Formal Synthesis

of

Salinosporamide A

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Canción tonta

Mamá.
Yo quiero ser de plata.

Hijo,
tendrás mucho frío.

Mamá.
Yo quiero ser de agua.

Hijo,
tendrás mucho frío.

Mamá.
Bórdame en tu almohada.

¡Eso sí!
¡Ahora mismo!

Federico García Lorca

A mis padres

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained in this thesis is the original work of my own research since the registration of the PhD degree in September 2004, and any collaboration has been clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Isabel Villanueva Margalef

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Abstract

Salinosporamide A (**1**) is a secondary metabolite that was isolated in 2003 by Fenical and co-workers from marine actinomycete bacteria of *Salinospora* strain CNB-392. Salinosporamide A is a highly potent and specific inhibitor of the 20S proteasome. The proteasome, a multicatalytic proteolytic complex that regulates protein degradation within the cells, is receiving considerable attention as a target for treating cancer. Salinosporamide A is currently undergoing clinical trials as potential drug for cancer treatment. It contains a densely functionalised fused γ-lactam-β-lactone bicyclic ring structure, with five contiguous stereocentres. Due to the impressive biological activity, as well as its complex chemical structure, this compound has become an important target for the synthetic community.

1
salinosporamide A
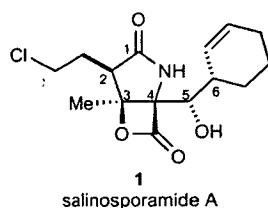
This thesis describes the investigations undertaken towards the synthesis of **1**. After studies on several different approaches, a concise formal synthesis was achieved. This route employed a sequential Ni-catalysed reductive aldol cyclisation-lactonisation reaction in the construction of the γ-lactam core of **1**, which contained the required stereochemistry. This approach represents an attractive method to install the C2 side-chain with simultaneous protection of the C5 oxygen and saves several steps over alternative routes. The product of the cyclisation-lactonisation sequence (**489**) was readily transformed into an intermediate in the synthesis of **1** by Corey and co-workers (**26**), which had been converted into salinosporamide A in four steps.
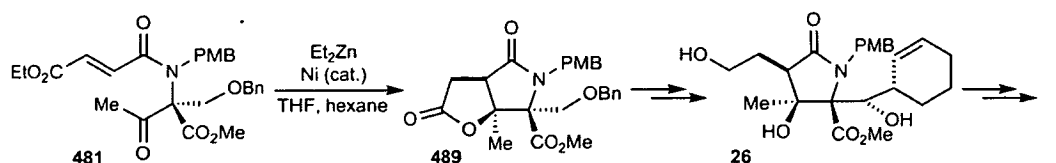
List of Abbreviations

α	observed optical rotation
°C	degrees celsius
Ac	acetyl
acac	acetyl acetonate
AIBN	2,2'-azobis(isobutyronitrile)
Aq	aqueous
Ar	aromatic group
Atm	atmosphere(s)
ATP	adenosine 5'-triphosphate
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
MeO-BIPHEP	(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine))
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOPCl	*N,N'*-bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
BOX	2,2'-isopropylidenebis-2-oxazoline
BroP	bromotris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
Bz	benzyl
Calcd	Calculated
CAN	Cerium(IV) ammonium nitrate
Cat	catalytic; catalyst
CDI	1,1'-carbonyldiimidazole
CloP	chlorotri(dimethylamino)phosphonium hexafluorophosphate
COD	cyclooctadiene
Cp	cyclopentadiene
CSA	camphor sulfonic acid
cy	cyclohexyl
d	doublet; day(s)
DBAD	dibenzylazodicarboxylate

DCC	*N,N'*-dicyclohexylcarbodiimide
dd	doublet of doublets
DEPT	distortionless enhancement by polarization transfer
DIBAL–H	diisobutylaluminium hydride
DIC	*N,N'*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	dimethylether
DMF	dimethylformamide
DMIPS	dimethylisopropylsilyl
DMPU	1,3-dimethyl hexahydro-2-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
Dpm	dipivaloylmethane
DPPB	1,2-bis(diphenyl-phosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
(*S,S*)-Et-DuPhos	(+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ES	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
FDA	Food and Drug Administration
g	gram(s)
GI$_{50}$	concentration to achieve 50% growth inhibition
GSH	glutathione
h	hour(s)
HBTU	*O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIV	human immunodeficiency virus
HMPA	hexametylphosphoramide

HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half maximal (50%) inhibitory concentration
^{i}Pr	*iso*-propyl
IR	infra red
IκB	inhibitor of nuclear factor κB
J	coupling constant
KHMDS	potassium bis-(trimethylsilyl)amide
L	litre(s)
LAB	lithium triamidoborohydride
LDA	lithium diisopropylamide
LHMDS	lithium bis-(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
LTMP	lithium 2,2,6,6-tetramethylpiperidine
M	Molar; metal
m.p.	melting point
Me	methyl
MeCN	acetonitrile
Me-DuPhos	1,2-Bis(2,5-dimethylphospholano)benzene
mg	milligram
min	Minute(s)
mL	millilitre
mmol	millimole
mol	mole(s)
MsCl	methanesulfonyl chloride
NaHMDS	sodium bis-(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCI	National cancer institute
NF-κB	nuclear factor κB
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide

NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*p*-methoxybenzyl
PMHS	polymethylhydrosiloxane
PMP	*p*-methoxyphenyl
ppm	parts per million
PPY	4-pyrrolidinopyridine
pr	propyl
p-TsOH	*p*-toluenesulfonic acid
pybox	2,6-bis(oxazolinyl)pyridine
PyBrop	bromotri(pyrrolidino)phosphonium hexafluorophosphate
q	quartet
rac-BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
rt	room temperature
SAR	structure-activity relationship
SEGPHOS	(*S*)-(4,4-bi-1,3-benzodioxole)-5,5-diylbis(diphenylphosphine)
t	triplet
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBTU	*O*-benzotriazol-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate
t-Bu	*tert*-butyl
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
THP	tetrahydropyrane
Thr	threonine
TLC	thin layer chromatography
TMDS	1,1,3,3-tetramethylhydrosiloxane
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Contents

1. Introduction

Salinosporamide A **(1)** is a secondary metabolite that was isolated in 2003 by Fenical and co-workers from the marine actinomycete bacteria of *Salinospora* strain CNB-392 (Figure 1.1).[1] Salinosporamide A is structurally related to omuralide **(2)**, a transformation product of the soil microbial metabolite (+)-lactacystin **(3)** isolated by Omura *et al.* in 1991.[2] Omuralide was the first specific 20S proteasome inhibitor identified. The proteasome is a multicatalytic proteolytic complex that regulates protein degradation within cells and is receiving considerable attention as a target for treating cancer. Omuralide **(2)** has an IC_{50} value of 49 nM when tested against purified 20S proteasome, but salinosporamide A **(1)** was found to be approximately 35 times more potent than omuralide, with an IC_{50} value of 1.3 nM in the same assay. Salinosporamide A also exhibited high *in vitro* cytotoxicity with a mean GI_{50} value of less than 10 nM when tested against the NCI's 60 cell-line panel. 20S Proteasome inhibitors are of interest for the treatment of several types of cancer and the drug Velcade® (bortezomib) **(4)** has been approved by the FDA for the treatment of multiple melanoma.[3] Salinosporamide A (NPI-0052) is currently in phase I human clinical trials for the treatment of multiple myeloma and other cancers.[4]
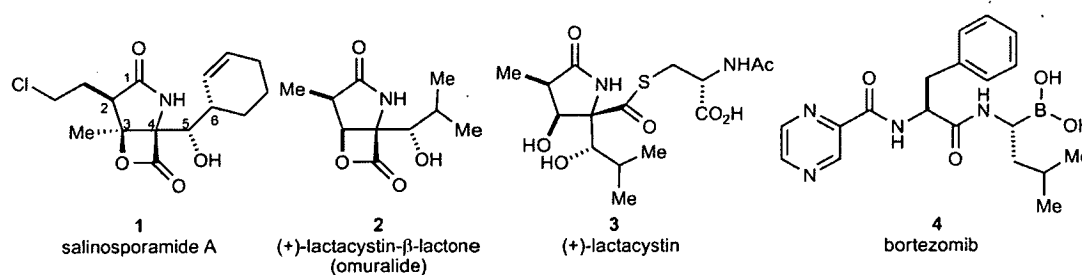
**Figure 1.1** *Salinosporamide A, omuralide, lactacystin and bortezomib*

The synthesis of proteasome inhibitors such as omuralide and salinosporamide A is therefore of great pharmaceutical value, since it would allow greater quantities to be produced which would permit more extensive testing, as well as the synthesis of analogues. The aim of this project was to investigate synthetic approaches to salinosporamide A, the most interesting 20S proteasome inhibitor recently isolated.

1.1. Ubiquitin-mediated proteolysis and proteasome inhibitors

1.1.1. The discovery of ubiquitin-mediated proteolysis

While there had been great interest and much research on understanding how the cell controls the synthesis of certain proteins, control of the degradation of proteins had for a long time not received so much attention. The first system known for protein degradation in eukaryotic cells was the lysosomal apparatus, a membrane-enclosed vacuole containing multiple acid proteases and other hydrolases. It was long believed to be the only site for protein breakdown but, from studies initiated in the fifties, it was established that the bulk of cytosolic proteins are hydrolysed by a distinct pathway which is highly specific and requires ATP and the 26S proteasome. Knowledge in this area developed rather slowly but in the early nineties the studies were greatly simplified thanks to the availability of proteasome inhibitors.[5] Avram Hersko, Aaron Ciechanover and Ernie Rose were awarded the Nobel Prize in chemistry in 2004 for their studies of this system.[6]

Ubiquitination is the process, present both in the nucleus and the cytosol, whereby proteins are marked for degradation by covalent linkage to the protein ubiquitin. This process requires the initial ATP-dependent activation of ubiquitin's terminal carboxy group by the ubiquitin-activating enzyme, E1 (Figure 1.2). The activated ubiquitin is then transferred to the ubiquitin carrier proteins, E2s. There is some selectivity in this step but the great selectivity of this process comes from the ubiquitin ligases, or E3s, which reorganise one or a set of protein substrates and catalyse the transfer of the activated ubiquitin from the E2 to the substrate, forming processively a chain of ubiquitin molecules. A chain composed of four or more ubiquitin molecules leads to the degradation of the protein in the proteosome.[3]
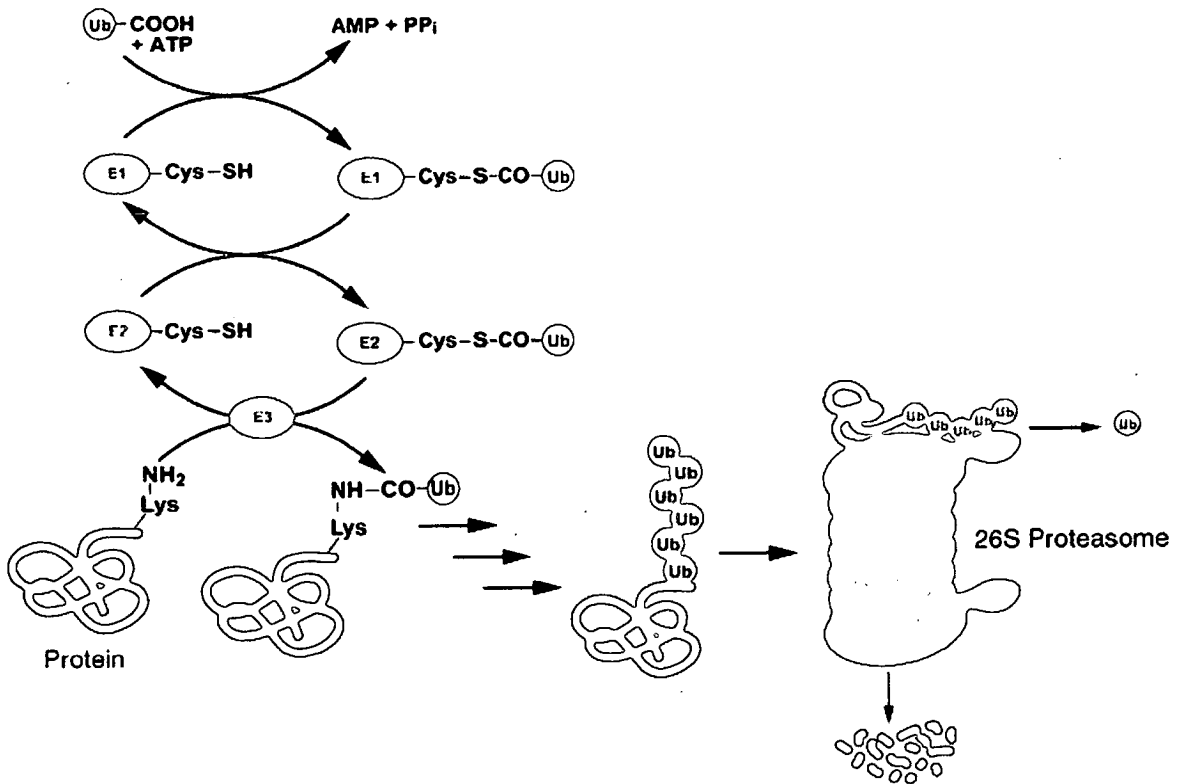
Figure 1.2 *Mechanism of the E1/E2/E3-catalysed attachment of ubiquitin to proteins[7]*

The 26S proteasome is an ATP-dependent proteolytic complex, formed by two 19S (890 kDa) "cap" complexes, which provide the specificity and regulation, and the central 20S proteosome (720 kDa), where proteins are degraded. The 19S complexes contain binding sites for ubiquitinated proteins, enzymes that depolymerise the ubiquitin chain, and six different ATPases that unfold the substrate and make the entry to the 20S complex easier. The barrel-shaped 20S proteasome is formed from four stacked rings that enclose a central chamber where proteolysis occurs. This proteasome uses the hydroxyl group of a terminal threonine residue as the catalytic nucleophile that attacks and breaks peptide bonds. A protein, once taken up by the proteasome, is completely degraded into small peptides of 3-20 residues that are further hydrolysed into amino acids by other peptidases. The isolation of the active sites within the 20S complex away from cytosolic proteins and the restriction of substrate entry must have evolved to avoid non-specific degradation of cell proteins.[8]

1.1.2. Biological functions of the ubiquitin mediated proteolysis

The availability of proteasomal inhibitors with increasing specificity and potency has helped greatly in understanding the role of the proteasomal-ubiquitin protein degradation in many biological processes.[5] Since the late 1980s a number of physiologically important substrates involved in this proteolysis pathway have been identified. Only as an illustration, a few examples will be briefly described.

IκB was the first substrate of the ubiquitin-proteasome pathway identified with the help of proteasome inhibitors.[9] It is an inhibitor of transcription factor NF-κB, which activates the expression of many genes encoding inflammatory mediators. The signal for the initiation of the inflammatory response is the rapid destruction of the inhibitory protein IκB. Consequently, proteasome inhibitors, by stabilising IκB, maintain NF-κB in the inhibited state and prevent production of the inflammatory proteins.[3]

The proteasome is also involved in degradation of numerous proteins regulating the cell cycle. Inhibition of the proteasomal activity was reported to stop the cell cycle at different stages. Several studies demonstrated that cancer cells are usually more sensitive to proteasome inhibitors than normal cells. The use of proteasome inhibitors also demonstrated that the proteasomal-ubiquitin pathway has a decisive effect on cell death and survival: several substrates of this proteolytic pathway are short-lived proteins which are critical for cell progression and transcriptional regulation, and they can therefore become the key players in the control of the cell death program.[10]

Proteasome inhibitors have been associated with suppression of angiogenesis.[11] Cancerous tissues stimulate angiogenesis and that leads to increased tumour formation and possible metastases. Many of the factors involved in angiogenesis are regulated by the proteasome.

The ability of proteasome inhibitors to inhibit cell growth and selectively induce apoptosis in cancer cells, together with the ability to inhibit angiogenesis, renders these agents attractive candidates as anticancer drugs. The development of proteasome inhibitors in cancer treatment is therefore one of the fastest growing fields in modern biomedical science.[8]

1.1.3. Proteasome inhibitors and mode of action

More than 90% of cell protein degradation occurs through the ubiquitin-proteasomal pathway. The proteasome is the main component of this mechanism and the regulation of its activity is very important for an enormous number of essential biological processes. For that reason, compounds that inhibit or modulate proteasomal activity have great biological importance. Proteasome inhibitors can be used as tools to investigate regulation of the ubiquitin-proteasomal system, and also as leads for possible drug development. They are generally classified based on the pharmacophore with preference for the proteasome's active site, the hydroxyl group of an *N*-terminal threonine. They are also classified based on the specificity and the reversibility of binding.[12]

Peptide aldehydes (Scheme 1.1) were the first proteasome inhibitors to be developed and are still the most widely used inhibitors. Aldehyde inhibitors enter the cell rapidly and their effect is reversible. They have fast dissociation rates, are rapidly oxidised into inactive acids by cells and are easily transported out of the cell. Consequently, the effects of these inhibitors can be rapidly reversed by removal of the inhibitor.

Peptides with a vinyl sulfone are another class of proteosomal inhibitor. These bind to proteasomes irreversibly but are less reactive than aldehydes. Vinyl sulfones act as conjugate addition acceptors for the hydroxyl group of the proteasome's catalytic threonine, forming a covalent bond.
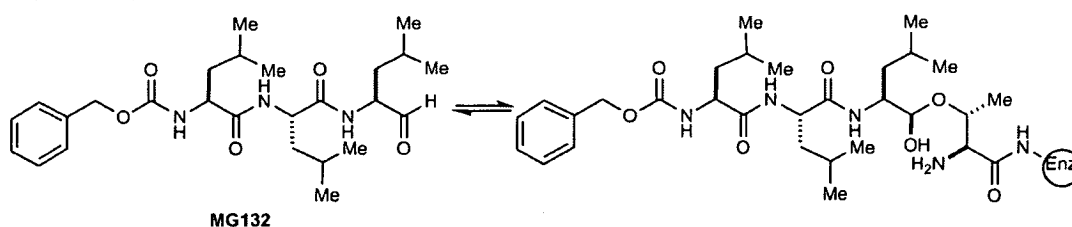

Scheme 1.1 *Peptide aldehydes and peptide vinyl sulfones proteasome inhibitors*

Peptide boronates (Scheme 1.2) are much more potent inhibitors than aldehydes and vinyl sulfones. Although boronates are considered reversible inhibitors, the inhibition is practically irreversible over the duration of several hours. Their high inhibition efficiency, high selectivity (they do not inhibit other cellular proteases) and low dissociation rates render these chemical compounds the focus of intense research. The boronate derivative bortezomib (**4**) has already passed through clinical trials and represents a new drug against multiple myelanoma.[4]

Apart from synthetic peptide inhibitors, there are a variety of natural compounds, like peptide epoxyketones and β-lactones. Epoxyketones act by an interesting and unique mechanism. They react with both the hydroxyl and amino groups of the catalytic *N*-terminal threonine of the proteasome. Due to their unique mechanism, they are the most selective inhibitors of the proteasome known.
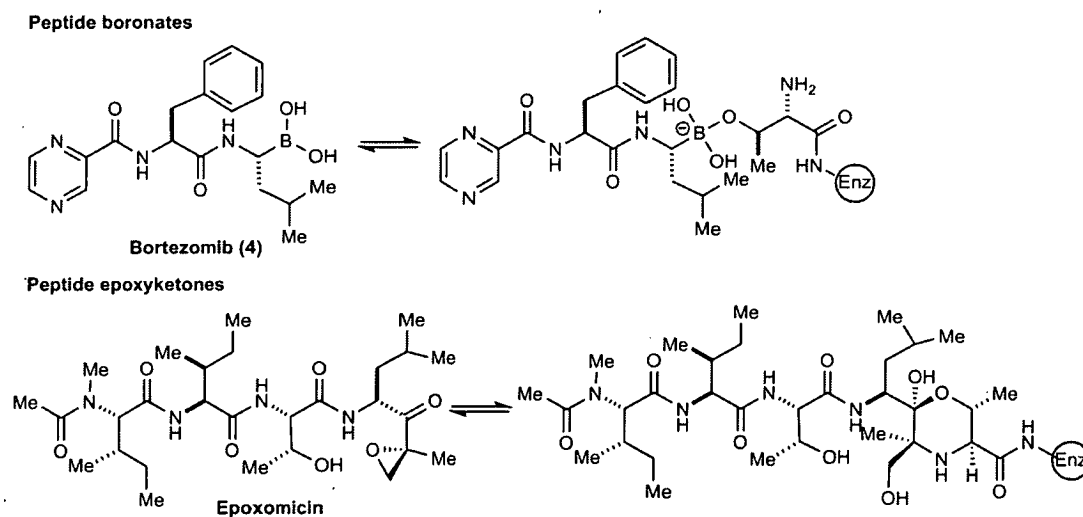

Scheme 1.2 *Peptide boronates and peptide epoxyketones proteasome inhibitors*

Lactacystin, omuralide and salinosporamide A are β-lactone inhibitors and their mode of action and reactivity will be explained in more detail in the next section.

1.1.3.1. Lactacystin, omuralide and salinoporamide A. Mode of action and Structure-Activity Relationships (SAR) studies

In 1991, Omura's group isolated and characterised (+)-lactacystin (**3**), a secondary metabolite derived from a *Streptomyces* bacterial strain.[2] It was initially considered a neurotrophic agent but has since found application in models of arthritis, ischemia, and asthma. By further interpretation of the biological activity, Fenteany discovered that its molecular target was the 20S proteasome.[13] Experiments done by Fenteany and co-workers as well as the crystallographic work of Huber[14] clearly defined the mode of inhibition of (+)-lactacystin and explained its high potency and selectivity.

(+)-Lactacystin was shown to be in fact a pro-drug for the active inhibitor omuralide (**2**), which is the only species to enter the cell.[15] (+)-Lactacystin spontaneously eliminates *N*-acetylcysteine in a reversible manner to produce the β-lactone. Once inside the cell, omuralide either: (i) is hydrolysed by water to give the carboxylic acid **5**; (ii) reacts with glutathione to form the glutathione derivative (lactathione) **6** which acts as a reservoir of the drug; or (iii) binds to the 20S proteasome to form ester **7**, as illustrated in Scheme 1.3.[16]
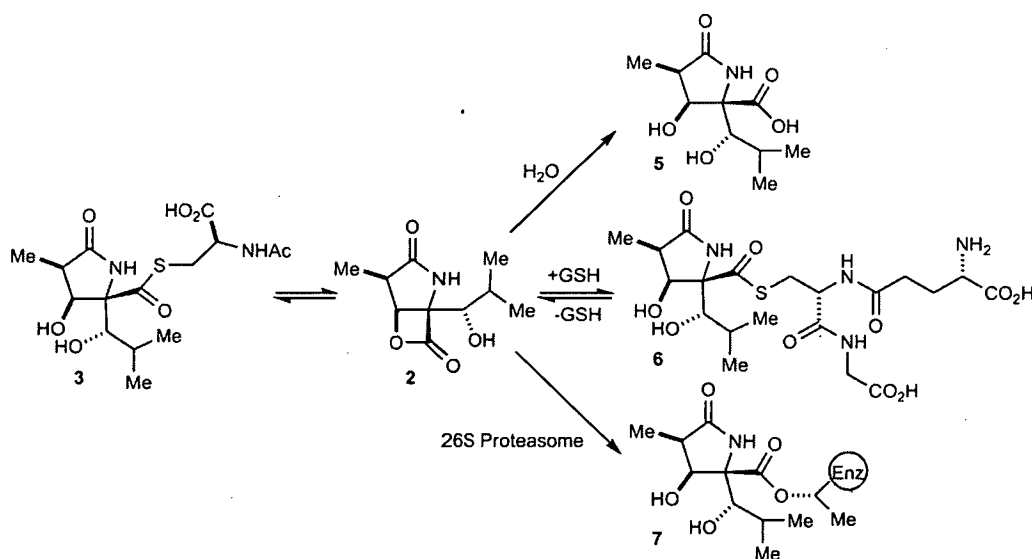
Scheme 1.3 *Formation of omuralide (2) from (+)-lactacystin 3 and its subsequent reaction inside the cell with water, glutathione (GSH) and the 20S proteasome*

The electrophilic centre of the inhibitor is the β-lactone. Omuralide binds to the 20S proteasome through a covalent bond in the form of an ester between the C4 carbonyl and the hydroxyl group of an *N*-terminal threonine residue in the active site. Although the inhibitor is covalently bound the resultant ester is subject to hydrolysis and the inhibition is therefore reversible, with enzymatic activity restored in a matter of hours.[8]

The synthesis of (+)-lactacystin has received widespread attention since its isolation in 1991. The first synthesis of **2** was reported by Corey and co-workers in 1992.[17] Many refinements to the synthesis have been reported by the Corey group, allowing (+)-lactacystin to be synthesised *via* omuralide and allowing the synthesis of C2 and C5 analogues.[16] It was found that replacing the C2 methyl group with larger alkyl substituents increased the potency of proteasome inhibition relative to omuralide but that alteration of the isopropyl group at the C5 position resulted in a loss of activity.[18] The β-lactone has been shown to be essential for biological activity through synthesis of the '3*R* diastereoisomer' (**8**) of (+)-lactacystin (**3**) which is unable to form the β-lactone but shares all of the other structural features.[19] This compound was found to be inactive which is consistent with the mechanism of inhibition.
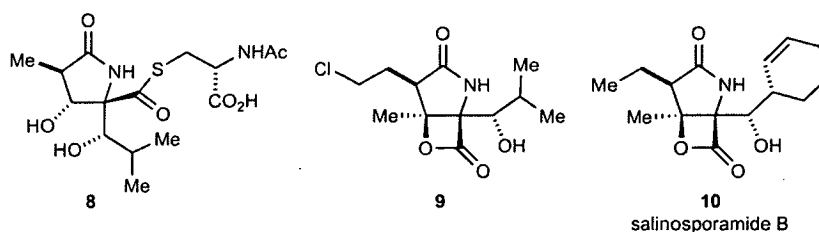

Figure 1.3 *Lactacystin, omuralide and salinosporamide A analogues*

Salinosporamide A not only represents a more attractive synthetic target than omuralide due to its increased biological activity, but it is also a more challenging one. It is even more densely functionalised than omuralide, containing five contiguous stereogenic centres. Salinosporamide A shares the key γ-lactam-β-lactone pharmacophore with omuralide but differs in the C2, C3 and C5 substituents. It contains a cloroethyl group at C2, it is methylated at C3 creating a second quaternary

stereogenic centre and carries a cyclohexenyl group at C5 in place of the isopropyl group of omuralide. It is this unique substitution that, collectively, makes salinosporamide A approximately 35 times more potent that omuralide in proteasome inhibition.

Given the structural similarities between omuralide and salinosporamide A, a similar binding mode with the proteasome could be expected, namely attack of the Thrl-OH of the proteasome to the β-lactone carbonyl, opening the ring and forming an ester. This was confirmed by a crystal structure analysis of salinosporamide A in complex with the 20S proteasome, by Potts and co-workers (Figure 1.4).[20]
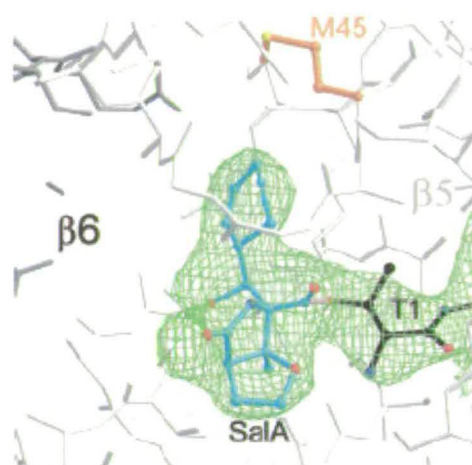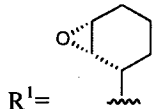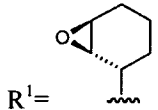
Figure 1.4 *Crystal structure analysis of salinosporamide A (1) in complex with the 20S proteasome* [20]

The β-lactone is therefore recognised as the key pharmacophore, but the enhanced potency of salinosporamide A must be due to certain substituents of the bicyclic ring. Therefore, full structure-activity relationship (SAR) studies of salinosporamide A were undertaken.[21] Table 1.1 outlines some biological data of *in vivo* (cytotoxicity against multiple myeloma cell line RPMI 8226) and *in vitro* proteasome inhibition. This SAR study together with the analysis of the crystal structure of salinosporamide A (1) and of the des-chloro analogue (10, Figure 1.3) in complex with the proteasome, provided explanations for its enhanced potency.[20] This des-chloro analogue 10 (salinosporamide B) was isolated, in smaller quantities, from the same microbial strain.

The fact that the cyclohexenyl group of **1** does not result in a loss of activity (Table 1.1) contradicts the SAR data obtained for omuralide (**2**) by Corey and co-workers and suggests that salinosporamide A may interact with the proteasome in a different manner to omuralide. The C5 isopropyl analogue of salinosporamide A (**9**, Figure 1.3, *vide supra*) has been synthesised by the Corey group[22] and was found to be 2.5 times more potent than **2** but less active than **1** against the purified proteasome.[23] Various C5 analogues were synthesised by modifying the cyclohexene substituent but all were found to be less potent than the parent compound (Table 1.1, entries 3-5). The hydrogen bonds formed between C5-OH and the proteasome also have an important role in causing inhibition. Epimerisation of this centre or oxidation to the ketone results in analogues without proteosomal inhibition (entry 6).

It was observed that the C3 methyl group points toward a small pocket and interacts weakly with the protein. Both a hydrogen atom and a methyl group fit into this pocket, but an analogue containing an ethyl group at this position does not inhibit the proteasome (entry 7). The ethyl group is too big and causes steric interactions that do not allow binding.

|	Modification from salinosporamide A (1) (R^2= CH₂CH₂Cl, R^3= Me, R^1= cyclohexenyl)	Biological activities (IC50 nM)	
		Cytotoxicity RPMI 8226 (MM)	Proteasome Inhibition
1	None (**1**)	8.2 ± 2.0	21 ± 3
2	Omuralide (**2**)	3300 ± 1600	540 ± 60
3	cyclohexyl	52 ± 13	250 ± 30
4	R^1=	32 ± 3	92 ± 6
5	R^1=	320 ± 5	770 ± 50
6	*epi*-C-5(OH)	>20000	>20000
7	R^3 = CH₂CH₃	1900 ± 400	3300 ± 200
8	R^2 = CH₂CH₂Br	7.4 ± 1.6	14 ± 2
9	R^2 = CH₂CH₂I	6.8 ± 0.8	13 ± 3
10	R^2 = *epi*-CH₂CH₂Cl	1900 ± 300	2500 ± 500
11	R^2 = CH₂CH₃	6100 ± 3300	640 ± 60

Table 1.1 *Biological activities of salinosporamide A, omuralide and analogues*

The hydrolysis of the β-lactone was also evaluated. In aqueous solutions salinosporamide A hydrolyses to the acid **11** which rapidly eliminates HCl to give the bicyclic product **12**, as illustrated in Scheme 1.4.
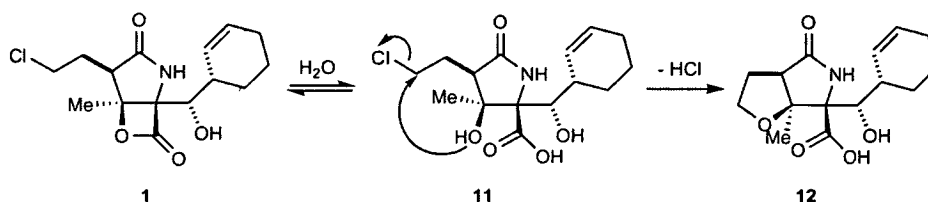
Scheme 1.4: *Formation of the bicyclic tetrahydrofuran derivative 12 following displacement of the C2-chloro substituent*

A potential problem with salinosporamide A as a pharmaceutical agent is therefore its instability in aqueous solution at pH 7 ($t_{1/2}$=5-10 min). In an attempt to get round this problem, Corey and co-workers have synthesised β-lactam **13** which is stable at pH 7 for at least 24 hours (Figure 1.5).[24] This is proposed to compensate for the decreased potency of proteasome inhibition exhibited for this compound.
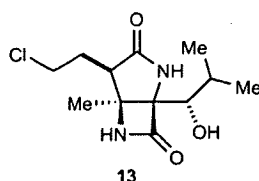
Figure 1.5 *β-Lactam 13*

Salinosporamide A (**1**) contains a chloroethyl group at the C2 position; the des-chloro analogue of salinosporamide A, salinosporamide B (Figure 1.3), is found to be 500-fold less cytotoxic than salinosporamide A against the human colon HCT-116 cancer cell line.[25] Substitution of chlorine with bromine or iodine (Table 1.1, entries 8 and 9) gave analogues of similar potency. The C2 epimer (entry 10) also resulted in a marked decreased potency.

The chloride substituent is proposed to be responsible for the increase in potency by ensuring that the covalent attachment to the proteasome is irreversible. It is suggested a two-step binding mechanism, in which β-lactone ring opening (**14**) is followed by the facile chloride displacement from the side chain by the free hydroxyl

at C3, forming a bicyclic tetrahydrofuran derivative (**15**) (Scheme 1.5). For omuralide (**2**), the formation of the ester bond with the proteasome is reversible because the hydroxyl at C3 is free and can attack the carbonyl again, but this is not possible for salinosporamide A.
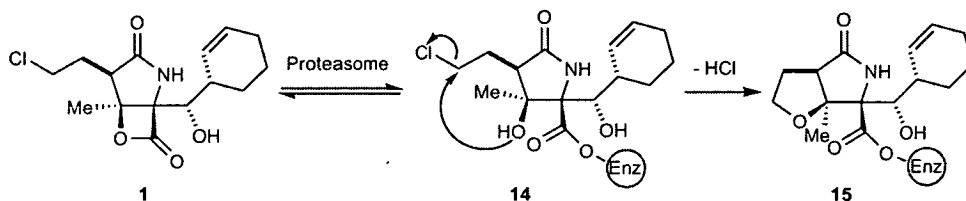
Scheme 1.5 *Salinosporamide A binds irreversibly*

Cleavage of the acyl ester by a nucleophilic water molecule is challenged by the spatial arrangement of C3-O in the tetrahydrofuran derivative. Proteasome activity is only slowly recovered after 7 days in mice treated with **1**, which could be attributed to red blood cell turnover.[4]

1.2. Previous syntheses of salinosporamide A

The discovery of proteasome inhibitors has facilitated a greater understanding of the mechanism of the proteasome and an increased awareness of its biological importance. They have shown the proteasome as a viable target for drug development.

Because of the potent biological activity, as well as its complex structure, salinosporamide A (**1**) has generated considerable interest in the synthetic community. Corey completed the first total synthesis in 2004[26]. Since then, other total syntheses (Danishefsky,[27] Macherla,[28] Pattenden[29] (racemic) and Romo[30](racemic)) and a formal synthesis (Langlois)[31, 32] have been reported. The remainder of this section will review the synthetic strategies towards the natural product.

1.2.1. Corey's Synthesis

The first total synthesis of salinosporamide A was achieved by Corey and co-workers in 2004,[26] following on from extensive work by the group on the synthesis of (+)-lactacystin, omuralide and related analogues.[17, 33, 34] This synthesis is outlined in Scheme 1.6

(*S*)-Threonine methyl ester was treated with 4-methoxybenzoyl chloride to give the *N*-acylated product **16** which cyclised to an ozaxoline in the presence of *p*-TsOH. Stereoselective alkylation of the oxazoline with benzyloxymethyl chloride afforded a new oxazoline **17**, with the required stereochemistry at the tetrasubstituted C4 carbon. Selective reductive ring-opening of **17** using NaBH$_3$CN/HOAc gave the *N*-PMB-protected amino alcohol **18**. This intermediate was acylated in a one-flask sequence: temporary protection of the secondary alcohol with a trimethylsilyl group, *N*-acylation with acryloyl chloride, followed by desilylation, to yield the *N*-acrylyl-*N*-PMB derivative **19** in 96% yield. Oxidation of **19** with Dess-Martin periodinane[35] produced keto-acrylamide **20**.

The key formation of the γ-lactam was successfully achieved *via* a Baylis-Hillman cyclisation, operation that installs the stereocentre at C3. Using quinuclidine as the catalyst in DME at 0 °C for 7 days, **20** cyclised to give the desired

diastereomer of the γ-lactam with high diastereoselectivity (9:1). Silylation of the cyclised products allowed separation of the two diastereomers and desired **21** was isolated in 95% yield. Subsequent tributyltin-mediated radical-chain cyclisation of **21** gave the *syn*-fused γ-lactam **22**, setting up the desired stereochemical relationship at C2 and C3. Cleavage of the benzyl ether and oxidation of the resulting primary alcohol afforded aldehyde **23**.
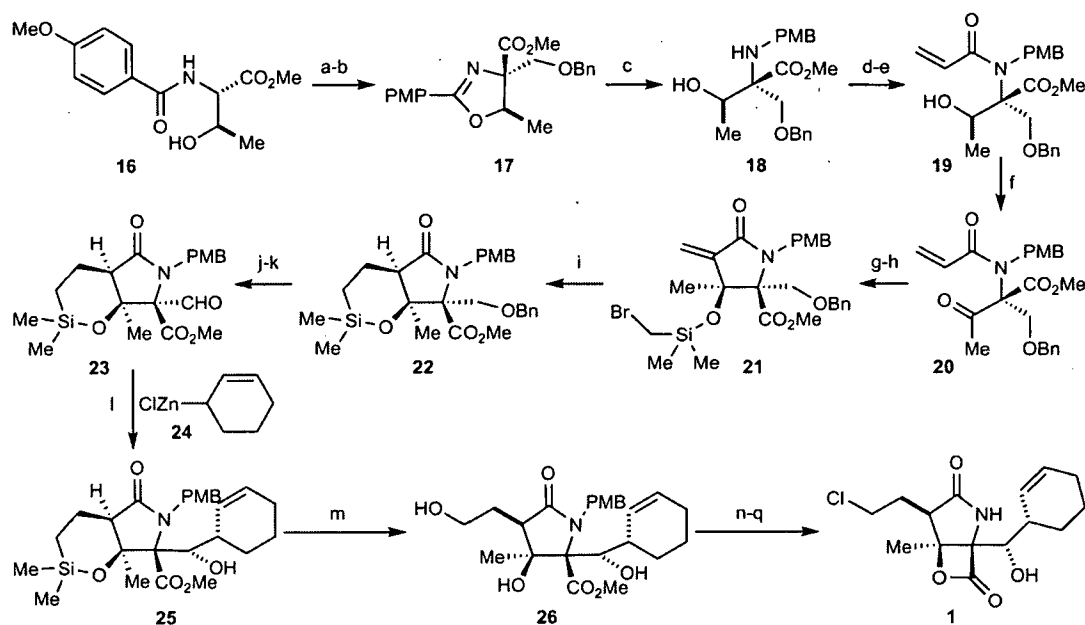

Reagents and conditions: (a) *p*-TsOH, toluene, reflux, 12 h, 80%; (b) LDA, THF-HMPA, −78 °C then ClCH$_2$OBn, 4 h, 69%; (c) NaCNBH$_3$, AcOH, 40 °C, 12 h, 90; (d) TMSCl, Et$_2$O, 23 °C, 12 h; (e) Acryloyl Chloride, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, 1 h, 0 °C then H$^+$, Et$_2$O, 23 °C, 1 h, 96%; (f) Dess-Martin periodinane, 23 °C, 1 h, 96%; (g) Quinuclidine, DME, 0 °C, 7 d, 90%; (h) BrCH$_2$Si(CH$_3$)$_2$Cl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 30 min, 95%; (i) Bu$_3$SnH, AIBN, Benzene, reflux, 8 h, 89%; (j) Pd-C, EtOH, H$_2$ (1 atm), 18 h, 95%;. (k) Dess-Martin periodinane, 23 °C, 1 h, 95%; (l) **24**, THF, −78 °C, 5 h, 88%; (m) KF, KHCO$_3$, H$_2$O$_2$, THF-MeOH (1:1), 23 °C, 18 h, 92%; (n) CAN, MeCN-H$_2$O; (3:1), 0 °C, 1 h, 83%; (o) 3N LiOH-THF (3:1), 5 °C, 4 d; (p) BOPCl, pyridine, CH$_2$Cl$_2$, 23 °C, 1 h; (q) Ph$_3$PCl$_2$, MeCN, pyridine, 23 °C, 1 h, 65% (3 steps).

Scheme 1.6: *First total synthesis of 1*

The next step was the installation of the 2-cyclohexenyl group *via* an organometallic addition of 2-cyclohexenylzinc chloride[36] (**24**) into aldehyde **23**. This reaction proceeded with excellent diastereoselectivity (20:1), setting up the desired stereochemical relationship at C5 and C6 (Scheme 1.6).

Tamao-Fleming oxidation[37] of **25** afforded triol **26**. This intermediate was successfully converted into **1** in four final steps: cleavage of the PMB group using CAN (83% yield), hydrolysis of the methyl ester employing LiOH, β-lactone formation with BOPCl, and finally chlorination of the primary alcohol with triphenylphosphine dichloride (65% yield over three steps).

The Baylis-Hilman cyclisation step was revised by Corey and co-workers in 2005 to give complete diastereoselectivity (dr >99:1).[22, 23] In this new methodology, keto-acrylamide **20** was reacted with the Kulinkovich[38] reagent **27**, formed from reaction of four equivalents of Ti(^{i}PrO)$_4$ with seven equivalents of cyclopentylmagnesium chloride (Scheme 1.7). The reaction mixture was treated then with iodine to form the α-iodomethyl-γ-lactam **28**. Finally, the addition of triethylamine afforded the γ-lactam **29** in 83% overall yield.
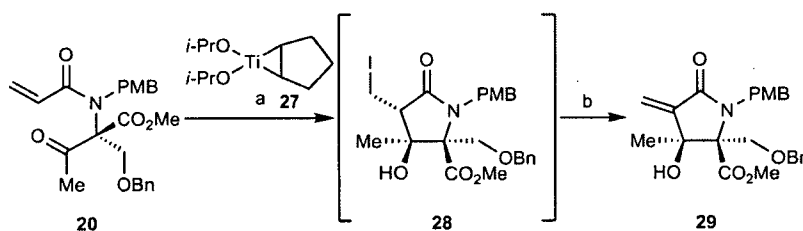
Reagents and conditions: (a) Ti(O*i*-Pr)$_4$ (4 eq), c-C$_5$H$_9$MgCl (7 eq), *t*-BuOMe, –40 °C, 30 min, I$_2$ (5 eq), -40 °C, 2 h then 0 °C, 2 h.; (b) NEt$_3$, CH$_2$Cl$_2$, 30 min, 83%.

**Scheme 1.7** *Improved γ-lactam formation*

This new methodology was also employed in the synthesis of 3-methyl-2-*epi*-omuralide **32**.[39] Keto acrylamide **30** was added to the Kulinchovich reagent in a similar procedure but the cyclised titanium-containing intermediate formed was then quenched with 1 N HCl, an operation that afforded γ-lactam **31** in 95 % yield and as a single diastereomer (Scheme 1.8).
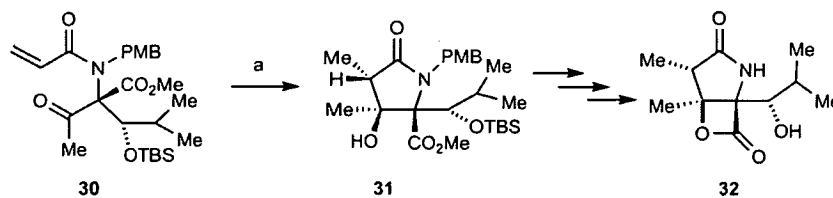
Reagents and conditions: (a) Ti(Oi-Pr)$_4$ (4 eq), c-C$_5$H$_9$MgCl (7 eq), t-BuOMe, -40 °C to -20 °C, then 1 N aq HCl, 95%.

Scheme 1.8 *Synthesis of 3-methyl-2-epi-omuralide* **32**

It was surprising that γ-lactam **31** was obtained with a *anti* relationship between the methyl substituent at C2 and the hydroxyl group at C3. The Ti-mediated cyclisations of γ,ε-unsaturated ketones[40] have been proposed to occur through a bicyclic organotitanium intermediate such as **33** (Scheme 1.9). However, the *anti* arrangement in γ-lactam **31** of substituents at C2 and C3 suggested that the cyclisation occurs *via* a monocyclic intermediate such as **34**. The formation of **34** could be explained *via* a two-step mechanism involving transfer of (RO)$_2$Ti from the Kulinchovich reagent **27** to the acrylamide α,β-double bond of **30**, followed by radical addition[41] of that intermediate to the methyl ketone, which is chelated through MgCl with the methyl ester carbonyl.
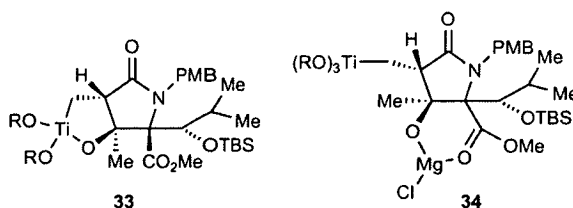
Scheme 1.9 *Bicyclic organotitanium intermediate vs radical mechanism*

Novel methodology for the methyl ester cleavage, β-lactone formation and the chlorination procedure was also reported.[22, 23] A novel sequence of three reactions was developed and applied in the transformation of dihydroxylactam **35** to the salinosporamide-omuralide hybrid **9** (Scheme 1.10). The cleavage of the methyl ester was a challenging step due to the strong steric hindrance of the CO$_2$Me carbonyl and the tendency of **35** to undergo retroaldol cleavage and other undesired reactions. A new reagent was successfully developed, (Me$_2$TeAlMe)$_2$, readily generated by

16

heating tellurium powder and $AlMe_3$ in toluene for 6 h and cooling the product to room temperature.[42] This reagent selectively attacks the methyl group of the methyl ester, instead of the carbonyl, and it can operate under mild conditions in terms of temperature and basicity.

Without further purification, the resulting carboxylic acid was reacted with Ph_3PCl_2 in dry 1:1 MeCN-pyridine to give directly **36** in 89% yield. This efficient operation combined the side chain chlorination with a novel method of β-lactonisation in a single step. Finally, desilylation afforded the salinosporamide-omuralide hybrid **9**.
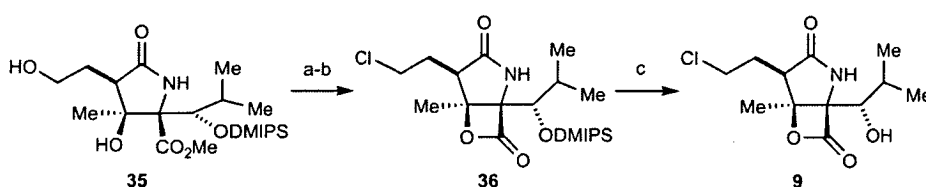
Reagents and conditions: (a) $[MeTeAlMe]_2$ Toluene, 23 °C, 12 h; (b) PPh_3Cl_2, CH_2Cl_2, pyridine, 12 h, 89%; (c) NEt_3•3HF, THF, 23 °C, 4 h, 92%.

Scheme 1.10 *Completion of the synthesis of salinosporamide-omuralide hybrid 9 via a novel sequence of three reactions*

Corey's total synthesis of salinosporamide A *via* a Baylis-Hillman cyclisation to construct γ-lactam **29** was achieved in 8.7% overall yield over eighteen steps. This was improved with a less time consuming, very efficient and completely diastereoselective cyclisation reaction employing the Kulinkovich reagent **27**, methodology that allows the synthesis of salinosporamide A in eightteen steps and an improved 9.1% overall yield.

1.2.2. Danishefsky's synthesis

The second total synthesis of **1** was published by Danishefsky in 2005.[27] This synthetic route afforded salinosporamide A from **37** in twenty-eight steps and in 1.8% overall yield . It started from the pyroglutamate derivative **37** derived from *L*-glutamic acid (Scheme 1.11).[43] The strong facial bias of this bicyclo[2.2.0] compound **37** allowed the creation of the stereocentre at C3 through treatment with divinyl cuprate, attacking from the α-face (addition completely diastereoselective).

This was followed by alkylation at C2 with β-benzyloxy iodoethane, with attack now from the β-face, to give lactam **38** as a 14:1 mixture of diastereoisomers.

Acylation at C4 would be achieved *via* conversion of the vinyl group into a carbonate ester acylating agent. Ozonolysis of **38** and reductive treatment with sodium borohydride produced alcohol **39**. Carbonate formation and aminal cleavage using TfOH afforded alcohol **40**, which was subjected to Jones oxidation to the carboxylic acid, *tert*-butyl ester formation and imidate formation with Meerwein's reagent (Et_3OBF_4) to produce **41**.
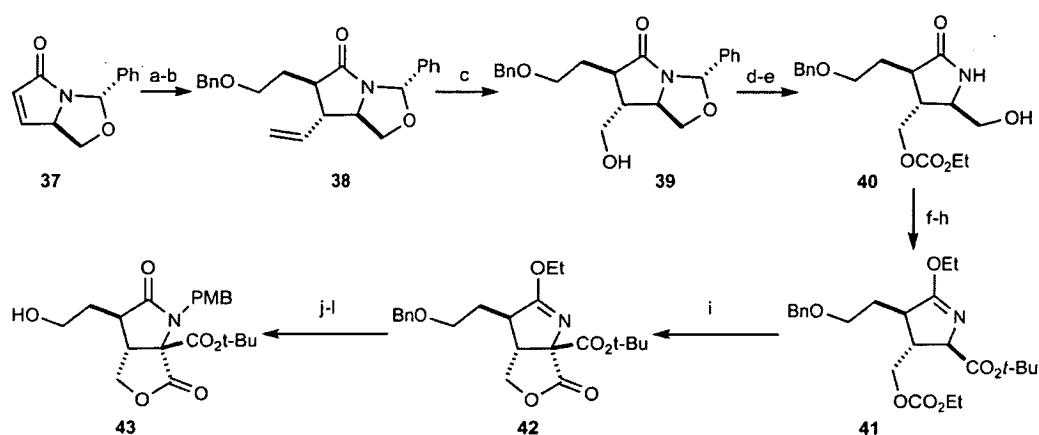
Reagents and conditions: (a) vinylmagnesium bromide, TMSCl, CuI, −78 °C, 75%; (b) [(2-iodoethoxy)methyl]benzene, LDA, THF, rt, 77%, dr = 14:1; (c) O_3, CH_2Cl_2-MeOH (3:1), -78 °C then $NaBH_4$, 0 °C (86%); (d) $ClCO_2Et$, pyridine, rt, 96%; (e) TfOH, THF-H_2O (9:1), rt, 100%; (f) Jones reagent, acetone, rt; (g) $Me_2NCH(Ot\text{-}Bu)_2$, toluene, reflux, 72% over 2 steps; (h) Et_3OBF_4, K_2CO_3, CH_2Cl_2, rt, 88%; (i) LHMDS, THF, -20 °C, 82%; (j) 1 M HCl aq, THF, 0 °C, 90%; (k) PMBCl, NaH, DMF, rt, 61%; (l) $Pd(OH)_2$-C, H_2, EtOH, rt, 100%.

Scheme 1.11 *Danishefsky's synthesis (I)*

With the lactam functionality thus masked, internal acylation of C4 with the pendant carbonate occurred in good yield using LHMDS, forming intermediate **42**. In this step, the stereogenic centre at C4 was constructed. The lactam was unmasked under acidic conditions, the amide was then protected with PMBCl and the benzyl ether was cleaved to give lactam **43**.

Nucleophilic lactone ring-opening of **43** with a phenylselenium anion generated from $(PhSe)_2$ and $NaBH_4$ followed by benzyl ester formation of the resulting carboxylic acid afforded **44** (Scheme 1.12). The subsequent selenide

oxidation/elimination sequence afforded a mixture of the expected alcohol **45** (72%), along with aldehyde **46** (22%). Upon purification, the unoxidised material was converted into aldehyde **46** *via* a Dess-Martin periodinane[35] oxidation (89% in three steps from **44**).
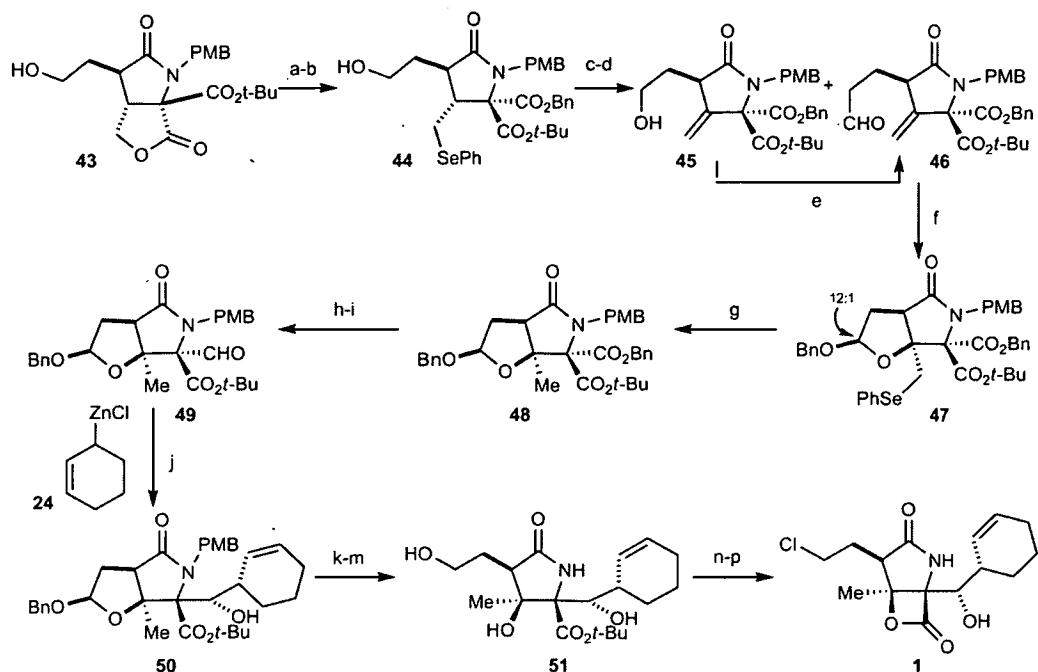
Reagents and conditions: (a) PhSeSePh, NaBH$_4$, EtOH, 60 °C; (b) BnBr, K$_2$CO$_3$, DMF, rt, 72% over 2 steps; (c) 30% H$_2$O$_2$ aq, THF, rt; (d) toluene, 100 °C, 72% **45** + 22% **46** over 2 steps; (e) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 92% (89% in three steps from **44**); (f) PhSeBr, AgBF$_4$, BnOH, CH$_2$Cl$_2$, −20 to 0 °C, 74% as an anomeric mixture (12:1); (g) AIBN, nBu$_3$SnH, toluene, 100 °C, 98%; (h) NaBH$_4$, THF-EtOH (3:1), rt, 85%; (i) Dess-Martin periodinane, CH$_2$Cl$_2$, rt, 95%; (j) cyclohexenyl zinc chloride **24**, THF, −78 °C; (k) CAN, CH$_2$Cl$_2$-H$_2$O, 0 °C, 90%; (l) Na, liq NH$_3$, −78 °C; (m) NaBH$_4$, THF-H$_2$O (2:1), rt, 97% over two steps; (n) BCl$_3$, CH$_2$Cl$_2$, 0 °C; (o) BOPCl, NEt$_3$, CH$_2$Cl$_2$, rt; (p) PPh$_3$Cl$_2$, pyridine, CH$_2$Cl$_2$, rt, 51% over 3 steps.

Scheme 1.12 *Danishefsky's synthesis (II)*

Treatment of **46** with phenylselenium bromide and AgBF$_4$ in the presence of benzyl alcohol gave acetal **47**, setting up the desired stereochemical relationship at C2 and C3. Subsequent radical deselenenylation of **47** yielded **48**, which contains the desired C3 methyl substituent. Selective reduction of the benzyl ester of **48** to the alcohol followed by a Dess Martin oxidation[35] afforded aldehyde **49**. Stereoselective introduction of the cyclohexenyl group was conducted using Corey's procedure[26]:

treatment of the PMB protected γ-lactam **49** with the cyclohexenyl zinc reagent **24**, produced **50** with an excellent yield and diastereoselectivity. It was reported that the use of this methodology on the corresponding imidate aldehyde derived from **42** (Scheme 1.11) instead of on **49** resulted in poor diastereoselectivity (78% yield, 4:3, configuration not determined). This showed that the PMB group played a critical role in diastereoselection in this novel addition.

Removal of the PMB group, followed by reductive opening of the benzyl glycoside, gave rise to triol **51**. Lewis acidic cleavage of the *tert*-butyl ester was effected through treatment with BCl_3, and the crude trihydroxy acid was then subjected to lactonisation-chlorination to provide salinosporamide A (**1**).

1.2.3. Pattenden Racemic Synthesis

Pattenden and co-workers reported in 2006 a racemic synthesis of salinosporamide A, outlined in Scheme 1.13.[29] In this route, (±)-**1** was obtained from **52** in fourteen steps and 11.5% overall yield.

Protection of known ketone **52**[44] as an acetal was followed by ester hydrolysis and coupling of the resulting acid with dimethyl 2-aminomalonate to afford amide **53**. This intermediate was transformed into amide γ-lactam (±)-**54** *via* a diastereoselective acid catalysed intramolecular cyclisation. When a solution of **53** in acetic acid/water (4:1) was heated at 65 °C for 4 days, deprotection of the dioxolane and *in situ* cyclisation occurred, leading to a single diastereomer of (±)-**54**.

The tertiary alcohol of (±)-**54** was then TMS-protected and the lactam nitrogen was protected with a PMB group, forming (±)-**55**. The ester *anti* to the protected alcohol was then selectively reduced to the aldehyde using lithium superhydride. The cyclohexenyl side chain was inserted into (±)-**56** following Corey's procedure,[26] obtaining the addition product (±)-**57** with excellent diastereoselectivity.
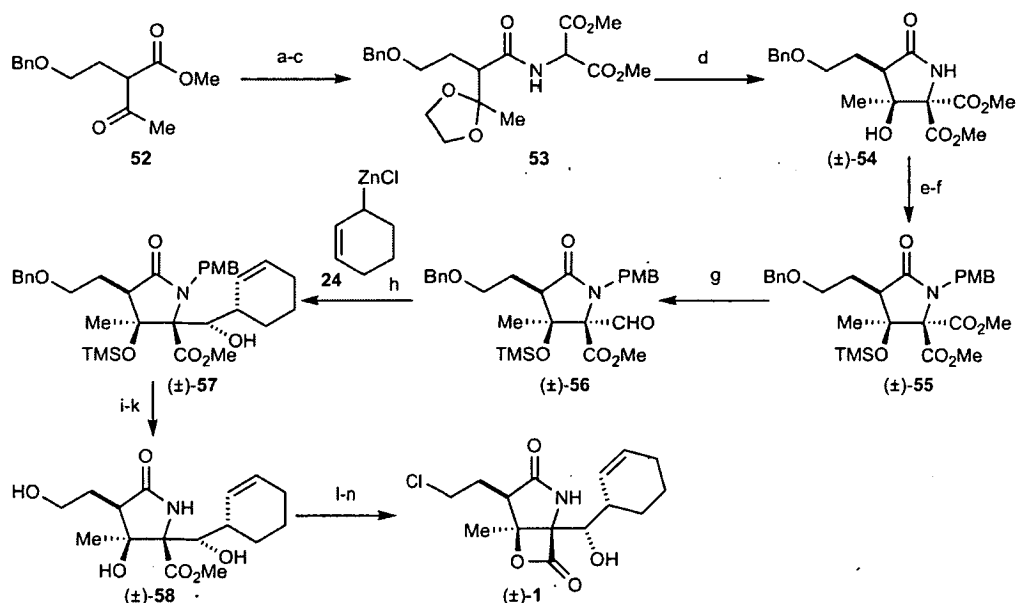
Reagents and conditions: (a) ethylene glycol, *p*-TsOH, benzene, 110 °C, 14 h; (b) 2M NaOH, EtOH, 70 °C, 3 h; (c) dimethyl aminomalonate·HCl, HOBt, EDC·HCl, CH_2Cl_2, NMM, 0 °C to rt (82% over 3 steps); (d) 4:1 AcOH–H_2O, 65 °C, 4 d (71%); (e) excess TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to 0 °C, then 1 M HCl (91%); (f) PMB-Br, NaH, DMF, 0 °C to rt, 14 h (82%); (g) Super-hydride (1.0 M in THF), CH_2Cl_2, −78 °C, 3 h (78%); (h) 2-cyclohexenylzinc chloride **24**, THF, −78 °C (87%); (i) BCl_3·DMS, CH_2Cl_2, 24 h, 0 °C to rt; (j) 48% HF in H_2O-MeCN (1:9), rt, 22 h; (k) CAN, MeCN, H_2O (3:1), 0 °C, 1 h (87% over 3 steps); (l) $[MeTeAlMe_2]_2$, toluene, rt, 24 h; (m) BOP-Cl, CH_2Cl_2, pyridine, rt, 3 h; (n) PPh_3Cl_2, MeCN, pyridine, rt, 4 h (45% over 3 steps).

Scheme 1.13 *Pattenden's synthesis*

Cleavage of the benzyl ether and trimethylsilyl ether, followed by deprotection of the PMB group on the lactam nitrogen afforded Corey intermediate (±)-**58**,[26] which was then converted into (±)-salinosporamide A following reported methods.[22, 23, 42]

1.2.4. Langlois's formal synthesis

In 2006, Langlois and co-workers reported a formal synthesis of Salinosporamide A.[31, 32] As it has been shown, Corey's synthesis involved the highly functionalised α-methylene-lactam **29** as a key intermediate (Figure 1.6). Langlois first published a route to (±)-**59**, a closely related scaffold which contains all the required functionality to be transformed into racemic salinosporamide A. Their synthetic strategy was based on a regio- and stereoselective *N*-methylnitrone cycloaddition.
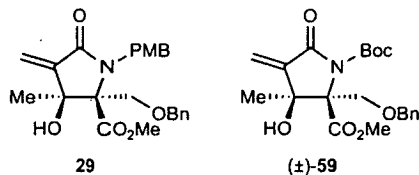
Figure 1.6 *α-Methylene-lactam key intermediates* **29** *and* (±)-**59**

Selective alkylation of methyl pyroglutamate **60** with chloromethylbenzylether was successfully achieved using LHMDS (Scheme 1.14). *N*-Boc protection afforded intermediate **61**. This protection improved the reactivity of the lactam carbonyl, allowing efficient classical introduction of the double bond to give **62**. A stereoselective methylcuprate addition was then performed (product obtained as a single diastereomer), followed by reintroduction of the double bond, yielding **63**. A regio- and stereoselective 1,3-dipolar cycloaddition of *N*-methylnitrone with **63** was achieved affording (±)-**64** in 57% yield. In this step the C3 hydroxyl group and the precursor for the C2 exo-methylene group are introduced. The cleavage of the isoxaline N-O bond was performed chemoselectively by hydrogenolysis using Pearlman's catalyst, without affecting the *O*-benzyl group. Finally, methylation with an excess of iodomethane and treatment with triethylamine afforded the target intermediate (±)-**59**.
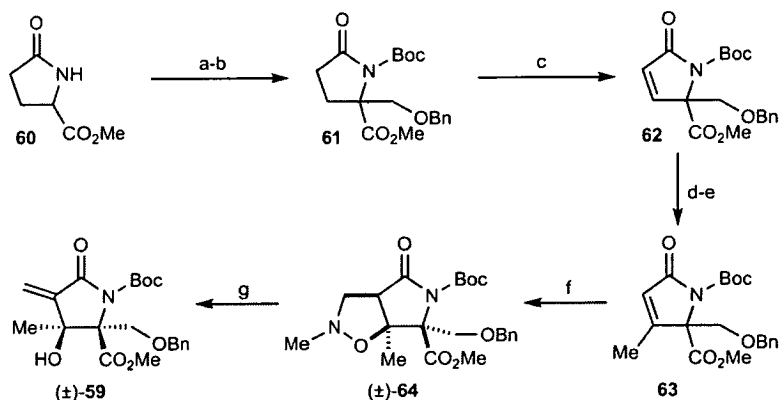
Reagents and conditions: (a) LHMDS, THF, BnOCH₂Cl (53%); (b) (Boc)₂O, DMAP, MeCN (100%); (c) (i) LHMDS, THF, PhSeCl; (ii) H₂O₂, CH₂Cl₂, pyridine (89%); (d) Me₂CuLi, THF, TMSCl (83%); (e) (i) LHMDS, THF, PhSeCl; (ii) H₂O₂, CH₂Cl₂, pyridine (75%); (f) *N*-methylnitrone, toluene, reflux (57%); (g) (i) H₂, Pd(OH)₂, EtOAc-MeOH (72%); (ii) MeI, THF, Et₃N (65%).

Scheme 1.14 *Racemic formal synthesis*

A second publication by Langlois reported an asymmetric route to **1**. To obtain enantiopure **29** and **59** (Figure 1.6), (*S*)-methyl 2-hydroxymethylpyroglutamate **67** was chosen as the chiral precursor (Scheme 1.15). This compound has been prepared before from bicyclic nitrile **65**.[45] Selective *O*-benzylation of **67** was successfully achieved using 2-benzyloxy-1-methylpyridinium triflate (**68**), leading to **69** in 75% yield. From intermediate **69**, the synthesis of enantiopure **59** (Figure 1.6) is achievable, because the subsequent steps of the racemic synthesis (Scheme 1.14) cannot produce racemisation.
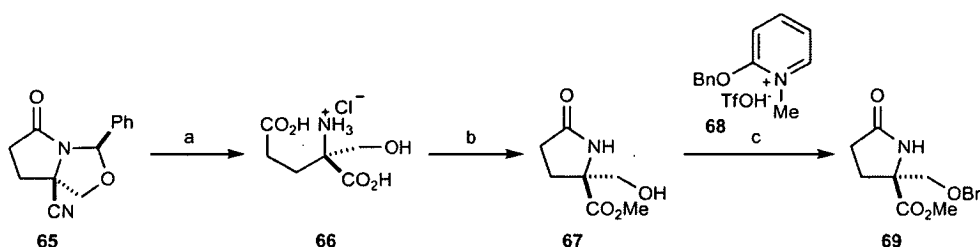
Reagents and conditions: (a) 6N HCl, reflux (98%); (b) CH_2N_2, Et_2O (67%); (c) **68**, MgO, $PhCF_3$, reflux (75%).

Scheme 1.15 *Langlois' formal synthesis*

This chemistry was also employed for the synthesis of Corey's intermediate **29**. Starting from PMB-protected **69**, the double bond introduction (Scheme 1.14) was achieved in a very low yield. Therefore **69** was transformed into the *N*-Boc derivative **59**, which was followed by removal of the Boc protecting group and PMB protection, to afford pyrrolinone **70** (Scheme 1.16).

The *N*-methylnitrone cycloaddition with **70** occurred with the expected regioselectivity, but slightly lower stereoselectivity (ratio 4:1), giving the desired diastereomer **72** in 54 % yield (14% of **71**). After hydrogenolysis (**73**), *N*-methylation using iodomethane and elimination in a biphasic mixture of aqueous Na_2CO_3, and CH_2Cl_2 afforded the target α-methylenelactam **29**. This route represents a formal synthesis of the natural product salinosporamide A from **67** in eighteen steps and 4% overall yield.
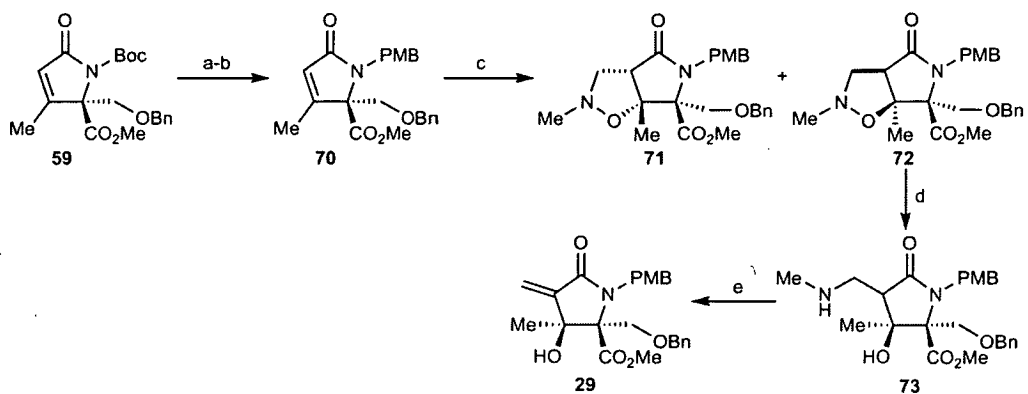
Reagents and conditions: (a) CF_3CO_2H, CH_2Cl_2 (100%); (b) $CsCO_3$, PMBBr, DMF (57%); (c) *N*-methylnitrone, toluene, reflux (14% for **71**, 54% for **72**); (d) H_2, Pd(OH)$_2$, EtOAc-MeOH (64%); (e) (i) MeI, MeOH; (ii) Na_2CO_3, CH_2Cl_2 (90%).

Scheme 1.16: *Langlois' formal synthesis*

1.2.5. Romo's synthesis

A racemic synthesis of salinosporamide A was published by Romo and co-workers in March 2007.[30] In this publication, they reported new methodology to form the bicyclic core of the natural product, *via* an intramolecular bis-cyclisation process which forms the C-C and the C-O bonds simultaneously (Scheme 1.17). This bis-cyclisation process permitted the synthesis of the (±)-bicyclic-β-lactone with the required relative configuration. Potential enolisation and subsequent racemisation at C2 was not problematic since, due to the conformationally controlled acidity of β-ketoamides owing to $A^{1,3}$ strain,[46] retention of this stereocentre occurred. This route allowed the synthesis of (±)-salinosporamide A in nine steps and 1.2% overall yield.
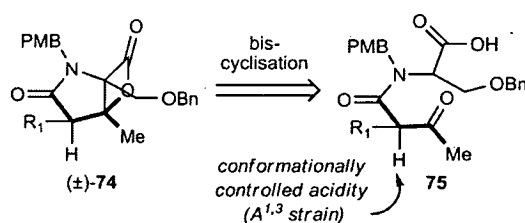

Scheme 1.17: *Racemic formal synthesis*

In this synthesis, *N*-PMB serine allyl ester **77** was obtained in two steps from benzyl protected serine **76** and then coupled with heteroketene dimer **78**, providing .

79, which afforded ketoacid **80** after Pd-mediated ester deprotection (Scheme 1.18). Bis-cyclisation of **80** gave bicyclic-β-lactones (±)-**82** and (±)-**83** in 25-35% yield, in favour of the relative configuration of salinosporamide A (dr 2-3:1). This was a much lower yield than the ones obtained in bis-cyclisation reactions with C4-unsubstituted substrates, most likely due to increased steric crowding.

Deprotection of the benzyl ether allowed enrichment of the major diastereomer (±)-**84** to 6-10:1 after purification. A modified Moffat oxidation[47] using EDCI and dichloroacetic acid, followed by addition of 2-cyclohexenyl zinc chloride gave two diastereomeric alcohols (dr 3.5:1) in 33% yield. Finally, PMB deprotection of (±)-**85** permitted isolation of diastereomerically pure (±)-salinosporamide A.
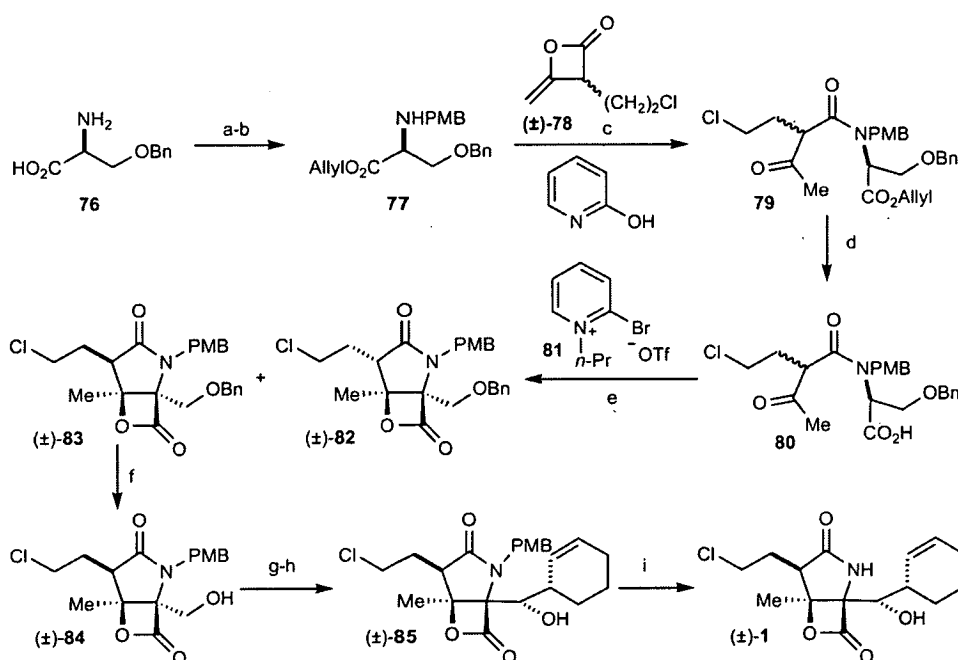
Reagents and conditions: (a) *p*-anisaldehyde, MeOH, NaBH$_4$; (b) *p*-TsOH, allyl alcohol (74%, 2 steps); (c) THF, 60 °C, 36 h (80%); (d) Pd(PPh$_3$)$_4$, morpholine (75%); (e) DIPEA, PPY, CH$_2$Cl$_2$, −10 °C, 6 h (25-35 %, dr 2-3:1); (f) H$_2$, Pd/C, THF, 25 °C (98%); (g) EDCI, DMSO, Cl$_2$CHCO$_2$H; (h) 2-cyclohexenylzinc chloride **24**, THF, −78 °C (33%, 2 steps, dr 3.5:1); (i) CAN, MeCN/H$_2$O (49%, major diast.).

Scheme 1.18 *Racemic formal synthesis*

1.2.6. Macherla's synthesis

Another enantioselective synthesis of salinosporamide A was reported by Macherla and co-workers in 2007.[28] This synthesis starts with a MsCl-mediated amide coupling of **86** and **87** to give protected β-ketoamide **88** (Scheme 1.19).

Oxazolidine **87** serves both as a group to induce chirality in the aldol cyclisation performed in a later step and as a protecting group. Deprotection of the ketone generated β-ketoamide **89** as a mixture of epimers at the α-carbon containing the allyl group.

The next step generated key intermediate **90**, *via* a novel enantioselective intramolecular aldol cyclisation that uses the self-regeneration of stereocentres principle[48] to generate simultaneously chiral stereocentres C2 and C3. β-Ketoamide **89** was treated with *t*-BuOK to give rise to **90** in 64% yield and 70% d.e., along with minor diastereomers and dehydration product. The chirality of C4 stereocentre was maintained in the reaction.

The highly functionalised intermediate **90** was then transformed into **91** (and its diastereomer, 5:1 ratio) *via* oxidative cleavage of the allyl group with OsO₄/NMO followed by treatment with NaIO₄ and then treatment with BnBr in the presence of *t*-BuOK. The methyl ester of **91** was reduced to the alcohol and reoxidised to the aldehyde **92** using a TPAP/NMO oxidation[49]. The use of Corey's methodology[26] to install the cyclohexene ring on **92** was not successful in this system and Brown's allylboration chemistry[50] had to be used instead. Aldehyde **92** was reacted with *B*-2-cyclohexen-1-yl-9-BBN (**93**) to give the expected *syn* addition product **94**, having the desired stereochemistry at C6, but the required stereocentre at C5 would have to be regenerated later.

The benzyl acetal in **94** was opened and transformed into the benzoyl protected alcohol **96**. This transformation aimed to obtain a protecting group that would withstand the strong acidic conditions of the aminal deprotection (1,3-propanedithiol, HCl, TfOH), because if the benzyl alcohol was deprotected, it could not be differentiated later in the synthesis from the other primary alcohol (C15 in **96**). Oxidation of the C15 alcohol was only possible after protection of the C5 hydroxyl group. It was found out that TMS protection of C5 hydroxyl followed by a 2-step oxidation afforded the corresponding carboxylic acid **97**.

Deprotection of the benzoyl group of **97** was followed by β-lactone formation with BOPCl and chlorination of the primary alcohol with Ph₃PCl₂ afforded **98**, the C5 epimer of **1**. The C5 hydroxyl group was oxidised to the ketone using Dess-

Martin periodinane[35], which was stereoselectively reduced by a ketoreductase enzyme to afford the desired (–)-**1**.

The synthesis of salinosporamide A was achieved in twenty-four steps and 0.2% overall yield. The key formation of **90** was accomplished *via* an impressive enantioselective intramolecular aldol cyclisation, but protecting group manipulations and the regeneration of the C5 stereocentre added extra steps and lowered the yield of this synthetic route.
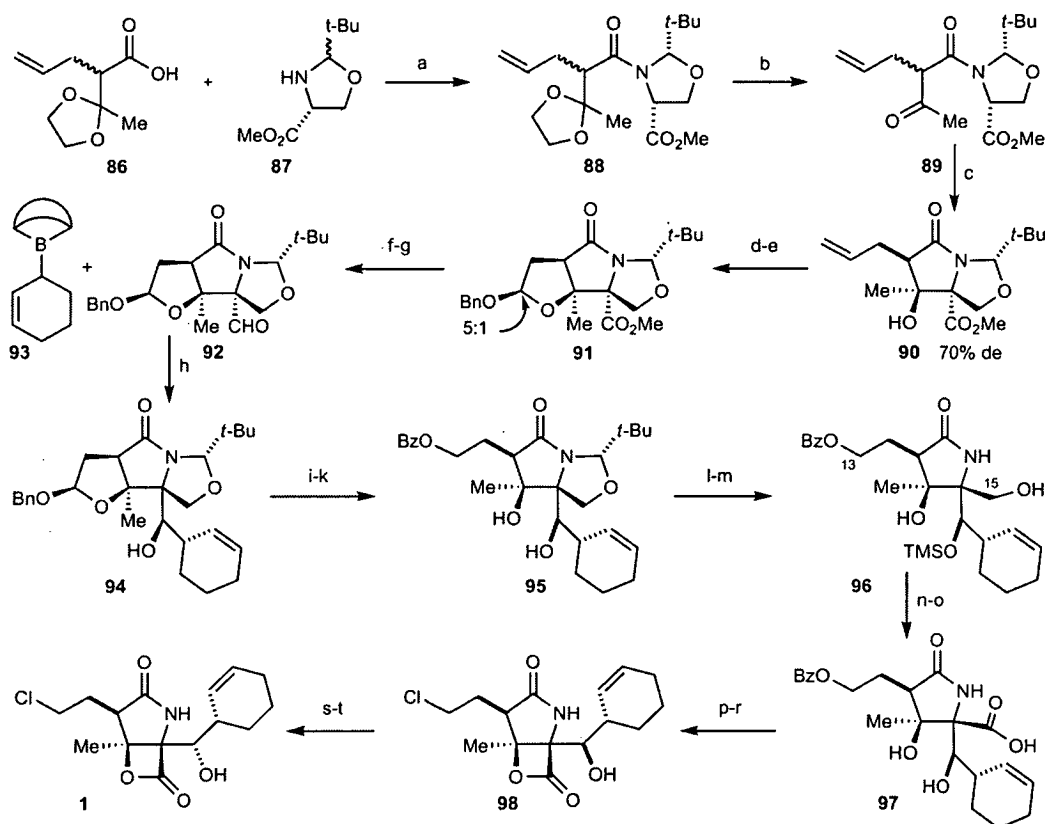

Reagents and conditions: (a) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C to rt, o/n (66%); (b) CeCl$_3$.7H$_2$O, NaI, MeCN, 60 °C, 4 h (84%); (c) *t*-BuOK, THF, rt, 15 min (64%, 70% de); (d) OsO$_4$, NMO, H$_2$O/THF, 3 h then NaIO$_4$, 2 h, (99%); (e) BnBr, *t*-BuOK, THF, 6 h, 76%; (f) LiBH$_4$, THF, 24 h (94%); (g) TPAP (cat.), NMO, CH$_2$Cl$_2$, 18 h (79%); (h) THF, –78 °C to rt, 11.5 h (80%); (i) HCl, THF, 60 °C, 10 h; (j) NaBH$_4$, THF/H$_2$O, 30 min (81%, 2 steps); (k) BzCl, Et$_3$N, CH$_2$Cl$_2$, 10 h (87%); (l) 1,3-propanedithiol, HCl, CF$_3$CH$_2$OH, 60 °C, 4 h (94%); (m) TMSCl, Et$_3$N, CH$_2$Cl$_2$, 12 h (53%); (n) Dess-Martin periodinane, CH$_2$Cl$_2$, 2 h; (o) NaH$_2$PO$_4$, NaClO$_2$, 2-methyl-2-butene, *t*-BuOH/H$_2$O, 0 °C, 1.5 h (63%, 2 steps); (p) K$_2$CO$_3$, MeOH, 15 h; (q) BOPCl, pyridine, MeCN, 2 h (60%, 2 steps); (r) Ph$_3$PCl$_2$, pyridine, MeCN, 18 h (57%); (s) Dess-Martin periodinane, CH$_2$Cl$_2$, 2 h (60%); (t) KRED-EXP-B1Y, NAD+, GDH-103, glucose, pH 6.9, 37-39 °C, 40 min (56%).

Scheme 1.19 *Macherla's total synthesis*

1.3. Objectives

The outstanding biological activity of salinosporamide A together with the challenge of synthesising the densely functionalised and compact structure prompted us to investigate a synthetic route to this natural product. The ultimate aim of this project was to develop a synthesis of salinosporamide A which is efficient, stereocontrolled and amenable to the preparation of significant quantities of the natural product.

Our objective was to integrate the development of new catalytic reaction methodologies into the synthesis of **1**. In parallel studies conducted by other PhD students within our group, the development of copper-, cobalt-, and nickel-catalysed reductive aldol cyclisations resulting in the production of β-hydroxylactones and β-hydroxylactams was being undertaken (Scheme 1.20). The successful application of a suitable variant of these methodologies within a complex setting, such as in a total synthesis of **1**, would serve to demonstrate the utility of this chemistry.
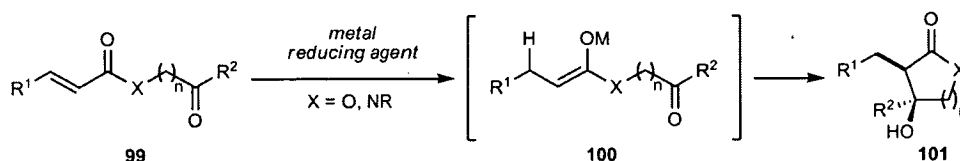
Scheme 1.20 *Reductive aldol cyclisation methodology*

To examine the feasibility of the use of this approach in our system, an amide represented by **102** would be first prepared (Scheme 1.21). With this substrate, the conditions for the reductive aldol cyclisation would be investigated, aiming to obtain γ-lactam **103** with good yields and diastereoselectivities. We envisaged this advanced intermediate could be converted into salinosporamide A (**1**) in a few straightforward operations.
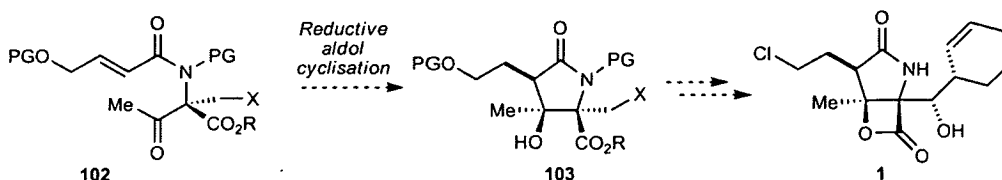
Scheme 1.21 *Reductive aldol cyclisation approach*

However, at the inception of our studies these methodologies were not available. Therefore, we would initially focus our efforts on a racemic synthetic approach that looked to be concise, allowing rapid assembly of much of the functionality of **1** (Scheme 1.22). The first target of this route was the synthesis of a γ-lactam such as **104**. Three key transformations would be then performed on this substrate: selective reduction to the aldehyde of the diester functionality, insertion of the cyclohexenyl side chain and alkylation at C2. If these three operations were successful, a few final transformations would afford (±)-**1**.
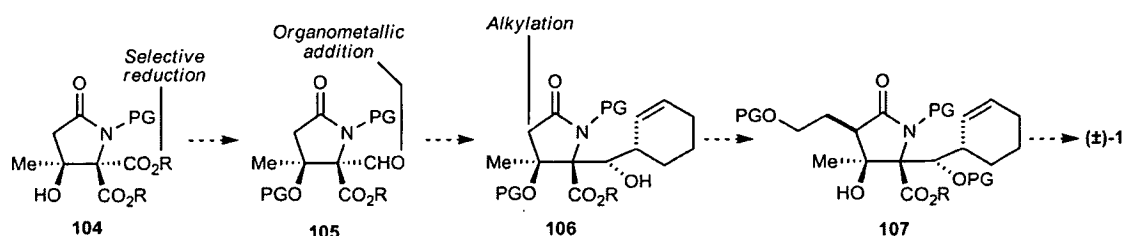
Scheme 1.22 *Initial investigations to (±)-1*

If this route was successful, we hoped to investigate the development of an asymmetric variant. With this approach we would also learn about the chemical behaviour of these γ–lactam intermediates and this knowledge could also be applied eventually into the route developed with the reductive aldol cyclisation approach.

2. Racemic approach based on amidomalonate aldol cyclisations

When this project began, the methodology studies on the catalysed reductive aldol cyclisation were simultaneously initiated. Until that methodology was developed, efforts were focused on another synthetic approach, the development of which is described herein.

2.1. Retrosynthetic analysis

Our first approach to salinosporamide A is outlined in Scheme 2.1. Disconnection of the β-lactone of **1**, transformation of the chlorine atom on the ethyl side chain and deprotection of the lactam nitrogen atom lead back to intermediate **107**. It was envisioned that the hydroxyethyl side chain of **107** could be inserted, after protecting group manipulations, *via* an enolate alkylation on **106**. Introduction of the side chain at C2 at a late stage in the synthesis would facilitate the preparation of derivatives of **1**.

Disconnection of the cyclohexenyl side chain of **106** reveals aldehyde **105** and cyclohexenyl zinc reagent **24**, methodology that had been successfully developed by Corey and co-workers in their total synthesis of **1**.[26] This reaction constructs stereoselectively the two contiguous stereogenic centres at C5 and at C6. It was anticipated that aldehyde **105** could be prepared by selective mono-reduction of the diester functionality of **104**. Our initial efforts targeted the construction of a γ-lactam such as **104**.
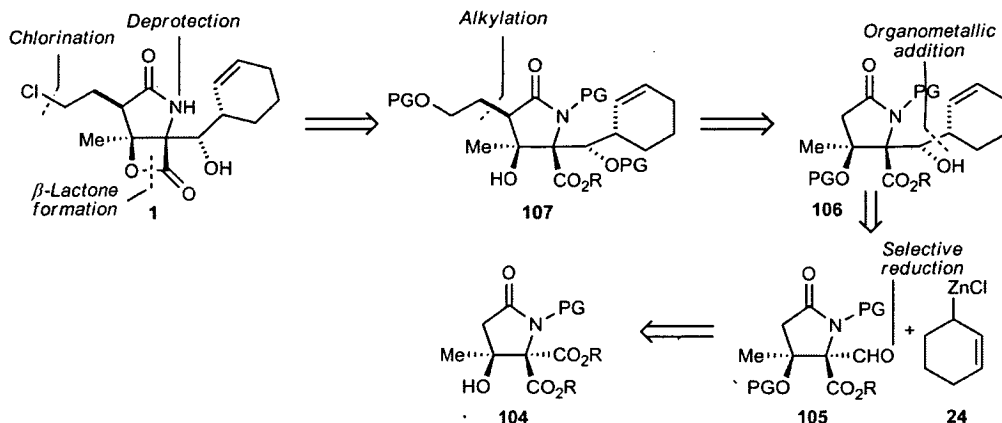
Scheme 2.1 *First retrosynthetic analysis of salinosporamide A (1)*

2.2. Results and discussion

2.2.1. Synthesis of the γ-lactam

Inspection of the literature revealed that a γ-lactam of general structure **104** had been prepared previously.[51] Pyrrolidinone **110** was obtained *via* an acid catalysed reaction of *N*-PMP diethyl aminomalonate **109** with diketene **108** (Scheme 2.2). γ-Lactam **110** was then transformed into β-lactam **111**, which was proposed as a suitable intermediate in the synthesis of β-lactam antibiotics such as thienamycin (**113**).[52]
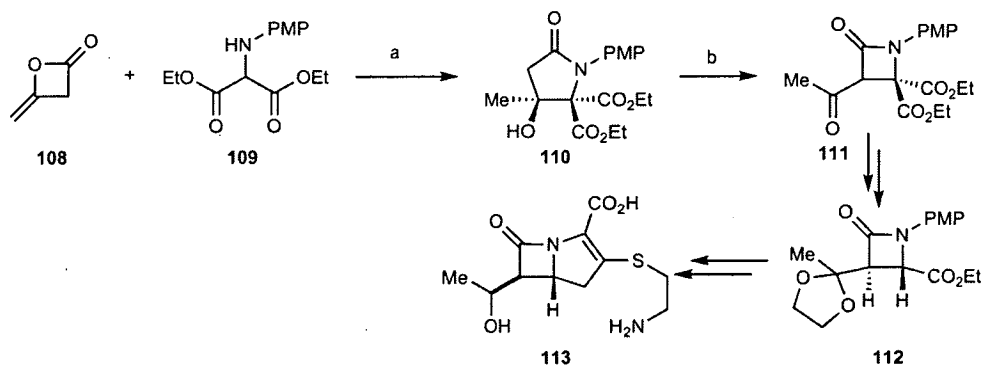
Reagents and conditions: (a) HOAc, reflux, 72%; (b) I_2, EtONa, 62%.

Scheme 2.2 *Reported example of the synthesis of 110 using diketene*

Diketene (**108**) is a reactive and versatile compound which is best known as a reagent for the preparation of acetoacetic acid derivatives (Scheme 2.3). It is a strained molecule which is readily ring-opened and therefore it frequently appears to

react as acetylketene (**114**).[53] It is known that aliphatic amines are rapidly acetoacetylated by diketene, without the need for a catalyst. Therefore, in this example, reaction of amine **109** with diketene presumably forms acetoacetamide **115**, which provides γ-lactam **110** *via* an acid catalysed aldol cyclisation.
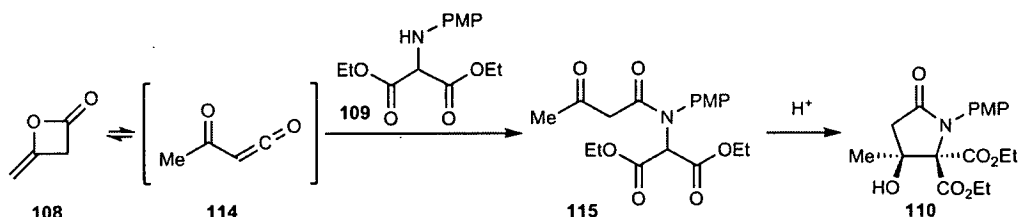
Scheme 2.3 *Synthesis of 110*

It was therefore decided to exploit this procedure in the preparation of the γ-lactam, which would be the starting point of our synthetic route. For this purpose, three aminomalonate derivatives were first prepared. The synthesis of *N*-PMP diethyl ester malonate **109** was successfully achieved reacting *p*-anisidine (**117**) and diethyl bromomalonate (**116**) in refluxing Et$_2$O. Following the reaction, a simple recrystallisation afforded amine **109** in 85% yield (Scheme 2.4).
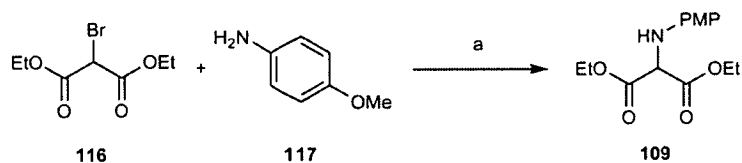
Reagents and conditions: (a) Et$_2$O, 2 h heating under reflux, 14 h rt, 85%.

Scheme 2.4 *Synthesis of amine 109*

N-PMB-protected aminomalonates **119** and **121** were also prepared (Scheme 2.5). The use of a PMB protecting group on the nitrogen was desirable, because although similar conditions are employed for the deprotection of both PMP and PMB groups (CAN reagent), the PMB group is much more readily cleaved than the PMP group.[54] In addition to this, Corey employed a *N*-PMB protecting group in the organometallic addition into aldehyde **23** (Scheme 1.6) to introduce the cyclohexenyl side chain.[26]

Diethyl bromomalonate (**116**) and *p*-methoxybenzyl amine (**118**) were reacted in the presence of Et₃N to yield amine **119** (52%), although with a lower yield than that obtained for the *N*-PMP equivalent. Similarly, **118** was reacted with dimethyl 2-bromomalonate (**120**), which afforded **121** in a 35-40% yield.
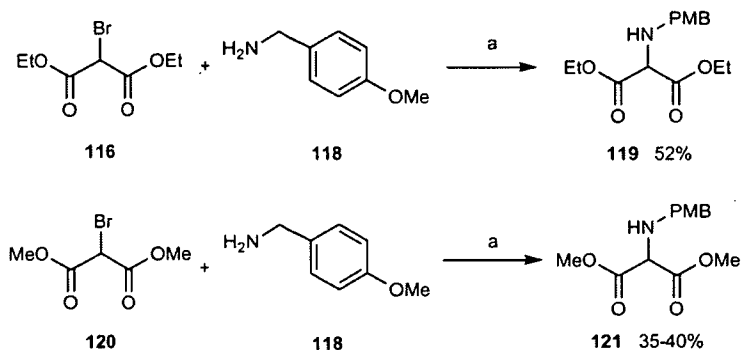
Reagents and conditions: (a) Et₃N (1 eq), MeCN, 0 °C to rt, 14 h.

**Scheme 2.5** *Synthesis of N-PMB protected amines 119 and 121*

We proceeded then to study the formation of the γ-lactam. Two procedures were investigated. Initially, we conducted the reported procedure, which involved reaction of diketene with the aminomalonate.[51] Due to the fact that diketene is now difficult to access from commercial sources, we decided to modify slightly the original procedure, by generating diketene *in situ*. Therefore, acetyl chloride was treated with Et₃N, followed by addition of amine **121**, to successfully afford γ-lactam **123**. Scheme 2.6 outlines the mechanism of this reaction. One equivalent of Et₃N reacts with acetyl chloride (**122**), eliminating HCl and forming ketene (**124**). A substoichiometric quantity of base then reacts with some of this ketene to form an ammonium enolate (**125**), which attacks ketene present in the media to give diketene **108**. Then, in the presence of DMAP as a catalyst, amine **121** reacts with diketene, forming the uncyclised amide **127**, which spontaneously cyclises to form γ-lactam **123** in good yield.
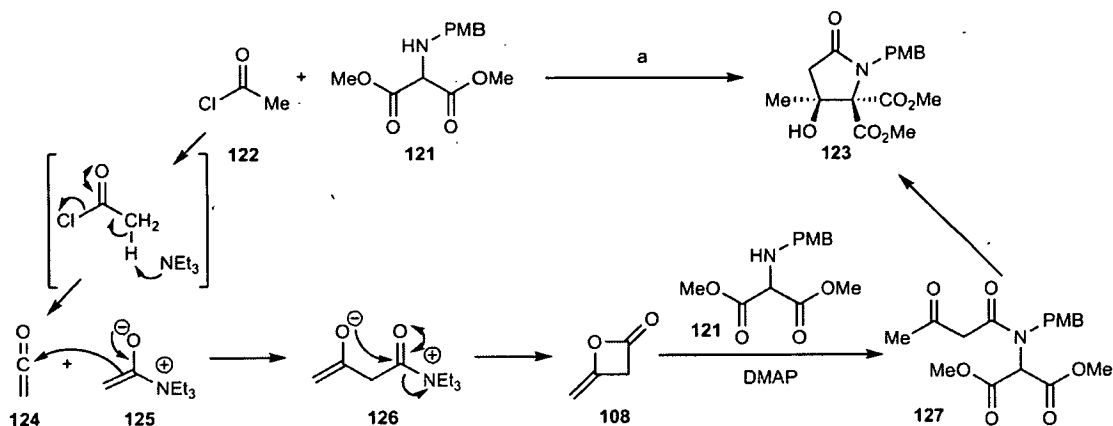
Reagents and conditions: (a) Et$_3$N (1.1 eq), DMAP (0.2 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 70-80%.

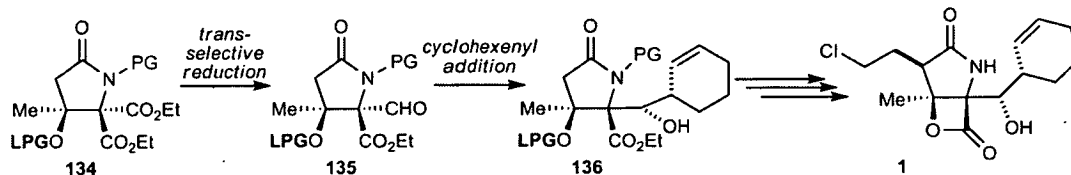**Scheme 2.6** *Mechanism of the formation of γ-lactam **123***

The second procedure investigated involved the reaction of an aminomalonate with dioxinone **129**. In 1952, Carroll and Bader described the acid catalysed reaction of diketene and acetone forming the dioxinone (Scheme 2.7). Subsequently, they reported that **129**, when pyrolysed, decomposes into acetylketene (**114**) and acetone, via a retro-Diels–Alder fragmentation.[55] Clemens reported in 1985 the pyrolysis of **129** in the presence of nucleophiles as a general purpose acetoacetylation procedure.[56] Dioxinone **129** is a commercially available liquid, which is easily handled and stored, and the acetylation reactions are rapid and provide only volatile products.
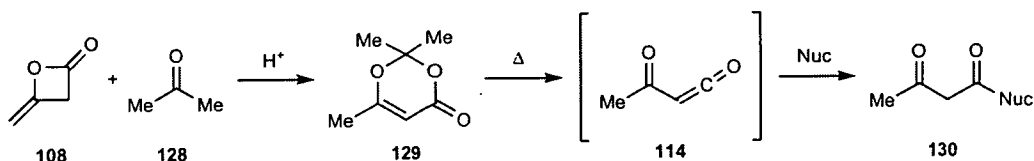
Scheme 2.7 *Synthesis and use of dioxinone **129***

We were pleased to find that γ-lactams **110** and **131** were readily prepared by mixing dioxinone **129** and the corresponding amine (**109** or **119**) in refluxing toluene (Scheme 2.8). Under the reflux conditions, the amine reacts with the acetylketene (**114**) formed in the reaction, to give an acetoacetamide which spontaneously affords the desired γ-lactam via an aldol cyclisation.

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Reagents and conditions: (a) Toluene, 110 °C, 14 h.

Scheme 2.8 *Synthesis of γ-lactams **110** and **131** using dioxinone **129***

This procedure was very easily performed and afforded the desired cyclised products in good yields. Due to this efficiency and practicality, it became our preferred method for the synthesis of the γ-lactam. It was decided to use amines γ-lactams **110** and **131** in parallel studies in the development of the synthesis, since amines **109** and **119** were obtained in higher yields than amine **121**. Moreover, the use of these two γ-lactams would keep consistency in the ester moiety, and only the nitrogen protecting group would vary. It was assumed that having an ethyl ester instead of a methyl ester as the intermediates in Corey's synthesis would not have an important effect in the synthetic route.

2.2.2. Regioselective reduction of the ester and cyclohexenyl insertion

With the γ-lactam in hand, the next step was the selective reduction of the ester *anti* to C3 hydroxyl to the aldehyde (Scheme 2.9). By having the aldehyde *anti* to the tertiary alcohol (**135**), the side chain at C5 would be correctly inserted at this position. It was anticipated that protection of C3 hydroxyl with a suitably bulky group (**134**) would be sufficient to direct reduction of the ester *anti* to it. The ester *syn* to the alcohol (**136**) is necessary in order to form the β-lactone of salinosporamide A.

Scheme 2.9 *Selective reduction of the diester functionality*

Several protection attempts using trimethylsilyl triflate or *tert*-butyldimethylsilyl triflate were unsuccessful, with none or very little desired product obtained. Finally, it was found that γ-lactams **130** and **131** were successfully protected with TMSCl to give the protected silyl ethers **137** and **138**, as shown in Scheme 2.10.
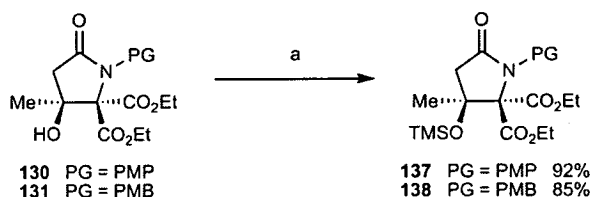
Reagents and conditions: (a) TMSCl (1.5 eq), DMAP (0.2 eq), Et$_3$N (3 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h.

Scheme 2.10 *TMS protection of C3 hydroxyl*

Initial investigations on the selective mono-reduction to the aldehyde, and subsequent addition of the side chain, were done employing the PMP-derivative. A selective reduction of diester **137** to yield an α-formyl ester was achieved using a method described by Burton.[57] In 1993, the Burton group reported the transformation of **139** to predominantly trans-1,4-dialdehyde **140** *via* a stereoselective low-temperature reduction with an excess of DIBAL–H (Scheme 2.11).
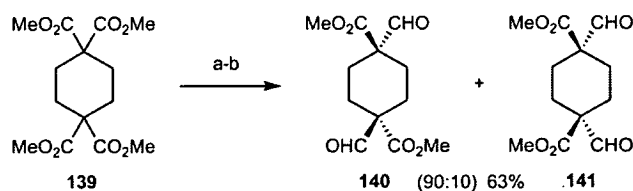
Reagents and conditions: (a) DIBAL–H (4 eq), CH$_2$Cl$_2$, –78 °C, 3 h; (b) HCl (aq), –65 °C, 63%.

Scheme 2.11 *Burton's stereoselective reduction using DIBAL–H*

After some investigation, the optimal conditions for the reduction of **137** were found to be a slow addition of 3.5 equivalents of DIBAL–H to a solution of the ester in CH_2Cl_2 at –78 °C. This reaction did in fact provide a mono-aldehyde product with high selectivity, and minimal traces of over-reduced or doubly reduced products were detected in the unpurified mixture. Initially, we assumed that reduction had occurred *anti-* to the bulky trimethylsilyloxy group to provide the desired aldehyde. In fact, reduction had occurred in the undesired sense to provide aldehyde **144** (Scheme 2.13, *vide infra*).

This outcome was discovered with the next transformation, the insertion of the cyclohexenyl side chain, which was done according to Corey's procedure.[26] 2-Cyclohexenyl tributyltin was first prepared, *via* a 1,4-palladium catalysed addition of tributyltin hydride into 1,3-cyclohexadiene (Scheme 2.12). Initially, this reaction was carried out following the reported method,[36, 58] which utilises $Pd(PPh_3)_4$ in THF. However, it was discovered that the reaction also proceeds using only 0.5 mol% of the less expensive $Pd_2(dba)_3$ and 4 mol% of PPh_3. Toluene was observed to be a better solvent than THF. After stirring overnight, the catalyst was removed by filtration of the reaction mixture through a silica plug and distillation of the crude product under high vacuum gave allylstannane **143** (85% purity)[i].
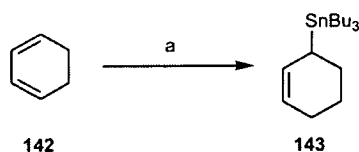
Reagents and conditions: (a) Bu_3SnH (1 eq), $Pd_2(dba)_3$ (0.5 mol%), PPh_3 (4 mol%), toluene, rt, 14 h, 52%.

Scheme 2.12 *Synthesis of 2-cyclohexenyl tributyltin **143***

Subsequently, 2-cyclohexenyl tributyltin **143** was transmetallated at –78 °C, first with *n*-BuLi and then with zinc chloride, forming a solution of 2-cyclohexenyl zinc chloride **24**. A solution of aldehyde **144** in THF at –78 °C was transferred into a solution of the zinc chloride reagent, which provided homoallylic alcohol **145** in 83% yield (Scheme 2.13).

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[i] The purity of **143** was assessed by ^1H NMR spectroscopy, calculating the amount of Bu_3SnH remaining in the sample by integration of the expected 15H from 3 x $CH_2CH_2CH_2CH_3$.

Reagents and conditions: (a) DIBAL–H (3.5 eq), CH_2Cl_2, –78 °C, 1.5 h, 69%; (b) 2-cyclohexenyl zinc chloride **24** (2.5 eq), THF, –78 °C, 4 h, 83%.

Scheme 2.13 *Synthesis of undesired addition product 145*

Alcohol **145** was isolated as a crystalline solid and it was possible to establish its connectivity and relative stereochemistry using X-ray crystallography (Figure 2.1), which unfortunately, revealed unambiguously that reduction of **137** had occurred in the undesired sense. Presumably, prior coordination of DIBAL–H to the oxygen atom of the TMS ether was responsible for the outcome of these reactions (chelate **146**, Scheme 2.13). Although not expected, similar effects have been observed by Evans and co-workers in carbonyl addition reactions of silyloxyaldehydes using aluminium Lewis acids.[59]

Figure 2.1 *X-ray crystal structure of 145*

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Therefore, a reducing agent without this coordinating ability was required, in the hope that the steric hindrance would this time be the determining factor for the selectivity of the reaction. A range of alternative procedures for selective monoreduction of **137** were evaluated and it was discovered that NaBH$_4$/LiCl in THF/EtOH[60] was efficient in this regard to provide alcohol **147** in 90% yield (Scheme 2.14). Re-oxidation of **147** with either Dess-Martin periodinane[35] or under Swern conditions[61] provided aldehyde **148**, which showed slight differences in its ^{1}H NMR spectra to aldehyde **144**. The introduction of the 2-cyclohexenyl chain was carried out following the same procedure as with undesired aldehyde **144**, to provide desired homoallylic alcohol **149** in 85 % yield (Scheme 2.14).
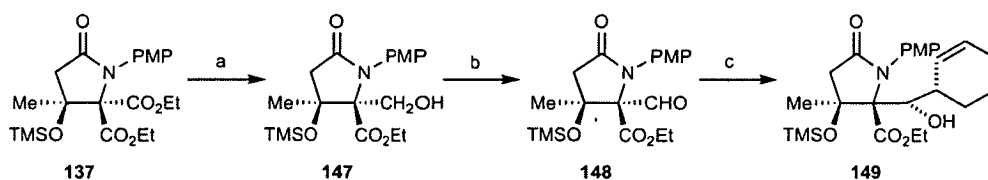
Reagents and conditions: (a) NaBH$_4$ (5.5 eq), LiCl (5.5 eq), THF, EtOH, 0 °C to rt, 14 h, 90%; (b) (COCl)$_2$ (2.1 eq), DMSO (4.2 eq), Et$_3$N (4.2 eq), CH$_2$Cl$_2$, −78 °C, 3 h, 90%; (c) 2-cyclohexenyl zinc chloride **24** (2.5 eq), THF, −78 °C, 4 h, 84%.

Scheme 2.14 *Synthesis of desired addition product 149*

The X-ray crystal structure of alcohol **149** was obtained, which further confirmed that reduction of **137** had occurred in the desired sense, in addition to showing that **149** possessed the desired relative stereochemistry (Figure 2.2).

Figure 2.2 *X-ray crystal structure of 149*
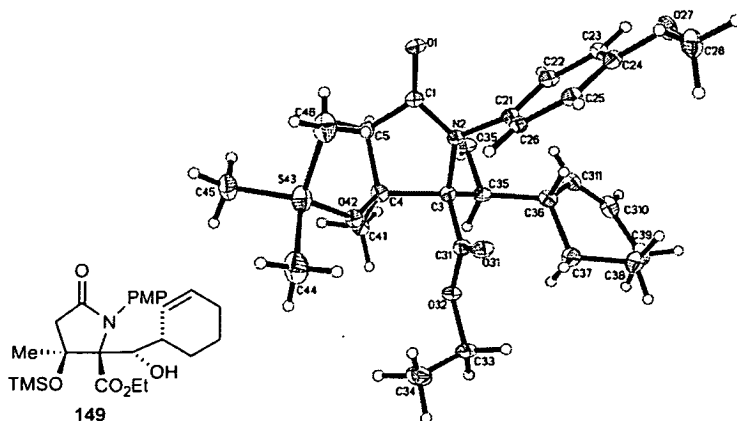
Once the optimal conditions for the mono-reduction and subsequent insertion of the cyclohexenyl group were found, these were applied to the PMB-derivative **138**. Selective reduction of **138** to the alcohol was successfully achieved (Scheme 2.15), but in slightly lower yields (68%) than those for the PMP γ-lactam. This was due to formation of the diol, product of reduction of both esters, before starting diester **138** was consumed. The cyclohexenyl side chain was inserted following the same procedure employed for **148** with good yield and high diastereoselectivity. An X-ray crystal structure of **151** was not obtained, but by analogy with the PMP-derivatives, it was assumed that alcohol **151** had the desired relative stereochemistry.
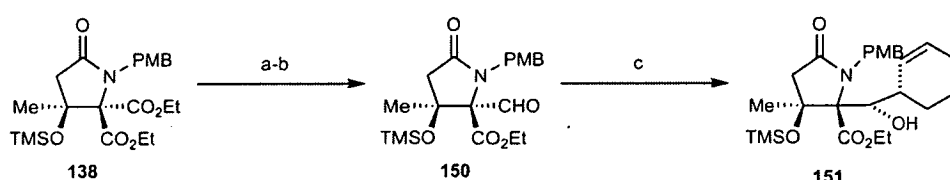
Reagents and conditions: (a) NaBH$_4$ (2 eq), LiCl (2 eq), THF, EtOH, 0 °C to rt, 14 h, 68%; (b) (COCl)$_2$ (2.1 eq), DMSO (4.2 eq), Et$_3$N (4.2 eq), CH$_2$Cl$_2$, -78 °C, 4 h, 78%; (c) 2-cyclohexenyl zinc chloride **24** (2.5 eq), THF, -78 °C, 4 h, 71%.

Scheme 2.15 *Synthesis of PMB protected alcohol **151***

2.2.3. Introduction of the C2 substituent

Focus was turned then to the installation of the side chain at C2 *via* enolate alkylation. The best available precedent for this transformation was found in the total synthesis of omuralide (**2**) by the Donohoe group.[62] In their route, β-hydroxylactam **152** was alkylated with MeI using LDA as base to provide **153** in 63% yield, along with the undesired diastereomer **154** in 10% yield (Scheme 2.16).
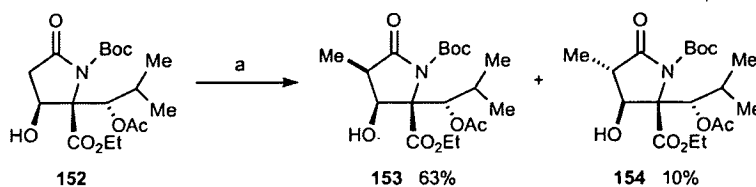
Reagents and conditions: (a) LDA (2.4 eq), HMPA (15 eq), MeI (9.3 eq), THF, −78 °C.

Scheme 2.16 *Donohoe's alkylation at C2 in the synthesis of omuralide*

40

γ-Lactam **152** had the C5 hydroxyl group acetate protected but a free C3 hydroxyl group. Surprisingly, no alkylation of the acetate ester was observed. However, we believed that the free C3 hydroxyl group was required to avoid undesired elimination to form the corresponding α,β-unsaturated lactam. The tertiary alcohol would be deprotonated under the basic conditions of the reaction and therefore a minimum of two equivalents of base was needed for the formation of the enolate.

In light of this precedent, we desired access to a β-hydroxylactam **157** (Scheme 2.17), in which the C5 secondary alcohol is protected and the C3 tertiary alcohol unprotected. Protection of the secondary alcohol of **149** was first attempted. Unfortunately, this hydroxyl group proved to be extremely unreactive, presumably due to steric crowding, and many attempts to install a suitable protecting group (such as acetate, benzyl, pivaloate, TBS etc) were fruitless. It was therefore decided to deprotect the C3 hydroxyl group and attempt a selective protection of the secondary over the tertiary alcohol. Diol **156** was easily obtained from **149** using CSA in EtOH. However, all efforts to protect selectively the secondary alcohol were unsuccessful and forcing conditions resulted in reprotection of the tertiary alcohol.
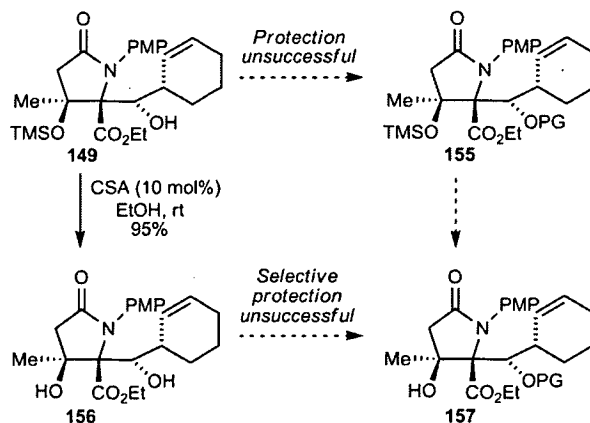
Scheme 2.17 *Unsuccessful attempts to β-hydroxylactam 157*

The protection of the secondary alcohol of the PMB derivative **151** also proved to be very challenging. Protection with a benzyl, pivaloate, TBS or TES group under several conditions were investigated but all attempts met with failure. However,

protection as the acetate ester was successful, and subsequent deprotection of the TMS ether provided β-hydroxylactam **159** (Scheme 2.18).
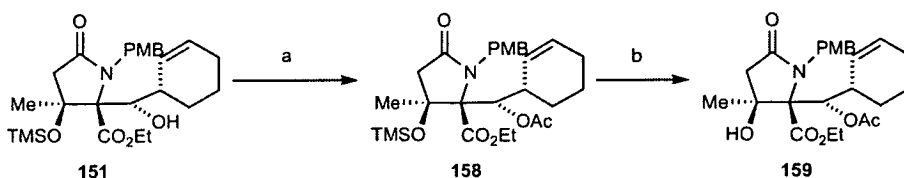
Reagents and conditions: (a) Ac_2O (3 eq), Et_3N (5 eq), DMAP (0.8 eq), CH_2Cl_2, 0 °C to rt, 14 h, 90%. (b) CSA (2 eq), EtOH, rt, 0.5 h, 91%.

Scheme 2.18 *Successful transformations to alkylation substrate 159*

γ-Lactam **159** was ready for alkylation. Although it displays differences to the compound that Donohoe and co-workers had successfully alkylated in their synthesis of omuralide (**152**),[62] most notably in a denser, more sterically crowded substitution pattern and a different nitrogen protecting group, we felt that there might be enough similarities to provide a good chance of success.

Donohoe's procedure involved the addition of methyl iodide (9.3 equivalents) to a solution of LDA (2.4 equivalents) at −78 °C, followed by the addition of a solution of alcohol **152** and HMPA (15 equivalents) in THF (Scheme 2.16). Additives such as HMPA, DMPU or TMEDA are often used as a cosolvent in reactions with organolithium reagents because they coordinate to the lithium cations, breaking up oligomers of lithium species and leaving a more reactive monomeric carbanion available for the reaction.[63] Because HMPA is highly toxic (it is a reported carcinogen), the use of DMPU or TMEDA is preferred. The influence of LiCl on the structure and reactivity of lithium enolates has also been reported.[64]

When we initiated the investigation of the alkylation reaction we decided to initially employ the very reactive MeI as alkylating agent, in order to test the reaction. Failure with this electrophile was likely to mean failure with a more complex alkylating agent required to give the desired chloroethyl side-chain. Numerous conditions were attempted: various multiple equivalents of LDA, NaHMDS or KHMDS as base, with or without HMPA or DMPU, with or without LiCl additive; but no evidence for the desired product **160** was obtained (Scheme

2.19). In some cases, only unreacted starting material was recovered, while in others, complex mixtures of products were obtained.
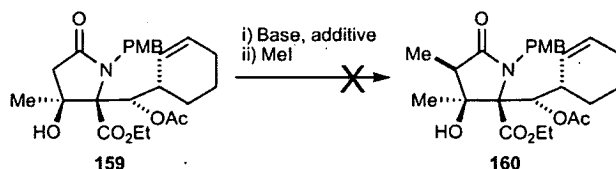
Scheme 2.19 *Alkylation reaction trials with substrate 159*

Model Studies

Analysis of the NMR spectra of the alkylation reactions performed on **159** proved to be complicated; furthermore, valuable 2-cyclohexenyl tributyltin **143** was being consumed during the study. Therefore, we decided to prepare a structurally less complex substrate, aiming for a more experimentally convenient preparation and also in order to facilitate the analysis of the NMR spectra. A thorough study of the alkylation reaction would then be undertaken on these derivatives. After finding the optimal conditions for the alkylation reaction, these would be applied to **159**, which would allow the synthesis of our natural product.

In one of the synthetic routes to omuralide (**2**) developed by Corey's group, the reaction of aldehyde **161** with isopropylmagnesium bromide **162** afforded alcohol **163** stereospecifically and in very good yields (Scheme 2.20).[33] In this transformation, the reaction of isopropenylmagnesium bromide with TMSCl at -40 °C is slower than with the aldehyde; attack of the Grignard reagent forms an alkoxide, which is rapidly silylated, avoiding a retroaldol cleavage. The isopropenyl group was then reduced to give the isopropyl side chain required for the synthesis of **2**.
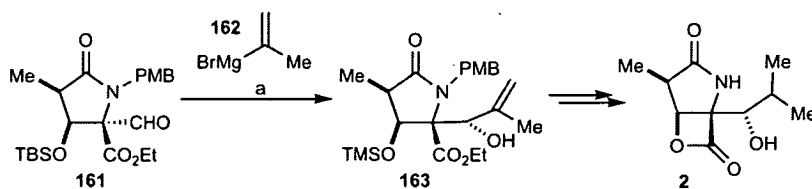
Reagents and conditions: (a) **162**, TMSCl, THF, –40 °C, 0.5 h, 97%.

Scheme 2.20 *Corey's insertion of the isopropenyl group in the synthesis of omuralide*

Consequently, for our model system we decided to insert an isopropyl group at C5 instead of the cyclohexenyl group, since this was an efficient and simple reaction, performed with a commercially available reagent. Moreover, if the route was successful, we would be preparing an omuralide-salinosporamide hybrid, compound that had also been recently synthesised by Corey.[23] Isopropenyl magnesium bromide was reacted with aldehyde **150**, in the presence of TMSCl to obtain alcohol **164** in good yield (Scheme 2.21). C5 of alcohol **164** was expected to have the desired stereochemistry, by analogy with Corey's reaction.
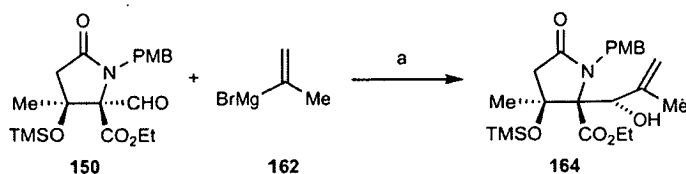
Reagents and conditions: (a) TMSCl (5 eq), **162** (3 eq), THF, -78 °C, 3 h, 76%.

Scheme 2.21 *Introduction of the isopropenyl side chain*

As previously described, before attempting the alkylating reaction, alcohol **164** needed to be transformed into a β-hydroxylactam with a free C3 hydroxyl group and the C5 hydroxyl group protected. Acetate protection of the secondary alcohol of **164** was readily achieved using acetic anhydride and pyridine as base (Scheme 2.22). It should be noted that, protection attempts using other protecting groups, such as benzyl or pivaloate, were fruitless. Deprotection of the TMS group of **165** in the presence of CSA was completed overnight, affording isopropenyl derivative **166**, which was then ready for alkylation.
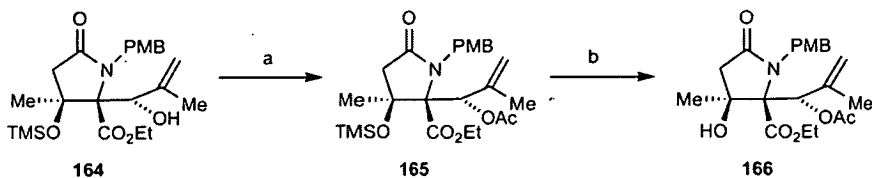
Reagents and conditions: (a) Ac$_2$O (6 eq), pyridine (3.5 eq), DMAP (0.2 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 92%; (b) CSA (4 eq), EtOH, rt, 14 h, 83%.

Scheme 2.22 *Obtention of β-hydroxylactam 166*

Hydrogenation of **166** using Pd/C afforded the new alcohol **167** containing the isopropyl group, albeit in low yield (Scheme 2.23).
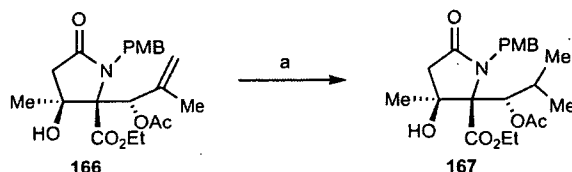
Reagents and conditions: (a) H_2, Pd/C (0.7 eq), EtOH, rt, 18 h, 50%.

Scheme 2.23 *Hydrogenation of 166 reveals the isopropyl side chain*

The investigation of the reaction was initiated employing alcohol **167** and again utilising the very reactive MeI as the alkylating agent. Numerous conditions were attempted. Firstly, Donohoe's conditions[62] were repeated, procedure that involved the addition of a solution of the alcohol to a solution of LDA and MeI; however, none of the desired methylated product was observed. This reaction was repeated without HMPA or using DMPU instead of HMPA. The use of other bases, such as KHMDS and LTMP, was also examined. An attempt was made altering the order of addition, therefore adding a solution of alcohol **167** into a solution of LDA, to form the enolate, followed by addition of MeI. The reaction was also performed using allyl iodide instead of methyl iodide. However, all efforts to obtain the alkylated product were unsuccessful (Scheme 2.24).
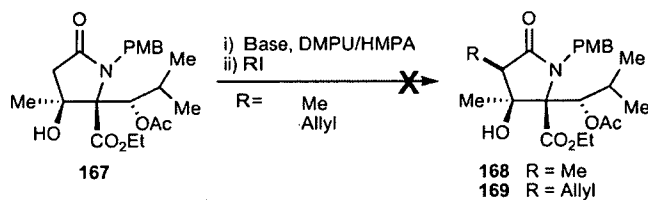
Scheme 2.24 *Alkylation reaction trials with substrate 167*

Several variables had been studied for this reaction but, in general, the procedure involved the addition of a base (typically LDA) to a solution of **167**, the reaction mixture was then stirred at −78 °C for 30-60 min, followed by the addition of MeI. In none of the conditions attempted desired alkylated product **168** was formed; however, a methylated product was obtained as a major product (50-75%). Careful

analysis of these reactions revealed the formation of a methylated compound, which displayed spectroscopic data consistent with the structure represented by enamide **172** (Scheme 2.25). We assumed that **172** was formed as a result of alkoxide **170** undergoing elimination of the acetate to provide ring-opened acetoacetamide **171**, which is then methylated under the reaction conditions. The ^{1}H NMR spectrum showed a doublet at high chemical shift (6.7 ppm) and there was no signal for the methyl of the acetate group. This doublet was assigned to the proton on the double bond formed in the elimination of the acetate group (H_A). When the ^{13}C NMR spectrum was examined, we observed a new quaternary carbon at 205.3 ppm, which was assigned to the newly formed methyl ketone. The ^{1}H NMR spectrum of this substrate showed in fact that **172** was a mixture of two compounds, due to the formation of either the double bond *Z/E* isomers or to a mixture of two amide rotamers.
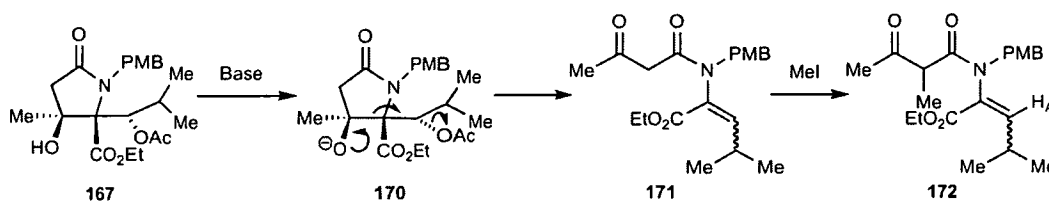
Scheme 2.25 *Fragmentation of 167: acetate elimination and ring opening*

When repeating the reaction in the absence of methyl iodide, the non-alkylated amide **171** was obtained (also as a mixture of two isomers or rotamers), thus demonstrating that the alkylation at C2 occurred in a second step, after the elimination and ring opening. The reaction was also performed using allyl iodide instead of methyl iodide and it afforded the analogous allylated amide.

The C2 alkylation of the isopropenyl derivative **166** was also investigated. The same combinations of conditions (different bases, addition of HMPA or DMPU, order of addition) were explored, however, all attempts failed to give the desired product (**173**). In this occasion, a methylated product, with spectroscopic data consistent with acetoamide **174** was isolated (Scheme 2.26). This product is a result

of a similar elimination and ring-opening process, followed by alkylation, to the one detailed for the formation of **172** (Scheme 2.25).
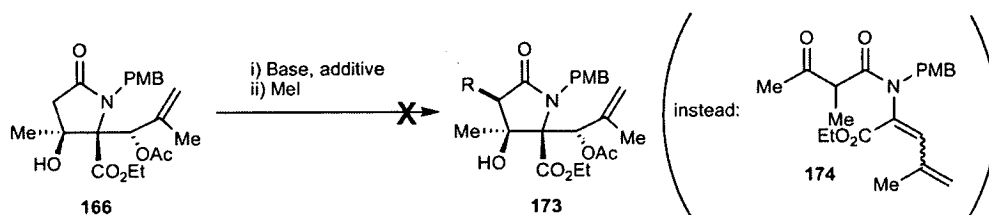
Scheme 2.26 *Failure in the preparation of **173** and formation of **174***

Employing the model substrates, we had identified the fragmentation process that was occurring under the reaction conditions. Despite this discouraging result, it was necessary to verify whether a similar ring-opened product was obtained when performing the reaction on γ-lactam **159**, the substrate with all the required functionalities for the synthesis of (±)-**1**.

The alkylation reactions attempted on **159** produced a slightly more complex mixture of products than **167** and **166**. However, now that we were able to recognise the pattern of the fragmentation product in the ^{1}H NMR spectrum, it was confirmed that the same ring-opening process was clearly taking place and compound **175** was being formed (Scheme 2.27).
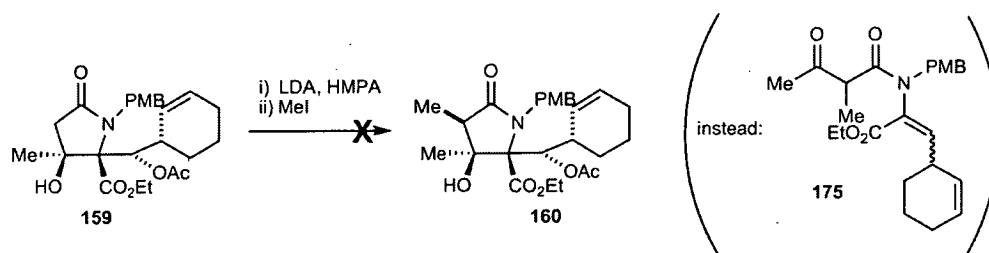
Scheme 2.27 *Final attempt of the alkylation on **159***

Although for C2 alkylation we had opted to target substrates containing a free alcohol at C3 to avoid hydroxide elimination, clearly this feature was resulting in the undesired ring-opening/acetate elimination described above. Therefore for comparative purposes, we attempted the alkylation of **158**, which has the C3 alcohol TMS protected (Scheme 2.28). Unreacted starting material was recovered when only

1.2 equivalents of base were employed. However, when using an excess of LDA (2.2 eq) in HMPA/THF for enolisation, followed by addition of MeI (9 equivalents), **177** was obtained in a rapid reaction, which is the product of methylation of the acetate ester. There was no evidence of methylation at C2, or elimination of the trimethylsilyloxy substituent.
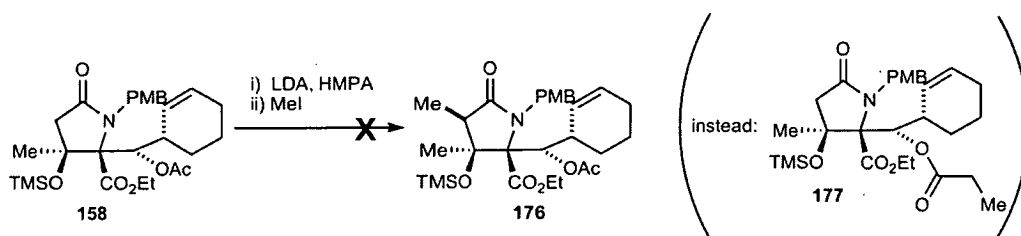
Scheme 2.28 *Acetate methylation of 158*

The reaction was also performed on **165**, and acetate methylation occurred again. Therefore, protection of the secondary alcohol at C5 with a non-enolisable protecting group was necessary. However, as previously described all efforts to protect the C5 hydroxyl group of **151** and also of **164** with any other group than acetate were unsuccessful.

The alkylation reaction was also performed with *N*-PMP diol **156** and γ-lactam **138** (Scheme 2.29), but mostly starting material was recovered in both cases. Comparing our substrates with Donohoe's (**152**, Scheme 2.29),[62] we wondered why the enolate formation and alkylation was unfavoured in our system. Although the presence of the C3 methyl made a more dense structure, we believed that the main difference with our system was the protecting group on the amide nitrogen. A possible explanation for the failure of these reactions was the lower reactivity of the *N*-PMP- or *N*-PMB-protected amides compared to the *N*-Boc substrate, due to electronic factors.
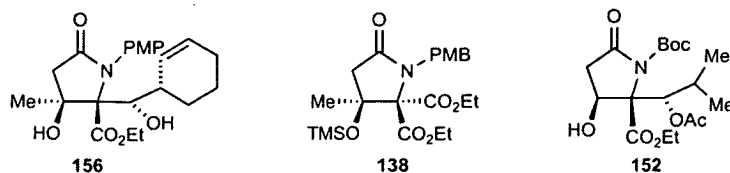
Scheme 2.29 *Comparison of our substrates with Donohoe's*

The *N*-Boc γ-lactam derivative could potentially be prepared, but Danishefsky reported[27] that the success of Corey's procedure[26] for the insertion of the cyclohexenyl side chain is very dependent on the protecting group of the amide. Therefore, a Boc group could be not beneficial for that step. The PMB group could have also been replaced by a Boc group only prior to the alkylation reaction, but this would mean adding extra steps to the synthesis.

2.3. Conclusions

We employed an easy and efficient way to prepare γ-lactams of general structure **104**. A selective mono-reduction of the ester to the aldehyde, followed by insertion of the cyclohexenyl side chain into the aldehyde were successfully performed.

The next key step in the synthetic sequence was the introduction of the side chain at C2. Unfortunately, all efforts to induce the formation of the enolate and subsequent reaction with the alkylating agent were fruitless, and the desired alkylated product was not obtained. When the reaction was performed on β-hydroxy γ–lactam substrates protected at C5, a fragmentation process ocurred. Throughout the study, we had no evidence for the formation of the amide enolate. It was speculated that changing the protecting group on the nitrogen could make the enolate more reactive.

The investigation of the racemic synthetic route proved more challenging than originally expected. Therefore, although we had managed to prepare compounds with much of the functionality required for salinosporamide A (**1**), the unsuccessful C2 alkylation studies prompted us to consider alternative strategies. Although we were not able to complete the route, with this approach we gained valuable insight into the reactivity and chemical behaviour of the γ-lactam substrates. This knowledge was fundamental for the development of the rest of the project. Most importantly, we were able to readily apply Corey's method for the insertion of the cyclohexenyl chain in the final approach, whereby we achieved the formal synthesis.

3. Reductive aldol cyclisation approach

A series of metal-catalysed reductive aldol cyclisation reactions for the formation of β-hydroxylactones and β-hydroxylactams in a highly diastereoselective fashion had been developed in our laboratories.[65-67] The studies carried out on the application of this methodology for the introduction of the γ-lactam moiety in salinosporamide A will be described in this chapter.

3.1. Aims

Disconnection of the β-lactone and the cyclohexenyl group of **1**, along with appropriate functional group manipulations/interconversions lead back to γ-lactam **103**. We envisaged that γ-lactam **103** could be synthesised from an amide enolate such as **178**, *via* an intramolecular aldol reaction with the methyl ketone moiety (Scheme 3.1). A crucial advantage over the previous approach is that the reductive aldol cyclisation is expected to afford the γ-lactam intermediate **103** having the side chain at C2 in place.
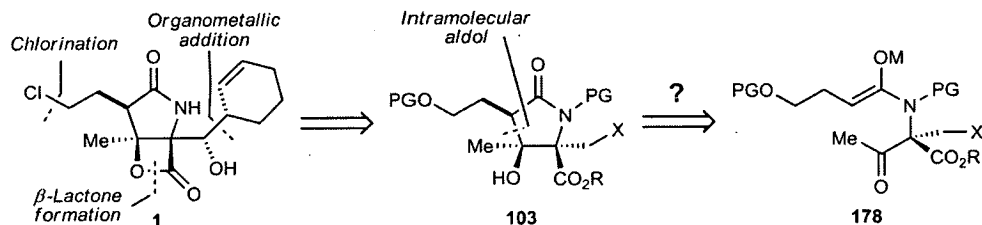
Scheme 3.1 *Formation of the γ-lactam via an intramolecular aldol reaction*

In order to obtain β-hydroxylactam **103** in an intramolecular aldol fashion, the main challenge was to regioselectively form the amide enolate over the ketone enolate. Control of the regioselectivity of the enolisation was essential, because under traditional aldol reaction conditions ketone enolate **180** would be the first to form, due to a higher acidity of the protons and also to a lower steric hindrance. (Scheme 3.2).
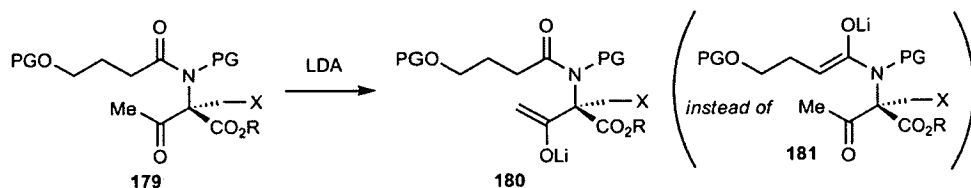
Scheme 3.2 *Favoured formation of ketone enolate 180 under classical aldol conditions*

We reasoned that the best approach to overcome this selectivity problem would be a reductive aldol protocol, which utilises an α,β-unsaturated amide as a latent enolate. Reductive enolate formation of α,β-unsaturated amide **102**, followed by aldol reaction with the methyl ketone, would provide access to the target γ-lactam **103**, as represented in Scheme 3.3.
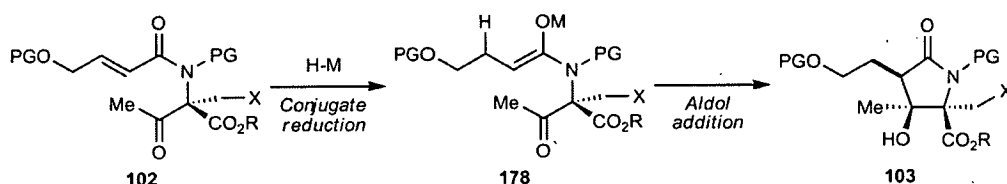
Scheme 3.3 *Reductive aldol approach for the preparation of γ-lactam 103*

Important advances have been made in the field of the reductive aldol chemistry in recent years. This technique has become an important tool in organic synthesis and the application of this methodology in synthesis of natural products has already been possible, as it will be described in the next section. Although the intramolecular aldol reaction of enones with ketones or aldehydes for the formation of carbocyclic rings had been widely described in the literature, when this project was started there were no examples of reductive aldol cyclisations of α,β-unsaturated amides to afford lactams. With this observation, our group initiated a programme for the development of d-block catalysed reductive aldol cyclisation of α,β-unsaturated amides and, although not relevant to this project of α,β-unsaturated esters, to yield heterocyclic products. The aim was to subsequently apply this methodology into the synthesis of the β-hydroxy-γ-lactam moiety of salinosporamide A.

3.2. The reductive aldol reaction

The aldol reaction

The aldol reaction is an extraordinarily important carbon-carbon bond-forming tool in organic synthesis, and is considered the most important method for the construction of β-hydroxy carbonyl compounds.[68] The addition of an enolisable carbonyl to a ketone or, more typically, to an aldehyde (due to its higher electrophilicity) affords a β-hydroxy carbonyl compound, forming a new C-C bond and setting two new stereogenic centres in a single transformation (Scheme 3.4).
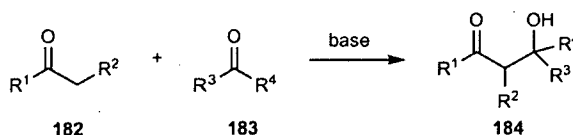
Scheme 3.4 *The aldol reaction*

The classic aldol reaction is a highly atom efficient process but the chemo- and regioselectivity in the formation of enolates from unsymmetrical precursors has represented a big challenge. The development of the asymmetric aldol reaction has been one of the most important topics in modern catalysis and the control of its stereoselectivity has now reached impressive levels. In natural product synthesis, control of the absolute stereochemistry when creating new stereocentres is fundamental and that is the reason why the asymmetric aldol reaction has been extensively used for the construction of complex molecules over the last three decades.[69]

In the early days of asymmetric synthesis, studies were limited to stepwise aldol approaches that utilised preformed enolates.[70] Two methods were extensively developed: the use of stoichiometric amounts of chirality in the form of auxiliaries or ligands (asymmetric modification of the enolate or of the electrophile) and the catalytic approach using chiral Lewis acids.

Crimmins[71], Evans[72], Oppolzer[73], Massamune[74], Paterson[75] and Denmark[76] groups have been the main contributors to the methodology employing chiral auxiliaries or highly efficient catalysts to generate aldol products with high enantioselectivity.

In order to avoid the use of stoichiometric amounts of chiral promoters, the catalytic version of the enantioselective aldol reaction was investigated. This methodology required a reaction catalyst to initiate and mediate the reaction. Therefore, the catalyst represented the vehicle for influencing reaction stereoselection. This reaction design needed the identification of a suitable latent enolate that would not react with the electrophile without the presence of the activating agent. Mukaiyama[77] first recognised enolsilanes as the requisite latent enolate equivalents to which the addition of a chiral metal-based Lewis acid would promote the asymmetric catalysed aldol reaction (Scheme 3.5). Since the discovery of the Mukaiyama aldol reaction, there has been a great progress in the development of the asymmetric catalytic aldol reaction, becoming thus a very reliable methodology.[78]
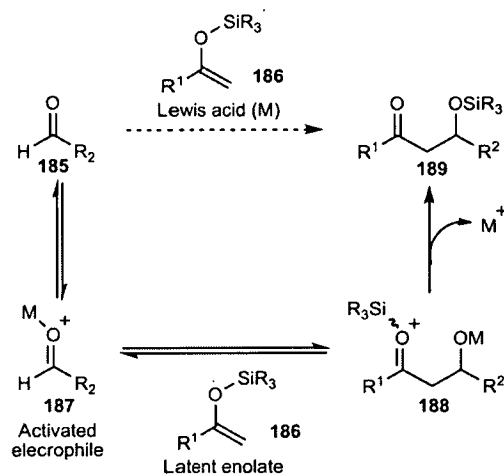
Scheme 3.5 *Lewis acid catalysed aldol reaction*

Although achieving high levels of diastereo- and enantioselectivity, these strategies always require the transformation of one of the reagents prior to the aldol addition. Ideally, catalytic methodologies should employ unmodified substrates. The direct catalytic asymmetric aldol reaction has been extensively developed in recent years, but these methodologies are still limited to the use of symmetric ketones, ketones possessing a single set of acidic hydrogens, or ketones which incorporate hydroxyl directing groups.[79]

The reductive aldol reaction

The use of enones represents an alternative way of achieving a selective enolate formation. Stork established that tandem enone reduction-enolate alkylation is an effective method to control the regiochemistry in enolate-mediated C-C bond formations (Scheme 3.6).[80]
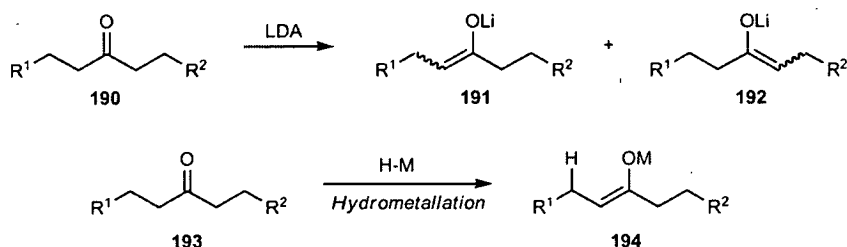
Scheme 3.6 *Control of the enolisation regioselectivity using enones as latent enolates equivalents*

The hydrometallation of α,β-unsaturated carbonyl compounds has proven to be a mild and versatile method for enolate formation, being amenable to catalysis.[81] The reductive aldol reaction involves the direct metal-catalysed reductive addition of α,β-unsaturated carbonyl compounds with aldehydes or ketones (Scheme 3.7).
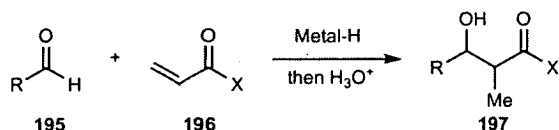
Scheme 3.7 *Transition metal-catalysed reductive aldol reaction*

The first example of a reductive aldol coupling was reported by Revis and Hilty in 1987.[82] They demonstrated that the reaction of α,β-unsaturated esters with ketones or aldehydes in the presence of substoichiometric amounts of $RhCl_3 \cdot 3H_2O$ (0.09 mol%) and trimethylsilane (1.3 mol%) represents a general and mild method to form β-siloxy esters (Scheme 3.8). The coupling proceeded well for several types of ketones and also for acetaldehyde. As nucleophiles, only esters were employed, since methyl vinyl ketone did not couple to acetone, and silyl enol ether (**200**) was formed instead.
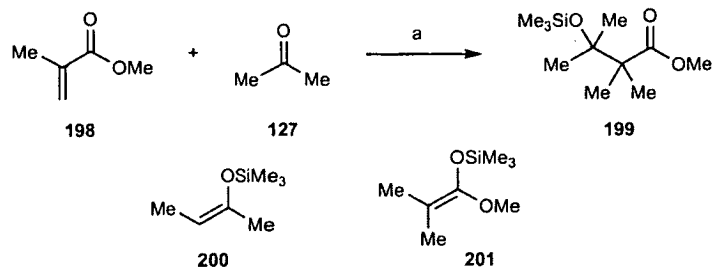
Reagents and conditions: (a) cat RhCl$_3$·3H$_2$O, Me$_3$SiH, rt, 95%.

Scheme 3.8 *First example of a catalytic reductive aldol reaction*

Silyl ketene acetal (**201**) was prepared independently and reacted with acetone in the presence of a substoichiometric quantity of RhCl$_3$·3H$_2$O, but only traces of the aldol product were formed. This eliminated the possibility of the Rh species acting as a Lewis acid in the reaction, thus supporting the conjugate reduction followed by aldol reaction mechanism.

Since the Revis and Hilty report, there have been numerous advances in the reductive aldol reaction, employing a broad variety of transition metal catalysts and reaction conditions. The reductive aldol reaction has already been fully reviewed in the literature;[81, 83, 84] the rest of this section will therefore focus on developments in the field that are directly related to this project. Two aspects will be covered: methodologies that have been successfully applied towards the synthesis of natural products and the methodologies reported for the formation of carbocyclic rings, which constitute the precedents for the methodology studies carried out in our group.

In 1990, Matsuda made an important contribution in the rhodium-catalysed reductive aldol reaction, reporting the first coupling of α,β-unsaturated ketones with aldehydes, to form β-siloxy ketone aldols, using Rh$_4$(CO)$_{12}$ as catalyst.[85] Nevertheless, Morken has been one of the main contributors to the Rh-catalysed reductive aldol reaction. As little was known about the mechanism, his aim was to find the most efficient catalyst system. A high-throughput evaluation of 192 independent catalytic systems was performed.[86] The reaction chosen for the screening was the reaction of methyl acrylate with benzyldehyde. He examined four complexes, Co(acac)$_2$·2H$_2$O, [Pd(allyl)Cl]$_2$, [Ir(COD)Cl]$_2$ and [Rh(COD)Cl]$_2$, six

hydride sources and seven chiral ligands. The combination of [Rh(COD)Cl]$_2$, Cl$_2$MeSiH and Me-DuPhos (**204**) was found to be the most successful one (Scheme 3.9), providing diastereoselectivities of up to 23:1 (_syn:anti_) and relatively high yields (15-82%).
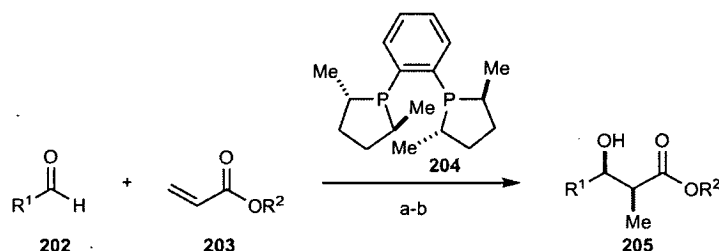
Reagents and conditions: (a) 5.5 mol% Me-DuPhos, 2.5 mol% [(COD)RhCl]$_2$, Cl$_2$MeSiH; (b) H$_3$O$^+$.

Scheme 3.9 _Morken's catalytic stereoselective reductive aldol reaction_

Morken also reported the first example of a catalytic asymmetric reductive aldol reaction.[87] Coupling of methyl acrylate with benzaldehyde in the presence of Rh(BINAP) as catalyst and Et$_2$MeSiH as reductant, afforded a _syn_ selective (1.7:1, 37% yield) reaction in which the _syn_ aldol product was obtained in 91% ee and the _anti_ in 88% ee. It was discovered that the yields were much more favourable using phenyl acrylate (**207**) (Scheme 3.10).

72% yield, 3.4:1 _syn:anti_

206   **207**   **208** (88% ee)   **209** (34% ee)
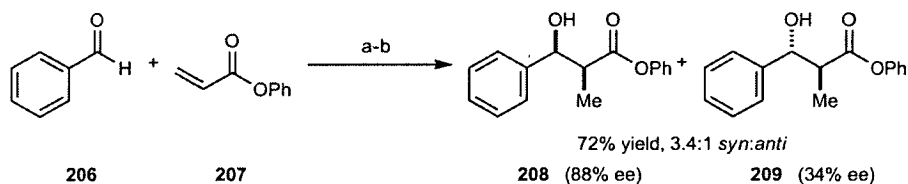
Reagents and conditions: (a) 2.5 mol% [(COD)RhCl]$_2$, 6.5 mol% _R_-BINAP, Et$_2$MeSiH; (b) H$_3$O$^+$.

Scheme 3.10 _First Rh-catalysed asymmetric reductive aldol reaction_

With the advances made in the Rh-catalysed reductive aldol reaction its application in total synthesis was now possible. Morken applied this methodology in the synthesis of the C10-C24 ketone fragment of the inostamycin family of compounds (Figure 3.1).[88] These compounds are known to possess anti-HIV and anticancer activity.

Inostamycin A: $R_1 = CO_2H$; $R_2 = Et$
Inostamycin B: $R_1 = CO_2H$; $R_2 = Me$
Inostamycin C: $R_1 = Et$; $R_2 = H$
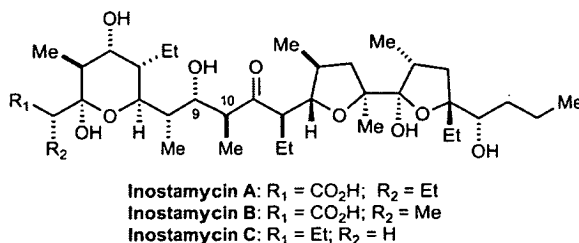
Figure 3.1 *Compounds of the Inostamycin family*

The Rh-catalysed asymmetric reductive aldol reaction between propionaldehyde (**210**) and phenyl crotonate (**211**) afforded the corresponding β-hydroxy ester **212** in 76% yield and with 4.3:1 *syn* diastereoselectivity and 88% enantiomeric excess (Scheme 3.11). This intermediate was then used for the synthesis of the C10-C24 ketone fragment **213**.

212 76%, 4.3:1 *syn:anti*
88% ee
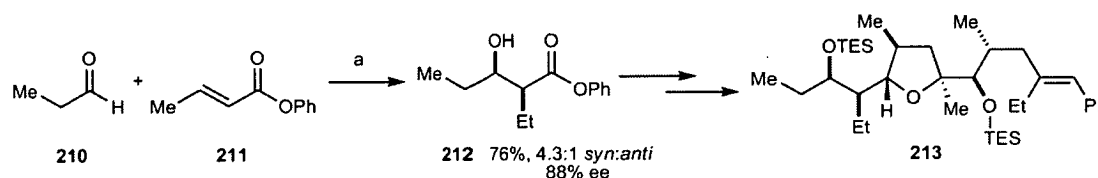
Reagents and conditions: (a) 2.5 mol% [Rh(COD)Cl]$_2$, 5.5 mol% *S*-BINAP, Et$_2$MeSiH (1.2eq), Cl(CH$_2$)Cl, rt; then H$_3$O$^+$, 76%.

Scheme 3.11 *Synthesis of the C10-C24 ketone fragment of the inostamycin family*

In 2001, Morken and co-workers reported that Ir(I) salts, when complexed to an appropriate 2,6-bis(oxazolinyl)pyridine (pybox) ligand (Figure 3.2), are able to catalyse reductive aldol reactions to give the products in good yields, good *syn*-diastereoselectivity and good to excellent enantioselectivities.[89]

214 R = Me
215 R = *i*Pr
216 R = *t*Bu
217 R = Ph

218
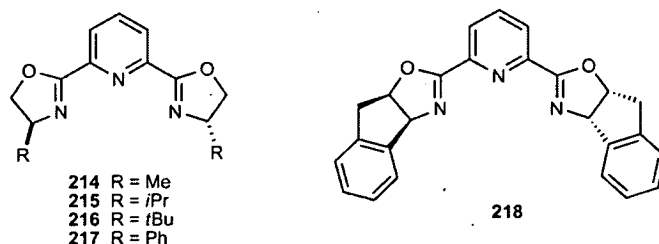
Figure 3.2 *Pybox ligands employed in the Ir-catalysed asymmetric reaction*

An initial survey of the impact of ligand architecture revealed that the nature of the pybox ligand substitution has a significant impact on stereoselectivity. These investigations identified the aminoindanol-derived indane pybox **218** as the best ligand with regards to both enantio- and diastereoselectivity.

Therefore, ligand **218** was successfully used in the iridium-based catalytic reductive aldol reaction of various aldehydes. This catalyst system showed remarkable enantioselectivity with benzaldehyde and α-alkoxy aldehydes, however poor reaction with simple aldehydes. It was also observed that oxygenation adjacent to the aldehydes enhances reactivity relative to non-oxygenated aliphatic substrates (Table 3.1).

Aldehyde	Yield (%)		*syn:anti*	*ee (syn)*
1 Ph-CHO	68	**221a**	6.6:1	94
2 EnC-CHO	49	**221b**	9.9:1	96
3 TESC-CHO	47	**221c**	8.2:1	96
4 Me-CHO	<5	**221d**	-	-
5 EnC-CHO	65	**221e**	2.7:1	82

Table 3.1 *Ir-Pybox catalysed asymmetric reductive aldol reaction*

Morken applied this methodology in the total synthesis of borrelidin (**222**), a potential anti-cancer agent.[90] The structure of borrelidin is characterised by an 18-membered macrolactone carrying a cyclopentane carboxylic acid and a unique conjugated cyanodiene (Figure 3.3).
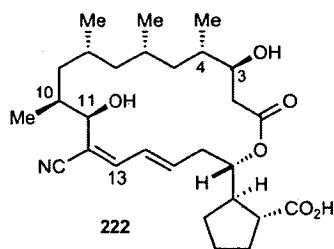
Figure 3.3 *Borrelidin*

Reductive aldol methodology was used to establish the stereogenic centres at C3, C4, C10 and C11. Both steps in which this methodology was used went in good yield, with high diastereoselectivity and good to excellent enantioselectivity (Scheme 3.12).
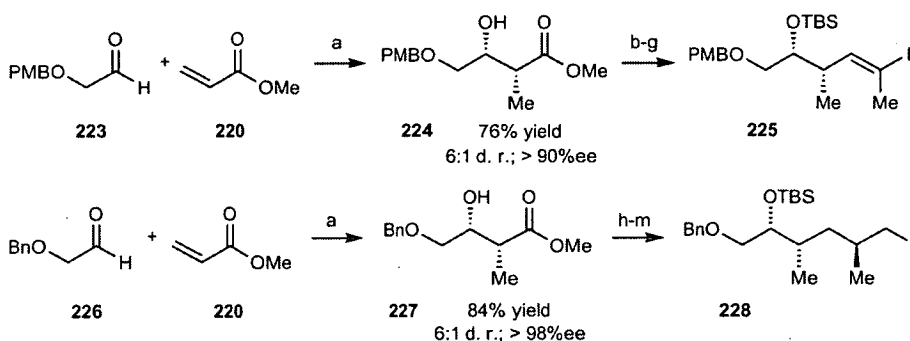
Reagents and conditions: (a) 2.5 mol% [Ir(COD)Cl]$_2$, Ligand **218**, 7.5 mol%, Et$_2$MeSiH, rt; (b) TBSOTf, 2,6-lutidine, 90%; (c) DIBAL–H, 79%; (d) Dess-Martin periodinane, 92%; (e) CBr$_4$, PPh$_3$, 94%; (f) *n*-BuLi, MeI, 97%; (g) (i) Cp$_2$ZrHCl, (ii) I$_2$, 89%; (h) TBSOTf, 2,6-lutidine, 99%; (i) DIBAL–H, 94%; (j) PPh$_3$, I$_2$, 96%; (k) pseudoephedrine propionamide, LDA, 93%; (l) LAB, 93%; (m) PPh$_3$, I$_2$, 95%.

Scheme 3.12 *Application of the Ir-Pybox catalysed asymmetric reductive aldol reaction in the synthesis of borrelidin*

Fragments **225** and **228** were coupled in a modified Negishi coupling. Alkyl iodide **228** was converted to the dialkyl zinc and reacted with vinyl iodide **225** yielding intermediate **229**, which ultimately allowed the synthesis of borrelidin (Scheme 3.13).
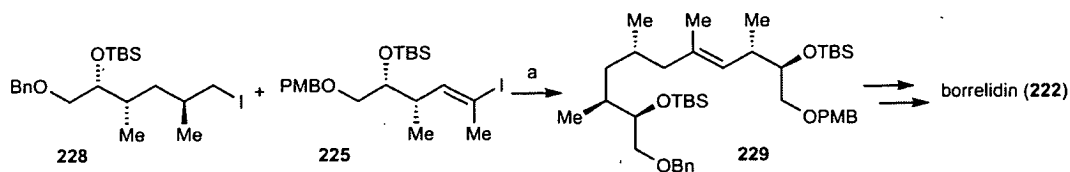
Reagents and conditions: (a) (i) *t*-BuLi, ZnCl$_2$, (ii) Pd(PPh$_3$)$_4$, 225, (58%).

Scheme 3.13 *Synthesis of borrelidin 222*

Motherwell reported in 2004 a Rh-catalysed intramolecular reductive aldol reaction of aldehyde-enoate derivatives.[91] 6-Oxo-enoates were cyclised with RhCl(PPh$_3$)$_3$ or RhH(PPh$_3$)$_4$ as the Rh source (1 mol%) and Et$_3$SiH (2.1 eq) as the hydride source, in toluene. Aldol products were obtained with *syn*-selectivity when using RhCl(PPh$_3$)$_3$, but RhH(PPh$_3$)$_4$ showed higher catalytic activity and high *anti*-selectivity, except for the cyclisation of **232** (Table 3.2).

	Substrate	Product	Catalyst	Yield (%)	*syn/anti*
1	**230**	**231**	RhCl(PPh$_3$)$_3$	81	3:1
2			RhH(PPh$_3$)$_4$	81	1:11
3	**232**	**233**	RhCl(PPh$_3$)$_3$	56	1:1
4			RhH(PPh$_3$)$_4$	62	6.4:1
5	**234**	**235**	RhCl(PPh$_3$)$_3$	93	2.2:1
6			RhH(PPh$_3$)$_4$	61	1:11

Table 3.2 *Rh-catalysed reductive cyclisation of 6-oxo-enoates derivatives*

They also applied this methodology in the synthesis of the highly potent anti-HIV carbocyclic nucleosides (-)-carbovir (**239**) and (-)-abacavir (**240**).[92] The Rh-catalysed reductive aldol reaction allowed access to key intermediate **237** from *cis*-cyclopentane **236** (Scheme 3.14). Protected triol **237** was converted into protected tetraol **238**, which is a key intermediate in the synthesis of the carbocyclic nucleosides.
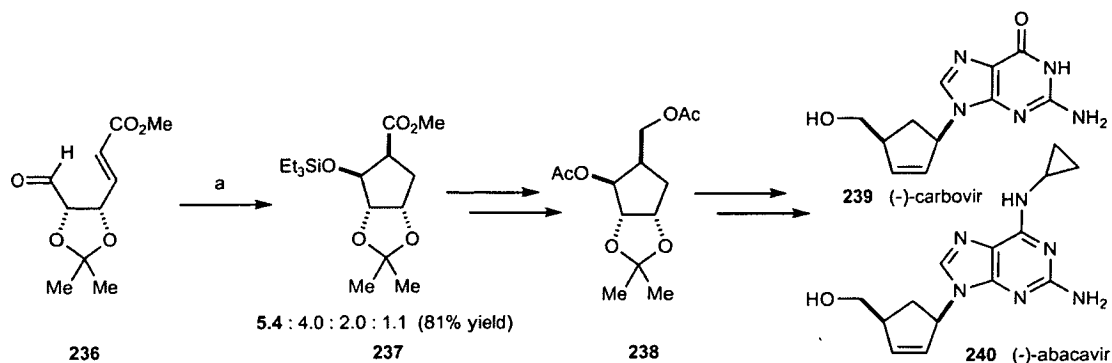
Scheme 3.14 *Use of the Rh-catalysed reductive aldol cyclisation*

We can then conclude that, due to the development of the reductive aldol reaction, the application of this methodology to the synthesis of natural products has been possible, with inter- and also intramolecular examples. In the remaining part of this section, we will describe methodologies for intramolecular reductive aldol reactions to form carbocyclic rings, which are therefore relevant to the methodology of our project.

In 1989, Mukaiyama reported the first cobalt-catalysed cross coupling reaction of α,β-unsaturated nitriles, amides and esters with aldehydes using phenylsilane as a hydride source to give the corresponding β-hydroxy nitriles, amides or esters.[93] Krische, in 2001, reported the first examples of intramolecular reductive aldol reactions catalysed by cobalt.[94] The optimised conditions for this transformation proved general for five-, six- and seven-membered ring formation. The aldol products were obtained in moderate to excellent yield (35-87%) and in all cases, irrespective of yield, only the *syn*-diastereomer was observed (Scheme 3.15). Studies into the mechanism of this cycloreduction were also performed.[81, 95]

242a	n = 1, R¹ = Ph	70%
242b	n = 2, R¹ = Ph	87%
242c	n = 2, R¹ = *p*-CF₃Ph	72%
242d	n = 2, R¹ = 2-Naph	68%
242e	n = 2, R¹ = Me	38%
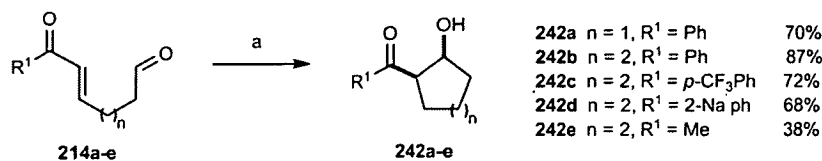
Scheme 3.15 *First example of a Co-catalysed intramolecular reductive aldol cyclisation*

Krische played a major role in the development of Rh based catalyst systems in the reductive aldol reaction. In 2002, he reported the first example of inter- and intramolecular reductive aldol reaction of enones in which the enolates were generated using elemental hydrogen as reductant.[96]

Generally, the accepted mechanism for the Rh-catalysed alkene hydrogenation has three steps: oxidative addition of $L_nRh(I)$ to elemental hydrogen, followed by alkene hydrometalation forming $L_nRh(III)(alkyl)(hydrido)$ intermediates and, finally, alkyl-hydrogen reductive elimination to give the saturated product and regenerate $L_nRh(I)$. If the double bond is part of an enone, an enolate will be generated. Therefore they hypothesised that if there was an electrophile, the alkyl-rhodium intermediate could be trapped, in competition with alkyl-hydrogen reductive. elimination (Scheme 3.16).
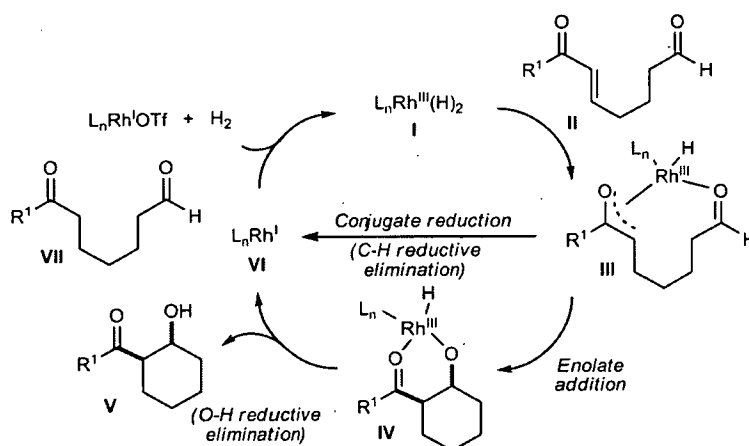
Scheme 3.16 *Proposed catalytic cycle of the reductive generation of enolates under hydrogenative conditions*

With this theory, they attempted the hydrogenative cycloreduction of monoenone monoaldehydes. A variety of Rh sources and phosphines were screened but when using $Rh(COD)_2OTf/PPh_3$, equal proportions of *syn*-aldol cycloreduction product (**244**) and 1,4-reduction product (**245**) were obtained (Scheme 3.17). Bearing in mind the proposed mechanism, they speculated that deprotonation of (hydrido)Rh species **I** or **III** would diminish the 1,4-reduction. Indeed, when the reactions were performed using potassium acetate **244** and **245** were obtained in 59% and 21% yield, respectively. A higher Lewis acidity of the metal was another important factor, since

when $(p\text{-}CF_3Ph)_3P$ was used as ligand, together with the base, the yield of **244** was increased to 89%, obtaining only 0.1% of **245**.

243   **244** 89% (10:1 *syn:anti*)   **245** 0.1%
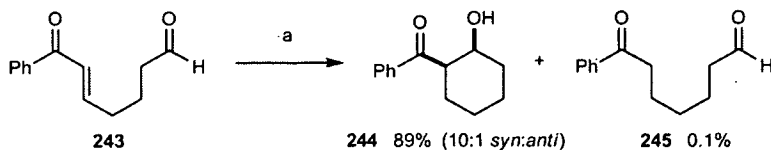
Reagents and conditions: (a) 10 mol% $[Rh(COD)_2]OTf$, 24 mol% $(p\text{-}CF_3Ph)_3P$, H_2 (1 atm), 30% KOAc, $Cl(CH_2)Cl$, rt, 89%.

Scheme 3.17 *Rh-catalysed hydrogenative aldol cycloreduction of 243*

Using these conditions, cycloreduction of aromatic, heteroaromatic, and aliphatic enone substrates yielded the five- and six-membered ring β-hydroxy ketone products in good to excellent yields (65-90%) and with high *syn* diastereoselectivities (up to 24:1) (Table 3.3).
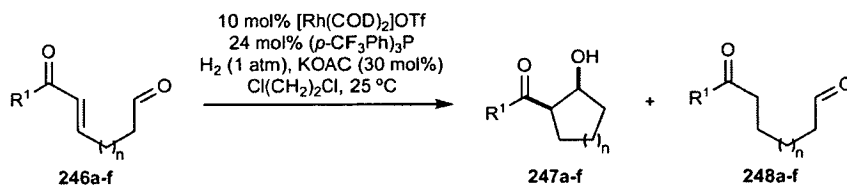
Substrate	Yield product (%) (*syn:anti*)		Yield 1,4-reduction (%)
1 $n = 2, R^1 = p\text{-}MeOPh$	74 (5:1)	**247a**	3
2 $n = 2, R^1 = 2\text{-naphthyl}$	90 (10:1)	**247b**	1
3 $n = 2, R^1 = 2\text{-thiophenyl}$	76 (19:1)	**247c**	2
4 $n = 2, R^1 = 2\text{-furyl}$	70 (6:1)	**247d**	10
5 $n = 1, R^1 = Ph$	71 (24:1)	**247e**	1
6 $n = 2, R^1 = Me$	65 (1:5)	**247f**	-

Table 3.3 *Rh-catalysed hydrogenative aldol cycloreduction of enone aldehydes*

The fact that 1,4-reduction had been practically eliminated led to the formulation of another possible mechanism and explanation of the role of the base (Scheme 3.18).[97] It was believed that Rh-monohydride was being formed *via* heterolytic cleavage of hydrogen (oxidative addition and reductive elimination by the base). Therefore, if enone hydrometalation occurred *via* a Rh-monohydride complex, the

resulting enolate would lack an extra hydride ligand and could not go under C-H reductive elimination (**II** *vs* **VI**, Scheme 3.18).[98] After enolate addition, **III** follows the catalytic cycle, suffering oxidative addition to form Rh(III) enolate **IV** that liberates the desired aldol product and Rh-monohydride, which reenters the cycle.
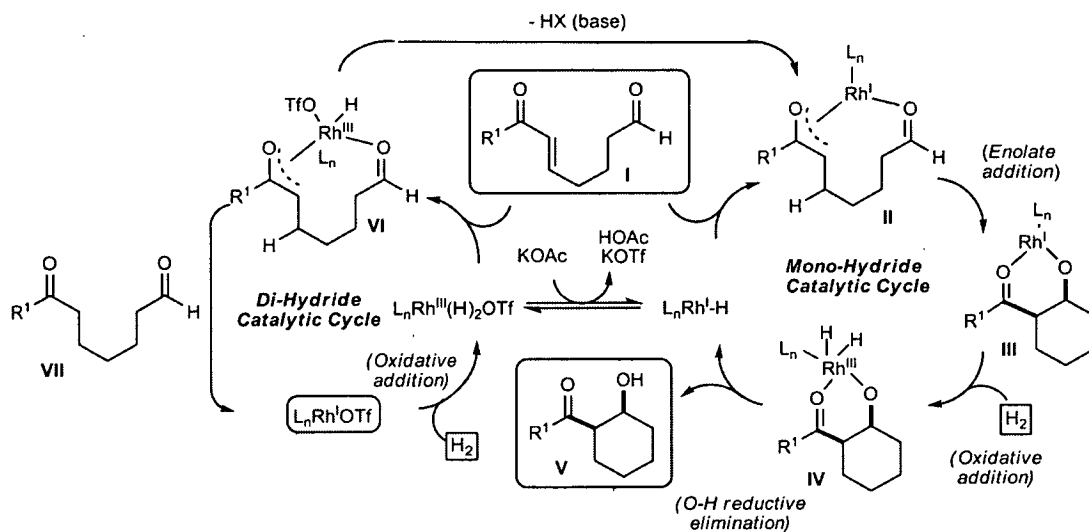
Scheme 3.18 *Formal heterolytic activation of hydrogen mitigates competitive conjugate reduction by enabling monohydride catalytic cycle*

Keto-enones were also cyclised using $Rh(COD)_2OTf/PPh_3$ and in the presence of K_2CO_3 as base, yielding the aldol products with good yields and exclusive *cis*-selectivity (*cis:trans* > 95:5) (Scheme 3.19).[98] Based on this system, there have been several other reports of Rh-catalysed reductive aldol reactions from the Krische group.[99]
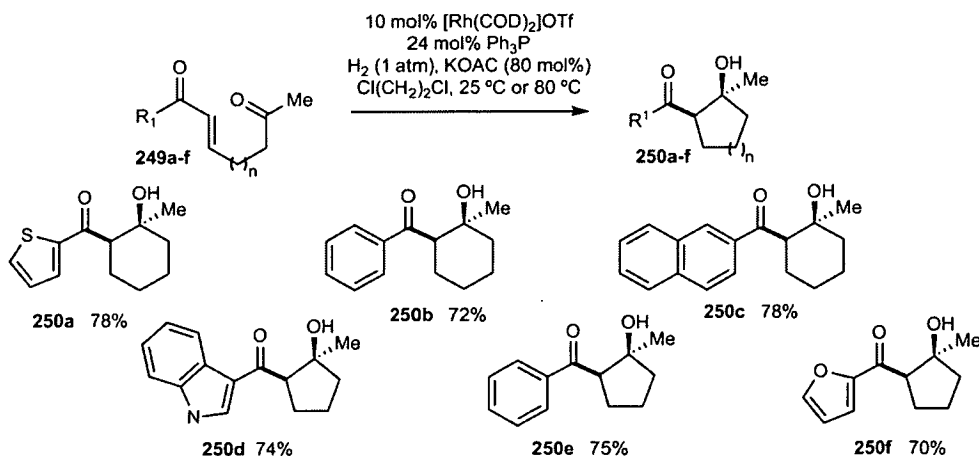
Scheme 3.19 *Catalytic hydrogenative cycloreduction of keto-enones*

In 2003, Krische reported a reductive aldol cyclisation of monoenone monoketones using catecholborane. In this intramolecular reaction, the reduction of either the enone or the ketone was avoided. The desired cyclised products were obtained in good yields and high levels of *syn*-diastereoselectivity (>99:1) (Scheme 3.20).[100]
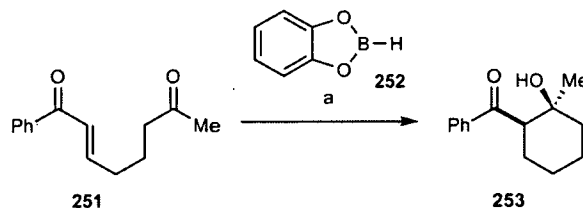
Reagents and conditions: (a) Catecholborane **252** (115 mol%), THF, 25 °C, 89%.

Scheme 3.20 *Catecholborane mediated aldol cycloreduction of monoenone monoketones*

Baba and co-workers reported a reductive aldol reaction of enones with aldehydes utilising InBr$_3$ and hydrosilanes as the hydride source.[101] In 2004 Hosomi and co-workers reported a similar indium catalysed reductive aldol cyclisation of enones with ketones, employing In(OAc)$_3$ and PhSiH$_3$ (Scheme 3.21).[102]
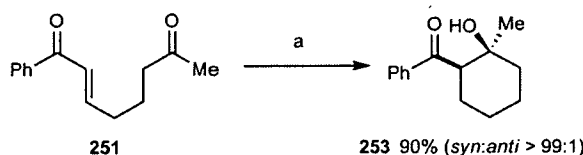
Reagents and conditions: (a) In(OAc)$_3$ (10 mol%), PhSiH$_3$ (1.2 eq), THF, EtOH, reflux.

Scheme 3.21 *Indium catalysed reductive aldol reaction of keto-enones.*

The Cu-catalysed reductive aldol reaction has also made a major contribution to the development of the intramolecular reductive aldol reaction forming carbocyclic rings. The copper hydride species [Ph$_3$PCuH]$_6$ (Stryker's reagent),[103] is a well characterised, stoichiometric source of hydride which chemoselectively reduces conjugate systems, being inert toward isolated olefins. In 1998 Chiu and co-workers were able to develop the first example of an intramolecular reductive aldol reaction using Stryker's reagent. Working on the synthesis of pseudolaric acid A, keto-enone

254 was successfully cyclised using [Ph₃PCuH]₆, to yield two bicyclic diastereomers, **255** (66%) and **256** (16%) (Scheme 3.22).[104]
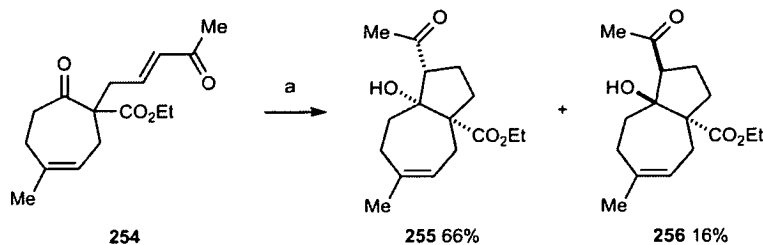
Reagents and conditions: (a) [Ph₃PCuH]₆ (2 eq), toluene, −23 °C.

Scheme 3.22 *First example of an intramolecular reductive aldol reaction using Stryker's reagent*

In· 2001, Chiu reported a more in-depth investigation of the intramolecular reductive aldol cyclisation reaction promoted by stoichiometric Stryker's reagent (Scheme 3.23).[105] When the reactions were performed at low temperatures (−40 to -25 °C), to avoid dehydration, β-hydroxyketones were obtained with good to excellent yields and exclusive *syn*-selectivity.
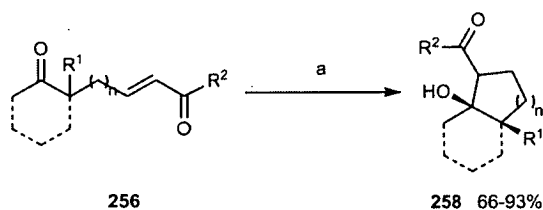
Reagents and conditions: (a) [Ph₃PCuH]₆ (2 eq), toluene, −40 °C

Scheme 3.23 *Reductive aldol cyclisation of enediones by Stryker's reagent*

This methodology was applied to the synthesis of lucinone (**261**) (Scheme 3.24).[106] Enedione **259** was transformed quantitatively and stereoselectively into **260** using two hydride equivalents of the Stryker's reagent in toluene at 0 °C to room temperature.
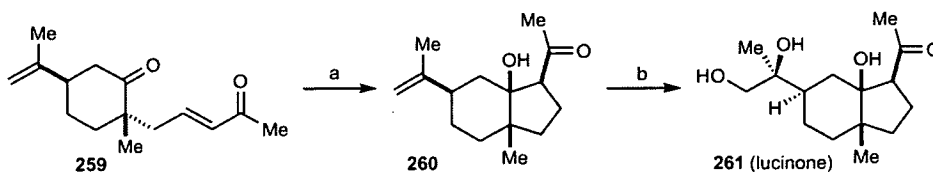
Reagents and conditions: (a) [Ph₃PCuH]₆ (2 eq), toluene, 0 °C, 99%; (b) cat OsO_4, $K_3Fe(CN)_6$, 38%.

Scheme 3.24 *Synthesis of lucinone*

The use of copper salts and organosilanes to form copper hydride species had been reported for conjugate reductive reactions by Mori and Hosomi in 1997.[107] Buchwald[108] and Lipshutz[109] had been great contributors in this area, reporting several excellent methods for enantioselective conjugate reductions.

In 2000, Lipshutz reported the catalytic reductive aldol reaction of enones and aldehydes using Stryker's reagent (5 mol%) in the presence of a silyl hydride (1.5 eq) such as dimethylphenylsilane (Me₂PhSiH), tetramethyldisiloxane (HMe₂SiOSiMe₂H) or polymethylhydrosiloxane (PMHS), to regenerate it.[110] This was a one pot- two step reaction and provided β-hydroxyketones in high yield. In the first step, silyl enol ethers were formed. In the second step, Lewis acids such as BF_3 or $TiCl_4$ were used to promote the aldol reaction.

Chiu reported, in 2004, the development of the intramolecular catalytic Cu-catalysed reductive aldol reaction using Strykers reagent (10 mol%) as the Cu source and PMHS (2.0 eq) as a hydride source.[83, 111] A variety of alkynediones were cyclised using these conditions, to afford the cyclic β-hydroxy bicycloalkenones with similar or improved yields that with the stoichiometric reaction. An example is represented in Scheme 3.25.
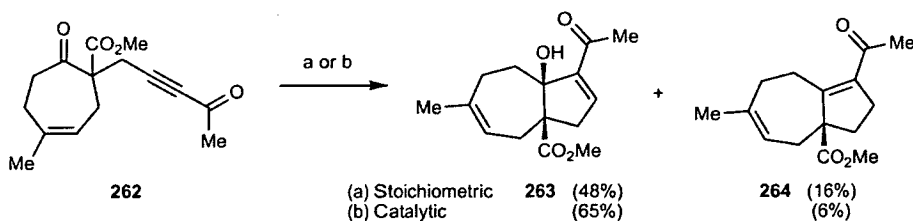
Reagents and conditions: (a) [Ph₃PCuH]₆ (1.5 eq), toluene, –40 °C. (b) [Ph₃PCuH]₆ (10 mol%), PMHS (2 eq), toluene, –40 °C.

Scheme 3.25 *Reductive aldol cyclisations catalysed by Stryker's reagent*

These were the precedents in the literature on intramolecular reductive aldol cyclisations when our group became interested in developing the reductive aldol methodology for the preparation of heterocyclic products. In the next section, the development within the group on this methodology will be described.

3.3. Development of the reductive aldol cyclisation in the Lam group

3.3.1. Copper-catalysed reductive aldol cyclisation

In 2004, with the aim of developing a methodology that ultimately allowed the synthesis of salinosporamide A, an investigation on the reductive aldol cyclisation of α,β-unsaturated amides and, although not related to our project, α,β-unsaturated esters was initiated in our group. As a result of these studies, in 2005 we reported the first intramolecular copper-catalysed reductive aldol reaction of α,β-unsaturated esters with ketones, affording five- and six-membered β-hydroxylactones with high yields and very high *syn*-stereoselectivity (>95:5).[66]

Initial efforts of this study focused on the cyclisation of α,β-unsaturated esters tethered to a ketone utilising phosphine-stabilised copper hydride complexes as catalyst system. As it was described before (Scheme 3.25), the use of substoichiometric amounts of Stryker's reagent in the presence of stoichiometric siloxane had proved successful in promoting reductive aldol cyclisations in carbocycle synthesis.[105, 111]

In optimising the reaction, several copper salts were investigated ($CuCl_2 \cdot 2H_2O$, CuF_2, $Cu(OAc)_2 \cdot H_2O$, $Cu(2\text{-ethylhexanoate})_2$, $Cu(OBz)_2$, and $Cu(acac)_2$), also several siloxanes (PMHS and TMDS) and bisphosphine ligands [DPPE, DPPB, DPPF, *rac*-BINAP, and (*S,S*)-Et-DuPhos] (Scheme 3.26).
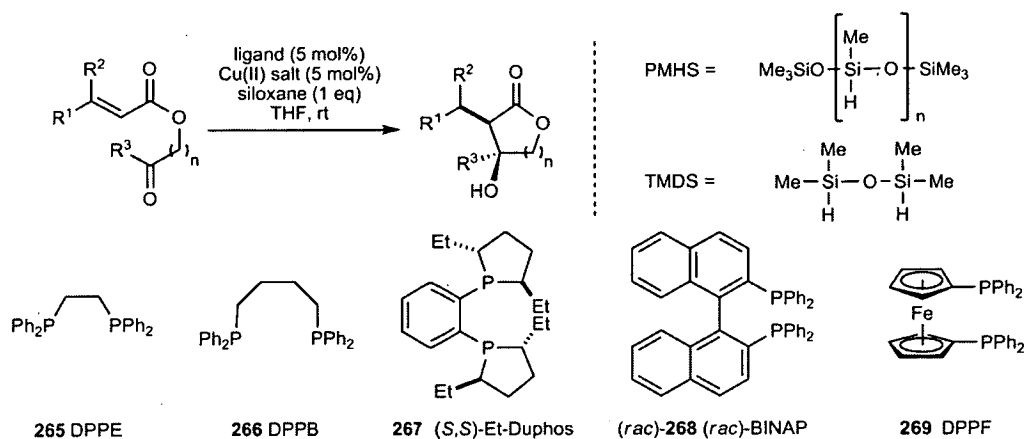
Scheme 3.26 *Optimisation of the Cu-catalysed reductive aldol cyclisation*

Finally, it was identified that $Cu(OAc)_2 \cdot H_2O$, TMDS and either DPPF or *rac*-BINAP, in THF, promoted the cyclisation with good yields and high diastereoselectivities (>95:5). Several α,β-unsaturated ester components were tolerated (Table 3.4); methyl ketone or phenyl ketone were both permitted and the process could also be applied to the formation of five-membered lactones.

Entry	Subtrate	R	Product		Yield (%)
1		PMP		**271a**	61
2		4-ClC$_6$H$_4$		**271b**	65
3		2-furyl		**271c**	63
4		*i*-Bu		**271d**	73
5		PhCH$_2$CH$_2$		**271e**	61
6				**271f**	62
7		H		**271g**	71
		Me		**271h**	50
		Ph		**271i**	47
8		H		**271j**	69
9		Me		**271k**	72
10		*i*-Bu		**271l**	65
11		PhCH$_2$CH$_2$		**271m**	60

Table 3.4 *Copper-catalysed reductive aldol cyclisations*

The use of nonracemic chiral bisphosphines (Figure 3.4) was also investigated and asymmetric cyclisations were performed with good enantioselectivities. The Roche MeO-BIPHEP Ligands (**272-274**) and SEGPHOS ligand **275** afforded slightly higher enantioselectivities than (*S*)-BINAP **268** (Table 3.5).
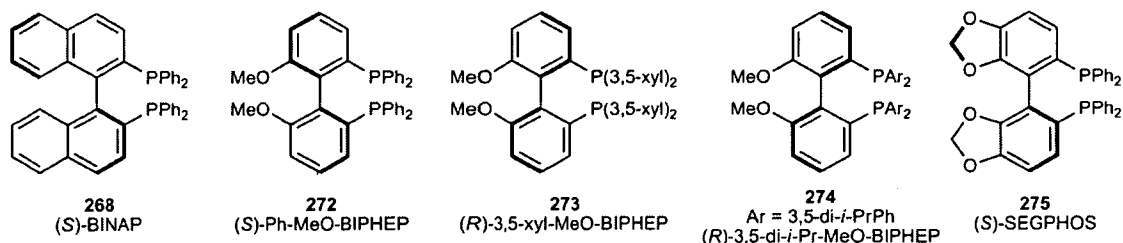
Figure 3.4 *Biphosphine ligands employed in asymmetric cyclisations*
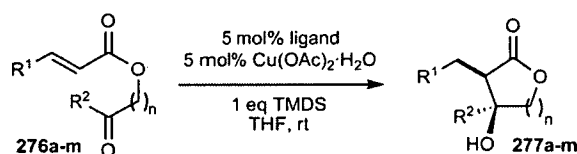
entry	Substrate	Ligand	Yield (%)		ee %
1		268	72	277a	62
2		272	73	277b	73
3		273	69	277c	70
4		274	64	277d	77
5		275	62	277e	74
6		268	79	277f	73
7		272	71	277g	76
8		273	71	277h	83
9		275	73	277i	82
10		268	60	277j	72
11		272	60	277k	72
12		273	61	277l	80
13		275	68	277m	80

Table 3.5 *Cu-catalysed asymmetric reductive aldol cyclisations*

A catalytic cycle of the reaction was proposed (Scheme 3.27). This involves the generation of (bisphosphine)Cu-H species, from the reduction of the Cu(II) salt in the presence of bisphosphine and TMDS. Conjugate reduction occurs to generate the copper enolate, which is followed by aldol addition and finally, σ-bond metathesis with the siloxane liberates the silylated product, deprotected upon workup.
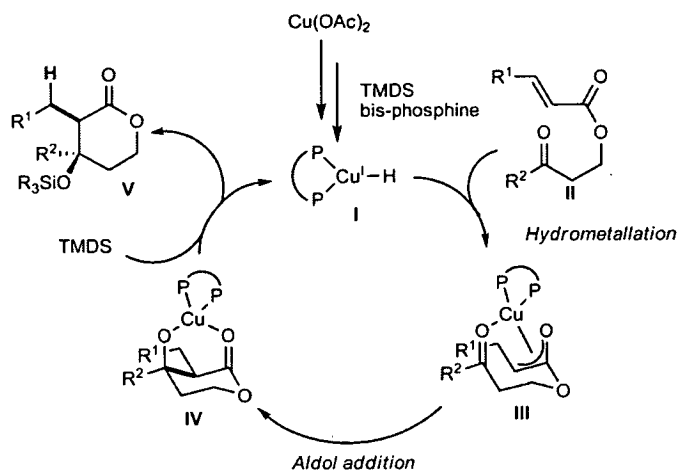
Scheme 3.27 *Proposed catalytic cycle of the copper-catalysed reductive aldol cyclisation*

These results made a significant contribution to the copper-catalysed reductive aldol methodology, but since we were aiming to apply this approach into the synthesis of salinosporamide A, our interest was centred on the reductive aldol cyclisation of α,β-unsaturated amides. Therefore, we were very pleased to see that the same copper catalyst system was also successfully applied to the reductive aldol cyclisation of α,β-unsaturated amides, to form 4-hydroxypiperidin-2-ones in a highly diastereoselective fashion (>95:5).[65]

The reaction was tolerant to wide variation in the ketone component, since alkyl, aromatic, and hetereoaromatic ketones were reacted in good yields (Table 3.6). However, the α,β-unsaturated amide component did not allow much variety. Acryloyl amides were found to be the best substrates and crotonoyl amides were also cyclised but with lower reaction rates and conversions. Unfortunately, the formation of five-membered lactams was not possible.
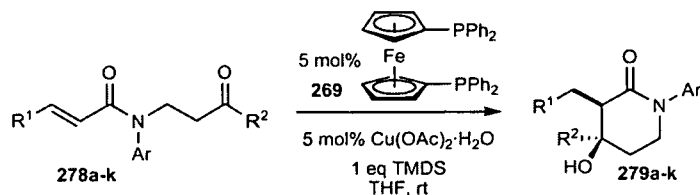
	Subtrate	R	Product	Time (h)	Yield (%)
1		Me	279a	2.5	66
2		Et	279b	5.5	61
3		*i*-Bu	279c	24	64
4		Ph	279d	21	69
5		4-MeC$_6$H$_4$	279e	24	64
6		2-furyl	279f	24	53
7		Me	279g	22	55
8		Et	279h	24	52
9			279i	4	70
10		Me	279j	24	70
11		Ph	279k	23	65

Table 3.6 *Catalytic Cu-catalysed reductive aldol cyclisation to form 4-hydroxypiperidin-2-ones*

The effect on the diastereoselectivity of the cyclisation of pre-existing centres in the tether linking the amide and the ketone was also studied. Formation of C5- and C6- substituted 4-hydroxypiperidi-2-ones was achieved with moderate to excellent levels of diastereoselectivity, due to the 1,2- or 1,3-asymmetric induction in the cyclisation (Table 3.7).
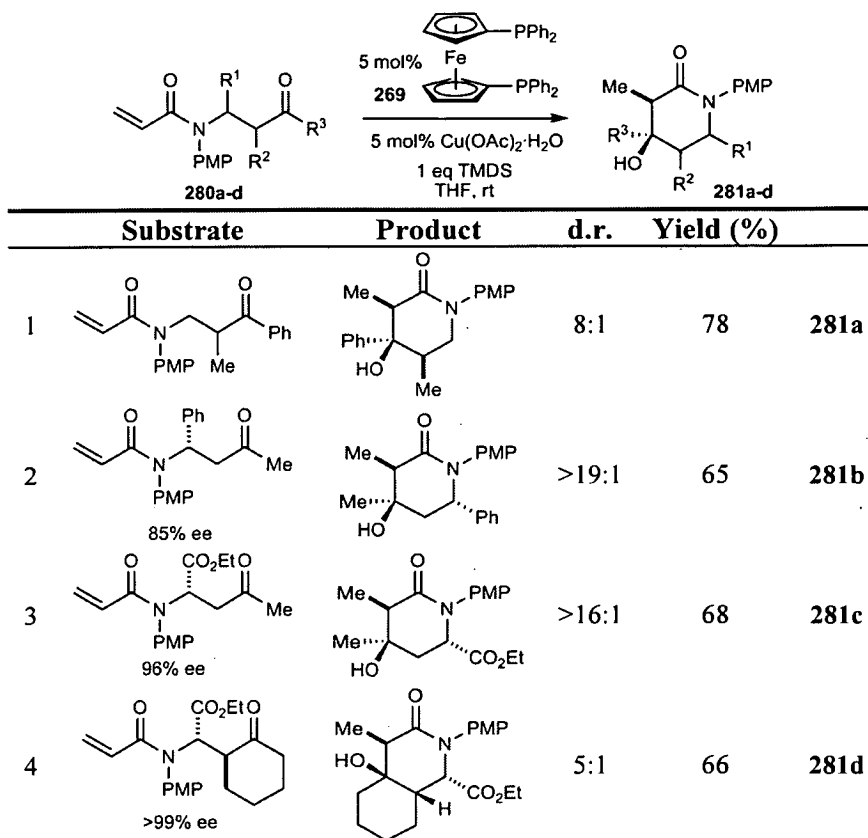
Table 3.7 *Formation of C5- and C6-substituted 4-hydroxypiperidin-2-ones*

3.3.2. Cobalt-catalysed reductive aldol cyclisation

The copper(I)-bisphosphine-catalysed reductive aldol cyclisation developed in our laboratories proved to be very efficient for the synthesis of β-hydroxylactones and β-hydroxylactams. The products were obtained with high diastereoselectivities and with moderate enantioselectivities in some cases.

However, there were two main limitations in this methodology, first, that the yields were only moderate at best (60-70%) and second and more importantly regarding the synthesis of 1, that due to the lower electrophilicity of α,β-unsaturated amides, the range of amides permitted in this reaction was very limited, with acryloyl and crotonyl amides being the only competent substrates. Moreover, the cyclisation to five-membered lactams was not achieved. With this substrate limitation, the application of this methodology to the synthesis of salinosporamide A was not feasible. Therefore, a search for a new catalyst system that could overcome these limitations was initiated.

After trying different combinations of Cu(I) salts, hydrosilanes and ligands without any improvement of the reaction, the use of other metals was investigated. The combination of Co(II) salts and hydrosilanes, combinations that had been employed in intermolecular reductive aldol reactions,[93-95] also proved ineffective.

Several methods had been reported in which organometallic reagents with β-hydrogen-containing alkyl groups were employed as stoichiometric reductants for transition metal-catalysed reductive couplings.[112] Thus, the use of Et_3B and Et_2Zn in the reaction was examined. In the presence of $Co(acac)_2 \cdot 2H_2O$ (5 mol%), Et_3B resulted in no reaction, but when Et_2Zn was employed, the desired product was obtained in 89% yield.[67a]

The scope of the reaction with these new conditions was next explored. It was discovered that it allowed the cyclisation of substrates with a wide range of substitution at both the α,β-unsaturated amide and the ketone; to give five- and six-membered rings β-hydroxylactams, in moderate to excellent yields and with high diastereoselectivities (Table 3.8). The standard conditions used $Co(acac)_2 \cdot 2H_2O$ (5 mol%) as the precatalyst (method A), but in some cases a combination of $CoCl_2$ (5 mol%) and the electron-rich phosphine ligand Cy_2PPh (5.5 mol%) proved to be more efficient (method B). Most of these substrates were not cyclised under the copper conditions.

Method A: Co(acac)$_2$·2H$_2$O (5 mol%)
Method B: CoCl$_2$ (5 mol%), Cy$_2$PPh (5.5 mol%)
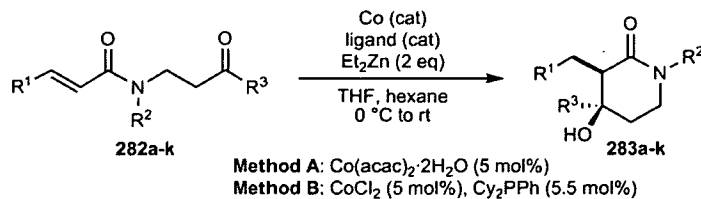
	Subtrate	R	Method	Product		dr	Yield (%)
1		Me	A		283a	12:1	89
2		Et	A		283b	9:1	79
3		H	A		283c	9:1	88
4		i-Pr	A		283d	>19:1	>99
5		Ph	A		283e	>19:1	97
6		2-furyl	A		283f	>19:1	>99
7		Me	A		283g	>19:1	94
8		i-Bu	A		283h	>19:1	94
9		H	B		283i	9:1	56
10		Me	B		283j	>19:1	80
11		Ph	B		283k	>19:1	88

Table 3.8 *Cobalt-catalysed reductive aldol cyclisations*

More importantly, the cyclisation to five-membered lactams ·was also successfully achieved (Scheme 3.28), and although with slightly lower yields and diastereoselectivities. This was a very encouraging result towards the possible application of this methodology to form γ-lactam **103**, intermediate in the route to **1**.
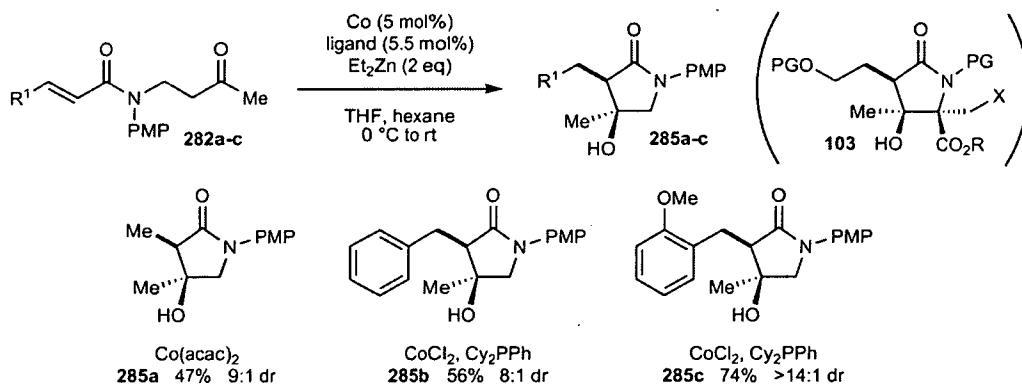
Scheme 3.28 *Cobalt-catalysed reductive aldol cyclisations to 5-membered lactams*

The cyclisation to obtain five-membered lactams from α,β-unsaturated amides containing phenyl ketones was very low yielding (<20%) when using Et_2Zn. However, when the reaction was performed using Et_3Al instead, the desired cyclised products were obtained in modest yields (Scheme 3.29).

286 R = PMP
287 R = PMB

288 57 % yield, >19:1 dr
289 53 % yield, 8:1 dr
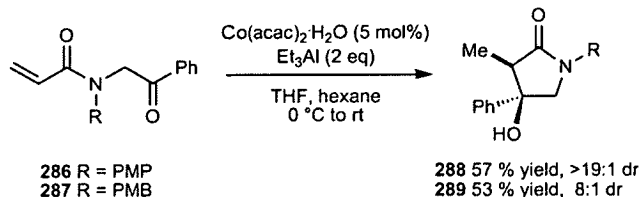
Scheme 3.29 *Cyclisations to five-membered ring lactams using Et₃Al*

The mechanism for this Co-catalysed cyclisation reaction is explained in the next section, together with the Ni-catalysed methodology.

3.3.3. Nickel-catalysed reductive aldol cyclisation

In the search for new, and more efficient, catalyst systems for the reductive aldol cyclisation of α,β-unsaturated esters and amides with ketones, the use of nickel was also contemplated. It was surprising that there is an extended development of catalytic reductive aldol couplings and cyclisations of α,β-unsaturated carbonyl substrates mediated by other metals, but not using nickel. Only recently, Montgomery reported a Ni-catalysed reductive aldol addition of acrylates and aldehydes, using Et_3B, $Ni(COD)_2$ and in the presence of an aryl iodide, which was shown to be linked to an initiation step.[113]

However, it has been demonstrated in our laboratories that the use of the combination of $Ni(acac)_2$ with Et_2Zn is not only as active as the cobalt catalyst system[67a] but also very efficient in the reaction of substrates that were completely inert or reacted inefficiently (Table 3.9).[67b]

The substrates containing the fumaric acid ethyl esters were successfully reacted to give the bicyclic products due to lactonisation of the alkoxide produced into the pendant ester (Table 3.9, entries 14 and 15).
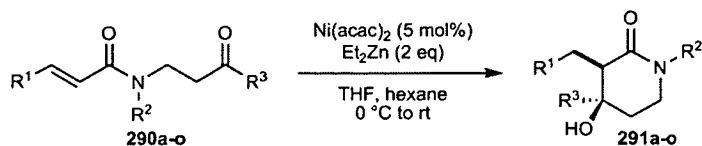
	Subtrate	R =	Product		dr	Yield (%)
1		Me		291a	>19:1	97
2		*i*-Pr		291b	12:1	98
3		CH₂CH₂Ph		291c	>19:1	95
4		Ph		291d	>19:1	97
5		2-furyl		291e	>19:1	>99
6				291f	>19:1	75
7				291g	>19:1	82
8				291h	>19:1	62
9		Me		291i	9:1	84
10		*i*-Bu		291j	12:1	84
11		2-furyl		291k	>19:1	79
12		Me		291l	>19:1	62
13		Ph		291m	>19:1	50
14		R¹ = PMP R² = Ph		291n	>19:1	79
15		R¹ = Bn R² = Me		291o	>19:1	89

Table 3.9 *Nickel-catalysed reductive aldol cyclisation to form 4-hydroxypiperidin-2-ones*

Most encouragingly towards the synthesis of **1**, the reaction was also possible for the synthesis of five-membered lactams (Scheme 3.30).
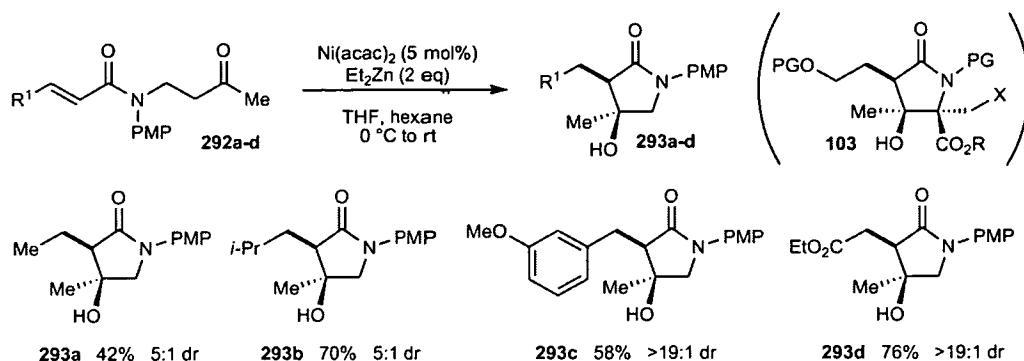
Scheme 3.30 *Successful Ni-catalysed cyclisations to form γ-lactams*

The cyclisations of esters was also performed using this new catalytic system. These substrates did not react under the cobalt conditions, but the Ni(acac)$_2$/Et$_2$Zn combination gave productive cyclisations affording a range of β-hydroxylactones in good to excellent yields and with high diastereoselectivities (Table 3.10).
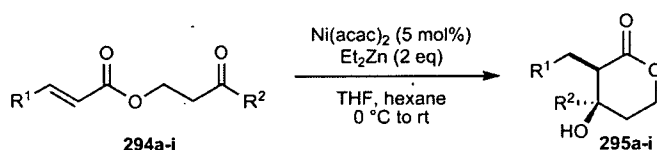
Subtrate	R =	Product		dr	Yield (%)
1	*i*-Bu		**295a**	>19:1	77
2	CH$_2$CH$_2$Ph		**295b**	>19:1	85
3	4-MeOPh		**295c**	>19:1	76
4	2-furyl		**295d**	>19:1	81
5	*i*-Bu		**295e**	5.5:1	99
6	CH$_2$CH$_2$Ph		**295f**	>10:1	76
7	Me		**295g**	>19:1	88
8	*i*-Pr		**295h**	>19:1	74
9	Ph		**295i**	>19:1	73

Table 3.10 *Nickel-catalysed reductive aldol cyclisation to form*
β-hydroxylactones

Several mechanistic possibilities have been proposed for the nickel-catalysed reductive couplings and cyclisations.[114] It is known that Ni(acac)$_2$ in the presence of Et$_2$Zn is reduced from Ni(II) to Ni(0), forming what is accepted to be the active

catalytic species. It is believed that $Co(acac)_2 \cdot 2H_2O$ or $CoCl_2$ in the presence of Et_2Zn behave in a very similar manner. Two possible reactive pathways were proposed in our group in order to explain the nickel- and cobalt-catalysed reductive aldol reaction.[65b]

The oxidative cyclisation of Ni(0) with two π-components, forming metallacyclic intermediates, has been proposed as one of the possibles mechanisms for the three-components couplings of two π-components with a main-group organometallic complex. In this mechanism, oxidative cyclisation of Ni(0) with two π-components forms metallacycle **II**, which is followed by transmetallation with a metal alkyl MR to afford **III** and, finally, reductive elimination affords **IV** (Scheme 3.31).[114]
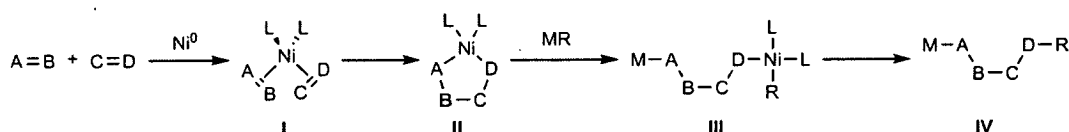
Scheme 3.31 *Oxidative cyclisation of Ni(0) with two π-components*

A possible catalytic cycle *via* the formation of metallacycles was proposed and is illustrated in Scheme 3.32. Oxidative cyclisation of M(0) with the alkene and the ketone of α,β-unsaturated substrate **I** would form metallacycle **II**. Diethylzinc would facilitate oxidative cyclisation by Lewis acid activation of the ketone through binding with zinc and by Lewis basic activation of M(0) through a three-center-two-electron bridging of a zinc-ethyl bond.[115] Transmetallation would cleave the metallacycle and would provide metal-ethyl species **III**, which undergo β-hydride elimination to generate metal hydride **IV**. Finally, reductive elimination affords alkoxide **V**, ethylene and M(0) which would reenter the catalytic cycle. Alkoxide **V** would be protonated during workup to give the desired product.

With this reaction mechanism, the relative *syn*-stereochemistry of the major diastereomer obtained in the reaction could be explained by the preference for the formation of the bicyclic metallacycle **II**, containing a *cis*-ring junction.
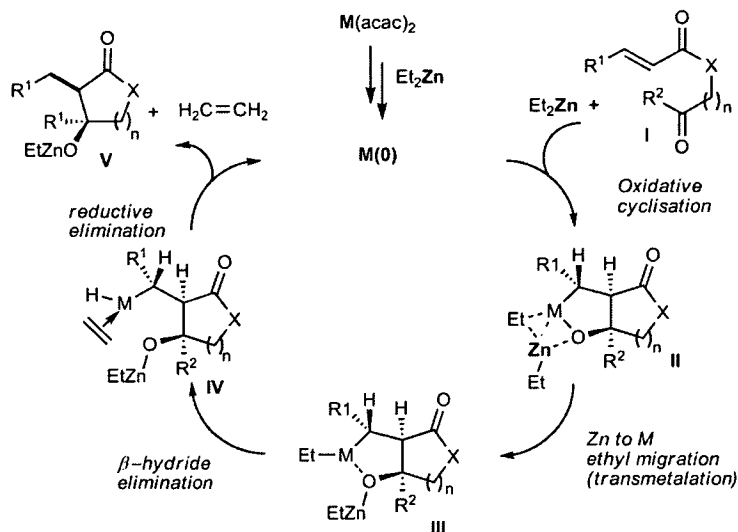
Scheme 3.32 *First possible reaction mechanism: via formation of metallacycles*

A second possible mechanism involving the formation of discrete enolates was proposed (Scheme 3.33). Interaction of M(0) and Et_2Zn forms intermediate **I**, a three-centre-two-electron bridging interaction, product of an oxidative addition of M(0) with the ethyl-zinc bond. Coordination of this intermediate to substrate **II** would provide **III**, which undergoes β-hydride elimination to form metal hydride **IV**. Reorganization of **IV** provides **V** and M(0), that can reenter the cycle. Enolate **V** undergoes aldol cyclisation to form **VII**, which is protonated during workup to give the desired product. The *syn*-stereochemistry of the major diastereomer can be explained by preferential formation of the Z-zinc enolate and the chelated Zimmerman-Traxler transition state **VI**.
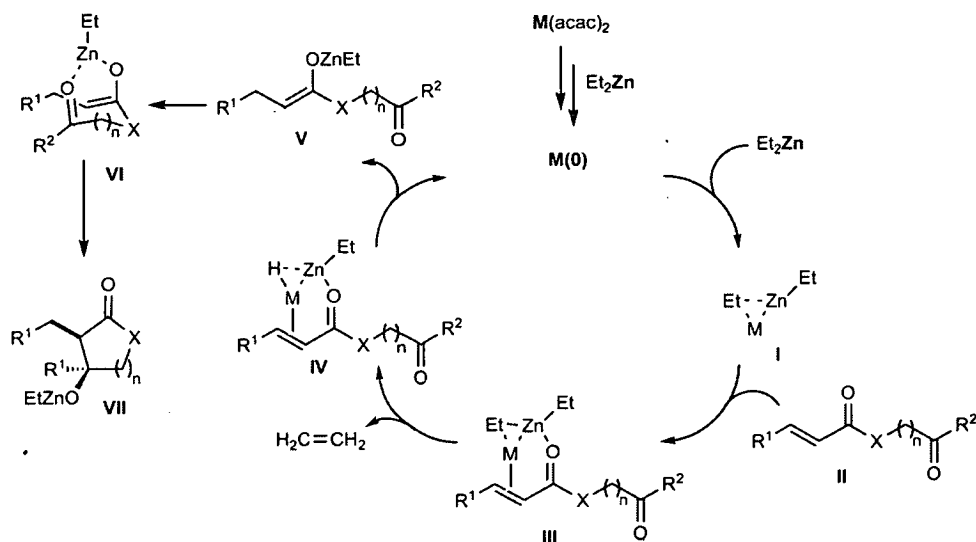
Scheme 3.33 *Second possible reaction mechanism: via formation of a zinc enolate*

3.4. Retrosynthetic analysis

The development in our group of the Cu-, Co- or Ni- catalysed reductive aldol cyclisation of α,β-unsaturated amides and esters has hugely contributed to the scope and strength of the reductive aldol methodology.[65-67] Regarding the application of these methodologies to the synthesis of salinosporamide A, the copper methodology was very substrate limited, showing poor reactivity with highly functionalised α,β-unsaturated amide substrates and the formation of γ-lactams was not achieved. However, the Co- and mostly the Ni-catalysed methodology had a significantly expanded substrate scope. Most importantly towards the synthesis of **1**, more examples of successful cyclisations affording 5-membered lactams were achieved (Scheme 3.28 and Scheme 3.30).

The full retrosynthetic analysis for this approach devised towards the synthesis of the natural product is outlined in Scheme 3.34. Initial disconnections on **1** lead to γ-lactam intermediate **296**. The aldehyde group of **296** would arise from transformation of group X of **103**, X representing an alcohol or an alcohol equivalent functionality.

We envisaged that γ-lactam **103** could be synthesised from α,β-unsaturated amide **102** *via* a reductive aldol cyclisation reaction. The objective was to find the optimal catalyst system that would allow this cyclisation with good yields and diastereoselectivities. Moreover, if the cyclisation reaction proved successful with several α,β-unsaturated amides, the synthesis of derivatives of **1** would also be possible. Amide **102** could be constructed by coupling of an α,β-unsaturated acid **298**, having a protected hydroxyl at the γ-position, with an amine **297**.
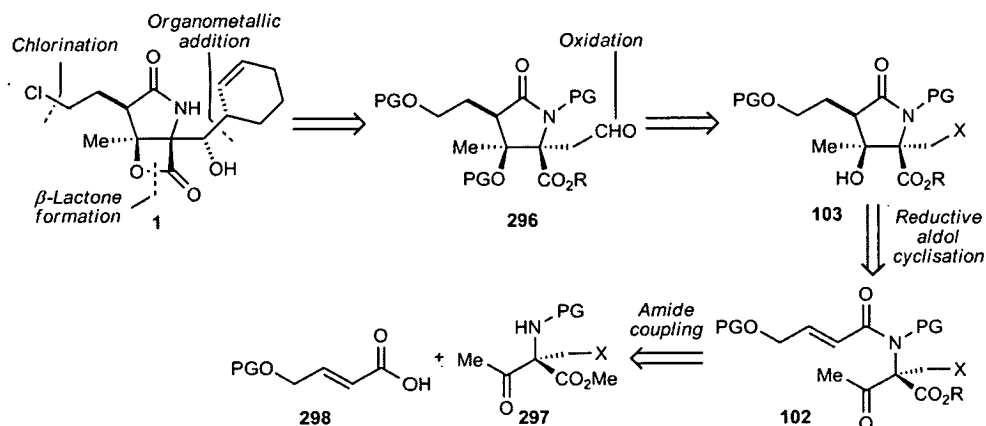
Scheme 3.34 *Retrosynthetic analysis for the reductive aldol cyclisation approach*

The required functionalities of α,β-unsaturated amide **102** to be converted into the final target **1** were then identified. Amide **299**, with a methyl ester, PMB protected amide, and a CH_2SiR_3 group, was selected as a suitable substrate for this route (Scheme 3.35). This substitution of amide **299** was also chosen in order to avoid employing similar functionality to the one employed by Corey and co-workers in their reported synthesis of **1** (Scheme 1.6).[26] A synthetic route to amine **300** would be developed.
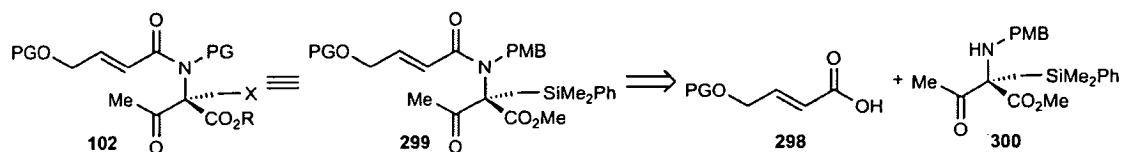
Scheme 3.35 *Design of amide 102*

After cyclisation of amide **299**, the silyl group would be converted into the alcohol *via* a Tamao-Flaming oxidation (Scheme 3.36).[37] Oxidation of alcohol **302** would afford aldehyde. **303**. We chose to have a PMB protecting group on the amide nitrogen because it was known that the insertion of the cyclohexenyl side chain at C5 following Corey's procedure[26] worked best in the presence of a PMB group on that position. Ideally, it was desired to install also a PMB protecting group on the alcohol of the acid, so that deprotection of both PMB groups at a later stage could be performed simultaneously. However, the alcohol of the α,β-unsaturated acid could also be protected with other groups, in order to prepare several α,β-unsaturated amides and have a wider variety of substrates for the study of the reductive aldol cyclisation. If the preparation of triol **26** was achieved, this route would represent a formal synthesis of salinosporamide A, since **26** is a final intermediate in the synthesis of **1** reported by Corey[26] and also in the one reported by Pattenden.[29]
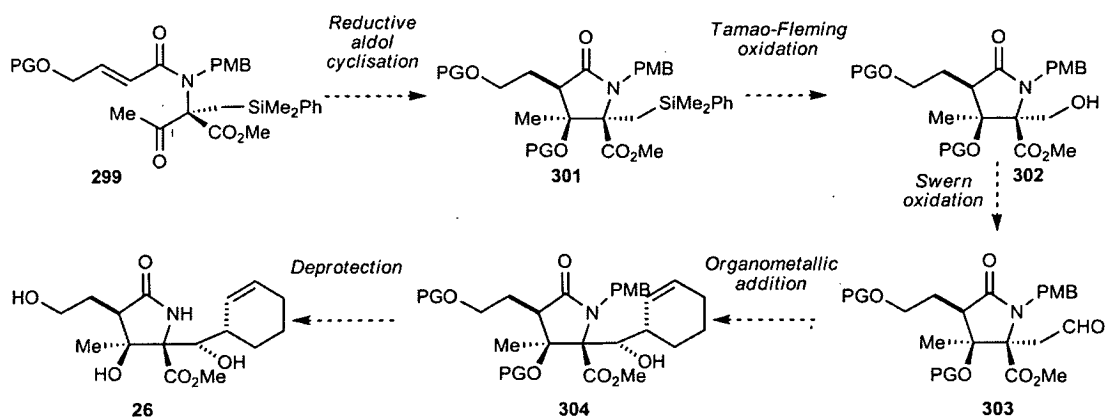
Scheme 3.36 *Main key steps after the cyclisation reaction*

It is worth pointing out that, with this approach, several steps to **26** are saved compared to Corey's synthesis. In the reported route, acrylamide **20** was prepared and successfully cyclised (Scheme 3.37). The γ-lactam product of the cyclisation was then silylated, affording **21**. A tributyltin-mediated radical-chain cyclisation was performed on **21** to obtain cis-fused γ-lactam **22**. This step introduced the ethyl chain at C2, setting up the desired stereochemical relationship at C2 and C3. In our route, the γ-lactam obtained in the cyclisation (**301**) would already contain the side chain at C2. From intermediate **22**, they prepared triol **26** in further four steps.
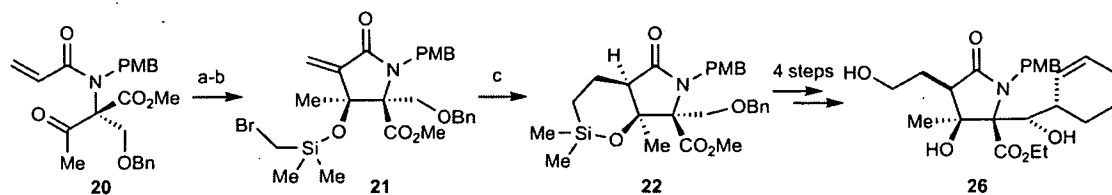
Reagents and conditions: (a) i) Ti(O*i*Pr)$_4$, c-C$_5$H$_9$MgCl, ^{t}BuOMe, –40 °C, 30 min, I$_2$, –40 °C, 2 h then 0 °C, 2 h.; (ii) NEt$_3$, CH$_2$Cl$_2$, 30 min, 83%; (b) BrCH$_2$Si(CH$_3$)$_2$Cl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 30 min, 95%; (c) Bu$_3$SnH, AIBN, Benzene, reflux, 8 h, 89%.

Scheme 3.37 _Extra steps for the insertion of the C2 side chain in Corey's total synthesis of 1_

3.5. Results and discussion

Our initial efforts focused on the synthesis of amine **300** and initially a racemic synthetic route was developed. Coupling of **300** with several acids would afford a range of α,β-unsaturated amides that would allow us to study the feasibility of the cyclisation reaction with highly substituted substrates. If the cyclisation proved successful, this route would lead to the synthesis of (±)-**1**. We would then develop an asymmetric route to amine **300** and work towards the synthesis of **1**.

3.5.1. Preparation of amine 300

Retrosynthetic analysis of **300** leads to the unprotected amine **305** (Scheme 3.38), which might be readily prepared _via_ hydrogenolysis of **306**. This intermediate is the product of the addition of dibenzylazodicarboxylate (DBAD) into **307**, which arises from the alkylation of methyl acetoacetate **308** with chloromethyldimethylphenyl silane.
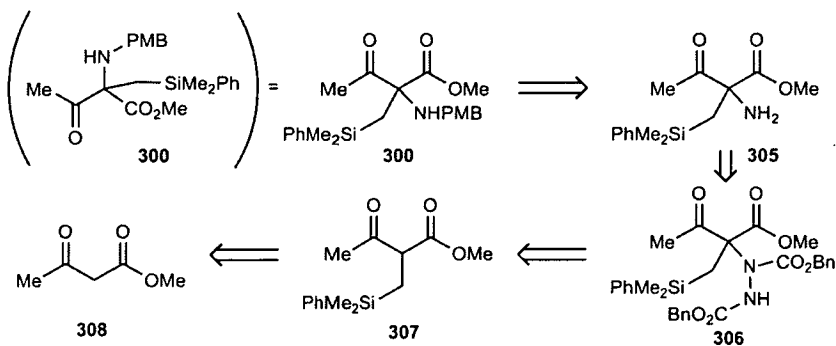
Scheme 3.38 _Retrosynthetic route to amine **300**_

84

The synthesis of amine **300** began with the alkylation of methyl acetoacetate **308** with (chloromethyl)dimethylphenyl silane. The reaction was first attempted *via* deprotonation of methyl acetoacetate with NaH, followed by addition of $ClCH_2SiMe_2Ph$. Several attempts using different solvents, such as THF, DMF or Et_2O, were carried out. These were conducted at a range of temperatures varying from room temperature to reflux, and for a variety of reaction times. Unfortunately, no product was observed even after heating under reflux for several days.

Formation of the desired product was only observed when an iodide source was added. Sequential addition of methyl acetoacetate and chloromethyl dimethylphenylsilane (1.1 eq) to a suspension of KI (0.6 eq) and NaH (1.1 eq) in DMF:THF (1:1) followed by heating under reflux for 14 h yielded the desired alkylated product in 45% yield.[116] The same procedure was repeated in THF only as solvent but product **307** was not formed. When a mixture of THF with other polar solvents (acetonitrile or DMSO) was employed, traces of product were obtained but the yield could not be improved.

The number of equivalents and the source of iodide were also investigated. It was demonstrated that the optimal amount of KI was 0.6 equivalents. When Bu_4NI was used, only traces of the desired alkylated product were formed. The use of NaI instead of KI also afforded the desired alkylated product but in slightly lower yield (40%). The yield of the reaction could finally be improved to 65% by increasing the amount of NaH (1.5 equivalents) and alkylating agent (1.2 equivalents) (Scheme 3.39).
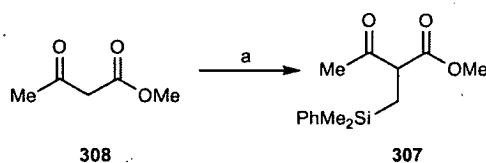
Reagents and conditions: (a) NaH (1.5 eq), KI (0.6 eq), $ClCH_2SiMe_2Ph$ (1.2 eq), THF:DMF (1:1), reflux, 14 h, 65%.

Scheme 3.39 *Alkylation of methyl acetoacetate to afford 307*

The next step involved the amination of **307**. Jorgensen reported in 2003 a catalytic enantioselective α-amination of α-substituted β-ketoesters catalysed by a chiral copper(II)-bisoxazoline complex with azodicarboxylates as the nitrogen

fragment source.[117] With only 0.5 mol% of the catalyst, the corresponding products were obtained in high yields and excellent enantioselectivities (Table 3.11).

	R^1	R^2	R^3		10 mol% cat.		0.5 mol% cat.	
					Yield (%)	ee (%)	Yield (%)	ee (%)
1	Me	Me	Et	312a	98	98	91	96
2	Et	Me	Et	312b	94	98	98	98
3	Ph	Me	Et	312c	85	95	81	87
4	*i*-Pr	Me	*t*-Bu	312d	96	98	89	98
5	Bn	Me	*t*-Bu	312e	84	98	79	98
6	Me	Allyl	*t*-Bu	312f	-	-	80	98
7	Me	Me	*t*-Bu	312g	86	98	-	-
8	(CH$_2$)$_3$		Et	312h	98	99	96	99
9	(CH$_2$)$_4$		Et	312i	98	99	96	99
10	(CH$_2$)$_5$		Et	312j	76	98	70	99

Table 3.11 *Jorgensen's (S)-Ph-Box-Cu(OTf)$_2$ catalysed enantioselective amination*

The newly formed stereogenic carbon centre was proved to be of *R* stereochemistry by X-ray crystallography of a derivative of one of the addition products. On the basis of this result, a reaction mechanism involving the approach of dibenzyl azodicarboxylate to the β-ketoester coordinated to the catalyst was proposed (Figure 3.5).
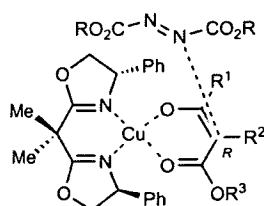
Figure 3.5 *Proposed reaction mechanism*

Consequently, it was planned to apply this methodology in the synthesis of amine **300**, which also had a quaternary stereocentre with *R* stereochemistry (Scheme 3.40).
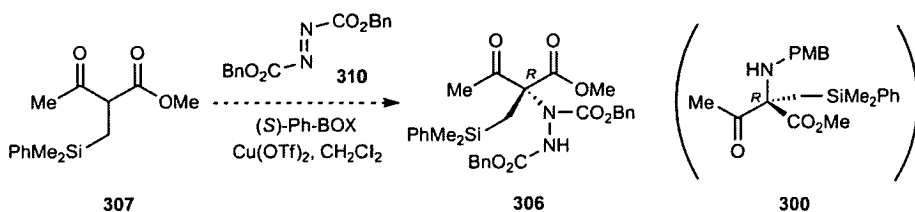
Scheme 3.40 *Possible application of Jorgensen's methodology to our system*

The need to test the feasibility of the key cyclisation step however, led us to first develop a simple and efficient route to racemic **300**. Amination of **307** was carried out *via* a phosphine-catalysed addition of **307** to azodicarboxylates.[118] We were very pleased to see that when β-keto ester **307** was reacted with a substoichiometric amount of tributylphosphine and with dibenzyl azodicarboxylate (**310**) in acetonitrile, the desired addition product **306** was easily prepared and isolated in 86% yield (Scheme 3.41).
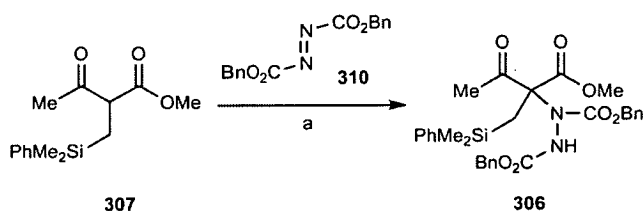
Reagents and conditions: (a) PBu₃ (0.2 eq), DBAD (**310**) (1.1 eq), MeCN, rt, 30 min, 86%.

Scheme 3.41 *Phosphine catalysed α-amination of 307*

The proposed mechanism for this reaction is outlined in Scheme 3.42. The phosphine attacks the electronically deficient double bond of the azodicarboxylate, forming a phosphonium ylide intermediate **313** that deprotonates the dicarbonyl compound **314** generating its conjugate base (**316**). The conjugate base can now attack the nitrogen of the phosphonium cation **315**, affording the addition product and releasing the phosphine (pathway A). Another alternative (pathway B) involves a

cyclic mechanism with attack of the conjugate base onto the double bond of the azodicarboxylate followed by transprotonation.

Pathway A

Pathway B
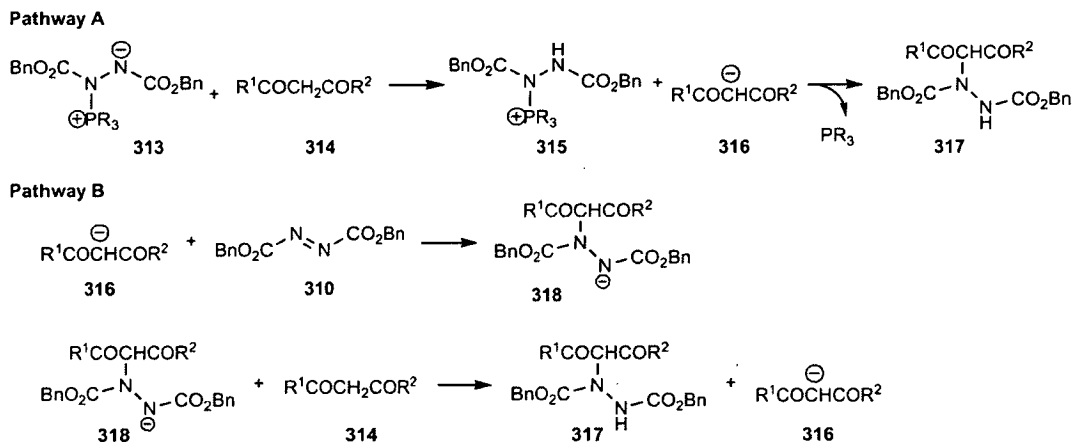
Scheme 3.42 *Proposed mechanism of the phosphine catalysed addition of β-keto esters to azodicarboxylates*

We next looked at the hydrogenolysis of **306**, to obtain the amine moiety. When compound **306** was treated with PtO_2 or Pd/C as catalyst under a hydrogen atmosphere, no reaction was observed. The reaction with Ra-Ni was slow, it did not go to completion and it only afforded an inseparable mixture of products. However, the starting material was consumed when the reaction was performed in a high pressure reactor (45 bar) and using a large excess of Ra-Ni. Purification of the crude reaction mainly afforded a diastereomeric mixture of aminoalcohols **319a** and **319b** (approximately 2.4:1), arising from the reduction of both the N-N bond and the ketone of **306** (Scheme 3.43). Unfortunately, the yield of this reaction was inconsistent, ranging from 50 to 70%. This is a problem that would need to be addressed in the future.
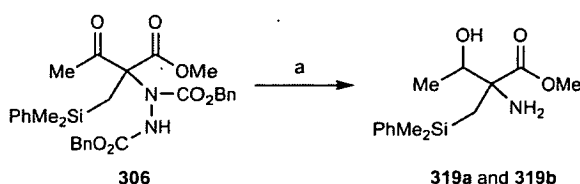
Reagents and conditions: (a) Ra-Ni, HOAc, MeOH, H_2, 40 °C, 16 h, 50-70%.

Scheme 3.43 *Hydrogenolysis of 306*

PMB protection on the nitrogen of **319a** and **319b** was first attempted using NaHCO₃ and PMBCl, conditions that afforded some desired product but the yield was low and inconsistent (25-40%). Formation of the product protected both on the oxygen and on the nitrogen was problematic. Several attempts were carried out using different bases and different number of reagent equivalents, and also using iodide additives (KI, NaI), but in none of these was the yield of the reaction significantly improved. We were pleased to find that reductive amination with *p*-anisaldehyde gave the desired product in a consistent and good yield (65-70%) (Scheme 3.44). The reaction was performed on the mixture of both diastereomers **319a** and **319b**, which yielded a mixture of both diastereomers **320a** and **320b**. Oxidation to the aminoketone was achieved under Swern conditions.[61] The yield of this oxidation was good (>80%) when the reaction was performed on a small scale, but on scaling (>0.75 mmol), the yield was only moderate (60-70%).
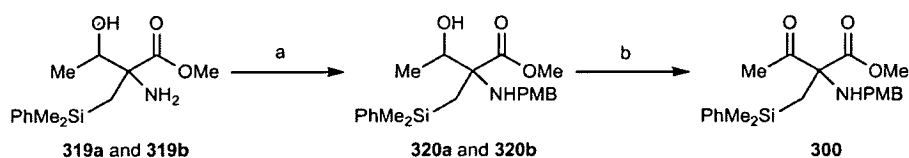
Reagents and conditions: (a) NaCNBH₃ (1.5 eq), *p*-anisaldehyde (1.2 eq), HOAc (2 eq), MeOH, rt, 18 h, 65%; (b) (COCl)₂ (2.1 eq), DMSO (4.2 eq), Et₃N (4.2 eq), CH₂Cl₂, −78 °C, 3h, 60-80%.

Scheme 3.44 *Final steps of the synthesis of amine 300*

The five step route shown in Scheme 3.45 allowed us to prepare sufficient amounts of amine **300** and studies on the reductive aldol reaction could be undertaken. However, a general improvement of the synthetic route, focusing on the hydrogenolysis of **306** and on the final oxidation step, was necessary.
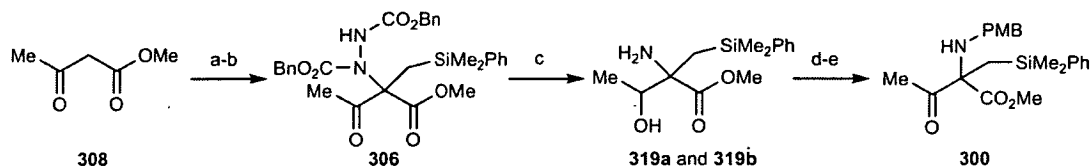
Reagents and conditions: (a) NaH, KI, ClCH₂SiMe₂Ph, THF:DMF (1:1), reflux, 14 h, 65%; (b) PBu₃, DBAD (**310**), MeCN, rt, 30 min, 86%; (c) RaNi, HOAc, MeOH, H₂, 40 °C, 16 h, 50-70%; (d) NaCNBH₃, *p*-anisaldehyde, HOAc, MeOH, rt, 18 h, 65%; (e) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, −78 °C, 3h, 60-80%.

Scheme 3.45 *Full synthetic route to amine 300*

3.5.2. Studies on the amide coupling and reductive aldol cyclisation

We next examined the preparation of the protected 4-hydroxy α,β-unsaturated acid. Ideally, the 4-hydroxy group should be protected with a PMB group, so that it could be simultaneously deprotected with the PMB-protected amide nitrogen. It was envisaged that alcohol **322** could derive from ethyl *trans*-4-oxo-2-buteanoate **321** (Scheme 3.46). Fortunately, Luche reduction[119] of **321** afforded alcohol **322** in excellent yield. PMB trichloroacetimidate **323** was next prepared[120] and reacted with alcohol **322** yielding ester **324**. Hydrolysis of the ester afforded acid **325** in 70 % yield.
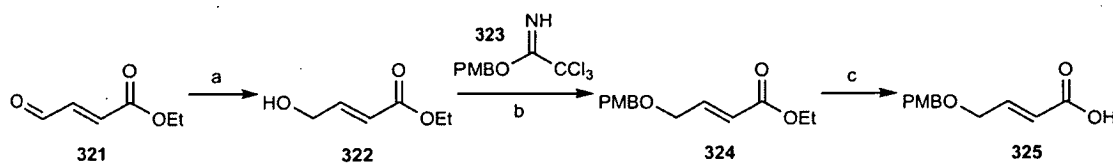
Reagents and conditions: (a) NaBH$_4$ (1 eq), CeCl$_3$ (1 eq), EtOH, 0 °C to rt, 14 h, 95%; (b) acetimidate **323** (1.5 eq), CSA (1 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 57%; (c) NaOH (1.1 eq), EtOH, rt, 14 h, 70%.

Scheme 3.46 *Preparation of PMB-protected acid 325*

The formation of the amide derived from acid **325** and amine **300** was attempted mainly *via* two methods: 1) formation of the acid chloride followed by coupling with the amine and 2) activation of the acid with a coupling agent followed by reaction with the amine.

In the first method, the acid chloride of **325** was formed and then reacted with a solution of amine **300** in the presence of a base. Corey and co-workers have reported interesting results on the coupling reaction of structurally similar amine **327** and acid chlorides (Scheme 3.47).[121] They reported a novel reaction that produced bicyclic β-lactones **328** and **329**, from the reaction of acryloyl chloride **326** and amino ketone **327** with pyridine as base. However, this discovery originated from the study of the formation of the corresponding acrylamide, which proved to be unexpectedly troublesome. It was observed that the formation of the acrylamide was only achieved when highly hindered tertiary amines, like triisobutylamine or 2,6-di-*tert*-butylpyridine, were employed as base. Instead, in the presence of less

hindered bases, like pyridine or triethylamine, the main products were the bicyclic β-lactones **328** and **329** (4:1 ratio). Due to the low basicity and high steric hindrance of amine **327**, the reaction rate of the coupling with the acid chloride is so slow that the side reaction that affords the β-lactones becomes dominant.
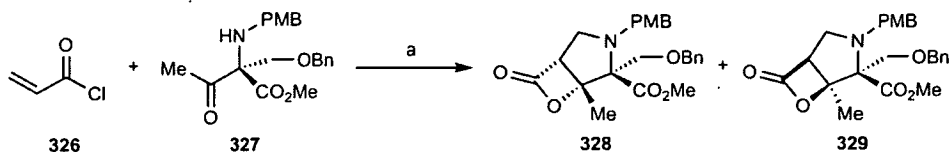
Reagents and conditions: (a) Pyridine (3 eq), CH_2Cl_2, 80% (4:1).

Scheme 3.47 *Formation of β-lactones **328** and **329** using a less hindered amine*

It was proposed that the most likely mechanism for the β-lactone formation in the presence of pyridine involved the formation of an *N*-acryloylpyridinium complex **331**, which suffers an addition of the secondary amine **327** at the carbon β to the carbonyl group instead of at the carbonyl, probably due to steric reasons. Keto ketene **332** is then formed and cyclises *via* an internal [2+2]-cycloaddition giving β-lactones **328** and **329** (Scheme 3.48).
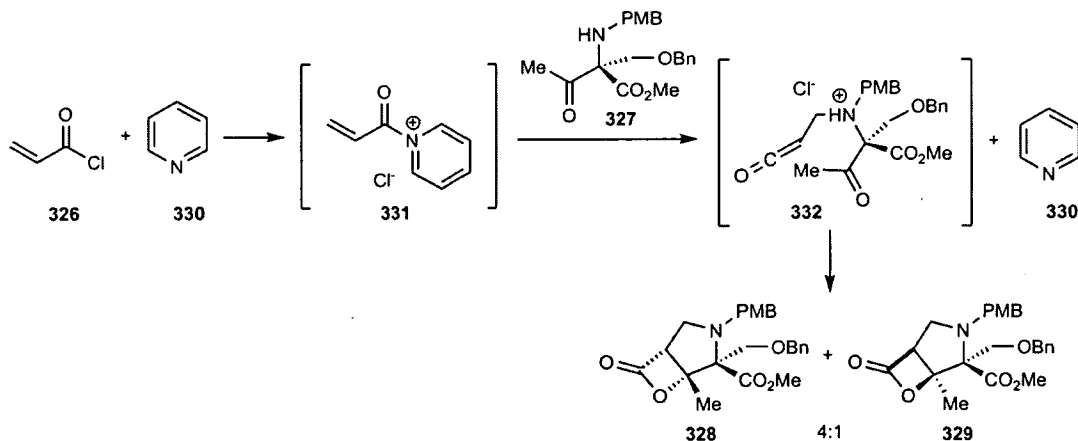
Scheme 3.48 *Proposed mechanism for the formation of β-lactones **328** and* ***329***

When more hindered bases are used, the activated *N*-acryloylammonium species is not formed and the amine is exclusively functioning as base, and *N*-acylation of amine **327** is the main reaction (Scheme 3.49).
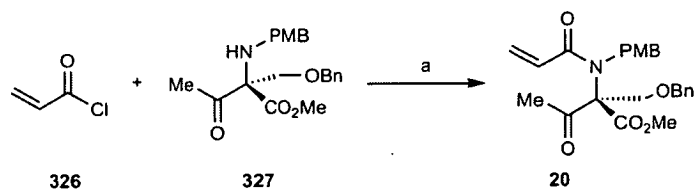
Reagents and conditions: (a) Triisobutylamine (3 eq), CH_2Cl_2, 78%.

Scheme 3.49 *Acylation of amine **327** using hindered amines*

Bearing this example in mind, we proceeded to perform the amide coupling of our substrates. Acid **325** was reacted with oxalyl chloride and a substoichiometric amount of DMF and stirred for 6 h. The formation of the acid chloride was also carried out using thionyl chloride and allowing the reaction to stir at room temperature overnight. The solution containing the acid chloride was then concentrated *in vacuo*, redissolved in CH_2Cl_2 and transferred into a solution of the base and amine **300** (Scheme 3.50). This coupling reaction was initially attempted in the presence of 2,6-di-*tert*-butylpyridine or triisobutylamine as base, but without success. The reaction was also attempted at various temperatures, using different number of equivalents of both reagents and also using other bases (Na_2CO_3 (aq) and pyridine). However, all efforts to obtain amide **334** were unsuccessful.

The main reason of the failure of this reaction was the cleavage of the PMB protecting group of the alcohol during the formation of the acid chloride of **325**, due to the acidic conditions produced in the reaction. This cleavage, combined with the low basicity and high steric hindrance of amine **300**, did not allow the formation of amide **334**. All reactions yielded a complex mixture of products and remaining starting amine **300**, but the desired amide was not isolated.
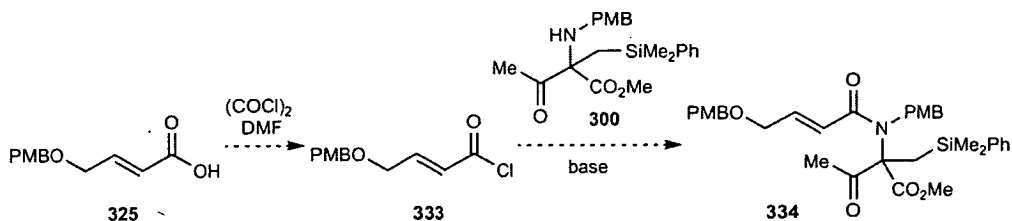
Scheme 3.50 *Preparation of **334** via formation of the acid chloride of **325***

The use of peptide coupling agents was next investigated. In a peptide coupling reaction, the carboxylic acid is typically activated by an appropriate peptide coupling reagent followed by reaction with the amine of a second amino acid. Carbodiimide coupling reagents (**335-337**) have been extensively used in peptide synthesis because of their moderate activity and because they are relatively inexpensive (Figure 3.6). Additives like 1-hydroxybenzotriazole (HOBt) or DMAP are successfully used to enhance the reaction rate and reduce racemisation. Another coupling reagent extensively used is the imidazolium CDI.
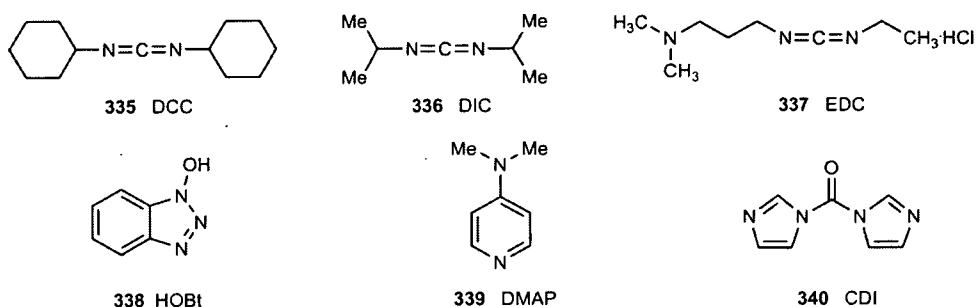
Figure 3.6 *Examples of coupling agents and additives*

Phosphonium reagents as CloP and BroP were introduced in the early 1970s but they showed high racemisation in their reactions (Figure 3.7). After HOBt was discovered as an antiracemisation agent, a new CloP-HOBt combined reagent (BOP) was introduced. Later, reagents like PyBroP were employed, in which the dimethylamine moiety has been replaced by a pyrrolidine. These reagents avoid the formation of the toxic hexamethylphosphoramide (HMPA) in the reaction.

Uronium reagents, like HBTU or TBTU, are also extensively used in peptide chemistry (Figure 3.7). Tetrafluoroborate or hexafluorophosphate anions are generally the non-nucleophilic counteranion used in these reagents. It has been reported that the active species of these reagents is the *N*-guanidium rather than the *O*-uronium salt.
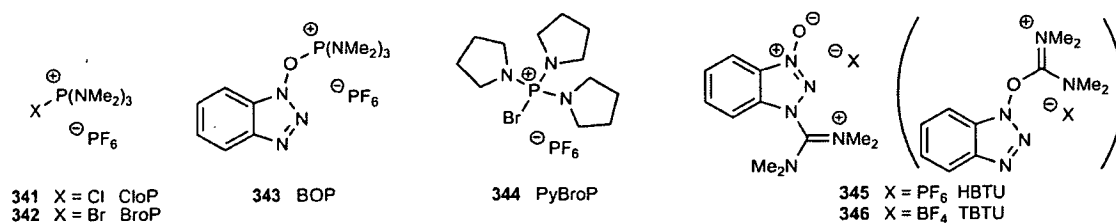
Figure 3.7 *Phosphonium and uranium coupling reagents*

We carried out different attempts using several coupling reagents, but all of them met with failure and no pure products could be isolated from the reactions. Table 3.12 summarises the different conditions employed for this reaction.

Attempts using DCC or EDC were performed in the presence of additives HOBt or DMAP (entries 1-4). These reactions were carried out in several solvents, under different temperatures, using different number of equivalents of the reagents and different reaction times. Even if under some conditions degradation of the starting material occurred, in every case unreacted amine **300** was recovered. An attempt was made using CDI in CH_2Cl_2 as solvent (entry 5), but no reaction was observed. Similarly disappointing results were obtained when HBTU, PyBrop or BOP was used in the presence of diisopropylamine (entries 6-9).
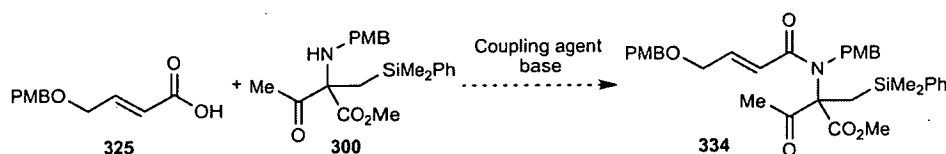
	Coupling agent	**Solvent**
1	DCC, DMAP	Tol
2	DCC, HOBt	CH_3CN
3	EDC, DMAP	CH_2Cl_2 or DMF
4	EDC, HOBt	CH_2Cl_2 or DMF
5	CDI	CH_2Cl_2
6	HBTU, DIPEA	DMF
7	HBTU, HOBt, DIPEA	DMF
8	PyBrop, DIPEA	CH_2Cl_2
9	BOP, DIPEA	CH_2Cl_2

Table 3.12 *Attempts for the formation of amide **334** using coupling agents*

In order to confirm that amine **300** is nucleophilic enough to couple with acid chlorides, reactions were repeated using commercially available acid chlorides. Amine **300** was successfully reacted with acroloyl or crotonoyl chloride (3 eq) in the presence of triisobutylamine,[121] yielding amides **347** and **349**, respectively, in good yields (Scheme 3.51). This suggests that decomposition of the acid was the main factor impeding the formation of amide **334**.
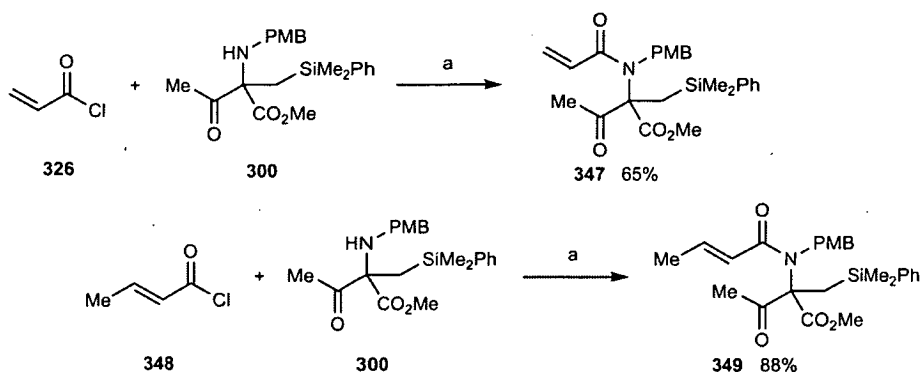
Reagents and conditions: (a) Triisobutylamine (3 eq), CH_2Cl_2, 0 °C to rt, 14 h.

Scheme 3.51 *Succesful coupling of amine **300** with commercially available acid chlorides*

Consequently, we decided to prepare another α,β–unsaturated acid, this time with a less acid-labile protecting group on the alcohol. We chose to use a benzyl protecting group, which is more stable under acidic conditions and should not cleave during the acid chloride formation.

Protection of alcohol **322** with a benzyl group was performed using the same method employed in the PMB protection. Benzyl trichloroacetimidate **350** was easily prepared and it was then reacted with alcohol **322** in the presence of an acid (Scheme 3.52). The first attempt was performed employing CSA but, although some desired product was formed, the reaction afforded a complex mixture of products and it did not go to completion, even when a large excess of acid was used. The use of triflic acid in a similar benzyl protection had been reported.[122] We were pleased to see that under these conditions, a fast and clean reaction afforded the desired ester **351** in moderate yield (60% to 70%). Hydrolysis of the ester using LiOH in H_2O/THF[123] gave access to the desired protected acid **352** in 85% yield after purification (Scheme 3.52).
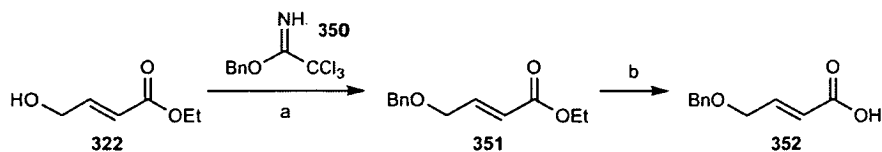
Reagents and conditions: (a) Benzyl acetimidate **350** (1.5 eq), TfOH (0.1 eq), CH_2Cl_2, rt, 24 h, 60-70 %, (b) LiOH (2 eq), H_2O/THF, rt, 18 h, 85%.

Scheme 3.52 *Synthesis of benzyl protected acid 352*

The coupling of amine **300** with acid **352** was next attempted. After some experimentation, it was found that 4.5 equivalents of acid chloride were necessary in the reaction. Therefore, 4.5 equivalents of acid **352** were reacted with oxalyl chloride for 18 h and this solution was concentrated, redissolved in CH_2Cl_2 and then added to a solution of amine **300** and triisobutylamine in CH_2Cl_2. Amide **354** was obtained in 60% yield, after tedious column chromatography purification (Scheme 3.53).
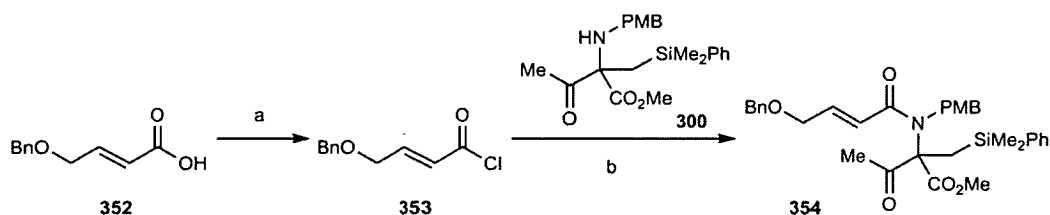
Reagents and conditions: (a) $(COCl)_2$ (13.5 eq), CH_2Cl_2, 14 h, rt; (b) amine **300**, triisobutylamine (4.5 eq), CH_2Cl_2, 0 °C to reflux, 14 h, 60%.

Scheme 3.53 *Successful amide coupling of 300 with acid 352*

We could now proceed to attempt the reductive aldol cyclisation of **354**. For these trials we would screen the most effective catalyst systems discovered within the group. Therefore, amide **354** was treated with Et_2Zn as the stoichiometric reductant and either Co salts ($Co(acac)_2 \cdot 2H_2O$ or $CoCl_2$ and Cy_2PPh) or $Ni(acac)_2$ as precatalyst. Unfortunately, in all cases the reaction only afforded a complex mixture of products, together with unreacted starting material (Scheme 3.54). The analysis of the reactions proved very difficult and desired products were never isolated. The reactions were also carried out using Et_3Al instead of Et_2Zn, but again a complex mixture of products was obtained.
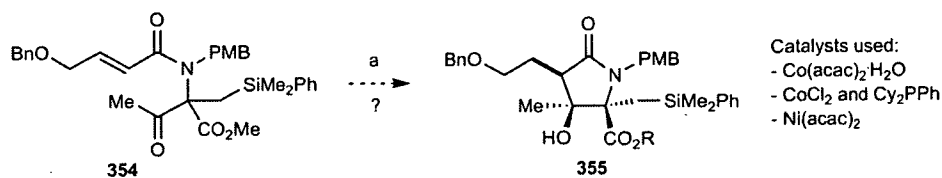
Reagents and conditions: (a) Catalyst (10 mol%), ligand (11 mol%), Et$_2$Zn or Et$_3$Al (2 eq), THF.

Scheme 3.54 *Inconclusive cyclisation trials of amide 354*

As mentioned previously, amides **347** and **349** (Scheme 3.51) were synthesised to confirm whether amine **300** was nucleophilic enough to react with an acid chloride to form an amide. These substrates do not contain the 4-hydroxy functionality in the acyl moiety of the amide required for the synthesis of **1**, but we questioned whether the cyclisation of these substrates would be possible. If these cyclisations were successful, more information about the optimal catalyst system and about the reaction conditions would be gained. Furthermore, we would learn that it was the functionalisation of the acyl part of the amide what was preventing the cyclisation of amide **354** from occurring.

Cyclisation of **347** and **349** was attempted employing the same catalyst systems as previously. These substrates were treated with Et$_2$Zn as the stoichiometric reductant and either Co salts (Co(acac)$_2$·2H$_2$O or CoCl$_2$ and Cy$_2$PPh) or Ni(acac)$_2$ as precatalyst (Scheme 3.55). In all cases the reaction resulted in a complex mixture of products and the desired product was never isolated.
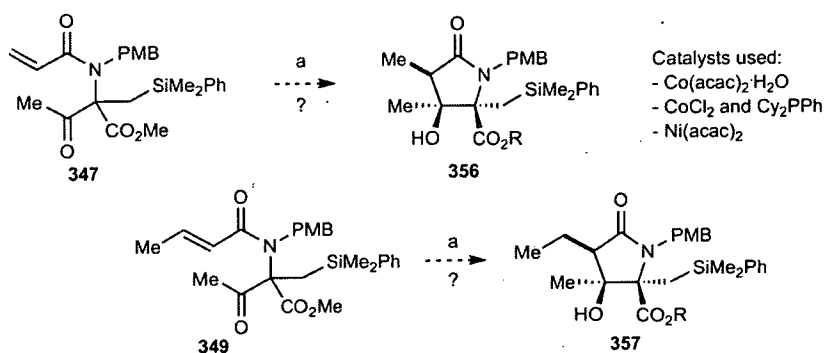
Reagents and conditions: (a) Catalyst (10 mol%), ligand (11 mol%), Et$_2$Zn (2 eq), THF.

Scheme 3.55 *Inconclusive attempts of cyclisation of 347 and 349*

In order to verify that the failure of the cyclisation could be attributed to the highly substituted amide, we decided to couple the simpler amine **359**[i] with the benzyl protected acid **352** (Scheme 3.56). The formation of the acid chloride (2.5 eq) was achieved reacting acid **352** with oxalyl chloride, stirring at room temperature for 14 h,[123] followed by the reaction with a solution of the amide and triisobutylamine in CH_2Cl_2. Amide **360** was obtained in very good yield (>94%). The fact that the conditions needed for amide coupling with **359** were less harsh than for the coupling with amine **300** (where 4.5 equivalents of the acid chloride were needed), demonstrates the low reactivity of the latter.
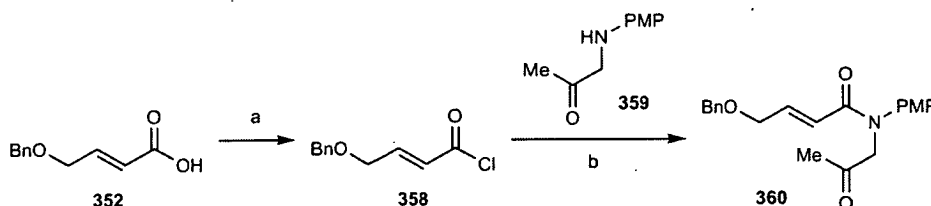
Reagents and conditions: (a) $(COCl)_2$ (12.5 eq), CH_2Cl_2, 14 h, rt; (b) amine **359**, triisobutylamine (3 eq), CH_2Cl_2, rt, 12 h, 94%.

Scheme 3.56 *Preparation of amide 360*

When substrate **360** was treated with Et_2Zn and $Co(acac)_2 \cdot 2H_2O$, some new products were formed, but most of the starting material remained unreacted. Surprisingly, exposure of **360** to Et_2Zn and $CoCl_2$ and Cy_2PPh as precatalyst afforded, in a very clean reaction, two cyclised products in a total conversion of 85% and in a 2:1 ratio (Scheme 3.57). The relative stereochemistry of each product was not assigned, although due to the known *syn*-selectivity of the cyclisation reaction,[67] we assumed that the major diastereomer would be the *syn*-product. The reaction using $Ni(acac)_2$ also afforded the two cyclised products, but with slightly lower conversions.

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[i] Kindly donated by Dr. G. J. Murray
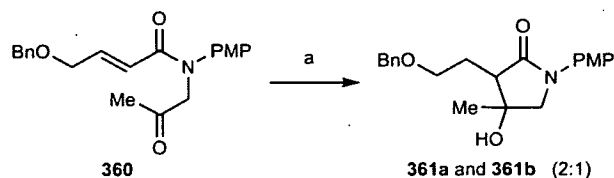
Reagents and conditions: (a) CoCl$_2$ (10 mol%), Cy$_2$PPh (11 mol%), Et$_2$Zn (2 eq), THF, 0 °C to rt, 18 h, 85 % (2:1).

Scheme 3.57 *Successful cyclisation of amide 360*

We decided to prepare yet another substrate, containing a sorbyl acyl fragment.[124] A substrate with the sorbyl functionality was potentially useful since ozonolysis of the double bond followed by a reductive work-up would reveal the ethyl hydroxyl side-chain at C2 needed for the synthesis of **1** (Scheme 3.58).
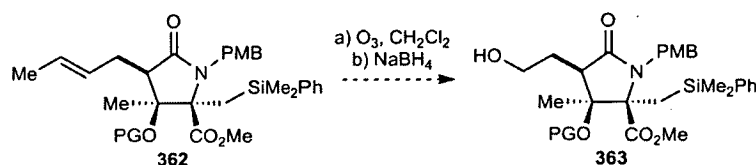
Scheme 3.58 *Obtention of the ethyl hydroxyl chain at C2 via ozonolysis of 362*

Therefore, sorbyl chloride was readily prepared[125] and reacted in the first place with amine **359** (Scheme 3.59). The cyclisation of this simpler amide would be attempted, hoping to gain knowledge of the cyclisation reaction.
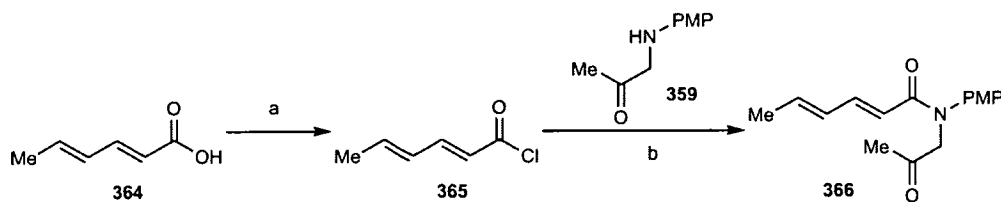
Reagents and conditions: (a) SOCl$_2$ (2 eq), DMF (cat), 1 h, reflux; (b) amine **359**, triisobutylamine (3 eq), CH$_2$Cl$_2$, rt, 12 h, 62%.

Scheme 3.59 *Preparation of sorbyl amide 366*

When substrate **366** was reacted using Co(acac)$_2$·2H$_2$O and Et$_2$Zn, most of the starting material was recovered. Surprisingly, when the reaction was performed using Ni(acac)$_2$ as precatalyst, the reaction went practically to completion and several

products were obtained. The crude mixture of this reaction was purified, and the major product isolated was a cyclisation product **367**, in 20-25% yield. The relative stereochemistry of this compound was not known. Some traces of what was tentatively identified as the alternative diastereomer of **367** and also of the double bond isomer **368** were isolated. The overall conversion was approximately 50% (Scheme 3.60). The reaction employing CoCl$_2$ and Cy$_2$PPh also afforded **367** and the other isomers in a very similar reaction to the one with Ni(acac)$_2$.

Although the cyclisation of amide **366** had only afforded small amounts of cyclised product, this example demonstrated again that the cyclisation could take place with amides that were not prepared from amine **300**.
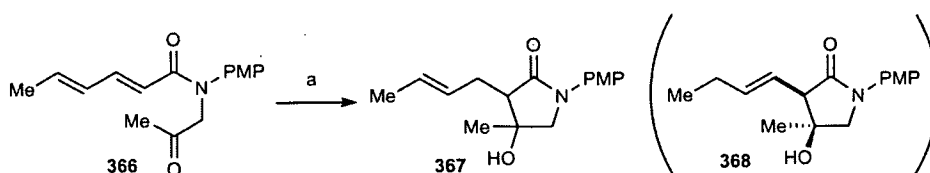
Reagents and conditions: (a) Ni(acac)$_2$, Et$_2$Zn, THF, 0 °C to rt, 18h, 25%.

Scheme 3.60 *Cyclisation of 366*

We then moved on to prepare amide **369** and attempt the cyclisation reaction. Sorbyl chloride was prepared and reacted with amine **300**, employing the same procedure as for the coupling of amide **366**. Unfortunately, although amide **369** was formed, the complete purification was not successfully achieved and therefore we were not able to use this substrate to study the cyclisation reaction (Scheme 3.61).
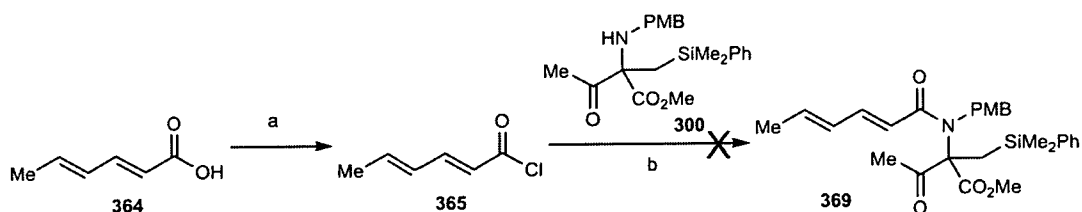
Reagents and conditions: (a) SOCl$_2$ (2 eq), DMF (cat), 1 h, reflux; (b) amine **300**, triisobutylamine (3 eq), CH$_2$Cl$_2$, rt, 12 h.

Scheme 3.61 *The coupling of amine 300 with sorbyl chloride was not successful*

3.6. Conclusions

Due to the successful advances in the development of the reductive aldol cyclisation reaction within the group, especially some encouraging results in the synthesis of five-membered lactams, we decided to use this approach in the synthesis of salinosporamide A.

Amide **354**, containing the required substitution to be transformed into **1**, was prepared and employed in several attempts of the cyclisation reaction. Unfortunately, in all cases only a complex mixture of products, together with unreacted starting material, was obtained and the isolation of cyclisation products proved impossible. Simpler amides **360** and **366** afforded cyclised products but all cyclisation attempts of highly substituted amides **354**, **347** and **349** were unsuccessful.

The failure of these cyclisations was attributed to the dense functionalisation of these substrates. Other side reactions, like conjugate reduction or reduction of the ketone, could be taking place, instead of the cyclisation reaction. Moreover, if some substrate had cyclised and the reaction was not diastereoselective, up to four cyclised products could be formed in similar ratios. All these factors could explain the formation of a complex mixture of compounds, from which the isolation of cyclisation products was not possible.

Disappointingly, due to these negative results the use of amine **300** was abandoned and a new approach towards the synthesis of the natural product was investigated.

4. Reformatsky reaction approach in the synthesis of salinoporamide A

The following chapter will concentrate on the route we adopted next. On this occasion we envisaged that the γ-lactam of **1** could be constructed *via* an intramolecular Reformatsky reaction. It was believed that the cyclisation could be achieved with high yield and high stereoselectivity.

4.1. Retrosynthetic analysis

The retrosynthetic plan adopted for this approach is outlined in Scheme 4.1. As described previously, initial disconnections of **1** lead to a γ-lactam intermediate represented by **370** (Scheme 4.1). We envisaged that this γ-lactam could be constructed from an α-halo amide such as **371**, *via* an intramolecular Reformatsky reaction.
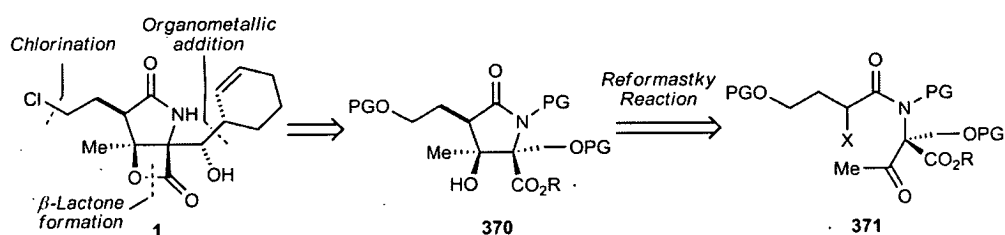
Scheme 4.1 *Retrosynthetic analysis using the Reformastky reaction approach*

Amide **371** could be readily prepared from the coupling of an α-halo acid **373** with the corresponding amine (Scheme 4.2). For this route, it was decided not to employ amine **300**, due to the unsuccessful results obtained when it was used in the reductive aldol approach (Chapter 3). It was decided to use amine **327** (Scheme 4.2), which had been utilised by Corey and co-workers in their synthesis of. **1**.[26] Amine **327** had proved successful in inducing diastereoselectivity in the cyclisation performed in Corey's synthesis. It was hoped that the quaternary stereocentre would also result in some internal asymmetric induction in the Reformatsky cyclisation of amide **372**. Moreover, amine **327** could be prepared following reported methods and

since it was prepared from (L)-threonine, we would be already working on an asymmetric route to **1**.
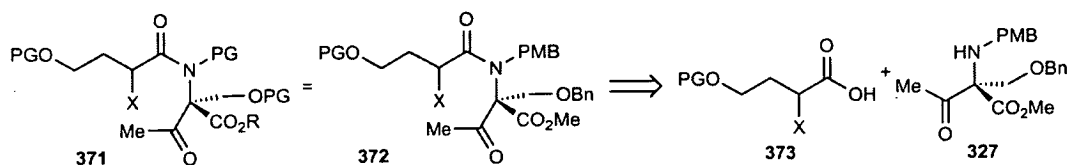
Scheme 4.2 *Retrosynthetic analysis of α-halo amide 372*

Amide **372** contains all the required functionalities for the synthesis of salinosporamide A. If **372** was successfully cyclised to afford γ-lactam **374** (Scheme 4.3), only a few operations would be necessary (transformation of the protected alcohol into the aldehyde, insertion of the cyclohexenyl chain, protecting group manipulations), to yield triol **26**. This intermediate is the same compound we were aiming to obtain *via* the reductive aldol approach (Chapter 3, Scheme 3.36), which is an intermediate in Corey's[26] and also in Pattenden's[29] reported syntheses of **1**.
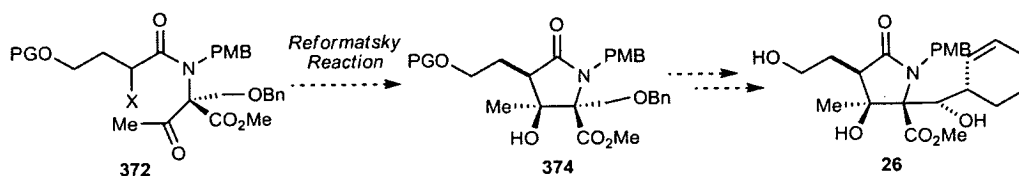
Scheme 4.3 *Application of the Reformatsky reaction in the cyclisation to γ-lactam 374 and transformation to intermediate 26*

If the proposed route to intermediate **26** was successful, we would have developed a concise and effective formal synthesis of salinosporamide A. The challenge was to find the optimal conditions for the Reformatsky cyclisation of amide **372** to obtain β-hydroxy γ-lactam **374**. In the next section, we will briefly review the Reformatsky reaction focusing on methodologies that have been successfully employed in intramolecular systems.

4.2. The Reformatsky reaction

The classical Reformatsky reaction, as it was reported for the first time in 1887,[126] consisted of a zinc-induced formation of β-hydroxy alkanoates from ethyl haloacetates and aldehydes or ketones (Scheme 4.4). However, since then the reaction has been found to be applicable to other alkyl 2-haloalkanoates, the scope of the reaction has also been extended beyond aldehydes and ketones as electrophiles and, moreover, other metals and catalysts have been found to promote the reaction in a similar way to zinc.[127-129] Therefore, a more general definition for the Reformatsky reaction was needed and it is now formulated as "all reactions resulting from metal insertions into carbon-halogen bonds activated by carbonyl or carbonyl-derived groups in vicinal or vinylogous positions with practically all kinds of electrophiles".[127]

$$XCH_2CO_2Et \xrightarrow{Zn} XZnCH_2CO_2Et \xrightarrow{R^1\overset{O}{\underset{}{C}}R^2} R^1\underset{R^2}{\overset{OZnX}{\underset{}{C}}}CH_2CO_2Et \xrightarrow{H_3O^+} R^1\underset{R^2}{\overset{OH}{\underset{}{C}}}CH_2CO_2Et$$

$$\mathbf{375} \qquad\qquad \mathbf{376} \qquad\qquad\qquad \mathbf{377} \qquad\qquad\qquad \mathbf{378}$$
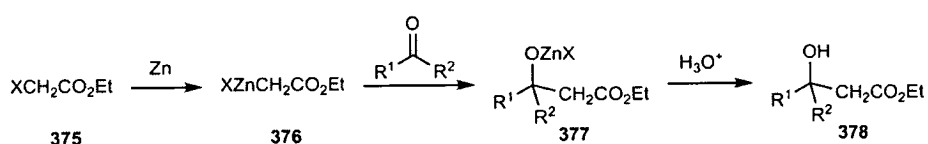
Scheme 4.4 *Classical Reformatsky reaction*

The Reformatsky reaction has become a very important carbon-carbon bond formation method in organic synthesis. In the field of enolate chemistry, it represents an alternative to base-induced aldol reactions. A separate treatment is due mainly to the specific mode of metal enolate formation from halo carbonyl compounds, with the site of the reaction being strictly determined by the halogen substituent. This may be advantageous with polycarbonyl compounds, for which a regioselective enolate formation is difficult to achieve *via* proton abstraction with a base.

The main disadvantage attributed to the Reformatsky reaction has been the lower yields and diastereoselectivities associated with it, compared to those of the aldol reaction. However, great improvements have been made in this area and there are now a great number of examples of highly diastereo- and enantioselective Reformatsky reactions. Therefore, it has become a perfectly suitable reaction for the synthesis of complex target molecules.

Several zinc-activation methods have been developed.[127] Activation is achieved either *via* effective removal of the zinc oxide layer from the metal surface or *via* a fine distribution of the metal, most efficiently accomplished by reduction of anhydrous zinc halides (e.g., Rieke zinc[130] is obtained from the reduction of anhydrous zinc chloride by potassium). The most common depassivating procedures employ reagents such as iodine, 1,2-dibromoethane, copper(I) halides, chlorotrimethylsilane or simple acid washing of the zinc.

Apart from the different available methods for zinc activation, there are numerous examples of additives or inductors in the Reformatsky reaction. Yamamoto and co-workers, in 1977, reported an aldol reaction of α-haloketones or α-haloesters with dialkylaluminium chloride and zinc.[131] An aluminium enolate was generated regiospecifically and then it was added to the carbonyl compounds affording the β-hydroxy carbonyl compounds after workup (Scheme 4.5).
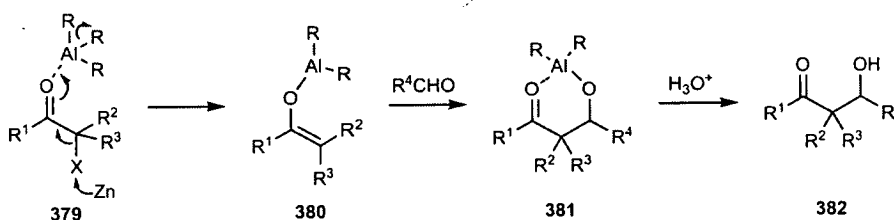
Scheme 4.5 *Yamamoto dialkylaluminium chloride mediated Reformatsky reaction*

This methodology was employed in an intramolecular cyclisation of **383** which afforded diastereomer **384** as the major product (Scheme 4.6).[132]
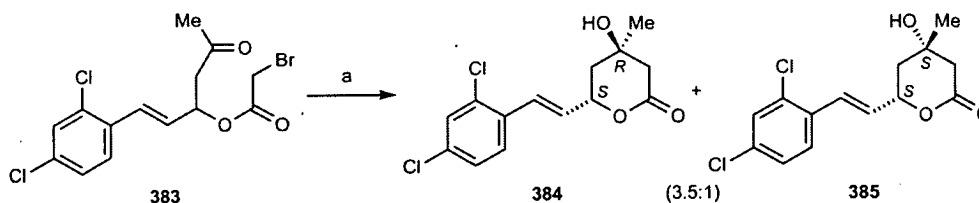
Reagents and conditions: (a) Et$_2$AlCl, Zn, THF, 5 h, rt, 50%.

Scheme 4.6 *Intramolecular example of Yamamoto's methodology*

More recently, this procedure was applied to the synthesis of the BCD framework of richardianidins (Scheme 4.7).[133] Treatment of **386** with diethylaluminium chloride

and zinc in the presence of a substoichiometric amount of $CuBr_2·SMe_2$ as zinc activator and at room temperature, afforded a diastereomeric mixture of *syn*-hydroxyester products **387** and **388** (1:20), due to the aluminium *Z*-enolate formation.
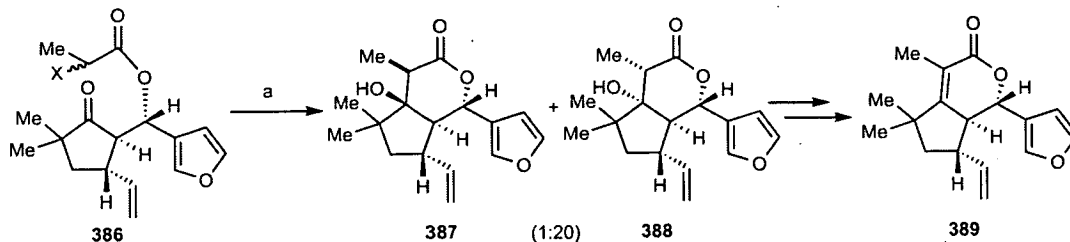
Reagents and conditions: (a) Et_2AlCl, Zn, $CuBr_2·SMe_2$, THF, 15 h, 57%.

Scheme 4.7 *Synthesis of richardianidin* **389**

Another relevant example of a zinc-mediated intramolecular Reformatsky reaction was reported by Heathcock and co-workers. During studies towards the synthesis of alkaloid daphnilactone A (**393**),[134] they developed a one-pot process that involved treatment of keto amide **390** with activated zinc in THF at 0 °C. This was followed by treatment with HMPA, affording lactam ether **392** in 73% yield (Scheme 4.8). This example was highly relevant, since the structure and cyclisation of α-halo amide **390** significantly resembles our system.
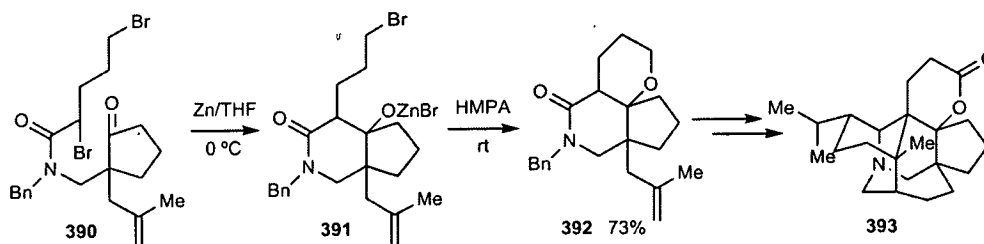
Scheme 4.8 *Synthesis of polycyclic lactam ether* **392** *via intramolecular Reformatsky reaction*

In 2000, Honda reported a rhodium-catalysed Reformatsky reaction using $RhCl(PPh_3)_3$ and Et_2Zn.[135] Surprisingly, prior to this work, there had been very few literature examples in the area of catalytic Reformatsky reactions.[136, 137] Honda and co-workers were especially encouraged by Ding's work, which employed zinc and a

catalytic amount of $Cp_2TiCl_2{}^{137}$, however, in this example it was thought that the active species was a titanium enolate.

Aromatic and aliphatic aldehydes or ketones were reacted successfully with ethyl bromoacetate or 2-bromopropionate in the presence of Wilkinson's catalyst and Et_2Zn to afford β-hydroxy esters within 5 minutes in moderate to good yields. The formation of the ethyl adduct was not observed. More encouragingly for us, the intramolecular version of the reaction was also developed and secondary and tertiary cycloalkanols were obtained in good to excellent yields and with moderate diastereoselectivities. Some of the examples of the intramolecular reactions with methyl ketones are represented in Scheme 4.9. A transition state of the zinc enolate (**400**) was proposed to explain the obtention of *cis*-hydroxyesters.
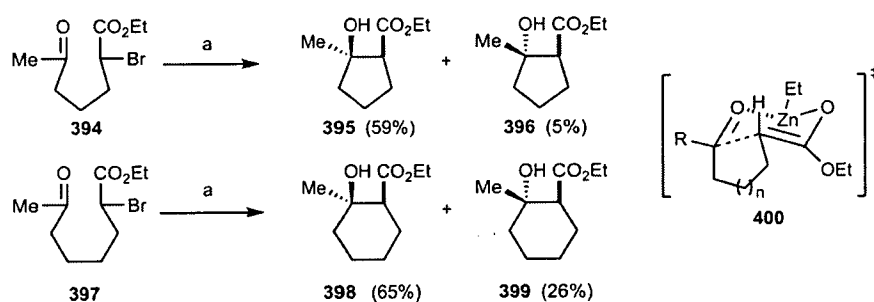
Reagents and conditions: (a) Et_2Zn (2.2 eq), $RhCl(PPh_3)_3$ (5 mol %), THF.

Scheme 4.9 *Intermolecular Rh-catalysed Reformatsky-type reaction*

The proposed mechanism for this reaction is shown in Scheme 4.10. Oxidative addition of α-haloester **I** into Rh(I) forms a Rh(III) complex **II** that, after transmetallation with Et_2Zn, produces the ethylzinc enolate **III** and Rh(I), which can start the cycle again. The zinc enolate adds to the carbonyl compound forming zinc alkoxide **IV** that affords β-hydroxy ester **V** after work-up.
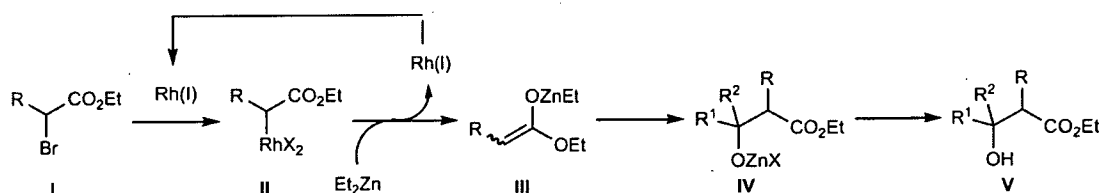
Scheme 4.10 *Mechanism of the Reformatsky reaction catalysed by $RhCl(PPh_3)_3$ and Et_2Zn*

This methodology was applied in the synthesis of 15-epi-haterumalide NA methyl ester **403**, a cytotoxic macrolide from an Okinawan sponge (Scheme 4.11).[138] When the cyclisation of **401** was attempted using Honda's conditions,[135] only decomposition of the starting material occurred. By monitoring the reaction it was observed that the β-hydroxy lactone was being formed but it was decomposing during workup. The addition of Ac$_2$O to trap the intermediate allowed the isolation of the desired (3*S*,4*Z*)-**402** in 9% yield, along with the (3*R*,4*Z*)- and (4*E*)- isomers.
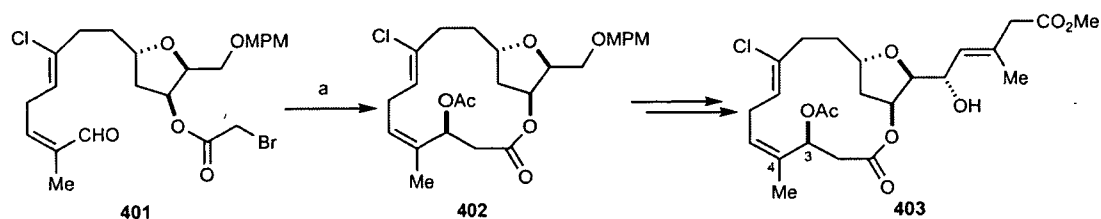
Reagents and conditions: (a) (i) Et$_2$Zn, RhCl(PPh$_3$)$_3$, THF-hexane; (ii) Ac$_2$O, 9%.

Scheme 4.11 *Application of Honda's methodology in total synthesis*

In 1977, Kagan introduced samarium(II) diiodide as a reagent for organic synthesis.[139] Three years later, the first studies on its use in deoxygenation of epoxides and sulfoxides, the chemoselective reduction of aldehydes in the presence of ketones, dehalogenations, and coupling between ketones and alkyl halides were reported.[140, 141] Since then, this polyvalent reducing agent has been used in a multitude of important synthetic transformations and in the synthesis of natural products.[142] One important use of this reagent is the SmI$_2$ mediated reaction of organic halides with an electrophile, including SmI$_2$ mediated Reformatsky reactions.

SmI$_2$ is commercially available as a solution in THF, however it can be prepared from the metal and diiodomethane, diiodoethane or iodine, in THF.[140, 143] SmI$_2$ is a single electron reducing agent, with Sm(II) wanting to revert to the more stable Sm(III) oxidation state. Therefore, the SmI$_2$ promoted reactions of organic halides are achieved using 2 molar equivalents of SmI$_2$ and occur by stepwise one-electron transfer to the halide. The most generally accepted mechanism for these reactions proceeds *via* organosamarium species which react with the electrophile (Scheme

4.12). These organosamarium species are formed *via* reduction of the alkyl halide to the radical by the first equivalent of SmI_2 and then further reduction to alkyldiiodosamariums by the second equivalent of SmI_2.[144]

$$R-X \xrightarrow[-[SmI_2X]]{SmI_2} [R^\cdot] \xrightarrow{SmI_2} R-SmI_2$$
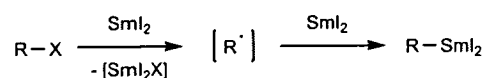
Scheme 4.12 *Formation of organosamarium species*

Most of the reactions employing SmI_2 are performed in THF, but other solvents employed have been tetrahydropyran (THP) and alkylnitriles.[145] The use of additives and cosolvents has also shown a crucial effect on the SmI_2 mediated reactions. The most commonly employed additive is the Lewis base HMPA.[146] It was reported that the redox potential (E°) of Sm^{+2}/Sm^{+3} in THF (vs. $Ag/AgNO_3$ reference electrode in THF) increased from -1.33 V to -1.95 V with 3 equivalents of HMPA and reached -2.05 V with 4 equivalents, remaining constant with more equivalents.[147] Hou and co-workers[148] isolated and characterised $SmI_2(HMPA)_4$, although it was suggested that the active species in solution are more closely represented by the formula [Sm-$(HMPA)_4(THF)_2]I_2$.[149] When HMPA was replaced for the less toxic HMPU, there was also an increase in the reduction potential, although more equivalents were required to achieve a similar level of activation.[150] The use of TMEDA as an additive has also been reported.[151]

The rate of SmI_2 mediated reactions can also be increased by the addition of inorganic salts like lithium chloride and bromide.[152] The chemoselectivity was also altered by the addition of lithium halide salts.[153] These reactions have also been markedly improved by the addition of catalytic amounts of transition metal salts.[154] Ferric salts ($FeCl_3$, $FeBr_3$, FeI_3) have been extensively employed, Kagan, in his first paper, already observed the enhanced reactivity when substoichiometric amounts of $FeCl_3$ were used.[140] CuI and NiI_2 have also shown to be efficient additives.[154, 155]

SmI_2 has efficiently been used to promote the Reformatsky-type reaction of α–halogenoesters, therefore becoming a useful alternative to the conventional Zn-mediated Reformatsky reactions. Due to the homogeneous conditions afforded by SmI_2, the reaction can proceed with enhanced reactivity and reproducibility, under

milder conditions, with even better chemoselectivity and, in intramolecular examples, with better stereoselectivity.

Intramolecular versions of the Reformatsky-like reactions have seen further developments and applications than their intermolecular versions. In fact, SmI_2 is one of the most exploited reagents for intramolecular Reformatsky-like reactions, especially due to the yields and diastereoselectivities. It is believed that the reaction proceeds through a samarium (III) enolate and cyclisation occurs through a rigid cyclic transition structure enforced by chelation, where the large ionic radius, the flexible coordination and the high oxophilicity of samarium play an important role.[156]

Molander studied the 1,2-, 1,3-, and 1,4-asymmetric induction in intramolecular SmI_2 mediated Reformatsky reactions.[157] The trends of diastereoselectivity observed could be all explained through an eight membered ring samarium chelate (**405**) (Scheme 4.13). The products were obtained in excellent yields and very high diastereoselectivities.
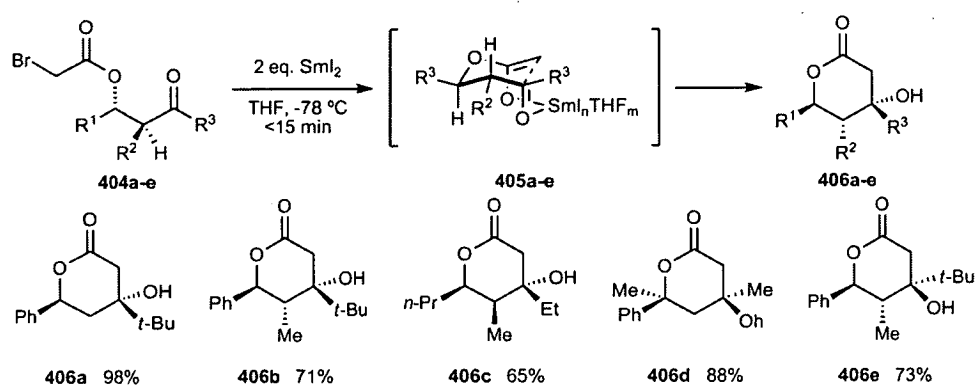
Scheme 4.13 *Molander SmI_2 mediated intramolecular Reformatsky reactions*

The stereoselectivity of this reaction was also very high with γ-bromoacetoxy ketones which lead to the related seven-membered lactones (Scheme 4.14).
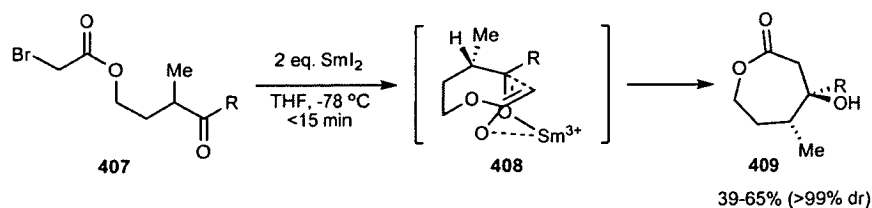
Scheme 4.14 *SmI_2 mediated cyclisations of γ-bromoacetoxy ketones*

Finally, it is worth highlighting a very interesting example due to the resemblance with our system, reported by Kocikowski in 1999.[158] Treatment of **410** and **412** with SmI$_2$ afforded γ-lactams **411** and **413** as single diastereomers (Scheme 4.15). No rationale was provided for the stereochemical outcomes of these reactions.

410 R = H	**411** 91% Single
412 R = OBn	**413** 80% diastereomer
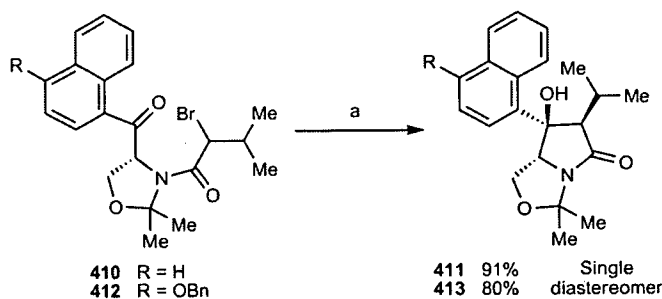
Reagents and conditions: (a) SmI$_2$, FeCl$_3$ (cat), THF-HMPA, rt.

Scheme 4.15 *Kocikowski SmI$_2$ mediated γ-lactam formation*

4.3. Results and discussion

Initial efforts centred on the preparation of amine **327**, using a slightly modified synthetic route from the one previously reported by Corey and co-workers.[26] Amine **327** was then successfully coupled to a number of α-halo acids affording several substrates which were used in the investigation of the intramolecular Reformatsky reaction.

4.3.1. Synthesis of amine 327

Methyl ester **415** was readily prepared from reaction of (*L*)-threonine (**414**) with thionyl chloride in MeOH heated to reflux overnight, and it was used in the next step without further purification (Scheme 4.16). 4-Methoxybenzimidate hydrochloride (**417**) was obtained from an overnight reaction of *p*-methoxybenzonitrile (**416**) and acetyl chloride in MeOH. Purification of **417** only involved several washings with Et$_2$O.
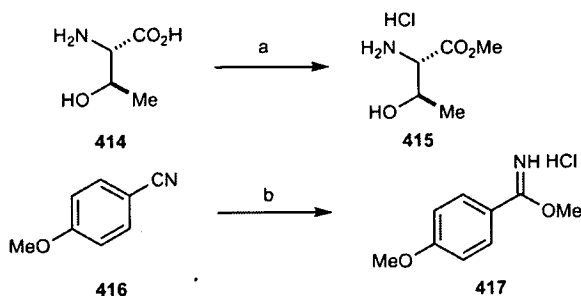
Reagents and conditions: (a) SOCl$_2$ (1 eq), MeOH, 0°C to rt, 18 h, quantitative; (b) Acetyl chloride (8 eq), MeOH, rt, 18 h, 91%.

Scheme 4.16 *Preparation of compounds 415 and 417*

Reaction of methyl ester **415** with triethyl amine and hydrochloric acid salt **417** in CH$_2$Cl$_2$ afforded oxazoline **418** (Scheme 4.17), in a moderate yield of 40%, due also to a difficult purification. The yield of this step was improved to 65% when K$_2$CO$_3$ was employed as base instead of triethyl amine.[i] Although the yield was a little low, the procedure was simpler and more convergent than the one reported by Corey, which involved acylation of methyl ester **415** with 4-methoxybenzoyl chloride followed by acid catalysed cyclisation (Scheme 1.6).[26] Moreover, it was amenable to a large scale preparation.
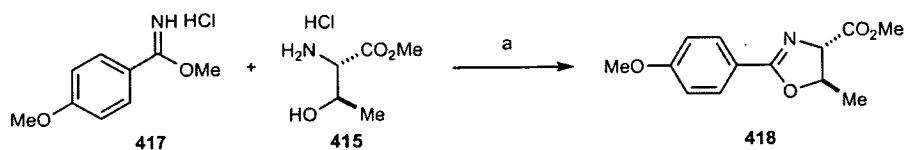
Reagents and conditions: (a) Et$_3$N (2 eq), CH$_2$Cl$_2$, reflux, 14 h, 40%.

Scheme 4.17 *Oxazoline 418 formation*

We next examined the alkylation of oxazoline **418**, an operation that introduces the CH$_2$OBn group, and sets the stereochemistry of the quaternary centre C4 (Scheme 4.18). In Corey's procedure[26] deprotonation was achieved using LDA in the presence of HMPA, and the enolate was reacted with chloromethyl benzyl ether affording the desired product in 69% yield. Using the commercially available base LHMDS instead of LDA, alkylated oxazoline **17** was obtained with an increased 75 % yield.

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[i] Step improved by Leszek Rupnicki
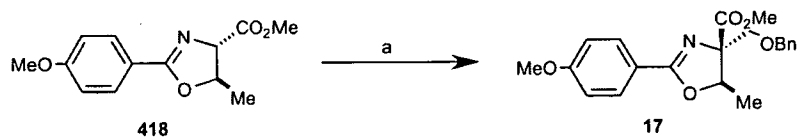
Reagents and conditions: (a) LHMDS (1.1 eq), HMPA (4.3 eq), ClCH₂OBn (1.2 eq), THF, −78 °C, 4 h, 75%.

Scheme 4.18 *Successful alternative procedure for the alkylation of* **418**

Transformation of oxazoline **17** into amine **327** was successfully performed following Corey's reported procedure (Scheme 4.19).[26] Reductive opening of oxazoline **17** was achieved using sodium cyanoborohydride in acetic acid to give amino alcohol **18** in good yield (from 65 to 80%). Finally, amine **327** was readily obtained *via* Swern[61] oxidation.
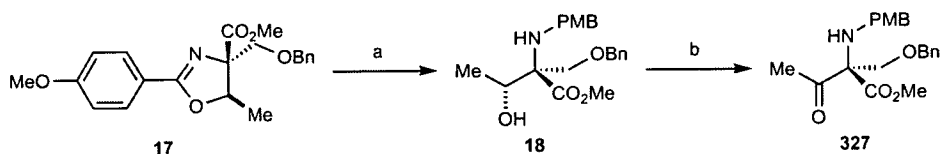
Reagents and conditions: (a) NaCNBH₃ (3.3 eq), HOAc, 50 °C, 18 h, 65%; (b) (COCl)₂ (2.1 eq), DMSO (4.2 eq), Et₃N (4.2 eq), CH₂Cl₂, -78 °C, 3 h, 72%.

Scheme 4.19 *Final steps of the synthesis of amine* **327**

4.3.2. Study of the Reformatsky cyclisation reaction

To investigate the viability of the Reformatsky cyclisation in the proposed route to **1**, an advanced model system was used. Ideally, this model substrate should be easily prepared and it should allow the optimisation of the reaction. This way, once the optimal conditions had been found, they could be applied to the real system, the substrate with the required functionalities to be transformed into **1**.

With this in mind, we chose to couple amine **327** to the commercially available 2-bromobutyryl bromide (**419**), to give α-bromo amide **420** (Scheme 4.20). This amide was an optimal compound to investigate the reaction, since it was readily prepared from a commercially available starting material and it was structurally similar to the real substrate, only lacking the hydroxyl group in the acyl fragment.
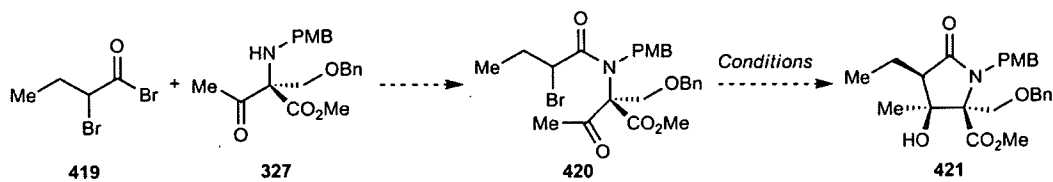
Scheme 4.20 *Model studies for the Reformatsky cyclisation reaction*

As expected, treatment of amine **327** with the hindered base triisobutylamine[121] followed by addition of 2-bromobutyryl bromide **419** afforded the two expected diastereomers of the amide in an excellent overall yield (93%) and approximately a 3:2 ratio (Scheme 4.21). The diastereomers were differentiated on the basis of their polarity on the silica plate: the more polar and major diastereomer (57% yield) was referred to as **420a** and the less polar and minor diastereomer (36% yield) as **420b**; but the absolute stereochemistry of the bromine bearing carbon of each compound was not known. As the two diastereomers could differ in reactivity, they were separated by column chromatography and were used independently in the study of the cyclisation reaction.
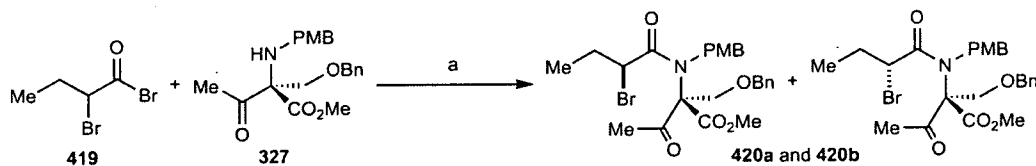
Reagents and conditions: (a) Triisobutylamine (1.3 eq), CH_2Cl_2, rt, 16 h, 93% (**420a** 57% and **420b** 36%).

Scheme 4.21 *Synthesis of amides 420a and 420b*

The initial studies on the reaction focused on the application of the conditions of the "classical" Reformatsky reaction. The substrates prepared would be reacted with activated zinc on its own and also in the presence of additives. For instance, bearing in mind the examples using Yamamoto's conditions (Scheme 4.6),[131-133] the reaction would also be attempted in the presence of Et_2AlCl.

Although being an intermolecular system, it was found in the literature another interesting example of a Reformatsky reaction. It involved the addition of azetidin-2-ones (**422**) to aldehydes and nitriles, and the effect of the addition of Lewis acids was also investigated (Table 4.1).[159] The organozinc was prepared in

THF and when it was reacted with benzaldehyde at room temperature the condensation product was not obtained (entry 1). However, when AlMe$_2$Cl was added as an activator of the electrophile, both diastereomeric products, **423** and **424**, were obtained within two hours and in good yield. The formation of the debrominated starting material (about 15%) was observed. The reaction was attempted also with several other Lewis acids. It was discovered that when the reaction was activated with BF$_3$·OEt$_2$ or Ti(O*i*-Pr)$_4$, the products were obtained in good yields within two hours (entries 5 and 6) and, in the case of the titanium-catalyzed reaction, some diastereoselectivity was observed.

	Additive	Time (h)	Yield of 423 + 424 (%) (*syn:anti*)
1	-	18	-
2	AlMe$_2$Cl	2	63 (50:50)
3	Sc(OTf)$_2$	24	-
4	ZrCl$_4$	6	30 (50:50)
5	BF$_3$·OEt$_2$	2	79 (50:50)
6	Ti(O*i*-Pr)$_4$	2	76 (70:30)

Table 4.1 *Use of Lewis acids in the classical Reformatsky reaction*

Several attempts of the cyclisation employing the classical Reformatsky conditions were carried out. Unfortunately, no reaction was observed when α-bromoamides **420a** and **420b** were treated only with zinc, which had been activated either with HCl washings or with I$_2$, and unreacted starting material **420** was recovered (Scheme 4.22).

The effect of the addition of Lewis acid additives was next investigated. Attempts were carried out in the presence of Et$_3$Al[160] or Et$_2$AlCl. These reactions were started at –40 °C and, since no reaction occurred at this temperature, they were then allowed to warm up slowly to room temperature over 4 hours, while monitoring the reaction by TLC. Disappointingly, amides **420a** or **420b** suffered quantitative debromination

to form **425**. Other Lewis acids were also evaluated: the reaction with $TiCl_4$ or $BF_3.Et_2O$ afforded the debrominated amide **425**; $Zn(OTf)_2$, $Mg(OTf)_2$ or AgOTf failed to furnish any product and starting material was recovered even after long reaction times.
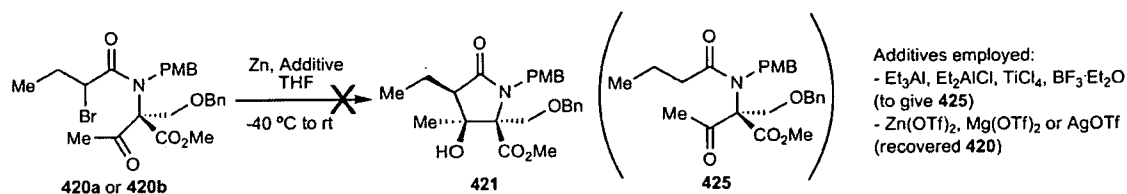
Scheme 4.22 *Failure of cyclisation trials using "classical" Reformatsky conditions*

Next, it was decided to attempt the cyclisation using Honda's conditions (Scheme 4.9).[135] Substrates **420a** and **420b** were treated with Et_2Zn and $RhCl(PPh_3)_3$. Unfortunately, a complex mixture of products was obtained, from which it was only possible to identify unreacted starting material and debrominated **425** (Scheme 4.23).
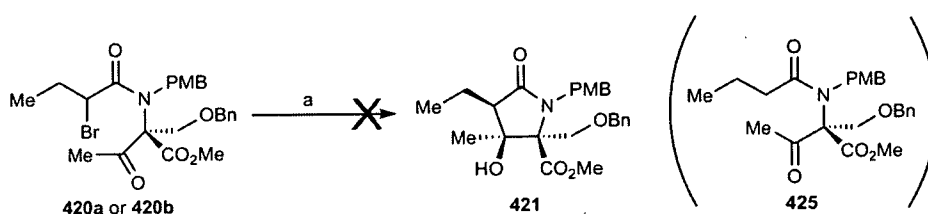
Reagents and conditions: (a) Et_2Zn (2.2 eq), $RhCl(PPh_3)_3$ (5 mol%), -78 °C to 0 °C, 5 h, THF.

Scheme 4.23 *Unsuccessful attempt of the cyclisation using Honda's methodology*

A related methodology was reported in 2003, which consisted of a Ni-catalysed Reformatsky-type three-component condensation reaction that combined an aldehyde, aniline and an α-bromocarbonyl affording β-amino carbonyl compounds (Scheme 4.24).[161] Using Et_2Zn, several catalysts [$RhCl(PPh_3)_3$, $PdCl_2(PPh_3)_2$, $Cr(acac)_2$, $Co(acac)_2 \cdot 2H_2O$] were surveyed for the reaction before discovering that $Ni(acac)_2$ was a very effective catalyst and afforded the desired product in 95% yield. Further optimisation of the reaction revealed $NiCl_2(PPh_3)_2$ as a better catalyst and the

use of the less nucleophilic dimethyl zinc instead of diethyl zinc avoided the formation of traces of the ethyl adduct
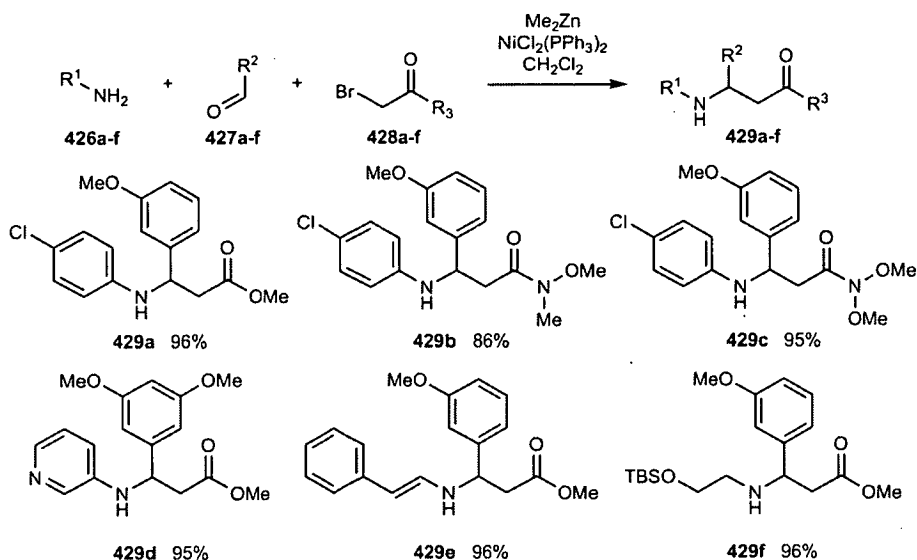
Scheme 4.24 *3-Component coupling Ni-catalysed Reformatsky reaction*

The proposed catalytic cycle of the reaction starts with the *in situ* generation of the active Ni(0), followed by formation of **II** *via* an oxidative addition to the α-halo carbonyl (Scheme 4.25). Then, transmetallation with dimethylzinc forms the methylzinc enolate **III** and the Ni(II) complex **IV**, which undergoes reductive elimination liberating the active Ni(0) that can start the cycle again. Zinc enolate **III** reacts with the imine affording the β-amino carbonyl (**VII**) after workup.
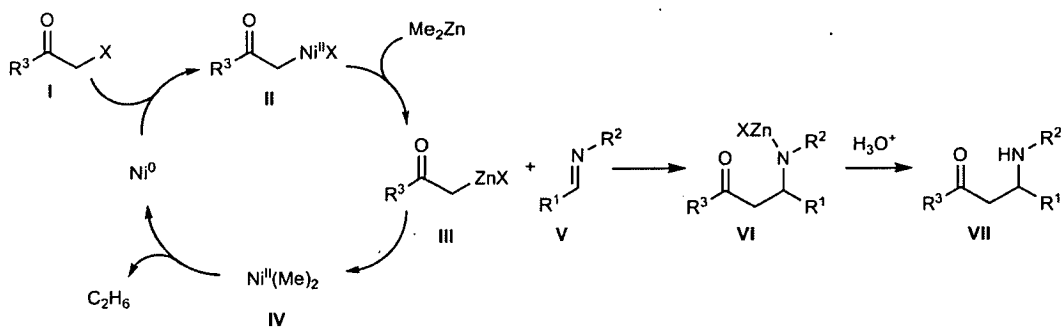
Scheme 4.25 *Proposed catalytic cycle for the nickel-catalysed Reformatsky-type reaction*

This intermolecular methodology was applied to our model substrates (Table 4.2). When amides **420a** and **420b** were exposed to Et₂Zn and Ni(acac)₂, the reaction went to completion but only to form a complex mixture of products, from which it was only possible to identify the debrominated amide **425**. An intractable mixture of compounds was also obtained when using CoCl₂ and Cy₂PPh (entry 2). When the reaction was carried out in the presence of Co(acac)₂·2H₂O (entry 3), no reaction occurred and starting material **420a** or **420b** was recovered.

Catalyst	Reaction time (h)	Product
1	Ni(acac)₂	4	complex mixture
2	CoCl₂, Cy₂PPh	18	complex mixture
3	Co(acac)₂·2H₂O	14	**420** recovered
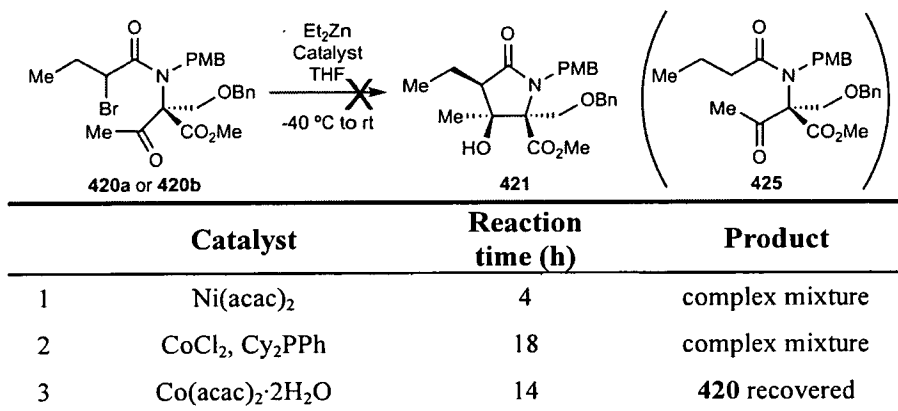
Table 4.2 *Reactions using Et₂Zn as the zinc source*

The Cr-mediated Reformatsky reaction was then investigated, although this methodology had been developed on intermolecular systems. Since the 1970s, Nozaki and Hiyama were the pioneers of the use of organochronium reagents in organic synthesis.[131] They demonstrated the insertion of Cr(II) into allyl-, alkyl-, alkynyl-, propargyl- and aryl halides or sulfonates under aprotic conditions, forming the corresponding organochromium(III) reagents that can react as nucleophiles in organic transformations. In 1986, both Kishi and Nozaki independently discovered a catalytic effect of nickel salts in the reaction, which improved the reproducibility of the reaction.[162] This was explained *via* the mechanism represented in Scheme 4.26. Ni(II) is reduced to Ni(0) with 2 equivalents of Cr₂Cl. Then oxidative addition to the alkenyl halide occurs, followed by transmetallation with Cr(III), forming the alkenylchromium (III) reagent, which is the species that reacts with the carbonyl.
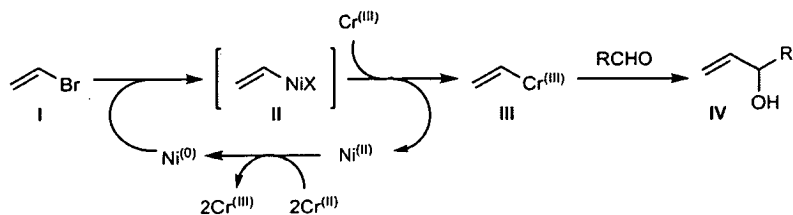
Scheme 4.26 *Explanation of the role of Ni(II) salts in the Cr(II)-mediated coupling reaction*

The major drawback of the Nozaki-Hiyama-Kishi (NHK) reaction is that, since Cr(II) is a one-electron donor, at least 2 mole are needed per mole of halide and, in reality, huge excesses (4-16 eq) of Cr(II) are used in the reaction. Because of the toxicity of Cr and Ni salts, a catalytic version of the reaction was highly desirable.

In 1995, Furstner and co-workers developed the Nozaki-Hiyama-Kishi (NHK) reaction catalytic in chromium (Scheme 4.27).[163] They reasoned that, in the reaction, the formation of the highly stable Cr(III) alkoxide drives the reaction to conversion but also traps the metal, impeding catalysis. It was hypothesised that if the chromium alkoxide (**III**) was reacted with a chlorosilane, a exchange of ligands (*via* σ bond metathesis) could occur, liberating the silyl ether of the desired product (**IV**) and liberating the second mole of Cr(III). The liberated Cr(III) species could be rereduced in situ by a non toxic reducing agent, this enabling the catalytic cycle. They found that use of the cheap and non-toxic Mn in combination with TMSCl and catalytic amounts of $CrCl_2$ allowed the first NHK reactions catalytic in chromium.
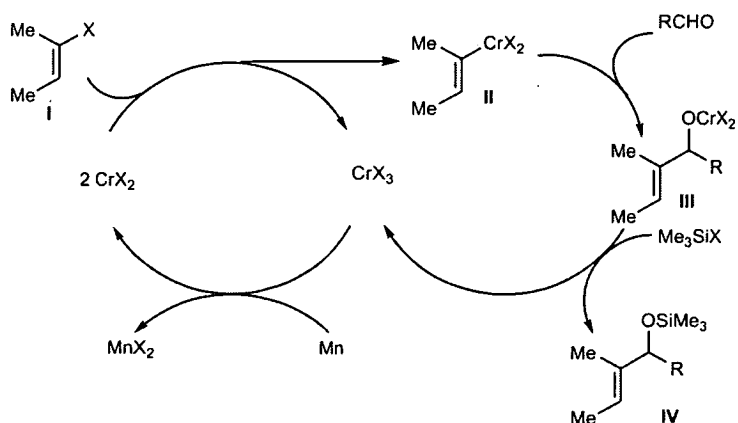
Scheme 4.27 *Mechanism of the NHK reaction catalytic in chromium*

α-Halo ketones, esters, amides, nitriles and other Reformatsky substrates[128, 164] have been reacted with Cr(II) salts, forming Cr(III) enolates *via* oxidative addition of the low valent metal salt into the carbon-halogen bond activated by the carbonyl group. In the presence of carbonyl compounds, the aldol products are obtained. For instance, intermolecular reaction of α-bromo ketones with aldehydes in the presence of $CrCl_2$ yielded the aldol products in good yields and with complete *syn*-diastereoseletivity (Scheme 4.28).[165]
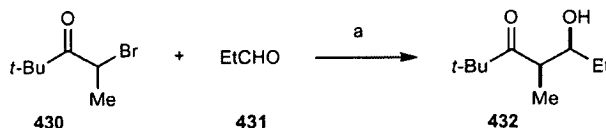
Reagents and conditions: (a) $CrCl_2$, THF, 81%.

Scheme 4.28 *Intermolecular Cr-mediated Reformatsky reaction*

The Cr-mediated Reformatsky reactions tend to proceed in THF, DMF or acetonitrile. This reaction is highly chemoselective towards aldehydes,[166] although reactions with ketones as electrophiles are also possible.[167] However, when α-bromoamides **420a** and **420b** were subjected to standard catalytic NHK reaction conditions (Mn, TMSCl and $CrCl_3$ doped with $NiCl_2$ in THF), debrominated product **425** was obtained quantitatively (Scheme 4.29). The same result was obtained when the reaction was performed in DMF. Wessjohann reported increased yields in NHK reactions in the presence of a catalytic amount of LiI, due probably to a general Lewis acid effect and to its ability to solubilise and modify $CrCl_2$.[168] A last attempt incorporating 10 mol% of LiI also failed, with **425** being again the only product of the reaction. With these results we concluded that the chromium enolate was being formed but it was not reacting with the methyl ketone and instead it was being immediately quenched.
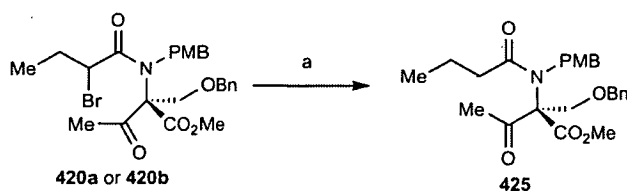
Reagents and conditions: (a) Mn (1.7 eq), CrCl$_3$ (0.15 eq), TMSCl (2.4 eq), NiCl$_2$ (0.03 eq), THF or DMF, rt, 2 h.

Scheme 4.29 *Unsuccessful Cr-mediated Reformatsky reaction*

At this point, the Reformatsky reaction had been attempted with several different metals but these were not successful in the formation of the cyclisation product and in most cases the debrominated starting material was obtained. The investigation next focused on the SmI$_2$ mediated Reformatsky reaction. It was hoped that, in this case, the substrates would cyclise into the ketone due to the known chelating ability of Sm^{3+}.

Initially, both diastereomers **420a** and **420b** were treated with 2.2 equivalents of SmI$_2$ (commercially available 0.1 M solution) in THF. The reaction did not proceed at −78 °C, but it quickly went to completion at room temperature (Scheme 4.30). We were very pleased to find that this reaction afforded the desired cyclised product **421** (30% yield), although it was accompanied by amide **433**, obtained in approximately 40% yield and debrominated amide **425** (10% yield).
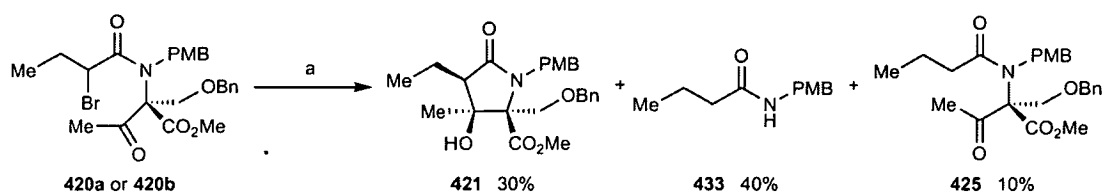
Reagents and conditions: (a) SmI$_2$ (2.2 eq), THF, rt, 2 h.

Scheme 4.30 *Preliminary result for the SmI$_2$ mediated Reformatsky reaction*

Although **421** was obtained in low yield, the good news was also that it was obtained as a single diastereomer (only one diastereomer of product was observed by ^{1}H NMR spectroscopy). Furthermore, the relative configuration was confirmed by a 2D NOESY experiment (**421** was not crystalline), which indicated that **421** was the desired diastereomer. Two cross peaks were observed to support this fact: the **CH$_3$** at C3 with **CH$_2$OBn** at C4 and the same **CH$_3$** at C3 with the **CH** at C2 (Figure 4.1).
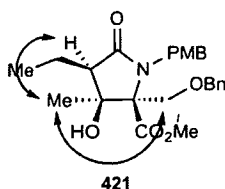
Figure 4.1 *2D NOESY experiment*

A proposed mechanism for the cyclisation to γ-lactam **421** is represented in Scheme 4.31. A first equivalent of SmI₂ reduces α-bromo amide **420** to form **434**, which then receives another electron from a second equivalent of SmI₂, to form enolate **435**. Finally, this enolate is trapped by the methyl ketone, forming γ-lactam **421**. A proposed transition state to explain the stereoselectivity of the reaction is represented by **436**.
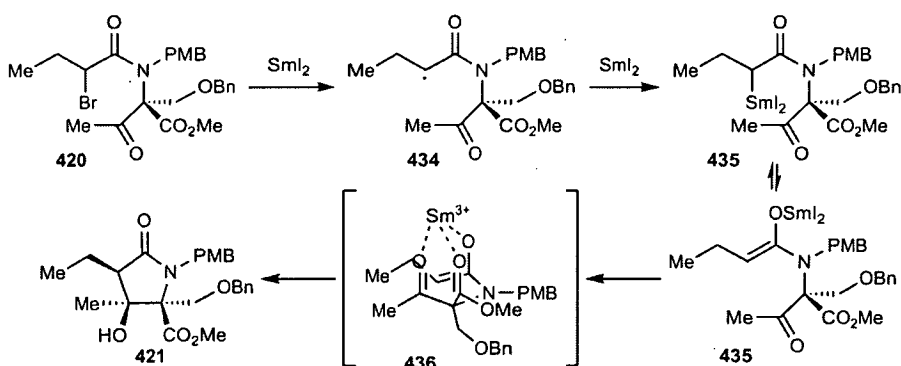
Scheme 4.31 *Proposed mechanism of the formation of 421*

A similar reductive mechanism is proposed for the formation of amide **433** (Scheme 4.32). Probably after loss of the bromine atom of **421**, the carbonyl of the ketone is reduced by a first equivalent of SmI₂. Then, a second equivalent forms anion **438** which rearranges, facilitated by the anion-stabilising effect of the ester, causing the C-N bond cleavage and yielding **433**.
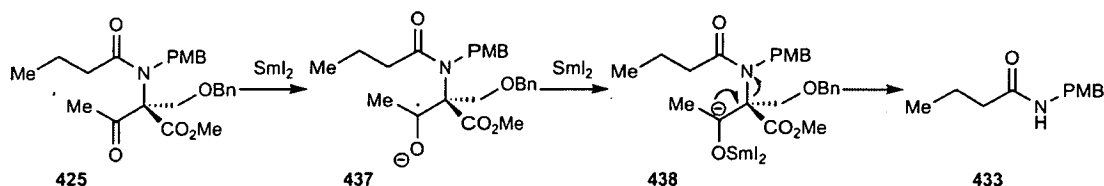
Scheme 4.32 *Proposed mechanism of the formation of 433*

Similar observations were made by Matsuda and co-workers, in an interesting example of an intramolecular Reformatsky cyclisation of 3-ketouridine derivatives promoted by SmI_2.[169] When **439** was reacted with 2.0 equivalents of SmI_2 in THF at room temperature, the Reformatsky reaction proceeded giving **440** in 71% yield (Scheme 4.33). The reaction performed at 0 °C afforded **440** in 75% yield and at −78 °C the yield was 90%. When the reaction was performed at −78 °C but using HMPA as an additive, the yield of **440** was decreased to 76% and **441** was obtained in 11% yield.
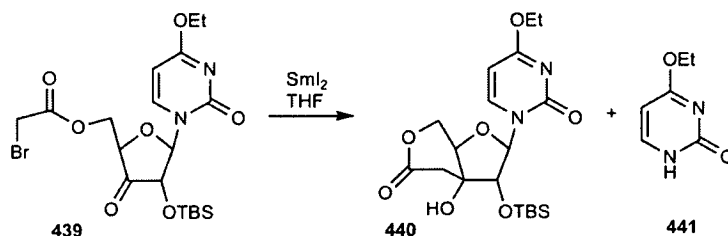
Scheme 4.33 *Matsuda intramolecular cyclisation to 439*

When **439** was reacted with zinc as a reductant in toluene, **440** was not formed and only debrominated starting material (**442**) was isolated. To study the mechanism of the formation of **441**, **442** was treated with SmI_2 and HMPA in THF at room temperature, which produced **441** in 64% yield (Scheme 4.34). This could be explained *via* an electron transfer from SmI_2 to the 3′-carbonyl of the 3′-ketouridine derivative, followed by reductive cleavage of the carbon-oxygen bond at the 4′-position.
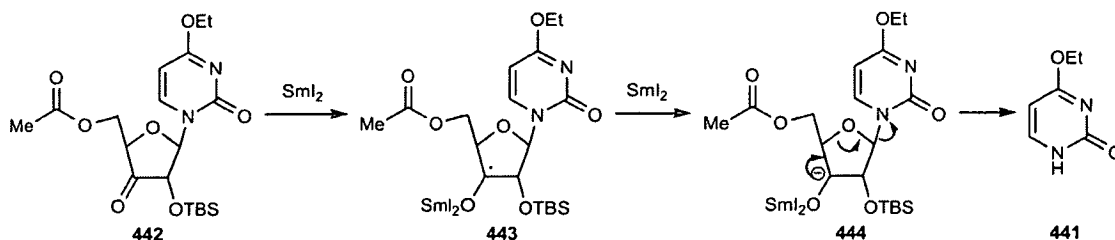
Scheme 4.34 *Proposed mechanism form the formation of 441*

They also reasoned that the ability of SmI_2 in promoting the reaction was due to the ability of Sm^{3+} to chelate to the 5′-enolate and the 3′-carbonyl (Figure 4.2). It was because of the formation of this chelate that the enolate addition to the carbonyl

occurred. That was the reason why, in the reaction with zinc as a reductant, the 5'-enolate was generated, but the addition into the 3'-carbonyl did not proceed, due to the lack of chelating ability of zinc.
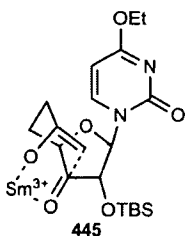
Figure 4.2 *Chelating ability of Sm^{+3}*

Based on the encouraging preliminary result of the desired cyclised product, work proceeded on the optimisation of the reaction. When the reaction was performed using 2.2 equivalents of SmI$_2$, but at 0 °C instead of at room temperature, the reaction was slowed down and did not go to completion; the main product obtained was debrominated amide **425**. The reaction was repeated in other solvents, for example CH$_3$CN and toluene, but THF remained the solvent of choice since it gave cleaner and better conversions.

The use of additives did not afford any improvement in the reaction. In the presence of HMPA or DMPU the reaction was again slower and would not go to completion. The same result was obtained with the addition of substoichiometric amounts of FeCl$_3$. Performing the reaction in the presence of Et$_2$AlCl afforded debrominated amide **425** only, in a very fast reaction. This example resembled to the attempts of the cyclisation using other metals than Sm, where presumably chelation with the ketone was not occurring and debrominated amide **425** was the only product obtained.

The amount of samarium iodide required was next revised. The number of equivalents employed was slowly raised from 2.2 to 12 equivalents. We discovered that when the reaction was performed using a large excess of SmI$_2$ (10-12 equivalents) at 0 °C, only traces of debrominated product **421** were obtained. The large excess of SmI$_2$ resulted in a fast reaction (completed in a matter of minutes) which seemed to be beneficial since the debromination had been practically eradicated and, by TLC, the desired cyclised product seemed to be the major product.

However, when the crude reaction was purified and the products isolated by column chromatography, amide **433** was again obtained in 40% yield and the yield of **421** had only increased slightly from 30% to 40% (Scheme 4.35). Under these conditions, the use of additives like HMPA, DMPU or $FeCl_3$, also resulted in lower conversions and more debrominated **425** was formed. There was no reaction when the temperature was lowered further (-40 °C or -20 °C).
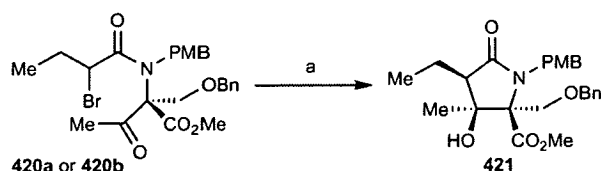
Reagents and conditions: (a) SmI_2 (10 eq), THF, 0 °C, 40%.

Scheme 4.35 *Improved yield towards γ-lactam **421***

A catalytic SmI_2-mediated Reformatsky reaction had been reported in the literature, using Mg metal to carry out the reduction of Sm(III) to Sm(II).[170] We speculated whether a catalytic procedure could favour the cyclisation at the expense of the C-N bond cleavage. However, little reaction occurred under these conditions.

It is important to note that the formation of the cyclised product only occurred when reacting the major diastereomer **420a**. Diastereomer **420b** reacted slightly faster and at lower temperatures than **420a** did, but to yield mainly debrominated amide **425** and amide **433**, and only traces of the desired product. The fact that **420a** was slightly less reactive turned out to be beneficial. However, being able to use only one diastereomer worsened the overall yield of a possible route to **1**.

In the next stages of the investigation, the α-iodo derivative was prepared, in order to determine if the nature of the halide had an effect on the cyclisation reaction. The synthesis of 2-iodo butanoic acid (**448**) was easily achieved from commercially available butanal (**446**) (Scheme 4.36). α-Iodo butanal (**447**) was prepared *via* a *DL*-proline catalysed α-iodination of **446** with NIS,[171] which afforded **447** as a racemic mixture. Oxidation of **447** to acid **448** was successfully performed using $KMnO_4$, in *t*-BuOH and a NaH_2PO_4 buffer to adjust the pH.[172] In a similar manner to that of the bromo-derivative preparation, from the racemic α-iodo carboxylic acid

both diastereomers of the amide would be obtained, they would be separated and the cyclisation reaction of each diastereomer would be studied independently. If one of the diastereomers were to react more efficiently, it could be selectively prepared with the same methodology but employing the chiral non-racemic organocatalyst.
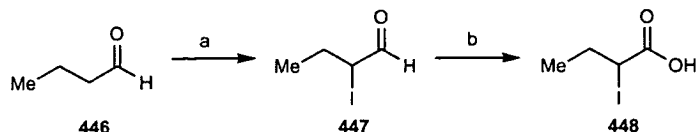
Reagents and conditions: (a) *DL*-Proline (0.3 eq), NIS (1.3 eq), CH$_2$Cl$_2$,
0 °C to rt, 5 h, 42%; (b) KMnO$_4$ (6 eq), 5% NaH$_2$PO4, *t*-BuOH, rt, 3 h, 95%.

Scheme 4.36 *Successful preparation of 2-iodo butanoic acid* **448**

The amide coupling of amine **327** and 2-iodo butanoic acid **448** was successfully achieved using triisobutylamine[121] as base, which yielded two diastereomers of the amide **(449a** and **449b)** in 75% overall yield (Scheme 4.37). In this case both diastereomers were obtained in practically the same proportion (1.2:1 ratio).
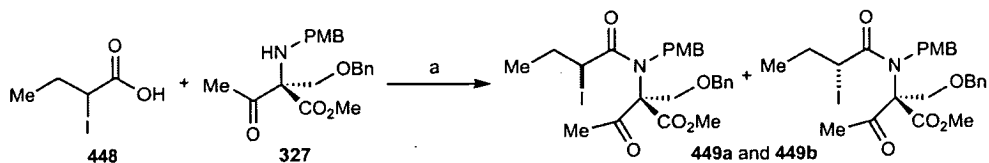
Reagents and conditions: (a) Oxalyl Chloride (11 eq), DMF (cat), CH$_2$Cl$_2$, rt,
1 h; (b) amine **327**, triisobutylamine (1.2 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 75%.

Scheme 4.37 *Successful amide coupling to α-iodo amides* **449**

The Reformatsky reaction with the iodo-derivatives was investigated, using from 2.2 to 12 equivalents of SmI$_2$ at different temperatures (from −40 °C to room temperature). In this case, neither the amount of SmI$_2$ nor the temperature led to any significant variation in the reaction. In all cases, amide **433** was the main product, obtained in 40-50% yield, followed by the debrominated amide **425** in 15-30% yield. γ-Lactam **421** was isolated only in a maximum yield of 10-15% (Scheme 4.38). The use of additives (HMPA, FeCl$_3$ or NiI$_2$) was again not beneficial in the reaction.

126
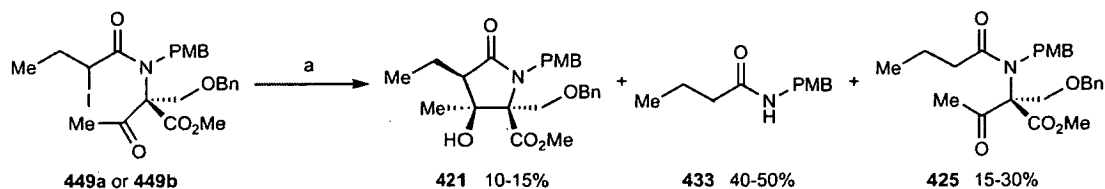
Reagents and conditions: (a) SmI_2 (12 eq), THF, 0 °C, 2 h.

Scheme 4.38 *Cyclisation reaction of iodo-derivative **449***

It was concluded that the iodo-derivative had a similar reactivity to the bromo-diastereomer **420b**, which only afforded traces of the desired product. The reaction of **420b** and the iodo derivatives **449** was faster and less controllable, and the cyclised product was formed in a lesser proportion than with the bromide diastereomer **420a**. Consequently, only α-bromo amides were employed for the rest of the investigation.

After this thorough study, an increase in the yield of the desired product had been achieved by reduction of the debromination of the starting material, but amide **433** was still being formed as a major product. An ideal set of conditions were required that, without completely stopping the reaction, would favour the formation of the desired cyclised product **421** at the expense of the formation of **433**.

Since γ-lactam **421** would only lead to the synthesis of salinosporamide B (Scheme 4.39), it was next decided to investigate further the optimisation of the reaction employing a substrate that would allow the synthesis of salinosporamide A.
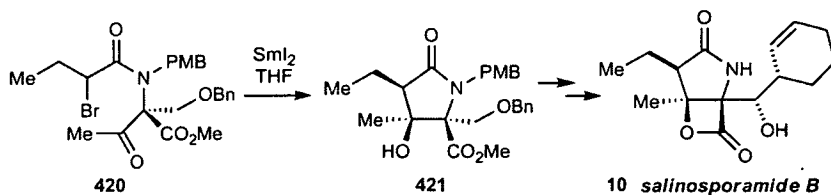
Scheme 4.39 *Cyclisation of **420** allows the formation of Salinosporamide B*

For this purpose, amine **327** would be coupled to an α-bromo acid such as **450**, which contained a protected alcohol on the γ-position (Scheme 4.40). If the amide obtained was successfully cyclised, the desired γ-lactam **374** would be formed.
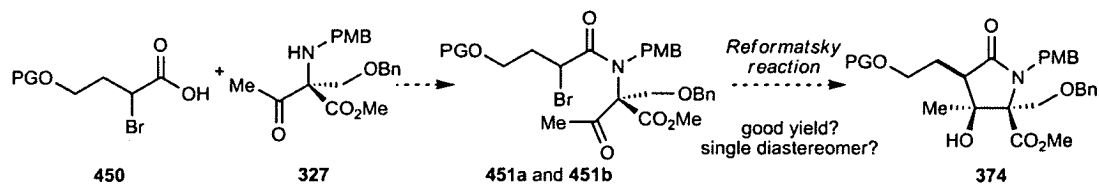
Scheme 4.40 *Synthesis and cyclisation reaction of the real substrate*

The formation of the amide was initially attempted *via* the ring opening of α-bromo-γ-butyrolactone with amine **327** (Scheme 4.41). Amine **327** and butyrolactone **452** were reacted under reflux,[173] but there was no reaction after 5 days. The reaction was also attempted in the presence of several bases (triisobutylamine, pyridine, KHMDS), in several solvents (CH_3CN, xylene, THF) and varying reaction times, but there was either no reaction or only a complex mixture of products was obtained.
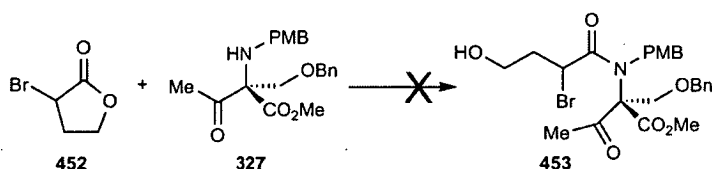
Scheme 4.41 *Failure of the ring opening of α-bromo-γ-butyrolactone 452*

We centred then on the preparation of an α-bromo acid for acylation of amine **327**. As described previously in the reductive aldol approach (Scheme 3.36), ideally the alcohol would be protected with a PMB group. The PMB protected acid **456** was easily prepared in good yield from 1,4 butanediol (Scheme 4.42).[174]
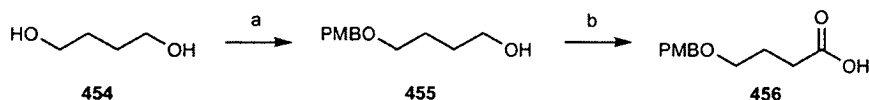
Reagents and conditions: (a) PMBCl (0.49 eq), KOH (1.05 eq), DMSO, 0 °C to rt, 14 h, 85%; (b) PDC (3.5 eq), DMF, rt, 14 h, 71%.

Scheme 4.42 *Preparation of PMB protected acid 456*

Treatment of acid **456** with bromine[175] or bromine and PCl_3[176] did not afford the desired α-brominated acid (**457**). The cleavage of the PMB group occurred instead,

due to the HBr released in the reaction. α-Bromination of carboxylic acids can also be achieved *via* the formation of the acid chloride.[177, 178] However, when acid **456** was treated with thionyl chloride, followed by the addition of bromine, the cleavage of the PMB group also occurred. The use of acid **456** was therefore abandoned (Scheme 4.43).
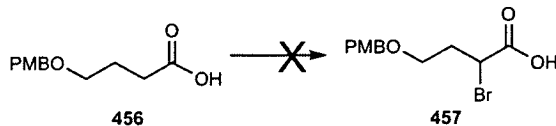
Scheme 4.43 *Failure of the α-bromination of acid 456*

Acid **459**, containing a TBDPS protecting group on the alcohol, was next prepared (Scheme 4.44).[179] Monoprotection of 1,4-butanediol (**454**) was followed by oxidation of **458** with PDC, which afforded acid **459** in moderate yield. The bromination was attempted employing the same procedures: acid **459** was reacted with bromine or bromine and PCl$_3$ in Et$_2$O or CCl$_4$ and also *via* the formation of the acid chloride, followed by reaction with bromine or NBS.[177] All attempts to brominate on the α-position of the acid failed to furnish the desired acid **460**.
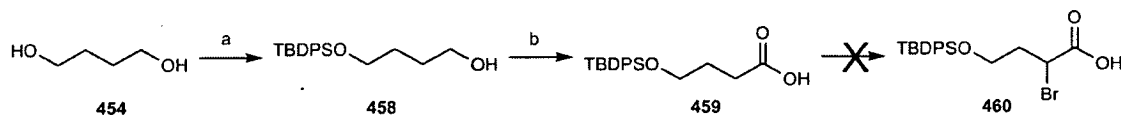
Reagents and conditions: (a) *n*-BuLi (0.33 eq), TBDPSCl (0.33 eq), THF, −78 °C to rt, 2 h, 97%; (b) PDC (3.5 eq), DMF, 0 °C to rt, 14 h, 51%.

Scheme 4.44 *Unsuccessful preparation of brominated acid 460*

Bromination of the acid was not being achieved; therefore, we decided to attempt the bromination on the aldehyde. Aldehyde **461** was prepared in good yield from alcohol **458** *via* a Swern oxidation (Scheme 4.45).[61]
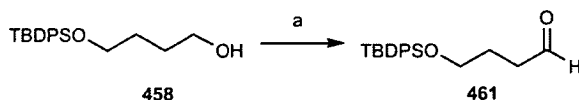
Reagents and conditions: (a) (COCl)$_2$ (2.1 eq), DMSO (4.2 eq), Et$_3$N (4.2 eq), CH$_2$Cl$_2$, -78 °C, 3 h, 79%.

Scheme 4.45 *Swern oxidation of alcohol 458*

Aldehyde **461** was reacted with bromine in Et$_2$O, CCl$_4$ or dioxane, but no reaction occurred. However, when the reaction was carried out in a mixture of Et$_2$O and dioxane,[180] brominated aldehyde **463** was successfully obtained (Scheme 4.46). This successful bromination procedure was also carried out with acid **459**, so that the oxidation step would be avoided, but with no success.

After bromination of **461**, the crude product was employed without further purification in the oxidation reaction to acid **463**, using KMnO$_4$, in *t*-BuOH and a NaH$_2$PO$_4$ buffer.[172] The yield of the oxidation was low due to partial cleavage of the TBDPS group. Consequently, the overall yield for the two-step sequence was 38%.
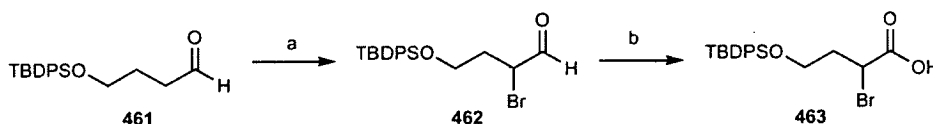
Reagents and conditions: (a) Br$_2$ (1 eq), dioxane, Et$_2$O, 0 °C to rt, 2 h; (b) KMnO$_4$ (6 eq), 5% NaH$_2$PO4, *t*-BuOH, rt, 3 h, 38% in two steps.

Scheme 4.46 *Bromination and oxidation of aldehyde 461*

With acid **463** in hand, we next centred on the coupling with amine **327**. The acid chloride of **463** was prepared and transferred into a solution of amine **327** and triisobutylamine (Scheme 4.47).[121] The two expected diastereomers of the amide (**464a** and **464b**) were obtained in an overall 73% yield, and in approximately a 1.2:1 ratio.
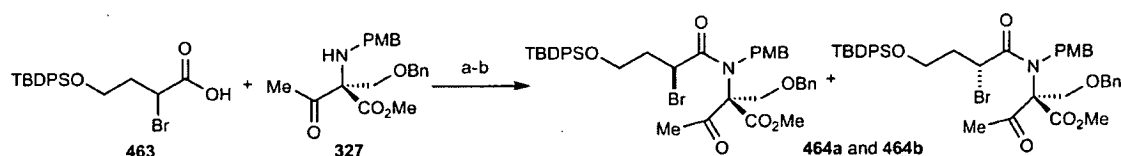
Reagents and conditions: (a) (COCl)$_2$ (11 eq), DMF (cat), CH$_2$Cl$_2$, 0 °C to rt, 1 h; (b) amine **327**, triisobutylamine (1.2 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 73% (40% and 33%).

Scheme 4.47 *Synthesis of amides 464a and 464b*

The α-bromo carboxylic acid containing an acetate protecting group (**468**) was also prepared, and it would be used in the study of the cyclisation reaction. The

acetate monoprotection of **454** was achieved, although in low yield, using Ac$_2$O and CeCl$_3$.[181] The yield of this reaction was not optimised. A PCC oxidation of **465** afforded aldehyde **466** in 65% yield (Scheme 4.48).
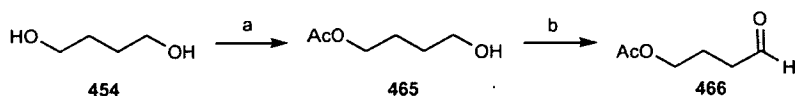
Reagents and conditions: (a) Ac$_2$O (10 eq), CeCl$_3$ (0.1 eq), THF, rt, 16 h, 43%; (b) PCC (1.5 eq), CH$_2$Cl$_2$, rt, 1.5 h, 65%.

Scheme 4.48 *Synthesis of aldehyde 466*

Aldehyde **466** was successfully brominated using *DL*-Proline and NBS in CH$_2$Cl$_2$ (Scheme 4.49). Oxidation to the carboxylic acid (**468**) was achieved in good yield using the same KMnO$_4$ protocol.
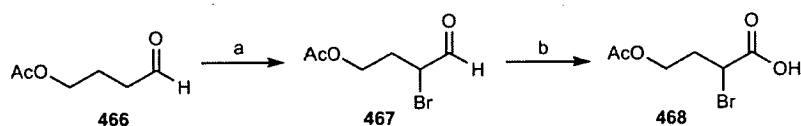
Reagents and conditions: (a) DL-Proline (0.3 eq), NBS (1.3 eq), CH$_2$Cl$_2$, rt, 4 h, 75%; (b) KMnO$_4$ (6 eq), 5% NaH$_2$PO$_4$, *t*-BuOH, rt, 3 h, 70%.

Scheme 4.49 *Bromination and oxidation of 466*

The amide coupling was performed under the same conditions employed for the rest of amide couplings (Scheme 4.50). However, this reaction proved troublesome, because although amides **469** were obtained, complete purification of the two diastereomers was not achieved. Therefore, it was not possible to attempt the cyclisation reaction on these substrates.
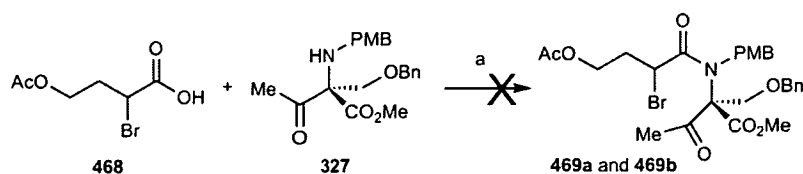
Reagents and conditions: (a) (COCl)$_2$ (11 eq), DMF (cat), CH$_2$Cl$_2$, 0°C to rt, 1 h; (b) amine **327**, triisobutylamine (1.2 eq), CH$_2$Cl$_2$, 0°C to rt, 14 h.

Scheme 4.50 *Unsuccessful amide coupling*

The cyclisation reactions with the TDBPS derivatives **464a** and **464b** were then investigated. Each diastereomer was treated independently with SmI$_2$ in THF, using from 2.2 to 12 equivalents, and at different temperatures (room temperature, 0 °C or −40°C). Both diastereomers had a similar and a reasonably high reactivity, since both substrates reacted at 0 °C and also at lower temperatures (−20 °C). However, the cyclisation product was not obtained and the only isolated product was amide **470** (40%), as well as traces of a compound that was tentatively characterised by ^{1}H NMR analysis as the debrominated starting material (**471**) (Scheme 4.51).

The reactivity of these compounds was comparable to the most reactive diastereomer of the model substrate **420b** or to the iodide derivatives, which reacted at lower temperatures than **420a** but forming only traces of the cyclised product. Therefore, this example also contributed to the idea that a higher reactivity meant a faster and more uncontrollable reaction, which did not allow the cyclisation to the γ-lactam.

Reagents and conditions: (a) SmI$_2$ (12 eq), THF, 0 °C, 1 h, 40%.
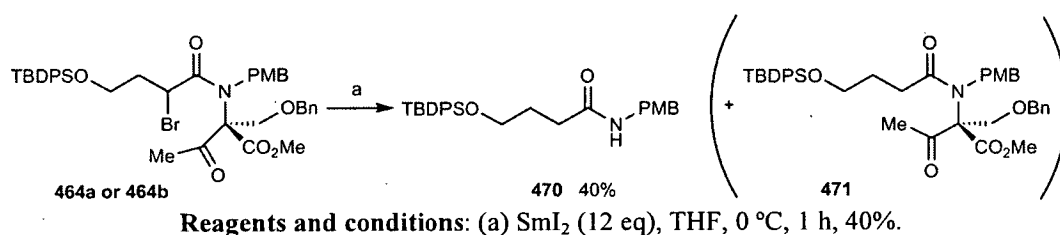
Scheme 4.51 *Unsuccessful cyclisation of amides **464a** and **464b***

4.4. Conclusions

In this approach we aimed to utilise a Reformatsky cyclisation of an α-halo amide to obtain the γ-lactam of **1**, having the side chain at C2 already in place. Initially, a model system of the α-bromo amide substrate was prepared and employed in the investigation of the reaction. The Reformatsky cyclisation employing different metals (Zn, Rh, Ni, Co and Cr) was attempted but the cyclised product was not obtained. As the precedent in the literature indicated, SmI$_2$ turned out to be the best reagent for this reaction, affording the desired cyclised product and as a single diastereomer, although in low yield. The fact that the cyclised product was formed only under the SmI$_2$ conditions was attributed to the known chelating ability of Sm^{3+},

which would make possible the enolate addition into the carbonyl of the methyl ketone.

After a thorough optimisation study, the yield was slightly improved to 40 %, but the formation of the main by-product was not avoided. From the two diastereomers of the substrate, only one afforded the cyclisation product. The other one reacted faster and at lower temperatures, but to yield only traces of the cyclised product. The effect of the nature of the halide was also investigated, but the iodo- derivatives were slightly more reactive and therefore afforded the cyclised product in lower yield.

The feasibility of the reaction with a substrate containing the required functionalities to obtain **1** was next studied. Efforts were made in the synthesis of several α-bromo amides. The cyclisation of the TBDPS derivative **464** was attempted, but the desired cyclised product was not obtained, and the amide resulting from a C-N bond cleavage was the only isolated product.

We concluded that the SmI₂ mediated Reformatsky reaction would either not progress at all at low temperatures or it would be too fast, yielding mainly the undesired by-product. At this stage, this approach was abandoned and work began on the next strategy.

5. Formal synthesis of salinosporamide A[i]

5.1. Aims

As described previously, our desire was to incorporate the reductive aldol methodology developed within our group[65-67] into a synthetic route to our natural product. We envisaged that a precursor such as **102** could be cyclised employing our methodology into γ-lactam **178**, and this intermediate could be converted into our final target **1** in only a few straightforward transformations.
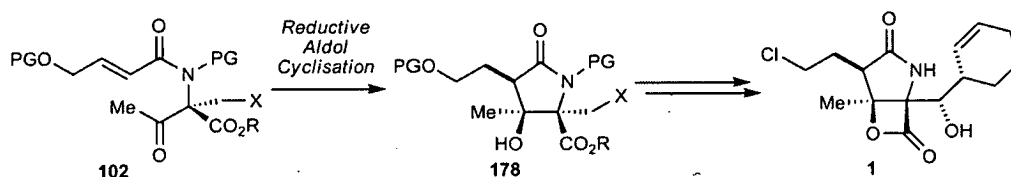
Scheme 5.1 *Application of the reductive aldol reaction into the synthesis of 1*

We had already undertaken investigations into the application of this approach into our synthetic route, which were described in Chapter 3. In these first studies, the α,β-unsaturated amide substrates for the cyclisation reaction were prepared from racemic amine **300** (Scheme 3.35). All attempts at the cyclisation reaction afforded a complex mixture of products and its analysis proved to be very difficult.

It was decided to reinvestigate the reductive aldol approach. On this occasion, we would utilise amine **327** to prepare the α,β-unsaturated substrates. This amine was utilised by Corey and co-workers in the synthesis of **1**, forming part of the acrylamide substrate of the cyclisation step that successfully afforded the γ-lactam core of **1**, with very good yield and diastereoselectivity.[22, 26] We had also employed amine **327** during the investigation of the Reformatsky cyclisation approach (Chapter 4). In this study a positive influence of the stereocentre of amine **327** was also observed, in that the cyclised product of the model substrate was achieved as a single diastereomer.

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[i] Work done in collaboration with Leszek Rupnicki, who developed the reductive aldol cyclisation-lactonisation reaction (Section 5.3).

We aimed to find out whether the use of amine **327** could also be beneficial in the reductive aldol methodology, facilitating the cyclisation and hopefully inducing diastereoselectivity in the reaction. In addition, unlike when this approach was first investigated, the Co- and Ni-catalysed methodologies were now completely developed, having been applied to a broader range of substrates. [65-67] Therefore we hoped to successfully utilise this reaction in our route to salinosporamide A.

The Co- and Ni-catalysed methodologies have afforded promising results in the formation of 5-membered lactams. In particular we should highlight the cyclisation of amide **292d**, containing the fumaric acid ethyl ester, which afforded γ-lactam **293d** in good yield and high *syn*-diastereoselectivity (Scheme 5.2). This example proved the high chemoselectivity of this methodology, because product **472**, resulting from cyclisation α- to the ester instead of α- to the amide was not observed. The formation of **293d** was especially encouraging, since the ethyl ester side chain could potentially be converted into the chloroethyl side chain at C2 of salinosporamide A.
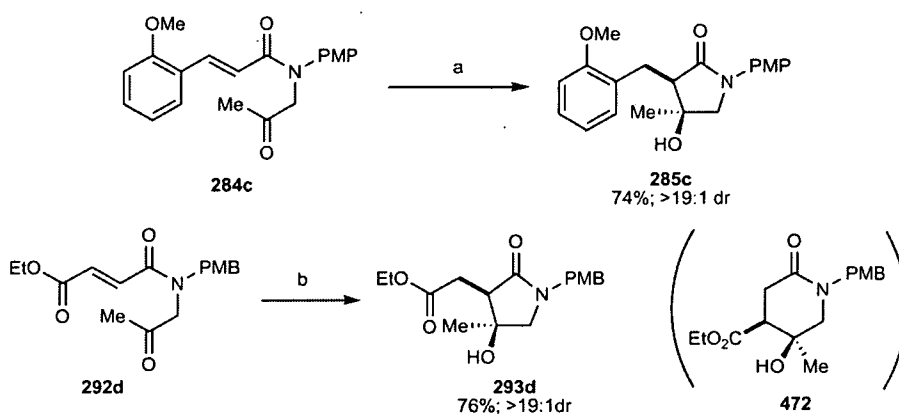
Reagents and conditions: (a) Co(acac)$_2$·2H$_2$O (5 mol%), Et$_2$Zn (2 eq), THF/hexane; (b) Ni(acac)$_2$ (5 mol%), Et$_2$Zn (2 eq), THF/hexane.

Scheme 5.2 *Relevant examples of successful cyclisations to 5-membered ring γ-lactams*

In conclusion, the reductive aldol approach was re-examined in order to employ in this occasion an α,β-unsaturated amide prepared from amine **327**. It was hoped that we could find the optimal substrate and catalyst which would allow cyclisation,

and hence provide the γ-lactam core of our natural product in good yield and with the desired relative stereochemistry.

5.2. Retrosynthetic analysis

The retrosynthetic analysis in this new study incorporates amine **327** into the retrosynthetic analysis outlined in Chapter 3 (Scheme 3.34) and it is briefly outlined in Scheme 5.3. γ-Lactam **374** represents the desired product of the reductive aldol cyclisation of α,β-unsaturated amide **473**. This amide could be obtained from the coupling of amine **327** with an α,β-unsaturated acid represented by **298**.
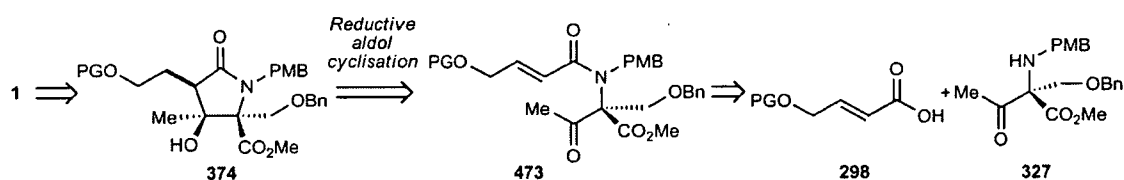
Scheme 5.3 *Retrosynthetic analysis of the reductive aldol cyclisation approach using amine **327***

If amide **473** cyclises to yield the desired γ-lactam **374**, this intermediate could be easily transformed into triol **26**, the same intermediate we were aiming to obtain during the first investigation of the reductive aldol approach (Chapter 3, Scheme 3.36), which is an advanced intermediate in Corey's synthesis[2] and also in Pattenden's synthesis.[29] Therefore, if the proposed route was successful, we would have developed a formal total synthesis of **1**.

5.3. Preliminary studies on the reductive aldol cyclisation reaction.

Initial work focused on the synthesis of the amide represented by **473** (Scheme 5.3). This amide would allow a thorough study of the reductive aldol cyclisation reaction, investigation that was carried out by another PhD student of the Lam group, Leszek Rupnicki and it is explained in this section.

Amine **327** was prepared following the method described in Chapter 4. The coupling of this amine with acid **325**, containing a PMB protecting group on the alcohol (for synthesis see Chapter 3, Scheme 3.52) was attempted, but all efforts were unsuccessful. The attempts of formation of the acid chloride of **325** followed by coupling with amine **327** also resulted in cleavage of the PMB group. Investigations into the use of coupling reagents also proved fruitless, presumably due to the low nucleophilicity and bulkiness of amine **327** (Scheme 5.4).
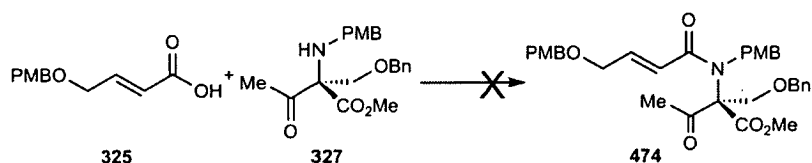
Scheme 5.4 *Unsuccessful preparation of amide 474*

Bearing in mind the successful cyclisation of **292d** (Scheme 5.2), it was next decided to couple amine **327** to the commercially available fumaric acid monoethyl ester **479**. However a potential problem was whether the ethyl ester on the C2 side chain of **476** could be, later in the synthesis, selectively reduced over the methyl ester at C4 (Scheme 5.5).
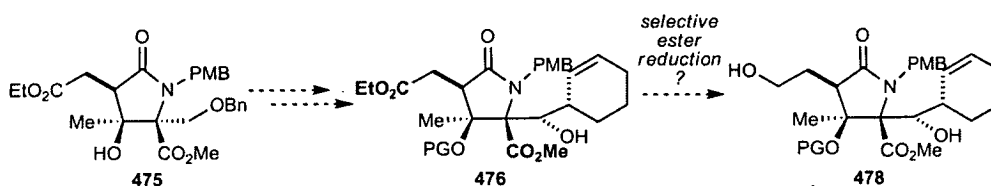
Scheme 5.5 *Possibly problematic selective ethyl ester reduction*

In spite of this, it was decided to prepare the substrate and investigate the cyclisation reaction. Amide **481** was successfully obtained *via* addition of a solution of acid chloride **480** into a solution of amine **327** and diisopropylethyl amine in CH$_2$Cl$_2$ (Scheme 5.6).
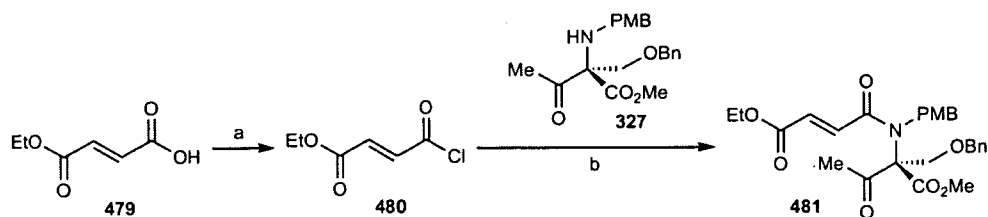
Reagents and conditions: (a) (COCl)$_2$ (1.2 eq), DMF (cat), CH$_2$Cl$_2$, 0 °C to rt, 2 h; (b) **327**, *i*-Pr$_2$EtN (1.7 eq), CH$_2$Cl$_2$, 0 °C to rt, 14 h, 95%.

Scheme 5.6 *Preparation of amide 481*

The cyclisation of amide **481** employing the reductive aldol methodology developed within the group was then investigated. The observed stereochemical outcome (*syn*-selectivity) of this methodology can be explained by preferential formation of the *Z*-enolate, along with a chelated chairlike Zimmerman-Traxler[182] transition state.[65-67] It was expected to observe a high *syn*-diastereoselectivity in the cyclisation of **481** and also to find out whether the quaternary stereocentre had an effect on the absolute configuration of the two newly formed stereocentres (Scheme 5.7).
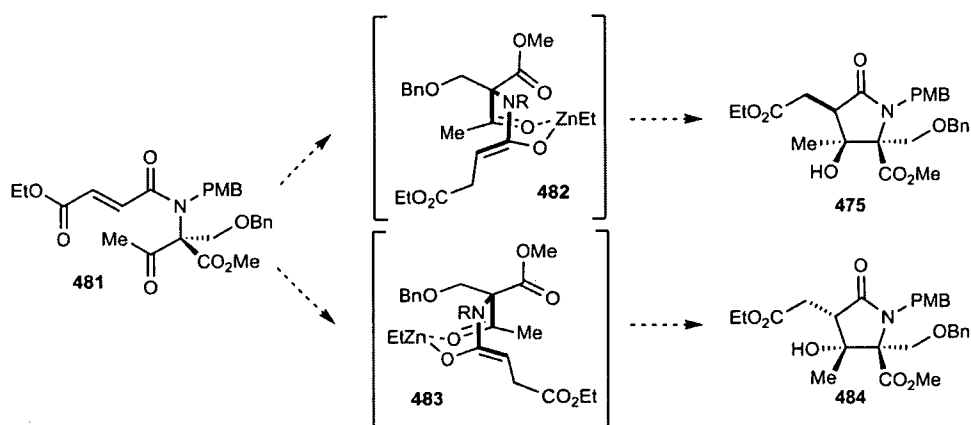
Scheme 5.7 *Desired transition state of the cyclisation reaction*

The catalyst could potentially bind, as well as to the enolate and the methyl ketone oxygens, to the carbonyl of the methyl ester forming **485**, which would yield the desired diastereomer **475** (Scheme 5.8). However, it could also bind to the benzyl ether (**486**) and therefore form the undesired diastereomer **484**. Ideally, formation of chelate **485** would be preferred and therefore product **475** would be obtained as the

major diastereomer, at the expense of the alternative *syn*-diastereomer **484**. However, the diastereoselectivity of this reaction was difficult to predict, since both proposed transition states could be formed in competition, or **486** could be the preferred one, and also neither of them could be occurring.
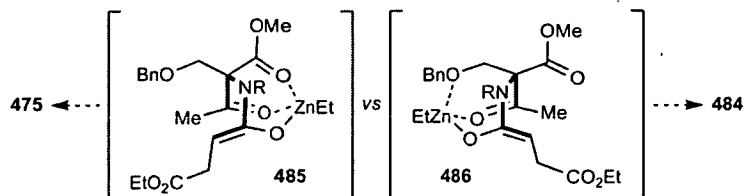
Scheme 5.8 *Influence of the quaternary stereocentre*

Initially, the cyclisation reaction was attempted using the standard Co and Ni conditions, but when **481** was exposed to Et_2Zn and $Ni(acac)_2$ or $CoCl_2$ and Cy_2PPh only an inseparable mixture of compounds was obtained (Table 5.1, entry 1 and 2). When $Co(acac)_2 \cdot 2H_2O$ was used, hardly any reaction was observed at all (entry 3). Et_2Zn was replaced with Et_3Al but again, a very complex mixture of compounds was obtained (entry 4 and 5).

The influence of phosphine ligands was next investigated. The use of $CoCl_2$ and PPh_3 proved unsuccessful, and unreacted starting material was recovered (entry 6). The combination of $CoCl_2$ and DPPF offered no improvement, since it afforded a complex mixture of compounds (entry 7). However, it was found that commercially available nickel–phosphine complexes were effective precatalysts. Complex $(Ph_3P)_2NiBr_2$ was able to promote the reductive cyclisation of **481** under dilute conditions to give bicyclic fused γ-lactone-γ-lactam **489** containing the desired stereochemistry in 35% yield. Unfortunately, this compound was accompanied by a comparable amount of the alternative diastereoisomer **490** (entry 8). This result was slightly improved when using $(Me_3P)_2NiCl_2$ and performing the reaction at an initial temperature of −15 °C. In this case, the yield of **489** increased to 42 % (entry 9).

Table 5.1 *Conditions attempted in the cyclisation of 481*
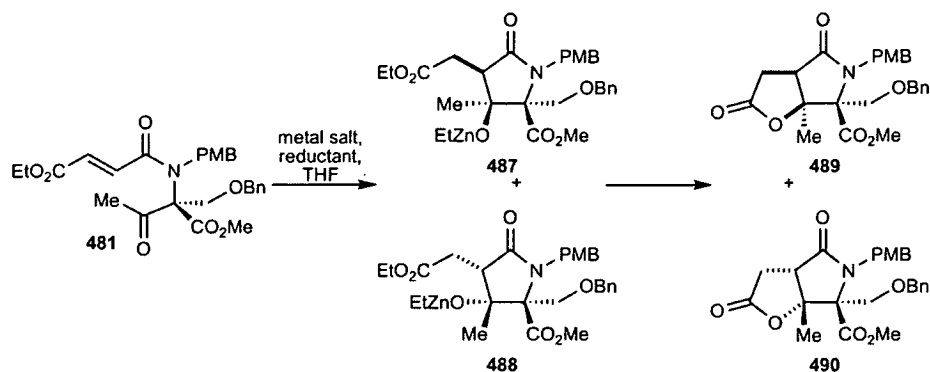
	Metal salt/ligand	Reductant	Results/yields
1	Ni(acac)$_2$	Et$_2$Zn	intractable mixture
2	CoCl$_2$, Cy$_2$PPh	Et$_2$Zn	intractable mixture
3	Co(acac)$_2 \cdot$2H$_2$O	Et$_2$Zn	<10% conversion
4	Ni(acac)$_2$	Et$_3$Al	intractable mixture
5	Co(acac)$_2 \cdot$2H$_2$O	Et$_3$Al	intractable mixture
6	CoCl$_2$ / PPh$_3$	Et$_2$Zn	**481** recovered
7	CoCl$_2$ / DPPF	Et$_2$Zn	intractable mixture
8	(Ph$_3$P)$_2$NiBr$_2$	Et$_2$Zn	35% of **489**, 30% of **490**
9	(Me$_3$P)$_2$NiCl$_2$	Et$_2$Zn	42% of **489**, 30% of **490**

The fact that both *syn*-diastereomers were obtained indicated that under these conditions, the pre-existing stereocentre in **327** was not effective in controlling the absolute configuration of the two new stereocentres formed in the reaction. The stereochemistry of diastereomer **490** was established by X-ray crystallography (Figure 5.1).
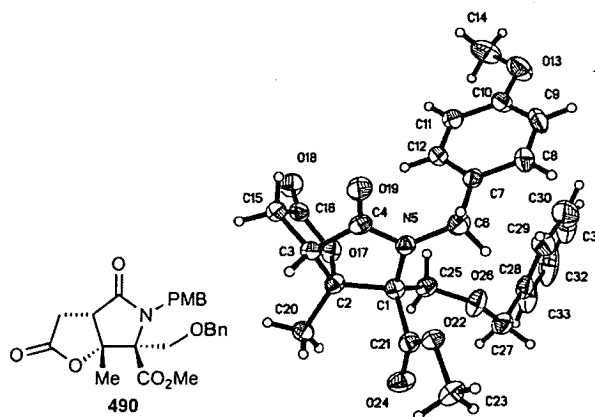
Figure 5.1 *X-ray crystallography of 490*

The lactones of **489** and **490** were formed as a result of the tertiary zinc alkoxides formed in the aldol reaction cyclising with the pendant ethyl esters. This lactonisation occurred in the Ni-catalysed cyclisation of 6-membered lactams **290n** and **290o** (Scheme 5.9), but this cyclisation had been observed only as a minor product (<10%) in the cyclisation to the γ-lactam **292d** (Scheme 5.2). Therefore, the lactonisation was unexpected in the cyclisation of our substrate **481**. However, it turned out to be a useful bonus because it protected the tertiary alcohol of **489** towards subsequent transformations.

290n R^1 = PMP, R^2 = Ph
290o R^1 = Bn, R^2 = Me

491
492

291n >19:1 dr, 79%
291o >19:1 dr, 89%
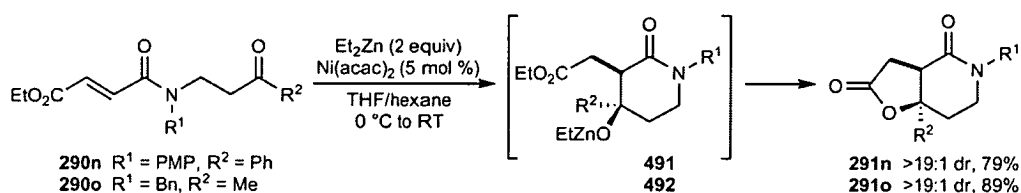
Scheme 5.9 *Sequential reductive cyclisation-lactonisation*

5.4. Completion of the formal synthesis

Once the reductive aldol cyclisation of **481** to afford the desired cyclised product **489** had been developed, we only needed to perform a few transformations to obtain intermediate **26**. After separation of diastereomers **489** and **490** by column chromatography, the next step was the deprotection of the alcohol. This was achieved *via* a palladium-catalysed debenzylation, which afforded alcohol **493** in good yield (Scheme 5.10). This alcohol was crystalline and X-ray crystallography[i] of this compound allowed confirmation of its stereochemistry and therefore that of **489**.

489   **493**
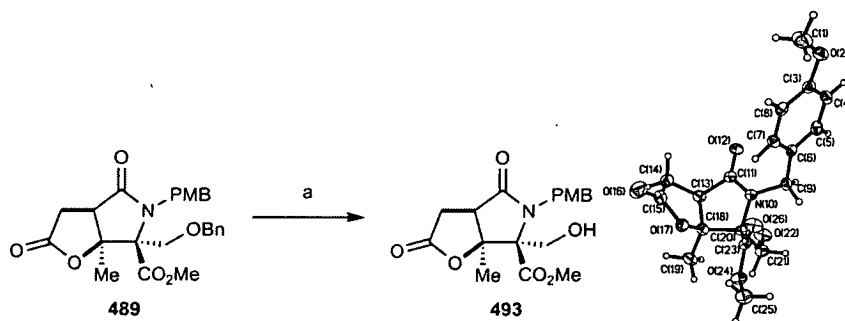
Reagents and conditions: (a) Pd/C (10%), EtOH, 23 °C, 12 h, 84%

Scheme 5.10 *Obtention of alcohol 493 and confirmation of its stereochemistry*

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[i] Crystal of **493** was obtained by Leszek Rupnicki

Oxidation of alcohol **493** to aldehyde **494** was performed using Dess-Martin periodinane reagent.[35] This aldehyde proved to be very unstable and therefore it had to be immediately reacted with 2-cyclohexenylzinc chloride, following Corey's procedure.[26] This step was readily performed, since we were already familiar with this transformation, which had been carried out during the first route we investigated for the synthesis of salinosporamide A (Chapter 2). Therefore, homoallylic alcohol **495** was successfully obtained with high diastereoselectivity (only one observable diastereoisomer by 1H NMR analysis). The overall yield for this two-step sequence was 61% (Scheme 5.11).
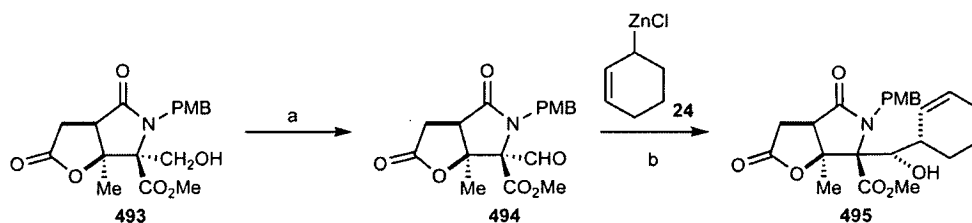
Reagents and conditions: (a) Dess-Martin periodinane (1.2 eq), CH_2Cl_2, rt, 1.5 h; (b) **24** (2.5 eq), THF, −78 °C, 5 h, 61%.

Scheme 5.11 *Oxidation to the aldehyde and immediate insertion of the cyclohexenyl chain*

Alcohol **495** was also crystalline and X-ray crystallography showed that the desired stereochemistry had been achieved in the insertion of the side chain (Figure 5.2).
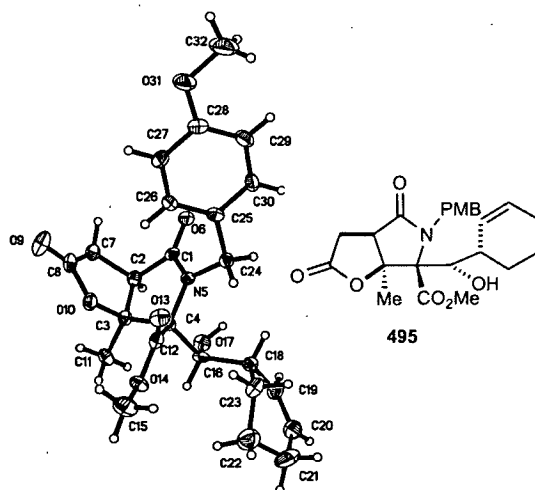
Figure 5.2 *X-ray crystallography of* **495**

The last step to complete the formal synthesis involved the selective reduction of the lactone over reduction of the methyl ester. We were pleased to find out that the lactone of **495** was selectively reduced with NaBH$_4$ to give triol **26** (Scheme 5.12), intermediate in the synthesis of Corey[26] and Pattenden[29] groups. A vast excess of NaBH$_4$ was necessary to obtain a satisfactory yield, otherwise, a small fraction of unreacted starting material was recovered. The conversion of **26** into salinosporamide A is performed in four steps and has already been described by these groups.
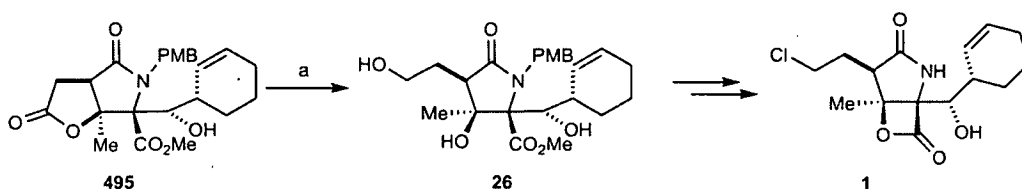
Reagents and conditions: (a) NaBH$_4$ (45 eq), EtOH, rt, 14h, 60%.

Scheme 5.12 *Final reductive ring-opening to triol **26***

Interestingly, the NMR data we obtained for triol **26** displayed subtle but appreciable differences to those reported by Corey and co-workers for the same compound,[26] most notably in the ^{13}C NMR chemical shifts.[i,ii] However, comparison of our spectra with that obtained by Pattenden for the same compound[29] showed good agreement. The most likely explanation for this observation is that the values of the ^{13}C NMR chemical shifts for triol **26** are concentration-dependent; both our and that obtained by Pattenden group ^{13}C NMR spectra were run at relatively low concentration, whereas the spectrum obtained by Corey was run at relatively high concentration.[ii]

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[i] Both the Corey group and the Pattenden group had kindly supplied us with a copy of their ^{13}C NMR spectrum

[ii] Both ^{13}C NMR data and spectrum included in the experimental section. The higher concentration of Corey's sample can also be observed.

5.5. Conclusions

In this chapter the reductive aldol approach was re-examined. On this occasion, we employed for the preparation of the α,β-unsaturated amides the amine used by Corey and co-workers (**327**) in the synthesis of **1**. α,β-Unsaturated amide **481** was prepared from monoethyl fumarate and amine **327**, and it was discovered that it successfully cyclised when treated with $(Me_3P)_2NiCl_2$ and Et_2Zn. The cyclisation reaction was followed by lactonisation due to the tertiary zinc alkoxide formed in the aldol reaction. The desired cyclised product was obtained in 42% yield and it was accompanied by a 30% yield of the alternative diastereomer. The lack of diastereoselectivity meant that the quaternary stereocentre of the amine was not effective in inducing stereoselection in the reaction.

The lactonisation step turned out to be beneficial, because an extra step for the protection of the tertiary alcohol formed was not necessary. This approach achieved the formation of the γ-lactam, installing the side-chain at C2 and with protection of the oxygen at C5 simultaneously, therefore saving several steps over alternative routes. The desired cyclised product was successfully transformed in four steps to an intermediate in the synthesis of **1** by Corey and co-workers, which had been converted into salinosporamide A in a further four steps. Consequently, a formal synthesis of **1** had been achieved.

Although very pleased with having been able to use the reductive aldol methodology developed in the group and with the success of the formal synthesis, the diastereoselectivity of the cyclisation reaction remains to be improved. Future work would involve more investigation to uncover alternative catalyst systems/reaction conditions that are able to promote the sequential reductive aldol cyclisation-lactonisation of **481**, in the hope of obtaining a highly diastereoselective reaction to give **489** at the expense of **490**.

At this point, our synthetic route to intermediate **26** was achieved in a 2.5% overall yield and over eleven steps, which represents a total synthesis of salinosporamide A with an overall yield of 1.4% over fiftten steps. The comparison of synthetic routes is not completely obvious, since the starting materials employed and the compounds obtained in the reported syntheses can differ significantly.

However, if our route is compared to the other enantioselective syntheses reported (Danishefsky, Langlois or Macherla's), it is clear that our route is already more efficient, since it achieves the synthesis of **1** over less steps and with a better overall yield (Table 5.2, entries 3, 5, 7 and 8).

If we compare our route with Corey's synthesis, which is the best reported synthesis of **1** so far, we observe that our synthetic route is 4 steps shorter, although the overall yield is notably lower (Table 5.2, entries 2 and 8). Nevertheless, if the diastereoselectivity of the key cyclisation step is improved, the overall yield of our route will increase significantly, and our synthesis of salinosporamide A will become as powerful as, if not more than, the one reported by Corey and co-workers.

	Synthesis	Number of steps	Overall yield	Asymmetric /racemic
1	Corey (Baylis-Hillman)[26]	18	8.7%	asymmetric
2	Corey (Kulinckovich)[22]	18 (8 steps to **29**) (14 steps to **26**) (10 steps from **18** to **26**)	9.1% (27.0% to **29**) (16.8% to **26**) (47.7% from **18** to **26**)	asymmetric
3	Danishefsky[27]	28 (from **37**)	1.8% (from **37**)	asymmetric
4	Pattenden[29]	14 (from **52**)	11.5% (from **52**)	racemic
5	Langlois (formal synthesis)[31]	8 (from **67** to **29**) (18 steps from **67** to **1**)	11.8% (from **67** to **29**) (4.0% from **67** to **1**)	asymmetric
6	Romo[30]	9 steps	1.2%	racemic
7	Macherla[28]	24 steps	0.2%	asymmetric
8	HWL (formal synthesis)	11 (to **26**) (15 steps to **1**) (7 steps from **18** to **26**)	2.5% (to **26**) (1.4% to **1**) (8.8% from **18** to **26**)	asymmetric

Table 5.2 *Comparison of the reported síntesis of salinosporamide A with the HWL synthetic route*

Another step in the synthesis we wish to modify is the installation of the cyclohexenyl side-chain. Practically all total syntheses of salinosporamide A[22, 26, 27, 29-32] reported so far employ the allylzinc reagent, as described by Corey and co-workers.[26] Although this chemistry works very well, the preparation of this reagent

requires access to an allylstannane, which is then subjected to a tin–lithium–zinc transmetallation sequence. In addition to employing a toxic reagent, this chemistry is atom-inefficient and somewhat experimentally inconvenient. Therefore, we intend to seek alternative methods to this chemistry involving more user-friendly precursors and reaction conditions. Particularly, we are interested in investigating the application to our system of the methodology reported by Tamaru and co-workers.[183] They developed a regio- and stereoselective Ni-catalysed homoallylation of aromatic and aliphatic aldehydes using Et_3B. The use of Et_2Zn instead of Et_3B in the reaction with sterically congested aliphatic aldehydes and ketones afforded improved yields and similarly high regio- and stereoselectivities (Scheme 5.13).
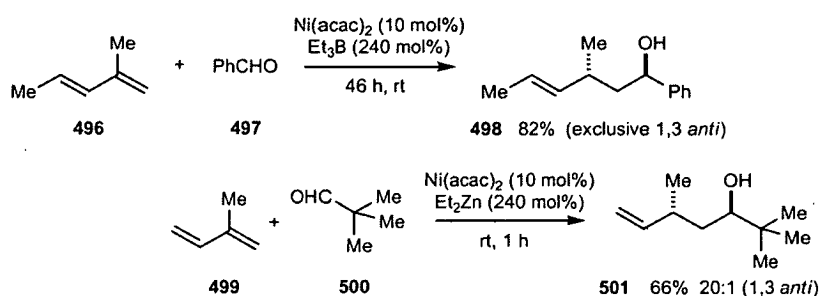
Scheme 5.13 *Ni-Catalysed homoallylation of aldehydes with 1,3-dienes*

The reaction with 1,3-cyclohexadiene was the only exception that resulted in an allylation, to yield **502** diastereoselectively and in good yield (Scheme 5.14). We therefore would like to investigate the application of this methodology to the insertion of the cyclohexenyl chain into aldehyde **494**.
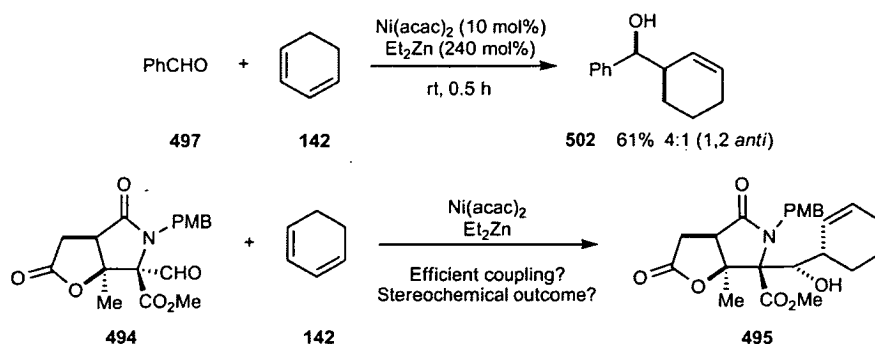
Scheme 5.14 *Application of Tamaru's methodology*

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6. Experimental

6.1. General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Only in section 6.2.1, CH_2Cl_2 and MeCN were distilled from CaH_2 and Et_2O and THF were distilled from sodium with benzophenone as an indicator. In the rest of sections, CH_2Cl_2, THF, MeCN and MeOH were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Anhydrous DMF was purchased from Aldrich. Pyridine, Et_3N and diisopropylamine were distilled from CaH_2. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin, potassium permanganate or ceric ammonium molybdate solution as appropriate. The compounds were purified by wet flash column chromatography using silica gel (Fisher Scientific 60Å particle size 35-70 micron) under a positive pressure.[184] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates. The wavelengths of maximum absorbance (v_{max}) are quoted in cm^{-1}. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), b (broad), bs (broad singlet). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence

with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the electron ionization (EI) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter with a path length of 0.5 dm at the sodium D line (589 nm).

6.2.   Experimental Procedures

6.2.1. Racemic approaches based on amidomalonate aldol cyclisations

Diethyl 2-(4-methoxyphenylamino)malonate (109)[51]
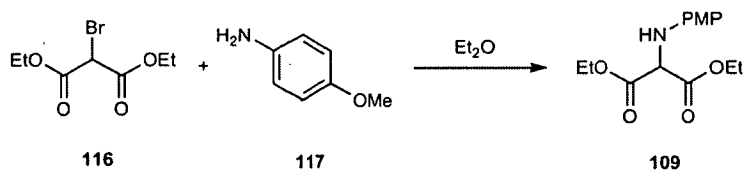
To a stirred solution of *p*-anisidine **117** (26.9 g, 218 mmol) in THF (120 mL) at room temperature was added 3-diethyl-2-bromomalonate **116** (20 mL, 109 mmol) *via* syringe. The reaction was heated to reflux for 2 h and stirred for 14 h at room temperature. The solution was then concentrated *in vacuo* and then redissolved in Et_2O. The reaction mixture was filtered, washing the solids with Et_2O and this solution was again concentrated *in vacuo*. This concentrate was now redissolved in EtOAc, filtered washing with EtOAc and concentrated *in vacuo*. A crystalline solid was formed and washed with petrol, obtaining pure amine **109** (26.2 g, 85%) as brown crystals. R_f (30% EtOAc in hexane) = 0.63; m.p. 65-67 °C, lit.[51] 64-65 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.78 (2H, d, J = 9.1 Hz, Ar**H**), 6.65 (2H, d, J = 9.1 Hz, Ar**H**), 4.69 (1H, s, C**H**($CO_2Et)_2$), 4.58 (1H, bs, N**H**), 4.27 (4H, q, J = 7.1 Hz, 2 x $CO_2C**H_2**CH_3$), 3.75 (3H, s, OC**H_3**), 1.28 (6H, t, J = 7.1 Hz, 2 x $CO_2CH_2C**H_3**$); [13]C

NMR (90 MHz, CDCl$_3$) δ 167.9 (2 x C), 153.1 (C), 139.4 (C), 115.1 (2 x CH), 114.8 (2 x CH), 62.2 (2 x CH$_2$), 61.8 (CH), 55.6 (CH$_3$), 14.0 (2 x CH$_3$).

^{1}H spectroscopic data in good agreement with the literature.[51]

Diethyl 2-(4-methoxybenzylamino)malonate (119)
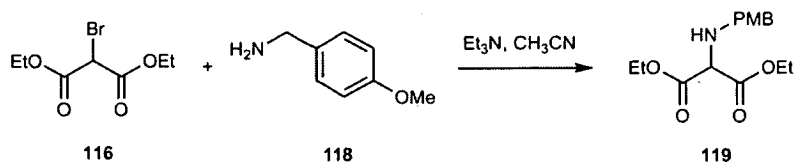
To a stirred solution of 4-methoxy benzylamine **118** (3.30 mL, 25.0 mmol) in MeCN (100 mL) at 0 °C, was added triethylamine (3.50 mL, 25.0 mmol), followed by the addition of 3-diethyl-2-bromomalonate **116** (4.60 mL, 25.0 mmol). The reaction was stirred for 14 h, allowed to warm up to room temperature, concentrated *in vacuo* and then redissolved in Et$_2$O. It was then washed with water (2 x 20 mL) and with saturated aqueous NaHCO$_3$ solution (2 x 20 mL). The combined aqueous layers were extracted with Et$_2$O (1 x 20 mL), and the organic layers were combined, dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amine* **119** (3.73 g, 52%) as a yellow oil. R$_f$ (20% EtOAc in hexane) = 0.33; IR (film) 2981 (NH), 1752 (C=O), 1734 (C=O), 1612, 1513, 1465, 1369, 1302, 1248, 1031 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.14 (2H, d, *J* = 8.5 Hz, ArH), 6.74 (2H, d, *J* = 8.5 Hz, ArH), 4.10 (4H, q, *J* = 7.1 Hz, 2 x CO$_2$CH$_2$CH$_3$), 3.92 (1H, s, CH(CO$_2$Et)$_2$), 3.67 (3H, s, OCH$_3$), 3.63 (2H, s, CH$_2$Ar), 2.33 (1H, bs, NH), 1.15 (6H, t, *J* = 7.1 Hz, 2 x CO$_2$CH$_2$CH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 166.4 (2 x C), 158.8 (C), 130.7 (C), 129.6 (2 x CH), 113.7 (2 x CH), 63.8 (CH), 61.6 (2 x CH$_2$), 55.1 (CH$_3$), 50.9 (CH$_2$), 13.9 (2 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{15}$H$_{21}$NO$_5$ [M+H]$^+$: 296.1492, found: 296.1494.

Dimethyl 2-(4-methoxybenzylamino)malonate (121)[51]
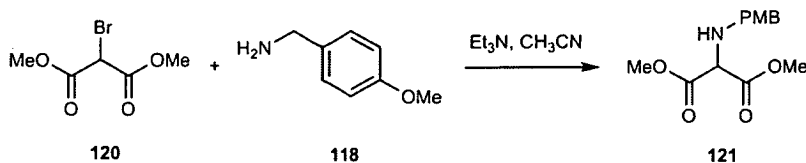
To a stirred solution of 4-methoxybenzylamine **118** (8.00 g, 60.0 mmol) in MeCN (60 mL) at 0 °C was was added triethylamine (8.40 mL, 60.0 mmol), followed by the addition of 3-diethyl-2-bromomalonate **120** (8.80 mL, 60.0 mmol). The reaction was stirred for 14 h at room temperature, concentrated *in vacuo* and then redissolved in Et$_2$O and saturated aqueous NaHCO$_3$ solution. This mixture was stirred for 30 min. The aqueous layer was separated and extracted with Et$_2$O (3 x 60 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (petrol/EtOAc, 10% to 30% in EtOAc) gave amine **121** (5.52 g, 35%) as a yellow oil. R$_f$ (40% EtOAc in hexane) = 0.50; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.25 (2H, d, J = 8.7 Hz, ArH), 6.86 (2H, d, J = 8.7 Hz, ArH), 4.08 (1H, s, CH(CO$_2$Me)$_2$), 3.80 (3H, s, OCH$_3$), 3.77 (6H, s, 2 x CO$_2$CH$_3$), 3.75 (2H, s, CH$_2$Ar), 2.32 (1H, bs, NH); ^{13}C NMR (90 MHz, CDCl$_3$) δ 168.9 (2 x C), 158.9 (C), 130.6 (C), 129.6 (2 x CH), 113.8 (2 x CH), 63.6 (CH), 55.2 (CH$_3$), 52.7 (CH$_3$), 51.0 (CH$_2$).

^{1}H spectroscopic data in good agreement with the literature.[51]

1-(4-Methoxybenzyl)-3-hydroxy-3-methyl-5-oxopyrrolidine-2,2-dicarboxylic acid methyl ester (123)
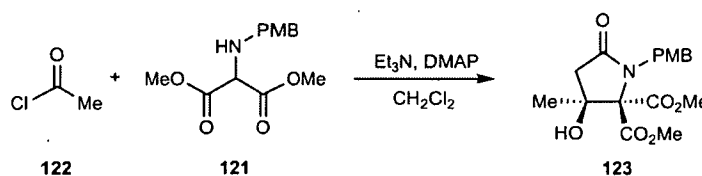
To a stirred solution of acetyl chloride **122** (2.75 mL, 38.4 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C, was added Et$_3$N (5.70 mL, 40.8 mmol) dropwise. After stirring for 1 h at 0 °C, a solution of amine **121** (3.26 g, 12.0 mmol) and DMAP (293 mg, 2.40 mmol) in CH$_2$Cl$_2$ (30 mL) was added *via* cannula. The reaction was stirred for 14 h at room temperature and then quenched with pH 7 phosphate buffer (20 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 80% EtOAc/petrol) gave *γ-lactam* **123** (2.95 g, 70%) as a yellow powder. R$_f$ (40% EtOAc in hexane) = 0.23; m.p. 125-128 °C; IR (film) 2954 (OH), 2360, 1742 (C=O), 1682 (C=O), 1612 (C=O),

1513, 1438, 1244, 1067 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.16 (2H, d, J = 8.7 Hz, Ar**H**), 6.79 (2H, d, J = 8.7 Hz, Ar**H**), 4.79 (2H, s, C**H$_2$**Ar), 3.76 (3H, s, OC**H$_3$**), 3.62 (3H, s, CO$_2$C**H$_3$**), 3.44 (3H, s, CO$_2$C**H$_3$**), 2.74 (1H, d, J = 16.8 Hz, C**H$_A$**H$_B$C=O), 2.68 (1H, d, J = 16.8 Hz, CH$_A$**H$_B$**C=O), 1.49 (3H, s, COHC**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.8 (C), 168.1 (2 x C), 167.7 (C), 159.1 (C), 130.2 (2 x CH), 128.9 (C), 113.9 (2 x CH), 79.5 (C), 55.6 (CH$_3$), 53.1 (2 x CH$_3$), 45.5 (CH$_2$), 45.3 (CH$_2$), 23.8 (CH$_3$); HRMS (ES) Mass calcd. for C$_{17}$H$_{22}$NO$_7$ [M+H]$^+$: 352.1391, found: 352.1393.

3-Hydroxy-1-(4-methoxyphenyl)-3-methyl-5-oxopyrrolidine-2,2-dicarboxylic acid ethyl ester (110)
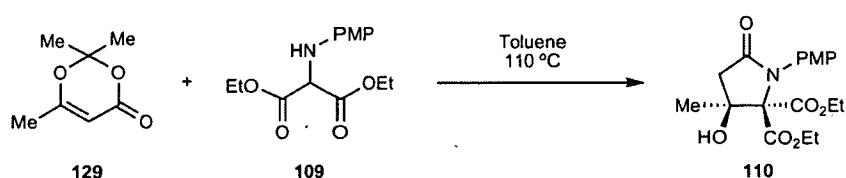
A stirred solution of dioxinone **129** (4.80 mL, 33.0 mmol) and amine **109** (8.44 g, 30.0 mmol) in toluene (25 mL) in a round bottom flask with an air condenser was placed in an oil bath preheated at 150 °C. The reaction was heated to reflux for 6 h and then concentrated *in vacuo*. Purification of the residue by column chromatography (25% to 45% EtOAc/petrol) gave γ-lactam **110** (8.72 g, 80%) as a yellow solid. R$_f$ (50% EtOAc in hexane) = 0.17; m.p. 127-130 °C, lit[51] 136-137 °C; IR (film) 2983 (OH), 1754 (C=O), 1727 (C=O), 1697 (C=O), 1512, 1366, 1297, 1250, 1031 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) 7.12 (2H, d, J = 9.1 Hz, Ar**H**), 6.86 (2H, d, J = 9.1 Hz, Ar**H**), 4.29 (2H, m, CO$_2$C**H$_2$**CH$_3$), 4.13 (2H, m, CO$_2$C**H$_2$**CH$_3$), 3.88 (1H, bs, CO**H**), 3.78 (3H, s, OC**H$_3$**), 2.82 (1H, d, J = 16.7 Hz, C**H$_A$**H$_B$C=O), 2.73 (1H, d, J = 16.7 Hz, CH$_A$**H$_B$**C=O), 1.58 (3H, s, COHC**H$_3$**), 1.27 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$C**H$_3$**), 1.07 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$C**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.2 (C), 167.6 (2 x C), 166.5 (C), 158.7 (C), 130.1 (C), 128.8 (2 x CH), 113.8 (2 x CH), 80.9 (C), 62.4 (CH$_2$), 62.0 (CH$_2$), 55.2 (CH$_3$), 44.6 (CH$_2$), 23.6 (CH$_3$), 13.8 (CH$_3$), 14.4 (CH$_3$).

^{1}H spectroscopic data in good agreement with the literature.[51]

3-Hydroxy-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2,2-dicarboxylic acid ethyl ester (131)
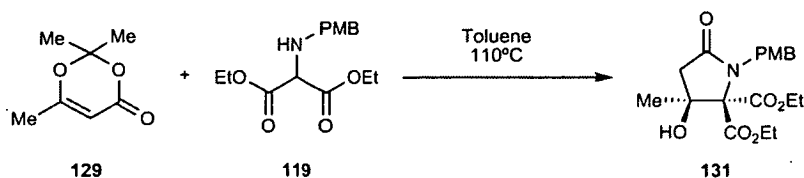
A stirred solution of dioxinone **129** (1.30 mL, 8.80 mmol) and amine **119** (2.30 g, 8.00 mmol) in toluene (25 mL) in a round bottom flask with an air condenser was placed in an oil bath preheated at 150 °C. The mixture was heated to reflux 14 h and then concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 25% EtOAc/petrol) gave *γ-lactam* **131** (2.65 g, 86%) as a brown oil. R_f (40% EtOAc in hexane) = 0.24; IR (film) 3392 (OH), 1738 (C=O), 1683 (C=O), 1612 (C=O), 1513, 1397, 1244, 1176, 1032 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.16 (2H, d, J = 8.7 Hz, Ar**H**), 6.78 (2H, d, J = 8.7 Hz, Ar**H**), 4.81 (1H, d, J = 14.9 Hz, C**H$_A$**H$_B$Ar), 4.74 (1H, d, J = 14.9 Hz, CH$_A$**H$_B$**Ar), 4.20-4.08 (1H, m, CO$_2$C**H$_C$**H$_D$CH$_3$), 4.05-3.95 (1H, m, CO$_2$CH$_{C'}$**H$_D$**·CH$_3$), 3.95-3.86 (1H, m, CO$_2$CH$_C$**H$_D$**CH$_3$), 3.86-3.77 (1H, m, CO$_2$CH$_{C'}$·**H$_D$**·CH$_3$), 3.75 (3H, s, OC**H$_3$**), 2.72 (1H, d, J = 16.5 Hz, C**H$_A$**H$_B$C=O), 2.65 (1H, d, J = 16.5 Hz, CH$_A$**H$_B$**C=O), 1.51 (3H, s, COHC**H$_3$**), 1.17 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$C**H$_3$**), 1.14 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$C**H$_3$**); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 174.5 (C), 167.2 (C), 166.8 (C), 158.6 (C), 129.4 (2 x CH), 128.8 (C), 113.4 (2 x CH), 79.1 (C), 76.4 (C), 62.2 (CH$_2$), 62.1 (CH$_2$), 55.2 (CH$_3$), 45.1 (CH$_2$), 44.9 (CH$_2$), 23.4 (CH$_3$), 13.7 (2 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{19}$H$_{26}$NO$_7$ [M+H]$^+$: 380.1704, found: 380.1703.

1-(4-Methoxy-phenyl)-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2,2-dicarboxylic acid ethyl ester (137)
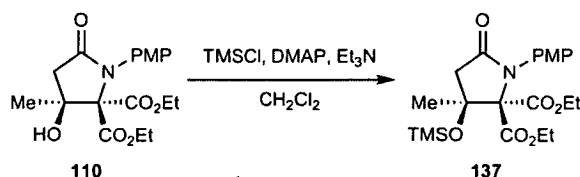
To a stirred solution of lactam **110** (4.00 g, 10.9 mmol) and DMAP (540 mg, 4.38 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C, was added Et$_3$N (4.60 mL, 33 mmol) dropwise, followed by the addition of TMSCl (2.15 mL, 16.4 mmol). The reaction

was stirred for 30 min at 0 °C and then quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol*)* gave *γ-lactam* **137** (4.27 g, 92%) as colourless crystals. R_f (50% EtOAc in hexane) = 0.80; m.p. 85-87 °C; IR (film) 2982, 1759 (C=O), 1746 (C=O), 1721 (C=O), 1512, 1250, 1063, 845 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.13 (2H, d, *J* = 8.9 Hz, ArH), 6.87 (2H, d, *J* = 8.9 Hz, ArH), 4.27 (2H, m, CO$_2$CH$_2$CH$_3$), 4.17 (2H, m, CO$_2$CH$_2$CH$_3$), 3.79 (3H, s, OCH$_3$), 2.97 (1H, d, *J* = 16.7 Hz, CH$_A$H$_B$C=O), 2.77 (1H, d, *J* = 16.7 Hz, CH$_A$H$_B$C=O), 1.67 (3H, s, COTMSCH$_3$), 1.27 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 1.24 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 0.17 (9H, s, 3 x SiCH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 173.5 (C), 167.1 (2 x C), 164.9 (C), 157.8 (C), 129.8 (C), 127.6 (2 x CH), 113.2 (2 x CH), 78.8 (C), 61.6 (CH$_2$), 60.8 (CH$_2$), 54.7 (CH$_3$), 45.2 (CH$_2$), 23.3 (CH$_3$), 13.3 (2 x CH$_3$), 1.2 (3 x CH$_3$); HRMS (ES) Exact mass calcd. for C$_{21}$H$_{32}$NO$_7$Si [M+H]$^+$: 438.1943, found: 438.1948 .

1-(4-Methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2,2-dicarboxylic acid ethyl ester (138)
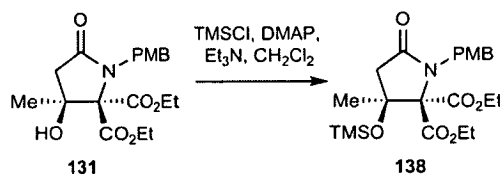
To a stirred solution of lactam **131** (2.50 g, 6.58 mmol) and DMAP (160 mg, 1.31 mmol) in CH$_2$Cl$_2$ (120 mL) at 0 °C, was added Et$_3$N (2.80 mL, 19.8 mmol) dropwise, followed by the addition of TMSCl (1.30 mL, 9.90 mmol) *via* syringe. The reaction was stirred for 14 h at room temperature and then quenched with saturated aqueous NaHCO$_3$ solution (40 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 30 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol*)* gave *γ-lactam* **138** (2.50 g, 85%) as a brown solid. R_f (40% EtOAc in hexane) = 0.67; m.p. 68-71 °C; IR (film) 2958, 1736 (C=O), 1707 (C=O), 1613 (C=O), 1513, 1387, 1302, 1248, 1064, 844 cm^{-1}; ^{1}H NMR (360

MHz, CDCl₃) δ 7.19 (2H, d, J = 8.7 Hz, ArH), 6.76 (2H, d, J = 8.7 Hz, ArH), 5.01 (1H, d, J = 14.9 Hz, CH$_A$H$_B$Ar), 4.64 (1H, d, J = 14.9 Hz, CH$_A$H$_B$Ar), 4.28-4.19 (1H, m, CO₂CH$_C$H$_D$CH₃), 4.14-4.06 (1H, m, CO₂CH$_C$H$_D$CH₃), 3.75 (3H, s, OCH₃), 3.68-3.59 (2H, m, CO₂CH₂CH₃), 2.80 (1H, d, J = 16.5 Hz, CH$_A$H$_B$C=O), 2.61 (1H, d, J = 16.5 Hz, CH$_A$H$_B$C=O), 1.57 (3H, s, COHCH₃), 1.27 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 1.07 (3H, t, J = 7.1 Hz, CO₂CH₂CH₃), 0.12 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.2 (C), 167.3 (C), 166.1 (C), 158.7 (C), 130.3 (2 x CH), 128.6 (C), 113.2 (2 x CH), 80.7 (C), 79.4 (C), 61.8 (CH₂), 61.4 (CH₂), 55.2 (CH₃), 45.7 (CH₂), 44.9 (CH₂), 23.5 (CH₃), 13.9 (CH₃), 13.6 (CH₃), 1.9 (3 x CH₃); HRMS (ES) Exact mass calcd for C₂₂H₃₃NO₇SiNa [M+Na]⁺: 474.1918, found: 474.1916.

(2*RS*,3*SR*)-2-Formyl-1-(4-methoxy-phenyl)-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylic acid ethyl ester (144)
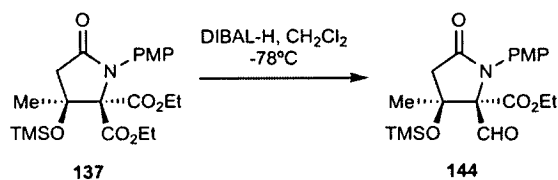
To a stirred solution of lactam **137** (3.53 g, 9.00 mmol) in CH₂Cl₂ (36 mL) at -78 °C, was added DIBAL–H (36 mL, 1 M in CH₂Cl₂, 36 mmol) dropwise over 40 min. The reaction was stirred for 1.5 h at −78 °C and then quenched with EtOH (3 mL), added dropwise. The mixture was stirred for 15 min and then it was poured into a solution of saturated Rochelle's salt (70 mL) and CH₂Cl₂ (70 mL). The resulting solution was stirred for 1 h. The aqueous phase was then extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 40% EtOAc/petrol) gave *aldehyde* **144** (2.16 g, 69%) as a yellow solid. R$_f$ (40% EtOAc in hexane) = 0.65; m.p. 69-72 °C; IR (film) 2959, 1754 (C=O), 1719 (C=O), 1643 (C=O), 1512, 1351, 1250, 1028, 844 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 10.01 (1H, s, CHO), 7.11 (2H, d, J = 9.0 Hz, ArH), 6.81 (2H, d, J = 9.0 Hz, ArH), 4.23 (2H, m, CO₂CH₂CH₃), 3.74 (3H, s, OCH₃), 2.77 (1H, d, J = 16.4 Hz, COCH$_A$H$_B$), 2.65 (1H, d, J = 16.4 Hz, COCH$_A$H$_B$), 1.57 (3H, s, COTMSCH₃), 1.19 (3H, t, J = 7.1

Hz, CO$_2$CH$_2$CH$_3$), 0.15 (9H, s, 3 x SiCH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 195.7 (CH), 172.3 (C), 166.8 (C), 157.9 (C), 129.6 (C), 126.9 (2 x CH), 113.6 (2 x CH), 81.9 (C), 80.8 (C), 62.0 (CH$_2$), 55.1 (CH$_3$), 45.3 (CH$_2$), 25.9 (CH$_3$), 13.7 (CH$_3$), 1.5 (3 x CH$_3$); HRMS (ES) Exact mass calcd. for C$_{19}$H$_{28}$NO$_6$Si [M+H]$^+$: 394.1680, found: 394.1678.

Tributyl(cyclohex-2-enyl)stannane (143) [185]
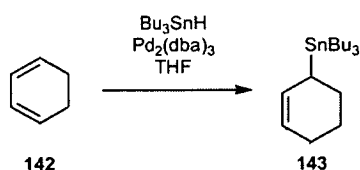
To a stirred solution of Pd$_2$(dba)$_3$ (65.2 mg, 71 μmol) and PPh$_3$ (150 mg, 0.56 mmol) in THF (45 mL), was added 1,3 cyclohexadiene (142) (4.2 mL, 42.7 mmol), followed by the slow addition of Bu$_3$SnH (3.95 mL, 14.2 mmol) at room temperature. The reaction was stirred for 14 h and then the solvent was concentrated *in vacuo*. The catalyst was filtered off through silica plug, obtaining a cloudy colourless oil (4.7 g) that was distilled *in vacuo* to afford 2-cyclohexenyltributyltin 143 (3.2 g, 85% purity assessed by ^{1}H NMR spectroscopy, 52%). R$_f$ (1% Et$_3$N in hexane) = 0.75; ^{1}H NMR (360 MHz, CDCl$_3$) δ 5.76 (1H, dm, J = 9.8 Hz, C**H**=CH), 5.41 (1H, dm, J = 9.8 Hz, CH=C**H**), 2.16 (1H, bs, SnC**H**CH$_2$), 2.09-1.96 (3H, m, CH$_2$CH$_2$CH$_2$), 1.85-1.76 (1H, m, CH$_2$CH$_2$CH$_2$), 1.72-1.63 (1H, m, CH$_2$CH$_2$CH$_2$), 1.60-1.42 (6H + 1H, m, 3 x SnCH$_2$**CH$_2$**CH$_2$CH$_3$ + CH$_2$CH$_2$CH$_2$), 1.31 (6H, m, 3 x SnCH$_2$CH$_2$**CH$_2$**CH$_3$), 0.88 (15H, m, 3 x Sn**CH$_2$**CH$_2$CH$_2$**CH$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ 131.6 (CH), 121.4 (CH), 29.2 (3 x CH$_2$), 27.5 (3 x CH$_2$), 26.8 (CH$_2$), 25.0 (CH$_2$), 23.2 (CH$_2$), 13.7 (3 x CH$_3$), 9.0 (3 x CH$_2$).

^{1}H spectroscopic data in good agreement with the literature.[185]

(2*SR*,3*SR*)-2-[(66*R*)-(7*R*)-Cyclohex-2-enylhydroxymethyl]-1-(4-methoxy-phenyl)-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylic   acid ethyl ester (145)
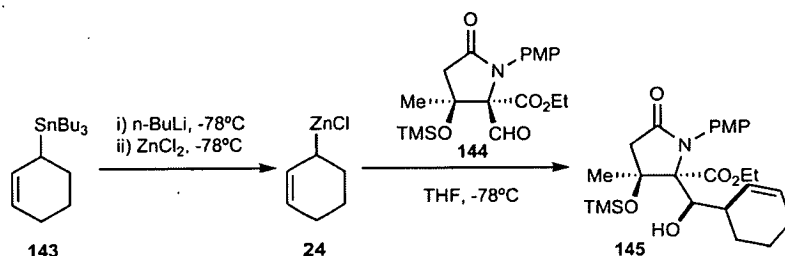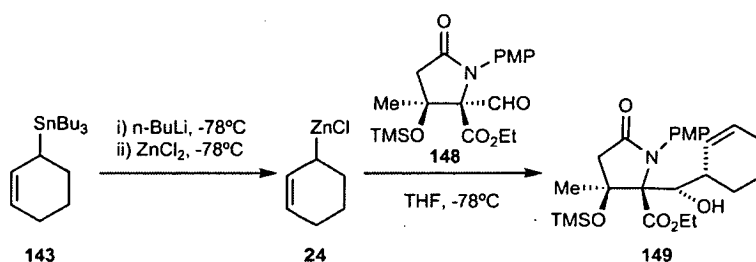

To a stirred solution of cyclohexenyltributyltin **143** (3.40 mL, 6.37 mmol) in THF (12 mL) at −78 °C was added *n*-BuLi (3.10 mL, 2.1 M solution in hexanes, 6.37 mmol). The reaction was stirred for 30 min stirring, $ZnCl_2$ (12.8 mL, 0.5 M solution in THF, 6.37 mmol) was added and stirring was continued for 30 min at −78 °C. To this solution was added a solution of aldehyde **144** (1.01 g, 2.55 mmol) in THF (20 mL) at −78 °C *via* cannula. After stirring for 2.5 h at −78 °C the reaction mixture was quenched with water (20 mL), extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 40% EtOAc/petrol) gave *homoallylic alcohol* **145** (1.1 g, 83%) as a colourless solid. R_f (40% EtOAc in hexane) = 0.69; m.p. 124-126 °C; IR (film) 2953 (OH), 1688 (C=O), 1644 (C=O), 1510, 1375, 1295, 1250, 1148, 1028, 844 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.06 (2H, d, J = 9.0 Hz, ArH), 6.61 (2H, d, J = 9.0 Hz, ArH), 5.28 (1H, dm, J = 10.4 Hz, CH=CH), 4.57 (1H, dm, J = 10.4 Hz, CH=CH), 4.03 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.88 (1H, t, J = 3.9 Hz, CHOH), 3.52 (3H, s, OCH_3), 3.21 (1H, s, J = 3.9 Hz, CHOH), 2.45 (1H, d, J = 16.7 Hz, CH_AH_BC=O), 2.38 (1H, d, J = 16.7 Hz, CH_AH_BC=O), 2.02-1.96 (1H, m, CHOHCH), 1.65-1.53 (2H, m, $CHCH_2CH_2$), 1.36-1.28 (2H, m, $CH_2CH_2CH_2$), 1.25 (3H, s, $COTMSCH_3$), 1.21-1.13 (2H, m, CH_2CH_2), 1.10 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), -0.01 (9H, s, 3 x $SiCH_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.1 (C), 169.0 (C), 156.9 (C), 128.8 (CH), 128.2 (C), 126.2 (CH), 125.4 (2 x CH), 112.1 (2 x CH), 80.9 (C), 79.5 (C), 73.8 (CH), 59.7 (CH_2), 53.3 (CH_3), 43.9 (CH_2), 36.4 (CH), 28.1 (CH_2), 23.4 (CH_3), 22.9 (CH_2), 19.1 (CH_2), 11.9 (CH_3), 0.00 (3 x $SiCH_3$); HRMS (ES) Mass calcd. for $C_{25}H_{38}NO_6Si$ [M+H]$^+$: 476.2463, found: 476.2466.

### (2*RS*,3*SR*)-2-(Hydroxymethyl)-1-(4-methoxyphenyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (147)
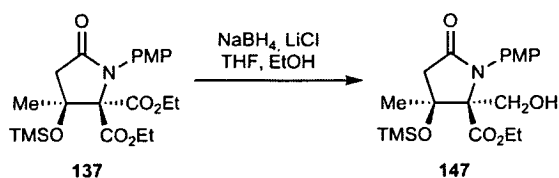
To a stirred solution of diester **137** (106 mg, 0.242 mmol) in THF (1 mL) at 0 °C was added anhydrous lithium chloride (57.3 mg, 1.33 mmol) and sodium borohydride (51.4 mg, 1.33 mmol), followed by the addition of EtOH (2 mL).The reaction was stirred for 14 h at room temperature, then quenched with saturated aqueous NH_4Cl solution (1 mL) and the THF removed *in vacuo*. The solution was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (50 % EtOAc/petrol) gave *alcohol* **147** (86.2 mg, 90%) as a colourless solid. R_f (50% EtOAc in hexane) = 0.56; m.p; 143-144 °C; IR (film) 3389 (OH), 2958, 1756 (C=O), 1685 (C=O), 1511, 1392, 1250, 1102, 1047, 916 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.08 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.89 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.29 (2H, q, *J* = 7.1 Hz, $CO_2C\textbf{H}_2CH_3$), 3.96 (1H, d, *J* = 11.6 Hz, $C\textbf{H}_AC\textbf{H}_BOH$), 3.79 (4H, s + d, *J* = 11.6 Hz, $OC\textbf{H}_3$ + $CH_AC\textbf{H}_BOH$), 3.04 (1H, d, *J* = 16.1 Hz, $C\textbf{H}_CH_DC=O$), 2.56 (1H, d, *J* = 16.1 Hz, $CH_C\textbf{H}_DC=O$), 1.36 (3H, s, $COTMSC\textbf{H}_3$), 1.36 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\textbf{H}_3$), 0.16 (9H, s, 3 x $SiC\textbf{H}_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.3 (C), 169.5 (C), 157.2 (C), 127.3 (2 x CH), 126.7 (C), 112.5 (2 x CH), 76.6 (C), 75.2 (C), 60.3 (CH_2), 59,7 (CH_2), 53.4 (CH_3), 44.9 (CH_2), 22.8 (CH_3), 12.3 (CH_3), 0.0 (3 x CH_3); HRMS (ES) Mass calcd. for $C_{19}H_{30}NO_6Si$ $[M+H]^+$: 396.1837, found: 396.1837.

### (2*SR*,3*SR*)-2-Formyl-1-(4-methoxy-phenyl)-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylic acid ethyl ester (148)
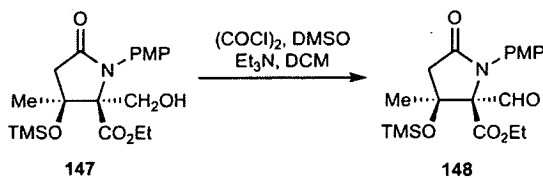
To a stirred solution of oxalyl chloride (0.047 mL, 0.52 mmol) in CH$_2$Cl$_2$ (2 mL) at −78 °C was added DMSO (0.075 mL, 1.1 mmol) dropwise over 1 min. After stirring for 15 minutes a solution of alcohol **147** (99.0 mg, 0.25 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added *via* cannula. This reaction was stirred at −78 °C for 1 h and Et$_3$N (0.15 mL, 1.1 mmol) was then added. The reaction was stirred at −78 °C for 2 h and then was quenched with saturated aqueous NH$_4$Cl solution (3 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 10 mL), and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30 % EtOAc/petrol) gave *aldehyde* **148** (88 mg, 90%) as a yellow oil. R$_f$ (40% EtOAc in hexane) = 0.54; IR (film) 3418, 2959, 1722 (C=O), 1644 (C=O), 1512, 1351, 1249, 1159,1024, 844 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 10.18 (1H, s, CHO), 7.12 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.84 (2H, d, *J* = 9.1 Hz, Ar**H**), 4.31-4.23 (2H, m, CO$_2$C**H$_2$**CH$_3$), 3.79 (3H, s, OC**H$_3$**), 2.94 (1H, d, *J* = 16.4 Hz, C**H$_A$**H$_B$C=O), 2.60 (1H, d, *J* = 16.4 Hz, CH$_A$**H$_B$**C=O), 1.52 (3H, s, COTMSC**H$_3$**), 1.26 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C**H$_3$**), 0.19 (9H, s, 3 x SiC**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ 195.3 (CH), 171.0 (C), 165.5 (C), 156.3 (C), 128.2 (C), 125.6 (2 x CH), 112.1 (2 x CH), 82.8 (C), 78.2 (C), 60.4 (CH$_2$), 53.5 (CH$_3$), 43.7 (CH$_2$), 23.5 (CH$_3$), 12.2 (CH$_3$), 0.0 (3 x CH$_3$); HRMS (ES) Mass calcd. for C$_{19}$H$_{28}$NO$_6$Si [M+H]$^+$: 394.1680, found: 394.1682.

(2*RS*,3*SR*)-2-[(6*S*)-(7*S*)-Cyclohex-2-enylhydroxymethyl]-1-(4-methoxy-phenyl)-3-methyl-5-oxo-3-trimethylsilanyloxy-pyrrolidine-2-carboxylic acid ethyl ester (149)

To a stirred solution of cyclohexenyltributyltin **143** (1.30 g, 3.35 mmol) in THF (7 mL) at −78 °C was added *n*-BuLi (1.3 mL, 2.5 M solution in hexanes, 3.2 mmol). The reaction was stirred for 30 min, ZnCl$_2$ (6.70 mL, 0.5 M solution in THF, 3.35 mmol) was added and stirring was continued for 30 min at −78 °C. To this solution

was added a −78 °C solution of the aldehyde **148** (0.53 g, 1.34 mmol) in THF (6 mL) *via* cannula. After stirring for 2.5 h at −78 °C the reaction mixture was quenched with water (20 mL), extracted with Et$_2$O (3 x 30 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30% to 40% EtOAc/petrol) gave *homoallylic alcohol* **149** (543 mg, 84%) as a colourless solid. R$_f$ (40% EtOAc in hexane) = 0.16; m.p. 175-177 °C; IR (film) 3406 (OH), 2932, 1755 (C=O), 1683 (C=O), 1509, 1456, 1382, 1250, 1137, 841 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.53 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.87 (2H, d, *J* = 9.0 Hz, Ar**H**), 5.79 (1H, dm, *J* = 10.2 Hz, C**H**=CH), 5.35 (1H, dm, *J* = 10.2 Hz, CH=C**H**), 4.25-4.13 (2H, m, CO$_2$C**H$_2$**CH$_3$), 4.01 (1H, t, *J* = 5.7 Hz, C**H**OH), 3.80 (3H, s, OC**H$_3$**), 2.84 (1H, d, *J* = 16.5 Hz, C**H$_A$**H$_B$C=O), 2.67 (1H, d, *J* = 16.5, CH$_A$**H$_B$**C=O), 2.25-2.19 (1H, bs, C**H**OHCH), 1.94-1.84 (3H, bs, C**H**C**H$_2$**CH$_2$), 1.70 (3H, s, COTMSC**H$_3$**), 1.63-1.59 (2H, m, CH$_2$C**H$_2$**CH$_2$), 1.55-1.47 (1H, m, C**H$_2$**CH$_2$), 1.34 (3H, t, *J* = 7.2 Hz, CO$_2$CH$_2$C**H$_3$**), 0.16 (9H, s, 3 x SiC**H$_3$**); ^{13}C NMR (90 MHz, CDCl$_3$) δ 172.2 (C), 167.4 (C), 156.8 (C), 130.1 (CH), 128.9 (C), 128.5 (CH), 124.8 (2 x CH), 111.5 (2 x CH), 81.9 (C), 78.7 (C), 73.9 (CH), 58.7 (CH$_2$), 53.3 (CH$_3$), 44.4 (CH$_2$), 36.5 (CH), 24.8 (CH$_2$), 22.9 (CH$_2$), 22.2 (CH$_3$), 18.3 (CH$_2$), 11.9 (CH$_3$), 0.0 (3 x CH$_3$); LRMS (ES) Mass calcd. for C$_{25}$H$_{38}$NO$_6$Si [M+H]$^+$: 476.2463, found: 476.2465.

(2*RS*,3*SR*)-2-(Hydroxymethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (503)
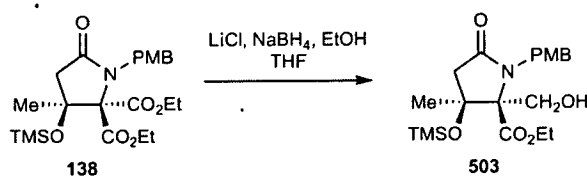
To a stirred solution of diester **138** (6.16 g, 13.6 mmol) in THF (38 mL) at 0 °C, was added anhydrous lithium chloride (1.20 g, 27.3 mmol) and sodium borohydride (1.03 g, 27.3 mmol), followed by the addition of EtOH (76 mL). The reaction was stirred for 14 h at room temperature, then quenched with saturated aqueous NH$_4$Cl solution (40 mL) and the THF removed *in vacuo*. The solution was extracted with CH$_2$Cl$_2$ (3 x 50 mL) and the combined organic layers were dried (MgSO$_4$), filtered

and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave *alcohol* **503** (3.82 g, 68%) as a colourless solid. R_f (40% EtOAc in hexane) = 0.20; m.p. 112-114 °C; IR (film) 3453 (OH), 2957, 2348, 1734 (C=O), 1678 (C=O), 1513, 1248, 1176, 1034, 841 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.29 (2H, d, J = 8.9 Hz, ArH), 6.80 (2H, d, J = 8.9 Hz, ArH), 4.73 (1H, d, J = 15.0 Hz, CH$_A$H$_B$OH), 4.38 (1H, d, J = 15.0 Hz, CH$_A$H$_B$OH), 4.12-4.02 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 3.96-3.88 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 3.87 (1H, d, J = 12.5 Hz, CH$_E$H$_F$Ar), 3.77 (3H, s, OCH$_3$), 3.72 (1H, d, J = 12.5 Hz, CH$_E$H$_F$Ar), 2.76 (1H, d, J = 16.2 Hz, CH$_A$H$_B$C=O), 2.47 (1H, d, J = 16.2 Hz, CH$_A$H$_B$C=O), 2.25 (1H, bs, OH), 1.47 (3H, s, COTMSCH$_3$), 1.19 (3H, td, J = 7.1, 2.6 Hz, CO$_2$CH$_2$CH$_3$), 0.09 (9H, s, Si(CH$_3$)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 174.2 (C), 170.4 (C), 158.9 (C), 129.8 (C), 129.7 (2 x CH), 114.0 (C), 113.8 (2 x CH), 78.2 (C), 62.1 (CH$_2$), 61.3 (CH$_2$), 55.2 (CH$_3$), 46.6 (CH$_2$), 44.1 (CH$_2$), 24.3 (CH$_3$), 14.0 (CH$_3$), 1.8 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{20}$H$_{32}$NO$_6$Si [M+H]$^+$: 410.1993, found: 410.1994.

(2*SR*,3*SR*)-2-Formyl-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (150)
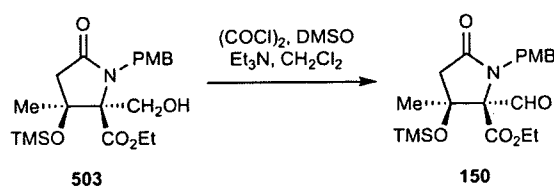
To a stirred solution of oxalyl chloride (0.74 mL, 8.46 mmol) in CH$_2$Cl$_2$ (40 mL) at −78 °C was added DMSO (1.20 mL, 16.9 mmol) dropwise over 1 min and this solution was stirred for 15 min. A solution of alcohol **503** (1.65 g, 4.03 mmol) in CH$_2$Cl$_2$ (40 mL) at −78 °C, was treated with Et$_3$N (2.40 mL, 16.9 mmol), followed by the addition of the Swern reagent *via* cannula. The reaction was stirred at −78 °C for 3 h and then quenched with NH$_4$Cl (30 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 20 mL) and the combined organic layers were washed with saturated aqueous NaHCO$_3$ solution (2 x 30 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave *aldehyde* **150** (1.28 g, 78%) as a yellow oil. R_f (30% EtOAc in hexane) = 0.45; IR (film) 2957, 1756 (C=O), 1724 (C=O), 1612 (C=O), 1513, 1378,

1282, 1250, 1025, 845 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 9.91 (1H, s, CHO), 7.09 (2H, d, J = 8.6 Hz, ArH), 6.75 (2H, d, J = 8.6 Hz, ArH), 4.89 (1H, d, J = 14.4 Hz, CH$_A$H$_B$Ar), 4.34 (1H, d, J = 14.4 Hz, CH$_A$H$_B$Ar), 3.96-3.87 (1H, m, CO$_2$CH$_A$H$_B$CH$_3$), 3.82-3.75 (1H, m, CO$_2$CH$_A$H$_B$CH$_3$), 3.74 (3H, s, OCH$_3$), 2.89 (1H, d, J = 16.0 Hz, CH$_A$H$_B$C=O), 2.41 (1H, d, J = 16.2 Hz, CH$_A$H$_B$C=O), 1.35 (3H, s, COTMSCH$_3$), 1.11 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 0.10 (9H, s, Si(CH$_3$)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 196.6 (CH), 172.6 (C), 167.0 (C), 158.4 (C), 130.5 (2 x CH), 126.9 (C), 112.9 (2 x CH), 80.5 (C), 78.9 (C), 61.2 (CH$_2$), 54.6 (CH$_3$), 45.3 (CH$_2$), 43.9 (CH$_2$), 25.1 (CH$_3$), 13.3 (CH$_3$), 1.2 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{20}$H$_{30}$NO$_6$Si [M+H]$^+$: 408.1837, found: 408.1836.

(2RS,3SR)-2-[(6S)-(7S)-Cyclohex-2-enylhydroxymethyl]-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (151)
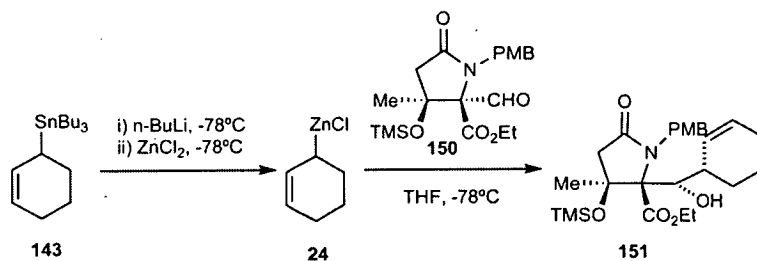
To a stirred solution of cyclohexenyltributyltin **143** (2.78 g, 6.44 mmol, 85%) in THF (5 mL) at −78 °C was added *n*-BuLi (2.50 mL, 2.5 M solution in hexanes, 6.31 mmol). The reaction was stirred for 30 min, ZnCl$_2$ (12.8 mL, 0.5 M solution in THF, 6.44 mmol) was added and stirring was continued for 30 min at −78 °C. To this solution was added a −78 °C solution of aldehyde **150** (1.05 g, 2.57 mmol) in THF (6 mL) *via* cannula. After stirring for 1.5 h at −78°C the reaction mixture was quenched with water (15 mL), extracted with Et$_2$O (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 30% EtOAc/petrol) gave *homoallylic alcohol* **151** (892 mg, 71%) as a colourless solid. R$_f$ (40% EtOAc in hexane) = 0.31; m.p. 169-171 °C; IR (film) 3429 (OH), 2923, 2666, 1748 (C=O), 1681 (C=O), 1513, 1442, 1247, 1034, 841 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.29 (2H, d, J = 8.8 Hz, ArH), 6.81 (2H, d, J = 8.8 Hz, ArH), 5.95 (1H, dm, J = 10.4 Hz, CH=CH), 5.69 (1H, dm, J = 10.4 Hz, CH=CH), 4.82 (1H, d, J = 15.2 Hz, CH$_A$H$_B$Ar), 4.47 (1H, d, J =

15.2 Hz, CH$_A$H$_B$Ar), 4.11-4.05 (2H, m, CO$_2$CH$_2$CH$_3$ + CHOH), 3.78 (3H, s, OCH$_3$), 2.85 (1H, d, J = 16.6 Hz, CH$_A$H$_B$C=O), 2.45 (1H, bs, CHOH), 2.39 (1H, d, J = 16.6 Hz, CH$_A$H$_B$C=O), 2.32-2.26 (1H, m, CHOHCH), 2.03-1.98 (2H, m, CHCH$_2$CH$_2$), 1.75-1.68 (3H + 2H, m, COTMSCH$_3$ + CH$_2$CH$_2$CH$_2$), 1.57-1.44 (2H, m, CH$_2$CH$_2$), 1.11 (3H, t, J = 7.0 Hz, CO$_2$CH$_2$CH$_3$), 0.16 (9H, s, Si(CH$_3$)$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 175.1 (C), 168.9 (C), 157.9 (C), 133.7 (CH), 130.6 (C), 127.6 (2 x CH), 124.4 (CH), 113.2 (2 x CH), 82.8 (C), 82.0 (C), 76.5 (CH), 60.9 (CH$_2$), 55.2 (CH$_3$), 47.5 (CH$_2$), 46.7 (CH$_2$), 38.0 (CH), 29.0 (CH$_2$), 25.0 (CH$_2$), 22.6 (CH$_3$), 20.5 (CH$_2$), 13.7 (CH$_3$), 2.1 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{26}$H$_{40}$NO$_6$Si [M+H]$^+$: 490.2619, found: 490.2616.

(2*RS*,3*SR*)-2-[(6*S*)-(7*S*)-Cyclohex-2-enylhydroxymethyl]-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid ethyl ester (156)
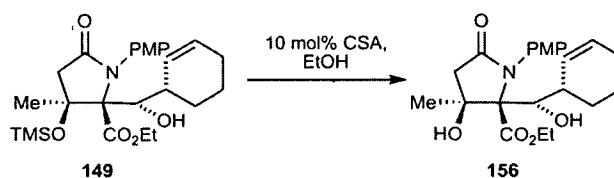
To a stirred solution of alcohol **149** (2.00 g, 4.80 mmol) in EtOH (10 mL) was added camphor sulfonic acid (245 mg, 1.03 mmol) at room temperature. This solution was stirred for 3 h and then quenched with Et$_3$N (0.14 mL, 1.04 mmol). The solution was concentrated *in vacuo*. Purification of the residue by column chromatography (60% to 80% EtOAc/petrol) gave *diol* **156** (1.92 g, 95%) as a colourless solid. R$_f$ (50% EtOAc in hexane) = 0.16; m.p. 184-186 °C; IR (film) 3393 (OH), 2933, 2359, 2341, 1753 (C=O), 1682 (C=O), 1509, 1372, 1249, 1030 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.57 (2H, d, J = 9.0 Hz, ArH), 6.86 (2H, d, J = 9.0 Hz, ArH), 5.77 (1H, dm, J = 10.3 Hz, CH=CH), 5.41 (1H, dm, J = 10.4 Hz, CH=CH), 4.41-4.28 (1H, m, CO$_2$CH$_A$H$_B$CH$_3$), 4.24-4.12 (2H, m, CO$_2$CH$_A$H$_B$CH$_3$), 4.12-4.06 (1H, m, CHOH), 3.81 (3H, s, OCH$_3$), 2.95 (1H, d, J = 16.8 Hz, CH$_C$H$_D$C=O), 2.93 (1H, s, CHOH), 2.55 (1H, d, J = 16.8 Hz, CH$_C$H$_D$C=O), 2.26-2.14 (2H, m, CHCH$_2$CH$_2$), 1.91-1.82 (2H, m, CHCH$_2$CH$_2$), 1.65 (3H, s, COHCH$_3$), 1.52-1.43 (1H, m, CHOHCH), 1.39 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 1.19-1.07 (2H, m, CHCH$_2$CH$_2$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 175.9 (C), 170.0 (C), 158.8 (C), 131.5

(2 x CH), 130.9 (CH), 130.6 (C), 126.2 (CH), 113.6 (2 x CH), 82.9 (C), 77.5 (C), 75.9 (CH), 61.4 (CH_2), 55.3 (CH_3), 46.6 (CH_2), 38.3 (CH), 26.9 (CH_2), 25.3 (CH_2), 23.2 (CH_3), 20.7 (CH_2), 14.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{30}NO_6$ [M+H]$^+$: 404.2068, found: 404.2063.

(2RS,3SR)-2-{(6S)-Acetoxy-[(7S)-cyclohex-2-enyl]methyl}-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (158)
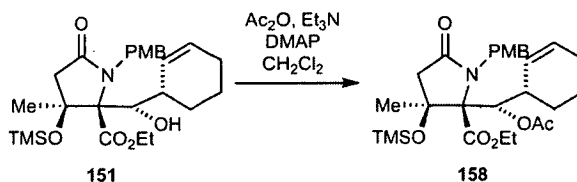
To a stirred solution of alcohol **151** (100 mg, 0.2 mmol) and DMAP (20.0 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C, was added Et_3N (0.14 mL, 1.02 mmol) dropwise, followed by the addition of Ac_2O (0.058 mL, 0.61 mmol) *via* syringe. The reaction was stirred for 14 h and then quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave *acetate protected homoallylic alcohol* **158** (96 mg, 90%) as a pale yellow solid. R_f (50% EtOAc in hexane) = 0.63; m.p. 146-148 °C; IR (film) 2938, 1748 (C=O), 1708 (C=O), 1613 (C=O), 1513, 1247, 1221, 1175, 1032, 842 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.31 (2H, d, J = 8.6 Hz, ArH), 6.81 (2H, d, J = 8.6 Hz, ArH), 5.76 (1H, dm, J = 10.4 Hz, CH=CH), 5.43 (1H, dm, J = 10.4 Hz, CH=CH), 5.36 (1H, d, J = 3.8 Hz, CHOAc), 4.79 (1H, d, J = 15.3 Hz, CH$_A$H$_B$Ar), 4.56 (1H, d, J = 15.3 Hz, CH$_A$H$_B$Ar), 4.19-4.10 (2H, m, $CO_2CH_2CH_3$), 3.78 (3H, s, OCH_3), 2.53-2.47 (1H, m, CHOHCH), 2.47 (1H, d, J = 16.8 Hz, CH$_C$H$_D$C=O), 2.41 (1H, d, J = 16.8 Hz, CH$_C$H$_D$C=O), 2.05 (3H, s, C=OCH$_3$), 1.99-1.92 (2H, m, CHCH$_2$CH$_2$), 1.80-1.72 (2H + 1H, m, CH$_2$CH$_2$CH$_2$), 1.57 (3H, s, COTMSCH$_3$), 1.52-1.39 (1H, m, CH$_2$CH$_2$), 1.18 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$), 0.16 (9H, s, Si(CH$_3$)$_3$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.9 (C), 169.5 (C), 167.9 (C), 157.9 (C), 130.4 (C), 130.1 (CH), 127.7 (2 x CH), 124.4 (CH), 113.2 (2 x CH), 82.0 (C), 81.1 (C), 77.1 (CH), 61.4 (CH_2),

55.2 (CH$_3$), 47.6 (CH$_2$), 46.2 (CH$_2$), 37.8 (CH), 29.4 (CH$_2$), 24.5 (CH$_2$), 22.6 (CH$_3$), 21.4 (CH$_2$), 21.1 (CH$_3$), 13.8 (CH$_3$), 2.0 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{28}$H$_{42}$NO$_7$Si [M+H]$^+$: 532.2725, found: 532.2721.

(2*RS*,3*SR*)-2-{(6*S*)-Acetoxy-[(7*S*)-cyclohex-2-enyl]methyl}-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid ethyl ester (159)
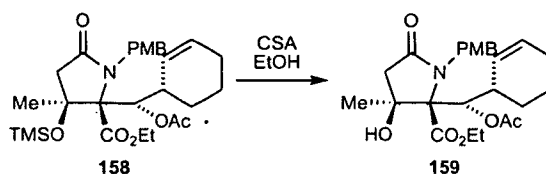
To a stirred solution of the lactam **158** (253 mg, 0.48 mmol) in EtOH (5 mL) was added camphor sulfonic acid (220 mg, 0.95 mmol). The reaction was stirred for 30 min and it was then quenched with Et$_3$N (0.13 mL, 0.95 mmol). The solvent was concentrated *in vacuo* and purification of the residue by column chromatography (80% EtOAc/petrol) gave *β-hydroxy-γ-lactam* **159** (195 mg, 91%) as a colourless solid. R$_f$ (50% EtOAc in hexane) = 0.22; m.p. 182-184 °C; IR (film) 3468 (OH), 2922, 1748 (C=O), 1703 (C=O), 1687 (C=O), 1513, 1220, 1032, 522 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.36 (2H, d, *J* = 8.5 Hz, ArH), 6.84 (2H, d, *J* = 8.5 Hz, ArH), 5.74 (1H, dm, *J* = 10.3 Hz, CH=CH), 5.38-5.31 (2H, m, CH=CH + CHOAc), 4.77 (1H, d, *J* = 15.1 Hz, CH$_A$H$_B$Ar), 4.57 (1H, d, *J* = 15.1 Hz, CH$_A$H$_B$Ar), 4.32-4.29 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 4.21-4.11 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 3.78 (3H, s, OCH$_3$), 2.69 (1H, bs, OH) 2.53-2.48 (1H, m, CHOHCH), 2.47 (1H, d, *J* = 17.2 Hz, CH$_E$H$_F$C=O), 2.39 (1H, d, *J* = 17.2 Hz, CH$_E$H$_F$C=O), 2.07 (3H, s, C=OCH$_3$), 1.99-1.92 (2H, m, CHCH$_2$CH$_2$), 1.79-1.69 (2H + 1H, m, CH$_2$CH$_2$CH$_2$), 1.49 (3H, s, COTMSCH$_3$), 1.49-1.41 (1H, m, CH$_2$CH$_2$), 1.23 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$CH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.2 (C), 169.4 (C), 168.2 (C), 158.2 (C), 130.2 (CH), 130.1 (C), 128.3 (2 x CH), 128.2 (C), 124.3 (CH), 113.4 (2 x CH), 80.9 (C), 77.1 (CH), 61.8 (CH$_2$), 55.2 (CH$_3$), 47.6 (CH$_2$), 46.1 (CH$_2$), 37.7 (CH), 29.1 (CH$_2$), 24.5 (CH$_2$), 22.1 (CH$_3$), 21.2 (CH$_2$), 21.1 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{34}$NO$_7$ [M+H]$^+$: 460.2330, found: 460.2329.

(2*RS*,3*SR*)-2-[(1*S*)-Hydroxy-2-methylallyl]-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (164)
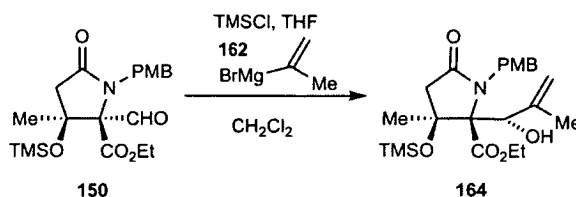

To a stirred solution of aldehyde **150** (1.26 mg, 3.10 mmol), in THF (150 mL) at -78 °C was added TMSCl (2.0 mL, 15.5 mmol), followed by the addition of isopropenylmagnesium bromide (18.6 mL, 0.5 M solution in THF, 9.31 mmol) *via* syringe. The reaction was stirred at −78 °C for 3 h and then slowly quenched with saturated aqueous NH_4Cl solution (30 mL). After warming up to room temperature and stirring for 30 min, the aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with water (1 x 30 mL), saturated NaCl aqueous solution (1x 30 mL) and then were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/petrol) gave *alcohol* **164** (1.06 g, 76%) as a colourless solid. R_f (40% EtOAc in hexane) = 0.14; m.p. 171-173 °C; IR (film) 3318 (OH), 2957, 2359, 1751 (C=O), 1680 (C=O), 1513, 1246, 1174, 1034, 841 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.21 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.78 (2H, d, *J* = 8.8 Hz, Ar**H**), 5.24 (1H, s, C**H**OH), 5.24 (1H, s, C=C**H**$_A$H$_B$), 5.08 (1H, s, C=CH$_A$**H**$_B$), 4.63 (1H, d, *J* = 15.7 Hz, C**H**$_A$H$_B$Ar), 4.31 (1H, d, *J* = 15.7 Hz, CH$_A$**H**$_B$Ar), 4.14-4.00 (2H, m, CO$_2$C**H**$_2$CH$_3$), 3.77 (3H, s, OC**H**$_3$), 2.91 (1H, d, *J* = 16.6 Hz, C**H**$_A$H$_B$C=O), 2.40 (1H, d, *J* = 16.5 Hz, CH$_A$**H**$_B$ C=O), 2.23 (1H, bs, C**H**O**H**), 1.81 (3H, s, CC**H**$_3$), 1.76 (3H, s, COTMSC**H**$_3$), 1.12-1.06 (3H, m, CO$_2$CH$_2$C**H**$_3$), 0.16 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.9 (C), 168.7 (C), 157.8 (C), 144.5 (C), 131.1 (C), 127.5 (2 x CH), 115.1 (CH$_2$), 113.1 (2 x CH), 82.1 (C), 82.0 (C), 75.7 (CH), 61.0 (CH$_2$), 55.2 (CH$_3$), 48.5 (CH$_2$), 46.8 (CH$_2$), 22.3 (CH$_3$), 21.2 (CH$_3$), 13.6 (CH$_3$), 2.1 (3 x CH$_3$); HRMS (ES) Exact mass calcd for $C_{23}H_{36}NO_6Si$ [M+H]$^+$: 450.2306, found: 450.2310.

(2*RS*,3*SR*)-2-[(1*S*)-Hydroxy-2-methylallyl]-1-(4-methoxybenzyl)-3-methyl-5-oxo-3-(trimethylsilyloxy)pyrrolidine-2-carboxylic acid ethyl ester (165)
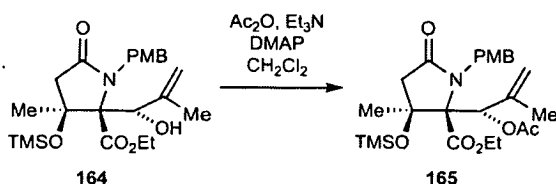
To a stirred solution of alcohol **164** (1.32 g, 2.92 mmol) and DMAP (71 mg, 0.58 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added pyridine (0.83 mL, 10.2 mmol) dropwise, followed by Ac_2O (1.70 mL, 17.6 mmol) *via* syringe. The reaction was stirred for 14 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petrol) gave *acetate protected allylic alcohol* **165** (1.32 g, 92%) as a pale yellow oil. R_f (40% EtOAc in hexane) = 0.38; IR (film) 2957, 2359, 1749 (C=O), 1707 (C=O), 1614 (C=O), 1513, 1247, 1222, 1175, 1033, 912 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.23 (2H, d, *J* = 8.8 Hz, ArH), 6.79 (2H, d, *J* = 8.8 Hz, ArH), 5.65 (1H, s, CHOAc), 5.09 (2H, s, C=CH$_2$), 4.68 (1H, d, *J* = 15.7 Hz, CH$_A$H$_B$Ar), 4.42 (1H, d, *J* = 15.7 Hz, CH$_A$H$_B$Ar), 4.22-4.01 (2H, m, CO$_2$CH$_2$CH$_3$), 3.77 (3H, s, OCH$_3$), 2.68 (1H, d, *J* = 16.7 Hz, CH$_C$H$_D$C=O), 2.49 (1H, d, *J* = 16.7 Hz, CH$_C$H$_D$C=O), 2.13 (3H, s, C=OCH$_3$), 1.77 (3H, s, CH$_3$COTMS), 1.60 (3H, s, CCH$_3$), 1.14 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 0.18 (9H, s, Si(CH$_3$)$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 179.9 (C), 168.8 (C), 167.6 (C), 157.8 (C), 139.8 (C), 130.6 (C), 127.4 (2 x CH), 116.1 (CH$_2$), 113.1 (2 x CH), 81.4 (C), 81.1 (C), 77.2 (CH), 61.4 (CH$_2$), 55.1 (CH$_3$), 48.6 (CH$_2$), 46.4 (CH$_2$), 22.1 (CH$_3$), 21.2 (CH$_3$), 20.9 (CH$_3$), 13.6 (CH$_3$), 2.0 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{38}$NO$_7$Si [M+H]$^+$: 492.2412, found: 492.2407.

(2*RS*,3*SR*)-2-[(1*S*)-Hydroxy-2-methylallyl]-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid ethyl ester (166)
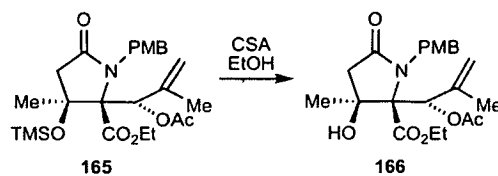

To a stirred solution of **165** (710 mg, 1.43 mmol) in EtOH (10 mL) was added camphor sulfonic acid (1.30 g, 5.70 mmol). The reaction was stirred for 14 h and then quenched with Et$_3$N (0.80 mL, 5.70 mmol) and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were concentrated *in vacuo* and purification of the residue by column chromatography (50% EtOAc/petrol) gave *β-hydroxy-γ-lactam* **166** (536 mg, 83%) as a colourless solid. R$_f$ (50% EtOAc in hexane) = 0.22; m.p. 194-196 °C; IR (film) 3386 (OH), 2922, 2663, 2347, 1749 (C=O), 1711 (C=O), 1682 (C=O), 1224, 1032 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.28 (2H, d, *J* = 8.7 Hz, ArH), 6.81 (2H, d, *J* = 8.7 Hz, ArH), 5.65 (1H, s, CHOAc), 5.08 (2H, s, C=CH$_2$), 4.67 (1H, d, *J* = 15.4 Hz, CH$_A$H$_B$Ar), 4.38 (1H, d, *J* = 15.4 Hz, CH$_A$**H$_B$**Ar), 4.28-4.19 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 4.15-4.06 (1H, m, CO$_2$CH$_C$**H$_D$**CH$_3$), 3.76 (3H, s, OCH$_3$), 2.64 (1H, d, *J* = 17.1 Hz, CH$_E$H$_F$C=O), 2.38 (1H, d, *J* = 17.1 Hz, CH$_E$**H$_F$**C=O), 2.14 (3H, s, C=OCH$_3$), 1.78 (3H, s, CCH$_3$), 1.49 (3H, s, CH$_3$COH), 1.17 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$CH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.1 (C), 168.7 (C), 167.9 (C), 158.0 (C), 139.7 (C), 130.5 (C), 127.9 (2 x CH), 116.1 (CH$_2$), 113.3 (2 x CH), 80.0 (C), 77.8 (CH), 77.2 (C), 61.8 (CH$_2$), 55.1 (CH$_3$), 48.6 (CH$_2$), 46.2 (CH$_2$), 21.9 (CH$_3$), 21.1 (CH$_3$), 21.0 (CH$_3$), 13.7 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{22}$H$_{29}$NO$_7$Na [M+Na]$^+$: 442.1836, found: 442.1837.

(2*RS*,3*SR*)-2-[(1*S*)-Acetoxy-2-methylpropyl]-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid ethyl ester (167)
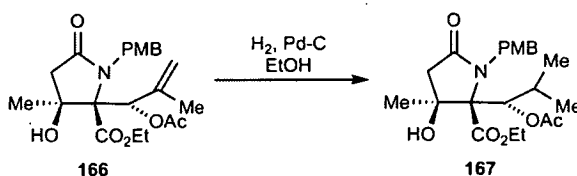
A mixture of alcohol **166** (180 mg, 0.43 mmol) and 10% Pd/C (23.0 mg, 0.22 mmol) in EtOH (4 mL) at room temperature was evacuated and flushed with H$_2$ (3

times) and then stirred vigorously under an atmosphere of H_2 (1 atm, H_2 balloon) at room temperature for 18 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol) gave *alcohol* **167** (91 mg, 50%) as a white powder. R_f (50% EtOAc in hexane) = 0.36; m.p. 182-184 °C; IR (film) 3365 (OH), 2359, 2341, 1749 (C=O), 1702 (C=O), 1682 (C=O), 1512, 1223, 1175, 1025 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.34 (2H, d, J = 8.7 Hz, ArH), 6.83 (2H, d, J = 8.7 Hz, ArH), 5.30 (1H, d, J = 6.5 Hz, CHOAc), 4.74 (1H, d, J = 15.2 Hz, CH$_A$H$_B$Ar), 4.62 (1H, d, J = 15.2 Hz, CH$_A$H$_B$Ar), 4.31-4.21 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 4.18-4.09 (1H, m, CO$_2$CH$_C$H$_D$CH$_3$), 3.77 (3H, s, OCH$_3$), 2.47 (1H, d, J = 17.1 Hz, CH$_E$H$_F$C=O), 2.36 (1H, d, J = 17.1 Hz, CH$_E$H$_F$C=O), 2.11 (3H, s, C=OCH$_3$), 2.04-1.94 (1H, m, CHOHCH), 1.47 (3H, s, CH$_3$COH), 1.23 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$CH$_3$), 1.05 (3H, d, J = 6.7 Hz, CHCH$_3$), 0.76 (3H, d, J = 6.7 Hz, CHCH$_3$); ^{13}C NMR (90 MHz, CDCl$_3$) δ 174.4 (C), 169.9 (C), 168.4 (C), 158.2 (C), 130.1 (C), 128.3 (2 x CH), 113.4 (2 x CH), 80.6 (C), 78.6 (CH), 77.6 (C), 61.7 (CH$_2$), 55.1 (CH$_3$), 47.7 (CH$_2$), 46.1 (CH$_2$), 30.6 (CH), 22.0 (CH$_3$), 21.9 (CH$_3$), 21.0 (CH$_3$), 18.7 (CH$_3$), 13.8 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{22}$H$_{31}$NO$_7$Na [M+Na]$^+$: 444.1993, found: 444.1989.

6.2.2. Reductive aldol cyclisation approach

Methyl 2-[(dimethylphenylsilyl)methyl]-3-oxobutanoate (307)
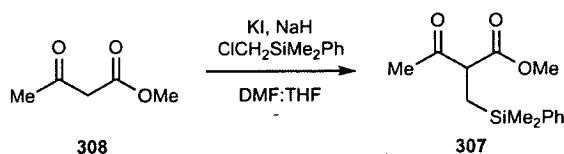
To a suspension of KI (9.90 g, 60.0 mmol) and NaH (6.00 g, 60% dispersion in mineral oil, 150 mmol) in a mixture of DMF:THF (1:1, 200 mL) at room temperature, was added methyl acetoacetate (**308**) (11.5 mL, 100 mmol) dropwise over 25 min. This solution was stirred for 30 min, until the effervescence stopped, when chloromethyl dimethylphenyl silane (22.0 mL, 120 mmol) was added and the solution was heated to reflux for 14 h. The reaction mixture was then diluted with Et$_2$O, washed with 2 M HCl (2 x 50 mL) and with saturated NaCl aqueous solution

(2 x 50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (2% to 6% EtOAc/petrol) gave *alkylated product* **307** (17 g, 65%) as a colourless oil. R_f (40% EtOAc in hexane) = 0.50; IR (film) 3070, 2953, 1744 (C=O), 1717 (C=O), 1428, 1357, 1249, 1113, 836, 701 cm^{-1}; ^{1}H NMR (360 MHz, CDCl₃) δ 7.51-7.45 (2H, m, Ar**H**), 7.39-7.34 (3H, m, Ar**H**), 3.58 (3H, s, CO₂C**H₃**), 3.41 (1H, dd, *J* = 9.1, 6.0 Hz, C**H**CH₂Si), 2.11 (3H, s, C**H₃**C=O), 1.43-1.27 (2H, m, SiC**H₂**), 0.31 (3H, s, C**H₃**Si), 0.30 (3H, s, C**H₃**Si); ^{13}C NMR (62.9 MHz, CDCl₃) δ 203.4 (C), 171.0 (C), 137.5 (C), 133.6 (2 x CH), 129.2 (CH), 127.8 (2 x CH), 55.3 (CH), 52.2 (CH₃), 27.9 (CH₃), 14.5 (CH₂), −2.9 (CH₃), −3.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₄H₂₀O₂SiNa [M+Na]$^+$: 287.1074, found: 287.1077.

Dibenzyl 1-{-2-[(dimethylphenylsilyl)methyl]-1-methoxy-1,3-dioxobutan-2-yl} hydrazine-1,2-dicarboxylate (306)
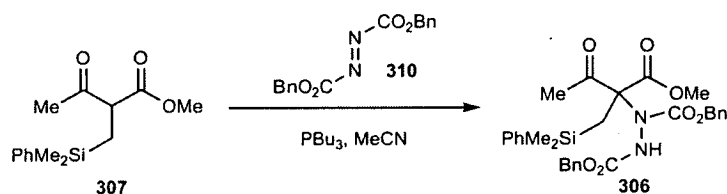
To a stirred solution of β-ketoester **307** (2.28 g, 8.62 mmol) in dry acetonitrile (60 mL) at room temperature was added tributylphosphine (0.12 mL, 1.72 mmol), followed by the addition of dibenzyl azodicarboxylate (3.15 g, 9.48 mmol). The solution was stirred for 30 min and then concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave *addition product* **306** (4.16 g, 86%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.43; IR (film) 3297 (NH), 3033, 1722 (4 x C=O), 1497, 1394, 1338, 1216, 1111, 979, 830 cm^{-1}; ^{1}H NMR (360 MHz, CDCl₃) δ 7.51 (2H, bs, Ar**H**), 7.37 (10H, bs, 2 x Ar**H**), 7.30 (3H, bs, Ar**H**), 6.53 (1H, bs, N**H**), 5.17 (4H, bs, 2 x CO₂C**H₂**Ar), 3.57 (3H, bs, OC**H₃**), 2.38 (3H, s, C**H₃**C=O), 1.66 (2H, bs, SiC**H₂**), 0.35 (3H, bs, C**H₃**Si), 0.31 (3H, bs, C**H₃**Si); ^{13}C NMR (62.9 MHz, CDCl₃) δ 199.7 (C), 169.4 (C), 156.1 (2 x C), 138.8 (2 x C), 135.2 (2 x C), 133.48 (2 x CH), 129.0 (2 x CH), 128.6 (4 x CH), 128.5 (4 x CH), 128.1 (CH), 127.8 (2 x CH), 68.7 (CH₂), 68.1 (CH₂), 52.4 (CH₃), 24.7 (CH₃), 20.6

(CH$_2$), -0.9 (CH$_3$), -2.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{30}$H$_{38}$N$_3$O$_7$Si [M+NH$_4$]$^+$: 580.2474, found: 580.2475.

## Methyl 2-amino-2-[(dimethylphenylsilyl)methyl]-3-hydroxybutanoate (319a and 319b)
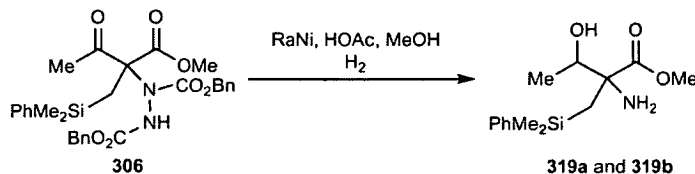
Raney nickel (17 g, suspension in MeOH) was pre-washed with methanol (3 x 10 mL). **306** (2.10 g, 3.72 mmol) was placed in the reaction vessel of the parr hydrogenator and then it was added a suspension of the catalyst in MeOH (100 mL), followed by HOAc (40 drops). The reaction mixture was stirred at 40 °C under hydrogen (45 bar) for 16 h. The reaction mixture was filtered over celite, the solids were washed with EtOAc and the combined organic layers were concentrated in vacuo. Purification of the residue by column chromatography (20% to 30% EtOAc/petrol) afforded the two *aminoalcohols* **319a** (386 mg, 40%) and **319b** (182 mg, 17%) as colourless oils.

Data for **319a**: R$_f$ (40% EtOAc in hexane) = 0.15; IR (film) 3404 (NH + OH), 2359, 2341, 1637 (C=O), 669, 524, 509 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.53-7.50 (2H, m, ArH), 7.38-7.35 (3H, m, ArH), 3.68 (1H, q, J = 6.4 Hz, CH$_3$CHOH), 3.51 (3H, s, CO$_2$CH$_3$), 2.41 (2H, bs, **OH + NH**), 1.52 (1H, d, J = 14.9 Hz, SiCH$_A$H$_B$), 1.41 (1H, d, J = 14.9 Hz, SiCH$_A$H$_B$), 0.97 (3H, d, J = 6.4 Hz, CH$_3$CHOH), 0.33 (3H, s, CH$_3$Si), 0.32 (3H, s, CH$_3$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.3 (C), 138.3 (C), 133.6 (2 x CH), 129.2 (CH), 127.9 (2 x CH), 73.1 (CH), 63.3 (C), 51.9 (CH$_3$), 24.6 (CH$_2$), 18.1 (CH$_3$), −1.8 (CH$_3$), −2.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{14}$H$_{24}$NO$_3$Si [M+H]$^+$: 282.1520, found: 282.1520.

Data for **319b**: R$_f$ (40% EtOAc in hexane) = 0.10; IR (film) 3382 (NH + OH), 1730 (C=O), 1587, 1427, 1249, 1112, 835, 701, 521 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.52-7.48 (2H, m, ArH), 7.37-7.34 (3H, m, ArH), 3.83 (1H, q, J = 6.3 Hz, CH$_3$CHOH), 3.47 (3H, s, CO$_2$CH$_3$), 2.20 (2H, bs, **OH + NH**), 1.33 (1H, d, J = 14.7 Hz, SiCH$_A$H$_B$), 1.14 (3H, d, J = 6.3 Hz, CH$_3$CHOH), 1.13 (1H, d, J = 14.7 Hz,

SiCH$_A$**H$_B$**), 0.33 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.5 (C), 138.3 (C), 133.5 (2 x CH), 129.1 (CH), 127.8 (2 x CH), 73.0 (CH), 63.5 (C), 51.9 (CH$_3$), 23.6 (CH$_2$), 16.6 (CH$_3$), −1.9 (CH$_3$), −2.1 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{14}$H$_{24}$NO$_3$Si [M+H]$^+$: 282.1520, found: 282.1521.

Methyl 2-(4-methoxybenzylamino)-2-[(dimethylphenylsilyl)methyl]-3-hydroxybutanoate (320a and 320b)
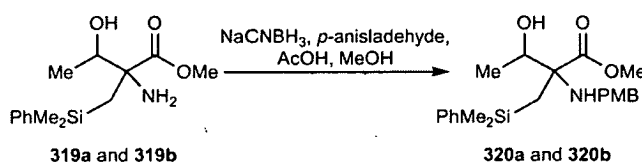
To a solution of a mixture of alcohols **319a** and **319b** (1.27 g, 4.50 mmol) in MeOH (40 mL) at room temperature was added HOAc (0.52 mL, 9.00 mmol), and the reaction flask was placed in a water bath. NaBH$_3$CN (450 mg, 6.77 mmol) was then added, followed by *p*-anisaldehyde (0.70 mL, 5.40 mmol). The reaction was stirred at room temperature for 18 h and it was then quenched with saturated aqueous NaHCO$_3$ solution. The suspension was concentrated *in vacuo*, and the crude mixture was partitioned between H$_2$O and CH$_2$Cl$_2$. The aqueous layer was extracted with CH$_2$Cl$_2$, and the combined organic extracts were dried (Na$_2$SO$_4$), filtered and concentrated. Purification of the residue by column chromatography (10% EtOAc/petrol) gave the mixture of *aminoalcohols* **320a** and **320b** (1.16 g, mixture of both diastereomers, 65%) as a colourless oil.

This reaction was typically performed on a mixture of both diastereomers **319a** and **319b** and it was isolated a mixture of both diastereomers of **320a** and **320b**. Only on one occasion was the reaction performed individually on each diastereomer for characterisation purposes

Data for **320a**: R$_f$ (30% EtOAc in hexane) = 0.48; IR (film) 2950 (NH + OH), 2348, 1727 (C=O), 1612, 1512, 1462, 1247, 1111, 1033, 833 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.56-7.53 (2H, m, ArH), 7.36-7.34 (3H, m, ArH), 7.12 (2H, d, *J* = 8.6 Hz, ArH), 6.84 (2H, d, *J* = 8.6 Hz, ArH), 3.99 (1H, q, *J* = 6.4 Hz, CH$_3$CHOH), 3.81 (3H, s, ArOCH$_3$), 3.58 (3H, s, CO$_2$CH$_3$), 3.55 (1H, d, *J* = 11.6 Hz, NHCH$_A$CH$_B$Ar), 3.46 (1H, d, *J* = 11.6 Hz, NHCH$_A$CH$_B$Ar), 3.23 (1H, bs, NH), 1.92 (1H, bs, OH), 1.57 (1H, d, *J* = 15.2 Hz, SiCH$_A$CH$_B$), 1.33 (1H, d, *J* = 15.2 Hz,

SiCH$_A$CH$_B$), 1.17 (3H, d, J = 6.4 Hz, CH$_3$CH), 0.39 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.9 (C), 158.7 (C), 139.4 (C), 133.6 (2 x CH), 131.9 (C), 129.2 (2 x CH), 128.9 (CH), 127.8 (2 x CH), 113.8 (2 x CH), 70.2 (CH), 68.1 (C), 55.2 (CH$_3$), 51.6 (CH$_3$), 47.1 (CH$_2$), 20.2 (CH$_2$), 17.3 (CH$_3$), −1.2 (CH$_3$), −1.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{22}$H$_{32}$NO$_4$Si [M+H]$^+$: 402.2095, found: 402.2096.

Data for **320b**: R$_f$ (30% EtOAc in hexane) = 0.48; IR (film) 2951 (NH + OH), 2348, 1729 (C=O), 1612, 1512, 1427, 1246, 1173, 1111, 832 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.55-7.51 (2H, m, ArH), 7.36-7.32 (3H, m, ArH), 7.07 (2H, d, J = 8.6 Hz, ArH), 6.81 (2H, d, J = 8.6 Hz, ArH), 4.04 (1H, q, J = 6.4 Hz, CH$_3$CHOH), 3.80 (3H, s, ArOCH$_3$), 3.61 (1H, d, J = 11.6 Hz, NHCH$_A$CH$_B$Ar), 3.58-3.52 (3H, s, CO$_2$CH$_3$ + 1H, d, J = 11.6 Hz, NHCH$_A$CH$_B$Ar), 3.31 (1H, bs, NH), 1.60 (1H, bs, OH), 1.43 (1H, d, J = 15.0 Hz, SiCH$_A$CH$_B$), 1.33 (1H, d, J = 15.0 Hz, SiCH$_A$CH$_B$), 1.23 (3H, d, J = 6.3 Hz, CH$_3$CHOH), 0.38 (3H, s, CH$_3$Si), 0.36 (3H, s, CH$_3$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.5 (C), 158.7 (C), 138.9 (C), 133.6 (2 x CH), 131.8 (C), 129.2 (2 x CH), 129.0 (CH), 127.8 (2 x CH), 113.8 (2 x CH), 70.2 (CH), 68.0 (C), 55.3 (CH$_3$), 51.7 (CH$_3$), 47.5 (CH$_2$), 20.5 (CH$_2$), 17.3 (CH$_3$), −1.2 (CH$_3$), −1.3 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{22}$H$_{32}$NO$_4$Si [M+H]$^+$: 402.2095, found: 402.2095.

Methyl 2-(4-methoxybenzylamino)-2-[(dimethylphenylsilyl)methyl]-3-oxobutanoate (300)
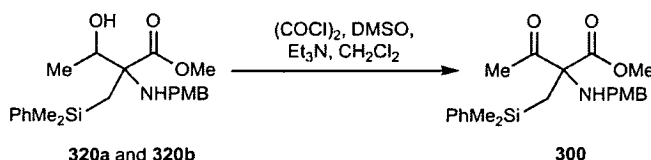
320a and 320b   **300**

To a stirred solution of oxalyl chloride (0.51 mL, 5.76 mmol) in CH$_2$Cl$_2$ (12 mL) at −78 °C was added DMSO (0.82 mL, 11.5 mmol) dropwise. After stirring for 15 minutes, a solution of the mixture of alcohols **320a** and **320b** (1.10 g, 2.74 mmol) in CH$_2$Cl$_2$ (12 mL) was added *via* cannula. The reaction was stirred at −78 °C for 1 h and Et$_3$N (1.61 mL, 11.5 mmol) was then added. The reaction was stirred at −78 °C for 1 h, allowed to warm up to −40 °C over 2 h and then quenched with saturated aqueous NH$_4$Cl solution (10 mL). The aqueous layer was separated and extracted

with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amino ketone* **300** (886 mg, 81%) as a yellow oil. R_f (30% EtOAc in hexane) = 0.53; IR (film) 2952 (NH), 2359, 1739 (C=O), 1717 (C=O), 1612, 1512, 1247, 1172, 1035, 832 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.56-7.52 (2H, m, Ar**H**), 7.36-7.33 (3H, m, Ar**H**), 7.09 (2H, d, *J*= 8.5 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.5 Hz, Ar**H**), 3.80 (3H, s, ArOC**H₃**), 3.52 (3H, s, CO₂C**H₃**), 3.40 (1H, d, *J* = 12.0 Hz, NHC**H**$_A$CH$_B$Ar), 3.32 (1H, d, *J* = 12.0 Hz, NHCH$_A$C**H**$_B$Ar), 2.28 (1H, bs, N**H**), 2.11 (3H, s, C**H₃**C=O), 1.73 (1H, d, *J* = 15.4 Hz, SiC**H**$_A$CH$_B$), 1.63 (1H, d, *J* = 15.4 Hz, SiCH$_A$C**H**$_B$), 0.35 (3H, s, C**H₃**Si), 0.34 (3H, s, C**H₃**Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 204.6 (C), 172.1 (C), 158.7 (C), 138.7 (C), 133.7 (2 x CH), 131.5 (C), 129.2 (2 x CH), 129.0 (CH), 127.7 (2 x CH), 113.7 (2 x CH), 73.6 (C), 55.3 (CH₃), 52.3 (CH₃), 46.8 (CH₂), 24.9 (CH₃), 19.2 (CH₂), -2.0 (CH₃), -2.1 (CH₃); HRMS (ES) Exact mass calcd for $C_{22}H_{30}NO_4SiNa$ [M+H]$^+$: 400.1939, found: 400.1933.

(*E*)-Ethyl 4-hydroxybut-2-enoate (322)[186]
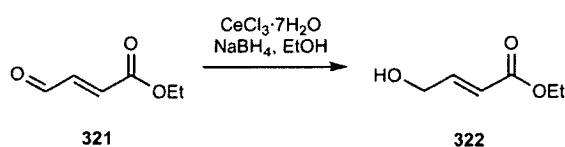
To a stirred solution of aldehyde **321** (5.60 mL, 44.6 mmol) in EtOH (200 mL) at 0 °C was added CeCl₃·7H₂O (16.6 g, 44.6 mmol) followed by NaBH₄ (1.72 g, 44.6 mmol), added portionwise over 20 minutes. The reaction was allowed to warm up to room temperature and stirred for 14 h and then quenched with saturated aqueous NH₄Cl solution. This mixture was concentrated *in vacuo* and the remaining mixture was taken up with Et₂O. The ether phase was washed with water (2 x 40 mL) and the combined aqueous layers were extracted with Et₂O (2 x 30 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to afford alcohol **322** (5.5 g, 95%) as a colourless oil which was used in the next step without further purification. R_f (30% EtOAc in hexane) = 0.26; ^{1}H NMR (250 MHz, CDCl₃) δ 6.99 (1H, dt, *J* = 3.9, 15.7 Hz, C**H**=CHC=O), 6.05 (1H, dt, *J* = 2.1, 15.7 Hz, CH=C**H**C=O), 4.29 (2H, bs, HOC**H₂**), 4.16 (2H, q, *J* = 7.1 Hz, C**H₂**CH₃), 3.06 (1H,

bs, OH), 1.25 (3H, t, $J = 7.1$ Hz, CH$_2$CH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 166.6 (C), 147.2 (CH), 119.8 (C), 61.5 (CH$_2$), 60.4 (CH$_2$), 14.1 (CH$_3$).

^{1}H spectroscopic data in good agreement with the literature.[186]

### (*E*)-Ethyl 4-(4-methoxybenzyloxy)but-2-enoate (324)[187]
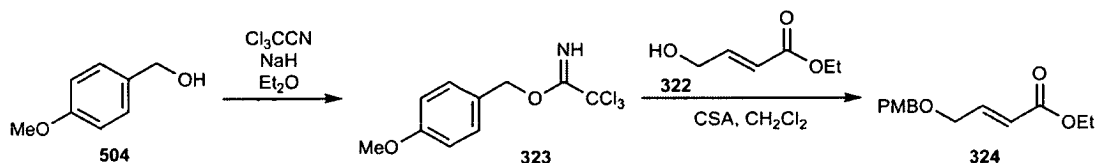
To a stirred suspension of sodium hydride (80 mg, 60% dispersion in mineral oil, 2.0 mmol) in Et$_2$O (25.0 mL) at 0 °C was added 4-methoxybenzyl alcohol **504** (2.50 mL, 20.0 mmol) dropwise over 3 min. The reaction was stirred at 0 °C for 5 min and trichloroacetonitrile (2.00 mL, 21.0 mmol) was added over 2 min. The reaction was allowed to warm up to room temperature, stirred for 12 h and then concentrated *in vacuo* to give crude *p*-methoxybenzyl trichloroacetimidate **323** (6.10 g), which was used in the next step without further purification.[120]

To a stirred solution of alcohol **322** (4.35 g, 33.3 mmol) in CH$_2$Cl$_2$ (80 mL) at 0 °C was added a solution of *p*-methoxybenzyl trichloroacetimidate (14.1 g, 49.9 mmol) in CH$_2$Cl$_2$ (30 mL) *via* cannula, followed by the addition of CSA (780 mg, 3.33 mmol) in one portion. The reaction was allowed to warm up to room temperature, stirred for 14 h and then filtered through celite. The solids were washed with CH$_2$Cl$_2$ (3 x 30 mL) and the combined organic layer was washed with NaHCO$_3$ (2 x 30 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave ester **324** (4.73 g, 57%, reaction not optimised) as a yellow oil. R$_f$ (10% EtOAc in hexane) = 0.26; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.20 (2H, d, $J = 8.3$ Hz, ArH), 6.94 (1H, dt, $J = 15.5$, 4.2 Hz, CH=CHC=O), 6.85 (2H, d, $J = 8.3$ Hz, ArH), 6.10 (1H, dt, $J = 15.5$, 2.3 Hz, CH=CHC=O), 4.50 (2H, s, ArCH$_2$O), 4.18 (2H, q, $J = 7.1$ Hz, CH$_2$CH$_3$), 4.10 (2H, dd, $J = 4.2$, 2.3 Hz, CH$_2$CH=CH), 3.8 (3H, s, CH$_3$O), 1.28 (3H, t, $J = 7.1$ Hz, CH$_2$CH$_3$).

^{1}H spectroscopic data in good agreement with the literature.[187]

## (*E*)-4-(4-Methoxybenzyloxy)but-2-enoic acid (325)
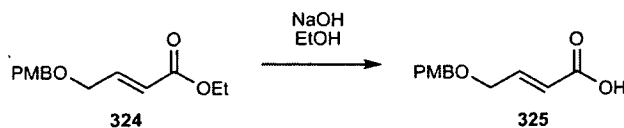
To a stirred solution of ester **324** (5.17 g, 20.6 mmol) in EtOH (100 mL) was added a 0.5 M NaOH aqueous solution (45 mL). The reaction was stirred at room temperature for 14 h, concentrated *in vacuo*, dissolved in water (40 mL) and washed with CH$_2$Cl$_2$ (1 x 30 mL). The pH of the aqueous layer was taken to pH = 4 and it was then extracted with CH$_2$Cl$_2$ (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*, to give *acid* **325** as a colourless solid (3.1 g, 70%), which was used in the next step without further purification. R$_f$ (30% EtOAc in hexane) = 0.23; m.p.= 83-85 °C; IR (film) 2838 (OH), 2360, 1685 (C=O), 1515, 1425, 1311, 1251, 1180, 1029, 821 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.43 (2H, d, *J* = 8.1 Hz, ArH), 7.24 (1H, dt, *J* = 15.7, 4.1 Hz, CH=CHC=O), 7.05 (2H, d, *J* = 8.1 Hz, ArH), 6.29 (1H, dt, *J* = 15.7, 2.0 Hz, CH=CHC=O), 4.67 (2H, s, ArCH$_2$O), 4.33 (2H, dd, *J* = 4.1, 2.0 Hz, CH$_2$CH=CH), 3.97 (3H, s, OCH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 171.4 (C), 159.3 (C), 147.1 (CH), 129.5 (C), 129.3 (2 x CH), 120.3 (CH), 113.8 (2 x CH), 72.5 (CH$_2$), 68.1 (CH$_2$), 55.2 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{12}$H$_{18}$NO$_4$ [M+NH$_4$]$^+$: 240.1230, found: 240.1232.

## Methyl 2-[*N*-(4-methoxybenzyl)acrylamido]-2-[(dimethylphenylsilyl)methyl]-3-oxobutanoate (347)
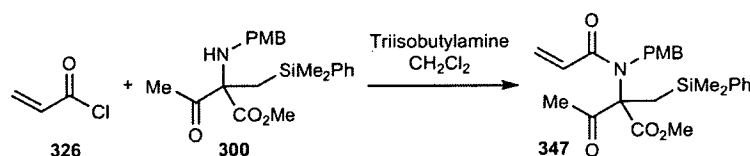
To a stirred solution of amine **300** (652 mg, 1.63 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C, was added triisobutylamine (1.20 mL, 4.89 mmol). The reaction was stirred at 0 °C for 10 min and acryloyl chloride (0.44 mL, 4.89 mmol) was then added. The reaction was stirred for 14 h and then quenched with 1 M HCl (10 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2 x 10 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amide*

347 (452 mg, 65%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.46; IR (film) 2952, 1741 (C=O), 1716 (C=O), 1652 (C=O), 1513, 1415, 1249, 1174, 829, 734 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.48-7.44 (2H, m, ArH), 7.37-7.33 (3H, m, ArH), 7.30 (2H, d, J = 8.4 Hz, ArH), 6.95 (2H, d, J = 8.4 Hz, ArH), 6.37 (1H, dd, J = 3.2, 16.7 Hz, CH$_A$H$_B$=CH), 6.34 (1H, dd, J = 9.1, 16.7 Hz, CH$_2$=CHC=O), 5.67 (1H, dd, J = 9.1, 3.2 Hz, CH$_A$H$_B$=CH), 4.62 (1H, d, J = 18.3 Hz, NHCH$_A$H$_B$Ar), 4.53 (1H, d, J = 18.3 Hz, NHCH$_A$H$_B$Ar), 3.86 (3H, s, ArOCH$_3$), 3.42 (3H, s, CO$_2$CH$_3$), 2.38 (3H, s, CH$_3$C=O), 1.79 (1H, d, J = 13.7 Hz, SiCH$_C$H$_D$), 1.47 (1H, d, J = 13.7 Hz, SiCH$_C$H$_D$), 0.30 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 201.9 (C), 169.9 (C), 168.2 (C), 158.9 (C), 138.9 (C), 133.7 (2 x CH), 130.1 (CH$_2$), 129.7 (C), 128.8 (CH), 128.2 (CH), 127.6 (2 x CH), 127.2 (2 x CH), 114.1 (2 x CH), 73.9 (C), 55.3 (CH$_3$), 52.1 (CH$_3$), 47.9 (CH$_2$), 28.0 (CH$_3$), 21.3 (CH$_2$), −1.2 (CH$_3$), -2.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{32}$NO$_5$Si [M+H]$^+$: 454.2044, found: 454.2044.

(*E*)-Methyl 2-[*N*-(4-methoxybenzyl)but-2-enamido]-2-[(dimethylphenylsilyl)methyl]-3-oxobutanoate (349)
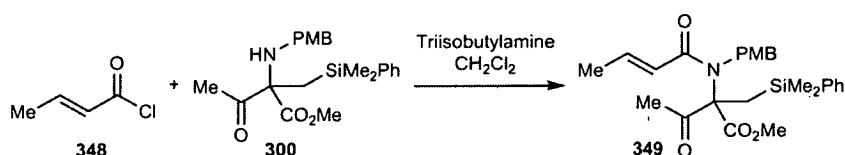
To a stirred solution of amine **300** (400 mg, 1.00 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C, was added triisobutylamine (0.73 mL, 3.00 mmol). The reaction was stirred at 0 °C for 10 min and crotonoyl chloride (0.29 mL, 3.00 mmol) was then added. The reaction was stirred for 15 h and then quenched with 1 M HCl (10 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2 x 10 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amide* **349** (413 mg, 88%) as a yellow oil. R_f (30% EtOAc in hexane) = 0.50; IR (film) 2952, 1740 (C=O), 1715 (C=O), 1660 (C=O), 1616, 1512, 1398, 1248, 1173, 829 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.44-7.40 (2H, m, ArH), 7.32-7.28 (3H, m, ArH), 7.26 (2H, d, J = 8.5 Hz, ArH), 6.98-6.88 (1H, m, CH=CHC=O), 6.92 (2H, d, J = 8.5 Hz, ArH), 6.00 (1H, dd, J = 15.0, 1.6 Hz, CH=CHC=O), 4.56 (1H, d, J = 18.3

Hz, NHCH$_A$**H**$_B$Ar), 4.49 (1H, d, J = 18.3 Hz, NHCH$_A$**H**$_B$Ar), 3.83 (3H, s, ArOC**H**$_3$),

3.36 (3H, s, CO$_2$C**H**$_3$), 2.33 (3H, s, C**H**$_3$CO), 1.79 (3H, dd, J = 6.9, 1.6 Hz,

C**H**$_3$CH=CH), 1.73 (1H, d, J = 13.8 Hz, SiCH$_C$**H**$_D$), 1.42 (1H, d, J = 13.8 Hz,

SiCH$_C$**H**$_D$), 0.26 (3H, s, C**H**$_3$Si), 0.25 (3H, s, C**H**$_3$Si); ^{13}C NMR (62.9 MHz, CDCl$_3$)

δ 201.8 (C), 170.0 (C), 168.4 (C), 158.8 (C), 144.3 (CH), 139.0 (C), 133.7 (2 x CH),

129.9 (C), 128.7 (CH), 127.5 (2 x CH), 127.3 (2 x CH), 122.3 (CH), 114.1 (2 x CH),

73.8 (C), 55.3 (CH$_3$), 52.0 (CH$_3$), 47.9 (CH$_2$), 28.0 (CH$_3$), 21.3 (CH$_2$), 18.2 (CH$_3$),

-1.2 (CH$_3$), −1.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{26}$H$_{34}$NO$_5$Si [M+H]$^+$:

468.2201, found: 468.2204.

(*E*)-Ethyl 4-(benzyloxy)but-2-enoate (351)[188]
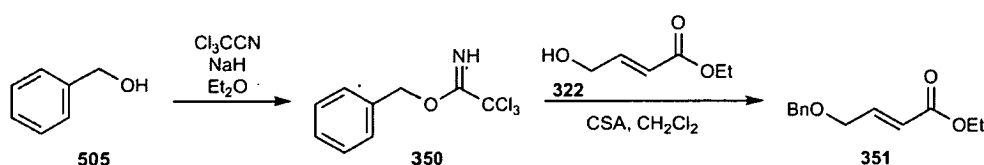
To a stirred suspension of sodium hydride (256 mg, 60% dispersion in mineral

oil, 6.40 mmol) in Et$_2$O (40.0 mL) at 0 °C was added benzyl alcohol **505** (6.6 mL, 64

mmol) dropwise over 4 min. The reaction was stirred at 0 °C for 5 min and

trichloroacetonitrile (13.2 mL, 128 mmol) was added over 3 min. The reaction was

allowed to warm up to room temperature, stirred for 12 h and concentrated *in vacuo*

to give crude benzyl trichloroacetimidate (**350**) (15.5 g, 95%), which was used in the

next step without further purification.[120]

To a stirred solution of alcohol **322** (2.40 g, 18.4 mmol) in CH$_2$Cl$_2$ (40 mL) and

toluene (20 mL) at room temperature was added a solution of benzyl

trichloroacetimidate (**350**) (7.80 g, 27.6 mmol) in CH$_2$Cl$_2$ (20 mL) and toluene (10

mL), followed by addition of a catalytic amount of triflouromethanesulfonic acid

(0.16 mL, 1.84 mmol). The reaction was stirred for 24 h and then filtered. The

filtrates were washed with CH$_2$Cl$_2$ and the combined organic layers were washed

with saturated aqueous NaHCO$_3$ solution (2 x 30 mL), water (1 x 30 mL) and then

were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue

by column chromatography (12 % EtOAc/petrol) gave ester **351** (2.5 g, 63%) as a

pale yellow oil. R$_f$ (30% EtOAc in hexane) = 0.57; ^{1}H NMR (250 MHz, CDCl$_3$) δ

7.46-7.40 (5H, m, Ar**H**), 7.06 (1H, dt, J = 15.7, 4.3 Hz, C**H**=CHC=O), 6.22 (1H, dt,

$J = 15.7$, 1.9 Hz, CH=CHC=O), 5.09 (2H, dd, $J = 4.3$, 1.9 Hz, CH$_2$CH=CH), 4.65 (2H, s, ArCH$_2$O), 4.32 (2H, q, $J = 7.1$ Hz, CH$_2$CH$_3$), 1.38 (3H, t, $J = 7.1$ Hz, CH$_2$CH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 166.2 (C), 144.1 (CH), 137.7 (C), 128.4 (2 x CH), 127.8 (CH), 127.6 (2 x CH), 121.4 (CH), 72.7 (CH$_2$), 68.6 (CH$_2$), 66.6 (CH$_2$), 14.2 (CH$_3$).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[188]

(*E*)-4-(Benzyloxy)but-2-enoic acid (352)[123]
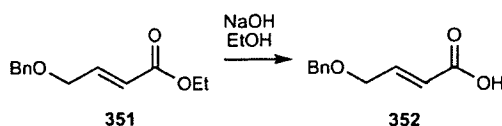
To a stirred solution of ester **351** (9.20 mg, 4.17 mmol) in THF (12 mL) and water (2 mL), was added LiOH (351 mg, 8.34 mmol). The reaction was stirred at room temperature for 18 h, diluted in water (6 mL) and concentrated *in vacuo*. This mixture was dissolved in water (40 mL) and washed with Et$_2$O (2 x 10 mL). The pH of the aqueous was taken to pH = 4 and it was then extracted with Et$_2$O (3 x 15 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20 % EtOAc/petrol) gave acid **352** (690 mg, 85%) as a pale yellow solid, which was used in the next step without further purification. R$_f$ (30% EtOAc in hexane) = 0.17; m.p. 46-48 °C, lit.[123] 46-47 °C; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.39-7.34 (5H, m, Ar**H**), 7.12 (1H, dt, $J = 15.7$, 4.0 Hz, OCH$_2$CH=CHC=O), 6.18 (1H, dt, $J = 15.7$, 2.1 Hz, OCH$_2$CH=CHC=O), 4.60 (2H, s, ArCH$_2$O), 4.24 (1H, d, $J = 2.1$ Hz, OC**H**$_A$H$_B$CH=CHC=O), 4.24 (1H, d, $J = 2.1$ Hz, OCH$_A$**H**$_B$CH=CHC=O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 171.6 (C), 147.1 (CH), 137.5 (C), 128.5 (2 x CH), 127.9 (CH), 127.6 (2 x CH), 120.4 (CH), 72.8 (CH$_2$), 68.4 (CH$_2$).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[123]

(*E*)-Methyl 2-[4-(benzyloxy)-*N*-(4-methoxybenzyl)but-2-enamido]-2-[(dimethylphenylsilyl)methyl]-3-oxobutanoate (354)
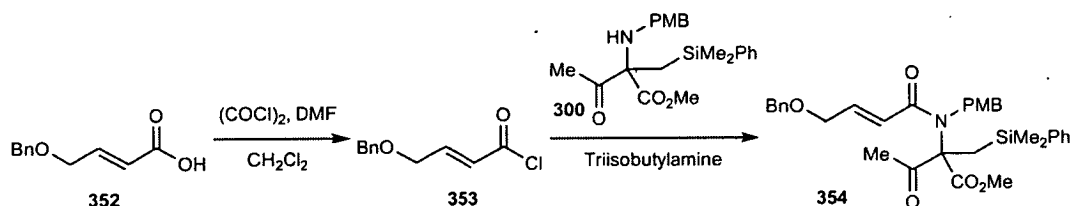
To a stirred solution of acid **352** (865 mg, 4.50 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (1.16 mL, 13.5 mmol) at room temperature. The reaction was stirred for 14 h, concentrated *in vacuo*, redissolved in CH_2Cl_2 (8 mL) and then transferred *via* cannula into a stirred solution of amine **300** (400 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) and triisobutylamine (1.10 mL, 4.50 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, heated to reflux for 14 h, and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave *amide* **354** (331 mg, 60%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.25; IR (film) 2952, 1741, 1718, 1654, 1513, 1249, 1174, 1033, 829 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46-7.42 (2H, m, ArH), 7.33-7.26 (8H, m, ArH), 7.17-7.14 (2H, m, ArH), 6.98-6.90 (2H + 1H, m, ArH + CH=CHC=O), 6.34 (1H, d, *J* = 15.1 Hz, CH=CHC=O), 4.58 (1H, d, *J* = 18.2 Hz, NHCH$_A$H$_B$Ar), 4.52 (1H, d, *J* = 18.2 Hz, NHCH$_A$H$_B$Ar), 4.42 (2H, s, ArCH$_2$O), 4.12-4.09 (2H, m, OCH$_2$CH=CHC=O), 3.82 (3H, s, ArOCH$_3$), 3.38 (3H, s, CO$_2$CH$_3$), 2.34 (3H, s, CH$_3$C=O), 1.75 (1H, d, *J* = 13.7 Hz, SiCH$_C$H$_D$), 1.45 (1H, d, *J* = 13.7 Hz, SiCH$_C$H$_D$), 0.27 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.8 (C), 169.9 (C), 168.1 (C), 158.8 (C), 144.0 (CH), 138.9 (C), 137.6 (C), 133.7 (2 x CH), 129.8 (C), 128.8 (CH), 128.3 (2 x CH), 127.6 (CH), 127.5 (2 x CH), 127.4 (2 x CH), 127.3 (2 x CH), 120.7 (CH), 114.0 (2 x CH), 73.9 (C), 72.5 (CH$_2$), 68.8 (CH$_2$), 55.2 (CH$_3$), 52.0 (CH$_3$), 47.9 (CH$_2$), 28.0 (CH$_3$), 21.3 (CH$_2$), −1.2 (CH$_3$), −1.9 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{33}H_{40}NO_6SiNa$ $[M+H]^+$: 574.2619, found: 574.2619.

(*E*)-4-(Benzyloxy)-*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)but-2-enamide (360)
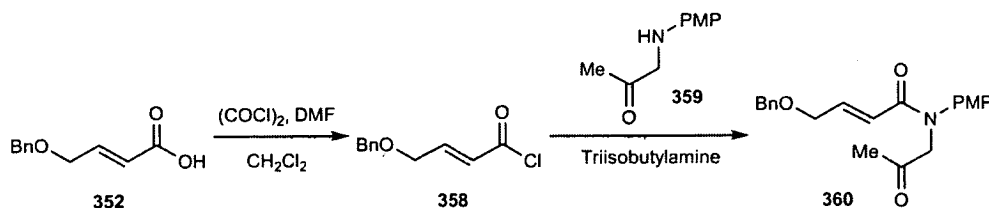
To a stirred solution of acid **352** (723 mg, 3.76 mmol) in CH_2Cl_2 (10 mL), was added oxalyl chloride (1.70 mL, 18.8 mmol) at room temperature. The reaction was stirred for 14 h, concentrated *in vacuo*, redissolved in CH_2Cl_2 (8 mL) and then transferred *via* cannula into a stirred solution of amine **359** (270 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) and triisobutylamine (1.10 mL, 4.51 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature, and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave *amide* **360** (497 mg, 94%) as a pale yellow solid. R_f (30% EtOAc in hexane) = 0.19; m.p. = 94-96 °C; IR (film) 2989, 2867, 1731 (C=O), 1666 (C=O), 1511, 1380, 1249, 1170, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.24-7.06 (7H, m, Ar**H**), 6.86 (1H, dt, *J* = 15.3, 4.4 Hz, C**H**=CHC=O), 6.82 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.04 (1H, dt, *J* = 15.3, 1.9 Hz, CH=C**H**C=O), 4.40 (2H, s, C**H₂**), 4.35 (2H, s, C**H₂**), 4.02 (2H, dd, *J* = 4.4, 1.9 Hz, OC**H₂**CH=CH), 3.74 (3H, s, OC**H₃**), 2.11 (3H, s, C**H₃**C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.4 (C), 165.8 (C), 159.0 (C), 141.9 (CH), 137.7 (C), 135.1 (C), 129.2 (2 x CH), 128.3 (2 x CH), 127.6 (CH), 127.4 (2 x CH), 120.6 (CH), 114.6 (2 x CH), 72.3 (CH_2), 68.8 (CH_2), 59.7 (CH_2), 55.4 (CH_3), 27.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1703.

## 3-(2-Benzyloxyethyl)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (361a and 361b)
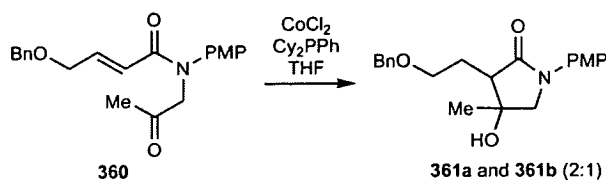
A solution of α,β-unsaturated amide **360** (53 mg, 0.15 mmol), CoCl$_2$ (2.0 mg, 15 μmol) and Cy$_2$PPh (4.5 mg, 16 μmol) in THF (1 mL) was stirred at room temperature for 30 min and then cooled to 0 °C. Et$_2$Zn (0.3 mL, 1 M solution in THF, 0.3 mmol) was then added. The reaction was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH$_4$Cl solution (2 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave the two diastereomers of the *cyclised products* **361a** (14.8 mg, 29%) and **361b** (29.8 mg, 55%) as pale yellow oils.

Data for **361a**: R$_f$ (30% EtOAc in hexane) = 0.50; IR (film) 3434 (OH), 2929, 2360, 1694 (C=O), 1511, 1397, 1246, 1102, 1030, 829 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.46 (2H, d, *J* = 9.1 Hz, ArH), 7.39-7.32 (5H, m, ArH), 6.90 (2H, d, *J* = 9.1 Hz, ArH), 4.62 (1H, d, *J* = 11.5 Hz, CH$_A$H$_B$Ph), 4.57 (1H, d, *J* = 11.5 Hz, CH$_A$H$_B$Ph), 3.89-3.72 (1H, m, OCH$_C$H$_D$CH$_2$), 3.80 (3H, s, OCH$_3$), 3.79 (1H, d, *J* = 9.0 Hz, NCH$_E$H$_F$), 3.63-3.52 (1H, m, OCH$_C$H$_D$CH$_2$), 3.79 (1H, d, *J* = 9.0 Hz, NCH$_E$H$_F$), 2.68 (1H, dd, *J* = 10.8, 2.4 Hz, CH$_2$CHC=O), 2.25 (1H, dm, *J* = 15.3 Hz, CH$_2$CH$_G$H$_H$CH), 2.05-1.8 (1H, m, CH$_2$CH$_G$H$_H$CH), 1.34 (3H, s, CH$_3$COH); 2D COSY experiment showed cross peak between: **CH$_E$H$_F$** and **CH$_G$H$_H$**; **CH$_G$H$_H$** and **CHCO**; ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 172.1 (C), 156.5 (C), 136.9 (C), 132.4 (C), 128.6 (2 x CH), 128.1 (CH), 127.9 (2 x CH), 121.5 (2 x CH), 114.0 (2 x CH), 73.7 (CH$_2$), 73.1 (C), 70.7 (CH$_2$), 59.6 (CH$_2$), 55.6 (CH), 55.4 (CH$_3$), 24.5 (CH$_2$), 23.7 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{21}$H$_{25}$NO$_4$ [M]$^+$: 355.1778, found: 355.1780.

Data for **361b**: R$_f$ (30% EtOAc in hexane) = 0.38; IR (film) 3425 (OH), 2931, 2868, 1682 (C=O), 1511, 1397, 1247, 1103, 829, 699 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.48 (2H, d, *J* = 9.2 Hz, ArH), 7.36-7.29 (5H, m, ArH), 6.89 (2H, d, *J* = 9.2 Hz, ArH), 4.58 (1H, d, *J* = 11.6 Hz, CH$_A$H$_B$Ph), 4.57 (1H, d, *J* = 11.6 Hz, CH$_A$H$_B$Ph), 3.87-3.79 (1H, m, OCH$_C$H$_D$CH$_2$), 3.80 (3H, s, OCH$_3$), 3.71 (1H, d, *J* = 10.2 Hz, NCH$_E$H$_F$), 3.66 (1H, d, *J* = 10.2 Hz, NCH$_E$H$_F$), 3.69-3.60 (1H, m, OCH$_C$H$_D$CH$_2$), 2.61 (1H, dd, *J* = 8.7, 4.3 Hz, CH$_2$CHC=O), 2.30-2.09 (2H, m, CH$_2$CH$_2$CH), 2.05 (3H, s, CH$_3$COH); 2D COSY experiment showed cross peak between: CH$_C$H$_D$CH$_2$

and **CH₂CH**; **CH₂CH** and **CH₂CH**; ¹³C NMR (62.9 MHz, CDCl₃) δ 172.1 (C), 156.5 (C), 136.9 (C), 132.4 (C), 128.6 (2 x CH), 128.1 (CH), 127.9 (2 x CH), 121.5 (2 x CH), 114.0 (2 x CH), 73.7 (CH₂), 73.1 (C), 70.7 (CH₂), 59.6 (CH₂), 55.6 (CH), 55.4 (CH₃), 24.5 (CH₂), 23.7 (CH₃); HRMS (EI) Exact mass calcd for $C_{21}H_{25}NO_4$ [M]⁺: 355.178, found: 355.1778.

(2E,4E)-N-(4-Methoxyphenyl)-N-(2-oxopropyl)hexa-2,4-dienamide (366)
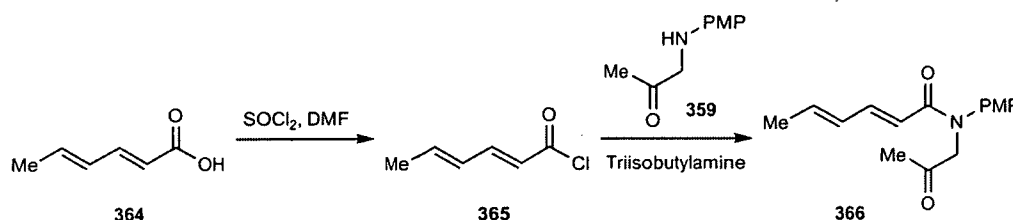
Sorbic acid (5.00 g, 44.6 mmol) was heated to reflux with thionyl chloride (6.50 mL, 89.2 mmol) and DMF (15 μL, 0.13 mmol) for 1 h. The reaction mixture was distilled under reduced pressure to give acid chloride **365** in quantitative yield.[125]

To a stirred solution of amine **359** (500 mg, 2.79 mmol) and triisobutylamine (2.00 mL, 8.37 mmol) in CH₂Cl₂ (15 mL) at 0 °C was transferred *via* cannula a solution of sorbyl chloride (1.1 g, 8.37 mmol) in CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, allowed to warm up to room temperature, stirred for 12 h and then quenched with saturated aqueous NH₄Cl solution (15 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 15 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 45% EtOAc/petrol) gave *amide* **366** (470 mg, 62%) as a brown oil. R_f (40% EtOAc in hexane) = 0.32; IR (film) 2975, 1729 (C=O), 1652 (C=O), 1511, 1384, 1249, 1170, 1029, 840, 561 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.21 (2H, d, *J* = 8.9 Hz, ArH), 6.89 (2H, d, *J* = 8.9 Hz, ArH), 6.02 (2H, m, CH=CH), 5.73 (2H, m, CH=CH), 4.46 (2H, s, CH₂), 3.83 (3H, s, OCH₃), 2.17 (3H, s, CH₃C=O), 1.77 (3H, d, *J* = 5.4 Hz, CH₃CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 202.7 (C), 192.4 (C), 166.8 (C), 158.9 (C), 142.9 (CH), 133.0 (CH), 130.1 (CH), 129.2 (2 x CH), 118.6 (CH), 114.5 (2 x CH), 59.7 (CH₂) 55.4 (CH₃), 27.2 (CH₃), 18.5 (CH₃); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_3$ [M+H]⁺: 274.1438, found: 274.1440.

(*E*)-3-(But-2-enyl)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (367)
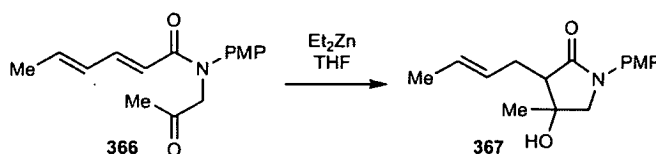
A solution of α,β-unsaturated amide **366** (50 mg, 0.18 mmol) and Ni(acac)$_2$ (4.8 mg, 18 μmol) in THF (1 mL) was stirred at room temperature for 30 min and then cooled to 0 °C. Et$_2$Zn (0.37 mL, 1 M solution in THF, 0.36 mmol) was then added. The reaction was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH$_4$Cl solution (2 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5% to 10% EtOAc/petrol) gave *cyclised product* **367** (13.5 mg, 25%) as a yellow oil. R$_f$ (30% EtOAc in hexane) = 0.52; IR (film) 3404 (OH), 2934, 1674 (C=O), 1511, 1400, 1248, 1180, 1033, 829 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.45 (2H, d, *J* = 9.2 Hz, ArH), 6.89 (2H, d, *J* = 9.2 Hz, ArH), 5.79-5.37 (2H, m, CH=CH), 3.79 (3H, s, OCH$_3$), 3.72 (1H, d, *J* = 9.6 Hz, NCH$_A$H$_B$), 3.55 (1H, d, *J* = 9.6 Hz, NCH$_A$H$_B$), 2.67 (1H, dd, *J* = 9.0, 5.0 Hz, CHC=O), 2.62-2.48 (1H, m, CH$_C$H$_D$CHC=O), 2.40-2.22 (1H, m, CH$_C$H$_D$CHC=O), 1.67 (3H, d, *J* = 5.3 Hz, CH$_3$CH), 1.42 (3H, s, CH$_3$COH); 2D COSY experiment showed cross peak of CH=CH protons with CH$_A$CH$_B$, CH$_2$CH and CH$_3$; 2D NOESY experiment showed cross peak of CH$_3$ at C3 with CHC=O proton and with CH$_C$H$_D$CHC=O protons; ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 172.9 (C), 156.6 (C), 132.2 (C), 127.9 (CH), 127.8 (CH), 121.7 (2 x CH), 114.0 (2 x CH), 74.3 (C), 60.5 (CH$_2$), 55.4 (CH), 54.7 (CH$_3$), 29.4 (CH$_2$), 22.8 (CH$_3$), 17.9 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{16}$H$_{21}$NO$_3$ [M]$^+$: 275.1516, found: 275.1519.

6.2.3. Reformatsky reaction approach

(*L*)-Threonine methyl ester (415)[189]
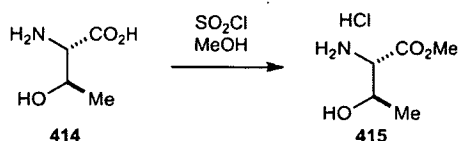
To a stirred solution of $SOCl_2$ (11.0 mL, 150 mmol) in MeOH (115 mL) at 0 °C was added (*L*)-threonine (18.2 g, 150 mmol) in portions. After stirring for 30 min at room temperature, the reaction was heated to reflux for 14 h and then concentrated *in vacuo*, to obtain a thick colourless oil. Methyl ester **415** was used in the next step without further purification. ^1H NMR (360 MHz, CD$_3$OD) δ 5.11 (3H, bs, NH$_2$ + OH), 4.52 (1H, dq, *J* = 6.5, 4.2 Hz, CHCH$_3$), 4.19 (1H, d, *J* = 4.2 Hz, CHCHOH), 4.08 (3H, s, OCH$_3$), 1.56 (3H, d, *J* = 6.5 Hz, CH$_3$CH); ^{13}C NMR (62.9 MHz, CD$_3$OD) δ 170.1 (C), 66.8 (CH), 60.3 (CH), 54.2 (CH$_3$), 20.9 (CH$_3$).

^1H and ^{13}C spectroscopic data in good agreement with the literature.[189]

4-Methoxybenzimidate hydrochloride (417)[190]
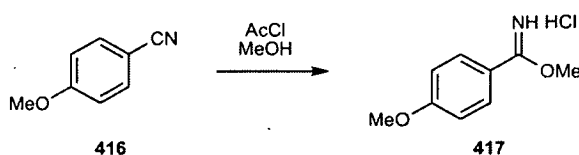
To a stirred solution of *p*-methoxybenzonitrile **416** (22.4 g, 168.6 mmol) in MeOH (85 mL, 2.0 mol) at 0 °C was added acetyl chloride (96.0 mL, 1.34 mol) slowly *via* syringe. The solution was stirred for 14 h at room temperature and then concentrated *in vacuo* which afforded **417** as a colourless solid. This solid was washed with Et$_2$O (5 x 30 mL), dried and used without further purification in the next step (30.5 g, 91%). m.p. 165-167 °C; ^1H NMR (360 MHz, CDCl$_3$) δ 11.60 (1H, bs, NH), 8.39 (2H, d, *J* = 9.0 Hz, ArH), 7.02 (2H, d, *J* = 9.0 Hz, ArH), 4.51 (3H, s, OCH$_3$), 3.88 (3H, s, OCH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 171.1 (C), 165.5 (C), 132.1 (2 x CH), 116.7 (C), 114.6 (2 x CH), 60.8 (CH$_3$), 55.6 (CH$_3$).

^1H spectroscopic data in good agreement with the literature.[190]

(4*S*,5*R*)-Methyl 4,5-dihydro-2 (4-methoxyphenyl)-5-methyloxazole-4-carboxylate (418)[26]
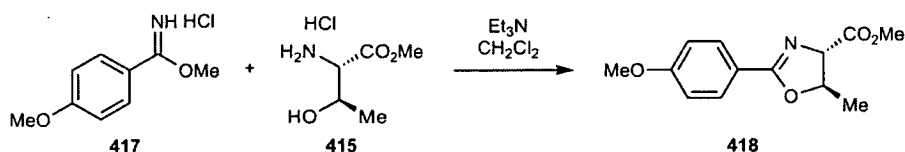
To a stirred solution of threonine methyl ester **415** (25.5 g, 150 mmol) in CH$_2$Cl$_2$ (175 mL) at room temperature was added Et$_3$N (41.0 mL, 300 mmol) slowly *via* syringe, followed by the addition of **417** in one portion. The reaction was stirred for 1 h at room temperature, heated to reflux for 14 h, then it was quenched with saturated aqueous NH$_4$Cl solution (150 mL) and extracted with CH$_2$Cl$_2$ (3 x 70 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 40% EtOAc/petrol) afforded oxazoline **418** (12.8 g, 40%) as a pale yellow solid. R$_f$ (30% EtOAc in hexane) = 0.29; m.p. 87-88 °C, lit.[26] 86-87 °C; [α]$_D^{22}$ +76.5 (*c* 1.98, CHCl$_3$), lit.[26] +69.4 (*c* 2.0, CHCl$_3$); ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.86 (2H, d, *J* = 8.9 Hz, ArH), 6.83 (2H, d, *J* = 8.9 Hz, ArH), 4.89 (1H, dq, *J* = 7.4, 6.3 Hz, OCHCH$_3$), 4.38 (1H, d, *J* = 7.4 Hz, NCH), 3.75 (3H, s, OCH$_3$), 3.73 (3H, s, OCH$_3$), 1.45 (3H, d, *J* = 6.2 Hz, CHCH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 171.4 (C), 165.0 (C), 162.1 (C), 130.0 (2 x CH), 119.4 (C), 113.4 (2 x CH), 78.4 (CH), 74.8 (CH), 55.0 (CH$_3$), 52.2 (CH$_3$), 20.7 (CH$_3$).

[1]H and ^{13}C spectroscopic data in good agreement with the literature.[26]

(4*R*,5*R*)-Methyl 4-[(benzyloxy)methyl]-4,5-dihydro-2-(4-methoxyphenyl)-5-methyloxazole-4-carboxylate (17)[26]
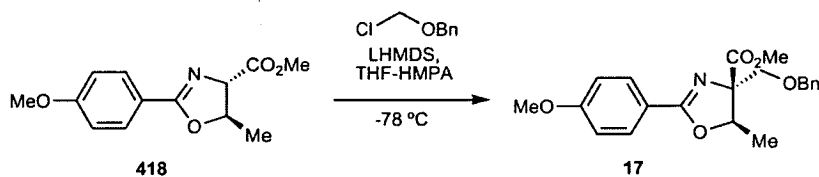

To a stirred solution of LHMDS (56.6 mL, 1 M solution in THF, 56.5 mmol), in THF (200 mL) at −78 °C was added HMPA (30.0 mL, 221 mmol), followed by the transfer of a solution of oxazoline **418** (12.8 g, 51.3 mmol) in THF (100 mL) *via*

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cannula. This solution was stirred at −78 °C for 1 h to allow enolate formation. Benzyloxy chloromethyl ether (14.3 mL, 61.7 mmol) was then added and the reaction was stirred at −78 °C for 3 h, when it was quenched with saturated aqueous NH_4Cl solution (150 mL) and warmed up to room temperature for 30 minutes. The aqueous layer was extracted with EtOAc (4 x 80 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 20% EtOAc/petrol) afforded alkylated oxazoline **17** (14.8 g, 75%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.53; $[\alpha]_D^{22}$ −6.0 (*c* 1.0, $CHCl_3$), lit.[26] −6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 9.0 Hz, ArH), 7.29-7.24 (5H, m, ArH), 6.90 (2H, d, *J* = 9.0 Hz, ArH), 4.78 (1H, q, *J* = 6.6 Hz, OC**H**CH₃), 4.61 (2H, s, OC**H₂**Ar), 3.87 (1H, d, *J* = 9.9 Hz, C**H**A**H**BO), 3.81 (1H, d, *J* = 9.9 Hz, CH**A**H**B**O), 3.80 (3H, s, OCH₃), 3.73 (3H, s, OCH₃), 1.35 (3H, d, *J* = 6.6 Hz, CHC**H₃**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.8 (C), 165.0 (C), 162.2 (C), 137.8 (C), 130. 2 (2 x CH), 128.0 (2 x CH), 127.4 (2 x CH), 127.3 (CH), 119.7 (C), 113.4 (2 x CH), 81.0 (C), 79.5 (CH), 73.5 (CH₂), 73.0 (CH₂), 55.1 (CH₃), 52.0 (CH₃), 16.5 (CH₃).

[1]H and ^{13}C spectroscopic data in good agreement with the literature.[26]

### (2*R*,3*R*)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3-hydroxybutanoate (18)[26]
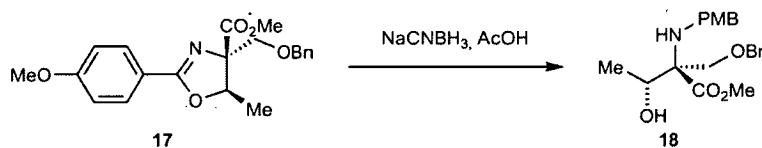
To a stirred solution of oxazoline **17** (14.8 g, 40.0 mmol) in HOAc (50 mL) at room temperature was added $NaCNBH_3$ (8.80 g, 132 mmol) in small portions over 2 h. The reaction mixture was stirred for 16 h at 50 °C, when it was diluted in water (100 mL), neutralised with solid Na_2CO_3 and the aqueous layer was extracted with ethyl acetate (5 x 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 25% EtOAc/petrol) afforded aminoalcohol **18** (9.3 g, 65%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.21; $[\alpha]_D^{22}$ −5.8 (*c* 1.03, $CHCl_3$), lit.[26] −9.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54-7.44 (5H, m, ArH), 7.43 (2H, d, *J* = 8.7

Hz, Ar**H**), 7.02 (2H, d, J = 8.7 Hz, Ar**H**), 4.71 (2H, s, OC**H₂**Ph), 4.15 (1H, q, J = 6.4 Hz, HOC**H**CH₃), 4.03 (1H, d, J = 9.8 Hz, NC**H**A**H**BAr), 3.98 (1H, d, J = 9.8 Hz, NC**H**A**H**BAr), 3.95 (3H, s, OC**H₃**), 3.92 (3H, s, OC**H₃**), 3.87 (1H, d, J = 11.8 Hz, C**H**C**H**DOBn), 3.79 (1H, d, J = 11.8 Hz, C**H**C**H**DOBn), 2.28 (1H, bs, O**H**), 1.35 (3H, d, J = 6.6 Hz, CHC**H₃**); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.8 (C), 158.8 (C), 137.5 (C), 131.7 (C), 129.5 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 127.7 (2 x CH), 113.8 (2 x CH), 73.5 (CH₂), 69.8 (C), 69.5 (CH₂), 69.4 (CH), 55.2 (CH₃), 52.1 (CH₃), 47.3 (CH₂), 17.9 (CH₃).

¹H and ¹³C spectroscopic data in good agreement with the literature.[26]

### (*R*)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3-oxobutanoate (327)
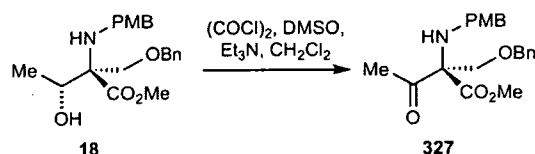
To a stirred solution of oxalyl chloride (1.70 mL, 18.8 mmol) in CH₂Cl₂ (40 mL) at −78 °C, was added DMSO (2.10 mL, 37.6 mmol) dropwise over 3 min. After stirring for 15 min, a solution of alcohol **18** (3.34 g, 8.94 mmol) in CH₂Cl₂ (30 mL) was added *via* cannula over 5 min. The reaction stirred at −78 °C for 1 h and Et₃N (5.25 mL, 37.6 mmol) was then added over 1 min. The reaction was stirred at −78 °C for 1 h, allowed to warm up to −40 °C over 2 h, and then quenched with saturated aqueous NH₄Cl solution (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amino ketone* **327** (2.39 g, 72%) as a pale yellow solid. R$_f$ (30% EtOAc in hexane) = 0.55; m.p. = 60-62 °C; [α]$_D^{22}$ -12.7 (*c* 1.02, CHCl₃); IR (film) 3347 (NH), 2952, 2836, 1741 (C=O), 1718 (C=O), 1511, 1245, 1178, 1033, 700 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.39-7.28 (5H, m, Ar**H**), 7.25 (2H, d, J = 8.7 Hz, Ar**H**), 6.85 (2H, d, J = 8.7 Hz, Ar**H**), 4.59 (1H, d, J = 12.4 Hz, OC**H**A**H**BPh), 4.53 (1H, d, J = 12.4 Hz, OC**H**A**H**BPh), 4.02 (1H, d, J = 10.1 Hz, NHC**H**C**H**D), 3.90 (1H, d, J = 10.1 Hz, NHC**H**C**H**D), 3.80 (3H, s, OC**H₃**), 3.74 (3H, s, OC**H₃**), 3.59 (1H, d, J = 12.3 Hz, C**H**E**H**FOBn), 3.46 (1H, d, J =

12.3 Hz, CH$_E$H$_F$OBn), 2.53 (1H, br s, NH), 2.21 (3H, s, CH$_3$C=O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 203.3 (C), 169.8 (C), 158.7 (C), 137.6 (C), 131.7 (C), 129.3 (2 x CH), 128.4 (2 x CH), 127.8 (3 x CH), 113.7 (2 x CH), 74.8 (C), 73.4 (CH$_2$), 68.1 (CH$_2$), 55.3 (CH$_3$), 52.7 (CH$_3$), 46.7 (CH$_2$), 25.7 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{21}$H$_{26}$NO$_5$ [M+H]$^+$: 372.1805, found: 372.1804.

(*R*)-Methyl 2-benzyloxymethyl-2-[2-bromo-*N*-(4-methoxybenzyl)butanamido]-3-oxobutanoate (420a and 420b)
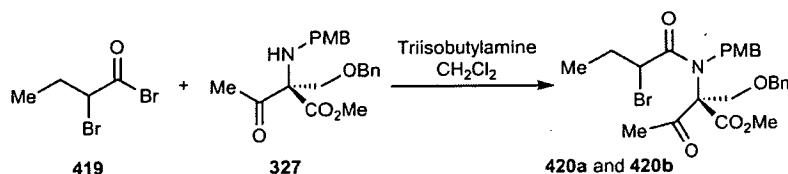
To a stirred solution of amine **327** (1.25 g, 3.36 mmol) in CH$_2$Cl$_2$ (15 mL) at room temperature was added triisobutylamine (1.10 mL, 4.37 mmol). The reaction was stirred for 10 min and 2-bromobutyryl bromide (0.55 mL, 4.04 mmol) was then added. The reaction was stirred for 16 h and then quenched with saturated aqueous NH$_4$Cl solution (10 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2 x 15 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10 % to 15% EtOAc/petrol) gave the two diastereomers of the *amide*, the more polar diastereomer **420a** (990 mg, 57%) and the less polar diastereomer **420b** (627 mg, 36%), as yellow oils.

Data for **420b**: R$_f$ (30% EtOAc in hexane) = 0.46; [α]$_D^{22}$ −63.3 (*c* 1.03, CHCl$_3$); IR (film) 2972, 1741 (C=O), 1709 (C=O), 1657 (C=O), 1513, 1433, 1246, 1177, 741, 510 (C-Br) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.31 (2H, d, *J* = 8.7 Hz, ArH), 7.22-7.17 (3H, m, ArH), 7.07-7.01 (2H, m, ArH), 6.84 (2H, d, *J* = 8.7 Hz, ArH), 5.01 (1H, d, *J* = 18.7 Hz, OCH$_A$H$_B$Ph), 4.75 (1H, d, *J* = 18.7 Hz, OCH$_A$H$_B$Ph), 4.27 (1H, d, *J* = 11.8 Hz, NHCH$_C$H$_D$), 4.19 (1H, d, *J* = 11.8 Hz, NHCH$_C$H$_D$), 4.00 (1H, dd, *J* = 8.6, 6.1 Hz, CHBr), 3.76 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 3.63 (2H, s, CH$_2$OBn), 2.42 (3H, s, CH$_3$C=O), 2.16-1.96 (1H, m, CHBrCH$_E$H$_F$CH$_3$), 1.90-1.76 (1H, m, CHBrCH$_E$H$_F$CH$_3$), 0.71 (3H, t, *J* = 7.3 Hz, CH$_A$H$_B$CH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 198.1 (C), 171.4 (C), 168.6 (C), 158.8 (C), 136.6 (C), 130.2 (C), 128.3 (2 x

CH), 127.9 (CH), 127.4 (2 x CH), 126.7 (2 x CH), 114.2 (2 x CH), 77.2 (C), 73.8 (CH$_2$), 70.3 (CH$_2$), 55.3 (CH$_3$), 52.9 (CH$_3$), 48.5 (CH$_2$), 44.5 (CH), 28.6 (CH$_2$), 28.1 (CH$_3$), 12.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{30}$^{79}BrNO$_6$Na [M+Na]$^+$: 542.1149, found: 542.1155.

Data for **420a**: R$_f$ (30% EtOAc in hexane) = 0.35; [α]$_D^{22}$ +41.0 (*c* 0.925, CHCl$_3$); IR (film) 2971, 2359, 1744 (C=O), 1735 (C=O) 1660 (C=O), 1513, 1413, 1247, 1176, 1095, 740, 503 (C-Br) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.38 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.34-7.30 (3H, m, Ar**H**), 7.21-7.18 (2H, m, Ar**H**), 6.95 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.95 (1H, d, *J* = 18.4 Hz, OC**H**$_A$H$_B$Ph), 4.86 (1H, d, *J* = 18.4 Hz, OCH$_A$**H**$_B$Ph), 4.42 (1H, d, *J* = 11.8 Hz, NHC**H**$_C$H$_D$), 4.38 (1H, d, *J* = 11.8 Hz, NHCH$_C$**H**$_D$), 4.22 (1H, dd, *J* = 8.5, 6.1 Hz, C**H**Br), 3.87 (1H, d, *J* = 10.5 Hz, C**H**$_E$H$_F$OBn), 3.93 (1H, d, *J* = 10.5 Hz, CH$_E$**H**$_F$OBn), 3.87 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 2.43 (3H, s, C**H**$_3$C=O), 2.28-2.15 (1H, m, CHBrC**H**$_G$H$_H$CH$_3$), 2.00-1.88 (1H, m, CHBrCH$_G$**H**$_H$CH$_3$), 0.88 (3H, t, *J* = 7.3 Hz, CH$_G$H$_H$C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.5 (C), 171.6 (C), 167.6 (C), 158.8 (C), 136.6 (C), 130.0 (C), 128.4 (2 x CH), 127.9 (CH), 127.6 (2 x CH), 126.9 (2 x CH), 114.1 (2 x CH), 77.8 (C), 73.8 (CH$_2$), 70.2 (CH$_2$), 55.3 (CH$_3$), 52.8 (CH$_3$), 49.7 (CH$_2$), 44.7 (CH), 28.6 (CH$_2$), 27.5 (CH$_3$), 12.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{30}$^{79}BrNO$_6$Na [M+Na]$^+$: 542.1149, found: 542.1153.

(2*R*,3*S*,4*R*)-2-Benzyloxymethyl-4-ethyl-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (421), *N*-(4-methoxybenzyl)butyramide (433) and (*R*)-methyl 2-benzyloxymethyl-2-[*N*-(4-methoxybenzyl)butyramido]-3-oxobutanoate (425)
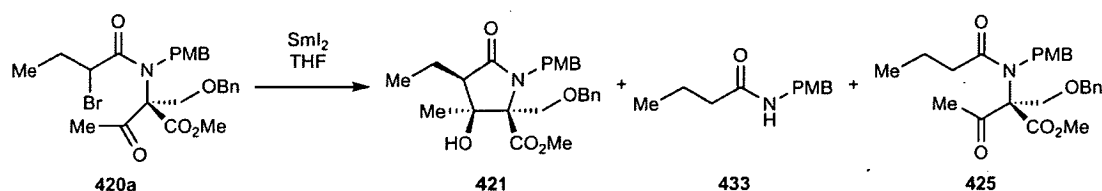
To a stirred solution of amide **420a** (more polar diastereomer, 30 mg, 57 µmol) in THF (3 mL) at 0 °C was added SmI$_2$ (0.1 M solution in hexanes, 6.90 mL, 0.69 mmol). The reaction was stirred at 0 °C for 1 h and then quenched with saturated aqueous NH$_4$Cl solution (5 mL). The aqueous layer was separated and extracted with

EtOAc (2 x 15 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10 % to 15% EtOAc/petrol) gave *γ-lactam* **421** (9.5 mg, 38%), *amide* **433** (4.5 mg, 40%) and *debrominated amide* **425** (2.6 mg, 10%).

Data for **421**: R$_f$ (30% EtOAc in hexane) = 0.10; $[\alpha]_D^{22}$ −24.6 (*c* 0.73, CHCl$_3$); IR (film) 3424 (OH), 2956, 1749 (C=O), 1670 (C=O), 1511, 1454, 1245, 1176, 1058, 736, 511 (C-Br) cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.30-7.20 (5H, m, Ar**H**), 7.07 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.69 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.97 (1H, d, *J* = 15.2 Hz, OC**H**$_A$H$_B$Ph), 4.19 (1H, d, *J* = 15.2 Hz, OCH$_A$**H**$_B$Ph), 3.89 (1H, d, *J* = 11.8 Hz, NHC**H**$_C$H$_D$), 3.83 (1H, d, *J* = 11.8 Hz, NHCH$_C$**H**$_D$), 3.73 (1H, d, *J* = 10.3 Hz, C**H**$_E$H$_F$OBn), 3.70 (3H, s, OC**H**$_3$), 3.69 (3H, s, OC**H**$_3$), 3.17 (1H, d, *J* = 10.3 Hz, CH$_E$**H**$_F$OBn), 2.44 (1H, t, *J* = 6.9 Hz, C**H**$_G$H$_H$CH), 1.83-1.71 (1H, m, CH$_G$**H**$_H$CH), 1.60-1.48 (1H, m, CH$_G$**H**$_H$CH), 1.40 (3H, s, CC**H**$_3$OH), 1.11 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH$_G$H$_H$); 2D NOESY experiment showed cross peak between: CC**H**$_3$OH and C**H**$_E$**H**$_F$OBn and between CC**H**$_3$OH and CH$_G$**H**$_H$C**H**; ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.5 (C), 169.3 (C), 158.7 (C), 137.2 (C), 130.4 (C), 130.0 (2 x CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.2 (CH), 113.5 (2 x CH), 78.4 (C), 77.2 (C), 72.8 (CH$_2$), 68.5 (CH$_2$), 55.2 (CH$_3$), 52.7 (CH), 52.4 (CH$_3$), 44.9 (CH$_2$), 21.1 (CH$_3$), 17.8 (CH$_2$), 13.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{32}$NO$_6$ [M+H]$^+$: 442.2224, found: 442.2227.

Data for **433**: R$_f$ (30% EtOAc in hexane) = 0.13; IR (film) 3289 (NH), 2930, 1632 (C=O), 1556, 1512, 1434, 1253, 1029, 813, 754 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.20 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.86 (2H, d, *J* = 8.7 Hz, Ar**H**), 5.75 (1H, bs, N**H**), 4.36 (2H, d, *J* = 5.6 Hz, OC**H**$_2$Ph), 3.79 (3H, s, OC**H**$_3$), 2.17 (2H, t, *J* = 7.6 Hz, C**H**$_2$C=O), 1.68 (2H, qt, *J* = 7.6, 7.3 Hz, CH$_3$C**H**$_2$CH$_2$), 0.95 (2H, t, *J* = 7.3 Hz, C**H**$_3$CH$_2$CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 172.6 (C), 158.9 (C), 130.5 (C), 129.1 (2 x CH), 114.0 (2 x CH), 55.2 (CH$_3$), 43.0 (CH$_2$), 38.6 (CH$_2$), 19.1 (CH$_2$), 13.7 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{12}$H$_{17}$NO$_2$ [M]$^+$: 207.1254, found: 207.1253.

Data for **425**: R$_f$ (30% EtOAc in hexane) = 0.32; IR (film) 2959, 2924, 2853, 1740 (C=O), 1716 (C=O), 1651 (C=O), 1513, 1247, 1096, 1029 cm^{-1}; ^{1}H NMR (250 MHz,

CDCl$_3$) δ 7.34 (2H, d, J = 8.7 Hz, Ar**H**), 7.30-7.26 (3H, m, Ar**H**), 7.15-7.10 (2H, m, Ar**H**), 6.91 (2H, d, J = 8.7 Hz, Ar**H**), 4.89 (1H, d, J = 18.3 Hz, OC**H$_A$**H$_B$Ph), 4.71 (1H, d, J = 18.3 Hz, OCH$_A$**H$_B$**Ph), 4.32 (1H, d, J = 11.9 Hz, NHC**H$_C$**H$_D$), 4.26 (1H, d, J = 11.9 Hz, NHCH$_C$**H$_D$**), 3.83 (3H, s, OC**H$_3$**), 3.79 (3H, s, OC**H$_3$**), 3.73 (2H, s, C**H$_2$**OBn), 2.42 (3H, s, C**H$_3$**C=O), 2.26 (2H, t, J = 11.9 Hz, C**H$_2$**C=O), 1.62 (2H, m, CH$_3$C**H$_2$**CH$_2$), 0.85 (3H, t, J = 7.4 Hz, C**H$_3$**CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.9 (C), 176.0 (C), 168.7 (C), 158.6 (C), 136.7 (C), 130.5 (C), 128.3 (2 x CH), 127.8 (CH), 127.4 (2 x CH), 126.9 (2 x CH), 114.0 (2 x CH), 77.2 (C), 73.7 (CH$_2$), 70.3 (CH$_2$), 55.2 (CH$_3$), 52.7 (CH$_3$), 48.6 (CH$_2$), 34.9 (CH$_2$), 28.0 (CH$_3$), 18.3 (CH$_2$), 13.6 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{25}$H$_{31}$NO$_6$ [M]$^+$: 441.2146, found: 441.2146.


2-Iodobutanal (447)[191]
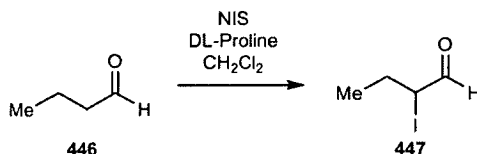
To a stirred solution of butanal **446** (1.80 mL, 20.0 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C was added *DL*-proline (690 mg, 6.00 mmol), followed by the addition of NIS (5.80 g, 10.1 mmol). This reaction mixture was stirred for 30 minutes at 0 °C, allowed to warm up to room temperature and then stirred for another 5 h. Hexane was added to the reaction mixture and the precipitated NIS, succinimide and catalyst were filtered off. The solvents were concentrated *in vacuo* and purification of the residue by column chromatography (10 % EtOAc/hexane) gave α-iodoaldehyde **446** (1.66 g, 42%) as a light pink oil. R$_f$ (30% EtOAc in hexane) = 0.55; ^{1}H NMR (250 MHz, CDCl$_3$) δ 9.27 (1H, s, C**H**O), 4.46-4.37 (1H, m, C**H**ICHO), 2.09-1.86 (2H, m, CH$_3$C**H$_2$**CHI), 1.09-1.00 (3H, m, C**H$_3$**CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 191.7 (C), 38.6 (CH), 25.6 (CH$_2$), 14.0 (CH$_3$).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[191]

2-Iodobutanoic acid (448)
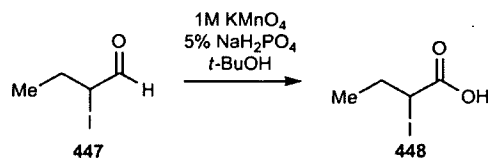
To a solution of the α-iodoaldehyde **447** (1.27 g, 6.40 mmol) in *t*-BuOH (38 mL) and 5% NaH$_2$PO$_4$ solution (26 mL) at room temperature was added KMNO$_4$ (38 mL, 1 M solution). The reaction mixture was stirred for 3 h and then quenched by the addition of solid Na$_2$SO$_3$ until the solution turned dark brown from the original purple colour. 1 M HCl (30 mL) was added to the reaction mixture until acidic pH. The reaction was then extracted with Et$_2$O (4 x 40 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol) gave *α-iodoacid* **448** (1.31 mg, 95%) as a light pink oil. R$_f$ (30% EtOAc in hexane) = 0.26; IR (film) 2970 (OH), 1705 (C=O), 1456, 1417, 1271, 1218, 1143, 930, 783, 506 (C-I) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 10.3 (1H, bs, OH), 4.27 (1H, t, *J* = 7.5 Hz, CHICO$_2$H), 2.00 (2H, dq, *J* = 7.5, 7.3 Hz, CH$_3$CH$_2$CHI), 1.01 (3H, t, *J* = 7.2 Hz, CH$_3$CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 177.6 (C), 29.2 (CH), 21.9 (CH$_2$), 13.9 (CH$_3$); HRMS (EI) Exact mass calcd for C$_4$H$_7$O$_2$I [M]$^+$: 213.9485, found: 213.9489.

(2*R*)-Methyl 2-benzyloxymethyl-2-[2-iodo-N-(4-methoxybenzyl)butanamido]-3-oxobutanoate (449a and 449b)
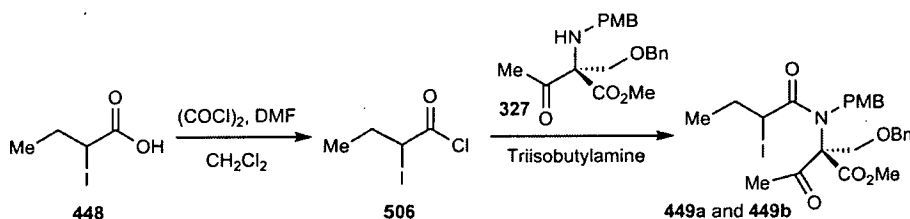
To a stirred solution of acid **448** (615 mg, 1.46 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C, was added oxalyl chloride (0.74 mL, 8.30 mmol) followed by DMF (1 drop). The reaction was stirred 5 min at 0 °C and then allowed to warm up to room temperature and stirred for another 30 min. The solution containing the acid chloride was concentrated *in vacuo*, redissolved in CH$_2$Cl$_2$ (8 mL) and then transferred *via* cannula into a stirred solution of amine **327** (270 mg, 0.73 mmol) in CH$_2$Cl$_2$ (10 mL) and

triisobutylamine (0.22 mL, 0.87 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature, stirred for 14 h and then quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) afforded the two diastereomers of *amide*, the more polar diastereomer **449a** (226 mg, 40%) and the less polar diastereomer **449b** (189 mg, 35%), as yellow oils.

Data for **449b**: R_f (30% EtOAc in hexane) = 0.62; $[\alpha]_D^{22}$ −62.9 (*c* 0.985, $CHCl_3$); IR (film) 2952, 2360, 1741 (C=O), 1708 (C=O), 1650 (C=O), 1513, 1358, 1246, 1097, 738, 504 (C-I) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (2H, d, J = 8.6 Hz, ArH), 7.25-7.19 (3H, m, ArH), 7.10-7.04 (2H, m, ArH), 6.87 (2H, d, J = 8.6 Hz, ArH), 5.03 (1H, d, J = 18.7 Hz, OCH$_A$H$_B$Ph), 4.59 (1H, d, J = 18.7 Hz, OCH$_A$H$_B$Ph), 4.31 (1H, d, J = 11.7 Hz, NCH$_C$H$_D$), 4.22 (1H, d, J = 11.7 Hz, NCH$_C$H$_D$), 4.03 (1H, dd, J = 8.9, 5.9 Hz, CHI), 3.80 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_3$), 3.65 (2H, s, CH$_2$OBn), 2.45 (3H, s, CH$_3$C=O), 2.15-1.95 (1H, m, CHICH$_E$H$_F$CH$_3$), 1.95-1.75 (1H, m, CHICH$_E$H$_F$CH$_3$), 0.67 (3H, t, J = 7.2 Hz, CH$_E$H$_F$CH$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.4 (C), 173.0 (C), 169.4 (C), 159.3 (C), 137.0 (C), 130.6 (C), 128.8 (2 x CH), 128.3 (CH), 127.9 (2 x CH), 127.1 (2 x CH), 114.6 (2 x CH), 77.6 (C), 74.3 (CH$_2$), 70.8 (CH$_2$), 55.7 (CH$_3$), 53.2 (CH$_3$), 49.7 (CH$_2$), 30.9 (CH$_2$), 28.5 (CH$_3$), 22.3 (CH), 14.3 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{25}H_{31}INO_6$ [M+H]$^+$: 568.1191, found: 568.1194.

Data for **449a**: R_f (30% EtOAc in hexane) = 0.52; $[\alpha]_D^{22}$ +28.0 (*c* 0.57, $CHCl_3$); IR (film) 2953 (OH), 2360, 1743 (C=O), 1730 (C=O), 1653 (C=O), 1513, 1410, 1247, 1094, 736, 503 (C-I) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 8.6 Hz, ArH), 7.27-7.20 (3H, m, ArH), 7.14-7.08 (2H, m, ArH), 6.86 (2H, d, J = 8.6 Hz, ArH), 4.78 (1H, d, J = 18.4 Hz, OCH$_A$H$_B$Ph), 4.67 (1H, d, J = 18.4 Hz, OCH$_A$H$_B$Ph), 4.36 (1H, d, J = 11.8 Hz, NCH$_C$H$_D$), 4.30 (1H, d, J = 11.8 Hz, NCH$_C$H$_D$), 4.13 (1H, dd, J = 8.9, 5.8 Hz, CHI), 3.93 (1H, d, J = 10.4 Hz, CH$_E$H$_F$OBn), 3.85 (1H, d, J = 10.4 Hz, CH$_E$H$_F$OBn), 3.77 (3H, s, OCH$_3$), 3.70 (3H, s, OCH$_3$), 2.33 (3H, s, CH$_3$C=O), 2.17-1.97 (1H, m, CHICH$_G$H$_H$CH$_3$), 1.96-1.75

(1H, m, CHICH$_G$**H$_H$**CH$_3$), 0.70 (3H, t, J = 7.2 Hz, CH$_G$H$_H$CH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.5 (C), 172.8 (C), 167.5 (C), 158.8 (C), 136.7 (C), 130.1 (C), 128.3 (2 x CH), 127.8 (CH), 127.6 (2 x CH), 126.9 (2 x CH), 114.2 (2 x CH), 78.0 (C), 73.8 (CH$_2$), 70.1 (CH$_2$), 55.3 (CH$_3$), 52.8 (CH$_3$), 50.6 (CH$_2$), 30.5 (CH$_2$), 27.5 (CH$_3$), 22.0 (CH) 13.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{31}$INO$_6$ [M+H]$^+$: 568.1191, found: 568.1191.

4-(4-Methoxybenzyloxy)butan-1-ol (455)[174]
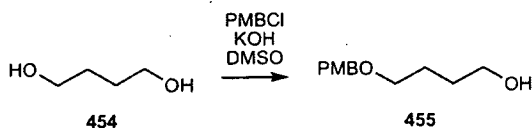
To a stirred solution of 1,4-butanediol (55.0 mL, 61.4 mmol) and KOH (powder, 4.16 g, 63.0 mmol) in DMSO (12 mL) at 0 °C was added *p*-(methoxy)benzyl chloride (4.15 mL, 30.0 mmol). The reaction was stirred at 0 °C for 2 h, allowed to warm up to room temperature, stirred then for 12 h and quenched with saturated aqueous NH$_4$Cl solution (30 mL). The aqueous layer was extracted with Et$_2$O (4 x 40 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (1 x 60 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30% to 40% EtOAc/petrol) gave monoalcohol **455** (5.32 g, 85%) as a colourless oil. R$_f$ (30% EtOAc in hexane) = 0.50; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.25 (2H, d, J = 8.6 Hz, ArH), 6.73 (2H, d, J = 8.6 Hz, ArH), 4.41 (2H, s, ArCH$_2$O), 3.75 (3H, s, OCH$_3$), 3.59 (2H, t, J = 5.1 Hz, OCH$_2$CH$_2$), 3.48 (2H, t, J = 5.3 Hz, CH$_2$CH$_2$OH), 2.30 (1H, bs, OH), 1.70-1.58 (4H, m, CH$_2$CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 159.1 (C), 130.1 (C), 129.2 (2 x CH), 113.7 (2 x CH), 72.5 (CH$_2$), 69.9 (CH$_2$), 62.4 (CH$_2$), 55.1 (CH$_3$), 29.9 (CH$_2$), 26.5 (CH$_2$).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[174]

4-(4-Methoybenzyloxy)butyric acid (456)[174]
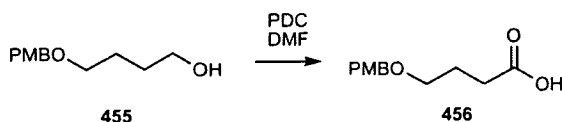
To a stirred solution of alcohol **455** (5.32 g, 25.3 mmol) in DMF (125 mL) at room temperature was added PDC (34.0 g, 88.5 mmol) portionwise. The reaction was stirred for 14 h and then quenched with water (250 mL) and extracted with Et_2O (5 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) afforded acid **456** (4.0 g, 71%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.25; ^1H NMR (360 MHz, $CDCl_3$) δ 10.5 (1H, bs, O**H**), 7.22 (2H, d, $J =$ 8.7 Hz, Ar**H**), 6.84 (2H, d, $J =$ 5.6 Hz, Ar**H**), 4.40 (2H, s, ArC**H₂**O), 3.76 (3H, s, OC**H₃**), 3.46 (2H, t, $J =$ 6.1 Hz, OC**H₂**CH₂), 2.43 (2H, t, $J =$ 7.3 Hz, C**H₂**C=O), 1.89 (2H, quint, $J =$ 7.3, 6.1 Hz, CH₂C**H₂**CH₂); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.9 (C), 159.0 (C), 130.2 (C), 129.1 (2 x CH), 113.7 (2 x CH), 72.4 (CH_2), 68.6 (CH_2), 55.1 (CH_3), 30.9 (CH_2), 24.7 (CH_2).

^1H and ^{13}C spectroscopic data in good agreement with the literature.[174]

## 4-(*tert*-Butyldiphenylsilyloxy)butan-1-ol (458)[179]
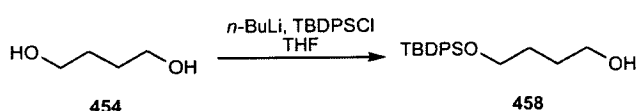
To a vigorously stirred solution of 1,4-butanediol (4.0 mL, 45 mmol) in THF (24 mL) at −78 °C was added *n*-BuLi (9.4 mL, 1.6 M in hexanes, 15 mmol) dropwise over 10 min. The reaction was stirred for 5 min and TBDPSCl (4.0 mL, 15 mmol) was then added dropwise. The reaction was allowed to warm up to room temperature (a white suspension was formed), stirred for 1.5 h and then quenched with water (20 mL) and saturated aqueous NH₄Cl solution (20 mL). The aqueous layer was separated and extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10 % to 20% EtOAc/petrol) gave mono-protected alcohol **458** (4.78 g, 97%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.50; ^1H NMR (360 MHz, $CDCl_3$) δ 7.72-7.68 (4H, m, Ar**H**), 7.48-7.38 (6H, m, Ar**H**), 3.73 (2H, t, $J =$ 5.6 Hz, C**H₂**OH), 3.68 (2H, t, $J =$ 5.7 Hz, TBDPSOC**H₂**), 1.74-1.65 (4H, m, C**H₂**CH₂), 1.09 (9H, s, C(C**H₃**)₃); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 135.5 (4 x CH),

133.6 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 63.9 (CH_2), 62.7 (CH_2), 29.7 (CH_2), 29.2 (CH_2), 26.8 (3 x CH_3), 19.1 (C).

^{1}H spectroscopic data in good agreement with the literature.[179]

4-(*tert*-Butyldiphenylsilyl)oxy butyric acid (459)[179]
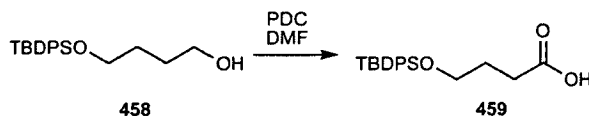
To a stirred solution of alcohol **458** (4.40 g, 13.3 mmol) in DMF (35 mL) at 0 °C was added PDC (18.0 g, 46.8 mmol) portionwise. The reaction was allowed to warm to room temperature, stirred for 14 h and then quenched with water (250 mL). The aqueous layer was extracted with Et_2O (5 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) afforded acid **459** (2.4 g, 51%) as a colourless solid. R_f (30% EtOAc in hexane) = 0.20; m.p. 68-70 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.70-7.65 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 3.71 (2H, t, J = 5.9 Hz, OCH_2), 2.53 (2H, t, J = 7.3 Hz, CH_2CO_2H), 1.90 (2H, q, J = 7.3, 5.9 Hz, $CH_2CH_2CH_2$), 1.06 (9H, s, $C(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 179.4 (C), 135.5 (4 x CH), 133.5 (2 x C), 129.6 (2 x CH), 127.6 (4 x CH), 62.7 (CH_2), 30.7 (CH_2), 27.4 (CH_2), 26.8 (3 x CH_3), 19.1 (C).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[179]

4-(*tert*-Butyldiphenylsilyl)oxy-1-butanal (461)[192]
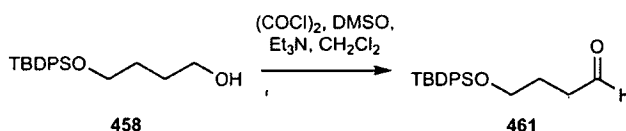
To a stirred solution of oxalyl chloride (1.10 mL, 12.7 mmol) in CH_2Cl_2 (30 mL) at −78 °C, was added DMSO (1.80 mL, 25.6 mmol) dropwise. After stirring for 15 minutes, a solution of alcohol **458** (2.0 g, 6.1 mmol) in CH_2Cl_2 (30 mL) was added *via* cannula. The reaction stirred at −78 °C for 1 h and then Et_3N (3.60 mL, 25.6 mmol) was added. The reaction was stirred at −78 °C for 1 h, allowed to warm up to −40 °C for 2 h and then quenched with NH_4Cl (40 mL). The aqueous layer was

separated and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave aldehyde **461** (1.57 g, 79%) as a colourless oil. R$_f$ (30% EtOAc in hexane) = 0.70; ^{1}H NMR (360 MHz, CDCl$_3$) δ 9.80 (1H, d, J = 1.6 Hz, CHO), 7.67 (4H, d, J = 7.9 Hz, ArH), 7.45-7.37 (6H, m, ArH), 3.71 (2H, t, J = 6.0 Hz, OCH$_2$CH$_2$), 2.56 (2H, dt, J = 7.1, 1.6 Hz, CH$_2$CHO), 1.94-1.87 (2H, m, CH$_2$CH$_2$CH$_2$), 1.07 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 202.5 (C), 135.5 (2 x CH), 135.2 (C), 134.8 (4 x CH), 133.6 (C), 129.7 (CH), 127.7 (4 x CH), 62.9 (CH$_2$), 40.7 (CH$_2$), 26.6 (3 x CH$_3$), 25.2 (CH$_2$), 19.2 (C).

^{1}H and ^{13}C spectroscopic data in good agreement with the literature.[192]
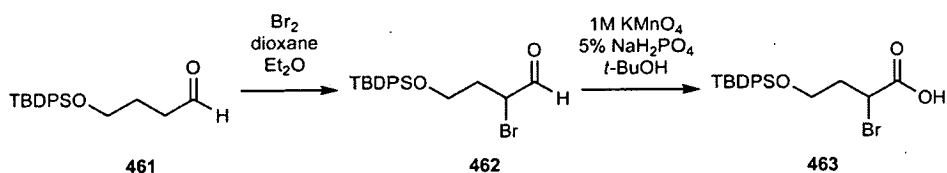
2-Bromo-4-(*tert*-butyldiphenylsilyl)oxy-1-butanoic acid (463)


To a stirred solution of aldehyde **461** (1.47 g, 4.52 mmol) and dioxane (1.20 mL) in dry Et$_2$O (18 mL) at 0 °C, was added bromine (0.23 mL, 4.52 mmol) dropwise over 1 min. The reaction was stirred for 30 minutes at 0 °C and then 1 h at rt when it was quenched with saturated aqueous NaHCO$_3$ solution. The aqueous layer was extracted with Et$_2$O (2 x 20 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude residue was used in the oxidation step without further purification.

To a stirred solution of the α-bromoaldehyde **462** in *t*-BuOH (29 mL) and 5% NaH$_2$PO$_4$ solution (19.5 mL) at room temperature was added KMnO$_4$ (1 M solution, 29 mL). The reaction was stirred for 3 h and then quenched by the addition of solid Na$_2$SO$_3$ until the solution turned dark brown from the original purple colour. 1 M HCl (30 mL) was added to the reaction mixture until acidic pH. The reaction was then extracted with Et$_2$O (4 x 40 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 20% EtOAc/petrol) gave *α-bromoacid* **463** (0.72 g, 38% in two steps) as a colourless solid. R$_f$ (30% EtOAc in hexane) = 0.20; m.p.= 73-75 °C;

IR (film) 2957 (OH), 2931, 2857, 1718 (C=O), 1428, 1277, 1111, 737, 701, 505 (C-Br) cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.72-7.66 (4H, m, ArH), 7.49-7.39 (6H, m, ArH), 4.66 (1H, dd, J = 8.1, 6.1 Hz, CHBr), 3.87-3.77 (2H, m, OCH$_2$CH$_A$H$_B$), 2.46-2.37 (1H, m, OCH$_2$CH$_A$H$_B$), 2.22-2.12 (1H, m, OCH$_2$CH$_A$H$_B$), 1.08 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.6 (C), 135.5 (4 x CH), 133.1 (2 x C), 129.8 (2 x CH), 127.7 (4 x CH), 60.6 (CH$_2$), 42.6 (CH), 37.2 (CH$_2$), 26.8 (3 x CH$_3$), 19.1 (C); HRMS (ES) Exact mass calcd for C$_{20}$H$_{29}$^{79}BrNO$_3$Si [M+NH$_4$]$^+$: 438.1095, found: 438.1093.

(*R*)-Methyl 2-benzyloxymethyl-2-[2-bromo-4-(*tert*-butyldiphenylsilyloxy)-*N*-(4-methoxybenzyl)butanamido]-3-oxobutanoate (463a and 463b)
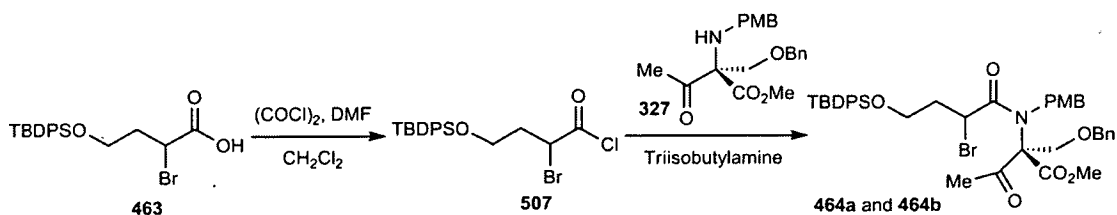

To a stirred solution of acid **463** (615 mg, 1.46 mmol) in CH$_2$Cl$_2$ (8 mL) at 0 °C, was added oxalyl chloride (0.74 mL, 8.30 mmol) followed by DMF (1 drop). The reaction was stirred 5 min at 0 °C and then allowed to warm up to room temperature and stirred for another 30 min. The solution containing the acid chloride was concentrated *in vacuo*, redissolved in CH$_2$Cl$_2$ (8 mL) and then transferred *via* cannula into a stirred solution of amine **327** (271 mg, 0.73 mmol) in CH$_2$Cl$_2$ (10 mL) and triisobutylamine (0.22 mL, 0.87 mmol) at 0 °C. The reaction mixture was stirred for 14 h at room temperature and then quenched with saturated aqueous NH$_4$Cl solution (10 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 15 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) afforded the two diastereomers of *amide*, the more polar diastereomer **464a** (226 mg, 40%) and the less polar diastereomer **464b** (189 mg, 33%), as yellow oils.

Data for **464b**: R$_f$ (30% EtOAc in hexane) = 0.48; [α]$_D^{22}$ −19.8 (*c* 0.98, CHCl$_3$); IR (film) 2929, 2856, 2360, 1741 (C=O), 1708 (C=O), 1654 (C=O), 1513, 1247, 1106, 701, 505 (C-Br) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.87-7.81 (4H, m, ArH),

7.70-7.52 (11H, m, Ar**H**), 7.40 (2H, d, J = 8.5 Hz, Ar**H**), 7.11 (2H, d, J = 8.5 Hz, Ar**H**), 5.38 (1H, d, J = 18.7 Hz, OCH$_A$**H**$_B$Ph), 5.21 (1H, d, J = 18.7 Hz, OCH$_A$**H**$_B$Ph), 4.99 (1H, dd, J = 8.3, 5.8 Hz, CH**Br**), 4.61 (1H, d, J = 11.7 Hz, NHCH$_C$**H**$_D$), 4.54 (1H, d, J = 11.7 Hz, NHCH$_C$**H**$_D$), 4.11 (3H, s, OC**H$_3$**), 4.01-3.98 (3H+2H+2H, m, OC**H$_3$**+C**H$_2$**OBn+OC**H$_2$**CH$_2$), 2.76 (3H, s, C**H$_3$**C=O), 2.50-2.40 (2H, m, CHBrC**H$_2$**), 1.13 (9H, s, C(C**H$_3$**)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.8 (C), 171.5 (C), 168.5 (C), 158.7 (C), 136.5 (C), 135.3 (4 x CH), 133.3 (C), 133.2 (C), 129.5 (2 x CH), 128.3 (2 x CH), 127.8 (CH), 127.6 (2 x C), 127.5 (4 x CH), 127.4 (2 x CH), 126.5 (2 x CH), 114.2 (2 x CH), 73.8 (CH$_2$), 70.1 (CH$_2$), 60.3 (CH$_2$), 55.1 (CH$_3$), 52.8 (CH$_3$), 48.7 (CH$_2$), 41.5 (CH), 37.3 (CH$_2$), 28.0 (CH$_3$), 26.6 (3 x CH$_3$), 18.9 (C); HRMS (ES) Exact mass calcd for C$_{41}$H$_{49}$^{79}BrNO$_7$Si [M+H]$^+$: 774.2456, found: 774.2460.

Data for **464a**: R$_f$ (30% EtOAc in hexane) = 0.35; [α]$_D^{22}$ +4.4 (*c* 0.905, CHCl$_3$); IR (film) 2931, 2857, 2360, 1745 (C=O), 1721 (C=O), 1660 (C=O), 1513, 1247, 1108, 701, 505 (C-Br) cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.70-7.64 (4H, m, Ar**H**), 7.51-7.35 (11H, m, Ar**H**), 7.24 (2H, d, J = 8.6 Hz, Ar**H**), 6.94 (2H, d, J = 8.6 Hz, Ar**H**), 5.12 (2H, d, J = 18.7 Hz, OC**H$_2$**Ph), 4.98 (1H, dd, J = 8.7, 5.6 Hz, CH**Br**), 4.23 (2H, s, NHC**H$_2$**Ar), 3.93 (2H, s, C**H$_2$**OBn), 3.88-3.84 (2H, m, OC**H$_2$**CH$_2$), 3.83 (3H, s, OC**H$_3$**), 3.81 (3H, s, OC**H$_3$**), 2.49 (3H, s, C**H$_3$**C=O), 2.42-2.23 (2H, m, CHBrC**H$_2$**), 0.99 (9H, s, C(C**H$_3$**)$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.5 (C), 171.7 (C), 167.6 (C), 158.7 (C), 136.5 (C), 135.3 (4 x CH), 133.3 (C), 133.1 (C), 129.5 (2 x CH), 129.3 (2 x C), 128.3 (2 x CH), 127.8 (CH), 127.6 (4 x CH), 127.5 (2 x CH), 126.7 (2 x CH), 114.1 (2 x CH), 73.7 (CH$_2$), 70.1 (CH$_2$), 60.4 (CH$_2$), 55.1 (CH$_3$), 52.7 (CH$_3$), 49.2 (CH$_2$), 41.6 (CH), 37.7 (CH$_2$), 27.7 (CH$_3$), 26.6 (3 x CH$_3$), 18.9 (C); HRMS (ES) Exact mass calcd for C$_{41}$H$_{49}$^{79}BrNO$_7$Si [M+H]$^+$: 774.2456, found: 774.2457.

**4-Hydroxybutyl acetate (465)**[193]
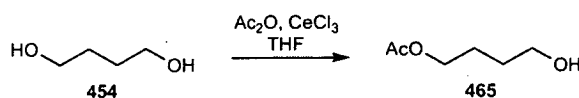
To a stirred solution of 1,4-butanediol (5.30 mL, 60.0 mmol) and $CeCl_3 \cdot 7H_2O$ (2.2 g, 6.0 mmol) in THF (170 mL) at room temperature was added acetic anhydride (57.0 mL, 600 mmol). The reaction was stirred for 16 h, diluted with Et_2O (100 mL) and then washed with a saturated aqueous $NaHCO_3$ solution (2 x 60 mL) and with saturated NaCl aqueous solution (1 x 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/hexane) gave monoacetate **465** (3.35 g, 43%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.20; ^1H NMR (250 MHz, $CDCl_3$) δ 4.09 (2H, d, J = 6.3 Hz, **CH$_2$OAc**), 3.67 (2H, d, J = 6.3 Hz, **CH$_2$OH**), 2.04 (3H, s, **CH$_3$C=O**), 1.79 (1H, bs, **OH**), 1.78-1.58 (4H, m, **CH$_2$CH$_2$**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.2 (C), 64.2 (CH_2), 62.3 (CH_2), 29.1 (CH_2), 25.0 (CH_2), 21.0 (CH_3).

^1H and ^{13}C spectroscopic data in good agreement with the literature.[193]

4-Oxobutyl acetate (466)[194]
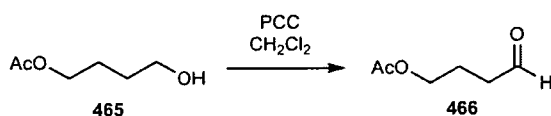
To a stirred solution of PCC (8.20 g, 38.0 mmol) in CH_2Cl_2 (70 mL) at room temperature was added a solution of monoalcohol acetate **465** (3.35 g, 25.3 mmol) in CH_2Cl_2 (7 mL) *via* cannula. The reaction was stirred for 1.5 h, when Et_2O (70 mL) was added. The solution was filtered through celite and the organics were concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 30% EtOAc/hexane) gave aldehyde **466** (2.13 g, 65%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.47; ^1H NMR (360 MHz, $CDCl_3$) δ 9.77 (1H, t, J = 1.3 Hz, **CHO**), 4.10 (2H, dt, J = 6.3, 4.8 Hz, **AcOCH$_2$**), 2.54 (1H, td, J = 7.1, 1.3 Hz, **CH$_2$CH$_A$H$_B$CHO**), 2.43 (1H, td, J = 14.0, 7.1 Hz, **CH$_2$CH$_A$H$_B$CHO**), 2.18 (3H, s, **CH$_3$C=O**), 2.17-2.05 (2H, m, **CH$_2$CH$_2$CH$_2$**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.2 (CH), 170.9 (C), 63.4 (CH_2), 40.4 (CH_2), 21.3 (CH_2), 20.8 (CH_3).

^1H spectroscopic data in good agreement with the literature.[194]

4-Acetyloxy-2-bromobutanal (467)[195]
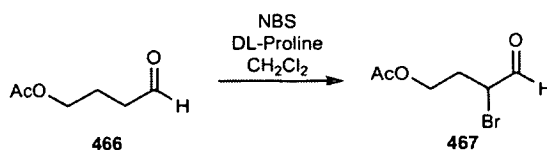
To a stirred solution of aldehyde **466** (2.40 g, 18.4 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added *DL*-proline (640 mg, 5.53 mmol), followed by the addition of NBS (4.60 g, 25.8 mmol). The reaction was stirred for 30 minutes at 0 °C and then allowed to warm up to room temperature and stirred for another 4 h. Hexane was added to the reaction mixture and the precipitated NBS, succinimide and catalyst were filtered off. The solvents were concentrated *in vacuo* and purification of the residue by column chromatography (15% to 20% EtOAc/hexane) gave α-bromoaldehyde **467** (2.92 g, 75%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.30; ^1H NMR (360 MHz, $CDCl_3$) δ 9.47 (1H, d, J = 2.0 Hz, CHO), 4.42-4.34 (1H, m, CHBrCHO), 4.31-3.98 (2H, m, OCH_2CH_2), 2.48-2.31 (1H, m, $CH_2CH_AH_BCHBr$), 2.24-2.07 (1H, m, $CH_2CH_AH_BCHBr$), 2.04 (3H, s, $CH_3C=O$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 191.7 (CH), 176.3 (C), 61.0 (CH_2), 51.3 (CH), 30.5 (CH_2), 20.6 (CH_3).

^1H spectroscopic data in good agreement with the literature.[195]

4-Acetyloxy-2-bromobutanoic acid (468)
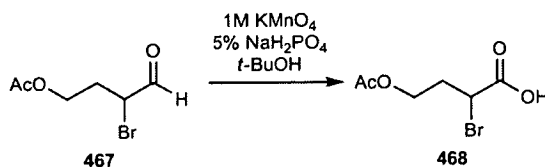
To a solution of α-bromoaldehyde **467** (500 mg, 2.38 mmol) in *t*-BuOH (14 mL) and 5% NaH_2PO_4 solution (9.5 mL) at room temperature was added $KMNO_4$ (14 mL, 1 M solution). The reaction was stirred for 3 h and then quenched by the addition of solid Na_2SO_3 until the solution turned dark brown from the original purple colour. 1 M HCl (10 mL) was added to the reaction mixture until acidic pH. The reaction was then extracted with Et_2O (4 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 20% EtOAc/petrol) gave *α-bromoacid* **468** (386 mg, 70%) as a colourless oil. R_f (30% EtOAc in hexane) = 0.12; IR (film)

2967 (OH), 1738 (2 x C=O), 1428, 1390, 1368, 1244, 1040, 806, 666, 607, 503 (C-Br) cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 10.3(1H, bs, OH), 4.40 (1H, dd, J = 8.3, 6.1 Hz, CHBrCO$_2$H), 4.29 (1H, td , J = 10.9, 5.4 Hz, AcOCH$_A$H$_B$), 4.20 (1H, ddd, J = 11.6, 8.1, 4.7 Hz, AcOCH$_A$H$_B$), 2.51-2.41 (1H, m, CH$_2$CH$_A$H$_B$CHBr), 2.34-2.25 (1H, m, CH$_2$CH$_A$H$_B$CHBr), 2.07 (3H, s, CH$_3$C=O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 173.9 (C), 171.2 (C), 61.4 (CH$_2$), 41.5 (CH), 33.5 (CH$_2$), 20.7 (CH$_3$); HRMS (EI) Exact mass calcd for C$_6$H$_9$^{79}BrO$_4$ [M]$^+$: 223.9679, found: 223.9677.

4-(*tert*-Butyldiphenylsilyl)oxy-*N*-(4-methoxybenzyl)butanamide (470)
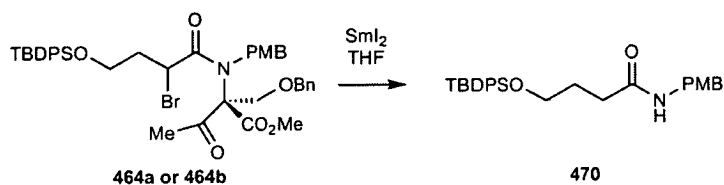
To a stirred solution of amide **464a** or **464b** (28 mg, 36 μmol) in THF (1 mL) at 0 °C, was added SmI$_2$ (3.6 mL, 0.1 M solution in hexanes, 0.36 mmol). The reaction was stirred at 0 °C for 1 h and then quenched with saturated aqueous NH$_4$Cl solution (3 mL). The aqueous layer was separated and extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 15% EtOAc/petrol) gave *amide* **470** (10 mg, 40%) as a pale yellow oil. R$_f$ (30% EtOAc in hexane) = 0.39; IR (film) 3287 (NH), 2930, 2857, 1644 (C=O), 1512, 1428, 1248, 1110, 822, 701 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.67-7.61 (4H, m, ArH), 7.44-7.33 (6H, m, ArH), 7.18 (2H, d, J = 8.7 Hz, ArH), 6.85 (2H, d, J = 8.7 Hz, ArH), 5.77 (1H, bs, NH), 4.34 (2H, d, J = 5.6 Hz, NHCH$_2$Ar), 3.83 (3H, s, OCH$_3$), 3.71 (2H, t, J = 5.9 Hz, OCH$_2$CH$_2$), 2.35 (2H, t, J = 7.3 Hz, CH$_2$C=O), 1.96-1.85 (2H, m, CH$_2$CH$_2$CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 172.5 (C), 158.9 (C), 135.4 (4 x CH), 133.6 (2 x C), 130.4 (C), 129.6 (2 x CH), 129.1 (2 x CH), 127.6 (4 x CH), 114.0 (2 x CH), 63.0 (CH$_2$), 55.2 (CH$_3$), 43.0 (CH$_2$), 33.1 (CH$_2$), 28.4 (CH$_2$), 26.8 (3 x CH$_3$), 19.2 (C); HRMS (EI) Exact mass calcd for C$_{28}$H$_{35}$NO$_3$Si [M]$^+$: 461.2381, found: 461.2382.

6.2.4. Formal synthesis

(*R*)-Ethyl (*E*)-3-[*N*-(1-benzyloxymethyl-1-carbomethoxy-2-oxopropyl)-*N*-(4-methoxybenzyl)carbamoyl]acrylate (481)
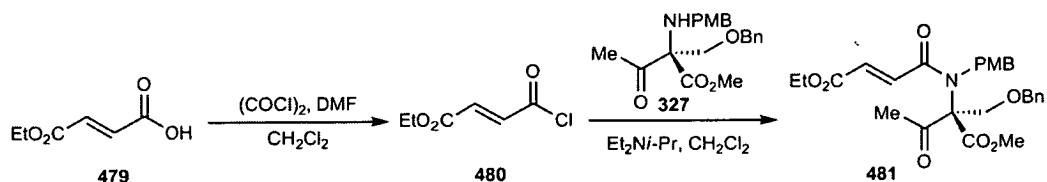
To a stirred solution of fumaric acid monoethyl ester (858 mg, 5.65 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C was added oxalyl chloride (0.56 mL, 6.40 mmol) followed by DMF (one drop). This solution was stirred at room temperature for 1 h, and then transferred *via* cannula to a solution of the amine **327** (1.34 g, 3.60 mmol) and diisopropylethyl amine (1.10 mL, 6.40 mmol) in CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 18 h, when it was quenched with saturated aqueous NH$_4$Cl solution (20 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 20 mL), and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave *amide* **481** (1.7 g, 95%) as a pale yellow oil. R$_f$ (30% EtOAc in hexane) = 0.45; $[\alpha]_D^{22}$ −18.2 (*c* 1.18, CHCl$_3$); IR (film) 2953, 2837, 1722 (C=O),1658 (C=O), 1513, 1408, 1294, 1175, 1032, 974 cm^{-1}; ^{1}H NMR (360 MHz, CDCl3) δ 7.35-7.27 (5H, m, Ar**H**), 7.22 (1H, d, *J* = 15.3 Hz, =C**H**), 7.17-7.12 (2H, m, Ar**H**), 6.95-6.89 (2H, dm, *J* = 8.8 Hz, Ar**H**), 6.80 (1H, d, *J* = 15.3 Hz, =C**H**), 4.95 (1H, d, *J* = 18.4 Hz, OC**H$_A$**H$_B$Ar), 4.81 (1H, d, *J* = 18.4 Hz, OCH$_A$**H$_B$**Ar), 4.32 (1H, d, *J* = 11.9 Hz, NC**H$_C$**H$_D$Ar), 4.28 (1H, d, *J* = 11.9 Hz, NCH$_C$**H$_D$**Ar), 4.19 (2H, q, *J* = 7.1 Hz, OC**H$_2$**CH$_3$), 3.83 (3H, s, OC**H$_3$**), 3.80 (3H, s, OC**H$_3$**), 3.78 (2H, s, C**H$_2$**OBn), 2.45 (3H, s, C**H$_3$**C=O), 1.26 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 197.6 (C), 168.0 (C), 167.5 (C), 165.2 (C), 158.9 (C), 136.5 (C), 133.3 (CH), 133.1 (CH), 129.7 (C), 128.4 (2 x CH), 127.9 (CH), 127.5 (2 x CH), 127.1 (2 x CH) 114.2 (2 x CH), 77.5 (C), 73.7 (CH$_2$), 70.1 (CH$_2$), 61.1 (CH$_2$), 55.2 (CH$_3$), 52.9 (CH$_3$), 48.9 (CH$_2$), 27.9 (CH$_3$), 14.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{27}$H$_{32}$NO$_8$ [M+H]$^+$: 498.2122, found: 498.2123.

(3a*R*,6*R*,6a*S*)-6-Benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (489) and (3a*S*,6*R*,6a*R*)-6-benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (490)
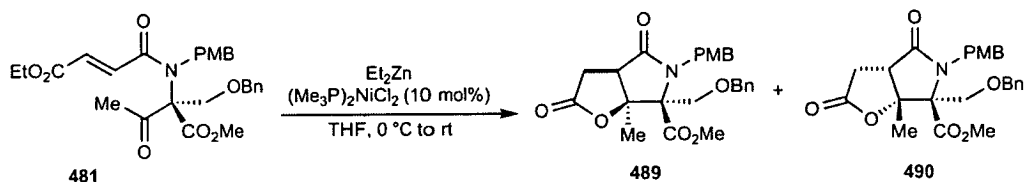
A solution of amide **481** (875 mg, 1.75 mmol) and (Me₃P)₂NiCl₂ (115 mg, 0.175 mmol) in THF (75 mL) was stirred at room temperature for 30 min and then cooled to −15 °C (ice-salt bath). Et₂Zn (3.52 mL, 1 M solution in THF, 3.52 mmol) was then added *via* syringe. The reaction was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH₄Cl solution (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 35 % EtOAc/petrol) gave the *double cyclization product* **489** (354 mg, 42%) as a pale yellow oil, followed by the *double cyclization product* **490** (253 mg, 30%) as a colourless solid. Recrystallization of **490** from EtOAc/petrol gave colourless crystals that were suitable for X-ray crystallography.

Data for *desired* **489**: R_f (30% EtOAc in CHCl₃) = 0.19; $[\alpha]_D^{22}$ −33.3 (*c* 1.02, CHCl₃); IR (film) 2955, 1789 (C=O), 1733 (C=O), 1699 (C=O), 1612, 1513, 1439, 1404, 1248, 1178 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.27-7.18 (3H + 2H, m, ArH), 7.04-6.99 (2H, m, ArH), 6.69 (2H, d, *J* = 8.7 Hz, ArH), 4.97 (1H, d, *J* = 15.2 Hz, OCH$_A$H$_B$Ph), 4.21 (1H, d, *J* = 15.2 Hz, OCH$_A$H$_B$Ph), 3.83 (1H, d, *J* = 11.5 Hz, NCH$_C$H$_D$Ar), 3.75 (1H, d, *J* = 10.4 Hz, CH$_E$H$_F$OBn), 3.73 (1H, d, *J* = 11.5 Hz, NCH$_C$H$_D$Ar), 3.73 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.13 (1H, d, *J* = 10.4 Hz, CH$_E$H$_F$OBn), 2.97 (1H, dd, *J* = 9.3, 1.5 Hz, CH$_G$H$_H$CH), 2.88 (1H, dd, *J* = 18.3, 1.5 Hz, CH$_G$H$_H$CH), 2.72 (1H, dd, *J* = 18.3, 9.3 Hz, CH$_G$H$_H$CH), 1.53 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.5 (C), 172.9 (C), 166.9 (C), 159.0 (C), 136.7 (C) 130.0 (2 x CH), 129.4 (C), 128.4 (2 x CH), 127.9 (CH), 127.3 (2 x CH), 113.6 (2 x CH), 88.4 (C), 75.8 (C), 72.8 (CH₂), 67.7 (CH₂), 55.2 (CH₃), 52.8 (CH₃), 47.5 (CH),

45.1 (CH$_2$), 30.7 (CH$_2$), 19.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{28}$NO$_7$ [M+H]$^+$: 454.1860 , found: 454.1856.

Data for *undesired* **490**: R$_f$ (30% EtOAc in CHCl$_3$) = 0.08; m.p. = 105 °C; [α]$_D^{22}$ -17.9 (*c* 1.01, CHCl$_3$); IR (film) 2952, 2870, 1789 (C=O), 1743 (C=O), 1703 (C=O), 1613, 1512, 1434, 1246, 1128 cm-1; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.38-7.21 (5H, m, ArH), 7.12 (2H, d, *J* = 8.7 Hz, ArH), 6.82 (2H, d, *J* = 8.7 Hz, ArH), 4.72 (1H, d, *J* = 15.2 Hz, OCH$_A$H$_B$Ph), 4.40 (1H, d, *J* = 15.2 Hz, OCH$_A$H$_B$Ph), 4.34 (1H, d, *J* = 11.7 Hz, NCH$_C$H$_D$Ar), 4.27 (1H, d, *J* = 11.7 Hz, NCH$_C$H$_D$Ar), 3.94 (1H, d, *J* = 10.1 Hz, CH$_E$H$_F$OBn), 3.82 (3H, s, OCH$_3$), 3.74 (1H, d, *J* = 10.1 Hz, CH$_E$H$_F$OBn), 3.67 (3H, s, OCH$_3$), 3.07 (1H, dd, *J* = 9.7, 1.8 Hz, CH$_G$H$_H$CH), 3.04 (1H, dd, *J* = 18.3, 1.9 Hz, CH$_G$H$_H$CH), 2.88 (1H, dd, *J* = 18.3, 9.7 Hz, CH$_G$H$_H$CH), 1.51 (3H, s, CH$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 173.4 (C), 173.2 (C), 169.2 (C) 158.7 (C) 137.1 (C) 129.2 (2 x CH), 129.0 (C), 128.3 (2 x CH), 127.7 (3 x CH), 113.6 (2 x CH), 86.6 (C), 75.3 (C), 73.6 (CH$_2$), 68.7 (CH$_2$), 55.2 (CH$_3$), 52.8 (CH$_3$), 46.9 (CH), 45.1 (CH$_2$), 30.9 (CH$_2$), 21.3 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{28}$NO$_7$ [M+H]$^+$: 454.1860, found: 454.1858.

(3a*R*,6*R*,6a*S*)-6-Hydroxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (493)
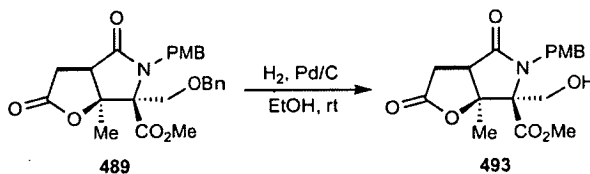
A mixture of benzyl ether **489** (354 mg, 0.78 mmol) and 10% Pd/C (99 mg, 0.093 mmol) in EtOH (5 mL) at room temperature was evacuated and flushed with H$_2$ (3 times) and then stirred vigorously under an atmosphere of H$_2$ (1 atm, H$_2$ balloon) at room temperature for 18 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol) gave *alcohol* **493** (240 mg, 84%) as a white powder. R$_f$ (100% EtOAc) = 0.52; m.p. 144-146 °C; [α]$_D^{22}$ -30.1 (*c* 0.95, CHCl$_3$); IR (film) 3437 (OH), 2955, 2253, 1787 (C=O), 1757 (C=O), 1692 (C=O), 1613, 1513, 1247, 1035, 951cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.37 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J*

205

= 8.6 Hz, Ar**H**), 5.22 (1H, d, *J* = 15.2 Hz, NC**H**$_A$H$_B$Ar), 4.24 (1H, d, *J* = 15.2 Hz, NCH$_A$**H**$_B$Ar), 3.95 (1H, dd, *J* = 13.0, 8.9 Hz, C**H**$_C$H$_D$OH), 3.83 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.43 (1H, dd, *J* = 13.0, 5.5 Hz, CH$_C$**H**$_D$OH), 3.04 (1H, dd, *J* = 9.1, 1.7 Hz, C**H**$_E$H$_F$CH), 2.96 (1H, dd, *J* = 18.1, 1.7 Hz, C**H**$_E$H$_F$CH), 2.85 (1H, dd, *J* = 18.1, 9.1 Hz, CH$_E$**H**$_F$CH), 1.69 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 173.7 (C), 172.7 (C), 167.1 (C), 159.5 (C), 129.6 (2 x CH + C), 114.6 (2 x CH), 88.3 (C), 77.3 (C), 60.9 (CH$_2$), 55.3 (CH$_3$), 52.8 (CH$_3$), 47.6 (CH), 44.9 (CH$_2$), 30.5 (CH$_2$), 19.8 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{18}$H$_{25}$N$_2$O$_7$ [M+NH$_4$]$^+$: 381.1656, found: 381.1660.
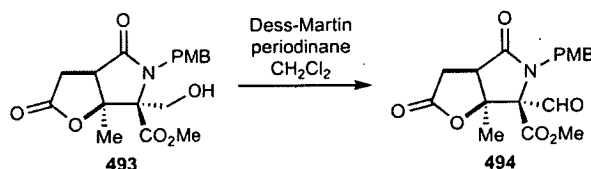
(3a*R*,6*R*,6a*S*)-6-Formyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (494)

To a solution of alcohol **493** (30 mg, 0.082 mmol) in CH$_2$Cl$_2$ (0.8 mL) at room temperature was added Dess-Martin periodinane (43 mg, 0.099 mmol). The reaction mixture was stirred for 1.5 h, quenched with water and extracted with EtOAc (3 x mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo as an oil. This aldehyde proved to be unstable and was generally used immediately in the next step without purification. On one occasion, purification of a small amount of crude product by column chromatography (50% EtOAc/petrol) was performed for characterisation purposes. R$_f$ (100% EtOAc) = 0.34; IR (film) 2956, 1788 (C=O), 1760 (C=O), 1728 (C=O), 1687 (C=O), 1513, 1438, 1246, 1176, 949 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 9.47 (1H, s, C**H**O), 7.05 (2, d, *J* = 8.7 Hz, Ar**H**), 6.81 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.86 (1H, d, *J* = 14.4 Hz, NC**H**$_A$H$_B$Ar), 4.39 (1H, d, *J* = 14.4 Hz, NCH$_A$**H**$_B$Ar), 3.90 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 3.08 (1H, dd, *J* = 9.7, 1.8 Hz, C**H**$_C$H$_D$CH), 2.99 (1H, dd, *J* = 18.4, 1.8 Hz, C**H**$_C$H$_D$CH), 2.85 (1H, dd, *J* = 18.4, 9.7 Hz, CH$_C$**H**$_D$CH), 1.52 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 195.5 (CH), 172.7 (C), 172.0 (C), 165.7 (C), 159.6 (C), 131.1 (2 x CH), 126.8 (C), 114.2 (2 x CH), 87.3 (C), 79.0 (C), 55.2 (CH$_3$), 53.4 (CH$_3$), 46.8 (CH), 45.6 (CH$_2$), 30.6 (CH$_2$),

20.5 (CH₃); LRMS (EI⁺) Mass calcd. for $C_{18}H_{19}NO_7Na$ [M+Na]⁺: 384.3, found: 383.7.
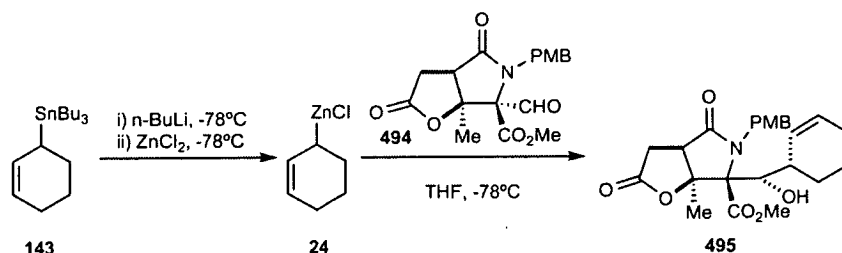
(3a*R*,6*R*,6a*S*)-6-[(7*S*)-(8*S*)-Cyclohex-2-enylhydroxymethyl]-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (495)

To a solution of cyclohexenyltributyltin (**143**)[36] (89.6 mg, 0.206 mmol) in THF (0.6 mL) at −78 °C was added *n*-BuLi (130 μL mL, 1.6 M solution in hexanes, 0.206 mmol). After stirring at −78 °C for 1 h, ZnCl₂ (0.42 mL, 0.5 M solution in THF, 0.21 mmol) was added and stirring was continued at this temperature for another 1 h. A solution of the crude aldehyde **494** from the above experiment (theoretically 0.082 mmol) in THF (0.4 mL) was then added *via* cannula, and after stirring for 3 h at −78 °C, the reaction was quenched with H₂O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*, and purification of the residue by column chromatography (50% EtOAc/petrol) gave the *homoallylic alcohol* **495** (22.4 mg, 61% over two steps) as a colourless solid. R$_f$ (100% EtOAc) = 0.61; R$_f$ (70% EtOAc in CHCl₃) = 0.45; m.p. = 114-116 °C; $[\alpha]_D^{22}$ +3.0 (*c* 1.47, CHCl₃); IR (film) 3438 (OH), 2931, 2359, 1790 (C=O), 1755 (C=O) 1687 (C=O), 1512, 1440, 1246, 1175, 807 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.18 (2H, d, *J* = 8.7 Hz, ArH), 6.84 (2H, d, *J* = 8.7 Hz, ArH), 5.91 (1H, dm, *J* = 10.2 Hz, CH=CH), 5.68 (1H, dm, *J* = 10.2 Hz, CH=CH), 4.79 (1H, d, *J* = 14.9 Hz, NCH$_A$H$_B$Ar), 4.54 (1H, d, *J* = 14.9 Hz, NCH$_A$H$_B$Ar), 4.12 (1H, t, *J* = 7.1 Hz, CHOH), 3.78 (6H, s, 2 x OCH₃), 3.13 (1H, dd, *J* = 6.8, 3.3 Hz, CH₂CHC=O), 2.92 (1H, br s, OH), 2.82-2.79 (2H, m, CH₂CHC=O), 2.32 (1H, bs, CHOHCH), 2.02 (2H, bs, CH₂), 1.81 (3H, s, CH₃CO), 1.76-1-66 (2H, m, CH₂), 1.57-1.46 (1H, m, CH₂), 1.44-1.33 (1H, m, CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 174.8 (C), 173.0 (C), 167.8 (C), 158.3 (C), 131.8 (CH), 129.3 (C), 127.6 (2 x CH), 125.2 (CH), 113.7 (2 x CH),

91.1 (C), 79.0 (C), 76.9 (CH), 55.2 (CH$_3$), 52.4 (CH$_3$), 47.9 (CH$_2$), 47.8 (CH), 38.3 (CH), 30.9 (CH$_2$), 27.0 (CH$_2$), 24.9 (CH$_2$), 20.6 (CH$_2$), 19.6 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{24}$H$_{33}$N$_2$O$_7$ [M+NH$_4$]$^+$: 461.2282, found: 461.2283.

(2R,3S,4R)-2-[(6S)-(7S)-Cyclohex-2-enylhydroxymethyl]-3-hydroxy-4-(2-hydroxyethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (26)
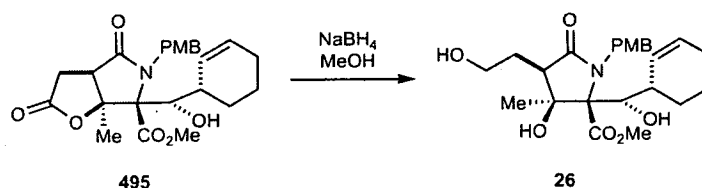
To a solution of the lactone **495** (19.3 mg, 0.043 mmol) in MeOH (0.6 mL) at room temperature was added NaBH$_4$ (75 mg, 2.0 mmol) portionwise over 2 min. The solution was stirred for 18 h, quenched with H$_2$O (4 mL) and extracted with EtOAc (3 x 4 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (70% EtOAc/petrol) gave triol **26** (11.7 mg, 60%) as a white foam. R$_f$ (70% EtOAc in CHCl$_3$) = 0.12; m.p. = 82-83 °C, lit.[26] 83-84 °C; [α]$_D^{22}$ +3.5 (*c* 0.56, CHCl$_3$), lit.[26] +5.2 (*c* 0.60, CHCl$_3$); IR (film) 3331(OH), 2925, 2853, 1752 (C=O), 1670 (C=O), 1512, 1441, 1245, 1175, 1034 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.29 (2H, d, *J* = 8.7 Hz, ArH), 6.85 (2H, d, *J* = 8.7 Hz, ArH), 5.93 (1H, dm, *J* = 10.2 Hz, CH=CH), 5.62 (1H, dm, *J* = 10.2 Hz, CH=CH), 4.76 (1H, d, *J* = 15.2 Hz, NCH$_A$H$_B$Ar), 4.39 (1H, d, *J* = 15.2 Hz, NCH$_A$H$_B$Ar), 4.15 (1H, t, *J* = 6.3 Hz, CHOH), 3.87-3.81 (1H, m, HOCH$_C$H$_D$CH$_2$), 3.80-3.75 (1H, m, HOCH$_C$H$_D$CH$_2$), 3.79 (3H, s, OCH$_3$), 3.71 (3H, s, OCH$_3$), 3.02 (1H, dd, *J* = 8.1, 4.8 Hz, COCH), 2.20 (1H, bs, CHOHCH), 2.01 (2H, bs, CH$_2$), 1.93- 1.78 (2H, m, CH$_2$), 1.76-1.65 (2H, m, CH$_2$), 1.64 (3H, s, CH$_3$CO), 1.54-1.41 (2H, m, CH$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 178.5 (C), 169.7 (C), 158.2 (C), 132.9 (CH), 130.2 (C), 128.0 (2 x CH), 124.8 (CH), 113.6 (2 x CH), 81.8 (C), 80.6 (C), 77.2 (CH), 61.7 (CH$_2$), 55.2 (CH$_3$), 51.9 (CH), 51.3 (CH$_3$), 47.8 (CH$_2$), 38.6 (CH), 28.2 (CH$_2$), 26.8 (CH$_2$), 25.0 (CH$_2$), 21.2 (CH$_3$), 20.6 (CH$_2$); HRMS (ES) Exact mass calcd for C$_{24}$H$_{33}$NO$_7$Na [M+Na]$^+$: 470.2149, found: 470.2150.

Comparison of ^{13}C NMR data (HWL, Corey and Pattenden's) for **26**

HWL ^{13}C NMR data (CDCl$_3$ referenced at 77.0 ppm)	Corey ^{13}C NMR data with CDCl$_3$ referenced at 77.38 ppm (data with CDCl$_3$ referenced at 77.0 ppm)	Δ ppm	Pattenden ^{13}C NMR data with CDCl$_3$ referenced at 77.03 ppm	Δ ppm
178.5	178.99 (178.61)	−0.11	178.8	−0.3
169.7	170.12 (169.74)	−0.04	169.7	0
158.2	158.27 (157.89)	+0.31	158.2	0
132.9	131.30 (130.92)	**+1.98**	132.6	+0.3
130.2	130.55 (130.17)	+0.03	130.7	−0.5
128.0	128.13 (127.75)	+0.25	128.2	−0.2
124.8	126.39 (126.01)	**−1.21**	125.1	−0.3
113.7	113.74 (113.36)	+0.34	113.7	0
81.8	81.93 (81.55)	+0.25	81.8	0
80.6	80.75 (80.37)	+0.23	80.6	0
77.2	76.87 (76.49)	**+0.71**	77.2	0
61.7	61.61 (61.23)	+0.47	61.6	+0.1
55.2	55.45 (55.07)	+0.13	55.2	0
51.9	51.97 (51.59)	+0.31	51.9	0
51.3	51.32 (50.94)	+0.36	51.3	0
47.8	48.07 (47.69)	+0.11	47.9	−0.1
38.6	39.17 (38.22)	+0.38	38.7	−0.1
28.2	27.71 (27.82)	+0.38	28.0	+0.2
26.8	27.13 (26.75)	+0.05	26.8	0
25.0	25.22 (24.84)	+0.16	25.0	0
21.2	21.35 (20.97)	+0.23	21.1	+0.1
20.6	21.22 (20.84)	−0.62	20.7	−0.1

6.2.5. NMR spectra

(*R*)-Ethyl (*E*)-3-[*N*-(1-benzyloxymethyl-1-carbomethoxy-2-oxopropyl)-*N*-(4-methoxybenzyl)carbamoyl]acrylate (481)

(3a*R*,6*R*,6a*S*)-6-Benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (489)

ppm (t1)

ppm (t1)
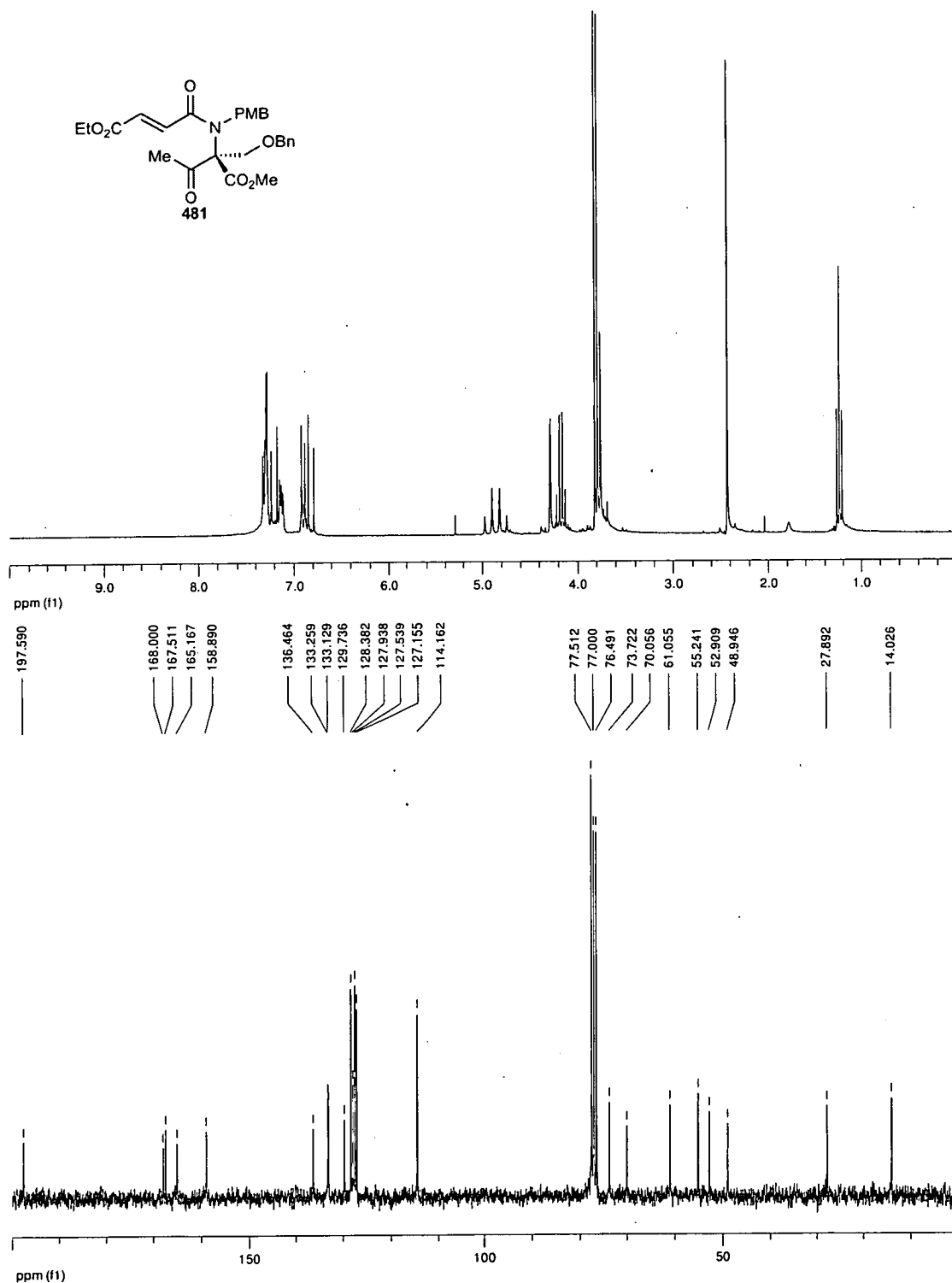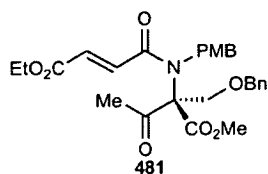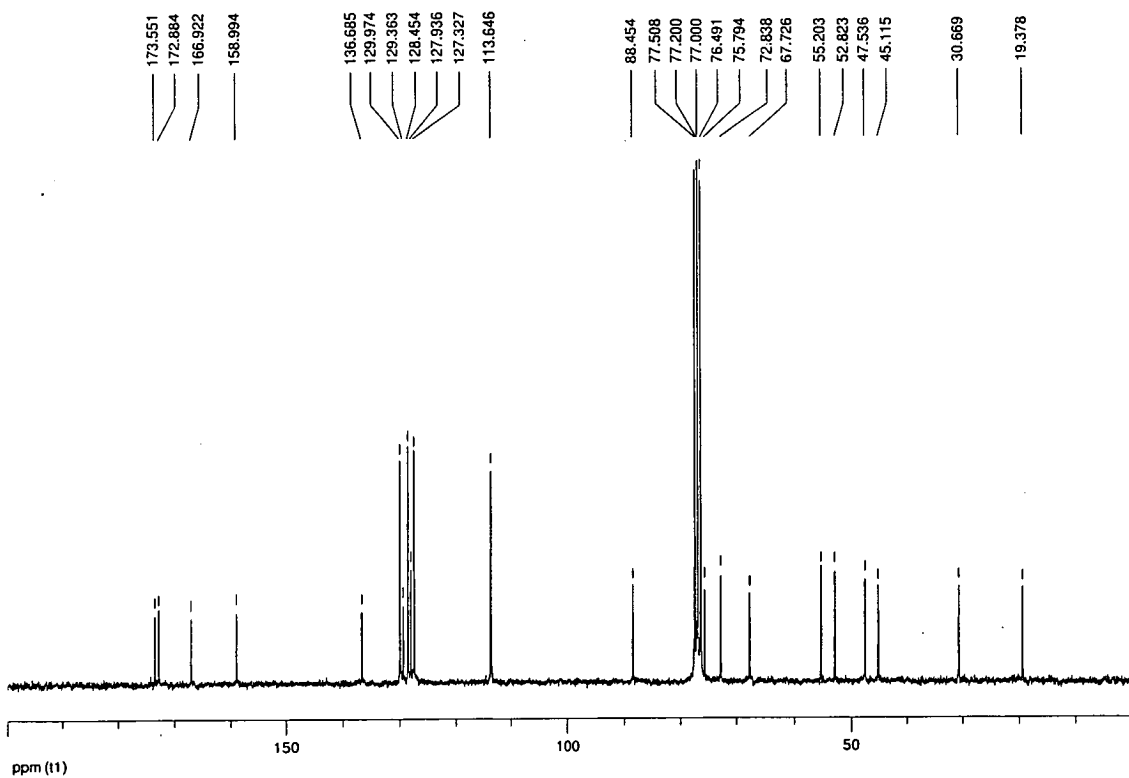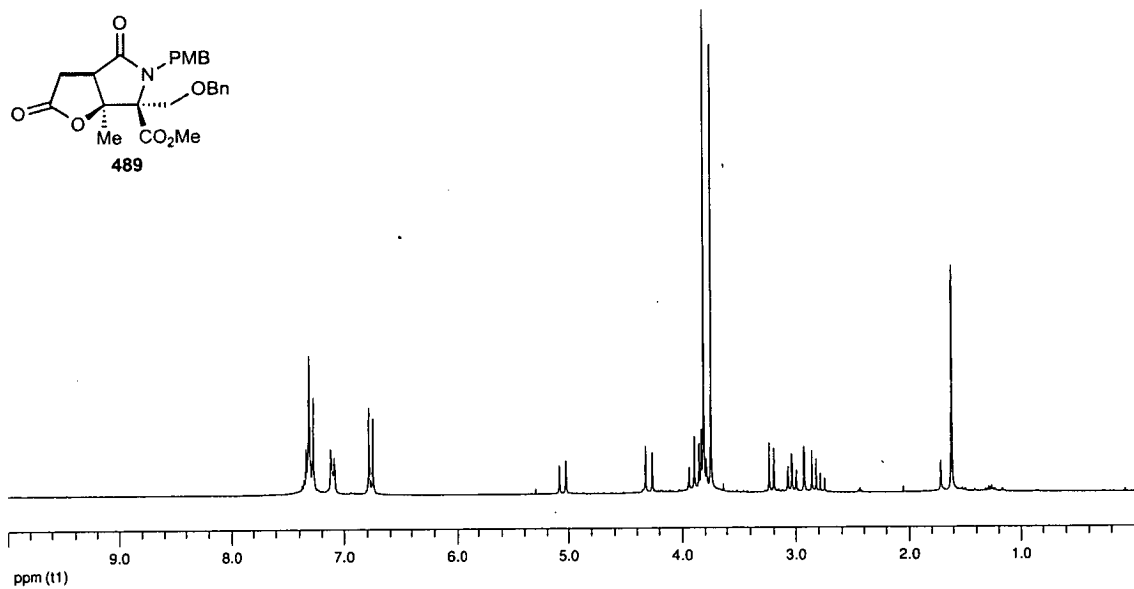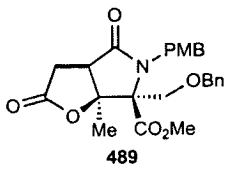
(3aS,6R,6aR)-6-benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (490)

490
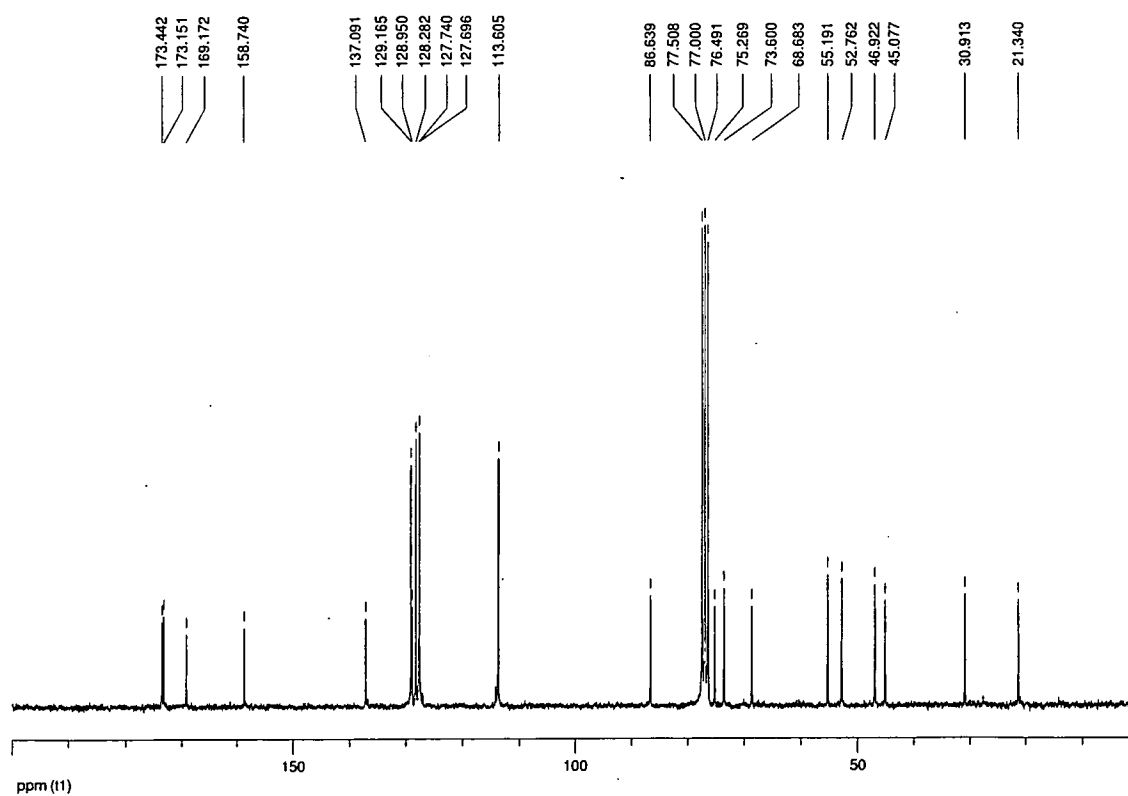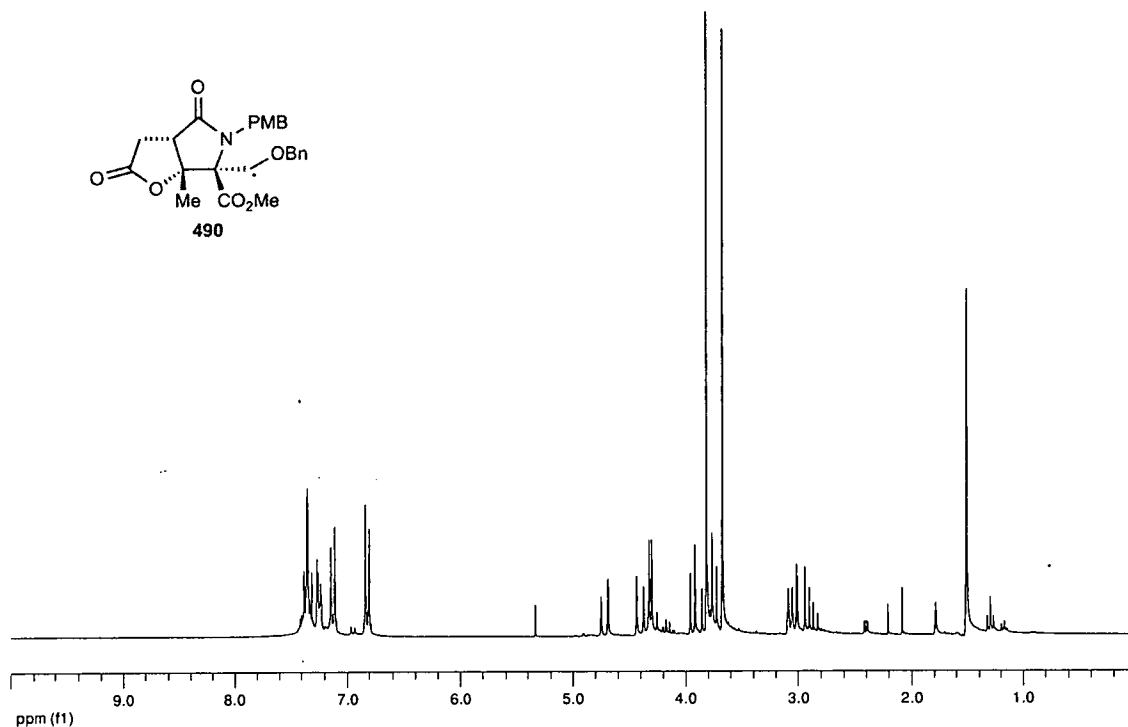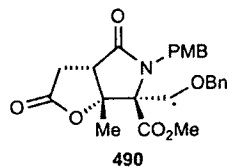
(3a*R*,6*R*,6a*S*)-6-Hydroxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (493)

(3a*R*,6*R*,6a*S*)-6-Formyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (494)

ppm (f1)

195.509

172.701
172.012
165.731
159.587

131.137
126.840

114.191

87.287
79.003
77.508
77.000
76.492

55.197
53.407
46.795
45.644

30.653

20.513

ppm (f1)
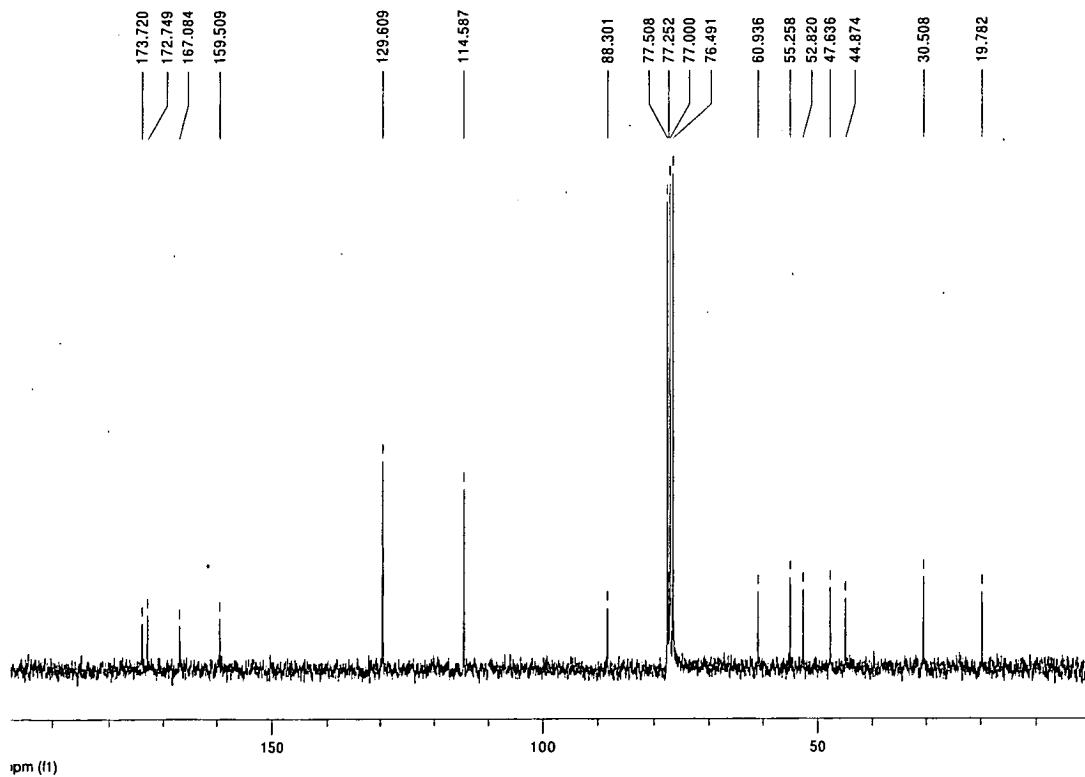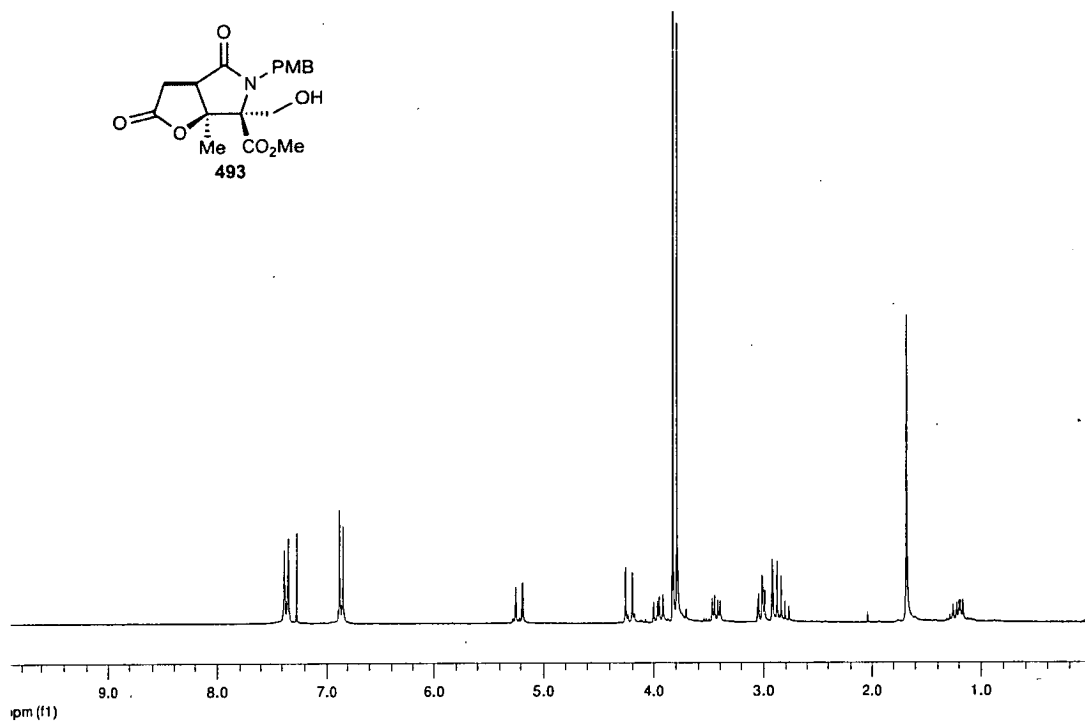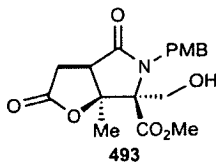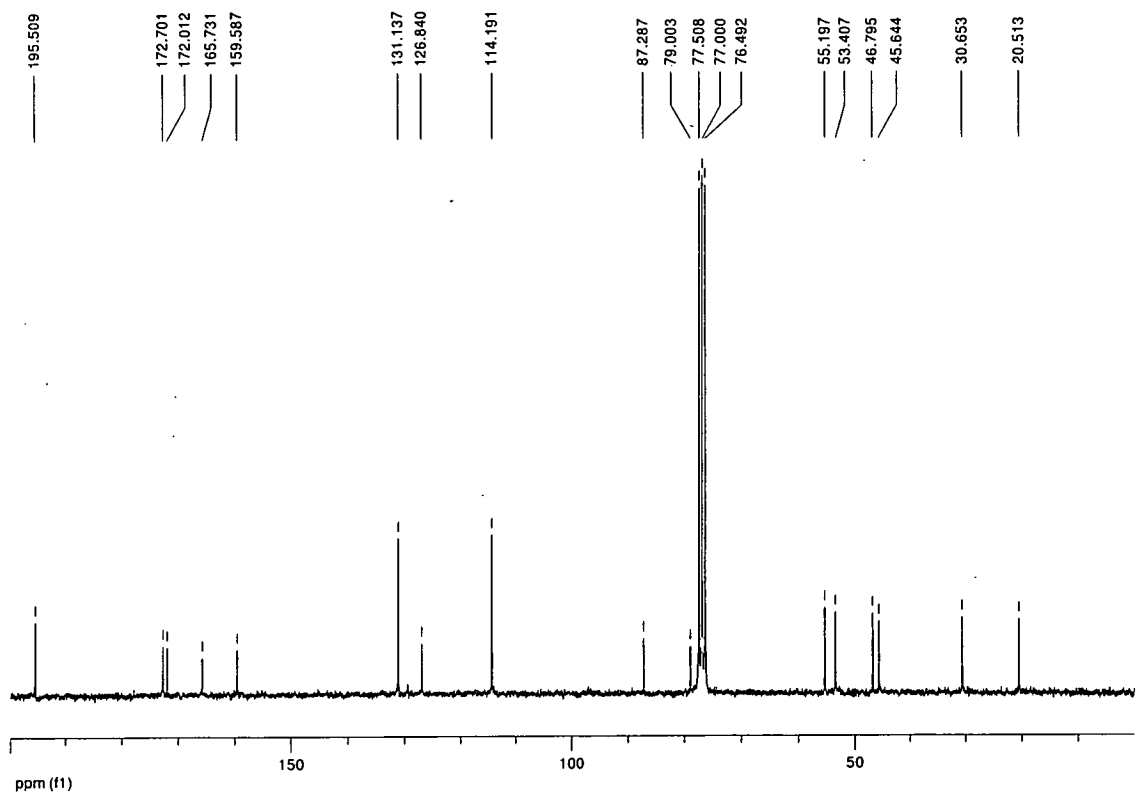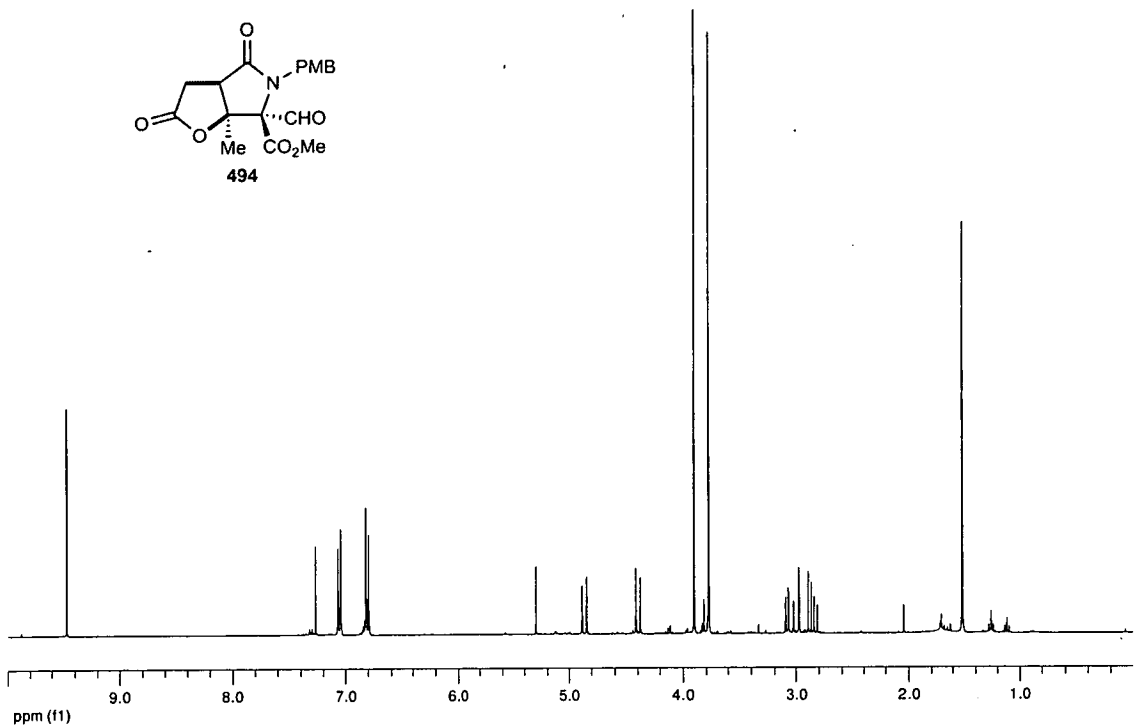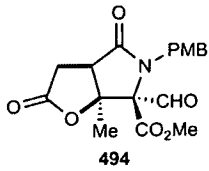
(3a*R*,6*R*,6a*S*)-6-[(*S*)-(*S*)-Cyclohex-2-enylhydroxymethyl]-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (495)

495

ppm (t1)

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0

174.794
172.975
167.802
158.317
131.840
129.307
127.569
125.202
113.747
91.088
79.000
77.508
77.000
76.914
76.492
55.164
52.407
47.927
47.807
38.326
30.898
26.962
24.900
20.623
19.582

ppm (f1)

150 100 50
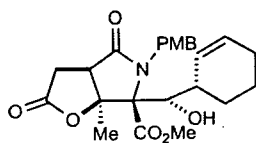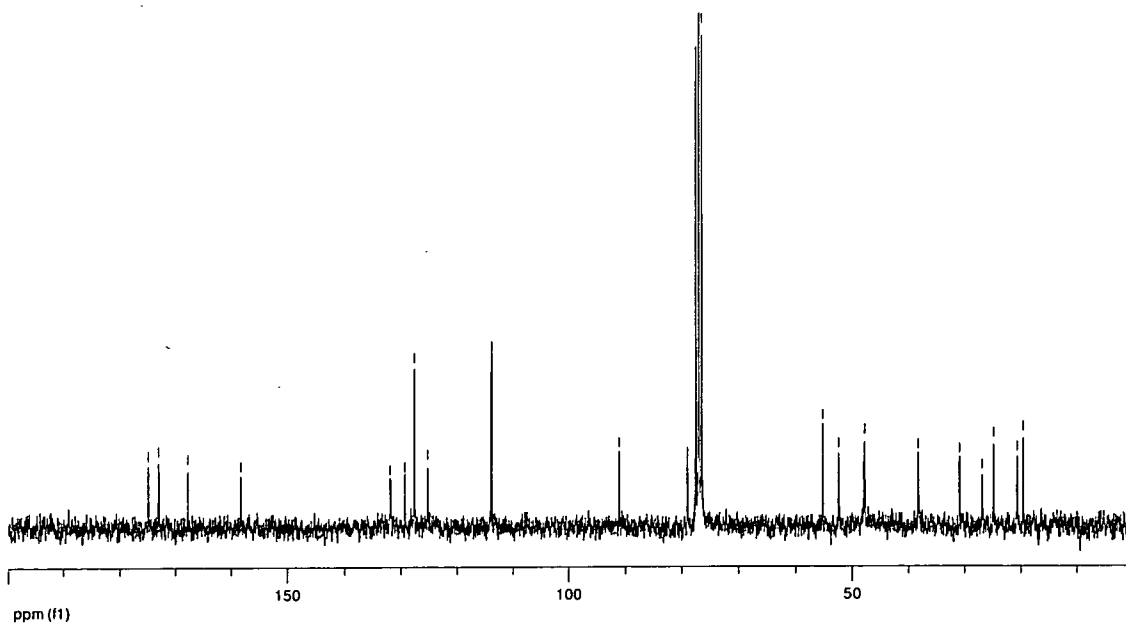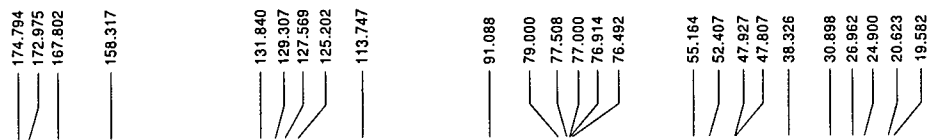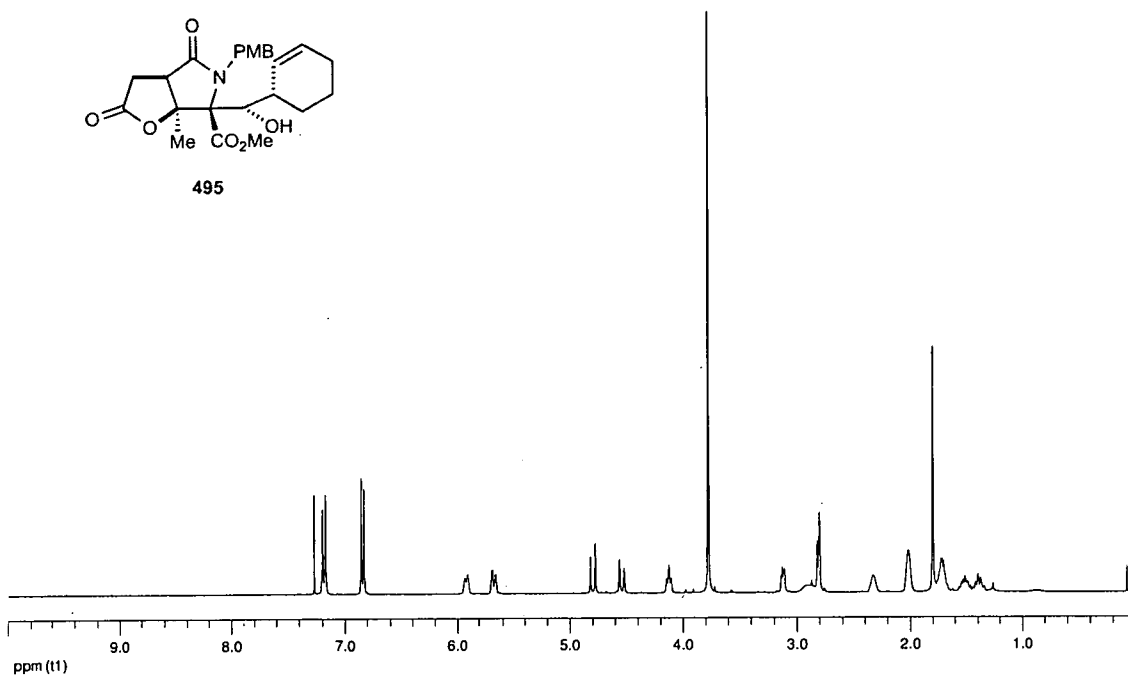
(2*R*,3*S*,4*R*)-2-[(*S*)-(*S*)-Cyclohex-2-enylhydroxymethyl]-3-hydroxy-4-(2-hydroxyethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (26)

ppm (t1)

ppm (f1)
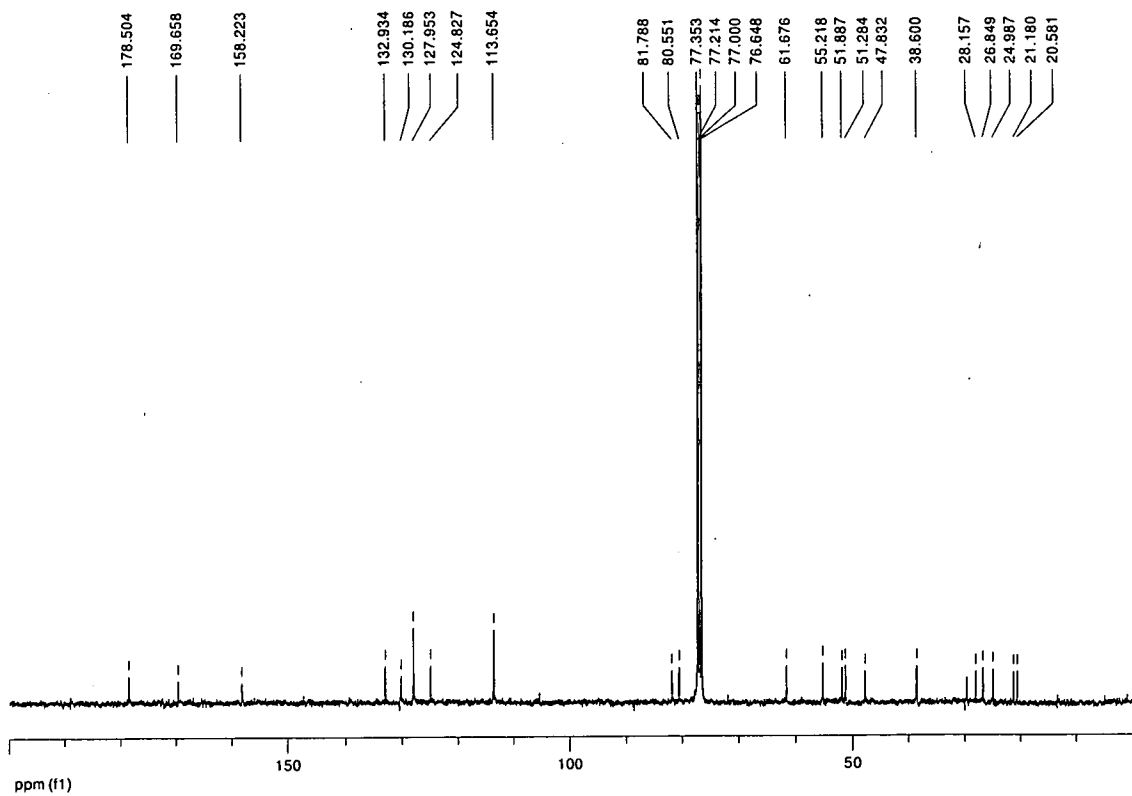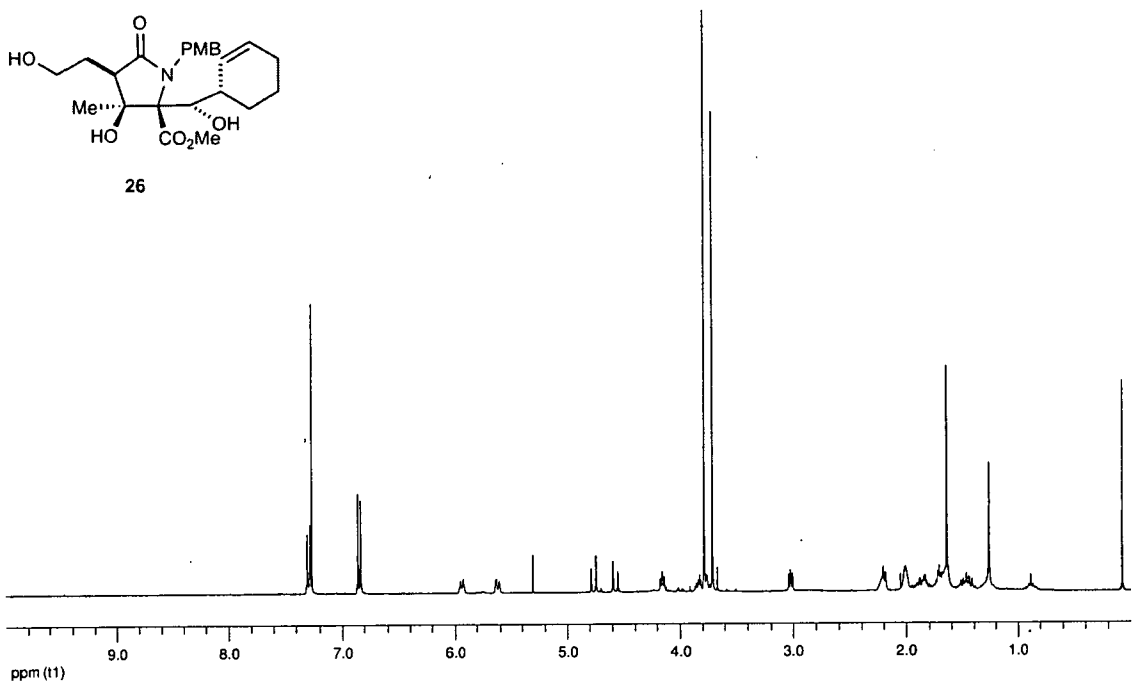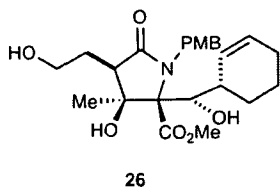
¹³C NMR Spectrum of triol 26 obtained by the Corey group

26

176.999
170.125
158.271
131.305
130.556
128.133
126.393
113.743
81.933
80.751
77.553
77.361
77.130
76.878
61.619
55.450
51.378
51.326
48.079
39.178
27.718
27.139
25.224
21.351
21.222
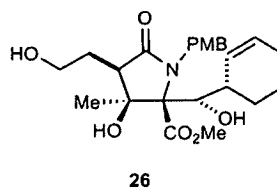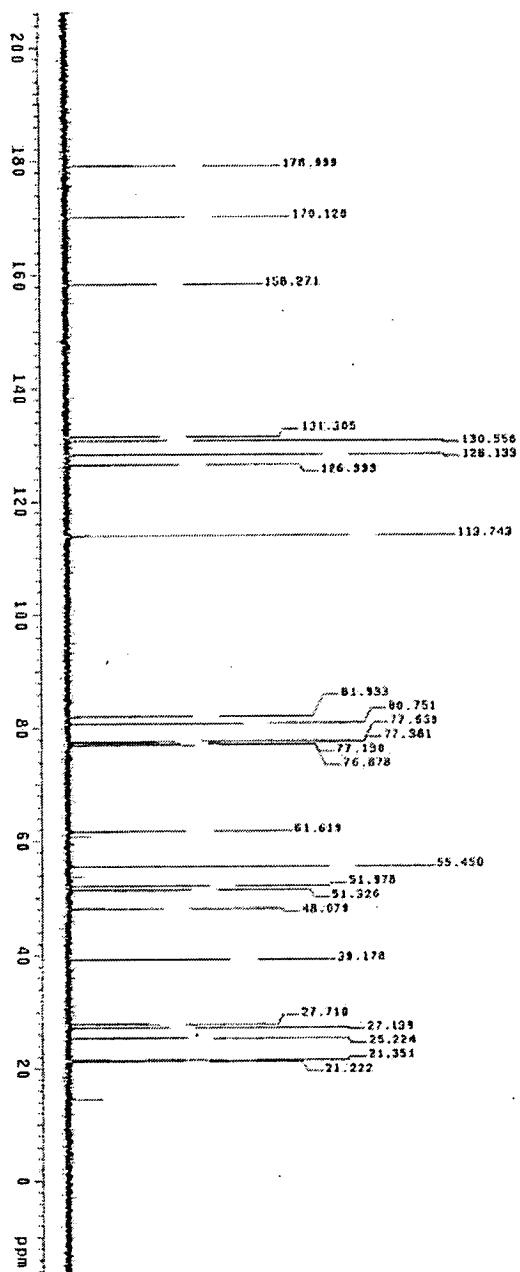
^{13}C NMR Spectrum of triol 26 obtained by the Pattenden group

26

Peak list (ppm):
- 178.764
- 169.690
- 158.250
- 132.613
- 130.721 ✗
- 130.145
- 128.158 ✗
- 127.983
- 125.097
- 113.676
- 81.879
- 80.592
- 77.351
- 77.237
- 77.034
- 76.717
- 76.640
- 61.639
- 55.243
- 51.910
- 51.711
- 47.889
- 38.688
- 28.007
- 26.836
- 25.000
- 21.161
- 20.677

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