior to the submission of this thesis.

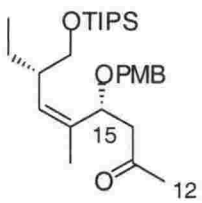
Paterson, Di Francesco and Kühn[206] reported the first partial synthesis of peloruside A in January 2003, and of the strategies reported thus far, this partial synthesis most closely resembles the strategy pursued by Stocker, Teesdale-Spittle and Hoberg.[193] The retrosynthetic disconnects for Paterson's synthesis of peloruside A are depicted in scheme 96. Here peloruside A has been divided into three key segments; the C-12 to C-24 fragment **113**, the C-7 to C-11 fragment **114** and the C-1 to C-6 fragment **115**.



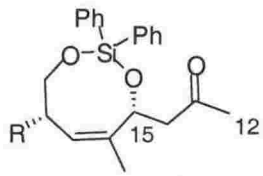
113 **114** **115**

Scheme 96: Paterson, Di Francesco and Kühn's retrosynthesis of peloruside A

The similarity between Paterson's strategy for the synthesis of the C-12 to C-24 fragment of peloruside A and the strategy pursued by Stocker *et. al.* for the synthesis of the similar carbon framework is most noteworthy. These two fragments are reviewed in figure 36.



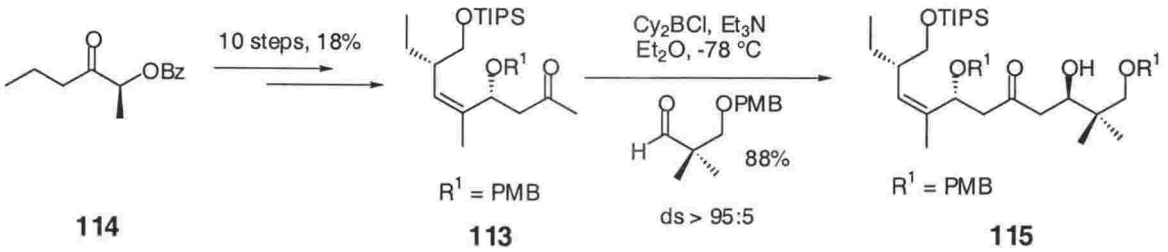
113



22a R = Et
22b R = H

Figure 36: The C-12 to C-24 fragments for Paterson's and Stocker's synthesis of peloruside A

Paterson's synthesis for **113** commences with the (*S*)-lactate-derived ketone **114** - itself synthesised in three steps in a 64% yield, scheme 97. A ten step synthesis is required for the formation of **113** and although the individual yields for each of the ten reactions are excellent, due to the linear nature of this strategy, **113** is synthesised in an overall yield of 18%. In contrast, **22b** is synthesised in four linear steps with an overall yield of 33%. Paterson subsequently utilizes boron mediated 1,5-*anti* aldol methodology to achieve the desired 1,5 *anti*- relationship between C-15 and C-11. However, in contrast to the synthesis developed by Stocker *et. al.*, whereby the cyclic silyl tether of **22** induces 1,5-*anti* induction, Paterson relied upon the more highly precedented PMB protecting group at the ß-position of **113** for diastereoselective induction.



114

R^1 = PMB

113

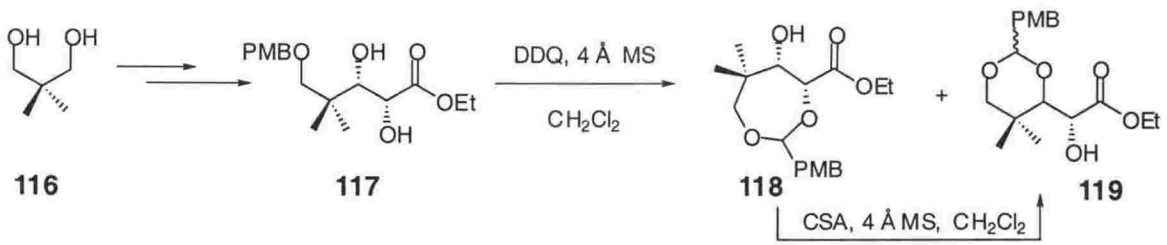
ds > 95:5

R^1 = PMB

115

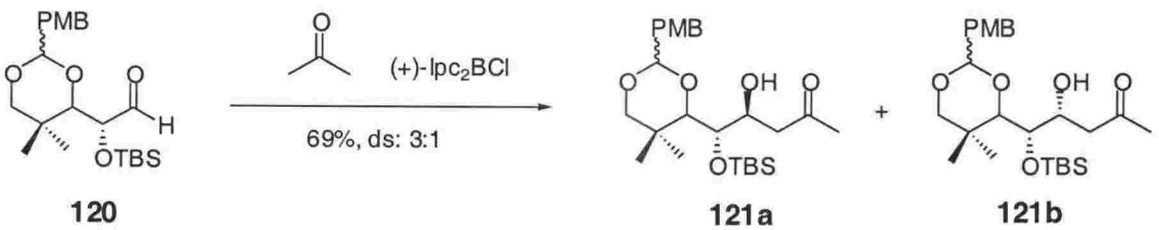
Scheme 97: Paterson, Di Francesco and Kühn's synthesis and aldol studies for the C-12 to C-24 fragment of peloruside A

Paterson's synthesis of the C-12 to C-7 fragment of peloruside A starts with neopentylglycol **116**. Glycal **116** is subjected to mono benzylation, a Swern oxidation, a Horner-Wadsworth Evans homologation and a Sharpless dihydroxylation, to give key intermediate **117**. Perhaps the most interesting feature of this strategy however, was the subsequent DDQ mediated oxidative cyclization of **117** that resulted in an unexpected mixture of PMP acetals **118** and **119**. Fortunately though, equilibration of this mixture of acetals with CSA afforded solely the desired, and thermodynamically more stable, six-membered cyclic acetal **119**.



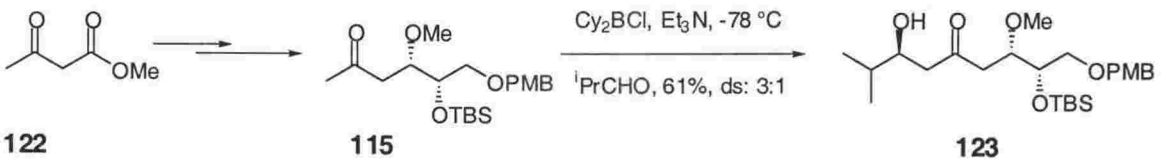
Scheme 98: Paterson, Di Francesco and Kühn's synthesis of the C-11 to C-7 fragment of peloruside A

The protection, reduction and oxidation of **119** gave the key retrosynthetic fragment **120**, which was subsequently subjected to a variety of aldol reactions, with acetone as a model substrate, in order to ascertain which conditions would favour formation of the desired *anti* diastereomer **121a**. (+)-Ipc_2BCl was reported to give the highest, although still rather modest, 3:1 ratio of diastereomers, scheme 99.



Scheme 99: Model aldol studies with key intermediate **120**.

Finally, Paterson's synthesis of the C-6 to C-1 fragment of peloruside A commenced with methylacetoacetate **122**, with the key retrosynthetic fragment **115** being synthesised in 12 steps, yet with an excellent overall yield of 28%, scheme 100. The desired C-2 and C-3 *syn* relationship was established by a Sharpless asymmetric dihydroxylation. Again, a boron-mediated 1,5- *anti* aldol reaction was used to control the diastereoselectivity of the subsequent aldol reaction. As depicted in scheme 100, isopropylaldehyde was used as a model substrate, and although the desired *anti* adduct **123** was synthesised in 61% yield, due to the presence of the methoxy substituent at the ß position, the diastereoselectivities were again, rather modest.



122 **115** **123**

Scheme 100: Synthesis of the C-6 to C-1 fragment of peloruside A and model aldol studies

Shortly following Paterson's fragment synthesis of peloruside A, De Brabander, Liao and Wu published the first, and to date, only total synthesis of peloruside A.[205] Although somewhat of a linear strategy was adopted, which in turn resulted in an overall yield of less than 2%, this was nonetheless elegant work given the complexity of the target molecule. Additionally, by completing the first total synthesis, De Brabander was able to establish the absolute stereochemistry of peloruside A – this being the opposite to that initially reported by West and Northcote.[15]

Only two fundamental disconnects were made by De Brabander in his retrosynthetic analysis, figure 37. It is interesting to note that De Brabander's synthesis of the C-14 to C-24 side chain commenced with the zirconium catalysed ethylmagnesation of 2,5-dihydrofuran **124**, in

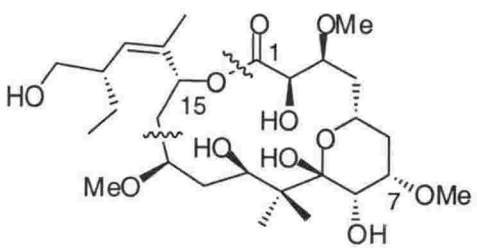
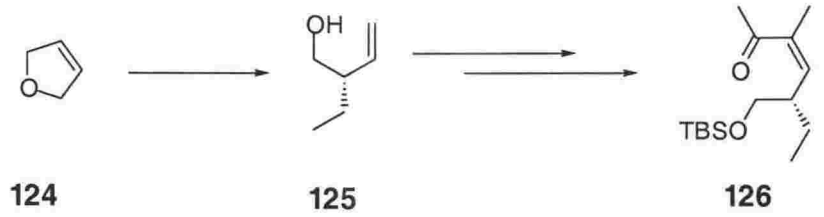


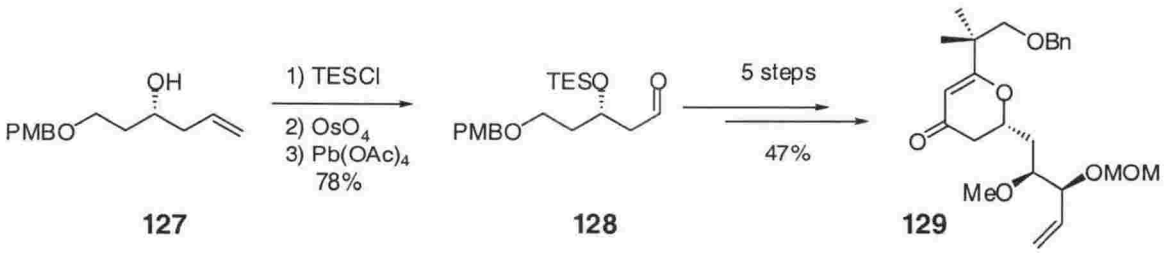
Figure 37: De Brabander's retrosynthesis

much the same manner as that proposed by Stocker *et. al.* The homoallylic alcohol **125** was subsequently acylated with methacryloyl chloride, subjected to RCM (using Grubb's second generation catalyst), the resulting lactone treated with methyl lithium and the ensuing hydroxyl silylated to give **126** in an overall yield of approximately 17%, scheme 101.



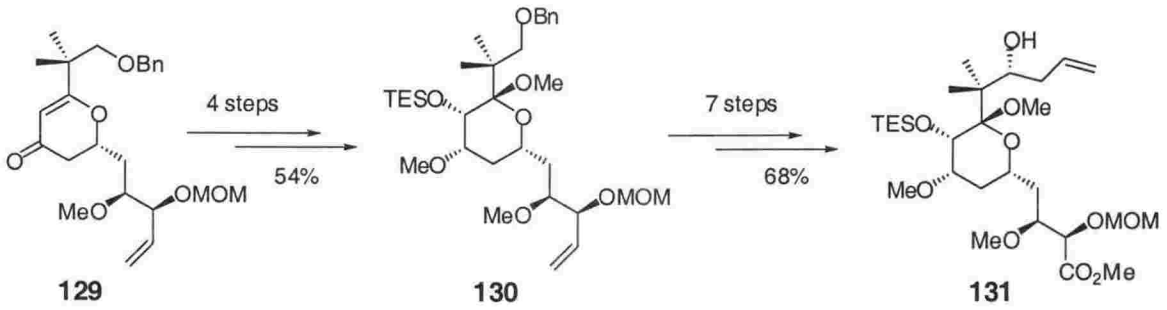
Scheme 101: De Brabander's synthesis of the C-14 to C-24 fragment of peloruside A

De Brabander's synthesis for the remainder of peloruside A began with the silylation and dihydroxylation of the previously reported alcohol **127**, scheme 102. A $Pb(OAc)_4$ assisted cleavage of the ensuing diol then gave alcohol **128**. A five step, linear strategy was then followed to give dihydropyranone **129**, in 47% overall yield.



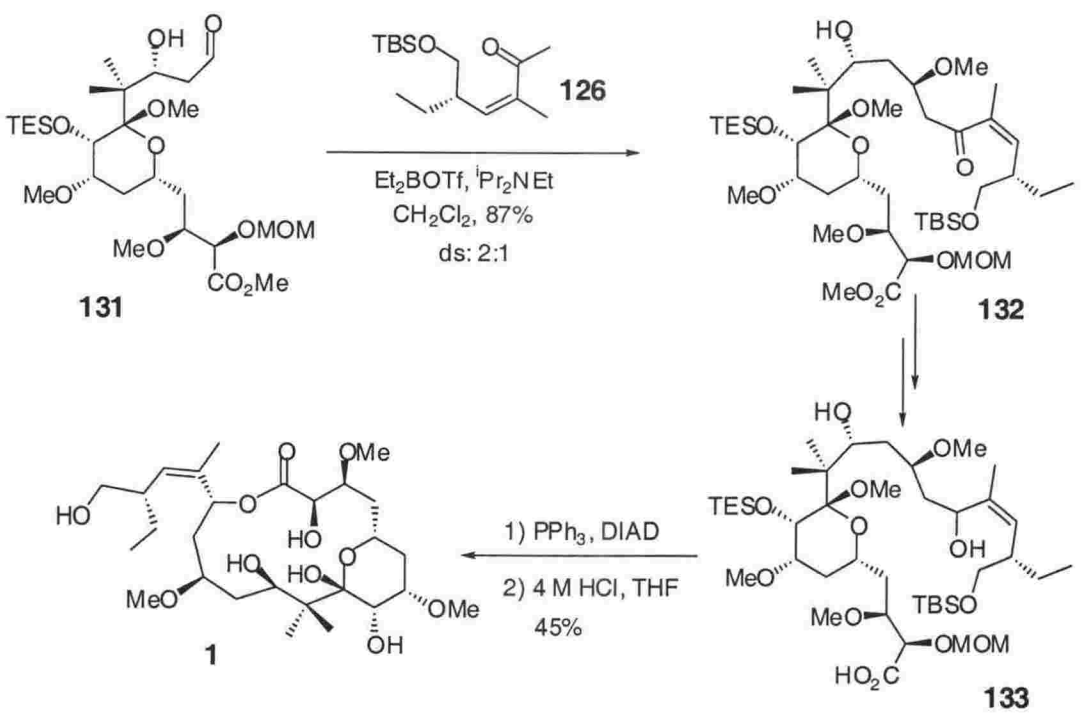
Scheme 102: De Brabander's synthesis of the key intermediate dihydropyranone **129**.

Formation of **129** thus provided a key starting point for establishing the correct stereochemistry of the pyranose ring of peloruside A. A five step strategy involving a Luche reduction, a hydroxyl-directed epoxidation followed by an *in situ* methylation, selective methylation of the ensuing equatorial hydroxyl and finally silylation of the remaining axial hydroxyl gave pyranose **130**, scheme 103. A series of functional group modifications then gave methyl ester **131**.



Scheme 103: De Brabander's synthesis of the key intermediate methyl ester **131**.

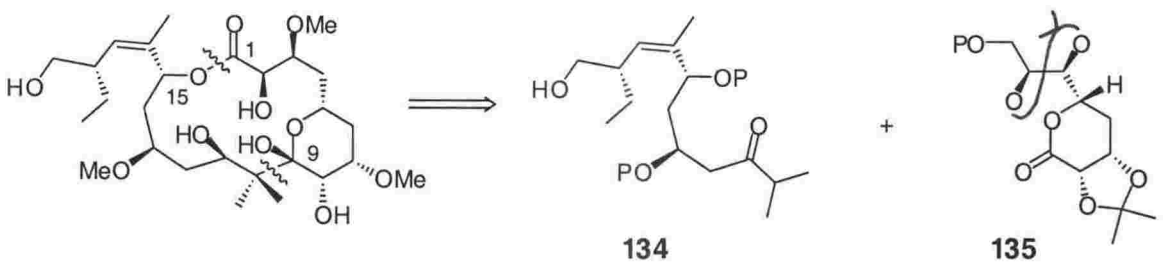
The final transformations required for De Branbander's synthesis of peloruside A first required a diastereoselective aldol reaction with the previously synthesised C-14 to C-24 fragment, scheme 104. Although the aldol reaction of **131** with **126** was rather unselective, the 2:1 ratio of diastereomers was nonetheless welcomed as previous problems had been encountered when attempting to synthesise peloruside by an alternative strategy. It is also interesting to note, that this aldol reaction was conducted in the presence of an unprotected hydroxyl group.



Scheme 104: The final chemical transformations required in De Brabander's total synthesis of peloruside A

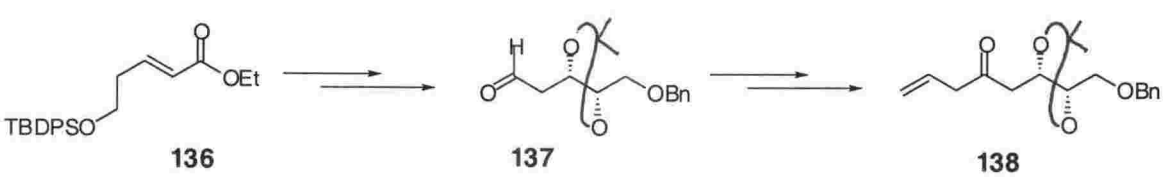
Perhaps the most salient feature of De Brabander's synthesis of peloruside A however, was the final Mitsunobu-type lactonisation, scheme 104. It was found that the same desired lactone was produced, regardless of the stereochemistry at C-15. It was subsequently speculated that geometrical/conformation constraints preclude formation of the C-15 epimeric lactone, forcing the cyclisation to occur via an alkoxyphosphonium intermediate, or the less familiar, acyloxyphosphonium intermediate.

Following De Brabander's total synthesis of peloruside A, Ghosh and Kim reported, in two separate papers, a synthesis for the C-1 to C-9 and C-10 to C-24 fragments of peloruside A.[207, 208] These fragments are highlighted in scheme 105.



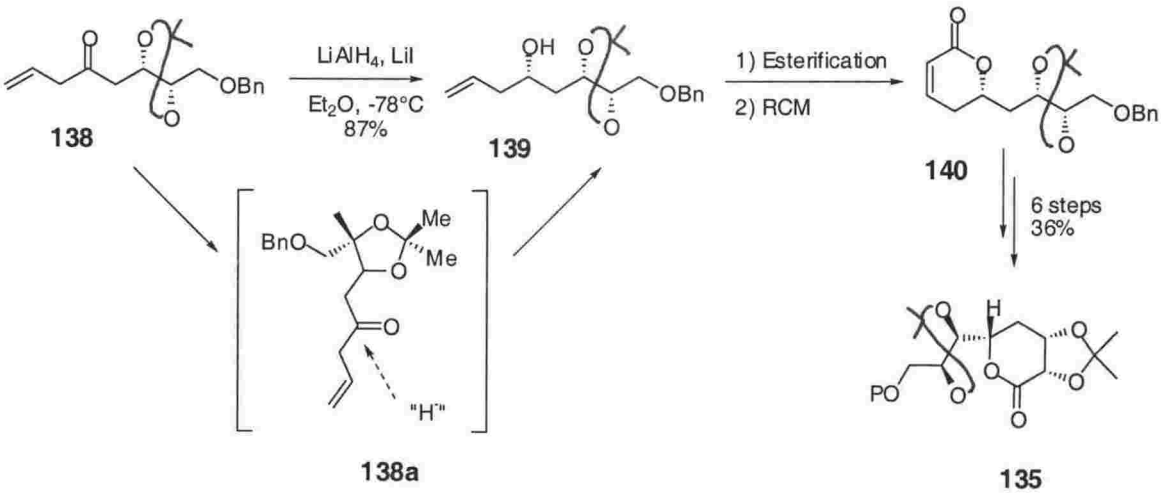
Scheme 105: Ghosh and Kim's retrosynthetic analysis of peloruside A

Of the two aforementioned fragments, synthesis of the C-1 to C-9 fragment **135** was reported first - commencing with the preparation of the α,ß-unsaturated ester **136** using known procedures. After installation of the C-2 to C-3 *syn* relationship using Sharpless asymmetric dihyroxylation methodology, a series of basic functional group transformations lead to aldehyde **137** in a 47% overall yield, scheme 106. Allylation of **137** using allyl magnesium bromide, followed by oxidation of the resulting alcohol gave ketone **138**.



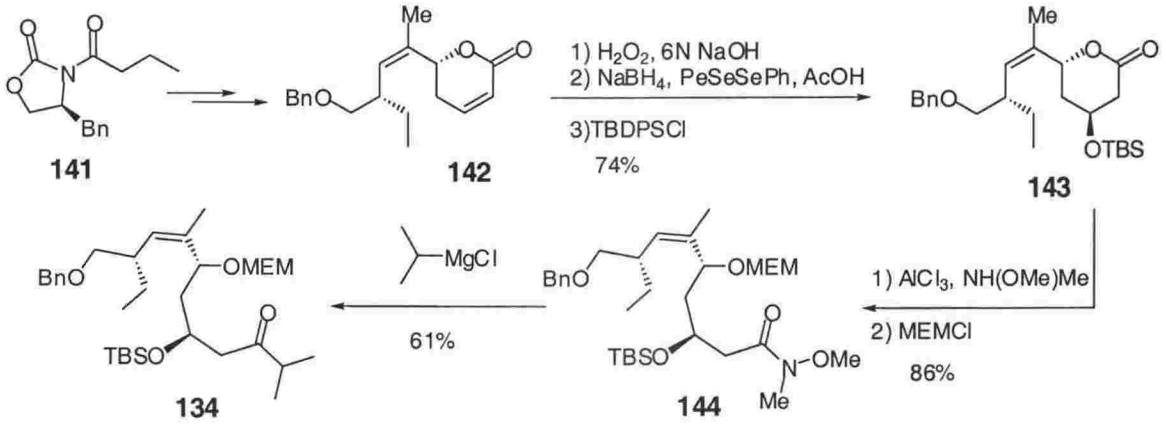
Scheme 106: Gosh and Kim's partial synthesis of the C-1 to C-9 fragment of peloruside

A unique feature of this C-1 to C-9 fragment synthesis was the subsequent chelation controlled asymmetric reduction of ketone **138** using a solution of $LiAl_4$ and LiI in diethylether, scheme 107. As depicted in transition state **138a**, the observed diastereoselectivity can be rationalised by the presence of the *gem*-dimethyl group on the ß-face, resulting in the reduction of the carbonyl from the less hindered α-face. Subsequent esterification with acrolyl chloride and RCM of the corresponding acrylated ester provided the α,ß-unsaturated δ-lactone **140**. A six-step strategy was then used to convert **140** into the desired C-1 to C-9 fragment **135**. Key features of this transformation include the saponification of lactone **140** and an asymmetric dihydroxylation (using A-D mix) to give the C-7 and C-8 *syn* relationship.



Scheme 107: Gosh and Kim's synthesis of the C-1 to C-9 fragment of peloruside A

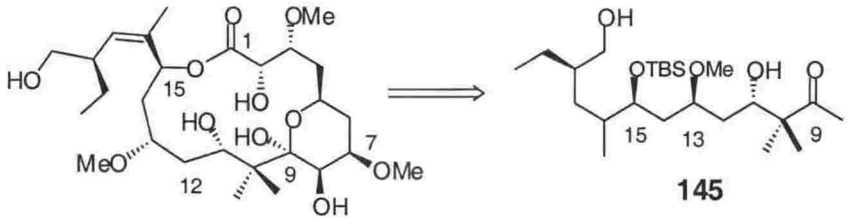
Gosh's synthesis of the C-10 to C-24 fragment of peloruside A commenced with the asymmetric allylation of Evan's chiral oxazolidinone **144**, using a slightly different procedure to that reported in this thesis for the synthesis of the enantiomerically pure side chain **39** (refer to page 37, chapter 2), scheme 108. Following some basic functional group transformations, the subsequent installation of the Z olefin using Horner-Emmons protocol and further functional group manipulations, the correct stereochemistry at C-15 was then established by using Brown's asymmetric allylboration protocol. Esterification and RCM protocol followed to give the α,ß-unsaturated lactone **142**.



Scheme 108: Gosh and Kim's synthesis of the C-10 to C-24 fragment of peloruside A

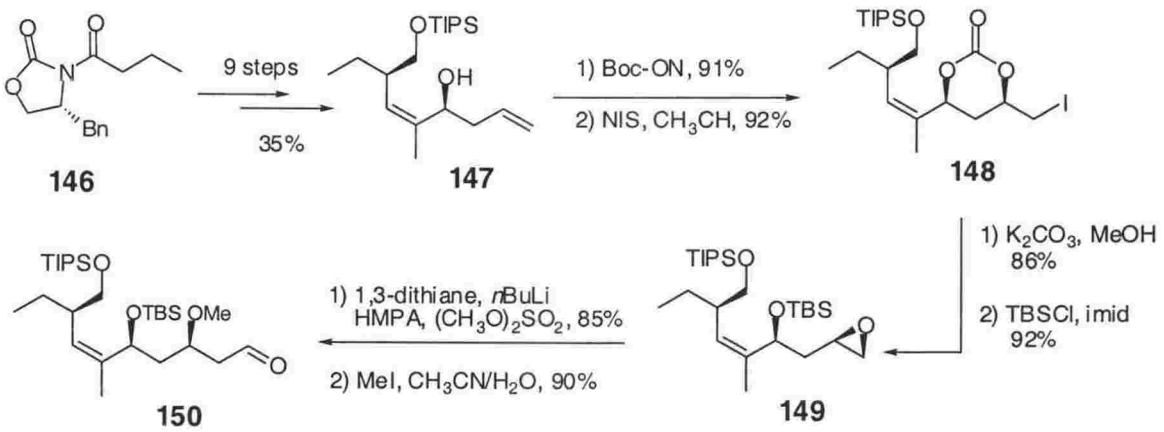
An elegant feature of Gosh's strategy for the installation of the correct stereochemistry at C-13 involved the stereoselective epoxidation of **142** and treatment of the resulting epoxide with diphenyldiselenide and sodium borohydride, scheme 108. Protection of the ensuing alcohol then gave **143** in a 74% overall yield for the three steps. It was initially anticipated that lactone **143** could be directly opened with isopropylmagnesium chloride, however this procedure proved elusive. Thus conversion of lactone **143** to the Weinred amide **144** was first required before synthesis of the final fragment **134** could be achieved.

Taylor and Jin[209] reported the first partial synthesis of the correct enantiomer of peloruside A. Although De Brabander had determined the absolute stereochemistry of peloruside A, Taylor and Jin previously compated the structural and conformational features of peloruside A and epothilone B using NMR and computer modelling techniques. Their modelling results also indicated that the enantiomer opposite to that initially reported by West and Northcote[15] was the correct enantiomer of peloruside A. Taylor and Jin initially focussed on the synthesis of the C-8 to C-24 fragment of peloruside A, as depicted in scheme **109**.



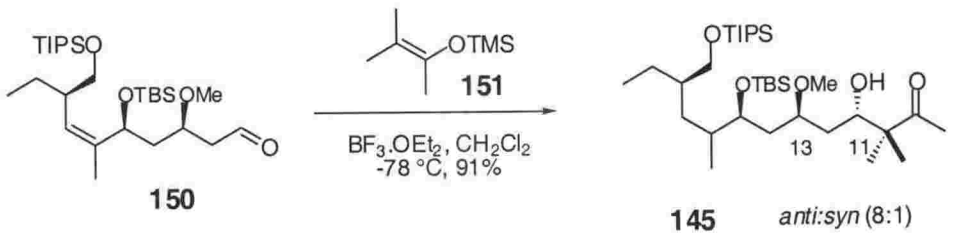
Scheme 109: Taylor and Jin's target C-8 to C-24 fragment of peloruside A

Taylor's synthesis of the C-8 to C-24 fragment of peloruside A commenced in a manner very similar to that previously reported by Gosh. Thus an asymmetric alkylation reaction using Evans's oxazolidinone, a Still-Gennari olefination and Brown's asymmetric allylation, were the key methodologies used during the nine-step synthesis of alcohol **147**. Establishment of the 1,3-*syn* relationship between C-13 and C-15 was achieved by an elegant regioselective, iodine-induced, carbonate cyclization to give carbonate **148** in excellent yield, scheme 110. Exposure of **148** to basic methanol solution and protection efficiently produced the *syn*-epoxy ether **149**. Ether **149** was then subjected to nucleophilic attack by the lithium anion of dithiane, methylated in situ, and the dithiane moiety hydrolysed to give aldehyde **150**.



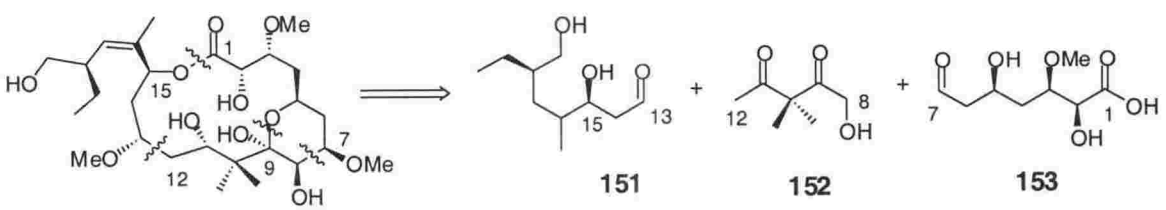
Scheme 110: Synthesis of key intermediate aldehyde **150**.

The final requirement in Taylor's synthesis of the C-8 to C-24 fragment of peloruside A involved a Mukaiyama aldol reaction of the ß-methoxy aldehyde **150** with the TMS silyl enol ether **151**, scheme 111. It is interesting to note that even though an achiral lewis acid was used, good 1,3 anti diastereoselectivity was nevertheless observed in this reaction.



Scheme 111: Synthesis of the C-8 to C-24 fragment of peloruside A

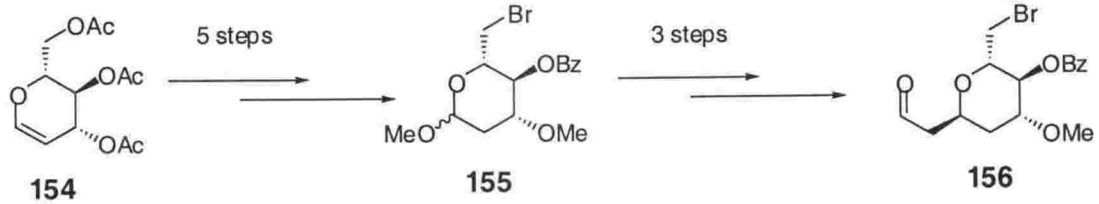
The final strategy towards the synthesis of peloruside A to be discussed in this thesis is the recently published partial synthesis of Pagenkopf, Engers and Bassindale.[210] This strategy has similar disconnects to those proposed by Stocker, Teesdale-Spittle and Hoberg.[193] These key disconnects are depicted in scheme 112.



Scheme 112: Pagenkopf, Engers and Bassindale's retrosynthesis of peloruside A

The unique difference between Pagenkopf's strategy, and the other strategies reported for the synthesis of peloruside A however, is Pagenkopf's use of the commercially available triacetal D-glucal for providing the chiral backbone for the pyranose segment of peloruside A. This strategy results in an elegant approach towards the synthesis of peloruside A.

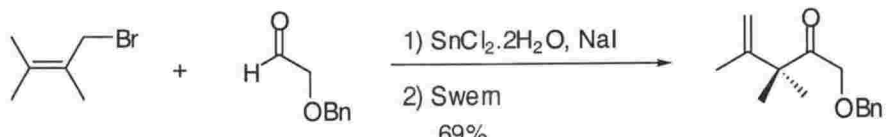
Thus, triacetal D-glucal **154** was converted in five steps to the known pyranose **155**, scheme 113. This transformation involved formation of a methoxy acetal, following treatment of glucal **154** with 10 mol % $Ph_3P.HBr$ and methanol, acetate cleavage, benzylidine acetal formation, methylation, and selective cleavage of the primary benzylidine acetal under Hanessian-Hullar radial bromination conditions. Allylation of **155**, followed by dihydroxylation and $NaIO_4$ oxidative cleavage of the resulting diol gave the desired C-1 to C-7 fragment **156**. Indeed, this eight-step synthesis has been performed on the 50 g scale, with a respectable overall yield of 46%.



154 **155** **156**

Scheme 113: Pagenkopf's synthesis of the C-1 to C-7 fragment of peloruside A

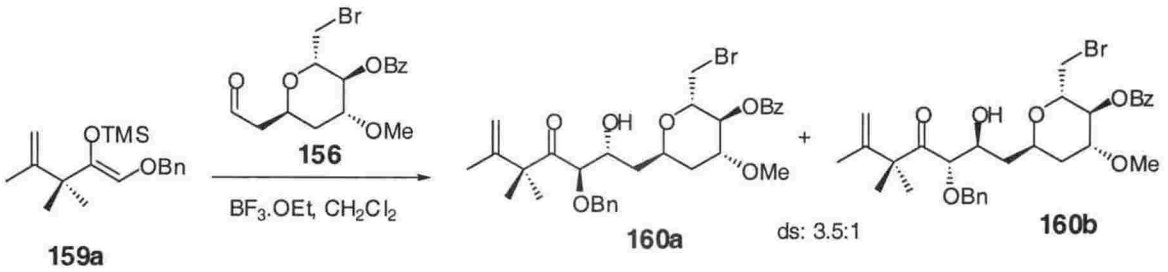
An equivalent of the central C-8 to C-12 piece was synthesised in 69% overall yield by the S_E2' addition of an allylic stannane generated in situ from Barbier-type reaction of **157** with $SnCl_2.2H_20$ and benzyloxy acetaldehyde **158**, scheme 114. A Swern oxidation then completed the synthesis of **159**.



157 **158** **159**

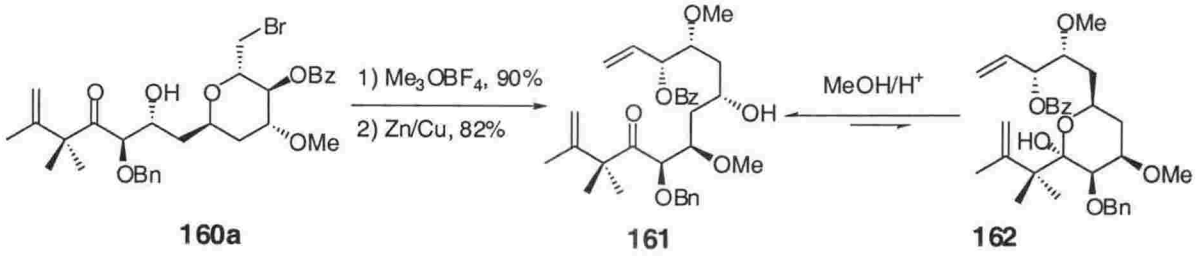
Scheme 114: Synthesis of the C-8 to C-12 fragment

Perhaps the most challenging step in Pakenkopf's strategy was in achieving the desired 1,2-*anti* relationship between C-7 and C-8 during the coupling of **156** and **159**. Thus a range of Lewis acids were explored during the coupling of **156** and the TMS enolate **159a**, with $BF_3.OEt$ giving the best, but still modest, diastereoselectivity, scheme 115.



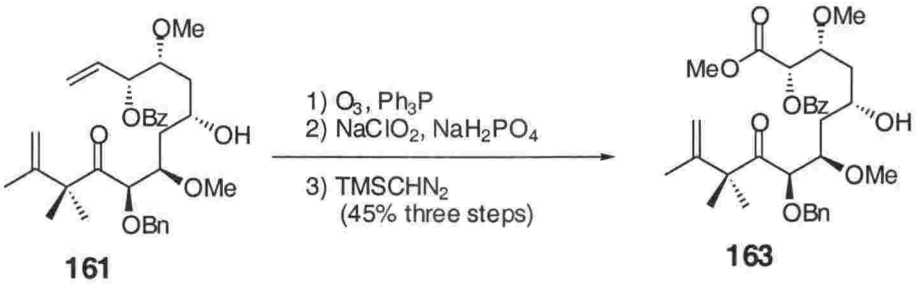
Scheme 115: Establishment of the C-7 to C-8 *anti* relationship

Diastereomer **160a** was then methylated and subjected to a suspension of zinc and copper in ethanol which resulted in Vasella ring cleavage by spontaneous ß-elimination of the alkyl zinc generated in situ by reduction of the alkyl bromide with the zinc-copper couple, scheme 116. For ease of characterisation, it was then anticipated that conditions could be established such that equilibration would favour the hemiacetal **162**. Unfortunately though, reliably obtaining **162** proved elusive, indicating that the pyranose fragment of peloruside may first need to be deprotected for cyclisation to occur.



Scheme 116: Attempted cyclisation of the C-1 to C-12 fragment of peloruside A

Finally, a series of basic functional group manipulations involving an ozonolysis, oxidation, and esterification of the resulting carboxylic acid gave the complete C-1 to C-12 carbon framework, scheme 117. By comparison to the previous synthesises of peloruside A, establishment of the correct stereochemistry in the C-5 to C-10 region appears to be the most challenging aspect of the synthesis. Thus the strategy adopted by Pakenkopf, Engers and Bassindale represents an elegant solution to this problem.



161 **163**

Scheme 117: Pagenkopf's synthesis of the C-1 to C-12 fragment of peloruside A

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