



**TOWARDS THE STEREOSELECTIVE
SYNTHESIS OF BICYCLIC AND TRICYCLIC
ALKALOID NATURAL PRODUCTS**

A Thesis Submitted to the Nanyang Technological University

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ABSTRACT

In this thesis we discuss the stereoselective synthesis of natural products containing bicyclic heterocycle with a bridgehead nitrogen atom. The unique structural feature of this core skeleton has inspired interest regarding to their stereochemistry and biological properties.

The first chapter describes efforts in the stereoselective total synthesis of amphorogynine C, a new class of pyrrolizidine alkaloids, which have not been reported in New Caledonian plants before. The key steps involve the stereoselective construction of *cis*-2,5-disubstituted isoxazolidines and the *N-O* bond cleavage of *cis*-2,5-disubstituted isoxazolidines to form the *cis*-1,3-amino-alcohol which can further cyclise to pyrrolidines by an intramolecular nucleophilic substitution.

In chapter 2, we report studies towards the stereoselective total synthesis of hydroxyindolizidine, an alkaloid isolated from the ant *Myrmecaria melanogaster* (Emery). The use of *N,O*-heterocycles, tetrahydro-1,2-oxazines, as synthetic intermediates to control the regio- and stereochemistry, is discussed. The key steps involve a tandem deprotection-intramolecular Michael addition and a tandem double hydrogenation-lactamization.

In chapter 3, we report studies towards the total synthesis of tuberostemospironine, an alkaloid extracted from the roots of *Stemona tuberosa* (Stemonaceae). Tuberostemospironine is a unique structure feature containing a spiro[furan-2-(5*H*), 9'[9*H*]pyrrolo[1,2-*a*]-azepin]-5-one nucleus which displays a spiro- γ -lactone at the basic azabicyclic nucleus. Three stereogenic centres of this natural product comprise a spiro- γ -butyro-lactone ring and the last chiral centre contains at the basic azabicyclic nucleus.

LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetyl
Acac	acetylacetyl
AIBN	azobisisobutyronitrile
Anal.	elemental analysis
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
b.p.	boiling point
br.	broad
°C	degree Celsius
CAN	ceric ammonium nitrate
cat.	catalytic
Calcd.	Calculated
Cbz	benzyloxycarbonyl
cm ⁻¹	wave number unit
COSY	correlated spectroscopy
Conc.	Concentrated
CSA	camphorsulfonic acid
d	doublet (spectral)
dd	double doublets (spectral)

LIST OF ABBREVIATIONS (Cont.)

δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undecane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(<i>1H</i>)-pyrimidinone
dr	diastereoisomeric ratio
E	electrophile
ee	enantiomeric excess
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EIMS	electron impact mass spectrometry
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram
h	hour (s)

LIST OF ABBREVIATIONS (Cont.)

HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared radiation
<i>J</i>	coupling constant
LDA	lithium diisopropylamide
Lit.	literature
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
m	multiplet (spectral)
M ⁺	molecular ion
MCPBA	3-chloroperoxybenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl
mg	milligram
MHz	megahertz
min	minute (s)
mL	millilitre
m.p.	melting point
MPM	4-methoxybenzyl
MS	mass spectrometry

LIST OF ABBREVIATIONS (Cont.)

m/z	a value of mass divided by charge
NaHMDS	sodium bis(trimethylsilyl)amide
<i>n</i> -Bu	butyl
<i>n</i> -BuLi	<i>n</i> -butyl lithium
NMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect spectroscopy
<i>n</i> -Pr	propyl
Nu	nucleophile (s)
<i>p</i>	para
PG	protecting group (s)
Ph	phenyl
Phth	phthaloyl
ppm	parts per million (in NMR)
PPTS	pyridinium <i>p</i> -toluenesulfonate
psi	pounds per square inch
q	quartet (spectral)
quint	quintet (spectral)
R	unspecified carbon substituent
rt	room temperature (°C)
RCM	ring closing metathesis
s	singlet (spectral)

LIST OF ABBREVIATIONS (Cont.)

Sat.	saturated
t	triplet (spectral)
<i>t</i>	tertiary
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl, tetramethylsilane
UHP	urea hydrogen peroxide
ν_{\max}	maximum absorption frequencies

CHAPTER 1

TOTAL SYNTHESIS OF AMPHOROGENINE C

1.1 Introduction

1.1.1 Introduction to Pyrrolizidine Alkaloids

Pyrrolizidine alkaloids are one of the more well-investigated classes of natural products contain a heterocyclic nitrogen atom, which consists of two fused five-membered rings with a bridgehead nitrogen (**Figure 1.1**). In general, pyrrolizidine alkaloids are esters of hydroxylated methyl pyrrolizidines, consisting of a necine base and a necic acid moiety. The necine base can either be 1,2-unsaturated (Retronecine) or saturated (Platynecine).^{1a}

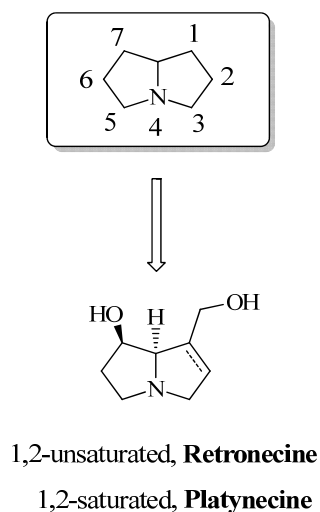


Figure 1.1 The 1-aza-[3.3.0]-bicyclic ring system

Pyrrolizidine alkaloids are naturally occurring toxins associated with harmful effects in both humans and animals and they are found in many species of plant. To date, pyrrolizidine alkaloids have been isolated from over 560 species, mainly belonging to the botanical families *Asteraceae*, *Boraginaceae*, *Fabaceae*, and *Orchidaceae*.¹ These compounds display a large number of biological activities, which include hepatotoxicity, pneumotoxicity, mutagenicity, carcinogenicity, embryotoxicity, weak virustatic, and antileukemic activities.^{1e} **Figure 1.2** shows a variety of pyrrolizidine alkaloids, most of which have a variety of hydroxy groups with different substitutions in the ring. This group has been synthesised and the analogues tested for biological activity.² Australine³ and alexine⁴ possess many hydroxy groups in the pyrrolizidine core. The necine bases such as lentiginosine,⁵ hyacinthacine A2,⁶ croalbinecine⁷ and rosmarinecine,⁸ have two hydroxy groups at the ring. Examples of monohydroxylated pyrrolizidines are (-)-hastanecine,⁹ turniforcidine,¹⁰ and platynecine¹¹. The hydroxylated methyl pyrrolizidine, isoretronecanol¹², has also been investigated for many years. The amphorogynines are a new class of pyrrolizidine alkaloids, bearing a hydroxyl group at the C-6 position of pyrrolizidine ring.¹³ Most of the known pyrrolizidine alkaloids is generally located at the C-7 position.

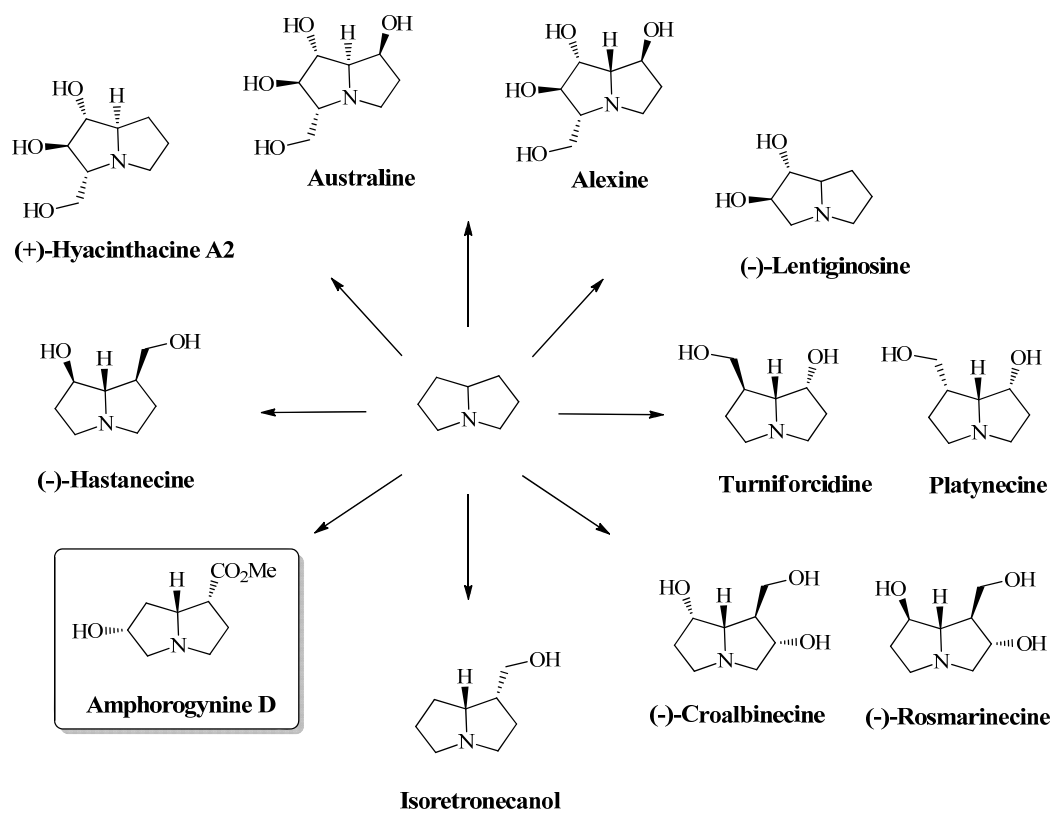


Figure 1.2 Structure of pyrrolizidine alkaloids

Nitrogen-containing natural products are remarkable source of biological activity. They have also been a target for total synthesis to demonstrate methodology. The functionalities of natural products have inspired the synthetic chemist to develop new methodologies.

1.1.2 Amphorogynines

Amphorogynines (A-D) have been isolated from the leaves of the New Caledonian plant *Amphorogynine spicata* (Santalaceae) (**Figure 1.3**). These pyrrolizidine alkaloids were first isolated by Païs and co-workers in 1998.^{13a} The structure and relative stereochemistry were elucidated by spectroscopic methods. The amphorogynines represented a new class of pyrrolizidines since these alkaloids possess substituents at both C-1 and C-6 positions, which have not been reported in New Caledonian plants before.^{13b} The substitution at the C-6 position was assigned to the phenyl propionic acid ester chain, whilst the COOMe group was attached to C-1. These alkaloids differ in the position of the substituents on the core structure pyrrolizidine ring. Whilst amphorogynines possess a hydroxyl group at the C-6 position, the well-known necines bear this substituent at the C-7 position of the pyrrolizidine ring. The alkaloids, amphorogynine B and C, were isomers of amphorogynine A. They differed from amphorogynine A by the configurations at C-1 and C-6 (amphorogynine B) or C-6 only (amphorogynine C). Amphorogynine D differs from the related natural products, displaying absence of the phenyl propionic acid ester chain. The configurations at C-1 and C-6 of amphorogynines A and D were identical.

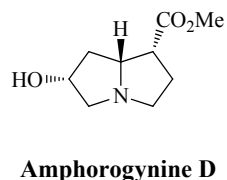
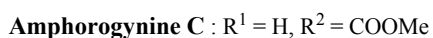
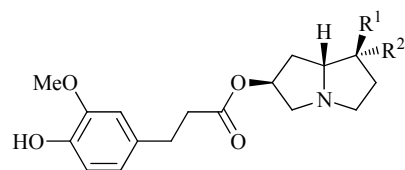
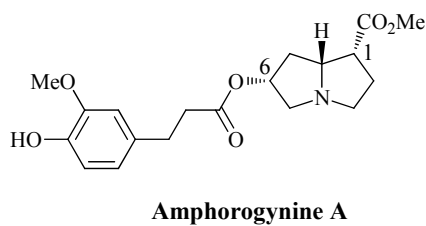
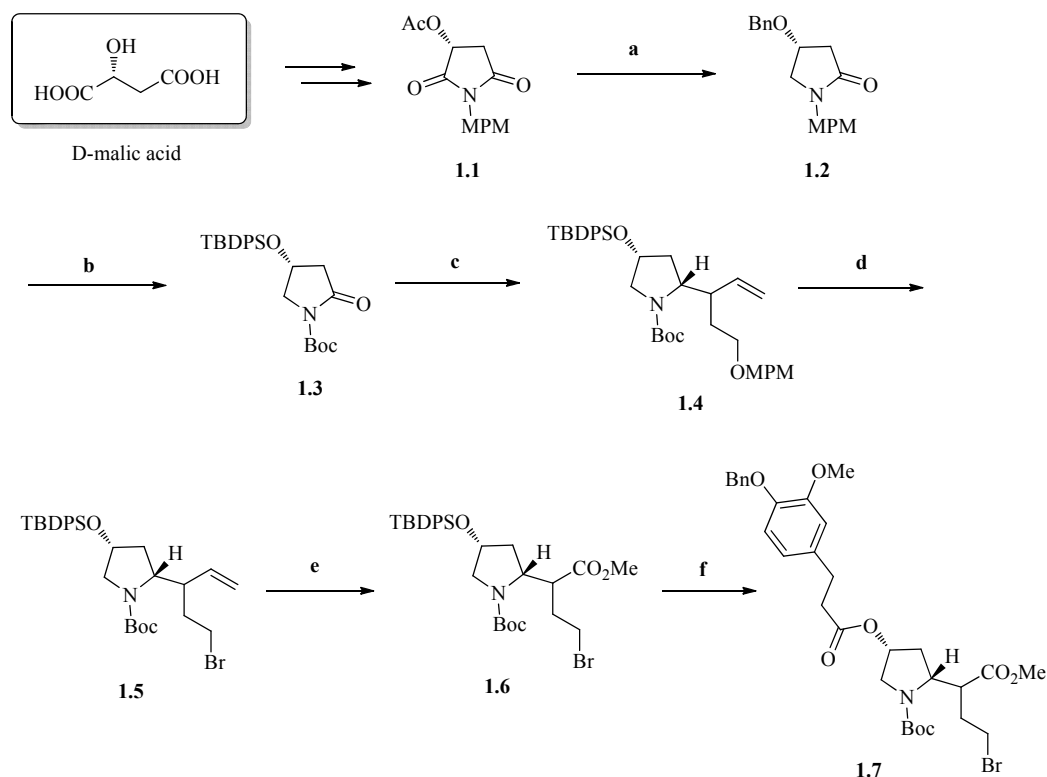


Figure 1.3 Structures of amphorogynine A-D

1.1.3 Synthesis of Amphorogynines

Currently, there have been two synthetic routes to amphorogynine A.^{14, 15} and only one group has synthesised amphorogynine D.¹⁶ Amphorogynine A was first synthesised by Yoda and co-workers in 2003 starting with the key 2,4-disubstituted pyrrolidine ring, which was constructed by the elaboration of a known chiral lactam derivative.¹⁴ The synthesis of the chiral lactam derivative was achieved in several steps from D-malic acid (**Scheme 1.1**). The imide (**1.1**) was regioselectively reduced with NaBH_4 , followed by reductive deoxygenation with Et_3SiH to give the acetyllactam intermediate (**1.1**). The acetyl group was exchanged for a benzyl group (**1.2**), then *N*- and *O*-deprotection and reprotection to the *N*-Boc and *O*-TBDPS derivative gave the cyclic

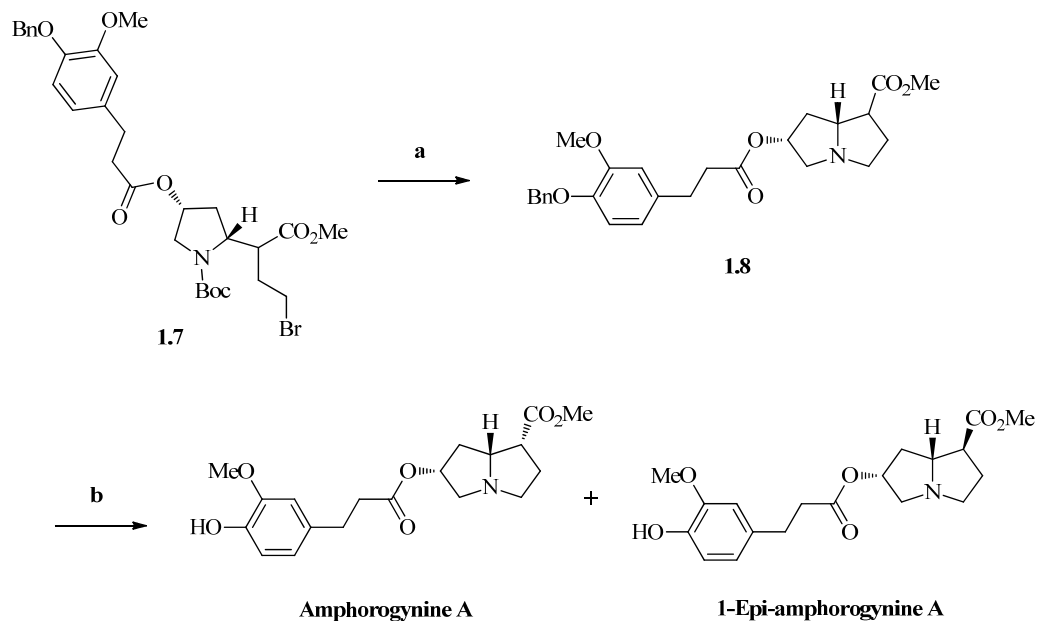
amide (**1.3**). The 2,4-disubstituted pyrrolidine (**1.4**) was obtained in 48% yield and about 55% d.e. by partial reduction and allylation *via* an *N*-acyliminium ion promoted by $\text{BF}_3 \cdot \text{OEt}_2$ at $-78\text{ }^\circ\text{C}$. The relative configurations of 2,4-disubstituted pyrrolidine (**1.4**) were in the *cis*-relationship but with about 55% d.e. at the allylic position. They confirmed the absolute stereochemistry of the newly created carbon centre by comparing its special data with a *trans*-2,4-disubstituted pyrrolidine derivative. Deprotection of MPM and bromination afforded (**1.5**), which was subjected to the Lemieux-Johnson oxidation *via* dihydroxylation of a double bond with OsO_4 and cleavage of the resulting diol with NaIO_4 to give the aldehyde, followed by bromine-induced oxidation to give the ester (**1.6**) in 89% yield. The remaining side unit in the amphorogynine was introduced *via* esterification with 2, 3-(*p*-benzyloxy-*m*-methoxyphenyl) propionic acid. After desilylation, the free hydroxy compound was treated with 2, 3-(*p*-benzyloxy-*m*-methoxyphenyl) propionic acid, EDCI, and DMAP in anhydrous dichloromethane at $0\text{ }^\circ\text{C}$ to afford ester (**1.7**).



Scheme 1.1 Selected steps for the first total synthesis of amphorogynine A and its 1-epimer

Reagents and conditions: (a) NaBH_4 , MeOH, 0 °C; $\text{BF}_3 \cdot \text{OEt}_2$, Et_3SiH , CH_2Cl_2 , 0 °C; 69% (two steps); K_2CO_3 , MeOH; 97%; BnBr , Ag_2O ; DMF; 92%; (b) CAN, $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (9:1); 93%; $(\text{Boc})_2\text{O}$, DMAP, Et_3N , CH_2Cl_2 , 0 °C; quant.; Pd (black), 4.4% $\text{HCOOH}-\text{MeOH}$, 45 °C; quant.; TBDPSCl , imidazole, CH_2Cl_2 ; 94%; (c) NaBH_4 , MeOH, 0 °C; $\text{MPMO}(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{SiMe}_3$, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78 °C; 47% (two steps); (d) DDQ, $\text{CH}_2\text{Cl}_2-\text{H}_2\text{O}$ (11:1), 0 °C; 90%; CBr_4 , PPh_3 , CH_2Cl_2 ; 96%; (e) OsO_4 , NMO, acetone- H_2O , 0 °C; NaIO_4 , ether-THF- H_2O (1:1:2); 88% (two steps); Br_2 , NaHCO_3 , MeOH- H_2O (9:1); 89%; (f) Bu_4NF , THF, 0 °C; 87%; 3-(*p*-benzyloxy-*m*-methoxyphenyl) propionic acid, EDCI, DMAP, CH_2Cl_2 ; 0 °C; 70%.

Deprotection of the *N*-Boc derivative (**1.7**) with $\text{BF}_3 \cdot \text{OEt}_2$ then cyclization under basic conditions afforded cyclic product (**1.8**), followed by debenzoylation with hydrogen and 5% Pd on carbon to produce amphorogynine A and its 1-epimer (**Scheme 1.2**).

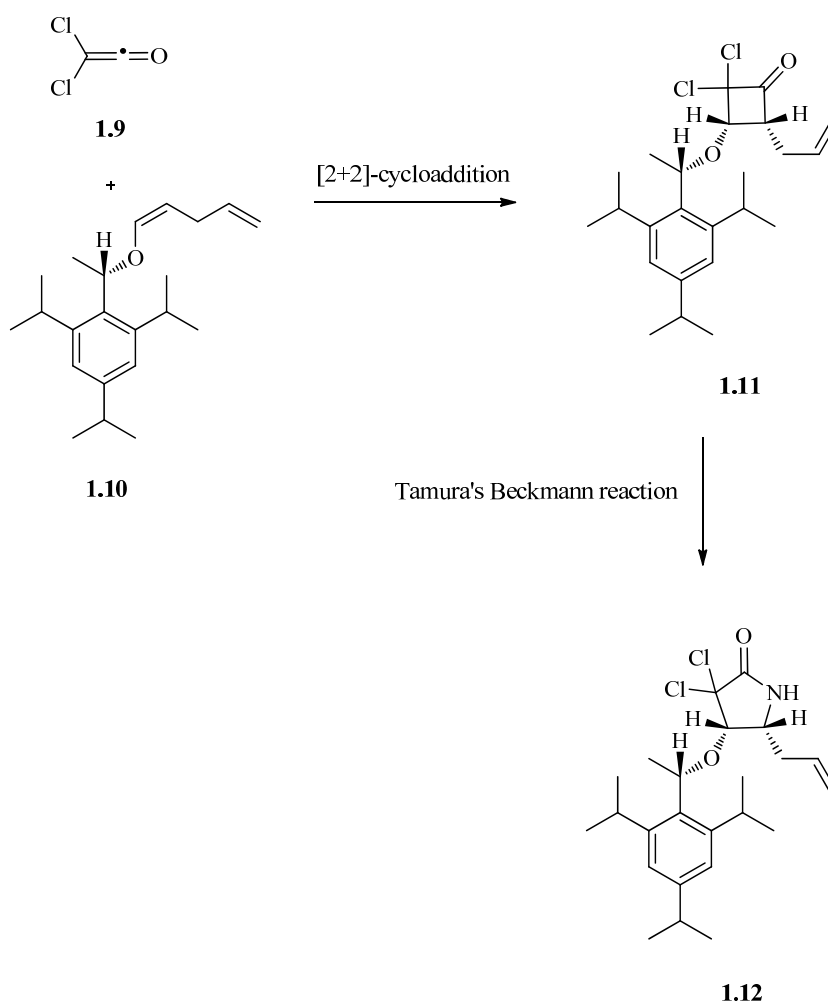


Scheme 1.2 Selected steps for the first total synthesis of amphorogynine A and its 1-epimer (Cont.)

Reagents and conditions: (a) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 ; $-15\text{ }^\circ\text{C}$; NaHCO_3 , H_2O ; 85% (two steps); (b) H_2 , Pd/C, CH_3OOEt ; 58% (amphorogynine A); 26% (1-epi-amphorogynine A).

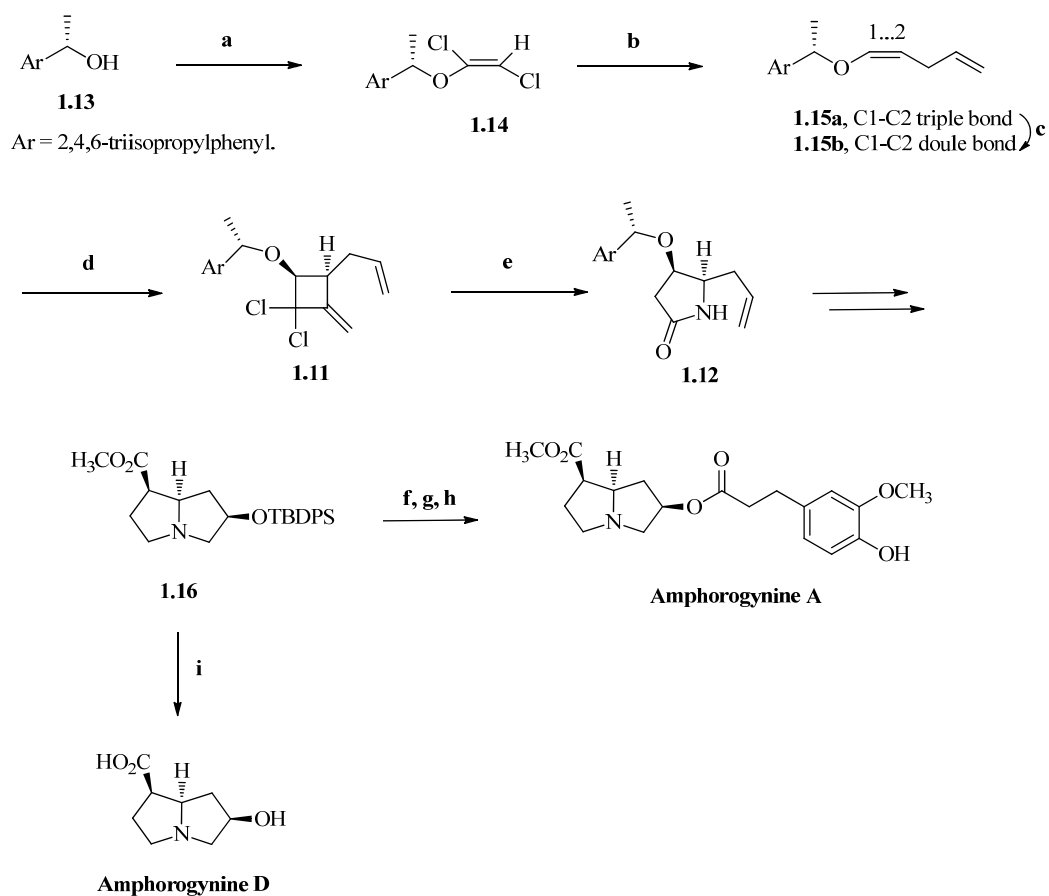
Yoda *et al.* successfully synthesised amphorogynine A in 19 steps, however, they could not selectively control the stereochemistry at the C-1 position in amphorogynine A. In the same year, Greene and co-workers reported a highly stereoselective route to amphorogynine A and D.¹⁵ The key step in their synthesis is a diastereoselective [2+2] dichloroketene–chiral enol ether cycloaddition. They employed the (*S*)-enantiomer of

1-(2,4,6-triisopropylphenyl)ethanol (**1.13**),¹⁶ a previously used and highly effective chiral controller, as the starting material. Thus, this chiral auxiliary was attached to dichlorocyclobutanone intermediate (**1.11**), which was constructed by a [2+2]-cycloaddition of dichloroketene (**1.9**) and chiral enol ether **1.10** (**Scheme 1.3**). The key intermediate pyrrolidinone derivative (**1.12**) was rapidly and highly regioselective formed under Tamura's Beckmann conditions because of electronic effects and Baeyer strain present in dichlorocyclobutanone (**1.11**).¹⁷



Scheme 1.3 The key step to pyrrolizidine alkaloids

A synthesis of chiral lactam derivative (**1.12**) was achieved using the *S* enantiomer of 1-(2,4,6-triisopropylphenyl)ethanol (**1.13**) as a chiral auxiliary. Treatment of the chiral alcohol (**1.13**) with potassium hydride, followed by trichloro-ethylene, provided the dichloroenol ether (**1.14**), which was converted into ynolether (**1.15a**) by reaction with *n*-BuLi and excess allyl iodide. Hydrogenation of (**1.15a**) with Pd on BaSO₄ in the presence of ethylenediamine afforded enol ether (**1.15b**), which was subjected to selective cycloaddition in the presence of *in situ* generated dichloroketene to give the cyclobutanone (**1.11**) (93:7 mixture). Beckmann ring expansion of the cyclobutanone (**1.11**) with Tamura's reagent,¹⁷ followed by dechlorination with a Zn-Cu couple in methanol saturated with ammonium chloride, provided the key pyrrolidinone intermediate (**1.12**) in 72% yield. Pyrrolidine (**1.12**) was induced to cyclize to provide pyrrolizidine (**1.16**) in several steps. Amphorogynine A was obtained by deprotection at the C-6 hydroxy group, which was esterified with *tert*-butyldimethylsilyl-protected hydroferulic acid. Removal of the phenolic silyl group in the ester was carried out with tetra-*n*-butylammonium fluoride in tetrahydrofuran. The ester (**1.16**) was converted into amphorogynine D by deprotection and hydrolysis (**Scheme 1.4**).



Scheme 1.4 Selected steps from Delair's synthesis of amphorogynine A and D

Reagents and conditions: (a) KH, THF; $\text{Cl}_2\text{CC=O}$; 79%; (b) *n*BuLi, THF; allyl iodide, HMPA; (c) Pd/BaSO₄, H₂, C₅H₅N, 1-hexene; (d) Al₂O₃, CH₃OH. (e) 1. NH₂OSO₂C₆H₂(CH₃)₃, CH₂Cl₂, Al₂O₃, CH₃OH; 2. Zn-Cu, NH₄Cl, CH₃OH; 84%; (f) TBAF, THF; 82%; (g) *O*-TBDMS hydroferulic acid, DIC, DMAP, CH₂Cl₂; 70%; (h) TBAF, THF; 77%; (i) 12 N HCl, dioxane; 77%.

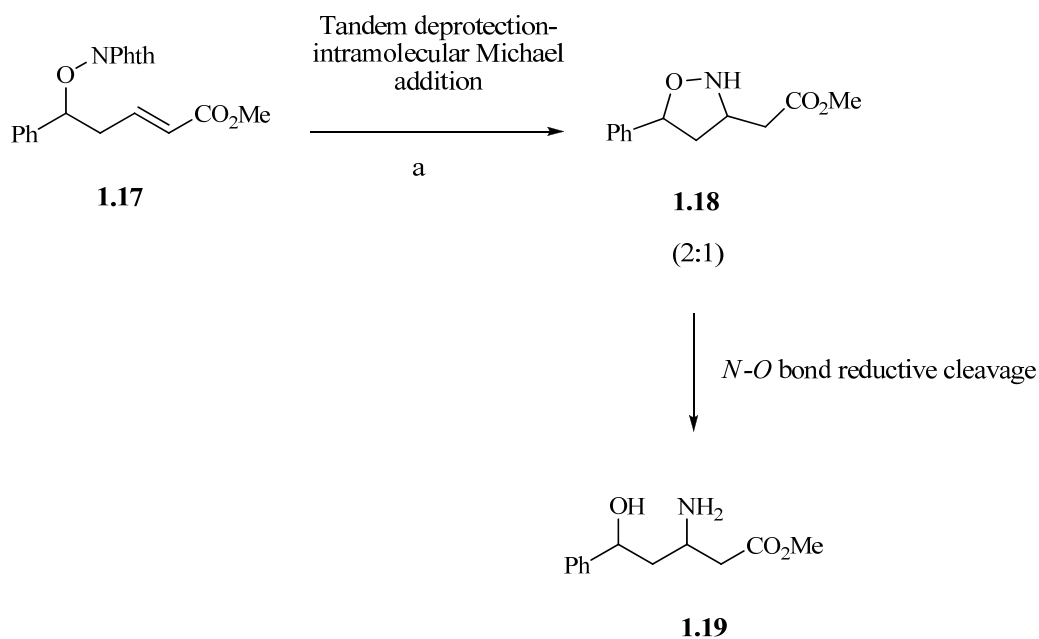
Greene and co-workers successfully synthesised amphorogynine A in 17 steps and amphorogynine D in 15 steps. Both of these synthetic routes outlined to amphorogynine A and D started with the key intermediate chiral lactam to set up the stereochemistry in the pyrrolidine ring. To date, the remaining natural products, amphorogynine B and C have not been synthesised.

1.2. Aim of Present Work

1.2.1 *N,O*-Heterocycles as Synthetic Intermediates

N,O-Heterocycles containing an *N-O* bond are cyclic hydroxylamines. We have been interested in the synthesis of *N,O*-heterocycles by intramolecular conjugate addition, and other methods, of a hydroxylamine to produce cyclic hydroxylamine derivatives as synthetic intermediates.¹⁸ Cyclic hydroxylamine derivatives, such as isoxazolidines have been extensively used in organic synthesis for the preparation of substituted amines and a variety of alkaloids.¹⁹ They have usually been prepared by the 1,3-dipolar cycloaddition of nitrones to alkenes. Methods developed in our group can make it easier to control the stereochemistry and can give different diastereoselectivity. Our interest in these heterocycles was as precursors of 1,3-amino-alcohols with control of the regio- and stereochemistry. Therefore, we employed hydroxylamines as a form of tethered nitrogen to set up the stereochemical relationship in the molecule, then cleavage of the *N-O* bond selectively under mild conditions would give the 1,3-amino-alcohol as shown in **Scheme 1.5**. More generally, a tandem reaction is series of

intramolecular organic reactions in which several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding reagents. As shown below, our group reported our recent results on the use of the tandem deprotection-intramolecular Michael addition of nitrogen of an *O*-substituted hydroxylamine, with introduction of the Michael acceptor by cross-methathesis.^{18d,20,21} *N*-phthaloyl derivative (**1.17**) was treated with hydrazine monohydrate in dichloromethane at 0 °C to room temperature to provide the isoxazolidine (**1.18**) in 88% yield as a 2:1 mixture of stereoisomers.^{18b} The *N*-*O* bond in isoxazolidine (**1.18**) may undergo reductive bond cleavage to give a 1,3-amino-alcohol (**1.19**) (Scheme 1.5).



Scheme 1.5 The intramolecular Michael addition of hydroxylamine to isoxazolidine

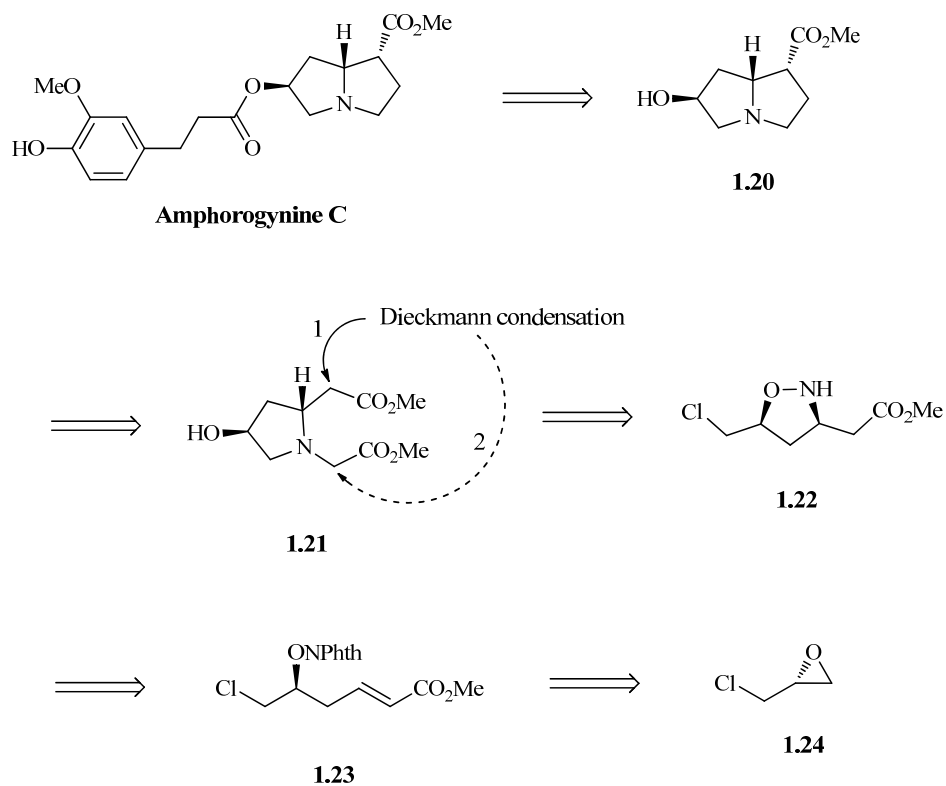
Reagents and conditions: (a) H₂NNH₂·H₂O, CH₂Cl₂, 0 °C to rt, 15-30 mins; 88%.

This work focused on the total synthesis of amphorogynine C by using the isoxazolidine as the key intermediate to set up the stereochemistry of the 1,3-amino-alcohol in the molecule.

1.2.2 Synthetic Plan

The retrosynthetic analysis of amphorogynine C is outlined in **Scheme 1.6**. Amphorogynine C has two substituents at C-1 and C-6 of the pyrrolizidine core. The substituent at the C-6 position could be prepared by esterification of phenylpropionic acid and the C-6 hydroxy group of pyrrolizidine (**1.20**). The COOMe group substituent at the C-1 position could be constructed by Dieckmann condensation of pyrrolidine (**1.21**). The regiochemical outcome of the Dieckmann condensation would provide the COOMe moiety substituent at the C-1 position of amphorogynine C. We expect that the base deprotonation, the proton at direction one, would occur generated to give the carbanion, which induces cyclisation to provide a bicyclic β keto ester. The remaining ketone would be reduced to provide the pyrrolizidine (**1.20**). The most important intermediate isoxazolidine (**1.22**) was expected to be the *cis* isomer, which gives the correct stereochemistry of pyrrolidine (**1.21**). After the *N-O* bond cleavage of the *cis*-isoxazolidine intermediate (**1.22**), we expect the 1,3-amino-alcohol to be formed and subsequently cyclise for pyrrolidine (**1.21**) by an intramolecular nucleophilic substitution. The *cis*-isoxazolidine (**1.22**) could be readily prepared from tandem deprotection intramolecular conjugate addition of the *N*-phthaloyl derivative (**1.23**). *N*-phthaloyl derivative (**1.23**) could be prepared by Mitsunobu reaction of the alcohol, which could

be prepared from selective ring opening at the less hindered terminus of commercially available (*R*)-epichlorohydrin (**1.24**) by Grignard reaction, as well as cross-metathesis.



Scheme 1.6 Retrosynthetic analysis for amphorogynine C

1.3. Results and Discussion

1.3.1 Synthesis of Amphorogynine C

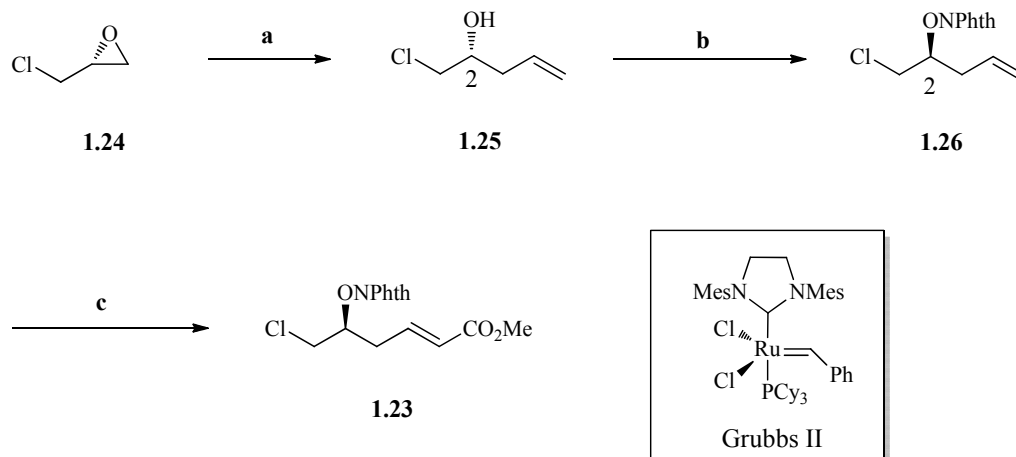
We began our synthesis by using commercially available (*R*)-epichlorohydrin (**1.24**). This material may also be obtained by hydrolytic kinetic resolution of the racemate (\pm)-epichlorohydrin.²² The ring-opening with a Grignard reagent, vinylmagnesium bromide, in the presence of copper iodide (CuI) catalyst in anhydrous tetrahydrofuran at -78 °C, provided the alcohol (**1.25**) in 95% yield, using a procedure reported by Blechert and co-workers²³ (**Scheme 1.7**). Only one product, arising from attack at the less hindered carbon of (*R*)-epichlorohydrin (**1.24**), was observed in the ¹H NMR analysis, in which only one multiplet was observed at 3.86 ppm for the H-2 proton. Generally terminal epoxides are opened at the unsubstituted epoxide carbon due to steric effects. The use of copper(I) in this reaction resulted in a transmetalation to promote the reaction by formation of an organocopper reagent *in situ*.

We then continued with the Mitsunobu reaction, which allowed the inversion of stereochemistry at the C-O bond. The Mitsunobu reaction allows the conversion of primary and secondary alcohol to a variety of functional groups with inversion of stereochemistry.²⁴ In our strategy we chose *N*-hydroxyphthalimide as the nucleophile^{18b,18d} which was sufficiently acidic for a Mitsunobu reaction. Another advantage of using *N*-hydroxyphthalimide as a nucleophile in this reaction as a hydroxylamine precursor, is that it deactivates the nitrogen atom to allow for cross-metathesis in the next step, as a free (basic) nitrogen can inhibit the metathesis catalyst.²⁵ Previously, our group has

reported a low yield of a cross-metathesis reaction with an NHBoc containing substrate.^{18b} This is commonly improved by using an electron withdrawing protecting group such as carbamate, sulfonate or an amide, thus *N*-hydroxyphthalimide is very useful. Hence, the alcohol (**1.25**) was treated with *N*-hydroxyphthalimide in the presence of triphenylphosphine and diisopropyl azodicarboxylate in anhydrous tetrahydrofuran at -20 °C to room temperature to obtain the *N*-phthaloyl hydroxylamine (**1.26**) in excellent yield. The enantiomeric excess of the *N*-phthaloyl hydroxylamine (**1.26**) was determined to be 98.2% by chiral HPLC analysis. The ¹H NMR analysis of the *N*-phthaloyl hydroxylamine (**1.26**) displayed a multiplet at 4.42 ppm for the H-2 proton, in which the chemical shift was strongly shifted to lower field. Two sets of aromatic protons were observed at 7.85-7.73 ppm corresponding to the phthalimide moiety. The ¹³C NMR spectrum showed a peak at 164.2 ppm, which was assigned to the carbonyl groups of the phthalimide moiety.

The construction of a Michael acceptor in *N*-phthaloyl derivative (**1.23**) was carried out by a cross-metathesis reaction.^{26,18b} We chose methyl acrylate as a terminal alkene to provide the ester moiety in the molecule. A subsequent cross-metathesis reaction of *N*-phthaloyl hydroxylamine (**1.26**) and 8 equivalents of methylacrylate in the presence of 5 mole percent Grubbs' second generation catalyst^{26a} in refluxing dichloromethane, gave *N*-phthaloyl derivative (**1.23**) in 86% yield. The ¹H NMR spectrum of *N*-phthaloyl derivative (**1.23**) indicated one singlet peak at 3.86 ppm for the COOMe group. One doublet of triplets was observed at 7.05 ppm with coupling constants of 15.5 and 7.3 Hz for one olefinic proton. The other one olefinic proton was detected at

6.04 ppm with coupling constant of 15.5 Hz. The large coupling constant is characteristic of the *trans* double bond in phthaloyl derivative (**1.23**).

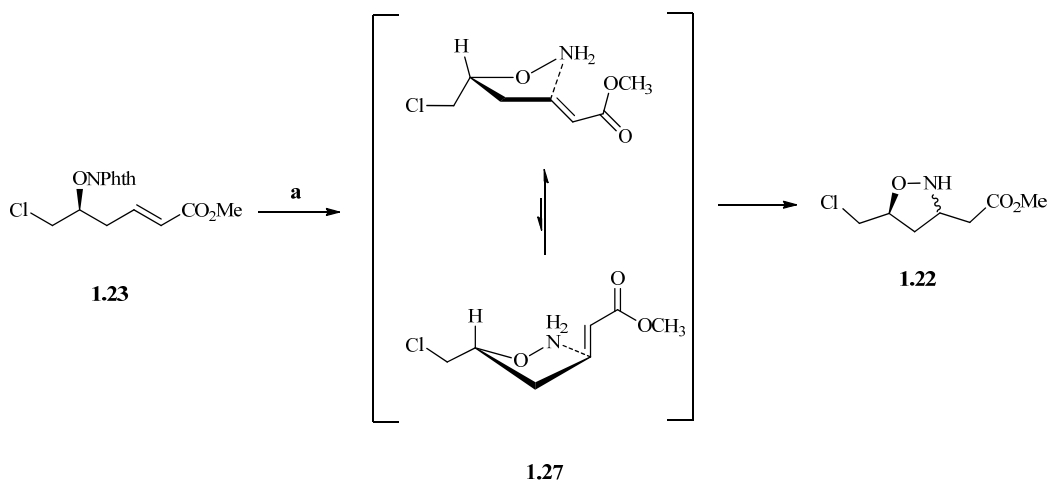


Scheme 1.7 Synthesis of phthaloyl derivative (**1.23**).

Reagents and conditions: (a) vinylmagnesium bromide, CuI, Et₂O, -68 °C, 1 h; 95%; (b) PhthNOH, PPh₃, DIAD, THF, -20 °C to rt, 6 h; 98%; (c) methyl acrylate, Grubbs II, CH₂Cl₂, reflux, 4 h; 86%.

The phthaloyl derivative (**1.23**) was then ready for the next step. Cleavage of the phthaloyl group of compound (**1.23**) was carried out with hydrazine monohydrate in dichloromethane at 0 °C to room temperature (**Scheme 1.8**). The reaction was complete in 15-30 minutes, providing the mixture of stereoisomeric isoxazolidines (**1.22**) quantitatively after simple filtration and evaporation. A copious precipitate of phthaloyl hydrazide was formed which could be easily removed by filtration.^{18b} Hydrazine was used to remove the phthaloyl group, using the Ing Manske modification of the Gabriel reaction²⁷, which involves mild and neutral conditions.²⁸ The ¹H NMR spectrum of the crude product showed the absence of the aromatic protons. Characterization by ¹H

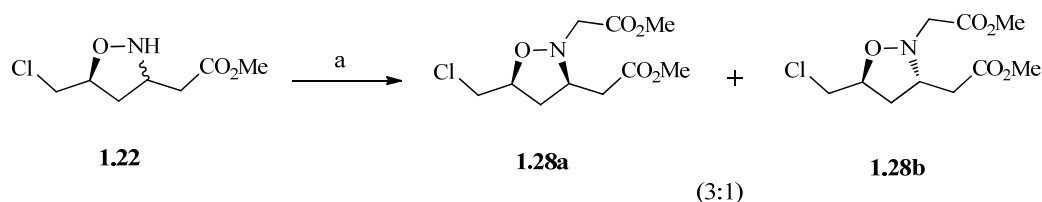
NMR showed a broad singlet at 4.77 ppm for NH group. The IR spectrum also exhibited a sharp peak at 3224 cm^{-1} for stretching of the N-H bond. The intermediate (**1.27**) was not observed; a tandem dephthaloylation-cyclisation occurred, to provide the crude mixture of isoxazolidines (**1.22**). A 3:1 ratio mixture of stereoisomeric isoxazolidines (**1.22**) was clearly formed by protonation of the intermediate enolate (**1.27**) produced by the intramolecular Michael addition. The conformational preference of the isoxazolidine gives rise to a distorted envelope or distorted half chair; depending on the substitution of the ring, but the preference is seldom well defined. The combination of molecular interactions related to both steric and electronic repulsion. Due to the difficult separation of the two diastereomers, we presumed the configuration of product isoxazolidine (**1.22**) was *cis* based on earlier work.^{18b} This was subsequently confirmed by conversion to the natural product. We then continued the next step without further purification.



Scheme 1.8

Reagents and conditions: (a) $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to rt, 15-30 mins; 89%.

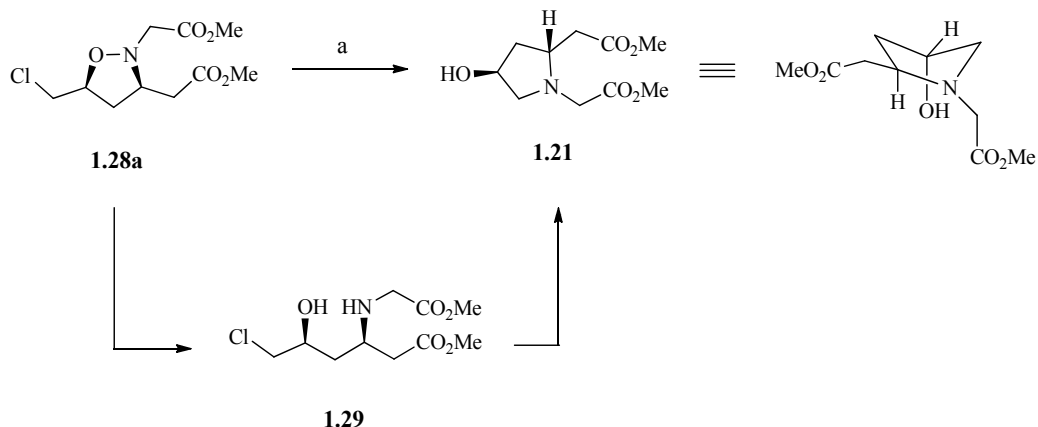
We carried out the *N*-alkylation using methyl bromoacetate as the electrophile. The remaining methylene ester moiety was introduced to the molecule at this step. *N*-Alkylation of the mixture of isoxazolidines (**1.22**) was carried out with methyl bromoacetate in the presence of sodium bicarbonate in dimethylformamide at room temperature for 24 hours. The reaction did not proceed well, rather it required heating to 60 °C for 24 hours to afford complete conversion, giving *N*-alkylated diester (**1.28a**) and (**1.28b**) in 80% yield as a 3:1 ratio. We were able to separate the diastereomers by column chromatography to obtain the *cis*-isomer (**1.28a**) as the major product in 58% yield and the *trans*-isomer (**1.28b**) as the minor product in 22% yield. The major isomer was presumed, on the basis of our previous results^{18b}, to be the *cis*-isomer (**Scheme 1.9**). The ¹H NMR spectrum of the *cis*-isomer (**1.28a**) showed methylene protons peak in the ring at 2.68 and 1.88 ppm, appearing as a doublet of triplets with coupling constants of 12.0, 8.0, and 8.0 Hz. The ¹H NMR spectrum of the *trans*-isomer (**1.28b**) displayed methylene protons peak in the ring at 2.40 and 2.17 ppm, appearing as doublet of triplets with coupling constants of 12.0, 8.0, and 1.3 Hz.



Scheme 1.9

Reagents and conditions: (a) methyl bromoacetate, NaHCO₃, DMF, 60 °C, 24 h; (58% for **1.28a**) and 22% for **1.28b**), 3:1).

Cleavage of the *N-O* bond of the *cis*-isoxazolidine (**1.28a**) could provide the 1,3-amino alcohol (**1.29**), which was expected to cyclise to give the pyrrolidine (**1.21**). The reductive cleavage of an *N-O* bond can be performed using a variety of different reagents.²⁹ Unexpectedly, the *N-O* bond of the *cis*-isoxazolidine (**1.28a**) turned out to be rather strong, possibly as a consequence of the steric bulk of the methylene group α to the oxygen and nitrogen. Several reducing agents, such as Zn/AcOH in tetrahydrofuran;^{29f-h} Mo(CO)₆ in acetonitrile:water (1:1);^{29j} Ni/Al (1.0 M KOH, in methanol);^{29e} catalytic hydrogenation over Pd-C^{29a} or/and PtO₂^{29b} under conventional conditions (1 atm); were tried. Unfortunately, the desired pyrrolidine (**1.21**) was obtained low yield and starting material (**1.28a**) was recovered. Nevertheless, a high yield of the pyrrolidine (**1.21**) was achieved using 100 psi hydrogen over Pd-C catalyst and one equivalent of calcium carbonate^{18d} in methanol at room temperature for 24 hours. The hydrogenation experiment revealed that a complete tandem *N-O* bond cleavage-cyclisation required more aggressive conditions. The 1,3-amino alcohol intermediate (**1.29**) was not observed; a tandem *N-O* bond cleavage-cyclisation occurred, to give the pyrrolidine (**1.21**) as a single isomer (**Scheme 1.10**). The chloride moiety at the molecule acted as a leaving group in the process of an S_N2 reaction. Addition of one equivalent of calcium carbonate in the reaction was to neutralise the hydrochloric acid, which was formed after completed cyclisation. The stereochemistry of the pyrrolidine (**1.21**) was presumed based upon the *cis*-isoxazolidine (**1.28a**). The ¹H NMR spectrum of pyrrolidine (**1.21**) displayed a broad singlet peak at 4.89 ppm indicating to OH group. The IR spectrum also demonstrated a sharp peak at 3434 cm⁻¹ for OH bond stretching.



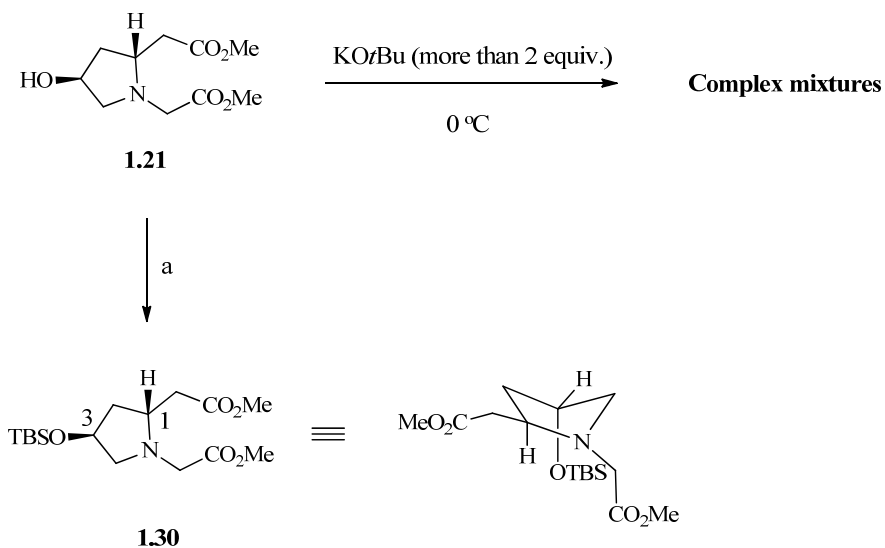
Scheme 1.10

Reagents and conditions: (a) H_2 , Pd-C, CaCO_3 , 100 psi, 24 h; 96%.

At this point two of the three chiral centres of the final product (**1.21**) had been created. The ester substituent could be formed by cyclisation under Dieckmann condensation to provide a bicyclic pyrrolizidine as proposed. The Dieckmann condensation is known as an intramolecular Claisen condensation in which diester compounds containing α -hydrogen deprotonates, promoted by a base such as sodium ethoxide, to afford β -ketoesters after cyclisation.³⁰ The Dieckmann condensation is the base-catalysed intramolecular nucleophilic acyl substitution, forming a cyclic β -ketoester, which usually produces 5- or 6-membered rings and the ring formed must not be strained.³⁰

It was found the necessary to protect the hydroxy group in the pyrrolidone ring (**1.21**) to prevent possible interference upon the Dieckmann cyclisation. Without prior protection, the use of one equivalent of potassium *tert*-butoxide (KO*t*Bu) in anhydrous tetrahydrofuran was tried at 0 °C, but gave only the recovered starting material (**1.21**). On

the other hand, with more than two equivalents of potassium butoxide, the reaction failed to give the desired product, and a complex mixture was formed (**Scheme 1.11**).

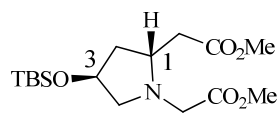
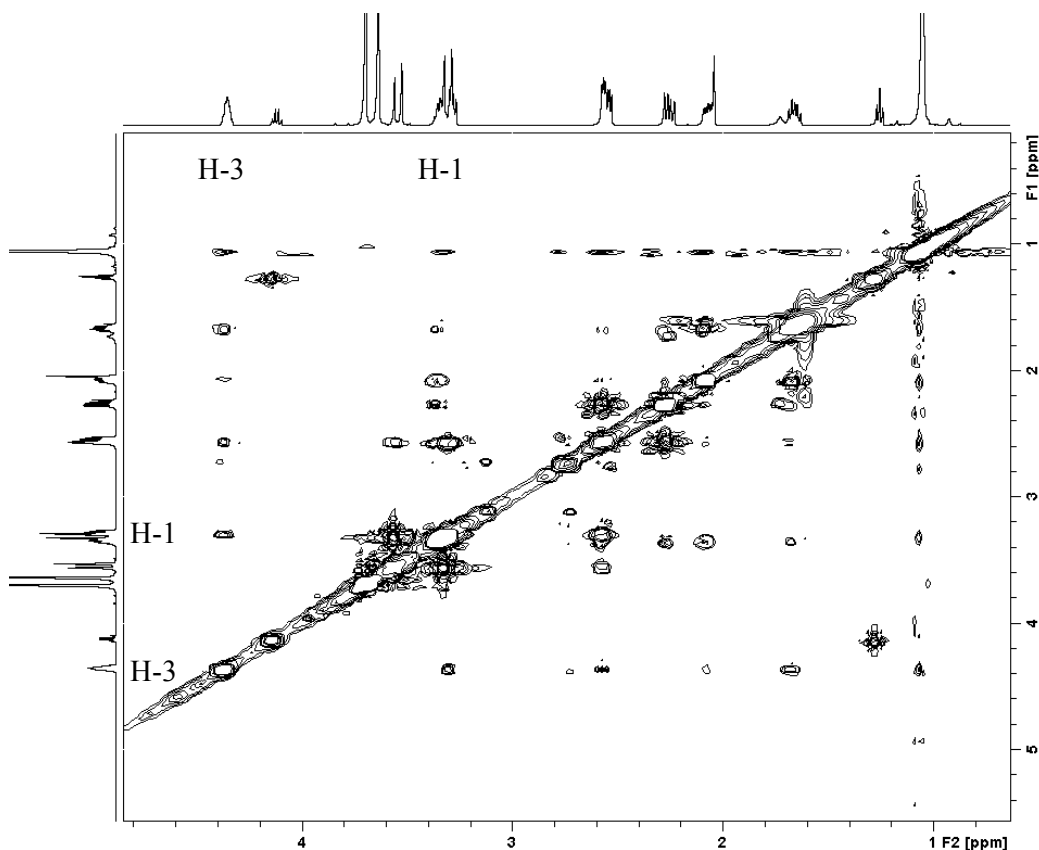


Scheme 1.11

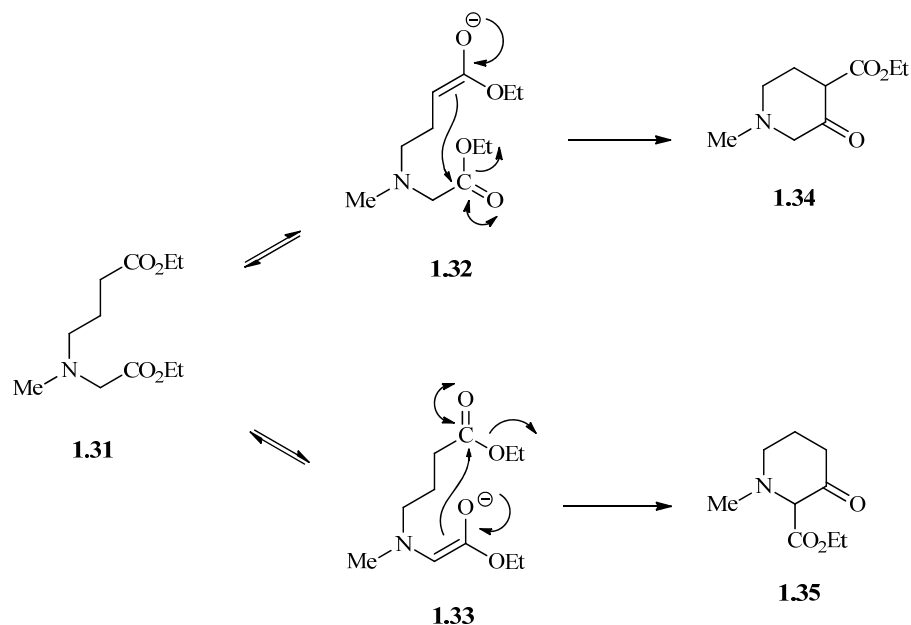
Reagents and conditions: (a) TBSCl, imidazole, DMF, 0 °C-rt, 24 h; 92%.

The presence of hydroxy group in pyrrolidine (**1.21**) obviously interfered with this reaction. Buchanan *et al.* reported that a silyl ether proved to be more tractable as a substrate for Dieckmann cyclisation.³¹ Therefore, the alcohol was converted to its silyl ether using the procedure reported by Corey and Venkateswarlu.³² The silyl ether (**1.30**) was obtained in good yield by treatment with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide at 0 °C to room temperature for 24 hours (**Scheme 1.11**). The ¹H NMR spectrum of the desired product (**1.30**) displayed a sharp singlet of the *tert*-butyl group at 0.84 ppm and the other singlet for the methyl group at 0.01 ppm. The desired protected product (**1.30**) was then ready for the next step.

The relative configuration at the C-1 and C-3 positions of the pyrrolidine (**1.30**) could not be confirmed by 2D NMR (NOESY) due to the protons at C-1 (3.24 ppm) superimpose with the other methylene proton at 3.22 ppm (CH_2N) (**Figure 1.4**). However, The relative configuration of the pyrrolidine (**1.30**) was assumed based on the *cis*-isoxazolidine (**1.28a**).^{18b}

**1.30****Figure 1.4** Part of NOESY spectrum of pyrrolizidine (**1.30**)

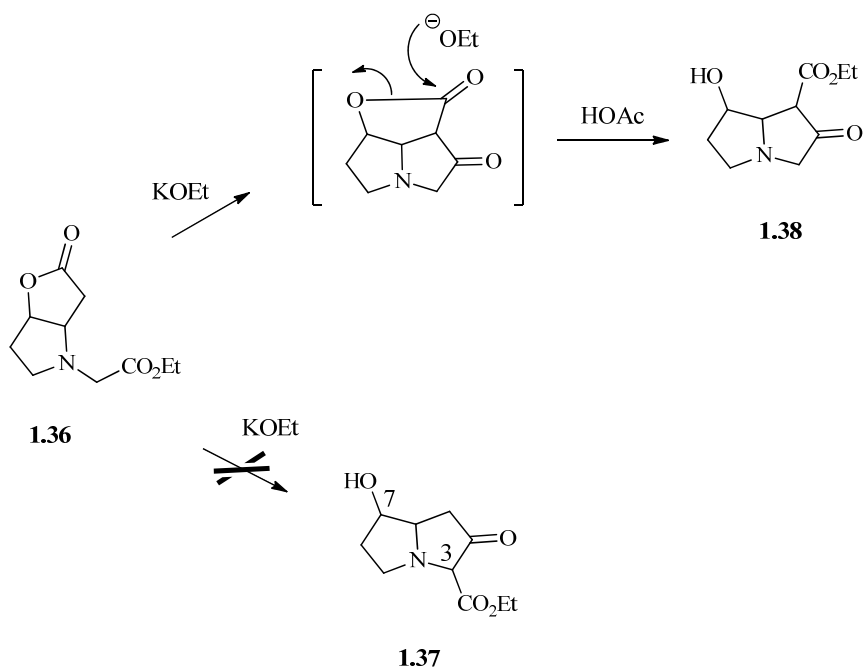
McElvain and Prill studied the Dieckmann condensation of di-ester amine (**1.31**) which could condense to piperidone (**1.34**) or/and (**1.35**) as shown in **Scheme 1.12**.³³ Two possible enolate anion intermediates (**1.32**) or/and (**1.33**) could be obtained, which lead to 6-membered piperidone (**1.34**) or/and (**1.35**). They found only one product, piperidone (**1.34**), was obtained in moderate yield in 30 minutes. They reported that the condensation of the enolate anion intermediate (**1.33**) proceeded very slow.



Scheme 1.12

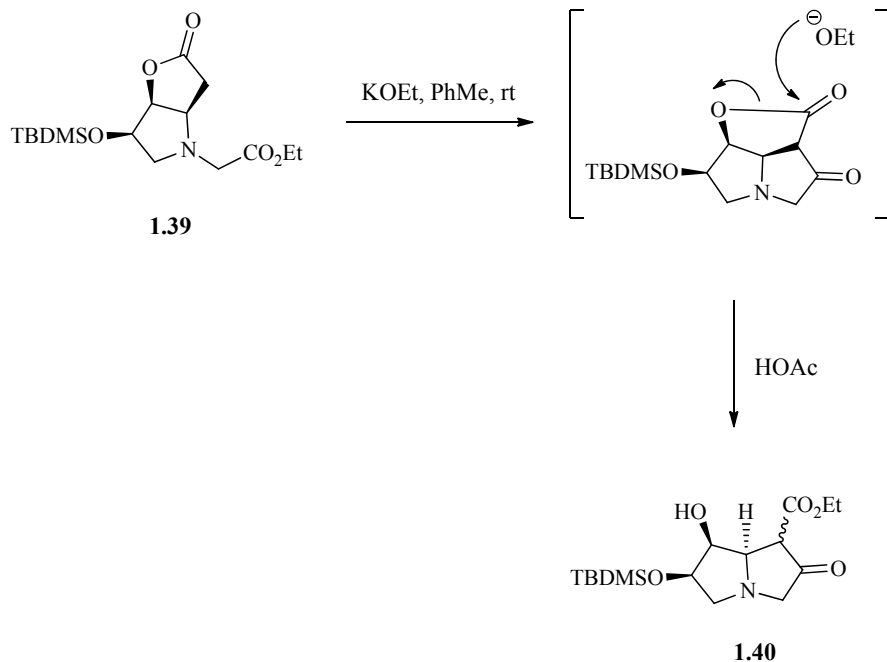
In the case of intramolecular condensation of bicyclic di-ester (**1.36**) by a Dieckmann reaction, this method has been reported to be useful for the synthesis of pyrrolizidine alkaloids.^{31,33-35} Geissman and Waiss³⁵ reported the Dieckmann condensation of lactone (**1.36**) was a direct consequence of the presence of the lactone ring (**Scheme 1.13**). They proposed that a carbonyl group at position 3 and a 7-hydroxyl group of the

pyrrolizidine (**1.37**) would involve substantial strain. Dieckmann already proposed that the ring formed must not be strained. Consequently, the formation of a carbanion next to the nitrogen atom is not preferred. They found the only one product bicyclic β -keto ester (**1.38**) was observed.



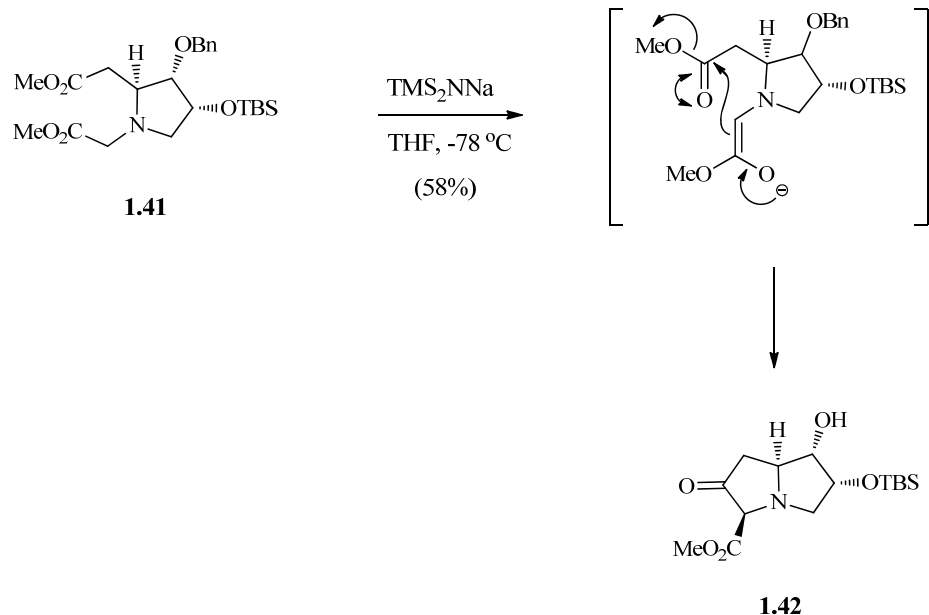
Scheme 1.13 Geissman's Dieckman condensation.

Buchanan and co-workers employed the Dieckmann condensation to bicyclic di-ester (**1.39**) followed a procedure developed by Geissman and Waiss.³⁵ This reaction was carried out in anhydrous toluene at room temperature and cyclisation occurred to give only one product β -keto ester (**1.40**) (**Scheme 1.14**).³¹



Scheme 1.14 Buchanan's Dieckman condensation.

Chmielewski and co-workers reported the regiochemistry of the deprotonation of the amine (**1.41**) in the Dieckman condensation is opposite to that reported by Buchanan's group. The formation of a carbanion next to the nitrogen is preferred.³⁶ In the case of Chmielewski's Dieckman condensation, the reaction was carried out in the presence of amide base (TMS_2NNa) in anhydrous tetrahydrofuran at $-78\text{ }^\circ\text{C}$. Cyclisation occurred to form pyrrolizidine (**1.42**) (**Scheme 1.15**).

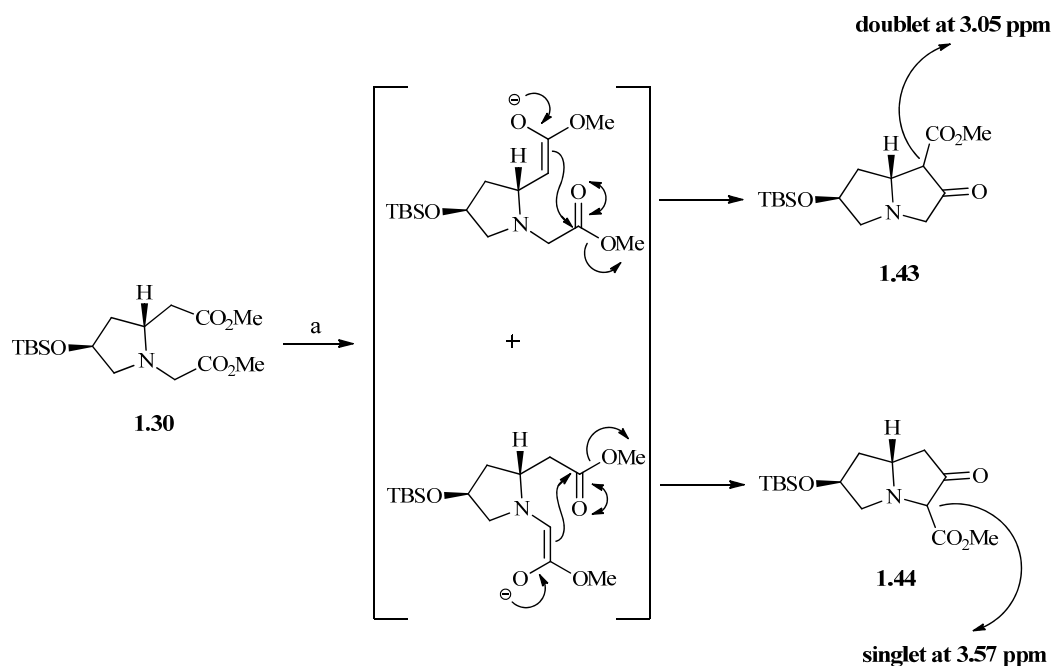


Scheme 1.15 Chmielewski's Dieckmann condensation.

With the method described in the literature above, the factor controlling the observed regiochemistry of the Dieckmann condensation of the cyclic di-ester amine, is the rate of the enolate anion reaction with the ester, leading to the thermodynamically more stable cyclic β -ketoester. The kinetically disfavored cyclic β -ketoester product is obtained in the case of Chmielewski's Dieckmann condensation.

From the limited information, it appears that the regiochemistry of the Dieckmann condensation can be controlled by rate and temperature of the reaction. Thus, we attempted to apply the standard conditions of the Dieckmann condensation to the silyl ether (**1.30**) to promote the formation of the five-membered ring. In the case of di-ester pyrrolidine (**1.30**), a carbanion next to the nitrogen or α -carbon of the other methyl

ester could condense to two different products as we proposed. The pyrrolidine (**1.30**) was then treated with potassium *tert*-butoxide in anhydrous tetrahydrofuran at 0 °C for 30 minutes; cyclisation occurred, to provide the crude mixture of keto ester (**1.43**) and (**1.44**) in a 1:1 ratio (Scheme 1.16). We were unable to control the regiochemistry of the Dieckmann condensation at 0 °C.



Scheme 1.16

Reagents and conditions: (a) KO^tBu, THF, 0 °C, 30 mins.

The ^1H NMR spectrum of the crude product showed two singlet peaks of ester groups at 3.76 and 3.78 ppm, which determined the mixture of keto ester (**1.43**) and (**1.44**) as 1:1. **Figure 1.5** shows the ^1H NMR spectrum of the crude mixture of keto esters (**1.43**) and (**1.44**). The signal of the singlet peak at 3.57 ppm was assigned as the proton of the CHCO_2Me moiety of the keto ester (**1.44**). The doublet peak at 3.05 ppm with coupling constant of 8.7 Hz indicated the characteristic proton in the $\text{CHCHCO}_2\text{CH}_3$ moiety of keto ester (**1.43**).

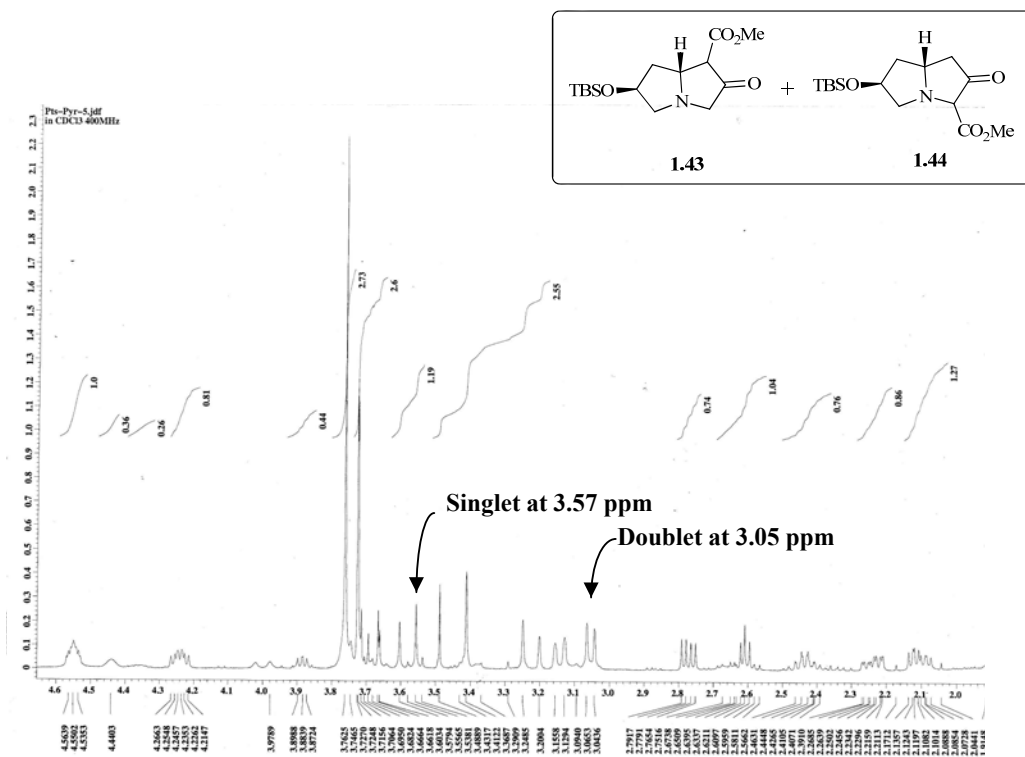


Figure 1.5 ^1H NMR spectrum of mixtures keto ester (**1.43**) and keto ester (**1.44**)

Column chromatography was required to isolate the desired product. Surprisingly, the keto ester (**1.44**) was isolated in 5% yield. The ^1H NMR spectrum showed the characteristic singlet peak at 3.57 ppm of one proton of the CHCO_2Me moiety of keto ester (**1.44**) (Figure 1.6).

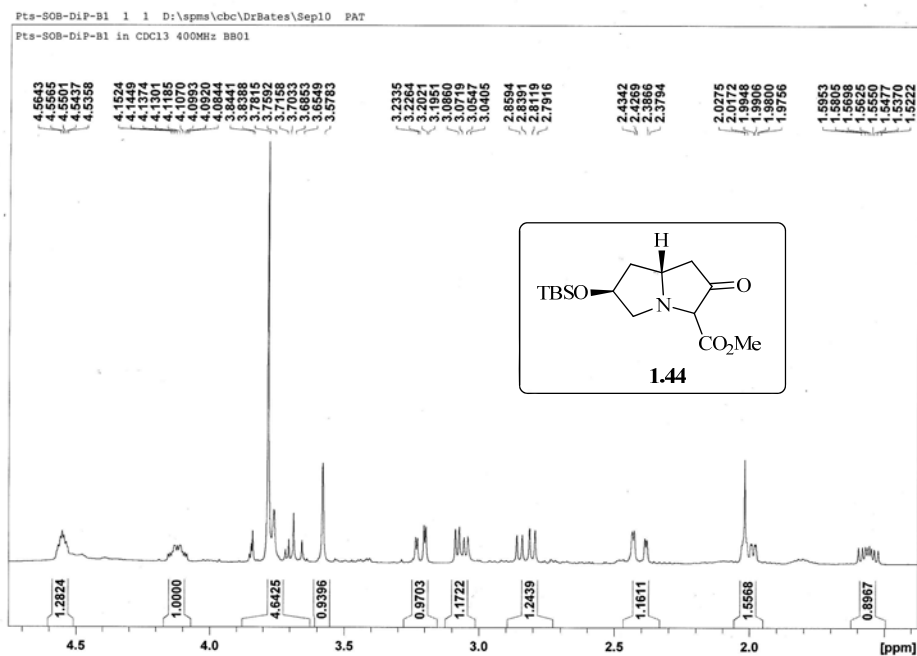


Figure 1.6 Part of ^1H NMR spectrum of keto ester (**1.44**)

We confirmed keto ester (**1.44**) was isolated by column chromatography. Nevertheless, after a period of time the keto ester (**1.44**) decomposed. Chemielewski and co-workers reported that this kind of keto ester skeleton is air sensitive.³⁶ However, the target keto ester (**1.43**) was not isolated by column chromatography. It could have also decomposed during the purification. According to Buchanan's result, the bicyclic keto ester (**1.43**) should be obtained under standard Dieckmann condensation conditions at room temperature or on warming to reflux in anhydrous toluene.³¹ Thus, we carried

out the reaction at room temperature. The pyrrolidine (**1.30**) was then treated with potassium *tert*-butoxide in anhydrous tetrahydrofuran at room temperature for 30 minutes. Cyclisation occurred to provide the crude product keto ester (**Scheme 1.17**). We found that the only one keto ester (**1.43**) was formed under this condition. The ^1H NMR spectrum of the crude product showed a doublet peak at 3.05 ppm with coupling constant of 8.7 Hz, corresponding to the characteristic of one proton of the $\text{CHCHCO}_2\text{CH}_3$ moiety of keto ester (**1.43**). **Figure 1.7** shows the ^1H NMR spectrum of the crude keto ester (**1.43**). Not surprisingly, after a short period of time, keto ester (**1.43**) decomposed.

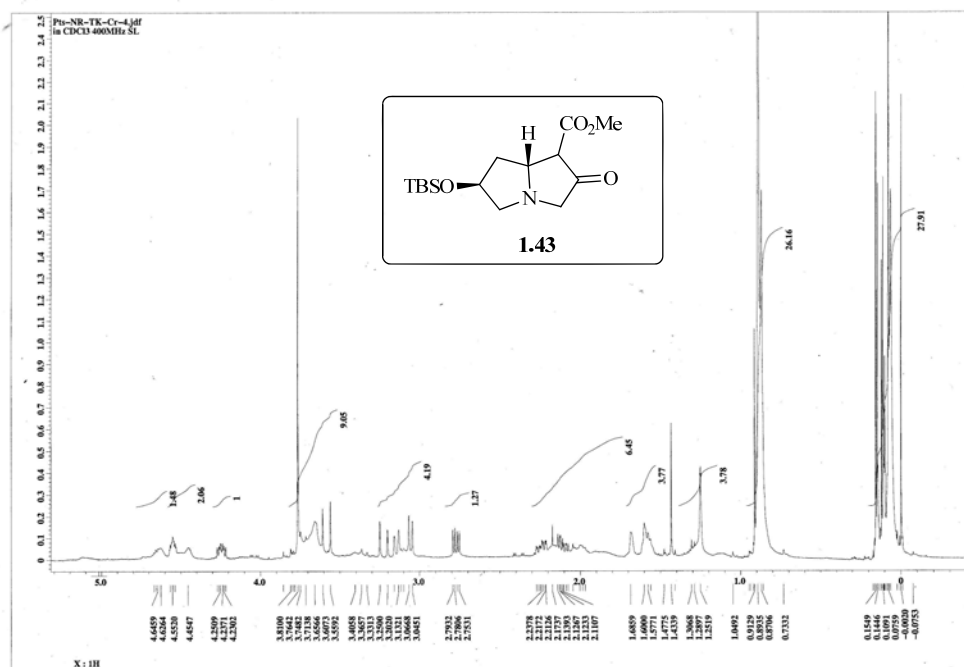


Figure 1.7 Part of the crude ^1H NMR spectrum of keto ester (**1.43**)

Several other amide bases such as lithium bis(trimethylsilyl)amide (LiHMDS),³⁷ sodium bis(trimethylsilyl)amide (NaHMDS),³⁸ and potassium bis(trimethylsilyl)amide (KHMDS),³⁹ were used.⁴⁰ The same results were obtained. The ¹H NMR spectrum of the crude product result from potassium bis(trimethylsilyl)amide, showed the cleanest desired keto ester (**1.43**). The configuration of the new stereochemistry was not determined as it was subsequently could led to a sp² hybridised carbon. As the material decomposed even a brief storage, we continued with the next step without further purification. The intermediate keto ester (**1.43**) was directly reduced with sodium borohydride in methanol under nitrogen at 0 °C to room temperature, providing intermediate (**1.45**). Mesylation of the intermediate (**1.45**) using methanesulfonyl chloride in the presence of excess triethylamine in dichloromethane at 0 °C to room temperature,⁴¹ gave the mesylate intermediate (**1.46**). This compound could not be isolated but underwent *in situ* elimination to give the conjugated ester intermediate (**1.47**) (**Scheme 3.17**).

Greene and co-workers reported the chemical shift of the proton at the endocyclic double bond of the pyrrolizidine (**1.49**) (**Figure 1.8**), appearing as a doublet of doublets of doublets (app. quartet) with coupling constants of 2.0, 2.0 and 2.0 Hz at 6.72 ppm.⁴² The ¹H NMR spectrum of the crude product (**1.47**) showed a peak at 6.65 ppm which appeared as a quartet with coupling constant of 2.2 Hz.

According to the results of Greene *et al.*, we decided not to isolate the unsaturated ester (**1.47**) and immediately continued with the next step. The unsaturated ester (**1.47**) was then hydrogenated over platinum(IV) oxide in methanol^{29b} to provide the expected pyrrolizidine (**1.48**). Lhommet *et al.* reported that the use of platinum(IV) oxide

as hydrogenation catalyst for the endocyclic double bond provided better selectivity than Pd.⁴³ The stereochemistry at the C-1 position of the pyrrolizidine (**1.48**) was presumed based on the Greene *et al.* previous results.⁴² The shape of the pyrrolizidines (**1.47**) showed that in the view of the folded geometry and the endo-face-encumbering silyl group, hydrogenation was expected to take place predominantly on the exo or convex face of the molecule.⁴⁴ With the limitation of instability of bicyclic keto ester (**1.43**), we continued the synthetic route without purification to an average yield of 70% for each step (**Scheme 1.17**).

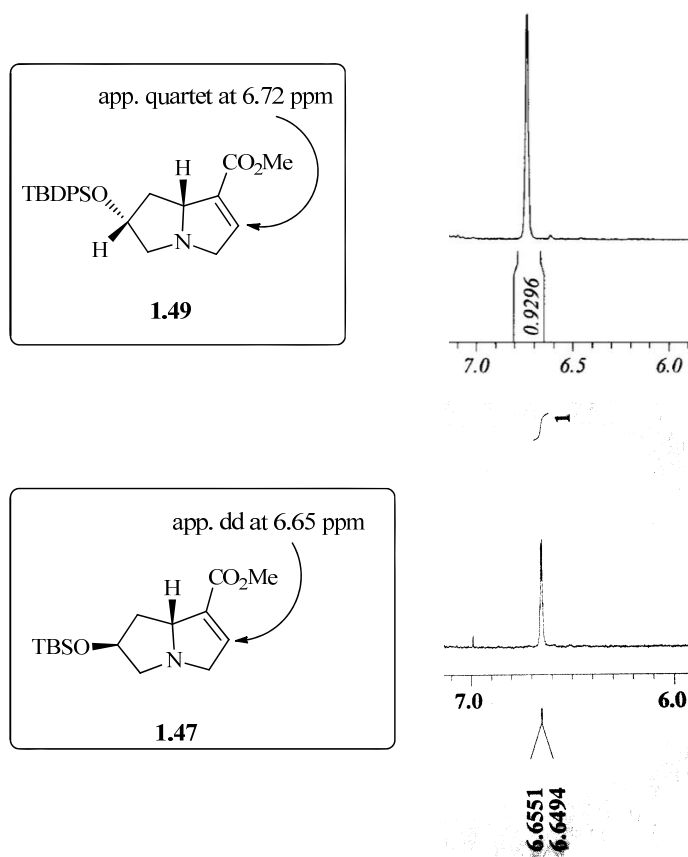
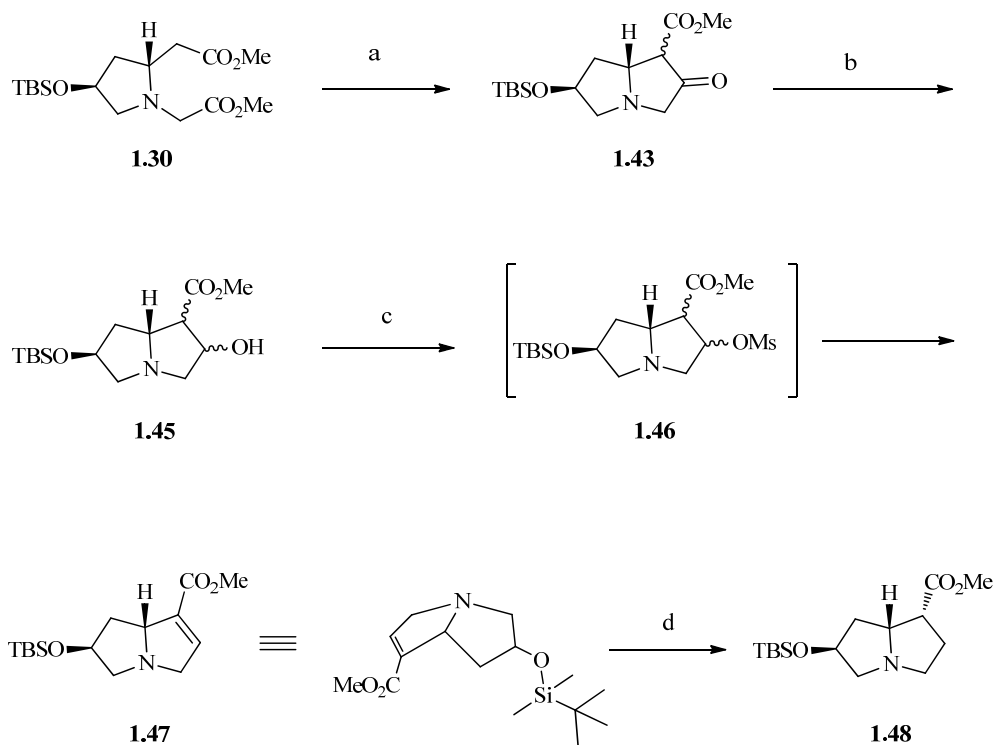


Figure 1.8 Compare part of ¹H NMR of Greene's pyrrolizidine (**1.49**) and compound (**1.47**)



Scheme 1.17

Reagents and conditions: (a) KHMDS, THF, rt, 30 mins; (b) NaBH₄, MeOH, 0 °C, 1 h; (c) MsCl, Et₃N (excess), CH₂Cl₂, 0 °C to rt, 2 h; (d) H₂, PtO₂, MeOH; 25% over 4 steps.

The ¹H NMR spectrum of pyrrolizidine (**1.48**) showed three protons of signals at 4.32 (quint), 3.72 (m) and 3.11 (q) assignable to H-6, H-8 and H-1 respectively. 2D COSY NMR experiments for compound (**1.48**) were conducted to determine the correlation of the quartet at 3.11 ppm (cross peak with H-8, H-2 and H-2') (**Figure 1.9**). The ¹³C NMR spectrum confirmed a peak (CO) at 173.5 ppm and 4 methylene carbons at 62.4, 53.9, 37.8, and 26.0 ppm.

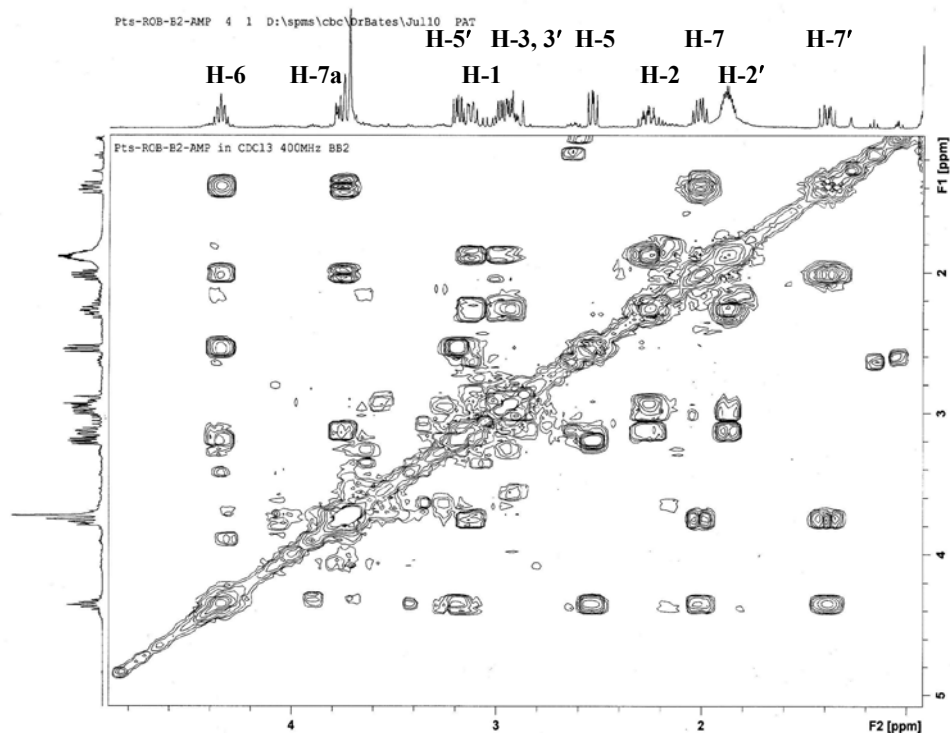
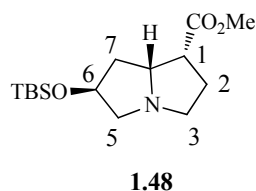
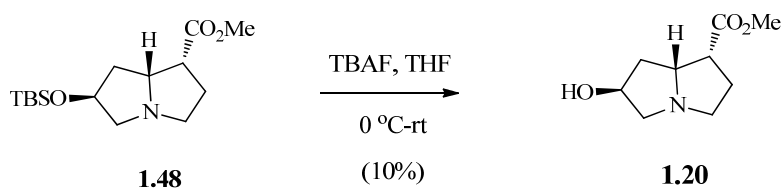


Figure 1.9 Part of COSY spectrum of the pyrrolizidine (**1.48**)

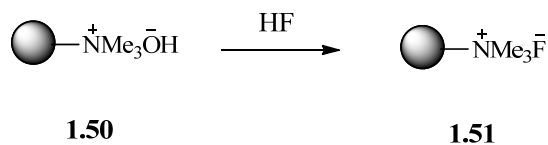
Next, with the bicyclic pyrrolizidine (**1.48**) in hand, we continued the next step, desilylation, simply using tetra-*n*-butylammonium fluoride as the usual reagent for deprotection of silyl ethers. Deprotection with TBAF often requires an excess amount of the reagent. The pyrrolizidine (**1.48**) was treated with excess TBAF in anhydrous tetrahydrofuran at 0 °C and warmed to room temperature overnight to give complete deprotection of the *tert*-butyldimethylsilyl ether. The tetra-*n*-butyl-ammonium by-product

was difficult to separate from the desired product (**1.20**), primarily because the polarity of such TBAF was much the same as that of the desired product (**1.20**). The pure product pyrrolizidine (**1.20**) was obtained in 10% isolated yield (**Scheme 1.18**). The concept of acid-catalysed deprotection of the silyl ether may also be applied to the pyrrolizidine (**1.48**). Despite this concern, the need for an aqueous-phase extraction method could be complicated by pyrrolizidine (**1.20**) being soluble in water.



Scheme 1.18

Given that the difficulty in the use of TBAF was in the removal of the by-product derived from the reagent, we investigated the use of polymer-supported reagents. These have been widely used in organic synthesis in the last few decades.⁴⁵ The major advantage of solid-supported reagents is the simplicity of workup, as they can be easily removed by simple filtration.⁴⁶ Thus, the use of solid-supported fluoride was chosen over TBAF because of the easier work-up.⁴⁷ The polymer-supported fluoride can be prepared using a procedure reported by Huang and co-workers.^{47c} Amberlyst A-26 anion exchange resin (hydroxide form) (**1.50**) can be converted to the fluoride form (**1.51**)^{47c} by treatment with dilute aqueous hydrogen fluoride (**Scheme 1.19**).



Scheme 1.19

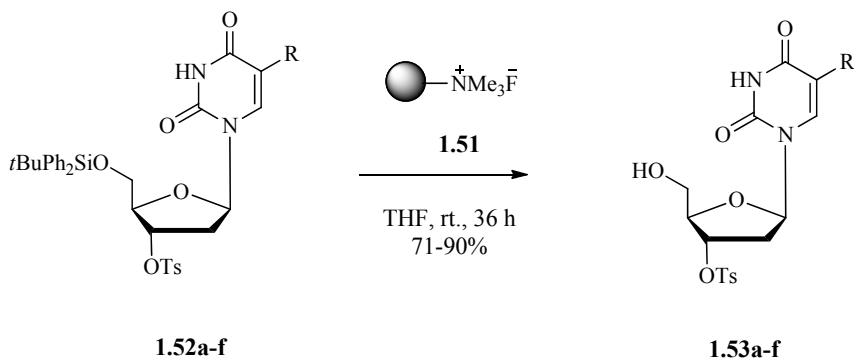
In 1983, Cardillo and co-workers employed Amberlite A-26 (F) (**1.51**) to promote the cleavage of the Si-O bond of a series of diphenyl-*tert*-butylsilyl monoprotected carbohydrates (**Table 1.1**, entry 1-5).^{47b} This polymer-supported fluoride is useful in this context as it allows the application of mild reaction condition and avoids aqueous work-up. The reaction was carried out in refluxing benzene using a 3:1 ratio of Amberlite A-26 (F) (**1.51**):substrate. After the reactions were completed, the corresponding polyhydroxylated products were attached to the resin and the by-product diphenyl-*tert*-butylsilyl fluoride was dissolved in benzene. The resin was filtered off and washed with methanol to release the pure products (**Table 1.1**, entry 1-5) in high yields.

Table 1.1 Deprotection reactions of diphenyl-*t*-butylsilyl monoprotected carbohydrates.

Entry	Substrate	Product	Yield (%)
1			92
2			92
3			89
4			91
5			94

Pederson and co-workers also used Amberlite A-26 (F) (**1.51**) as a source of fluoride to desilylate a series of diphenyl-*t*-butylsilyl monoprotected nucleosides (**1.52a-f**) (**Scheme 1.20**).^{47d} The reactions were performed in tetrahydrofuran at room tempera-

ture for 36 hours. Compounds (**1.53a-f**) were released from the resin through addition of MeOH.

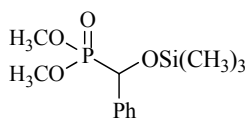
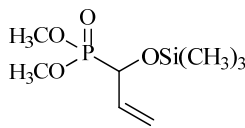
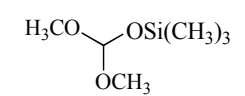


1.52, 1.53	R
a	H
b	CH ₃
c	C ₂ H ₅
d	F
e	Br
f	I

Scheme 1.20

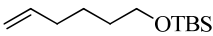
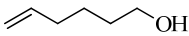
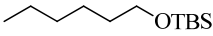
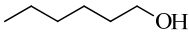
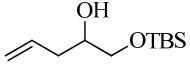
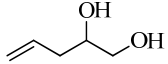
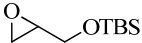
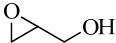
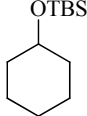
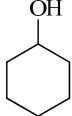
Huang and co-workers also employed this polymer-supported fluoride (**1.51**) to promote the cleavage of the Si-O bond of trimethylsilyl protected alcohols (**Table 1.2**, entry 1-5).^{47b} The reactions were completed in methanol at room temperature: the resin was filtered and the pure deprotected alcohols (**Table 1.2**, entry 1-5) were obtained in high yields.

Table 1.2 Si-O bond cleavage using Amberlite A-26 (F) (**1.51**)

Entry	R'OSi(CH ₃) ₃	Temp (°C)	Time (h)	R'OH (%) (Isolated Yield)
1	CH ₃ (CH ₂) ₇ OSi(CH ₃) ₃	20	2	98
2	Ph-CH ₂ -OSi(CH ₃) ₃	20	2	91
3		20	1.5	88
4		8	2	96
5		rt	2	72

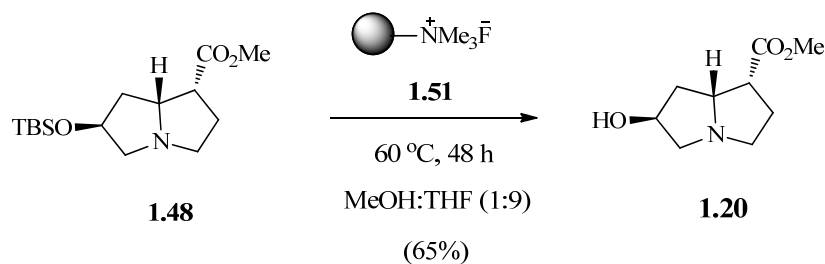
From the Si-O bond cleavage using Amberlite A-26 (F) (**1.51**) information, the deprotection of *tert*-butyldimethylsilyl protected alcohols was not found in the literature. Therefore, we first subjected several substrates (**Table 1.3**, entry 1-5) to desilylation with Amberlite A-26 (F) (**1.51**). All the substrates were completely deprotected in methanol at room temperature overnight to provide the free hydroxy products (**Table 1.3**, entry 1-5) in excellent yields.

Table 1.3 Si-O bond cleavage using Amberlyst A-26 (F) (**1.51**)

Entry	Substrate	Product	Yield (%)
1			92
2			90
3			93
4			95
5			97

Based on the above background concerning the use of polymer-supported fluoride, we then applied the solid supported resin Amberlyst A-26 (F) (**1.51**) with its simplified work-up procedure to the deprotection of the TBS silyl ether in our synthetic route. The pyrrolizidine (**1.48**) was subjected to desilylation with Amberlite A-26 (F) in methanol or/and tetrahydrofuran at room temperature overnight. The reaction did not proceed well at room temperature. We employed the combination of solvent, methanol and tetrahydrofuran, and heated the reaction to 50-60 °C. Disappointingly, upon completion of the reaction, the corresponding product alcohol (**1.20**) was obtained in low yield (**Scheme 1.21**). The literature reported that the deprotected product may be attached to the resin and cited the need for methanol to release the pure product from the resin. The best result for deprotection of the TBS group of the pyrrolizidine (**1.48**) required heating to 50-60 °C in methanol:tetrahydrofuran (1:9) for 2 days. After comple-

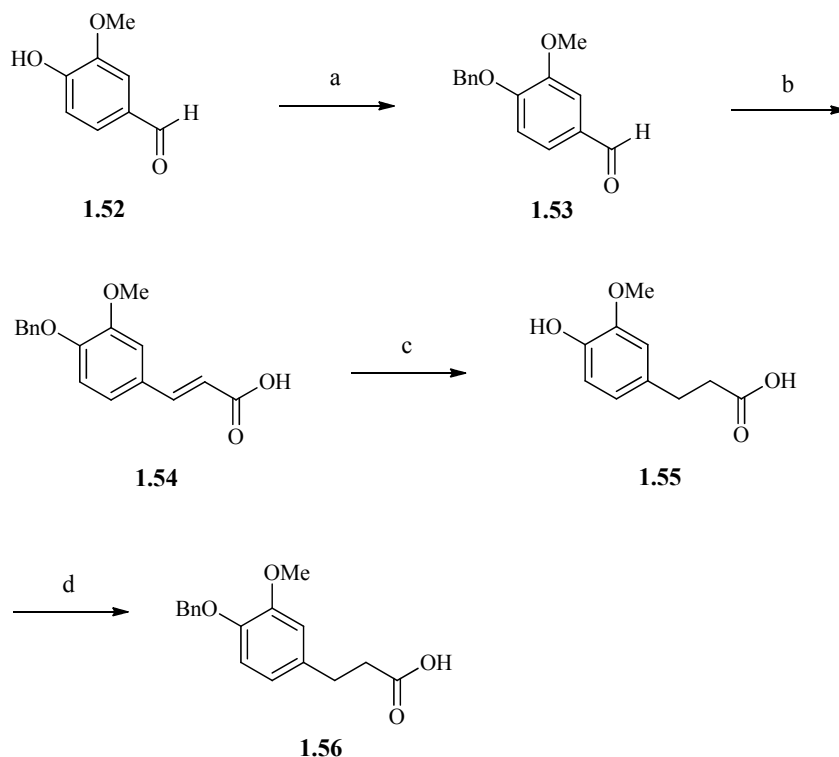
tion of the reaction, methanol was added and stirred for 2-3 hours. The resin was filtered off, the solvent was evaporated to afford the complete conversion, giving the desired product alcohol (**1.20**) in 65% yield. TBS-derived material was a contaminant in the crude product, which was purified by column chromatography. The IR spectrum showed a strong absorption band at 3287 cm^{-1} , indicating O-H stretching. The ^1H NMR spectrum showed the absence of the methyl groups at 0.01 ppm and the *tert*-butyl group at 0.89 ppm.



Scheme 1.21

The remaining side unit in amphorogynines C was prepared from vanillin (**1.52**). The benzyloxy aldehyde (**1.53**) was obtained in 93% yield by heating vanillin (**1.52**) in the presence of benzyl bromide, potassium carbonate at reflux in ethanol. Knoevenagel condensation, with the Doebner modification,⁴⁸ using malonic acid under basic conditions (pyridine and piperidine) led to α,β -unsaturated carboxylic acid (**1.54**) in 79% yield.⁴⁹ The double bond was then hydrogenated to compound (**1.55**) in 85% yield, followed by reprotection *via* treatment with benzyl bromide and potassium carbonate in refluxing acetone to afford 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid (**1.56**)

in 78% yield (**Scheme 1.22**). All spectroscopic data for 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid (**1.56**) agreed with those previously reported.⁵⁰

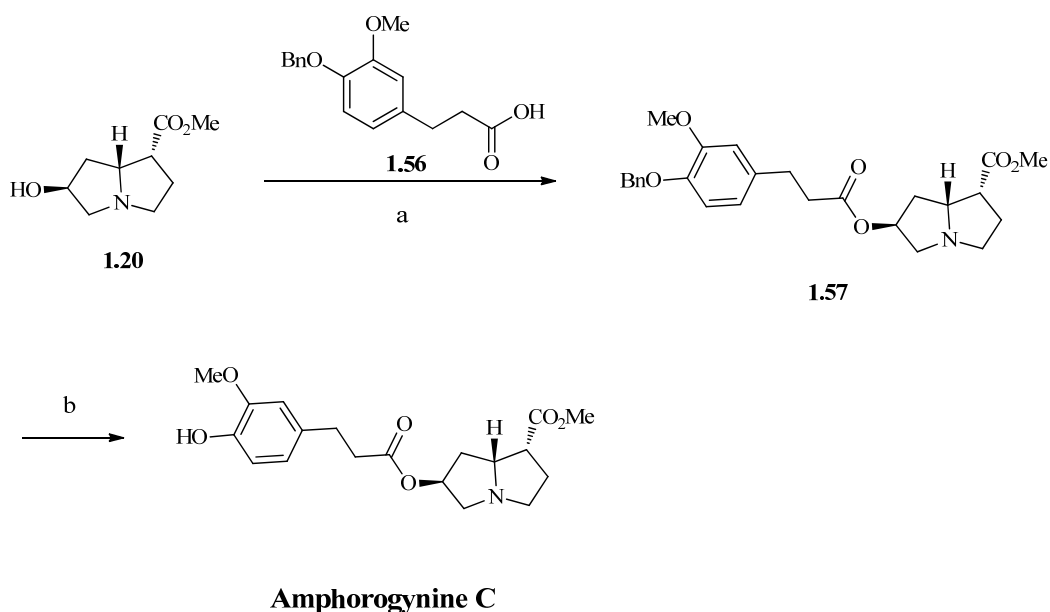


Scheme 1.22 Synthesis of 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid (**1.56**)

Reagents and conditions: (a) BnBr, K₂CO₃, EtOH, reflux; 93%; (b) malonic acid, pyridine:piperidine (1:1), reflux; 79%; (c) H₂, Pd-C, EtOAc; 85%; (d) BnBr, K₂CO₃, acetone, reflux; 78%.

The attachment of the ester side chain was achieved by treating the free hydroxy pyrrolizidine (**1.20**) and carboxylic acid (**1.56**) with 1-ethyl-3-(3-dimethylaminopropyl)-carbo-diimide hydrochloride and 4-dimethylaminopyridine in anhydrous dichloromethane at 0 °C to room temperature under a nitrogen atmosphere overnight to furnish the coupled product ester (**1.57**) in 68% yield.^{51,14} The ¹H NMR spectrum of ester

(**1.57**) showed the aromatic protons at 7.22-7.30 and 6.64-6.83 ppm and four methylene protons in the side chain at 2.86 (t) and 2.60 (t) ppm with coupling constant of 7.4 Hz. The final step was debenzoylation of the phenolic protecting group. Deprotection of benzyl ether was achieved by palladium catalysed hydrogenation, liberating the alcohol and toluene. This well-known procedure was reported by Bergmann and Zervas in 1932.⁵² Thus, debenzoylation of the phenolic protecting group was carried out at room temperature under an atmosphere of H₂ (1 atm) in the presence of Pd-C to provide the target amphorogynine C in 90% yield (**Scheme 1.23**). The loss of the aromatic signal at 7.30-7.22 ppm and methylene protons at 5.12 ppm in ¹H NMR spectrum confirmed the success of the reaction.



Scheme 1.23

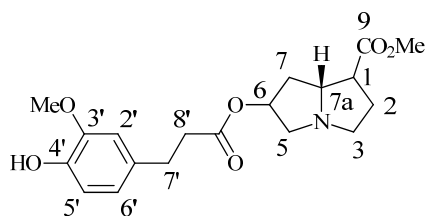
Reagents and conditions: (a) compound (**1.56**), EDCI, CH₂Cl₂, DMAP; 68%; (b) H₂, Pd-C, EtOAc; 90%.

The NMR spectroscopic data of amphorogynine C were in closely consistent with those reported in the original publication (**Table 1.4**).¹³ In our synthetic material the ¹³C NMR spectrum of the final product showed the absence of three quaternary carbons due to the low amount of compound.

Table 1.4 Comparison of physical and spectroscopic data for amphorogynine C.

	Literature ¹³	Our synthetic data
Optical rotation	$[\alpha]_D -2.0$ (<i>c</i> 1, CHCl ₃)	$[\alpha]_D^{21.1} -4.4$ (<i>c</i> 0.1, CHCl ₃)
¹ H NMR	300 MHz, CDCl ₃	400 MHz, CDCl ₃
	6.77 (d, <i>J</i> = 8 Hz) 6.65 (d, <i>J</i> = 2 Hz) 6.64 (dd, <i>J</i> = 8 Hz) 5.32 (m) 3.86 (s) 3.83 (ddd, <i>J</i> = 6 Hz) 3.66 (s) 3.21 (dd, <i>J</i> = 12 Hz) 3.14 (ddd, <i>J</i> = 8 Hz) 3.06 (m) 2.86 (m) 2.79 (m) 2.18 (t, <i>J</i> = 7.5 Hz) 2.53 (t, <i>J</i> = 7.5 Hz) 2.09 (m) 1.95 (m) 1.86 (ddd, <i>J</i> = 14, 7 Hz) 1.65 (ddd, <i>J</i> = 14, 7, 5 Hz)	6.77-6.67 (m) 5.37 (m) 3.87 (s) 3.86 (m) 3.72 (s) 3.36-3.26 (m) 2.99 (m) 2.94 (m) 2.86 (<i>J</i> = 7.4 Hz) 2.60 (<i>J</i> = 7.4 Hz) 2.25-1.90 (m) ~1.69-1.50 (m)
¹³ C NMR	75 MHz, CDCl ₃	125 MHz, CDCl ₃
	173.8 173.0 147.0 144.6 132.4 121.0 114.8 111.4 76.6 64.8 60.7 56.1 54.1 52.1 46.9 36.6 34.6 30.9 27.4	146.9 132.1 120.9 114.2 111.0 77.2 64.0 60.0 55.8 55.8 52.0 46.6 36.3 35.1 30.7 26.4

It has to be noted that one chemical shift of the methylene proton at the side chain of amphorogynine C, is a printing error. The ^1H NMR spectrum of H-7' in the natural product amphorogynine C was reported to have the chemical shift at 2.18 ppm with coupling constant of 7.5 Hz. Comparison of ^1H NMR data of amphorogynine A-C is shown in **Table 1.5**. In the spectra of amphorogynine A and B, the H-7' protons gives rise to a triplet at 2.81 ppm with coupling constant of 7.0 Hz and a triplet at 2.83 ppm with coupling constant of 7.5 Hz, respectively. The H-7' of amphorogynine C should therefore be a triplet at 2.81 ppm with coupling constant of 7.5 Hz, which is in good agreement with our synthetic amphorogynine C.



Amphorogynine A H-1 β , H-6 β

Amphorogynine B H-1 α , H-6 α

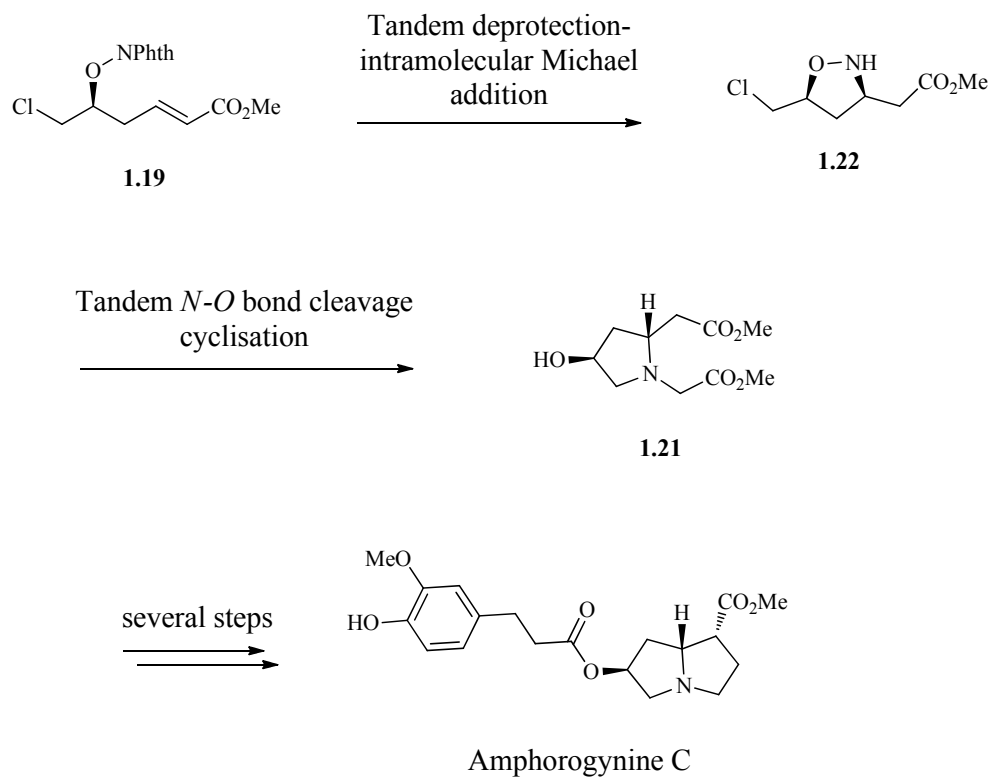
Amphorogynine C H-1 β , H-6 α

Table 1.5 ^1H NMR data for amphorogynine A-C in CDCl_3 ¹³

position	Amphorogynine A	Amphorogynine B	Amphorogynine C
	δ H (J Hz)	δ H (J Hz)	δ H (J Hz)
1	3.18 ddd (8)	2.63 m	3.14 ddd (8)
2	2.22 m	2.20 m	2.09 m
	1.90 m		1.95 m
3	2.78 μ	2.65 m	2.79 m
	3.05 ddd (11, 8, 6)	3.28 ddd (6)	3.06 m
5	2.72 dd (12, 6)	2.77 dd (12, 4, 5)	2.86 m
	3.26 dd (12, 5)	3.16 dd (12)	3.21 dd (12)
6	5.15 dddd (6)	5.36 m	5.32 m
7	1.48 ddd (14, 8, 5)	1.88 ddd (13, 7.5)	1.65 ddd (14, 7, 5)
	2.18 ddd (14, 8)	2.16 m	1.86 ddd (14, 7)
7a	3.75 ddd (8)	3.85 m	3.86 ddd (6)
9-OMe	3.64 s	3.68 s	3.66 s
2'	6.64 d (2)	6.67 d (2)	6.65 d (2)
5'	6.74 (8)	6.78 d (8)	6.77 d (8)
6'	6.62 dd (8, 2)	6.63 dd (8, 2)	6.64 dd (8)
7'	2.81 t (7)	2.83 t (7.5)	<u>2.18 t (7.5)</u>
8'	2.53 t (7)	2.55 t (7.5)	2.53 t (7.5)
3'-OMe	3.81 s	3.83 s	3.83 s

1.4 Conclusion

In conclusion, we have shown that the isoxazolidine route previously developed in our laboratory can be adapted to the synthesis of amphorogynine C as shown in **Scheme 1.24**. Our synthesis of amphorogynine C was successfully accomplished in 14 steps and 3.63% overall yield from commercially available (*R*)-epichlorohydrin (**1.24**). To our knowledge, this is the first stereoselective the total synthesis of amphorogynine C.



Scheme 1.24

CHAPTER 2

STUDIES TOWARDS THE TOTAL SYSTHESIS OF HYDROXYINDOLIZIDINE

2.1 Introduction

2.1.1 Introduction to Hydroxylated Indolizidine Alkaloids

The core structure of indolizidine is defined by the 1-*aza*-bicyclo[4.3.0]octane structure, a bicyclic heterocycle containing a six-membered ring fused to a five-membered ring (**Figure 2.1**). Indolizidine alkaloids have been found in microbial, plant and animal sources. Many natural products containing this ring system show interesting biological activities, especially polyhydroxylated members of this family due to their potential to act as glycosidase inhibitors. Accordingly, they are active against viral infections, cancer, diabetes, and glycosphingolipid storage diseases.⁵³

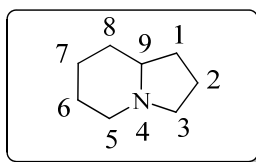


Figure 2.1 The 1-*aza*-[4.3.0]-bicyclic ring system

The interest in hydroxylated indolizidine alkaloids has continued over many years due to the stereochemistry and their potent biological activity.⁵⁴ For instance, some polyhydroxylated indolizidines (+)-lentiginosine⁵⁵ (an amyloglucosidase inhibitor), (-)-swainsonine⁵⁶ (a potent α -mannosidase inhibitor), (+)-castanospermine⁵⁷ (a potent α -glucosidase) and uniflorine A⁵⁸ have constantly attracted the attention and represent

good examples of dihydroxylated, trihydroxylated, tetrahydroxylated, and pentahydroxylated indolizidines, respectively (**Figure 2.2**).

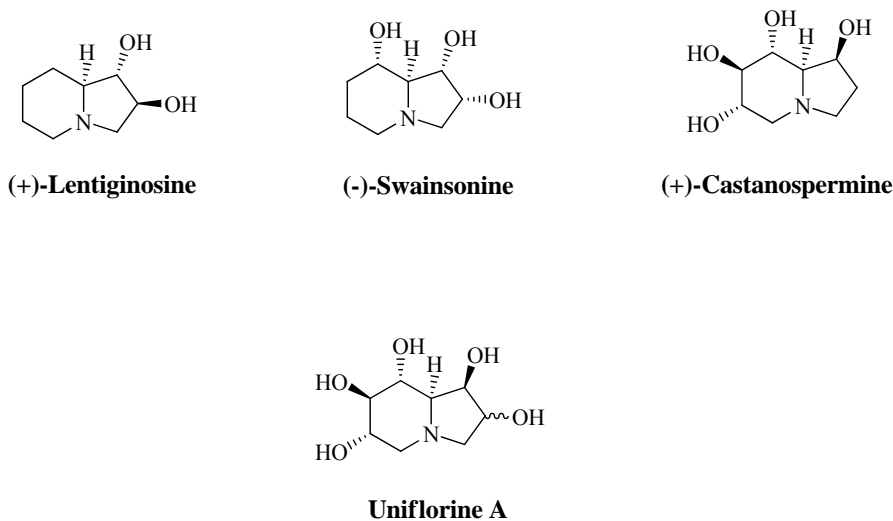


Figure 2.2 Examples of hydroxylated indolizidine containing natural products

Some monohydroxylated indolizidines, pumiliotoxin 237A⁵⁹ and 225F,⁶⁰ allopumiliotoxin 341A,⁶¹ and tylophorinine⁶² are biologically active substances. The structures are shown in **Figure 2.2**. The 8-hydroxyindolizidine moiety is presented in these alkaloids. This motif is encountered in many bioactive compounds and natural products. An unnamed hydroxyindolizidine (**2.1**) is included in this class.⁶³ An important subclass, the 2,6-disubstituted piperidin-3-ols, is encountered in hydroxyindolizidine (**2.1**). This motif is a common constituent of in bioactive compounds. These include (+)-spectaline,⁶⁴ (-)-morusimic acid D,⁶⁵ (-)-prosopinine⁶⁶ and (-)-cassine.⁶⁷ The structures are shown in **Figure 2.3**.

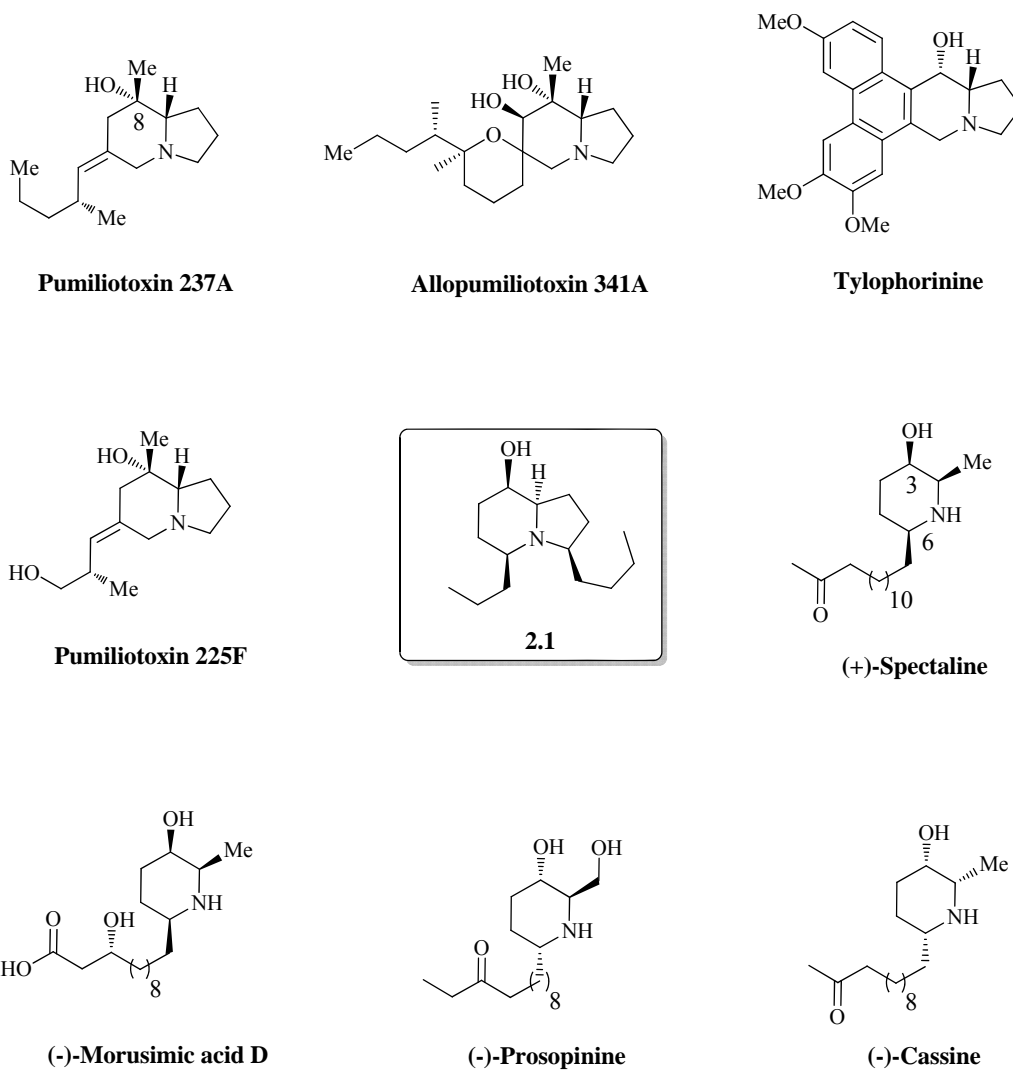


Figure 2.3 Examples of 8-hydroxyindolizidine and 3-hydroxypiperidine-containing natural products.

The bioactivity of the hydroxyindolizidine (**2.1**) has not yet been investigated. It has been reported to be involved in ant warfare. However the hydroxyindolizidine (**2.1**) has received considerable attention, soon after its elucidation.^{71,72}

2.1.2 Structural Elucidation of Hydroxyindolizidine (2.1)

The hydroxyindolizidine (**2.1**) was isolated from the ant *Myrmicaria melanogaster* (Emery), a species reported only in Borneo and collected in the sultanate of Brunei Darussalam in 2007.⁶³ Five new alkaloids, along with six known indolizidine and three known pyrrolidines, were found in the extract. These alkaloids were assigned as 3,5-disubstituted indolizidines (**2.5a-b**, **2.9**, **2.10**), 2,5-disubstituted pyrrolidines (**2.3**, **2.4**, **2.6a-b**, **2.7**) and (*10E*)-3-butyllehmizidine (**2.8**). These structures are shown in **Figure 2.4**. Analysis of the extracts of this ant by GC-MS and GC-IR discovered five new alkaloids, identified as (*9Z*)-3-propylindolizidine (**2.2**), *cis*- and *trans*-2-butyl-5-propylpyrrolidine (**2.3** and **2.4**), (*10E*)-3-butyllehmizidine (**2.8**), and (*5Z*, *8Z*, *9Z*)-3-butyl-5-propyl-8-hydroxyindolizidine (**2.1**), whose structures were established by comparison with synthetic samples. In the case of hydroxyindolizidine (**2.1**), the assignment of the stereochemistry was revealed using vapour-phase infrared analysis which showed the Bohlmann bands and an intramolecular hydrogen bond between the hydroxyl group and the nitrogen atom.

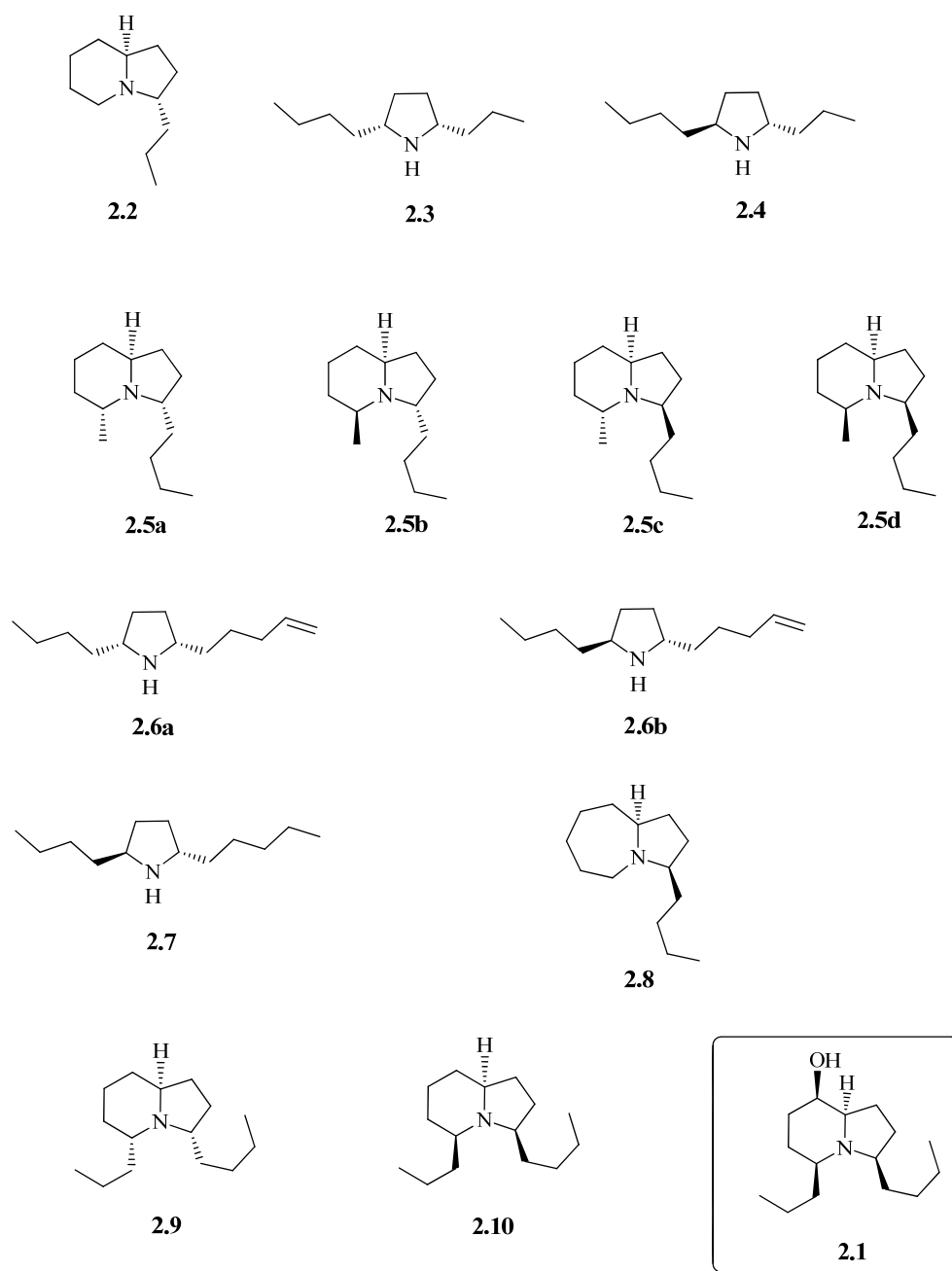


Figure 2.4 Alkaloids found in the ant venom extracts of *Myrmicaria melanogaster* by workers from Brunei

3,5-Disubstituted indolizidines are usually found in the venom of ants of the subfamily Myrmicinae, genera *Megalomyrmex*, *Monomorium* and *Solenopsis*.⁶⁸ (-)-Monomerine⁶⁹ is one of the earliest reported examples of these compounds. These include 5Z,9Z-233AB (**2.11**), which is often found among the skin alkaloids of dendrobatid frogs.⁷⁰ Structures of 3,5-disubstituted indolizidine alkaloids are shown in **Figure 2.5**. The hydroxyindolizidine (**2.1**) and 5Z, 9Z-223 AB (**2.11**) showed the same substitution and stereochemistry at the C-3 and C-5 positions, which located the butyl group at the C-3 position and the propyl group at the C-5 position, whereas the hydroxyindolizidine (**2.1**) bears a hydroxy group at the C-8 position. The synthesis of these alkaloids is considerably challenging due to the stereochemistry of the substituted indolizidine ring.⁵⁴

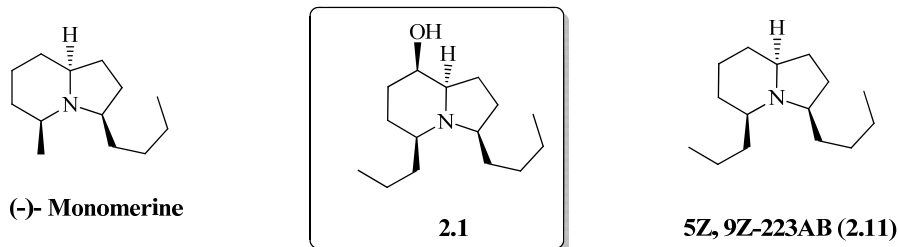


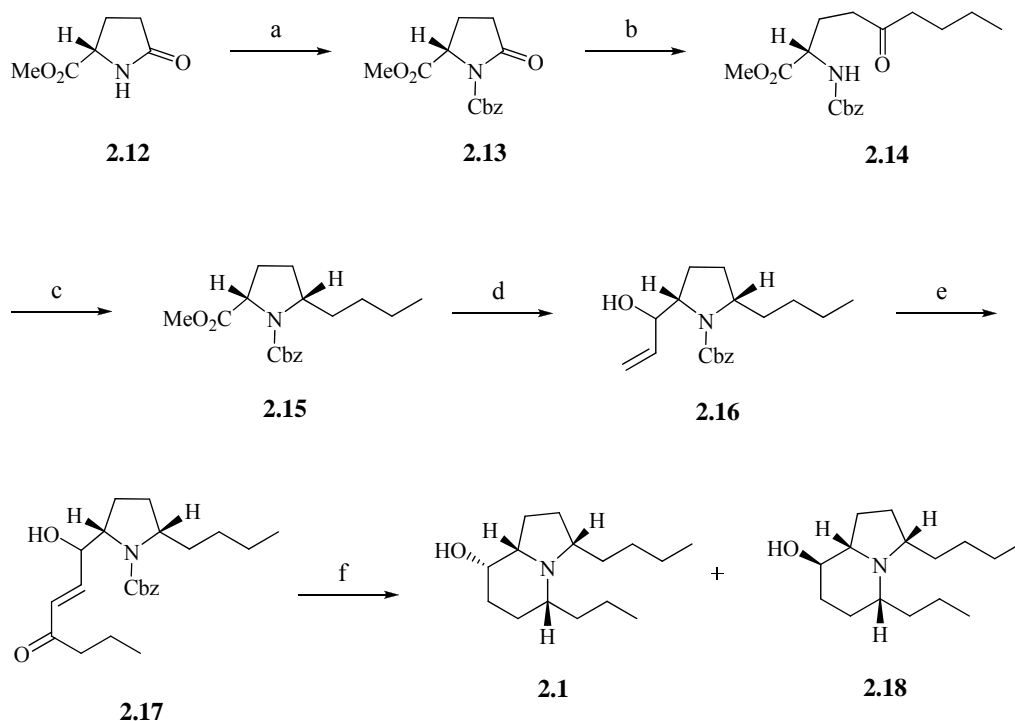
Figure 2.5 Structures of 3,5-dialkylindolizidine alkaloids

2.1.3 Previous Syntheses of Hydroxyindolizidine (2.1)

To date, there have been two synthetic routes outlined to the hydroxyindolizidine (2.1). The first enantioselective synthesis of the hydroxyindolizidine (2.1) was reported by Toyooka and co-workers in 2008.⁷¹ The synthesis of the hydroxyindolizidine (2.1) has been achieved in seven steps and 25% overall yield. The key hydroxyl group was introduced by chelation control of a Grignard reagent to an aldehyde moiety to give the alcohol as a mixture of diastereomers. Later, Huang and Lin reported a concise seven-step synthesis of the hydroxyindolizidine (2.1) with an overall yield of 29%.⁷² Huang and Lin used an oxazolidone as a key intermediate to introduce the stereochemistry of the hydroxyl group, which was envisioned to be introduced by halonium-initiated cyclization reaction. The syntheses by the two groups used the same strategy for construction of the *cis*-2,5-disubstituted pyrrolidine ring with excellent chemo-, regio- and/or diastereoselectivities. The following sub-section will give the details of the synthesis of the hydroxyindolizidine (2.1).

The first publication was a communication by Tokoooya and co-workers.⁷¹ In retrosynthetic terms, Tokoooya's approach, used the commercially available 5 membered lactam (2.12) to construct the 2,5-disubstituted pyrrolidine ring with control of the stereochemistry. The key hydroxyl functional group was introduced using a Grignard reagent attack on an aldehyde. Their synthesis, beginning with the commercially available lactam (2.12), is outlined in **Scheme 2.1**. The lactam (2.12) was protected as the *N*-Cbz-imide (2.13) in 92% yield. A subsequent treatment with *n*-butylmagnesium bromide and tetramethylethylenediamine at -78 °C afforded the ketone (2.14) in 65%

yield. The *cis*-2,5-disubstituted pyrrolidine (**2.15**) was formed in 98% yield using Martin's conditions.⁷³ The ketone (**2.14**) was subjected to an intramolecular reductive carbonylation with Ph_3SiH and $\text{BF}_3 \cdot \text{OEt}_2$ to give the *cis*-2,5-disubstituted pyrrolidine (**2.15**). Subsequent reduction with DIBAL yielded an aldehyde. Treatment of the aldehyde with vinylmagnesium bromide at -78°C gave a mixture of diastereoisomers (**2.16**) in 72% yield. Subsequent treatment with the Grubbs second-generation catalyst and 1-hexen-3-one provided the ketone (**2.17**). A tandem deprotection-hydrogenation-reductive amination of the ketone (**2.17**) afforded a mixture of the hydroxyindolizidine alkaloids (**2.1**) and (**2.18**). The mixture of hydroxyindolizidine alkaloids (**2.1**) and (**2.18**) was separated by column chromatography. The key feature of this synthesis was a tandem deprotection-condensation-hydrogenation was employed to construct the bicyclic system in one step.

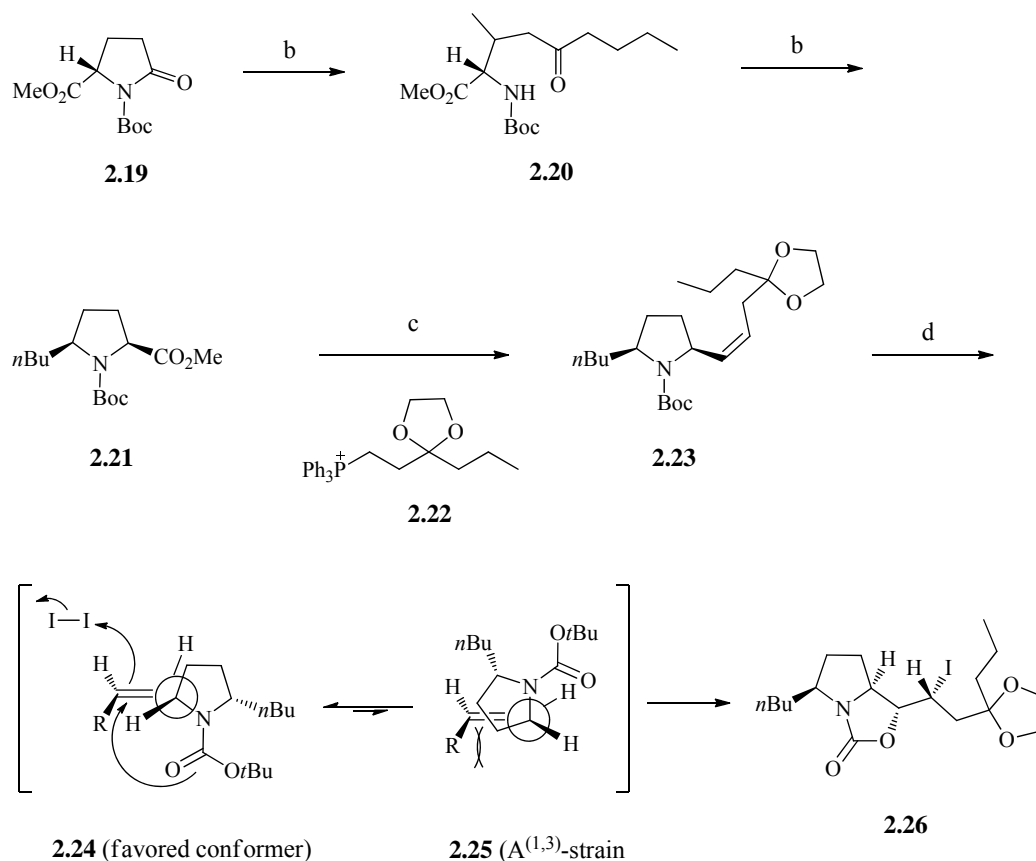


Scheme 2.1 Tokoooya's synthesis of hydroxyindolizidine alkaloid (**2.1**)

Reagents and conditions: (a) LiHMDS, CbzCl, THF, -78 °C; 92%; (b) *n*BuMgBr, TMEDA, THF, -78 °C; 65%; (c) Ph₃SiH, BF₃·OEt₂, CH₂Cl₂, -78 °C to rt; 98%; (d) DIBAL, CH₂Cl₂, -78 °C then vinylMgBr (3 equiv), THF, -78 °C to rt; 72%; (e) 1-hexen-3-one, Grubbs second generation catalyst (0.1 equiv), CH₂Cl₂, reflux; 97%; (f) 20% Pd(OH)₂, EtOH, 1 atm (**2.1**): 62%, (**2.18**): 19%).

Huang and Lin achieved the stereoselective synthesis of hydroxyindolizidine alkaloid (**2.1**), a total of 7 steps with an overall yield of 29%.⁷² They started with the commercially available *N*-Boc-(*S*)-pyroglutamate (**2.19**), which was the same starting material as Tokoooya and co-workers except with a different *N*-protecting group (**Scheme 2.2**). Huang and Lin elegantly demonstrated the synthetic route with a better overall yield

than that reported by Tokooya and co-workers. In retrosynthetic terms, they employed an electrophile-mediated heterocyclisation, in the stereoselective installation of the hydroxyl group of the hydroxyindolizidine alkaloid (**2.1**). Interestingly, the final step in their synthesis is a tandem deprotection-hydrogenation-cyclisation. The reaction produced the final product, the hydroxyindolizidine alkaloid (**2.1**), in good yield as a single diastereomer. Treatment of the *N*-Boc imide derivative (**2.19**) with *n*-butylmagnesium bromide at -78 °C afforded the keto urethane ester (**2.20**), which was subjected to an intramolecular reductive carbamoylation in the presence of Ph_3SiH and $\text{B}(\text{C}_6\text{F}_5)_3$ in dichloromethane at -78 °C to room temperature to obtain the *cis*-2,5-disubstituted pyrrolidine derivative (**2.21**) (Martin's conditions).⁷³ The chemoselective reduction of the ester group of the pyrrolidine derivative (**2.21**) with DIBAL-H in anhydrous diethyl ether furnished an aldehyde moiety, which further underwent a Wittig reaction with an ylide, generated *in situ* from phosphonium derivative (**2.22**) and KHMDS, to provide (*Z*)-olefin (**2.23**) as the sole stereoisomer in 72% yield. Subsequently iodocyclisation of the allylic urethane (**2.23**) with I_2 and NaHCO_3 in acetonitrile afforded iodooxazolidone (**2.26**) in 70% yield. The observed product iodooxazolidone (**2.26**) was formed through the intermediate (**2.24**), whereas the intermediate (**2.25**) is disfavored due to a 1,3-allylic strain-controlled interaction between the pyrrolidine moiety and the bulky carbon side chain R. The five membered oxazolidone (**2.26**) was formed by the carbonyl oxygen attacked to the iodonium ion intermediate in a 5-*exo-tet* fashion.⁷⁴

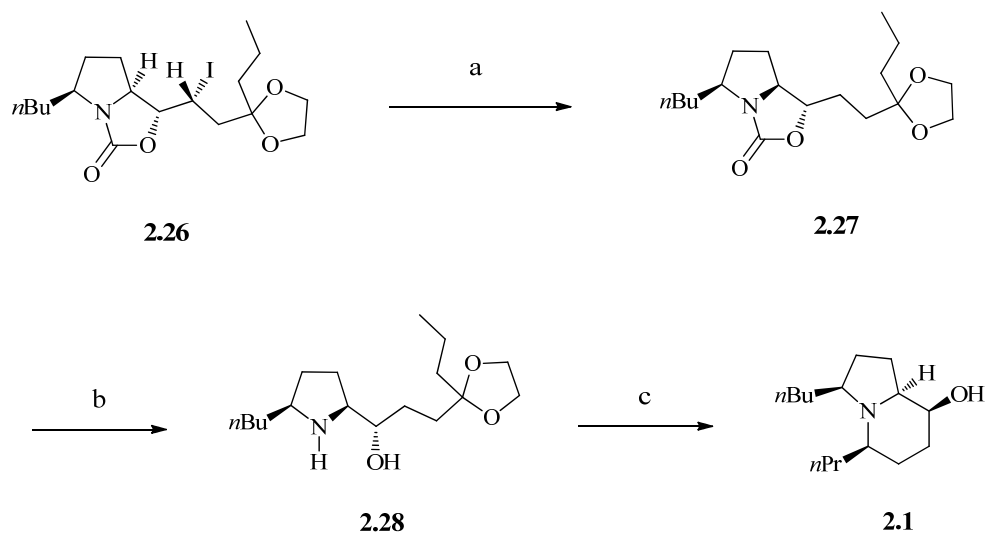


Scheme 2.2 Huang's synthesis of hydroxyindolizidine alkaloid (**2.1**)

Reagents and conditions: (a) *n*BuMgBr, THF, -78 °C; (b) Ph₃SiH, B(C₆F₅)₃, CH₂Cl₂, -78 °C to rt; 82% (2 steps); (c) DIBAL, Et₂O; KHMDS, THF; phosphonium (**2.22**); 72%; (d) I₂, CH₃CN, NaHCO₃; 70%.

Treatment of the iodo-oxazolidone (**2.26**) with *n*Bu₃SnH and AIBN gave the oxazolidone (**2.27**), which was hydrolyzed with Ba(OH)₂ in dioxane-H₂O to provide the amino alcohol (**2.28**). The hydroxyindolizidine (**2.1**) was successfully synthesised in a one

pot reaction using 1% HCl, Pd-C, under a hydrogen atmosphere (1 atm) for three days to form the amino alcohol (**2.28**) in 82% yield (**Scheme 2.3**).



Scheme 2.3 Huang' synthesis of hydroxyindolizidine alkaloid (**2.1**) (Cont.)

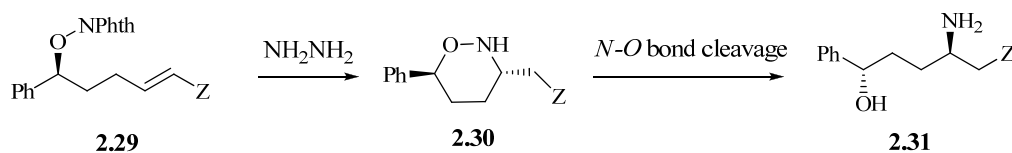
Reagents and conditions: (a) Bu_3SnH , AIBN, toluene, reflux; 90%; (b) $\text{Ba}(\text{OH})_2$, H_2O ; 95%; (c) H_2 , $\text{Pd}(\text{OH})_2$, 1% HCl, EtOH; 82%.

In summary, two groups reported the synthesis of hydroxyindolizidine alkaloid (**2.1**) by ring construction from the *cis*-2,5-disubstituted pyrrolidine ring with good chemo-, regio- and/or diastereoselectivities. Herein, the hydroxyindolizidine (**2.1**) makes an interesting target for us to study further. We had hoped methods developed in our group could control the stereochemistry of the hydroxyindolizidine (**2.1**).

2.2 Aim of Present Work

2.2.1 *N,O*-Heterocycles as Synthetic Intermediates

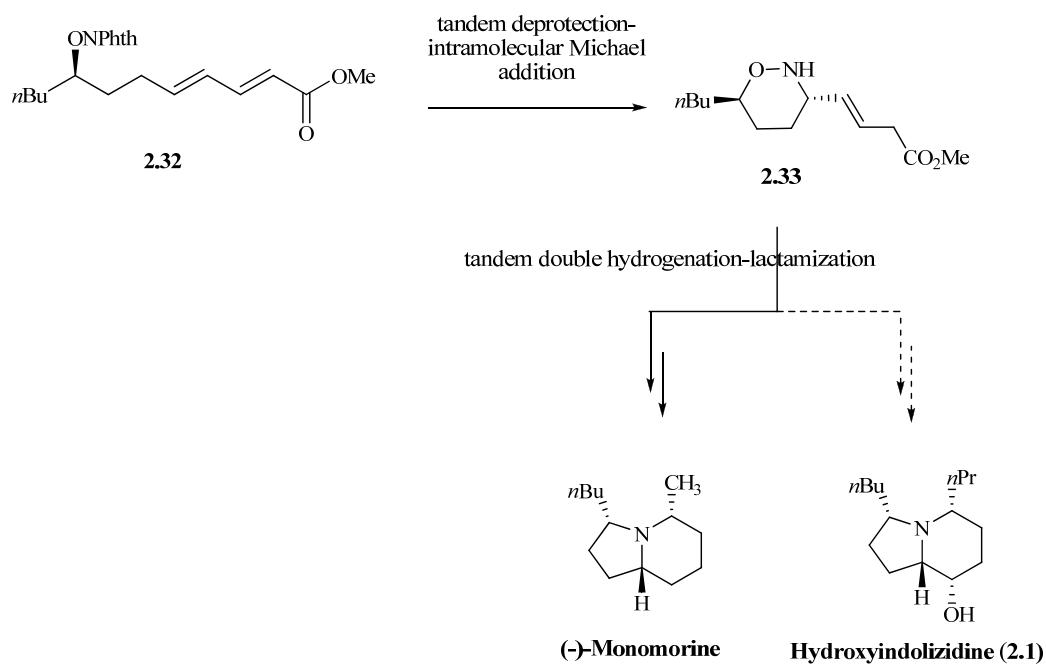
In first chapter, the total synthesis of amphorogynine C is reported using an isoxazolidine as a key intermediate with control of the regio- and stereochemistry. Therefore, in this chapter we continued using the *N,O*-heterocycles as synthetic intermediates. We employed cyclic hydroxylamine derivatives as a form of tethered nitrogen nucleophile whilst introducing ring closure onto an alkene. In our group, we have been particularly interested in the synthesis of a variety of tetrahydro-1,2-oxazines (**2.30**) (**Scheme 2.4**).^{18b,d} An intramolecular conjugate addition of nitrogen of an *O*-substituted hydroxylamine was employed to control the regio- and stereochemistry of the tetrahydro-1,2-oxazines. The tetrahydro-1,2-oxazine (**2.30**) were formed as the *trans* isomer. The *N-O* bond in the oxazine derivatives (**2.30**) may be subject to a reductive ring opening process leading to acyclic 1,4-amino alcohols (**2.31**).



Z = CO₂Me, CO₂tBu, SO₂Ph, COMe

Scheme 2.4 The intramolecular Michael addition of the hydroxylamine to the tetrahydro-1,2-oxazines

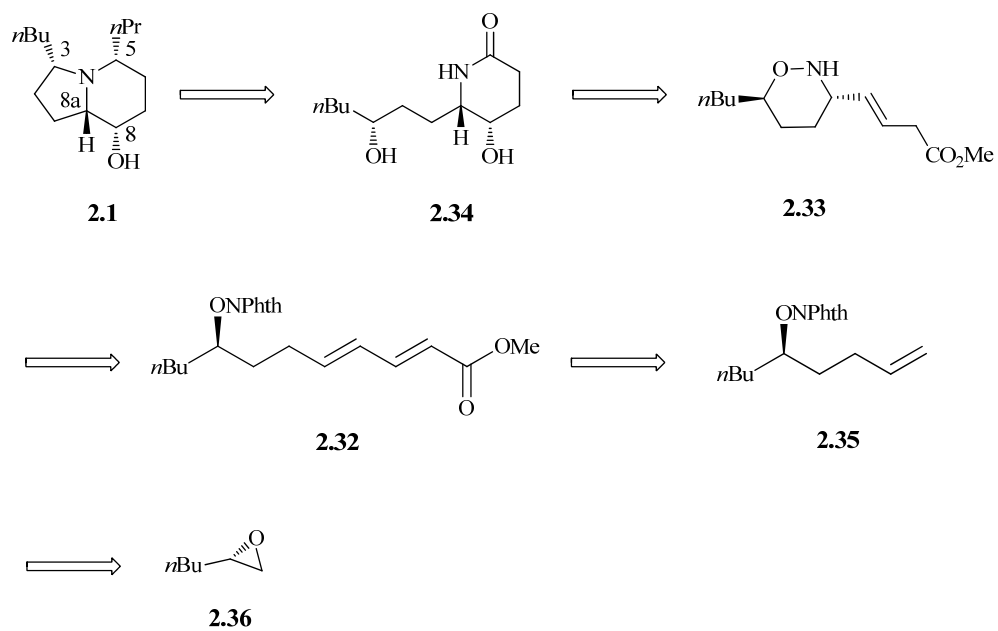
With this methodology, the stereoselective synthesis of (-)-monomorine *via* a tandem deprotection-intramolecular Michael addition and a tandem double hydrogenation-lactamization was accomplished.^{18d} Hence, we proposed that this same method could be applied to the synthesis of hydroxyindolizidine alkaloid (**2.1**) as shown in **Scheme 2.5**.



Scheme 2.5 Bates' synthesis of (-)-monomorine

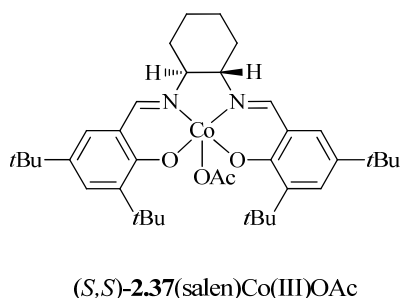
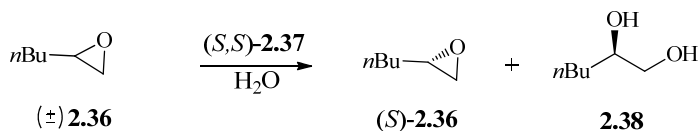
2.2.2 Synthetic plan

The retrosynthetic analysis of the hydroxyindolizidine (**2.1**) is outlined in **Scheme 2.6**. The hydroxyindolizidine (**2.1**) has three substituents at the C-3, C-5, and C-8 positions. This alkaloid tentatively possesses a (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine structure. The stereochemical control of the hydroxyindolizidine (**2.1**) would be incorporated gradually in each step. The *n*-propyl group substituent at the C-5 position could be constructed by a Grignard reaction with the lactam (**2.34**). The chiral centre at the C-3 position of the indolizidine ring could be established by a nucleophilic ring closure. After the *N-O* bond cleavage and dihydroxylation or epoxidation of the double bond of the *trans*-tetrahydro-1,2-oxazine intermediate (**2.19**), the 1,4 amino alcohol could be formed and subsequent cyclise to the 5-hydroxyl-2-piperidone (**2.34**) by lactamisation. The chiral centre at the C-8a position of the hydroxyindolizidine (**2.1**) would arise from the cyclic *trans*-tetrahydro-1,2-oxazine (**2.33**). The relative configuration of 1,4-disubstitution of the tetrahydro-1,2-oxazine (**2.33**) could be achieved from a tandem-deprotection-intramolecular Michael addition of the dienone (**2.32**). We envisaged that by using the α,β -unsaturated ester moiety as a Michael acceptor, the cyclic tetrahydro-1,2-oxazine skeleton could be readily prepared. The *trans* double bond of dienone (**2.32**) would be prepared through a cross metathesis reaction, followed by a Wittig reaction of the olefin (**2.35**). The *N*-phthaloyl derivative (**2.35**) could be prepared by Mitsunobu reaction of the alcohol, which could be prepared from selective ring opening at the less hindered terminus of the commercially available (*S*)-hex-1-ene oxide (**2.36**) by a Grignard reaction.

**Scheme 2.6** Retrosynthetic analysis for the hydroxyindolizidine (**2.1**)

2.3 Results and Discussion

We began our synthesis by using the commercially available (*rac*)-hex-1-ene oxide (**2.36**). (*S*)-Hex-1-ene oxide (**2.36**) was prepared by hydrolytic kinetic resolution (HKR). Jacobsen and co-workers reported a useful and efficient method, HKR, a standard method for synthesising both highly enantioenriched terminal epoxides and 1,2 diols from cheap racemic epoxides, using chiral (salen)Co(III) complexes (Jacobsen's catalyst).²² The Jacobsen catalyst are available in both enantiomeric forms. The commercially available (*rac*)-hex-1-ene oxide (**2.36**) was treated with 0.2 mol% of chiral (*S,S*) (salen)Co(III) complex (**2.37**) and 0.55 equivalent of water to afford the highly enantioenriched (*S*)-hex-1-ene oxide (**2.36**) and 1,2-diol (**2.38**) (**Scheme 2.7**). The resulting (*S*)-hex-1-ene oxide (**2.36**) was separated by simple distillation (25 °C at 10 mmHg). The target (*S*)-epoxide (**2.36**) was obtained in 45% yield.

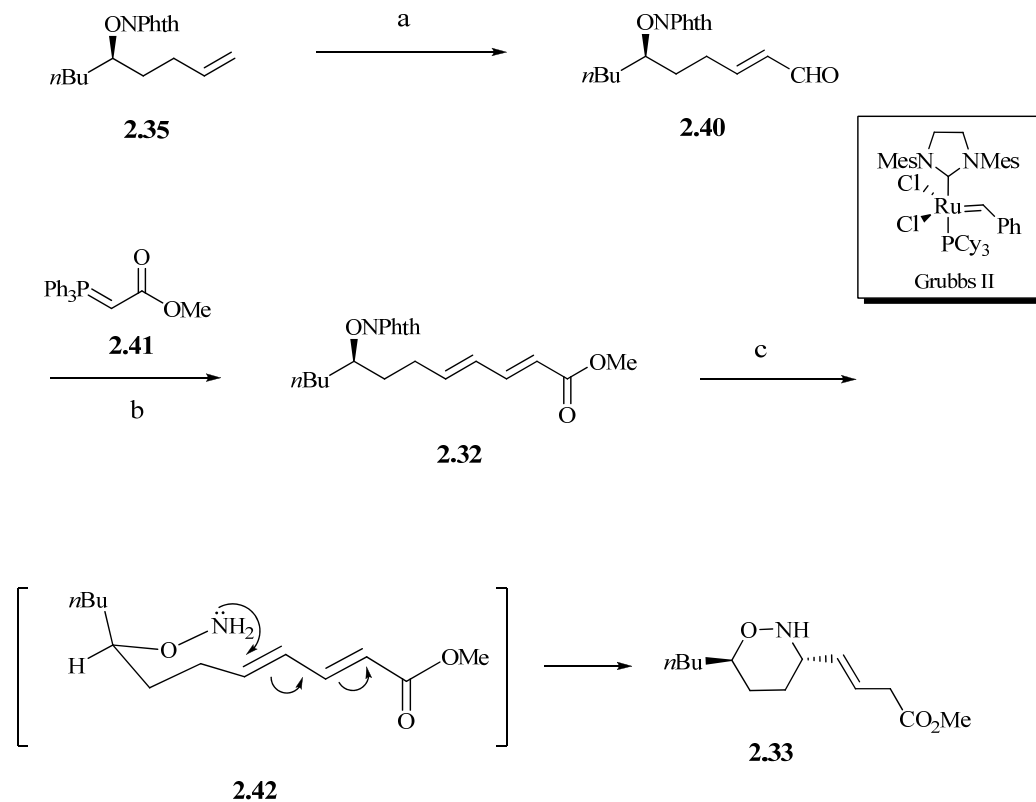


Scheme 2.7 Hydrolytic kinetic resolution reaction (HKR)

Subsequently, a cross-metathesis reaction was achieved by treatment of the terminal alkene (**2.35**) with crotonaldehyde in the presence of 5 mole percent Grubbs' second generation catalyst in refluxing dichloromethane, affording the α,β -unsaturated aldehyde (**2.40**) which was subjected to a Wittig reaction without further purification.^{26,76} After removal of excess crotonaldehyde under *vacuum*, the crude aldehyde (**2.40**) was treated with the ylide (**2.41**) in dichloromethane at room temperature to provide the corresponding diene (**2.32**) in good yield (**Scheme 2.9**).^{18d}

The phthaloyl derivative (**2.32**) was then ready for the following step. Cleavage of the phthaloyl group with hydrazine monohydrate was again carried out using the Ing-Manske modification of the Gabriel reaction.^{27,28} The phthaloyl derivative (**2.32**) was treated with hydrazine monohydrate in dichloromethane at room temperature for 12 hours to provide the hydroxylamine (**2.42**), which was further cyclised to the tetrahydro-1,2-oxazine (**2.33**) in good yield. The 1,4-amino alcohol intermediate (**2.42**) was not observed; a tandem *N*-deprotection-cyclisation occurred, to give the tetrahydro-1,2-oxazine (**2.33**) as a single isomer. The stereochemistry of two substituents of the cyclic tetrahydro-1,2-oxazine (**2.33**) were presumed, on the basis of our previous results, to be the *trans*-isomer.^{18b,d} This was subsequently confirmed by conversion to the natural product. Assuming the *trans*-isomer was formed, it is proposed that the substituents in each case adopt a pseudo equatorial position during cyclisation. As the cyclisation occurs in the absence of any acids or bases, alkene migration does not occur. The ¹H NMR spectrum of tetrahydro-1,2-oxazine (**2.33**) showed olefinic protons of the β,γ -unsaturated ester at 5.78 and 5.43 ppm, appearing as a doublet of triplets and a doublet of doublets with coupling constants of 15.6 and 7.0 Hz, respectively. All

spectroscopic data for the tetrahydro-1,2-oxazine (**2.33**) agreed with those previously reported by our group.^{18d}



Scheme 2.9

Reagents and conditions: (a) crotonaldehyde, 5 mol% Grubbs (II), CH₂Cl₂, reflux, 1 h; (b) compound (**2.41**), CH₂Cl₂, rt; (2 steps, 91%); (c) H₂NNH₂·H₂O, CH₂Cl₂, 0 °C to rt; 12 h; 89%.

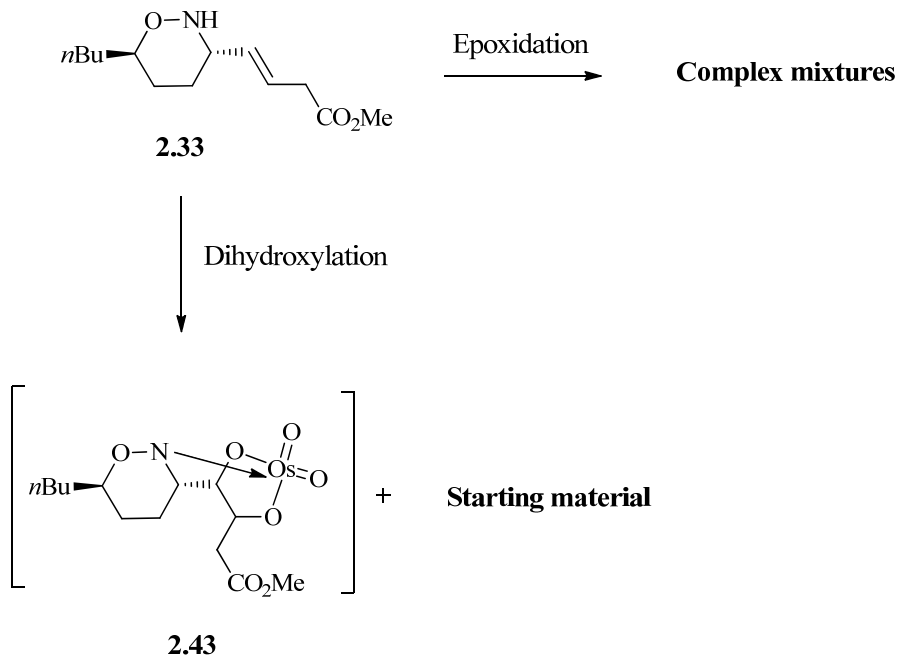
Consequently, we had hoped that the remaining double bond could be stereoselectively oxidised to introduce the hydroxy group at the C-8 position of the hydroxylated indolizidine (**2.1**). Epoxidation with most common peracids: 3-chloroperoxybenzoic acid

(MCPBA) and trifluoroperacetic acid, is directed by hydrogen bonding. The presence of hydrogen bond acceptor groups in close proximity to the olefin can influence the stereoselectivity. This is called Henbest epoxidation.⁷⁷ In our case, we expected the epoxidation of the allylic NH of the tetrahydro-1,2-oxazine (**2.33**) could direct the epoxidation by the peracid via hydrogen bonding. This was proposed by Kočovský and Starý who studied the steric control of epoxidation by carbamate and amide groups.⁷⁸ Unfortunately, the attempted epoxidation of the remaining double bond of the tetrahydro-1,2-oxazine (**2.33**) using either MCPBA or trifluoroperacetic acid (generated from urea hydrogen peroxide (UHP) and trifluoroacetic anhydride) failed, giving complex product mixtures or recovery of starting material. The procedure for epoxidation with UHP was reported by Heaney.⁷⁹ Urea-hydrogen peroxide (UHP) has been employed as a solid substitute for liquid hydrogen peroxide. It is relatively stable and safe alternative for the generation of anhydrous hydrogen peroxide.

However, we focused on the dihydroxylation of alkenes using osmium tetroxide (OsO_4) as a reagent of choice for the *syn*-dihydroxylation, originally introduced by Criegee in 1936.⁸⁰ We expected that the allylic NH of the tetrahydro-1,2-oxazine (**2.33**) could direct *syn*-dihydroxylation through hydrogen bonding. Upjohn's group reported a convenient and reliable procedure for dihydroxylation that involved sub-stoichiometric amounts of OsO_4 (typically 5 mol %) and *N*-methylmorpholine-*N*-oxide (NMO) as a stoichiometric co-oxidant. The osmylations under Upjohn conditions are carried out under homogeneous conditions.⁸¹ Whilst the Tsuji conditions are known as a two phase system, they represent one well-known method for osmylations using

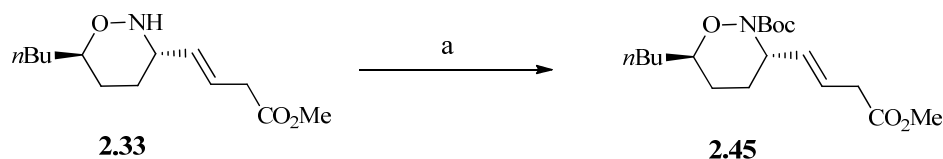
hexacyanoferrate(III) ion ($\text{K}_3\text{Fe}(\text{CN})_6$) as a cheap and convenient co-oxidant for osmium(VI).⁸²

Nonetheless, attempted *syn*-dihydroxylation of the tetrahydro-1,2-oxazine (**2.33**) under either Upjohn or Tsuji conditions largely returned starting material. It was suspected that the catalytic cycle may not turn over due to coordination of the osmium of the osmate ester by the oxazine nitrogen lone pair (**Scheme 2.10**). The requirements and considerations of the stoichiometric osmylation may help to promote the dihydroxylation of the tetrahydro-1,2-oxazine (**2.33**).⁸³ However, the stoichiometric osmylation is not an economically viable method because the cost (and toxicity) of osmium tetroxide.



Scheme 2.10

It was therefore necessary to protect the free amine group of the tetrahydro-1,2-oxazine (**2.33**) to prevent possible interference during the oxidation. The tetrahydro-1,2-oxazine (**2.33**) was protected with di-*tert*-butyl dicarbonate under basic conditions (Et_3N) in dichloromethane at room temperature overnight, affording the *N*-Boc derivative (**2.43**) in quantitative yield (**Scheme 2.11**). The *N*-Boc group was clearly visible in the ^1H NMR spectrum of the *N*-Boc derivative (**2.43**) as a sharp singlet at 1.44 ppm, corresponding to 9 protons of *tert*-butyl group. The ^{13}C NMR spectrum of *N*-Boc derivative (**2.43**) confirmed the structure with signals at 28.0 (q, (Me_3CO), 79.8 (s, Me_3CO) and 155.8 (s, CO) ppm.

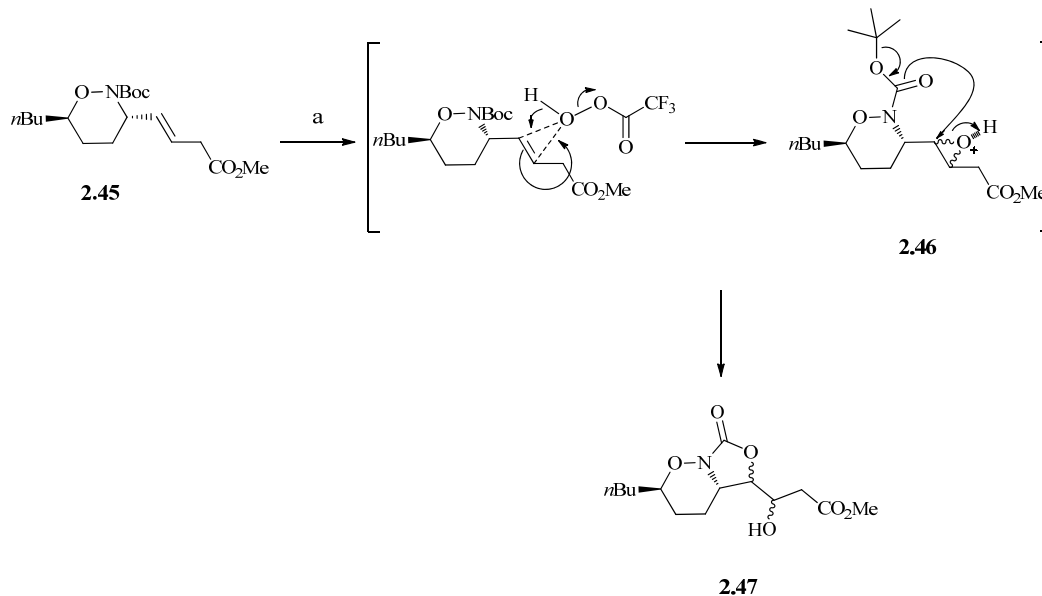


Scheme 2.11

Reagents and conditions: (a) Boc_2O , Et_3N , DMAP, CH_2Cl_2 , rt, 24 h; 98%.

According to Heaney's methodology, the *N*-Boc derivative (**2.30**) was subjected to epoxidation using urea-hydrogen peroxide. Treatment of the *N*-Boc derivative (**2.45**) with UHP in the presence of trifluoroacetic anhydride and sodium dihydrogen phosphate in dichloromethane at room temperature overnight, gave a sluggish reaction and starting material was recovered. We carried out the same reaction but with an addition of a NaHSO_4 . Unfortunately the reaction was slow as monitored by thin layer chroma-

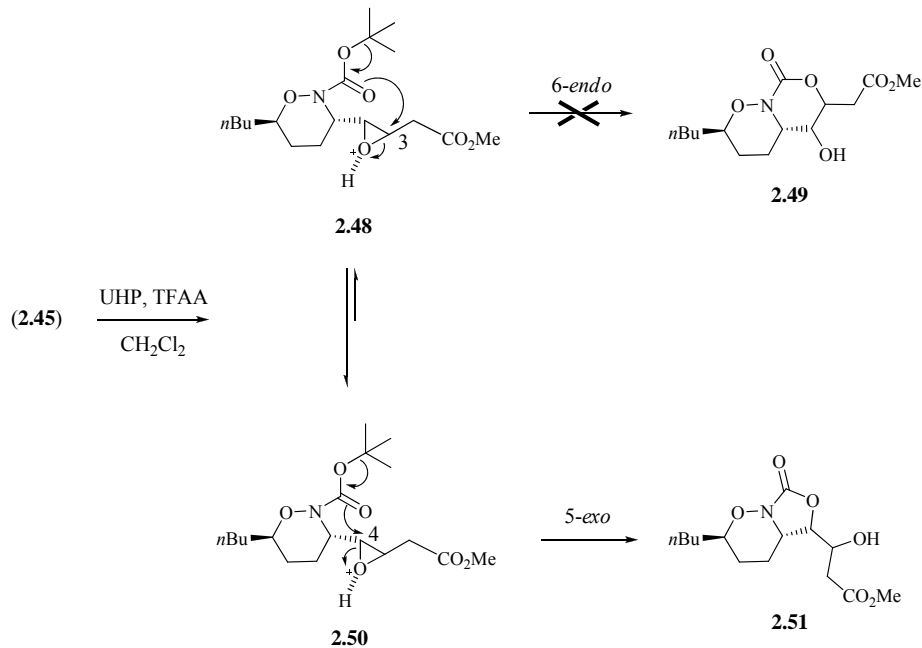
tography (TLC), and the starting material was recovered. We turned our attention to carrying out the reaction without adding any buffer or base. Thus, treatment of the *N*-Boc derivative (**2.45**) with urea-hydrogen peroxide in the presence of trifluoroacetic anhydride in dichloromethane at room temperature overnight, the reaction was still sluggish and did not produce the expected epoxide (**2.46**). The ^1H NMR spectrum of crude product showed the complete loss of the sharp singlet at 1.44 ppm of the *tert*-butyl group of the Boc protecting group, indicating the not unexpected results of the use of TFAA. We attempted to purify the crude mixture by column chromatography. The rigid bicyclic oxazolidinone (**2.47**) was formed as a 2:1 mixture of diastereoisomers in 18% yield, accompanied by the decomposition of the starting material. The rigid oxazolidinone (**2.47**) was formed by 5-*exo* ring opening of the epoxide intermediate (**2.46**) by the carbonyl oxygen (Scheme 2.12). The oxazolidinone (**2.47**) was identified by the ^1H NMR spectroscopy, which indicated a doublet of triplets with coupling constants of 8.2 and 2.2 Hz at 4.09 ppm, corresponding to one proton at oxazolidinone ring (*CHOCO*, major); the deshielding of the oxygen bearing CH, and a quartet with coupling constant of 8.2 Hz at 3.90 ppm, corresponding to one proton (*CHOH*, major). The IR spectrum of oxazolidinone (**2.47**) showed strong absorption bands at 3400 and 1774 cm^{-1} , indicating characteristic OH and C=O stretches, respectively.



Scheme 2.12

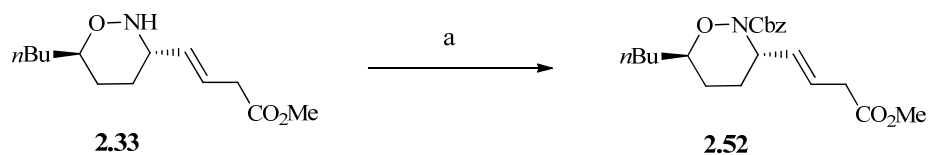
Reagents and conditions: (a) UHP, TFAA, CH₂Cl₂, rt, 24 h; 18%.

Under acidic conditions, the *tert*-butylcarbamate is known to undergo elimination of 2-methylpropene, leading to the *in situ* formation of a carbamic acid, so that the epoxide ring can be opened either by the carbamate, or by the carbamate carbonyl prior to loss of the *tert*-butyl group as already reported, by attack on the C-4 or C-3 carbon of the epoxide leading to the 5 or 6-membered ring respectively (**Scheme 2.13**).⁸⁴ According to Baldwin's rules,⁸⁵ we presumed the 5-*exo* ring-opening product was favored as shown in the conformation (**2.50**), leading to the 5-membered ring product (**2.51**). Whereas the conformation (**2.48**) disfavoured the 6-*endo* ring-closure product (**2.49**).



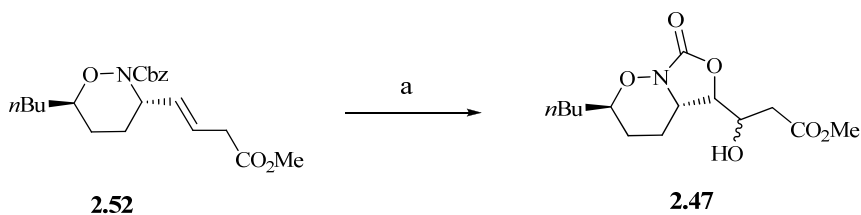
Scheme 2.13

We suspected that the low yield could be attributed to an undesirable loss of the *t*Boc group due to its instability under acidic conditions. Thus, attempts were made to change the protecting group to the Cbz group, which is more stable under acidic conditions. The oxazine (**2.33**) was treated with benzyl chloroformate and sodium bicarbonate in dichloromethane-water (1:1) to provide the *N*-Cbz derivative (**2.52**) in 82% yield (Scheme 2.14).

**Scheme 2.14**

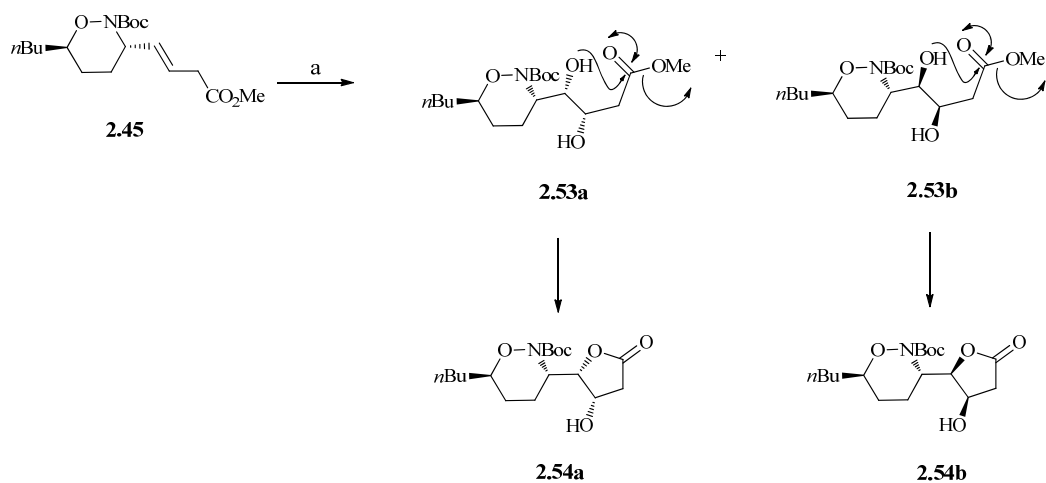
Reagents and conditions: (a) CbzCl, NaHCO₃, CH₂Cl₂:H₂O (1:1), rt, 24 h; 82%.

The alternative *N*-Cbz derivative (**2.52**) was subjected to epoxidation in the presence of urea-hydrogen peroxide and trifluoroacetic anhydride in dichloromethane. The oxazolidinone (**2.47**) was obtained in 68% yield as a 2:1 mixture of diastereoisomers (**Scheme 2.15**). Changing the protecting group to the Cbz group proved that the reaction proceeded well. We were unable to determine the identity of the diastereoisomers of the oxazolidinone (**2.47**). We next turned our attention to the introduction of a hydroxyl group by *syn*-dihydroxylation.

**Scheme 2.15**

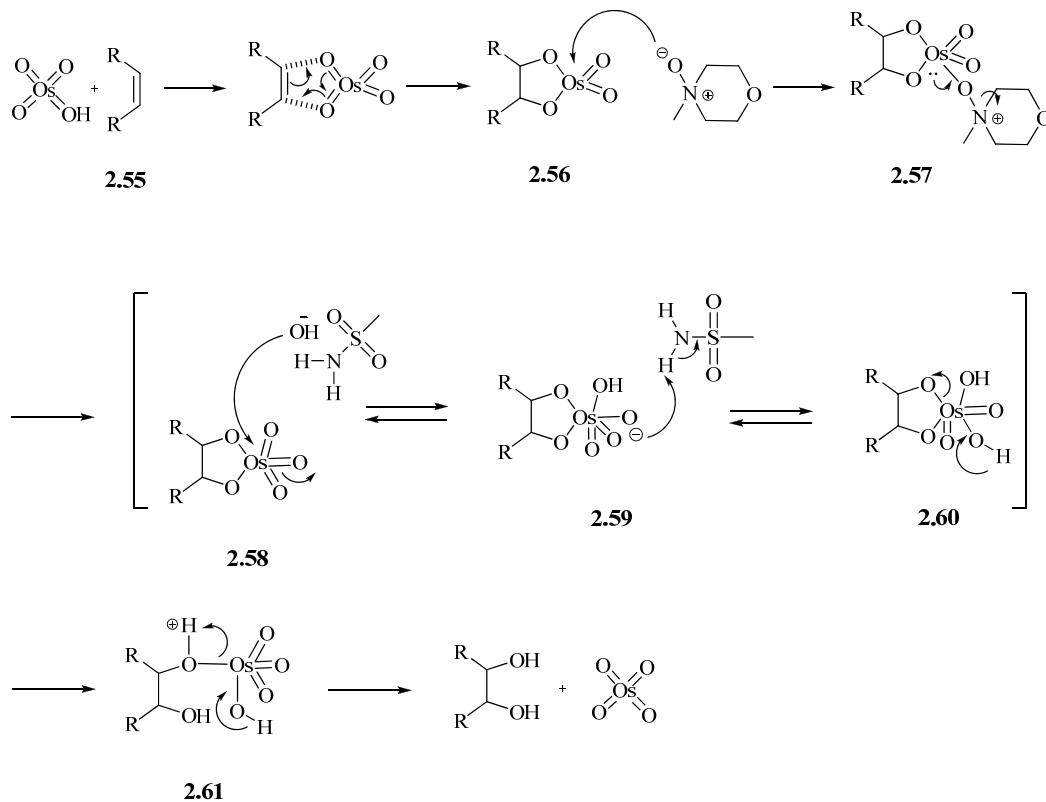
Reagents and conditions: (a) UHP, TFAA, CH₂Cl₂, rt, 24 h; 68%.

Dihydroxylation of the *N*-Boc tetrahydro-1,2-oxazine (**2.45**) was performed directly under Upjohn conditions.⁸¹ The reaction was carried out using *N*-methylmorpholine-*N*-oxide, methanesulfonamide and osmium tetroxide in acetone-water (9:1) at room temperature for 10 hours. NMO was used as co-oxidant and MeSO₂NH₂ was added to accelerate hydrolysis of the osmate ester, allowing a faster reaction.⁸⁶ After the reaction was worked-up, neither of the expected diol products (**2.53a** and **2.53b**) were observed. Two diastereisomeric lactones (**2.54a**) and (**2.54b**) were formed in 70% yield in a ratio of 1:2.5 (**Scheme 2.16**). The diastereomeric ratio of the products was determined by ¹H NMR spectroscopy. The corresponding peaks of the products were clearly identifiable in the ¹H NMR spectrum of the crude product, by integrating the methylene proton peaks in the lactone ring at ~ 2.50-2.80 ppm. The β position of the hydroxyl group relative to carboxylic acids or derivatives promoting the formation of a lactone under Upjohn conditions, was reported before by Paz and Sardina.⁸⁷ Therefore, we achieved the dihydroxylation under Upjohn conditions.

**Scheme 2.16**

Reagents and conditions: (a) 0.05 eq. K_2OsO_4 , NMO, MeSO_2NH_2 , Acetone- H_2O (9:1); (1:2.5, 70%).

The catalytic cycle and mechanism under Upjohn conditions is shown in **Scheme 2.17**.⁸¹ In terms of mechanism, OsO_4 adds to alkene (**2.55**) to provide osmate ester (**2.56**). The osmate ester (**2.56**) is then able to undergo fast oxidation with NMO, and subsequent hydrolysis release the osmate(VI). Methanesulfonamide or deprotonated methanesulfonamide reacts as a nucleophile towards the osmium centre in the intermediate osmate ester (**2.58**) prior to hydrolysis to give the vicinal diol and regenerates the oxidising species.



Scheme 2.17 Catalytic cycle and mechanism of Upjohn conditions

We attempted to oxidise the double bond under Tsuji conditions,⁸² which is a two-phase reaction. The reaction was carried out with $\text{K}_3\text{Fe}(\text{CN})_6$ as co-oxidant, potassium carbonate and osmium tetroxide in *tert*-butanol-water (9:1) at room temperature overnight. The use of $\text{K}_3\text{Fe}(\text{CN})_6$ as co-oxidant resulted in a very slow reaction. After 24 hours, no conversion of starting material was obtained. The reaction was monitored by thin layer chromatography (TLC). In consideration of the Upjohn conditions for this transformation, we settled for a one-step procedure since this reagent is capable of

both *syn*-dihydroxylation and lactonisation with modest stereoselectivity. While the oxidation was carried out in the absence of chiral ligands, a 1:2.5 mixture of lactone (**2.54a**) and (**2.54b**) was obtained (70% yield) (**Table 2.1**, entry 1). Addition of (1,4-diazabicyclo[2.2.2]octane (DABCO) as a coordination ligand for osmium(VI) in the reaction mixture had minimal effect on the diastereoselectivity,⁸⁸ giving only a 1:2.3 mixture of lactones (**2.54a**) and (**2.54b**) in 65% yield (**Table 2.1**, entry 2). However, the reaction rate was affected by adding DABCO as a coordination ligand for osmium(VI). An enhancement of the reaction rate was observed while using DABCO, a 2 times increase being achieved.

The improvement of the stereoselectivity is interpreted as asymmetric dihydroxylation using a chiral ligand in “matched” and “mismatched” pairings of stereoisomers.^{89,90} Previously in 1936 Criegee’ had already observed that pyridine accelerates the reaction.⁸⁰ Later, Sharpless recognized that the chirality of bases can be transferred to the substrates which allowed the development of asymmetric version of the reaction.⁹⁰ In 1979, quinuclidine derivatives were introduced to induce enantioselectivity in the osmylation. The cinchona alkaloids have been shown to give high enantiomeric excesses.^{90g} Thus, Sharpless asymmetric dihydroxylation of alkenes using dihydroquinine or dihydroquinidine ligands as the chiral ligand was applied to our synthetic route.⁹⁰ We carried out the asymmetric dihydroxylation in the presence of chiral ligands, 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, (DHQD)₂PHAL (**2.62**) and 1,4-bis(9-*O*-dihydroquininyl)phthalazine, (DHQ)₂PHAL (**2.63**) (**Figure 2.6**).

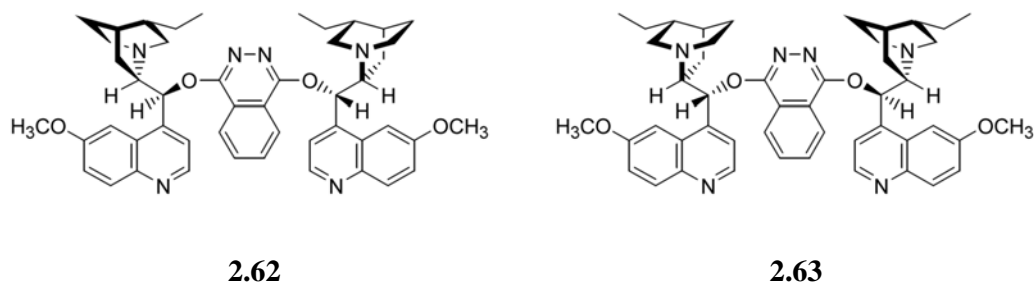
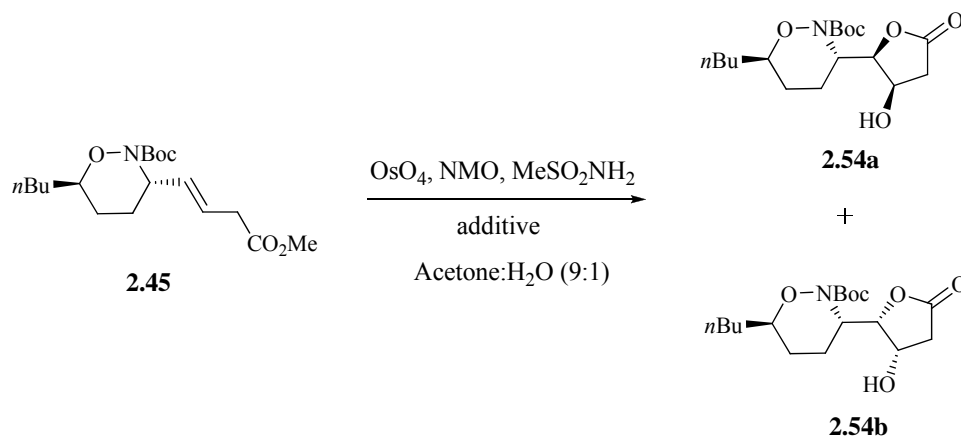


Figure 2.6 Structure of (DHQD)₂PHAL (**2.62**) and (DHQ)₂PHAL (**2.63**)

Addition of (DHQD)₂PHAL (**2.62**) gave an enhanced 1:10 ratio of diastereomers (**2.54a**) and (**2.54b**) (72% yield) (Table 2.1, entry 3). On the other hand, in the presence of (DHQ)₂PHAL (**2.63**) as a chiral ligand, a 6:1 mixture of lactones (**2.54a**) and (**2.54b**) was obtained in 71% yield (Table 2.1, entry 4). In addition, 2 times increases of the reaction rate were observed in comparison with the reactions carried out in the absence of the chiral ligands.

**Table 2.1** The tetrahydro-1,2-oxazine (**2.45**) dihydroxylation

Entry	Additive	Ratio (2.54a): (2.54b) ^a	Time (h)	Yield ^b %
1	None	1:2.5	24	70
2	DABCO	1:2.3	10	65
3	(DHQD) ₂ PHAL	1:10	12	72
4	(DHQ) ₂ PHAL	6:1	12	71

^a: Determined by ¹H NMR; ^b: Isolated yield

To our delight, a single crystal of lactone (**2.54b**) was obtained after isolation and its configuration was determined by X-ray crystallography. As shown in **Figure 2.7**, the stereochemistry of tetrahydro-1,2-oxazine ring was fixed at the C-8 and C-5 positions as *trans*, indicating that the proton at the C-4 position of the lactone ring was *trans* to the proton at the C-5 position of tetrahydro-1,2-oxazine ring. From the X-ray structure of (**2.54b**), we could determine the configuration of the proton at the C-4 of the lactone ring, indicating that lactone (**2.54b**) was the correct relative configuration. The relative configuration of lactone (**2.54b**) is shown that the “*anti*” diastereofacial selectivity imposed by the allylic carbamate of the tetrahydro-1,2-oxazine (**2.45**) using the

phthalazine ligand (DHQD)₂-PHAL (**2.62**) as the chiral ligand. The lactone (**2.54a**) was observed through “*syn*” diastereofacial selectivity induced by allylic carbamate of the tetrahydro-1,2-oxazine (**2.45**) using the phthalazine ligand (DHQ)₂-PHAL (**2.63**) as the chiral ligand.

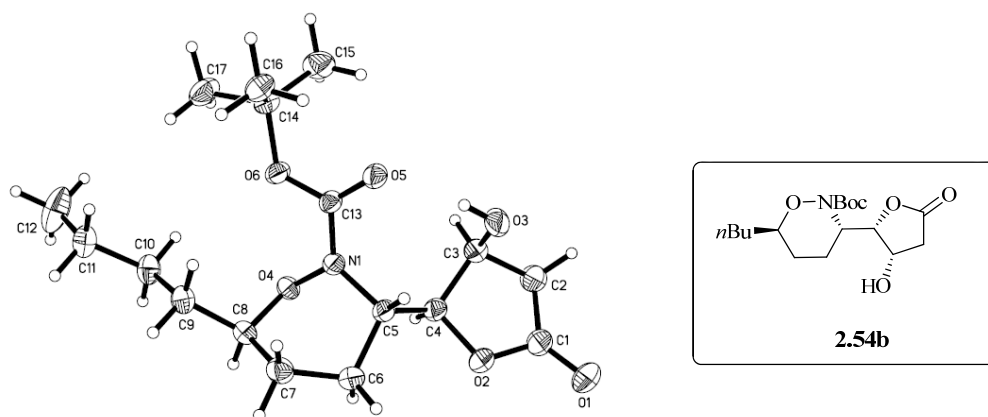
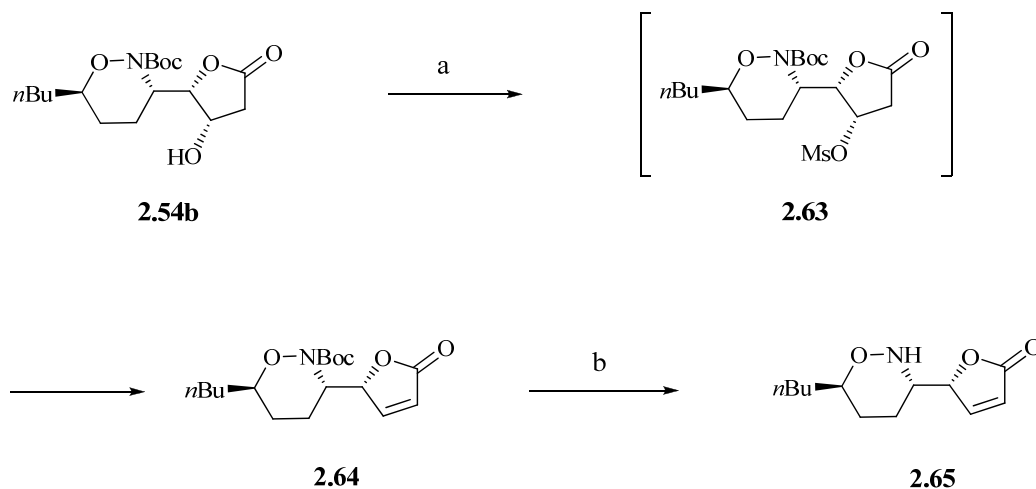


Figure 2.7 The X-ray structure of (**2.54b**)

With the correct stereochemistry of lactone (**2.54b**) in hand, we continued our synthesis of hydroxyindolizidine (**2.1**). The hydroxyl group in the lactone ring of (**2.54b**) was eliminated *via* mesylation followed by base-induced elimination.⁴¹ Treatment of lactone (**2.54b**) with methanesulfonyl chloride in the presence of excess triethylamine in dichloromethane at 0 °C to room temperature for 2 hours, provided the butenolide (**2.64**) in excellent yield. Subsequent removal of the *t*Boc group using trifluoroacetic acid in dichloromethane at 0 °C to room temperature for 3 hours afforded the liberated cyclic amine (**2.65**) in good yield (**Scheme 2.18**). In the ¹H NMR spectrum of butenolide (**2.65**), the liberated cyclic amine produced a broad singlet at 4.80 ppm; the olefinic protons gave rise to a triplet of doublets at 6.09 ppm with coupling constants

of 5.9 and 1.4 Hz and a doublet at 7.45 ppm with a coupling constant of 5.9 Hz. The ^{13}C NMR spectrum also confirmed the loss of the *tert*-butyl group and exhibited methine carbons at 153 and 121 ppm, corresponding to a double bond at the ring. The IR analysis of butenolide (**2.65**) showed a strong absorption band at 3425 cm^{-1} which resulted from NH stretch. The butenolide (**2.65**) was then ready for the next stages of the synthetic programme.

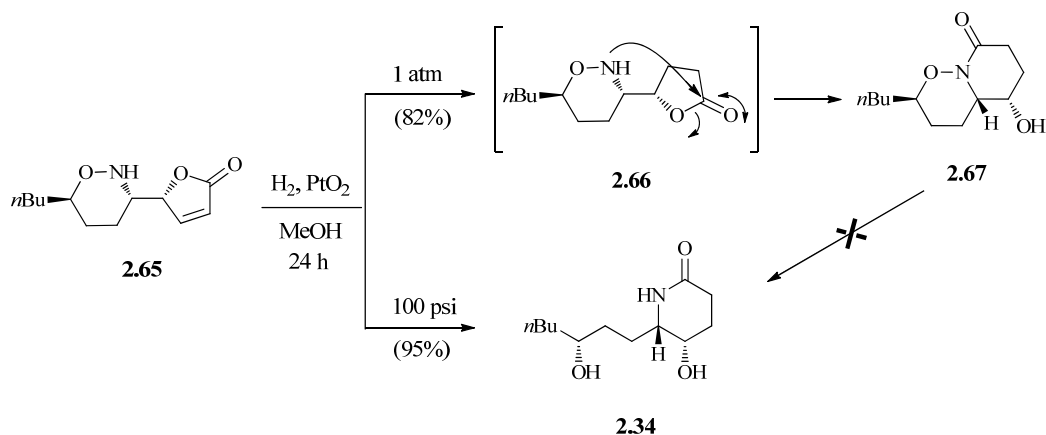


Scheme 2.18

Reagents and conditions: (a) MsCl, Et₃N, CH₂Cl₂, 0° to rt, 2 h; 95%; (b) TFA, CH₂Cl₂, 0° to rt, 3 h; 96%.

Surprisingly, when the butenolide (**2.65**) was subjected to hydrogenation conditions,^{29b} no sign of *N-O* bond cleavage was observed. The ^1H NMR spectrum of crude product did not reveal the expected amine peak which suggested that the *N-O* bond was not cleaved. Mass analysis confirmed the bicyclic lactam (**2.67**) with a mass of 228

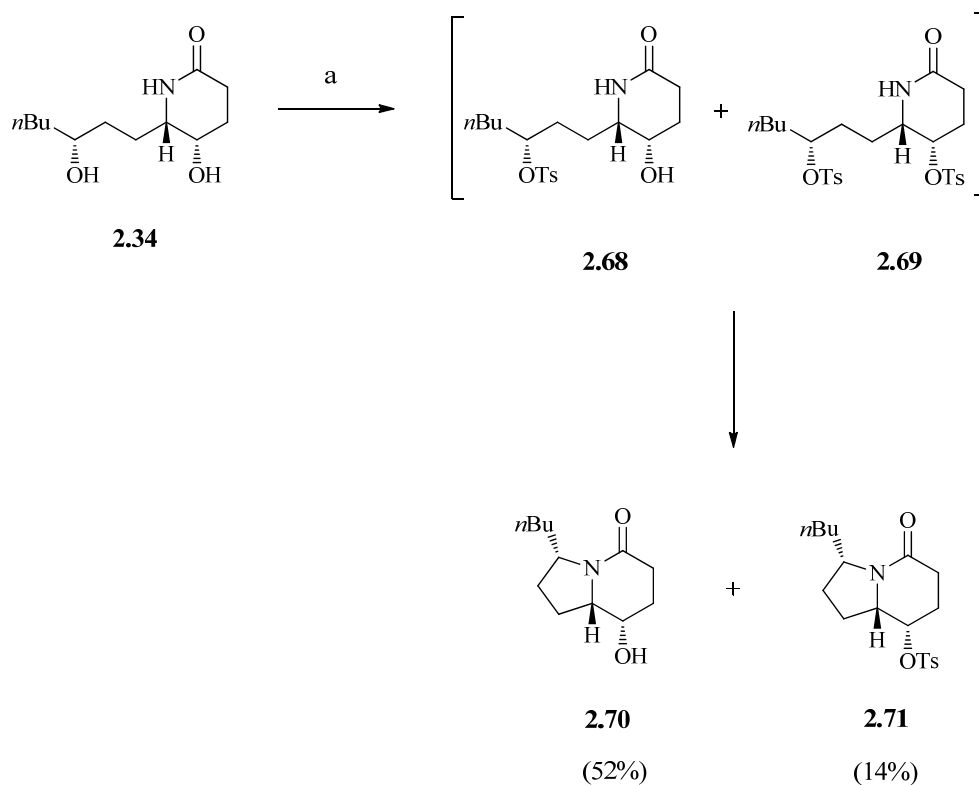
(M+H)⁺. We then attempted to vary the pressure of hydrogen gas by using Parr apparatus. It was found that the complete tandem alkene reduction and *N*-*O* bond cleavage-cyclisation required more aggressive conditions. The reaction proceeded at 100 psi of hydrogen over 24 hours to provide the lactam (**2.34**) as a single isomer in excellent yield (**Scheme 2.19**). The reaction proceeded through reduction of the alkene, lactamization by ring opening of lactone and then reductive *N*,*O*-bond cleavage. The ¹H NMR spectrum of the lactam (**2.34**) revealed a strong broad singlet at 6.8 ppm, indicating the presence of the NH proton.



Scheme 2.19

Initial attempts to form the bicycle (**2.70**) through a 2-step process by first selectively converting the side-chain secondary alcohol into an *O*-tosylate followed by cyclisation were unsuccessful. The di-*O*-tosylated product (**2.69**) was formed. We could not control regioselectivity of the tosylation. Therefore, we decided to use a procedure from Tanaka *et al.* for a one-pot synthesis of cyclic amides.⁹¹ Using Tanaka's procedure, the

second ring was constructed under basic conditions with the addition of 2.0 equivalents of *n*-butyllithium at -78 °C to form the lithium bis-alkoxide, followed by addition of 1.0 equivalent of *p*-toluenesulfonyl chloride to provide the *O*-tosylated intermediate (**2.68**) which subsequently underwent cyclisation to form the desired bicyclic lactam (**2.70**) in 52% yield, accompanied by the side product (**2.71**) in 14% yield (**Scheme 2.20**). We tentatively assigned the major product based on the mass analysis, showing m/z at 212 (M+H)⁺, which corresponds to the molecular mass of bicycle (**2.70**). The disappearance of the amine peak at 6.8 ppm in the ¹H NMR spectrum of bicyclic (**2.70**) also suggested that the reaction was successful. However, the ¹H NMR spectrum of the side product (**2.71**) clearly showed four aromatic protons at 7.80 (doublet) and 7.36 (doublet) ppm with a coupling constant of 8.2 Hz; and a sharp singlet at 2.49 ppm with an integration of 3 protons (ArCH₃). From the results obtained, it was shown that a competing reaction had occurred, whereby a side product was formed from the bicyclic product (**2.70**) and/or *O*-tosylated intermediate (**2.69**) thus reducing the yield. In order to increase the yield, the best approach available to us was to quench the reaction after 1 hour, whereby the bicyclic product (**2.70**) could be obtained (40-50% yield), together with some recovered starting material (**2.34**) (20-30%). Several attempts were made to optimise the condition but all failed to provide higher than 52% yield.

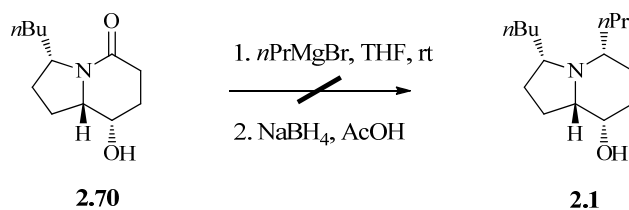


Scheme 2.20

Reagents and conditions: (a) *n*BuLi, THF, -78 °C, 30 min; TsCl, THF, -78 °C to rt, 1 h; (**2.70**, 52%), (**2.71**, 14%).

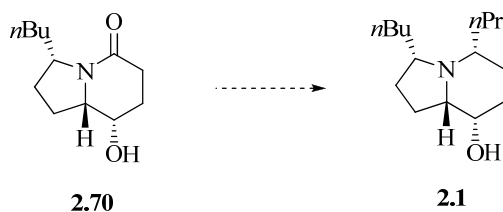
Each of three stereogenic centres of the lactam (**2.70**) possesses the correct relative configuration for the eventual synthesis of hydroxyindolizidine (**2.1**). The final step of the synthesis was to install the propyl group in the lactam ring. According to Orito's method,⁹² this could be achieved by adding propylmagnesium bromide to a solution of the lactam (**2.70**) in tetrahydrofuran at room temperature, followed by addition of acetic acid to form the iminium salt and subsequently, reduction with sodium borohydride

to give the target compound (**2.1**). It has to be noted that this was used previously in Bates's synthesis of (-)-monomorine using MeMgBr.^{18d} Unfortunately, a complex mixture was formed and the reaction failed to yield any of the desired product. This could be due to the interference of the hydroxyl group of the lactam (**2.70**) with the reaction (**Scheme 2.21**).

**Scheme 2.21**

2.4 Future work

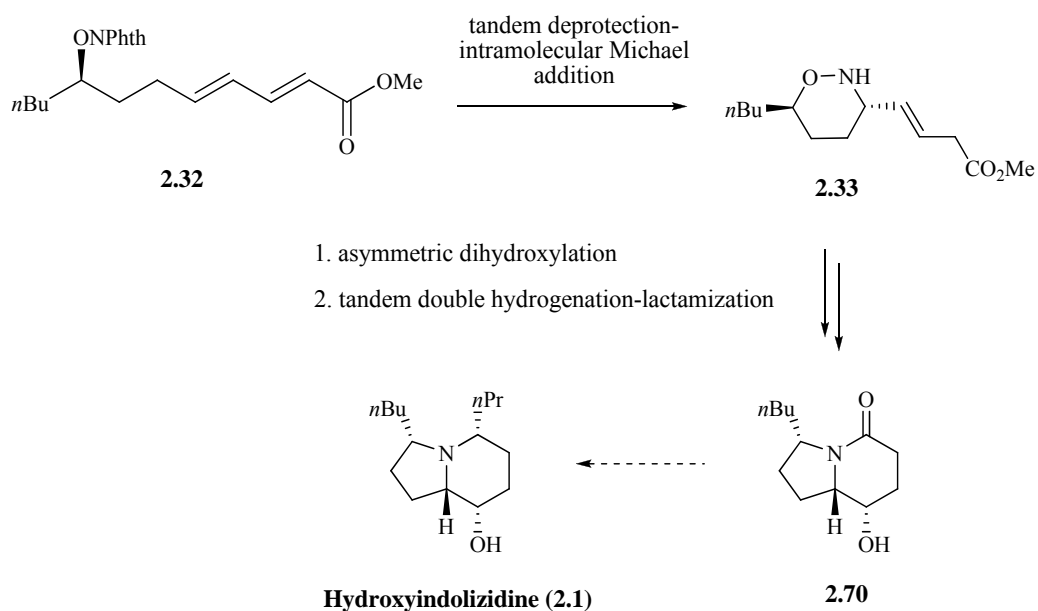
Unfortunately, despite being only one synthetic step away from our target natural product, due to time constraints, we were unable to complete the synthesis of hydroxyindolizidine (**2.1**). The completion of the synthesis of hydroxyindolizidine (**2.1**) will require a protection of the hydroxyl group at the indolizidine ring and stereoselective installation of the *n*-propyl group into the ring; follow by deprotection to afford the final target natural product (**2.1**).



Scheme 2.22

2.5 Conclusion

In conclusion, we have shown that the oxazine route previously developed in our laboratory can be adapted to the synthesis of hydroxylated indolizidines (**2.1**), but requires reagent-control of the stereochemistry of the asymmetric dihydroxylation, as shown in (**Scheme 2.23**).



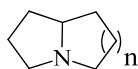
Scheme 2.23

CHAPTER 3

STUDIES TOWARDS THE TOTAL SYNTHESIS OF TUBEROSTEMOSPIRONINE

3.1 Introduction

In the first two chapters we have discussed the stereoselective synthesis of natural products that contain bicyclic nitrogen heterocycles, which consist of either five-membered rings or six-membered rings fused to a five-membered ring system. The bicyclic heterocycle containing a nitrogen atom in a seven-membered ring fused to a five-membered ring system is a pyrrolo[1,2-a]azepine, and this is the main architecture of the *stemona* alkaloids (**Figure 3.1**). The unique structural feature of this core skeleton has inspired interest regarding their chemical and biological properties.



n=1, Pyrrolizidine alkaloids

n=2, Indolizidine alkaloids

n=3, *Stemona* alkaloids

Figure 3.1 The 1-aza-[2+n.3.0]-bicyclic ring systems.

Alkaloids from *Stemona* plants have long been used in China and Southeast Asian countries for the treatment of respiratory disorders such as asthma, bronchitis, petusis and tuberculosis.^{93,94} Modern studies of biological activities have been hindered due to a lack of availability of the *Stemona* alkaloids. This has led to an increased interest in the synthesis of this class of *Stemona* alkaloids. These alkaloids might represent the main component responsible for their medicinal properties. All the *Stemona* alkaloids share the same pyrrolo[1,2-a]azepine nucleus. The substructure of an α -methyl- γ -butyrolactone is present in a majority of the alkaloids, which incorporate at least one

linked to the azabicyclic core in a spiro or fused manner or as a substituent. Pilli and co-workers have recently organised the *Stemona* alkaloids into eight groups (**Figure 3.2**): stenine (**I**), stemoamide (**II**), tuberospironine (**III**), stemonamide (**IV**), parvistemoline (**V**), stemofoline (**VI**) (all of which contain the pyrrolo[1,2-a]azepine core characteristic of the majority of the *Stemona* alkaloids), stemocurtisine (**VII**) displaying the pyrido[1,2-a]azepine nucleus, and a miscellaneous group formed by those alkaloids which do not display the same structure motif.^{93c}

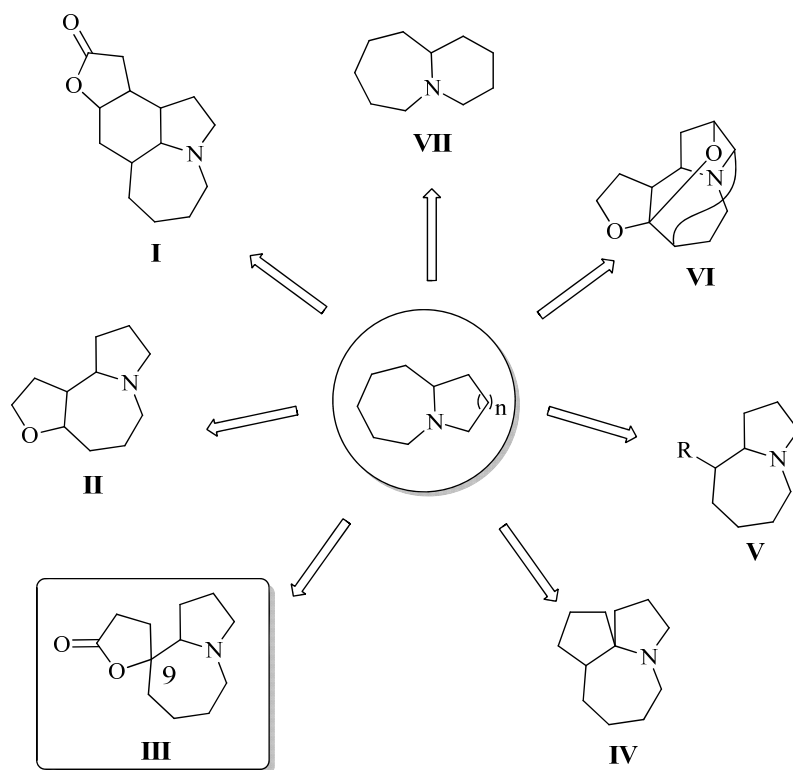


Figure 3.2 *Stemona* alkaloid groups.

One of these groups, the tuberostemospironine group is characterised by a spiro[furan-2-(5*H*), 9'[9*H*]pyrrolo[1,2-*a*]azepin]-5-one nucleus which displays a spiro- γ -lactone at C-9 of the basic azabicyclic nucleus (**III**, **Figure 3.2**). Selected examples of tuberostemospironine group alkaloids are shown in **Figure 3.3**. The relative configurations of the alkaloids tuberostemospironine (**3.1**),⁹⁵ stemonidine (**3.2**),⁹⁶ isostemotinine (**3.3**),^{96a} stemotinine (**3.4**),^{96a,97} 6- and 10-hydroxycroomine (**3.5**, **3.6**),^{95b,98} dehydrocroomine (**3.7**),^{98a} tuberospironine (**3.8**),^{95b,98a} sessilifoliamine A (**3.9**),⁹⁹ and didehydrocroomine (**3.10**)¹⁰⁰ were established by NMR studies. The absolute configurations of croomine (**3.11**)¹⁰¹ and stemospironine (**3.12**)¹⁰² were established by X-ray analyses (heavy-atom method). The parent alkaloid tuberostemospironine (**3.1**) is the only alkaloid in this group which lacks the α -methyl- γ -butyrolactone ring attached to C-3 of the pyrrolidine ring.^{95a} Tuberostemospironine (**3.1**), isostemotinine (**3.3**), stemonidine (**3.4**), and tuberospironine (**3.8**) show the opposite stereochemistry at C-9 to that found in croomine (**3.11**), stemospironine (**3.12**), stemotinine (**3.2**), 6- and 10-hydroxycroomine (**3.5**, **3.6**), dehydrocroomine (**3.7**), and sessilifoliamine A (**3.9**).

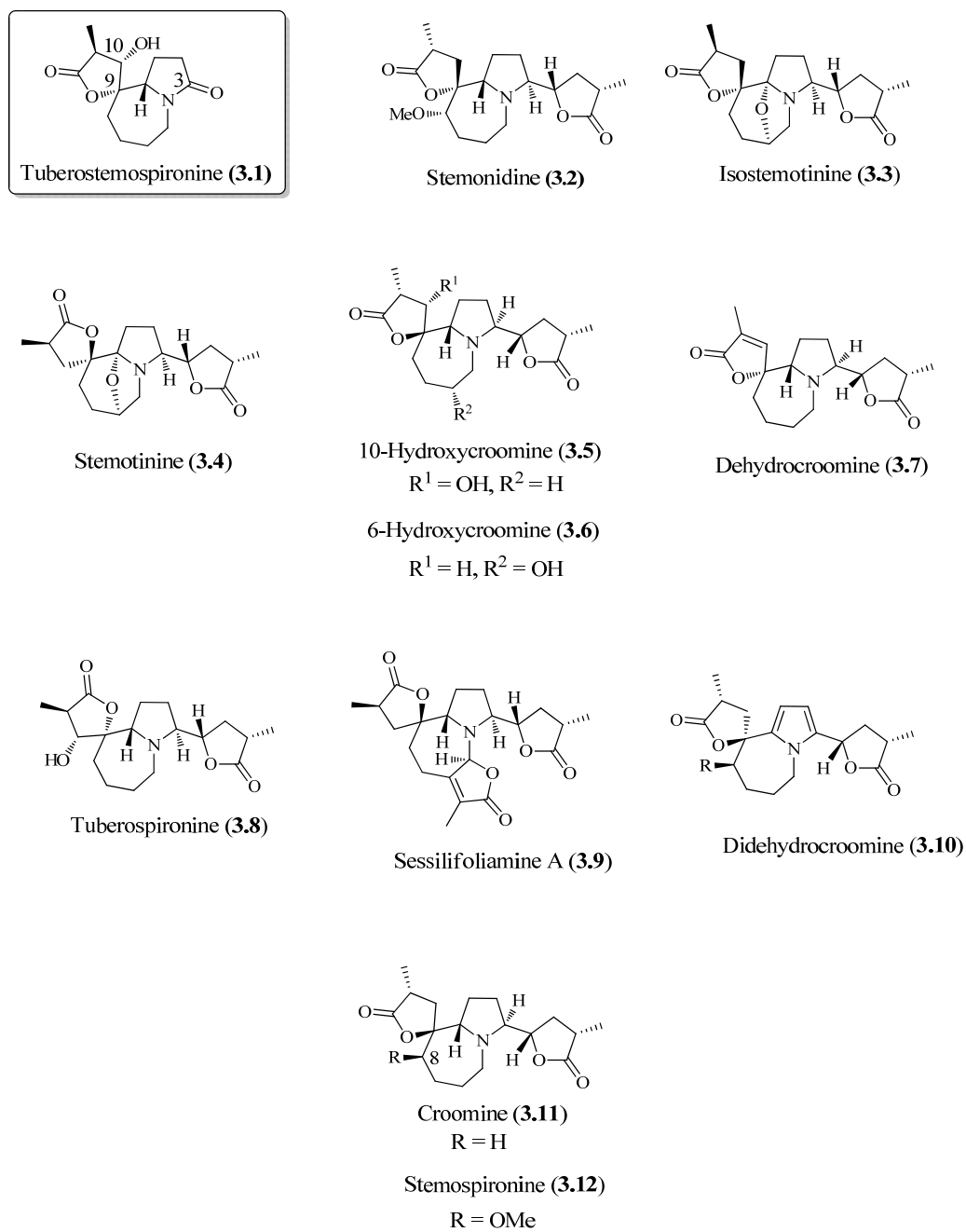
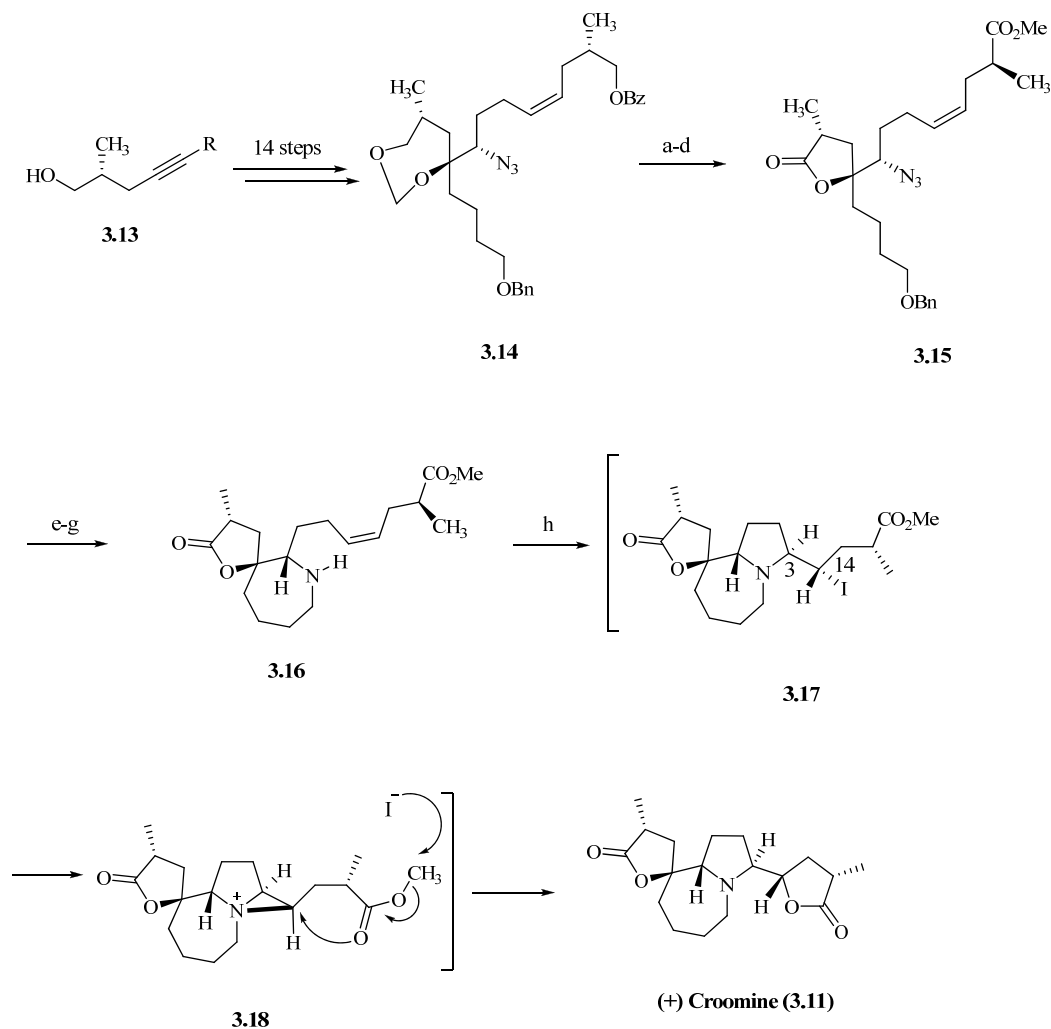


Figure 3.3 *Stemona* alkaloids of the tuberostemospirone group

3.1.1 Synthetic Sources of Tuberostemospirone Group

To date, the only total syntheses of alkaloids from the tuberostemospirone group, are those of (+)-croomine (**3.11**),^{103,104} (-)-stemospirone (**3.12**),¹⁰⁵ and stemonidine (**3.2**)¹⁰⁶. The syntheses of these three alkaloids are outlined below. Williams and co-workers reported the first total synthesis of croomine (**3.11**) and (-)-stemospirone (**3.12**). The synthesis of (+)-croomine (**3.11**) was the first accomplished in 1989,¹⁰³ whereas (-)-stemospirone (**3.12**) was successfully synthesised in 2001.¹⁰⁵ (+)-Croomine (**3.11**) and (-)-stemospirone (**3.12**) have different substituents at the C-8 position. (-)-Stemospirone (**3.12**) carries a methoxy group at this position whereas (+)-croomine (**3.11**) shows no substitution. The first total synthesis of (+)-croomine (**3.11**) was achieved in 26 steps and about 0.5% overall yield from methyl (*S*)-2-methyl-3-hydroxypropionate (**3.13**) (Scheme 3.1). The key steps in this synthesis were an intermolecular Staudinger reaction and iodoamination step to construct the pyrrolo[1,2-*a*]azepine nucleus and the γ -butyrolactone ring attached at C-3. The intermediate (**3.14**) was derived from methyl (*S*)-2-methyl-3-hydroxypropionate (**3.13**) in 14 steps. Treatment of azide (**3.14**) with aqueous fluoroboric acid (aq. HBF₄) in methanol, subsequent saponification, oxidation and esterification furnished the γ -butyrolactone (**3.15**). The γ -butyrolactone (**3.15**) was subjected to deprotection followed by Swern oxidation and subsequent an intramolecular Staudinger reaction followed by reduction to give the azabicyclic amine (**3.16**). The final natural product (+)-croomine (**3.11**) was obtained by iodoamination of bicyclic intermediate (**3.16**). This key step set the correct stereochemistries at C-3 and C-14. The iodine-induced intramolecular cyclisation favored formation of *trans*-2,5-disubstituted pyrrolidino iodides (**3.17**) which cy-

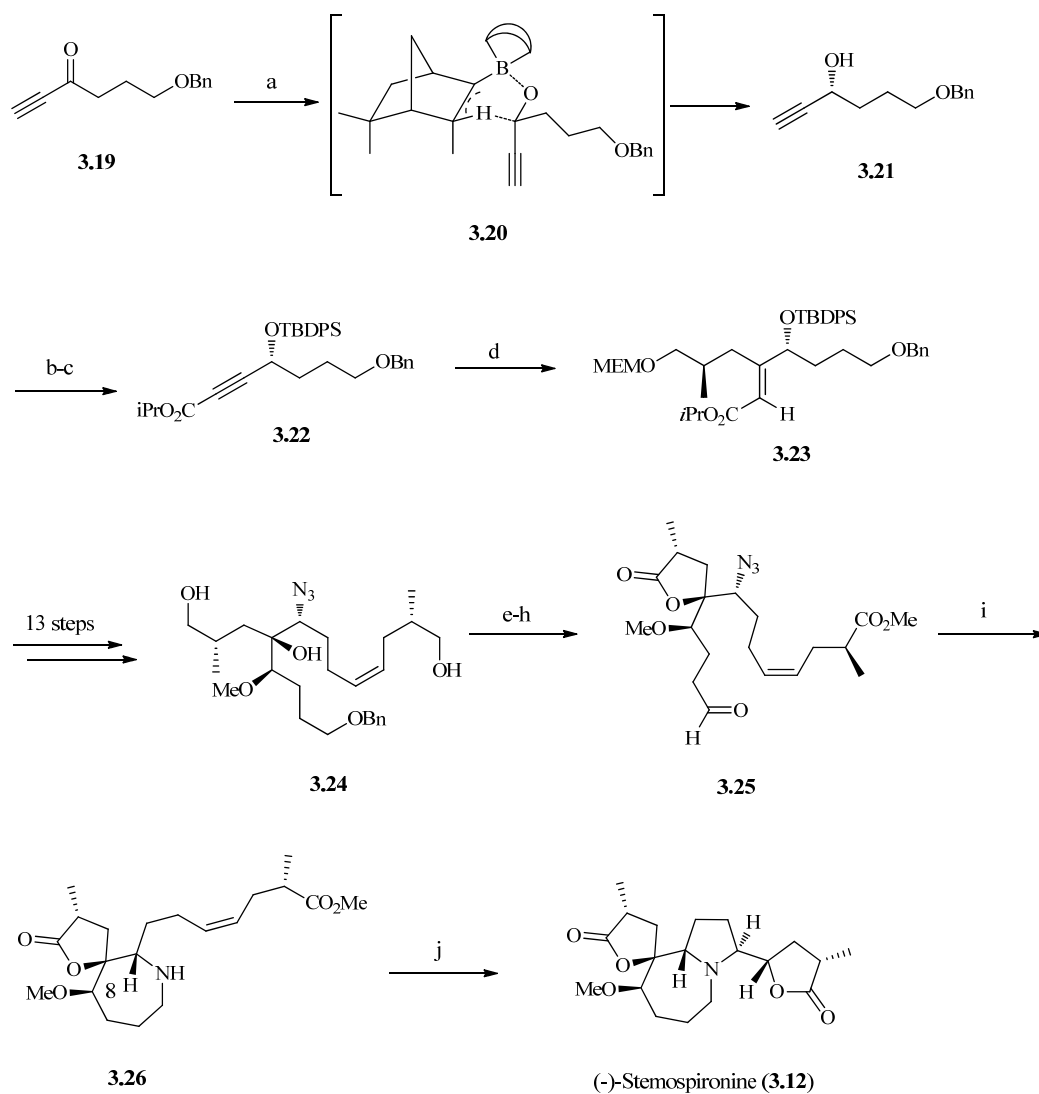
clised to the aziridinium species (**3.18**), followed by nucleophilic substitution by the neighbouring methyl ester for the retention of C-14 stereochemistry.



Scheme 3.1 Williams' synthesis of (+) croomine (**3.11**)

Reagents and conditions: (a) aq. HBF₄, MeOH (72%); (b) LiOH, THF, MeOH, H₂O, 22 °C (86%); (c) Jones' reagent, THF, 0 °C; (d) CH₂N₂, Et₂O (78%, 2 steps); (e) BCl₃, CH₂Cl₂, -78 °C → 0 °C; then, MeOH, -78 °C (77%); (f) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 °C to 0 °C (92%); (g) Ph₃P, THF, 22 °C; then, NaBH₄, MeOH (90%); (h) I₂, CH₂Cl₂, Et₂O, 22 °C (25%).

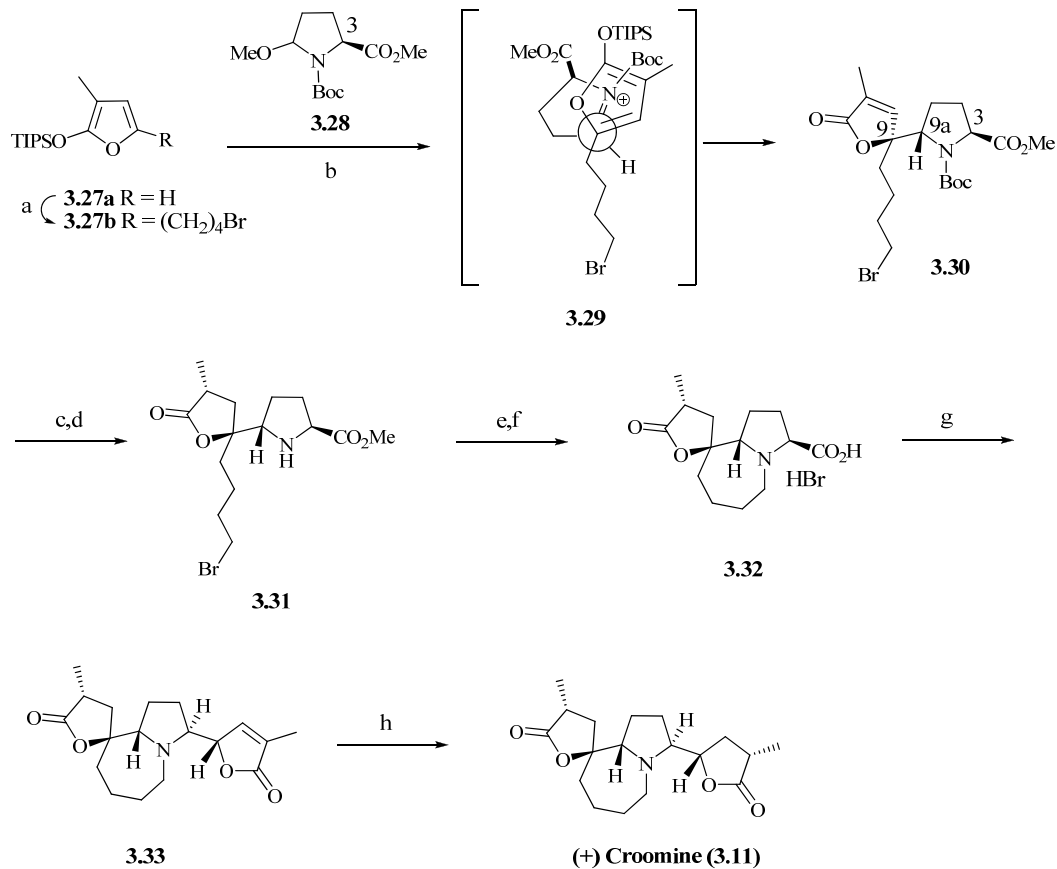
Since the first total synthesis of (+)-croomine (**3.11**) was achieved as described above, in 2001, Williams and co-workers extended this work and disclosed the first total synthesis of (-)-stemospironine (**3.12**) in 24 steps and less than 1% overall yield, using the same strategy as that reported previously (**Scheme 3.2**).¹⁰⁵ Only the substitution at C-8 is different from (+)-croomine (**3.11**). They started with the commercially available ketone (**3.19**). The chirality at C-8 was introduced *via* Midland Alpine borane reduction of the conjugated ynone (**3.19**) with (*R*)-Alpine-borane, leading to the corresponding alcohol (**3.21**) (88% ee). After hydroxyl protection and acylation of the terminal acetylene, ester (**3.22**) was subjected to stereoselective Cu(I)-catalysed conjugate addition of a Grignard reagent to provide unsaturated ester (**3.23**). After functional group manipulations, azide (**3.24**) was obtained in 13 steps from unsaturated ester (**3.23**). After Jones' oxidation, esterification, debenzoylation, and Dess-Martin periodination, the key intermediate azido aldehyde (**3.25**) was obtained in good yield. The key intermediate azido aldehyde (**3.25**) was then subjected to the Staudinger reaction to provide a seven-membered imine which was reduced *in situ* with sodium borohydride to give a bicyclic amine (**3.26**). Upon exposure to iodine the corresponding bicyclic amine (**3.26**) underwent the stereoselective double cyclisation to provide (-)-stemospironine (**3.12**) in 30% yield. Williams and co-workers' elegantly employed the iodocyclisation methodology in both cases but overall, this resulted in very lengthy syntheses.



Scheme 3.2 Williams' synthesis of (-)-stemospironine (3.12)

Reagents and conditions: (a) (*R*)-Alpine borane, THF, -10 °C to rt (95%, 88% ee); (b) TBDP-
 SCl, imidazole, CH₂Cl₂, rt (80%); (c) nBuLi, ClCO₂iPr, THF, -78 °C (90%); (d) (*S*)-
 MEMOCH₂CH(CH₃)CH₂MgBr, CuBr·DMS, THF, -78°C to rt (70%); (e) Jones' reagent, THF,
 -10 °C; (f) CH₂N₂, Et₂O, 0 °C (80%, two steps); (g) BCl₃, CH₂Cl₂, -78 °C to rt (60%); (h)
 Dess-Martin periodinane, CH₂Cl₂ (80%); (i) PPh₃, THF; then NaBH₄, MeOH, rt (60%); (j) I₂,
 CH₂Cl₂, Et₂O, rt (30%).

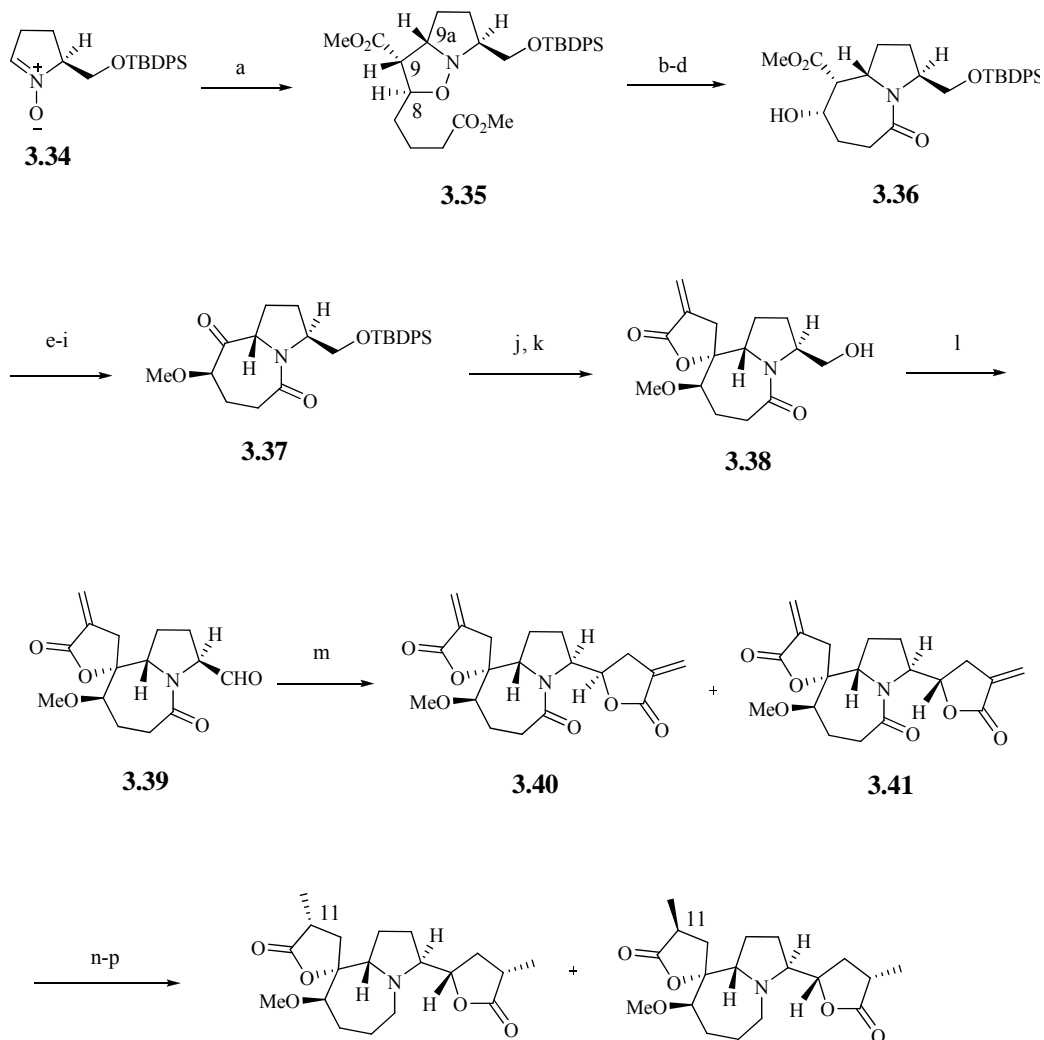
During the 1989-2001 period, Martin and co-workers devised an elegant synthesis of (+)-croomine (**3.11**) using a vinylogous Mannich reaction.¹⁰⁴ In 1999, they disclosed the total synthesis of (+)-croomine (**3.11**) in 8 steps and approximately 5% overall yield (**Scheme 3.3**). A shorter and efficiently devised method to this alkaloid started with furan (**3.27b**) by alkylation of the lithio derivative of silyloxyfuran (**3.27a**) with 1,4-dibromobutane. The first vinylogous Mannich reaction was achieved *via* addition of the chiral acyl iminium ion generated *in situ* by the triisopropylsilyl triflate-catalysed ionisation of aminal (**3.28**) to furan (**3.27b**) to obtain the *threo* adduct (**3.30**) in 32% yield. They established the structure of the *threo* adduct (**3.25**) by X-ray crystallography. The relative stereochemical relationships at C-9 and C-9a of (+)-croomine were set in a single step *via* a vinylogous Mannich reaction proceeding *via* a *threo* manifold (**3.29**) in which the furan approached the iminium ion from the face opposite the carboxyl function at C-3. After removal of the *N*-Boc group and hydrogenation of the double bond, amine (**3.31**) underwent an intramolecular nitrogen alkylation to provide the seven-membered amine which was converted into carboxylic acid (**3.32**) in 93% yield. The carboxylic acid (**3.32**) was then ready for the second vinylogous Mannich transformation. Treatment of the carboxylic acid (**3.32**) with phosphoryl chloride in dimethylformamide afforded an intermediate iminium ion which was trapped with 2-triisopropylsilyloxy-3-methylfuran (**3.27a**) to give the desired isomer (**3.33**) and its C-14 epimer (2:1 ratio) in 47% combined yield. The desired adduct (**3.33**) was subjected to a stereoselective hydrogenation to provide (+)-croomine (**3.11**) in 81% yield.



Scheme 3.3 Martin's synthesis of (+)-croomine (3.11)

Reagents and conditions: (a) *s*BuLi, TMEDA, THF, 0 °C; then, BrCH₂(CH₂)₂CH₂Br (83%); (b) (3.28), 5% TIPSOTf, CH₂Cl₂, 0 °C (32%); (c) CF₃COOH, CH₂Cl₂, rt.; (d) 3% Rh/C, H₂, EtOAc, EtOH (>96%, 2 steps); (e) *N*-methylmorpholine, DMF, reflux; (f) 3 M aq. HBr, 60 °C (74%, 2 steps); (g) POCl₃, DMF, rt, then, (3.27a) (ca. 32%); (h) 10% Pd/C, H₂ 10% HCl-EtOAc (85%).

The most recent synthesis of alkaloids from the tuberospironine group is that of stemonidine (**3.2**) which was accomplished in 16 steps by Figueredo and co-workers in 2007 (**Scheme 3.4**).¹⁰⁶ Stemonidine (**3.2**) and (-)-stemospironine (**3.12**) are spirocyclic diastereomers. Figueredo and co-workers devised a strategy in which the azabicyclic structure was generated at an early stage, and other specific fragments were then incorporated. They overcame the stereochemical control of stemonidine (**3.2**) at C-8, C-9 and C-9a using 1,3-dipolar cycloaddition of a chiral nitron (**3.34**) and (*E*)-diester (**3.43**). Nitron (**3.34**) was subjected to 1,3-dipolar cycloaddition with (*E*)-diester (**3.43**) in refluxing toluene to provide *endo*-isoxazolidine (**3.35**) and its *exo* isomer. *N-O* bond cleavage with zinc in glacial acetic acid, followed by treatment with aqueous ammonia and heating, afforded bicyclic lactam (**3.36**). After dehydration and dihydroxylation, the diol was subjected to regioselective methylation to provide a methyl ether which was converted into the ketone (**3.37**) by treatment with lithium borohydride and then lead tetraacetate. The spiro γ -methylene butyrolactone moiety was selectively introduced *via* the Barbier reaction of ketone (**3.37**) with ethyl bromomethylacrylate in the presence of zinc to give lactone (**3.38**) in 86% yield. After deprotection of the silyl ether and oxidation of the primary alcohol, the aldehyde (**3.39**) was treated with ethyl bromomethylacrylate in the presence of zinc to give a roughly 1:1 mixture of bislactones (**3.40**) and (**3.41**) in 73% yield. Hydrogenation of bislactone (**3.41**), followed by formation of the corresponding thiolactam and desulfurization with Raney[®] nickel, provided a mixture of C-11 epimeric azepines stemonidine (**3.2**) and (**3.42**).



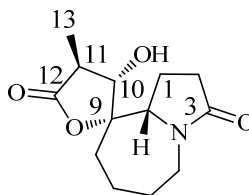
Scheme 3.4 Figueredo's synthesis of stemonidine (**3.2**)

Reagents and conditions: (a) (*E*)-MeO₂CCH₂CH₂CH=CHCO₂Me (**3.43**), toluene, reflux (78%); (b) Zn, AcOH; (c) aq. NH₃; (d) toluene, reflux (84%, three steps); (e) PPh₃, DIAD, BzOH, THF (88%); (f) OsO₄, NMO, acetone-H₂O (92%); (g) NaH, THF; then Me₂SO₄ (84%); (h) LiBH₄, THF (97%); (i) Pb(OAc)₄, THF (92%); (j) EtO₂CC(C=CH₂)CH₂Br, Zn, THF (86%); (k) Et₃N·3HF, THF (87%); (l) Dess-Martin, CH₂Cl₂ (92%); (m) EtO₂CC(=CH₂)CH₂Br, Zn, THF (73%, 1:1 mixture); (n) H₂ (6 bar), Pd/C, EtOH, HCl (68%); (o) Lawesson's reagent; (p) Raney[®] Ni, EtOH (45%, two steps).

The brief highlight of the different routes utilised to achieve the syntheses of alkaloids from tuberostemospironine group inspired us to study alternative approaches towards the total synthesis of tuberostemospironine (**3.1**). To date, no synthetic study towards tuberostemospironine (**3.1**) has been reported. Herein, we propose an approach to its synthesis.

3.1.2 Tuberostemospironine (3.1)

In 1992, Xu and co-workers isolated tuberostemospironine (**3.1**) from the roots of *Stemona tuberosa* (Stemonaceae).^{95a} The structure is shown in **Figure 3.4**. The relative configuration of the alkaloid tuberostemospironine (**3.1**) was characterised by 2D-NMR techniques. Tuberostemospironine (**3.1**) bears a carbonyl group at C-3, a hydroxyl group at C-10, and the spirooxygenated carbon at C-9. The spiro configuration of the γ -lactone was confirmed by the NOESY cross peaks between H-10 and Me-13, H-11 and H-1 α , and OH and H-1 α .

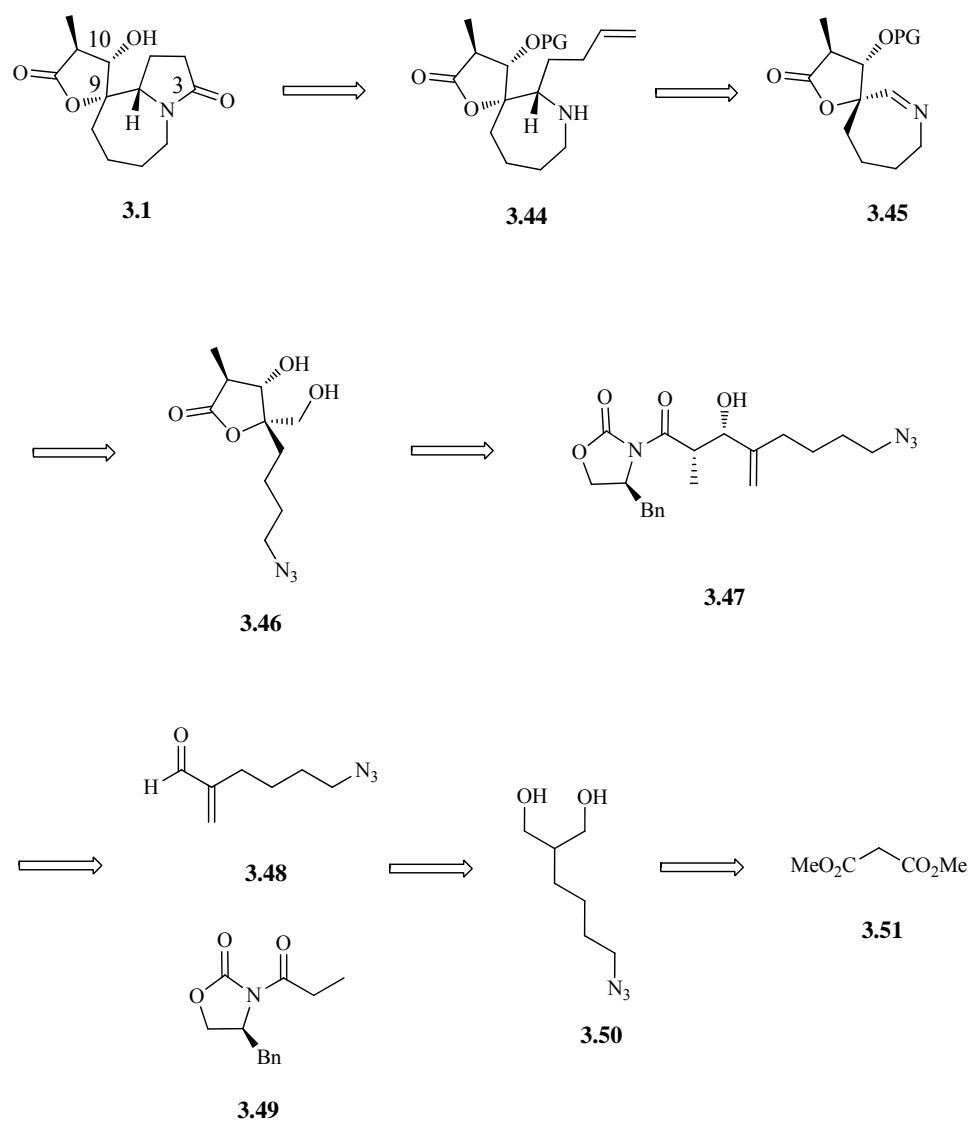


Tuberostemospironine (**3.1**)

Figure 3.4

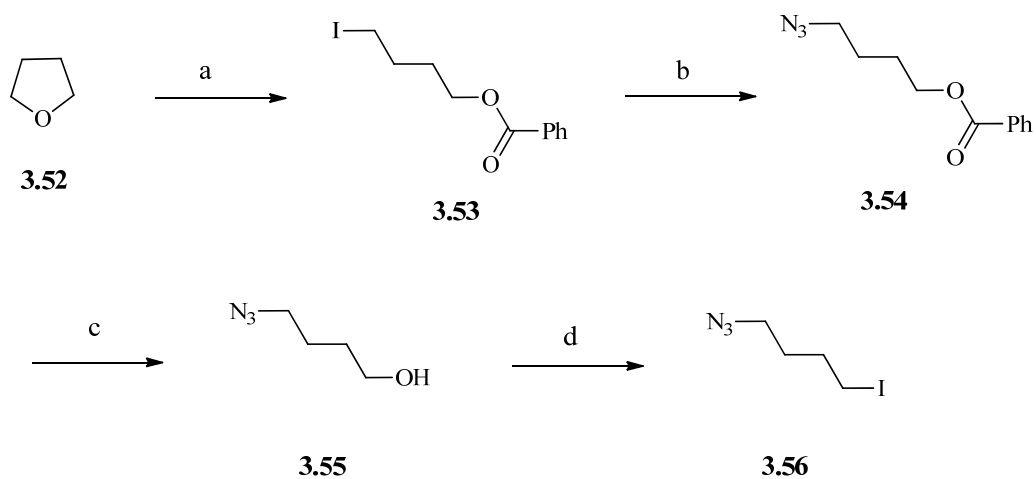
3.1.3 Synthetic Plan

The molecular framework of tuberostemospironine (**3.1**) contains a spiro- α -methyl- γ -butyrolactone ring at C-9 of the basic 1-azabicyclo[5.3.0]decane nucleus. This alkaloid contains four stereogenic centres, the three stereogenic centres at C-9, C-10 and C-11 of the γ -butyrolactone ring and one stereogenic centre at C-9a of the basic azabicyclic nucleus. Since the stereocentres of the α -methyl- γ -butyrolactone moiety are significant, we therefore proposed strategy in which a α -methyl- γ -butyrolactone moiety is generated at an early stage of the sequence and the azabicyclic core is then constructed. Our retrosynthetic analysis for tuberostemospironine (**3.1**) is outlined in **Scheme 3.5**. Tuberostemospironine (**3.1**) can be considered to ascend from lactamisation after oxidative cleavage of double bond of amine (**3.44**), which would arise from alkylation of bicyclic imine (**3.45**). As a cyclic imine, compound (**3.45**) could be formed *via* acid catalysed cyclisation or aza-Wittig reaction of an amine (after reduction of azide), and an aldehyde (after oxidation of primary alcohol). γ -Butyrolactone (**3.46**) could be prepared *via* ring opening epoxidation of alkene (**3.47**) by intramolecular nucleophilic attack of a carboxylic acid after removal of the chiral auxiliary oxazolidinone by hydrolysis. The *syn*-aldol compound (**3.47**) will be constructed via the asymmetric aldol condensation of chiral auxiliary oxazolidinone (**3.49**) and aldehyde (**3.48**). The aldehyde (**3.48**) could be prepared from diol (**3.50**) derived from the commercially available dimethyl malonate (**3.51**).

**Scheme 3.5** Retrosynthetic analysis for tuberostemospirone (3.1)

3.2 Results and Discussion

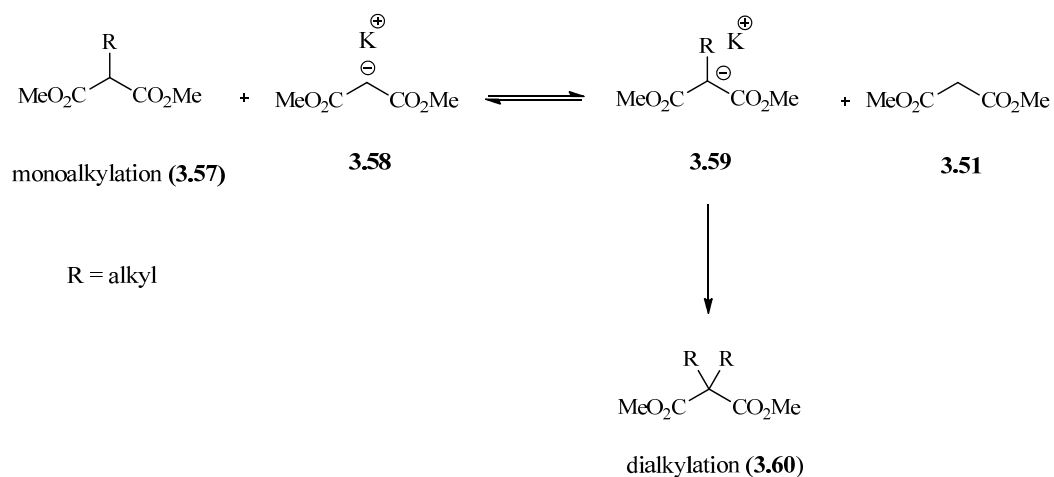
Our initial plan was the synthesis of 1-azido-4-iodobutane (**3.56**), which is a starting material for introducing the azide moiety into the molecule (**Scheme 3.6**). A tetrahydrofuran (**3.52**) ring-opening reaction with sodium iodide in the presence of benzoyl chloride in acetonitrile at room temperature provided 4-iodobutyl benzoate (**3.53**) in 90% yield, using a procedure reported by Oku *et al.*¹⁰⁷ A tetrahydrofuran provides an economical access to 1,4-disubstituted butanes. The iodide was displaced with azide by treatment of 4-iodobutyl benzoate (**3.53**) with sodium azide in dimethylformamide at room temperature overnight to provide 4-azidobutyl benzoate (**3.54**) in quantitative yield, which was used without further purification. The benzoyl ester was then saponified with a solution of lithium hydroxide in tetrahydrofuran-water-methanol (1:1:1) at room temperature for two hours to give the alcohol (**3.55**) in quantitative yield.¹⁶⁷ Iodination of alcohol (**3.55**) in the presence of iodine, imidazole and triphenylphosphine in diethyl ether-acetonitrile (3:1) furnished 1-azido-4-iodobutane (**3.56**) in 71% yield, following a procedure reported by Garegg and Samuelsson.¹⁰⁸ Column chromatography was required only after the last step in the purification of the 1-azido-4-iodobutane (**3.56**). All spectroscopic data for the 1-azido-4-iodobutane (**3.56**) agreed with those previously reported.¹⁰⁹



Scheme 3.6 Preparation of 1-azido-4-iodobutane (**3.56**)

Reagents and conditions: (a) BzCl, NaI, CH₃CN; 90%; (b) NaN₃, DMF, rt; quant; (c) LiOH, THF-H₂O-MeOH (1:1:1); 95%; (d) I₂, imidazole, PPh₃, Et₂O-CH₃CN (3:1), rt; 71%.

The alkylation of dimethyl malonate (**3.51**) with an alkyl halide under traditional condition often gives substantial amount of dialkylated product (**3.60**), but use of THF as solvent, in which the intermediate (**3.58**) is insoluble, suppresses the dialkylation. Low solubility of the intermediate (**3.58**) drives this undesirable equilibrium to the left hand side (**Scheme 3.7**) and an excess of dimethyl malonate (**3.51**) must be used to prevent formation of dialkylated product (**3.60**).

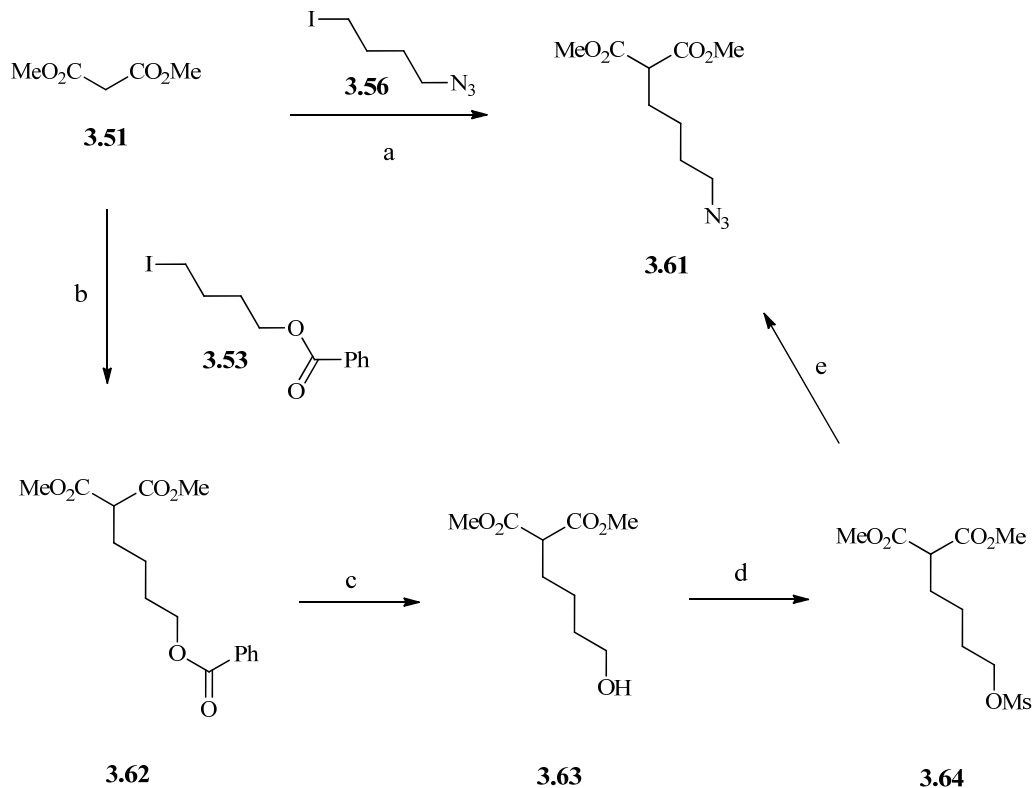


Scheme 3.7

The 1-azido-4-iodobutane (**3.56**) was then ready for the alkylation with dimethyl malonate. The malonate (**3.51**) was added dropwise to a mixture of potassium-*tert*-butoxide in anhydrous tetrahydrofuran at 0 °C for five minutes, followed by slow addition of a solution of 1-azido-4-iodobutane (**3.56**) in tetrahydrofuran at 0 °C to room temperature for 3 days (Scheme 3.7). The diester (**3.61**) was obtained in quantitative yield after distillation under reduced pressure (80 °C at 4 mmHg) to remove the excess of dimethyl malonate (**3.51**). The ¹H NMR of crude product showed only monoalkylate diester product (**3.57**).

We realized 4-iodobutyl benzoate (**3.53**) could also be a good electrophile in the alkylation step. We therefore carried out the alkylation using 4-iodobutyl benzoate (**3.53**) as the electrophile. Treatment of the dimethyl malonate (**3.51**) with potassium *tert*-

butoxide in anhydrous tetrahydrofuran at 0 °C for five minutes, and subsequent addition of a solution of 4-iodobutyl benzoate (**3.53**) in tetrahydrofuran at 0 °C to room temperature for 4 days furnished the diester (**3.62**) in 94% yield, after removal of excess dimethyl malonate (**3.51**) by distillation. Alkaline hydrolysis of the benzoate ester with potassium carbonate in the presence of methanol at room temperature for 2 hours, provided the corresponding alcohol (**3.63**) which underwent mesylation⁴¹ with methanesulfonyl chloride and triethylamine in anhydrous tetrahydrofuran at 0 °C to room temperature for 2 hours to provide diester (**3.64**) in 73% yield over two steps. Displacement of the methanesulfonate of (**3.64**) was carried out with sodium azide in dimethylformamide. The reaction was heated to 70 °C for 6 hours to provide the azide (**3.61**) in 94% yield. The procedures described in the alkylation step using 4-iodobutyl benzoate (**3.53**) as an electrophile, is preferable. Due to the synthesis of 1-azido-4-iodobutane (**3.56**) was required iodination in the last step, which was certainly not economical and also toxic.

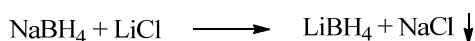


Scheme 3.8 Preparation of the diester azide (**3.61**)

Reagents and conditions: (a) KO t Bu, THF; (**3.56**), 0 °C to rt, 3 days; quant; (b) KO t Bu, THF; (**3.53**), 0 °C to rt, 4 days; quant; (c) K₂CO₃, MeOH, rt, 2 h; (d) MsCl, Et₃N, THF, 0 °C to rt, 2 h; 73%, 2 steps; (e) NaN₃, DMF, 70 °C, 6 h; 94%.

The diester (**3.61**) was then directly reduced with two equivalents of lithium aluminium hydride in anhydrous tetrahydrofuran at 0 °C to room temperature for two hours to afford the diol (**3.50**) in 38% yield (**Scheme 3.10**). The difficulties of separating the desired product (**3.50**) from the lithium and aluminium salt by-product resulted in the low yield. Thus, we investigated the use of lithium borohydride for reduction of the esters, using a procedure reported by Brown and co-workers.¹¹⁰ The convenient proce-

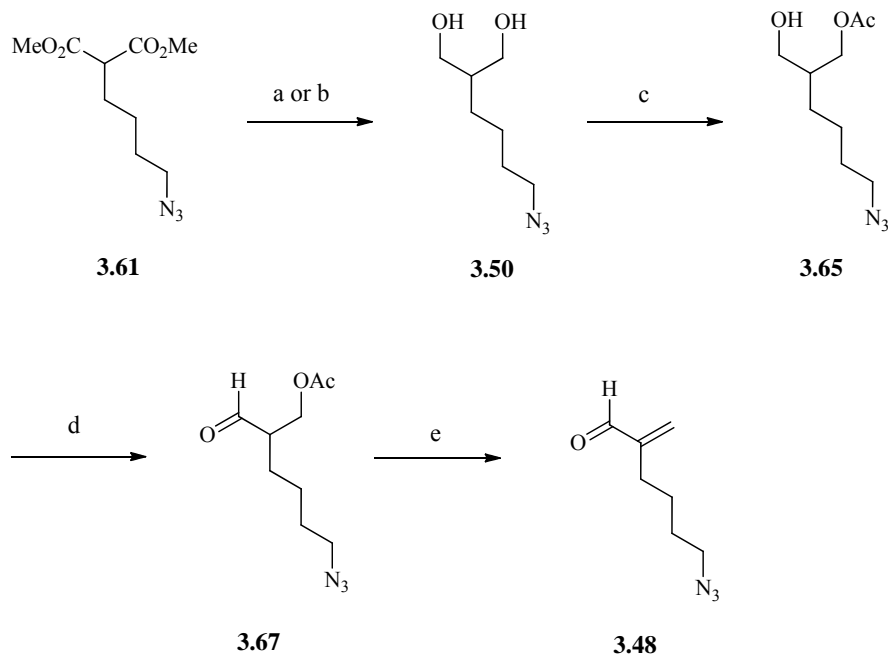
dure for the conversion of sodium borohydride into lithium borohydride, is used for the reduction of ester to the corresponding alcohols. This method makes lithium borohydride readily available, using an inexpensive reagent, and avoids handling the deliquescent LiBH_4 (**Scheme 3.9**). The dimethyl ester (**3.61**) was reduced with LiCl-NaBH_4 in ethanol:tetrahydrofuran (1:1) at 0°C to room temperature for two hours to provide the diol (**3.50**) in 83% yield.



Scheme 3.9

Triethyl orthoacetate is used in organic synthesis for the introduction of the acetate group to an alcohol. This method can be used as a selective acylation of one hydroxy group of a diol. The formation of *O,O*-acetals from alcohols proceeds *via* acid catalysis. Acid catalysts can be a mineral acid (HCl or H_2SO_4) or sulfonic acid (*p*-toluenesulfonic acid, camphorsulfonic acid, or a strongly acidic cation exchange resin). Treatment of diol (**3.50**) with triethyl orthoacetate in the presence of concentrated sulfonic acid as a catalyst (a few drops) in tetrahydrofuran at room temperature for 2 hours provided the cyclic orthoester which was straightforwardly reacted with aqueous 80% acetic acid for 2 hours to afford acetate (**3.65**) in 89% yield.¹¹¹ Aqueous 80% acetic acid was used in this step to accelerate the hydrolysis of cyclic orthoester to an acetyl group.¹¹² The monoacetate (**3.65**) was identified by its ^1H NMR spectrum with the acetyl group being observed as a sharp singlet at 2.01 ppm, whereas the free hydroxyl group was observed as a broad singlet at 2.46 ppm. The remaining primary alcohol of

compound (**3.65**) was then ready for the oxidation. The aldehyde functional group could be installed by simple oxidation such as Swern oxidation,¹¹³ Dess-Martin periodinane,¹¹⁴ 2-iodoxybenzoic acid (IBX),¹¹⁵ chromium-based oxidation agents such as Jones reagent,¹¹⁶ Sarett and Collins reagent,¹¹⁷ pyridinium dichromate (PDC),¹¹⁸ and pyridium chlorochromate (PCC)¹¹⁹. Based on Santagostino's report,¹¹⁵ oxidation of alcohol (**3.65**) with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide at room temperature for 18 hours provided the desired aldehyde product. The ¹H NMR spectrum of the crude product showed the characteristic of aldehyde proton as two singlet peaks at 9.68 and 9.51 ppm, indicated that two aldehyde products were obtained. Separation of the mixture by column chromatography eventually afforded the desired aldehyde (**3.67**) in 50% yield and the unsaturated aldehyde (**3.48**) in 39% yield. Presumably under mild acidic oxidation conditions, using 2-iodoxybenzoic acid may cause the β -elimination of the acetoxy group of the acetate (**3.67**) to give unsaturated aldehyde (**3.48**). Thus, in this case separation was not required prior to triethylamine treatment. The β -elimination of the acetoxy group could be obtained by treatment of acetate (**3.67**) with triethylamine in dichloromethane-dimethylsulfoxide (1:1) at room temperature for 2 hours to afford the unsaturated aldehyde (**3.48**) in excellent yield. The ¹H NMR spectrum of the product (**3.48**) confirmed a sharp singlet at 9.51 ppm indicating the aldehyde functional group and two singlet peaks at 6.24 and 6.00 ppm corresponding to the double bond unit at the molecule. The geminal coupling constant on a sp² carbon is very small. Thus, the geminal proton appeared as a singlet.



Scheme 3.10 Preparation of aldehyde (**3.48**)

Reagents and conditions: (a) LiAlH_4 , THF, 0 °C to rt, 2 h; 38%; (b) LiCl-NaBH_4 , EtOH-THF (1:1), 0 °C to rt, 2 h; 83%; (c) triethyl orthoacetate, H_2SO_4 (cat.), THF, rt, 2 h; 80% aq. CH_3COOH , rt, 2 h; 89%; (d) IBX, DMSO, rt, 18 h; (e) Et_3N , CH_2Cl_2 -DMSO (1:1), rt, 2 h; 93% (2 steps).

Using chiral auxiliaries is one of the most important and general methods for asymmetric synthesis.¹²⁰ Chiral auxiliaries are enantiomerically pure compounds which are linked to a substrate and influence the stereochemical course of a reaction via steric hindrance or directing groups to determine chirality and they can be removed afterwards. The use of chiral oxazolidinone auxiliaries,¹²¹ first introduced by Evans *et al.* in 1981,¹²² has attracted much interest in synthetic chemistry. Enantiomerically pure oxazolidinones are easily prepared and commonly available. Selected succeeding varia-

tions of chiral *N*-acyloxazolidinone (**3.68**)¹²² are shown in **Figure 3.5**. These chiral substituted imide auxiliaries, more highly substituted oxazolidinones (**3.70**),¹²³ (**3.71**)^{124,125}; super Quats (**3.73**),¹²⁶ (**3.74**)¹²⁷; imidazolidinones (**3.76**),¹²⁴ (**3.77**)¹²⁸; thiazolidinethiones (**3.69**)^{129,130}; imidazolidinethiones (**3.72**)¹³¹; and cyclic sultam (**3.75**)¹³², are becoming widespread and have been applied with success to many asymmetric transformations.

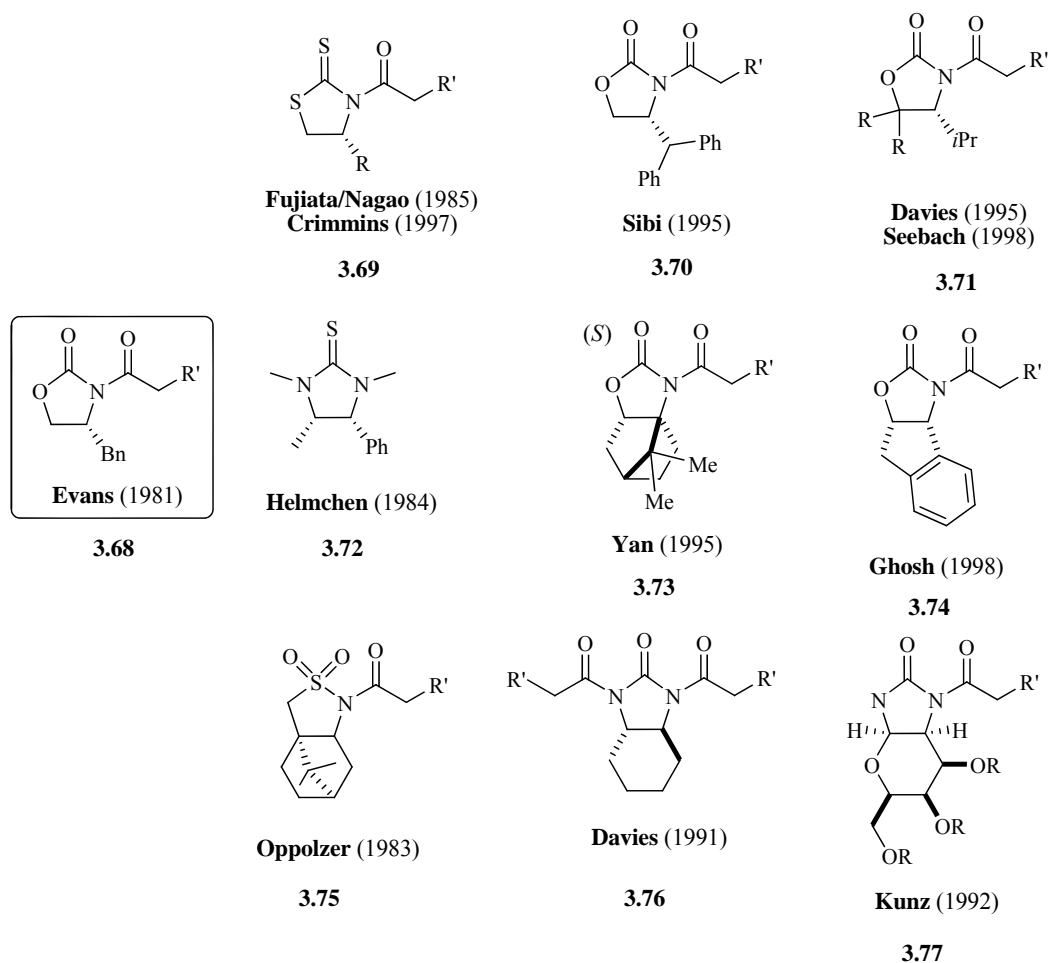
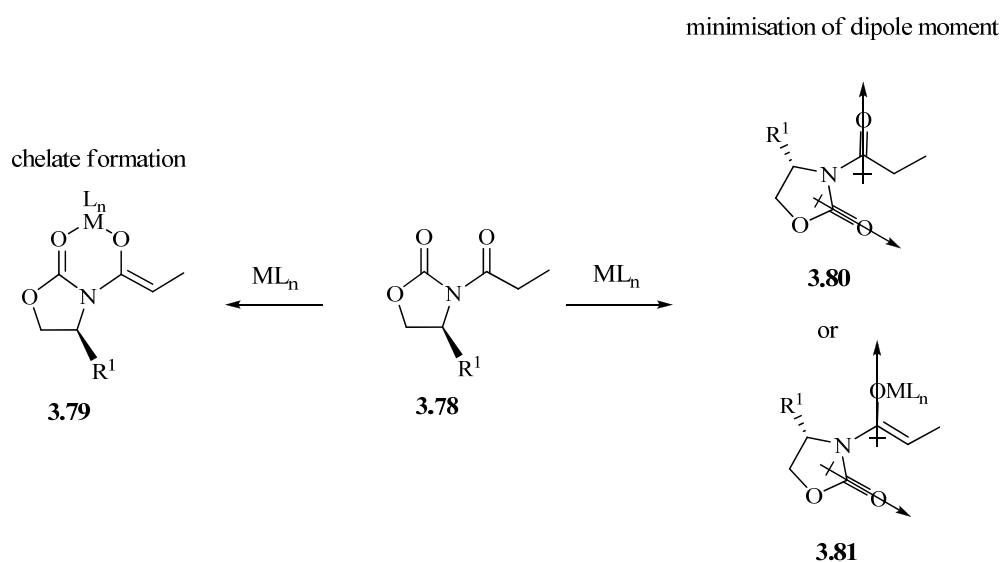


Figure 3.5 Selected succeeding variations of chiral *N*-acyloxazolidinone (**3.68**)

While oxazolidinones (**3.78**) are linked to the substrate via a single bond; additional factors like chelation (**3.79**)¹³³ or dipole-moment minimisation (**3.80**, **3.81**)^{120,134,135} often lead to preferred conformations in which the substituent R¹ of the oxazolidinone efficiently shields one of the molecule's diastereotopic faces (**Scheme 3.11**).¹²⁰

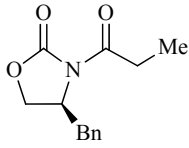
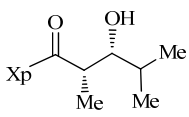


Scheme 3.11 Alternative modes of action of the oxazolidinone auxiliaries: chelation vs. dipole minimisation

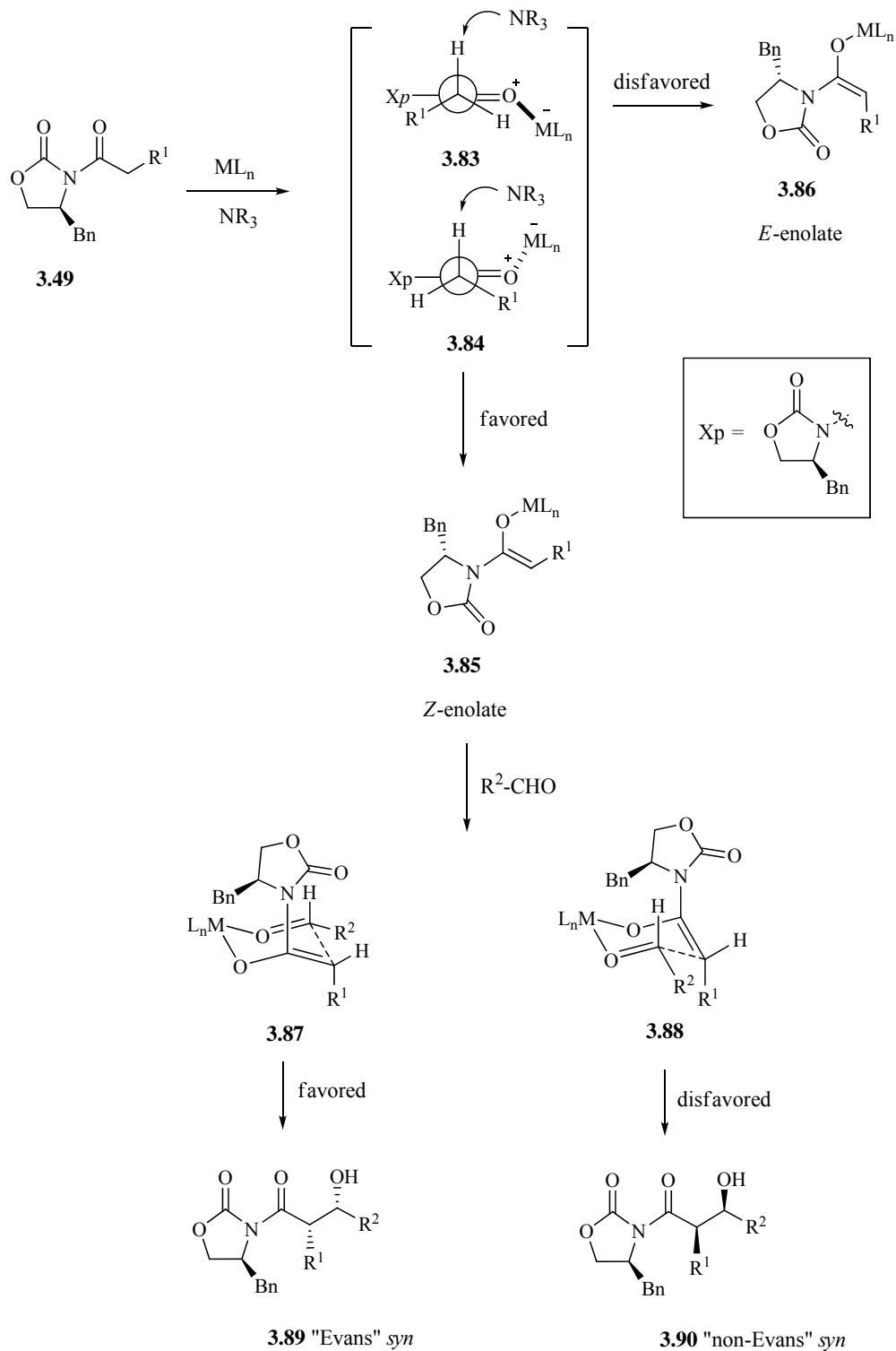
Evans and co-workers first developed the asymmetric aldol condensation using the chiral oxazolidinones *via* the boron, lithium or titanium enolates, resulting in highly enantioselective formation of the *syn* aldol product. For instance, the diastereoselective aldol reactions of chlorotitanium versus dialkylboron enolates with isobutyraldehyde are shown in **Table 3.1**, entry 1-3.^{134b} Evans and co-workers reported that in a kinetic enolisation process, *Z*- and *E*-enolates (**3.85**) and (**3.86**) are derived from deprotona-

tion of the *anti*- and *syn*-complexes (**3.84**) and (**3.83**), respectively (**Scheme 3.12**). The reactions showed the *Z*-enolate (**3.85**) with carbonyl functionalities in the preferred dipolar orientation with the benzene ring as the steric control element and the hindered bases' deprotonation of the *anti*-complexes (**3.84**) is preferred. In the case of *E*-enolate (**3.86**), additional transition state 1,3-allylic strain considerations between R¹ and the chiral oxazolidinone (*Xc*) may be involved. The chiral *Z*-enolate synthons (**3.85**) proceeded via a preferred chairlike transition state (**3.87**) involving cooperative metal ion ligation of both the enolate and carbonyl, which is called Zimmerman-Traxler model,¹³⁶ to give rise to the *syn* aldol product (**3.89**). For the non-Evans *syn* product (**3.90**), reaction via a chair-like transition state (**3.88**) is disfavored due to the sterically dominant considerations between the reacting aldehyde and the chiral oxazolidinone.

Table 3.1 Selected diastereoselective aldol reactions of chlorotitanium versus dialkylboron enolates with isobutyraldehyde

Entry	Substrate	Enolization	Major product	Yield ^a	Stereoselection
1		TiCl ₄ , <i>i</i> Pr ₂ NEt		87%	94:6 (HPLC)
2		TiCl ₄ , TMEDA		84%	98:2 (HPLC)
3	3.49	<i>n</i> Bu ₂ BOTf, Et ₃ N	3.82	83%	>99:1 (GLC)

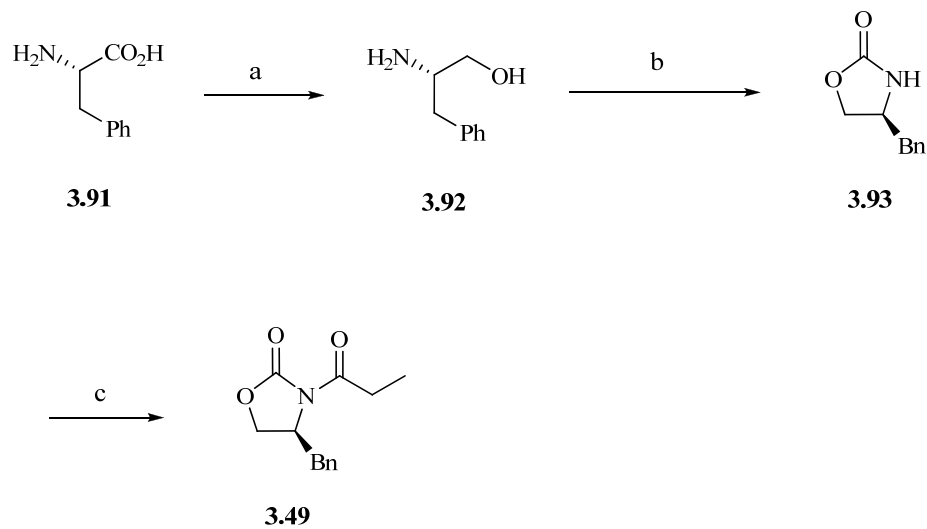
^aCombined isolated yield of all diastereomers. Xp = Evans'(*S*)-4-benzyloxazolidin-2-one.



Scheme 3.12

This method provides high levels of stereoselection and a predictable product. We have relied upon oxazolidinone (**3.49**) as a chiral auxiliary for absolute stereochemical control. Thus, the Evans *syn* aldol product (**3.47**) would be efficiently constructed via the asymmetric aldol reaction of chiral oxazolidinone (**3.49**) and the unsaturated aldehyde (**3.48**), which we already had in hand (**Scheme 3.14**).

The chiral oxazolidinone (**3.49**) was derived from (*S*)-phenylalanine (**3.91**) in 3 steps (**Scheme 3.13**).¹²² Treatment of (*S*)-phenylalanine (**3.91**) with sodium borohydride in the presence of boron trifluoride in anhydrous tetrahydrofuran at room temperature overnight gave the aminoalcohol (**3.92**) in 74% yield. Reaction of aminoalcohol (**3.92**) with potassium carbonate and diethyl carbonate, the mixture was carefully heated to 135 °C, and ethanol was allowed to distil out as it was formed. The (*4S*)-4-phenylmethyl-2-oxazolidinone (**3.93**) was obtained in 77% yield. *N*-Acylation of (*4S*)-4-phenylmethyl-2-oxazolidinone (**3.93**) with *n*-butyllithium followed by addition of propanoyl chloride in anhydrous tetrahydrofuran at -78 °C provided the chiral oxazolidinone (**3.49**) in 88% yield. All spectroscopic data of the chiral oxazolidinone (**3.49**) were consistent with those reported in the literature.^{122,134}

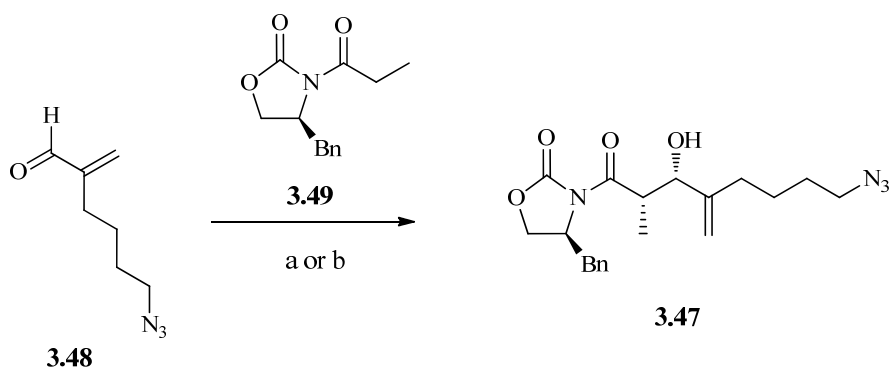


Scheme 3.13 Preparation of oxazolidinone (**3.49**)

Reagents and conditions: (a) NaBH_4 , $\text{BF}_3 \cdot \text{OEt}_2$, THF; 74%; (b) K_2CO_3 , diethyl carbonate, heat 135-140 °C; 77%; (c) $n\text{BuLi}$, THF; propanoyl chloride; 88%.

Because of the short *B-C* and *B-O* bonds of the *Z*-boron enolate, these enolates form tighter transition states generally leading to high selectivities for the formation of the *syn* aldol adduct.^{122,134} According to Mukaiyama's method,¹³⁷ Masamune and Evans used a dialkylboron trifluoromethanesulfonate (triflate) with a large steric requirement and the triflate as a good leaving group, to greatly influence the stereochemistry of the enol borinate formed, making it possible to produce preferentially the *Z*-enol borinate.^{134,138} Later Brown and co-workers also reported the use of 9-borabicyclo(3.3.1)nonane trifluoromethanesulfonate (9-BBN-OTf) and the hindered base ($i\text{Pr}_2\text{NEt}$) to achieve the conversion of representative ketones into pure (*Z*)-enol borinate.¹³⁹ Therefore, the first attempt at asymmetric aldol condensation, with the chi-

ral oxazolidinone (**3.49**) was carried out with 1.0 equivalents of 9-BBN-OTf and 1.2 equivalents of diisopropylethylamine in anhydrous dichloromethane at 0 °C for one hour followed by addition 1.2 equivalents of the unsaturated aldehyde (**3.48**) in anhydrous dichloromethane at -78 °C for two hours. The *syn* aldol adduct (**3.47**) was obtained in 64% yield as the major diastereomer with excellent *dr* (>99:1), combined with a 20% yield of recovered starting material (**3.48**). The diastereoselectivity was determined by ¹H NMR spectroscopy. Disappointingly, when the reactions were repeated several times under the same condition, the isolated yields of the major diastereomer after chromatographies were 39~47%. When the 9-BBN-OTf reagent was used for the first time, the yield was at a maximum. Subsequently, using the same bottle, we were unable to reproduce the yield of the *syn* aldol adduct (**3.49**). Therefore, for the enolisation of the chiral oxazolidinone (**3.49**) we changed to the titanium enolate. Thus, enolisation of chiral oxazolidinone (**3.49**) with 1.1 equivalents of titanium tetrachloride (TiCl₄) and 1.2 equivalents of diisopropylethylamine at 0 °C, followed by addition of 1.0 equivalents of the unsaturated aldehyde (**3.48**) at -78 °C produced the *syn* aldol adduct (**3.47**) as the major diastereomer in 75% yield with good *dr* (84:16). The isolated yields of the major diastereomer after chromatography were 70~75%. The titanium enolisation aldol reaction is considerably less selective than boron-enolisation. Nevertheless, the isolated yields of Evans *syn* adduct (**3.47**) is higher than boron enolisation. This method is operationally simple, no oxidative work-up is required, the reagents can be used as purchased, the method highly reproducible and repeatable and the cost is lower than aldol additions with 9-BBN-OTf. For these reasons, Crimmins and co-workers developed their method using TiCl₄ as a Lewis acid to produce the non-Evans *syn* aldol product.¹⁴⁰

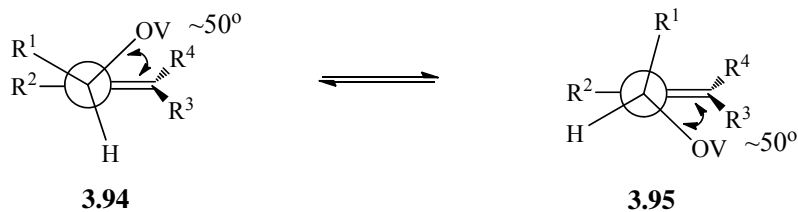
**Scheme 3.14**

Reagents and conditions: (a) 9-BBN-OTf, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; 2 h; 64%; $dr > 99:1$; (b) TiCl_4 , $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 2 h; 75%; dr 84:16.

Using the asymmetric Evans aldol condensation, the hydroxyl and methyl groups were assigned as the *syn*-aldol. This reaction created two stereogenic centers of tuberospirospirone (**3.1**) as proposed. The most important part in this molecule is the α -methyl- γ -butyrolactone moiety. The remaining allylic alcohol (**3.47**) could then be subjected to a hydroxyl-directed stereoselective epoxidation reaction, followed by ring-opening by intramolecular nucleophilic attack of the exocyclic carbonyl of the carboxylic acid after removal of the chiral auxiliary oxazolidinone through hydrolysis.¹⁴¹ The epoxidation of the 1,1-disubstituted alkene functionalities of secondary allylic alcohols can be influenced through hydrogen bonding or metal-alcoholate binding. For the stoichiometric oxidants MCPBA, dimethyldioxirane (DMD), and some molybdenum or tungsten peroxo complexes, hydrogen bonding has been documented,^{142,143} while metal-alcoholate binding has been proposed in the catalytic systems $\text{Ti}(\text{O}-i\text{-Pr})_4/t\text{-BuOOH}$,

$\text{VO}(\text{acac})_2/t\text{-BuOOH}$, $\text{Mo}(\text{CO})_6/t\text{-BuOOH}$, and $\text{H}_2\text{WO}_4/\text{H}_2\text{O}_2$.^{144,145} The stereodifferentiation by the hydroxyl-group directivity of chiral allylic alcohols depends on the type of bonding between the substrate and the oxidising species, which is expressed in the dihedral angles (O-C-C=C) of allylic alcohols and by conformation control from 1,2- and 1,3-allylic strain (R^1 , R^2 , R^3 and $\text{R}^4 = \text{alkyl}$) (**Scheme 3.15**).¹⁴⁶ The equilibrium between 1,2- and 1,3-allylic strain in the corresponding transition states for the epoxidation is expressed in terms of *threo* or/and *erythro* selectivities. On the basis of the diastereoselectivity data reported by Mihelich,^{144a} the dihedral angles (α) of these oxidation systems have been reported to lie in arrange from acute as 50° for $\text{VO}(\text{acac})_2$, to 120° for MCPBA.¹⁴⁴ These two structural types show the largest changes in the stereoselectivities. In the case of vanadium alcoholates, the *erythro* product is obtained with high stereoselectivity, which emphasises the dominance of 1,3-allylic strain, while the *threo* product may involve structure (**3.94**), the transition state with 1,2-allylic strain considerations between R^1 and R^2 . The transition state geometries for the oxygen transfer by MCPBA are very close to each other (structure (**3.96**) and (**3.97**), **Scheme 3.15**). The diastereoselective control is essentially lost using the peracid in acyclic systems. The 1,2- and 1,3-allylic strain does not manifest itself for both the transition state (**3.96**) and (**3.97**). Thus, the *threo* or/and *erythro* products are obtained.

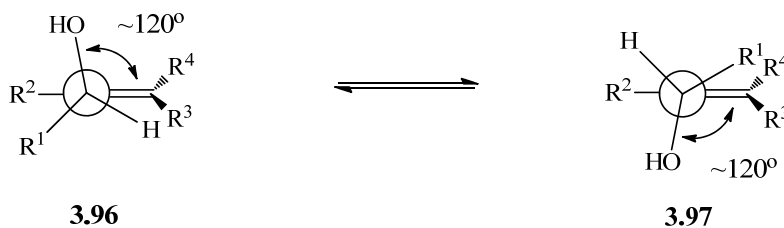
Predicted O-C-C=C dihedral angles: for V^{+5} , TBHP epoxidation



1,2-allylic strain, leads to *threo* product

1,3-allylic strain, leads to *erythro* product

Predicted O-C-C=C dihedral angles: for peroxy acid (MCPBA) epoxidations



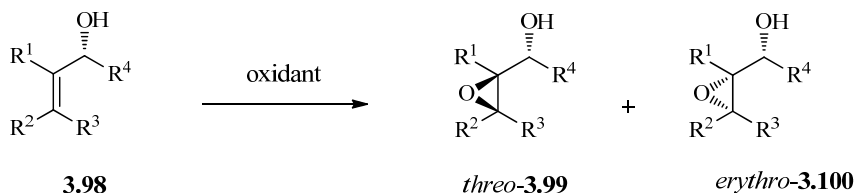
1,2-allylic strain, leads to *threo* product

1,3-allylic strain, leads to *erythro* product

Scheme 3.15 1,2- and 1,3-allylic strain (A) in the vanadium (V) catalyzed epoxidation and peroxy acid (MCPBA) epoxidation

Adam and co-workers studied the full details of the regio- and diastereoselective catalytic epoxidation of acyclic allylic alcohol (**3.98**), using a procedure reported by Sharpless *et al.*¹⁴⁴ They found out that a facile and stereoselective epoxidation of acyclic allylic alcohol (**3.98**) using $VO(acac)_2$ and *tert*-butyl hydroperoxide (TBHP) have proceeded with high levels of *erythro* diastereoselectivity (**Table 3.2**, entry 1-4).^{146g,147}

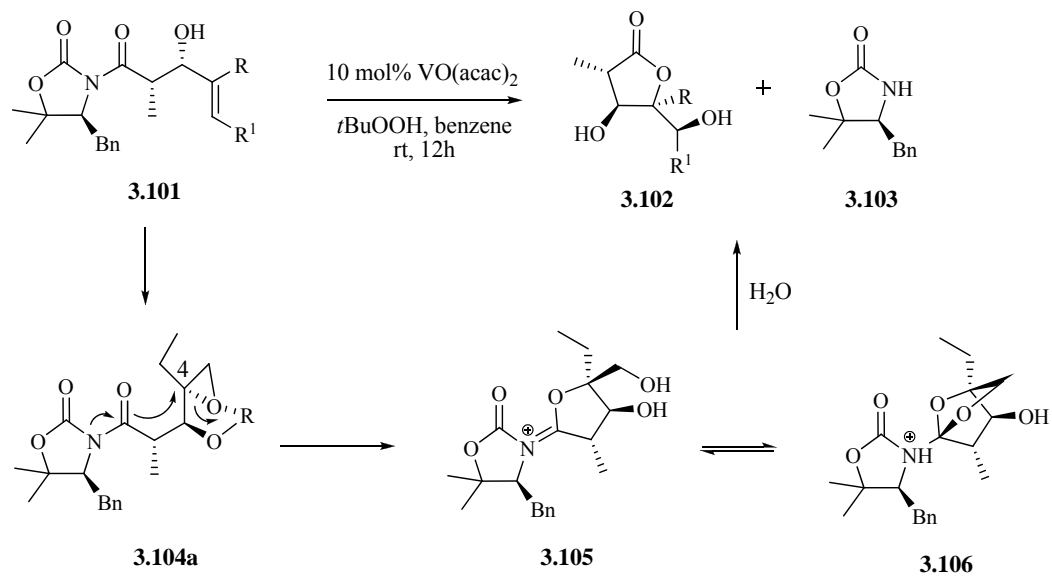
Table 3.2 Selected diastereomeric ratios (*dr*) for the epoxidation of the chiral allylic alcohols (**3.98**) with Ti(O-*i*-Pr)₄/TBHP, VO(acac)₂/TBHP, (MCPBA)



		diastereomeric ratios (<i>threo:erythro</i>) ^b		
		Catalyst: Ti(O- <i>i</i> -Pr) ₄ ^a	VO(acac) ₂	MCPBA
		Donor: TBHP	THBP	CH ₂ Cl ₂
		Solvent: CDCl ₃	C ₆ H ₆	CH ₂ Cl ₂
entry	substrate			
1		71:29	20:80	60:40
2		22:78	05:95	45:55
3		05:95	05:95	10:90
4		05:95	05:95	56:44

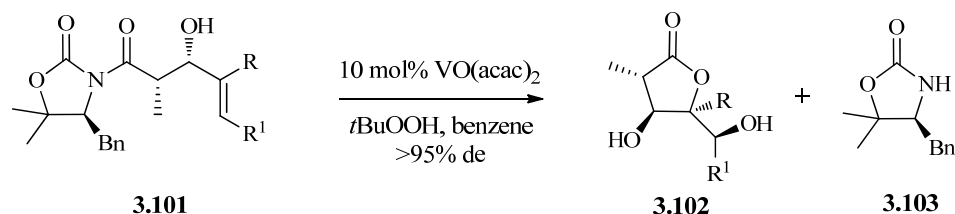
^a0.05 equiv of Ti(O-*i*-Pr)₄ was used in the presence of molecular sieves (4 Å) in CDCl₃; conversion was always complete. ^bDiastereomeric ratios (*dr*), determined by ¹H NMR analysis of the characteristic signals of the epoxides in the crude reaction mixture, error ±5% of the stated values.

According to the method developed by Adam *et al.*, Bull and co-workers reported an efficient asymmetric synthesis of chiral hydroxyl- γ -butyrolactones which derived from hydroxyl-directed epoxidation of β -hydroxy- β -vinyl-N-acyloxazolidin-2-ones (**Table 3.3**, entry 1-4). Epoxidation of the 1,1-disubstituted alkene functionalities of secondary allylic alcohols (**3.101a-d**) using VO(acac)₂ and *tert*-butylhydroperoxide has been shown to proceed with high levels of *erythro*-epoxide (**3.104a-d**) being formed, which could not be isolated but instead 1:1 mixture of 5,5-dimethyloxazolidin-2-one (**3.103**) and lactone (**3.102a-d**) was observed.¹⁴⁸ The reaction mechanism is outlined in **Scheme 3.16**. The hydroxyl-directed epoxidation of (**3.101a**) is predicted to afford an *erythro*-epoxide (**3.104a**). This unstable epoxide is then ring-opened by intramolecular nucleophilic attack of the exocyclic carbonyl of its *N*-acyl fragment with inversion of configuration at C-4 to afford an unstable iminium species (**3.105**) (that may be stabilized via reversible formation of *N,O,O*-orthoester (**3.106**) which is hydrolysed in workup.¹⁴⁸



Scheme 3.16 Stereoselective epoxidation of β -vinyl-*syn*-aldol (**3.101**) affords lactone (S,S,S)-(**3.102**)

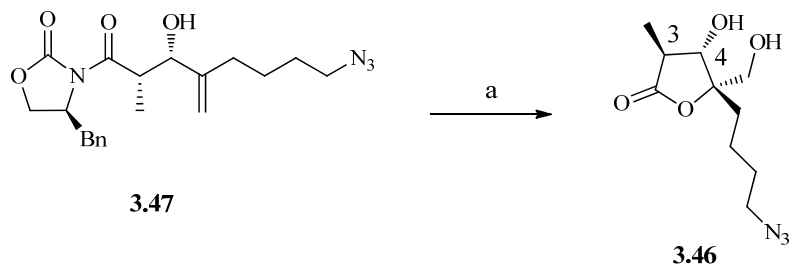
Table 3.3 Selected epoxidation of aldol (**3.101a-d**) using VO(acac)₂ and *tert*-butylhydroperoxide to afford hydro- γ -butyrolactones (**3.102a-d**)



entry	Substrate	Epoxides (not isolated)	Lactones	de (%) ^a	Yield (%) ^b
1	<p>3.101a</p>	<p>3.104a</p>	<p>3.102a</p>	>95	78
2	<p>3.101b</p>	<p>3.104b</p>	<p>3.102b</p>	>95	76
3	<p>3.101c</p>	<p>3.104c</p>	<p>3.102c</p>	>95	83
4	<p>3.101d</p>	<p>3.104d</p>	<p>3.102d</p>	>95	74

^a all *de*'s determined by ¹H NMR spectroscopic analysis of crude reaction products. ^b Yields of lactones (**3.102a-d**) calculated from aldols (**3.101a-d**). Xp = Evan's (*S*)-4-benzyloxazolidin-2-one.

We applied the hydroxyl-directed stereoselective epoxidation to our synthetic route using the procedure developed by Sharpless *et al.*. Treatment of aldol (**3.47**) with 10 mol % of VO(acac)₂ in anhydrous toluene for five minutes and subsequent reaction of the vanadyl-alcoholate intermediate with *tert*-butylhydroperoxide (*t*BuOOH) (70% in water) at room temperature for 24 hours provided the α -methyl- γ -butyrolactone (**3.46**) as a single stereoisomer in 66% isolated yield as confirmed by ¹H NMR analysis (**Scheme 3.17**). Due to the toxicity of benzene, we utilized toluene as solvent instead. The ¹H NMR spectrum of lactone (**3.46**) showed a broad singlet of 2 protons of the hydroxyl groups at 3.64 ppm, a doublet with coupling constant of 12.3 Hz of H-4 at 3.93 ppm, a doublet of doublet with geminal coupling constant of 11.8 Hz of the methylene protons (CH₂OH) at 3.82 ppm; a quintet with coupling constant of 6.9 Hz of H-3 at 2.88 ppm; a doublet with coupling constant of 7.3 Hz of the methyl group at 1.30 ppm.



Scheme 3.17

Reagents and conditions: (a) 10 mol% VO(acac)₂, *t*BuOOH, toluene, rt, 24 hr; 66%.

The NOESY spectrum of α -methyl- γ -butyrolactone (**3.46**) is shown in **Figure 3.6**. The relative configuration of the α -methyl- γ -butyrolactone (**3.46**) was confirmed by the NOESY cross peaks between H-4 and CH₃ and H-4 and H-1'.

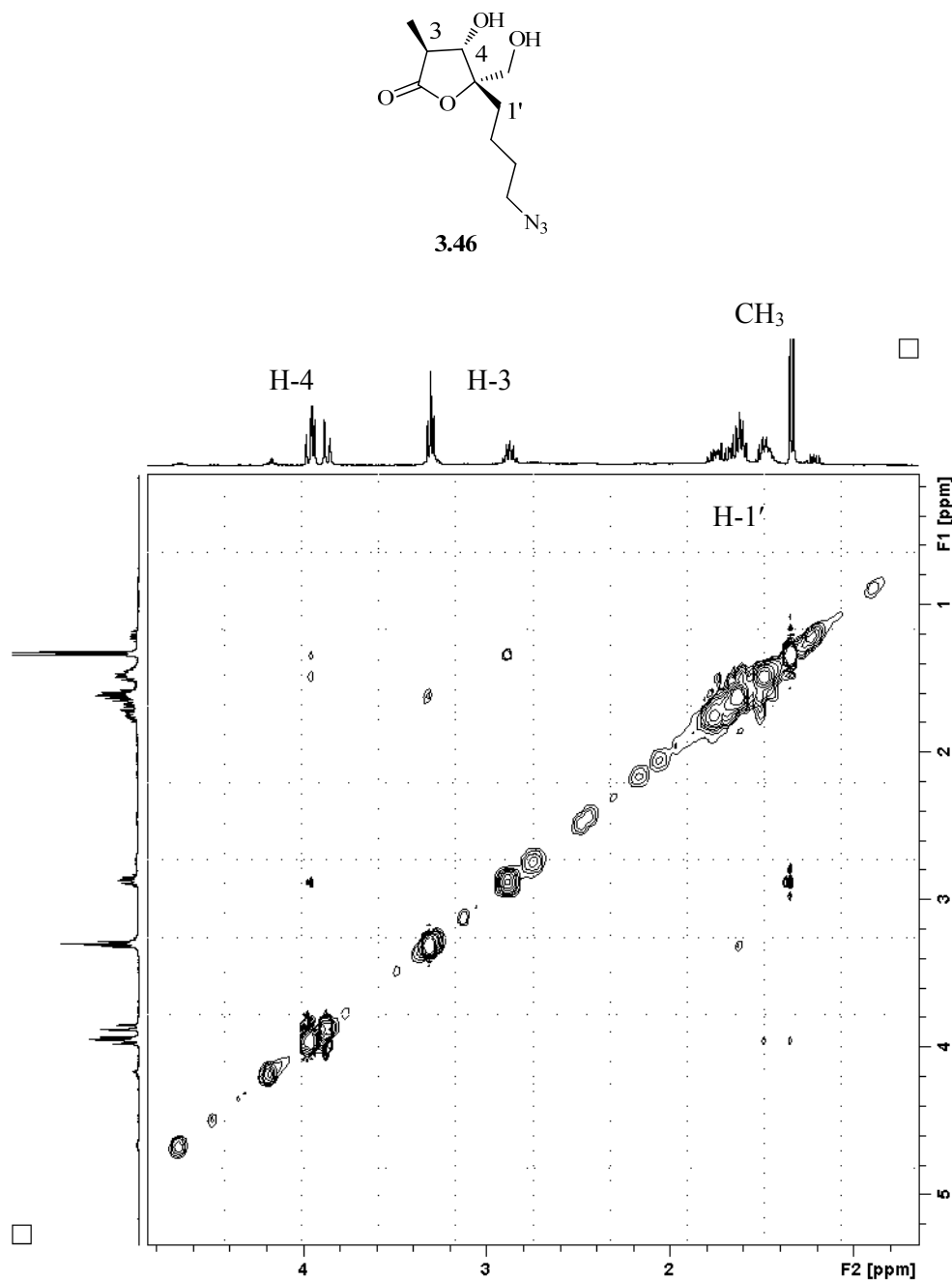
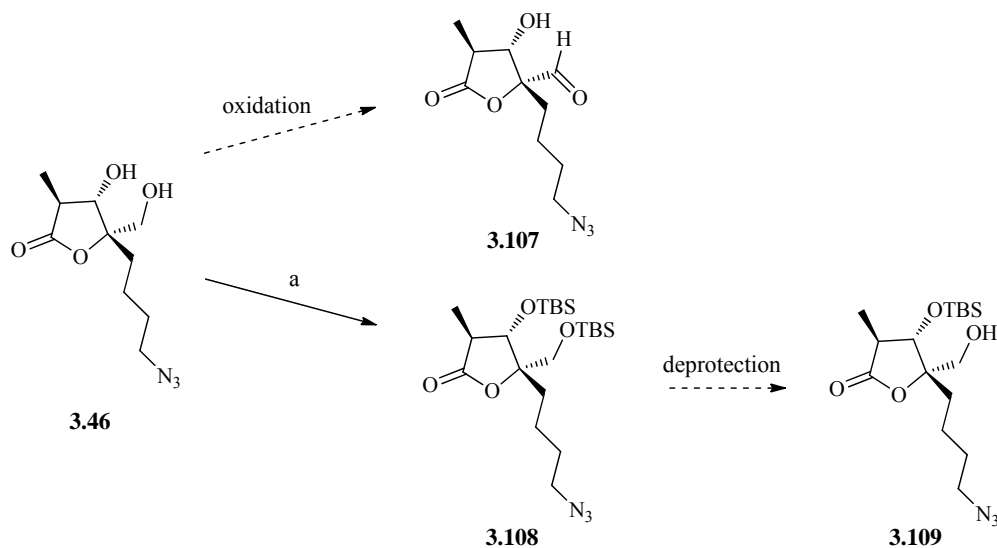


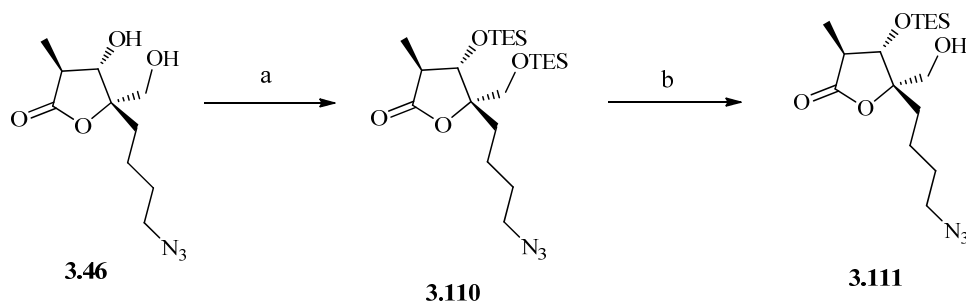
Figure 3.6 NOESY spectrum of α -methyl- γ -butyrolactone moiety of compound (**3.46**)

The reaction established the quaternary stereocentre of the α -methyl- γ -butyrolactone (**3.46**). The α -methyl- γ -butyrolactone moiety of compound (**3.46**) contained a primary alcohol which would be converted into an aldehyde by treatment with oxidising agents, and then reduction of the azide moiety to an amine could facilitate the cyclisation to provide a cyclic imine as proposed. Unfortunately, during first attempts to oxidise lactone (**3.46**) with IBX, the reaction failed to give the desired product aldehyde (**3.107**), rather decomposition occurred due to the γ -hydroxybutyrolactone being quite reactive and readily converted into its linear counterparts.¹⁴⁹ It was necessary to protect the secondary alcohol of γ -butyrolactone (**3.46**) before subjecting it to oxidation. Protection of γ -butyrolactone (**3.46**) as the bis-TBS ether (**3.108**), followed by selective removal of the primary TBS group was attempted,^{150a} but the reaction failed to provide the mono TBS product (**3.109**) (Scheme 3.18).

**Scheme 3.18**

Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 0 °C to rt, 24 h; quant.

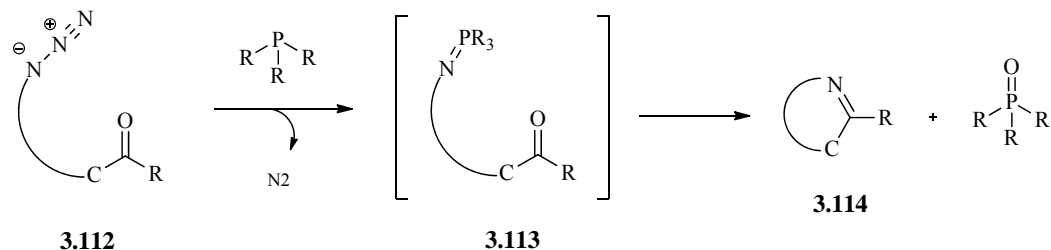
However, treatment of γ -butyrolactone (**3.46**) with triethylsilyl chloride and triethylamine in the presence of 4-dimethylaminopyridine in dichloromethane at room temperature formed the corresponding bis-TES-protected γ -butyrolactone (**3.110**) which was subjected to selective cleavage of the primary TES group with pyridinium *p*-toluenesulfonate¹⁵⁰ in methanol at room temperature for two hours to give mono-TES-protected γ -butyrolactone (**3.111**) in 88% yield (**Scheme 3.19**).



Scheme 3.19

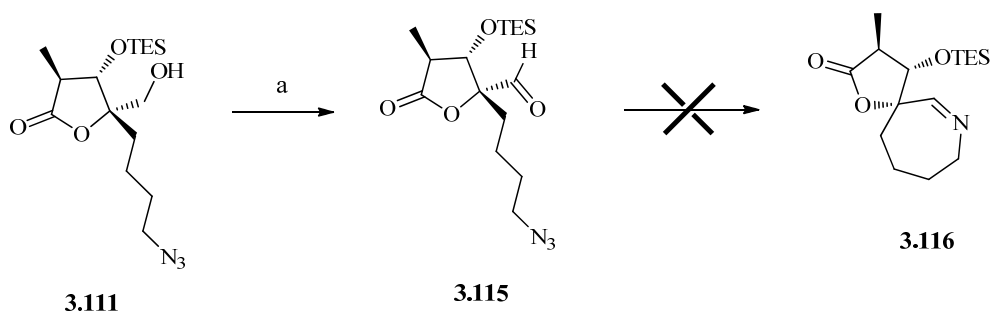
Reagents and conditions: (a) TESCl, Et₃N, DMAP, CH₂Cl₂, 0 °C to rt; 73%; (b) PPTS, MeOH, rt, 2 h; 88%.

The Aza-Wittig reaction refers to the synthesis of an imine (**3.114**) from an iminophosphorane (**3.113**) and an aldehyde or ketone.¹⁵¹ The iminophosphorane intermediate (**3.113**) is derived from the reaction of the azide (**3.112**) with a phosphine or phosphite, and is known as the Staudinger reaction (**Scheme 3.20**).¹⁵²



Scheme 3.20

It was anticipated that the intramolecular aza-Wittig reaction would be useful in our synthetic route due to the neutral reaction conditions, coupled with the simplicity of direct condensation with the aldehyde group. Exposure of primary alcohol γ -butyrolactone (**3.111**) to Dess-Martin periodinane in anhydrous dichloromethane in the presence of sodium bicarbonate at room temperature for one hour provided aldehyde γ -butyrolactone (**3.115**) in 91% yield (Scheme 3.21). After completion of the oxidation reaction, the trace amount of acetic acid present was typically neutralised by the addition of sodium bicarbonate. The TES protecting group is sensitive to acid and easily cleaved under acidic conditions. The mono-TES-protected γ -butyrolactone (**3.115**) would be deprotected to give γ -hydroxy-butylolactone which would decompose rapidly in the presence of acid. The aldehyde (**3.115**) was subjected to an intramolecular aza-Wittig reaction in the presence of one equivalent of tributylphosphine in anhydrous toluene under nitrogen. Unfortunately, the ^1H NMR spectrum of the crude product displayed an absence of the characteristic γ -butyrolactone moiety of spiroimine (**3.116**). We were unable to identify the spiroimine (**3.116**), and assumed that decomposition had occurred.



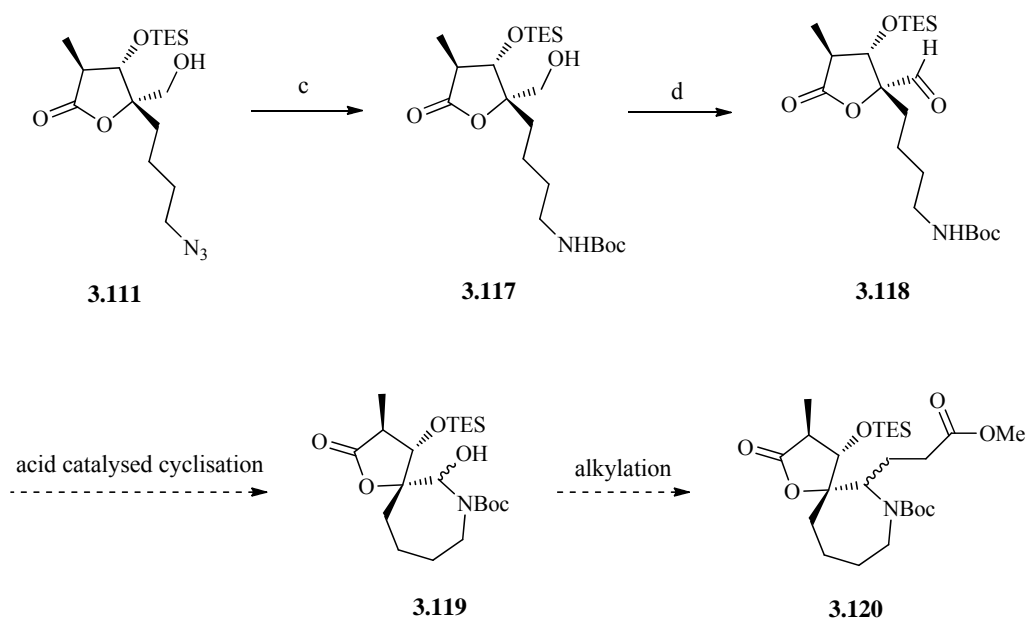
Scheme 3.21

Reagents and conditions: (a) DMP, NaHCO₃, CH₂Cl₂, rt, 1 h, 91%.

At this stage, we had planned to reduce the azido-group to an amine and protect it with a Boc group which is easier to handle in the cyclisation or alkylation steps. Saito and co-workers reported a convenient one-pot method for the conversion of an azido-group into a *N*-Boc amino group.¹⁵³ With this method, azide reduction via catalytic hydrogenation and *in situ* *N*-protection in the presence of an acylation agent, such as *tert*-butylpyrocarbonate is often used. We successfully applied this method to mono-TES-protected γ -butyrolactone (**3.111**). Treatment of mono-TES-protected γ -butyrolactone (**3.111**) with 10% Pd/C and *tert*-butylpyrocarbonate in ethyl acetate under hydrogen at room temperature for 24 hours provided *N*-Boc- γ -butyrolactone (**3.117**) in 82% yield. In the ¹H NMR spectrum of *N*-Boc- γ -butyrolactone (**3.117**), the amine (NH) group gives rise to a broad singlet at 4.54 ppm and *tert*-butyl group appears as a singlet at 1.43 ppm. The IR analysis of *N*-Boc- γ -butyrolactone (**3.117**) showed the absence of the azide group.

With the mono-*TES*-protected γ -butyrolactone (**3.117**) in hand, oxidation was then carried out using the Dess-Martin periodinane as the oxidising agent.¹¹⁴ Treatment of mono-*TES*-protected γ -butyrolactone (**3.117**) with Dess-Martin periodinane in anhydrous dichloromethane in the presence of sodium bicarbonate at room temperature for one hour furnished aldehyde (**3.118**) in 95% yield (**Scheme 3.22**). The formation of the aldehyde (**3.118**) was confirmed by ¹H NMR spectroscopy, which displayed the characteristic aldehyde peak at 9.61 ppm.

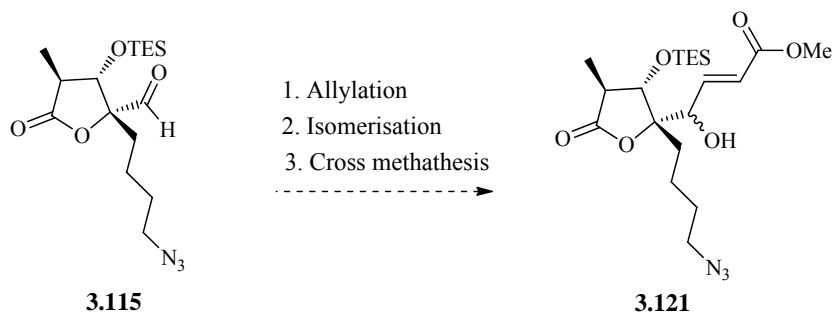
As a cyclic *N,O*-acetal (**3.119**) could be formed via acid catalysed cyclisation of the amine and aldehyde, subsequent alkylation of this cyclic *N,O*-acetal with silyl enol ether derivatives under Lewis acidic conditions should give compound (**3.120**).¹⁵⁴ However, overly acidic conditions may cause deprotection of *TES* group and give rise to decomposition. We therefore turned our attention to construct the 7-membered ring using the tandem Staudinger/intramolecular aza-Wittig reaction.¹⁵⁵



Scheme 3.22

Reagents and conditions: (c) H₂, Pd-C, Boc₂O, EtOAc, rt, 24 h; 82%; (d) DMP, NaHCO₃, CH₂Cl₂, rt, 1 h, 95%.

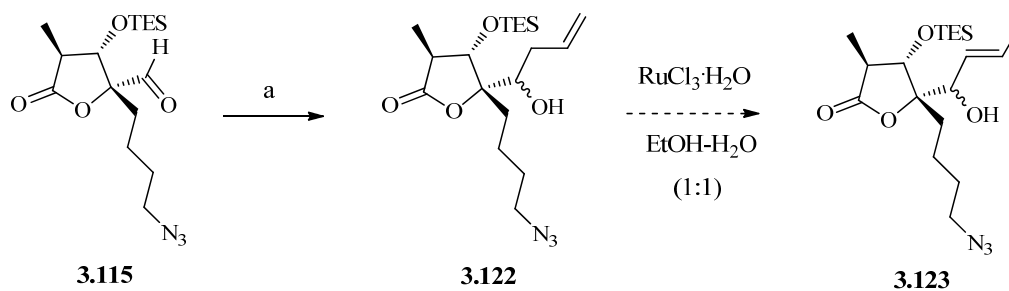
We were therefore unable to incorporate efficiently the azabicyclic framework at this stage. Nevertheless, we hoped that we could postpone the construction of azabicyclic core and turned our attention to C-C bond formation to build the side-chain for lactamisation; to achieve formation of the target natural product tuberostemospironine (**3.1**). We devised the first stage for C-C bond formation by allylation, follow by isomerisation a double bond and cross methathesis with methylacrylate to give the ester (**3.121**) as shown in **Scheme 3.23**.



Scheme 3.23

With the aldehyde (**3.115**) in hand, we considered a Barbier reaction as applicable for C-C bond formation due to the mild conditions and selectivity for the aldehyde over the lactone carbonyl.¹⁵⁶ The one-pot Barbier reaction, can be performed very effectively in aqueous media. The allylation of aldehydes or ketones under the Barbier conditions, has gained widespread interest, especially for coupling of the more reactive allyl halides.¹⁵⁷ Likewise, a number of metals are known to participate in the coupling reaction in aqueous media including zinc, indium, tin, manganese, antimony, bismuth, and magnesium.^{158,159} Zinc and indium are the mostly used metals under Barbier conditions.¹⁶⁰ Therefore, we decided to perform the Barbier allylation in the presence of indium. Thus, the allyl moiety was introduced *via* treatment of aldehyde (**3.115**) with allyl bromide in the presence of indium to give a mixture of epimers of the allyl alcohol γ -butyrolactone (**3.122**) in a 1.7:1 ratio and 80% yield (**Scheme 3.24**). We could not determine the stereochemistry of the major isomer. We moved on to the isomerisation reaction. Treatment of allyl alcohol γ -butyrolactone (**3.122**) with $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ in ethanol-water (1:1) at room temperature; unfortunately failed to give the isomerised product (**3.123**), rather a decomposed complex mixture was formed. This is probably

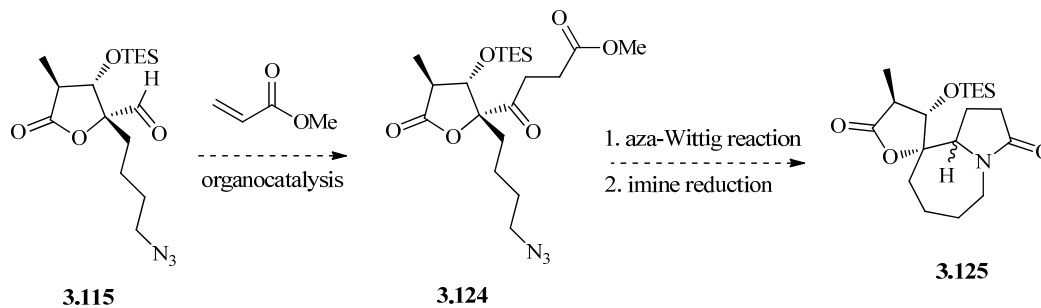
due to the presence of azide group in the γ -butyrolactone (**3.122**) interfering with this reaction or loss of the TES protecting group due to a trace of acid. Thus, we discontinued this plan.



Scheme 3.24

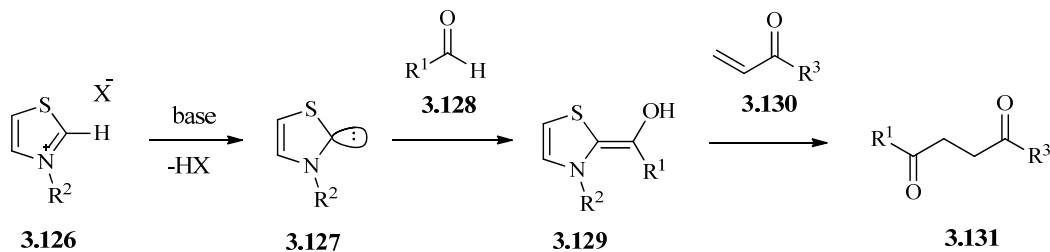
Reagents and conditions: (a) allyl bromide, In, THF-H₂O (1:1), rt, 18 h; 80% (1:1.7 dr)

The Stetter reaction is a superior method for construction of the α -ketoester in which the carbonyl function would later serve as a functional handle to direct the formation of an imine in the aza-Wittig reaction. The remaining ester function could then cyclise with imine after *in situ* reduction to give the lactam moiety (**Scheme 3.25**).



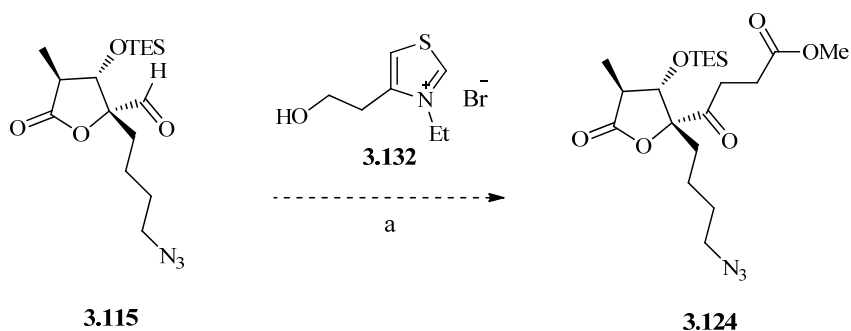
Scheme 3.25

The Stetter reaction is the 1,4-addition (conjugate addition) of an aldehyde to an α,β -unsaturated compound, catalysed by cyanide or a thiazolium salt.¹⁶¹ Following this procedure, aldehydes (**3.128**) can be turned into acylanion equivalents (**3.129**) through covalent activation with suitable thiazolium salts (**3.126**) which serve as precursors for nucleophilic carbenes (**3.127**) when treated with base (Scheme 3.26). The 1,4-addition of acylanion equivalent (**3.129**) to Michael acceptor (**3.130**) forms 1,4-dicarbonyl compound (**3.131**).



Scheme 3.26 General and reactions of acylanion equivalents

With the aldehyde (**3.115**) in hand, treatment of thiazolium salt (**3.132**) with triethylamine in anhydrous ethanol and subsequent reaction of the carbene intermediate with the aldehyde (**3.115**) gave an acylanion equivalent which was reacted with methyl acrylate (**Scheme 3.27**). Unfortunately, the reaction failed to give the desired product ketoester (**3.124**); instead an unknown product was obtained.¹⁶² Curiously, we suspected that the azide group might interfere with this reaction. The IR analysis of an unknown product showed the absence of the azide functional group $\sim 2100\text{ cm}^{-1}$, which confirmed our indication. However, we did not identify the unknown product.



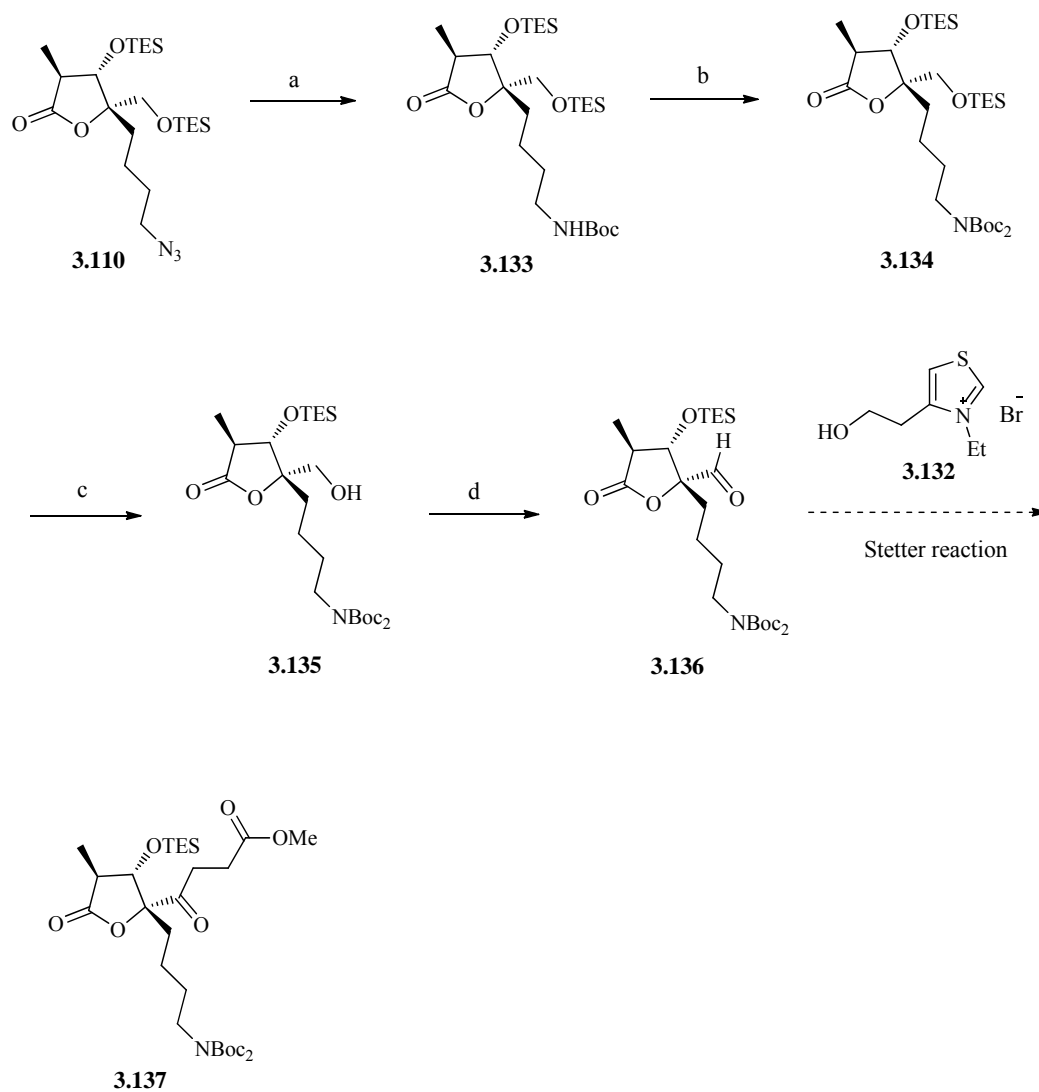
Scheme 3.27

Reagents and conditions: (a) cat. (**3.132**), Et₃N, methyl acrylate, EtOH, 60 °C, 8 h.

At this juncture, it was clear that the azide group was problematic to our synthetic route. It was necessary to reduce the azide functional group to the amine and protect with two Boc groups. We had hoped that the di-Boc-protected amine would possibly eliminate the problem. The preparation of di-Boc- γ -butyrolactone (**3.136**) is shown in

Scheme 3.28. Treatment of bis-TES-protected γ -butyrolactone (**3.110**) with 10% Pd/C and *tert*-butylpyrocarbonate in ethyl acetate under a hydrogen atmosphere at room temperature for 24 hours provided *N*-Boc- γ -butyrolactone (**3.133**) which was immediately reacted with *tert*-butylpyrocarbonate in anhydrous acetonitrile in presence of 4-dimethylaminopyridine at room temperature for 24 hours to give di-Boc- γ -butyrolactone (**3.134**) in 71% yield over two steps.¹⁶⁴ Selective cleavage of bis-TES-protected γ -butyrolactone (**3.134**) with pyridinium *p*-toluenesulfonate in methanol at room temperature for two hours provided mono-TES-protected γ -butyrolactone (**3.135**) in 93% yield. After selective removal of the silyl protecting group, subjecting the mono-TES-protected γ -butyrolactone (**3.135**) to the Dess-Martin periodinane in anhydrous dichloromethane in the presence of sodium bicarbonate at room temperature for one hour afforded aldehyde γ -butyrolactone (**3.136**) in 71% yield.

The aldehyde (**3.136**) was then ready for the Stetter reaction; however, a limited period of time, we were unable to try this reaction.

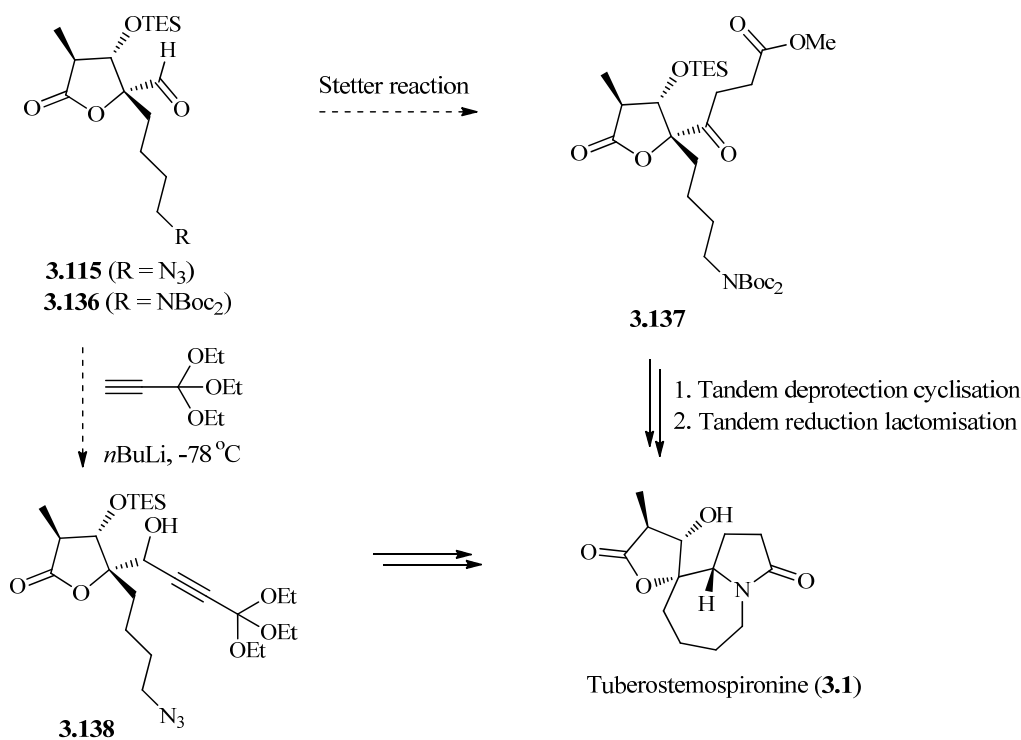


Scheme 3.28

Reagents and conditions: (a) H_2 , Pd-C, Boc_2O , EtOAc, rt, 24 h; (b) Boc_2O , CH_3CN , DMAP, rt, 24 h; 71% (2 steps); (c) PPTS, MeOH, rt, 2 h; 93%; (d) DMP, NaHCO_3 , CH_2Cl_2 , rt, 1 h, 71%.

3.3 Future work

Inopportunately, despite being only few synthetic steps away from our target natural product, due to time constraints, we were unable to complete the total synthesis of tuberostemospironine (**3.1**). The completion of the synthesis of tuberostemospironine (**3.1**) will require a C-C bond formation of an aldehyde (**3.136**) by a Stetter reaction to provide diketoester γ -butyrolactone (**3.137**) or an aldehyde (**3.115**) by alkylation to provide alkylated γ -butyrolactone (**3.138**). Subsequently, a tandem deprotection cyclisation should provide a spiro γ -butyrolactone and finally incorporation of the lactam moiety to form tricyclic framework by a tandem reduction lactamisation should afford the final target natural product tuberostemospironine (**3.1**) (**Scheme 3.29**).



S

cheme 3.29

3.4 Conclusion

In summary, the synthetic route described in this chapter describe our studies towards the total synthesis of tuberostemospironine (**3.1**). We have achieved a highly stereoselective synthesis of the α -methyl- γ -butyrolactone ring which is a major part of tuberostemospironine (**3.1**) since three stereogenic centres are contained in this moiety. Using an asymmetric aldol condensation to construct the *syn* aldol adduct and taking advantage of a hydroxy group for directed stereoselective epoxidation, the α -methyl- γ -butyrolactone ring was obtained in modest yield with excellent diastereoselectivity. Unfortunately, we were unable to accomplish the complete synthesis of the natural product tuberostemospironine (**3.1**). However, we are in progress to incorporate the last stereogenic centre in the azabicyclic ring. We hope to complete the molecule's synthesis in the near future.

CHAPTER 4

EXPERIMENTAL SECTION

4.1 General Methods

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran and ether were distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use, under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received.

Analytical TLC was carried out on precoated plates (silica gel 60, F254). Column chromatography was performed with silica gel 60 (230-400 mesh).

^1H NMR spectra were recorded in CDCl_3 solutions using JEOL ECA 400 and Bruker Advance DPX at 300, 400, 500 MHz spectrometers. ^{13}C NMR spectra were recorded in CDCl_3 solutions on the same instruments at 75, 100, 125 MHz. Chemical shifts are recorded in ppm using CDCl_3 as an internal standard (δ 7.26 ppm ^1H , δ 77.00 ppm ^{13}C). Coupling constants J are recorded in Hz. Multiplicities are recorded as singlet (s), broad singlet (brs), doublet (d), broad double (brd), triplet (t), quartet (q), multiplet (m).

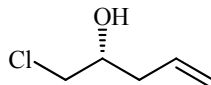
Mass spectra were recorded on a Finnigan LCQ DECA XP MAX Ultra instrument or Finnigan Polaris Q, GCMS XP mass spectrometer. High-resolution mass spectra were recorded on a Waters Q-ToF Premier instrument or Finnigan MAT95XP instrument.

Infrared spectra were recorded on a Shimadzu IR Prestige-21 FT-IR or a Bruker Alpha-E FT-IR.

Melting points were determined on an OptiMelt MPA 100 and are uncorrected. Optical rotations were recorded on a Jasco P-1030 polarimeter and are given with units of 10^{-1} deg cm²g⁻¹. The angles of rotations were measured at wavelength of 589 nm.

4.2 Experimental Section for Chapter 1

Synthesis of (*R*)-1-chloropent-4-en-2-ol (**1.25**)¹⁶⁵



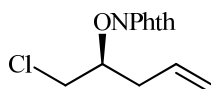
Vinyl magnesium bromide was prepared from 1.0 M vinylbromide (64 mL, 64.0 mmol) in THF and magnesium (2.48 g, 0.1 mol) in 100 mL anhydrous THF under N₂. After the addition, the reaction mixture was stirred at 50-60 °C for 1 hour to complete the formation of vinyl magnesium bromide. (*R*)-Epichlorohydrin, (2 mL, 25.5 mmol) was added to a suspension of CuI (0.5 g, 2.55 mmol) in anhydrous diethyl ether (100 mL) and the mixture cooled to -68 °C. The solution of Vinylmagnesium bromide (164 mL, 63.8 mmol) was added dropwise and stirred at -68 °C for 1 hour. Upon completion the reaction was quenched with saturated aq. NH₄Cl (50 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether and the combined organic extracts was washed with brine, dried with anhydrous MgSO₄ and the solvent was removed *in vacuo* to afford the title compound (**1.25**)¹⁶⁵ as a colourless oil (4.9 g, 95%).

¹H NMR (400MHz, CDCl₃) δ 5.76 (1H, ddt, *J* = 17.1, 7.2, Hz, CH₂CH=CH₂), 5.14 (2H, dd, *J* = 7.2, 1.3 Hz, CH₂CH=CH₂), 3.86 (1H, m, CHOH), 3.60 (1H, dd, *J* = 11.0, 3.7 Hz, CHH), 3.49 (1H, dd, *J* = 6.4, 3.7 Hz, CHH), 2.39 (1H, d, *J* = 4.6 Hz, CHH), 2.39 (1H, d, *J* = 4.6 Hz, CHH), 2.33 (2H, m, CH₂)

^{13}C NMR (100 MHz, CDCl_3) δ 133.2 (CH), 118.6 (CH_2), 70.5 (CH), 49.3 (CH_2), 38.6 (CH_2)

MS (ESI) m/z 121 [$\text{M} (^{35}\text{Cl})+\text{H}$] $^+$

Synthesis of (S)-(1-chloromethyl-but-3-enyloxy)-isoindole-1,3-dione (1.26)



Compound (**1.25**) (2.0 g, 16.50 mmol), *N*-hydroxyphthalimide (3.25 g, 19.90 mmol) and triphenylphosphine (6.53 g, 24.70 mmol) were dissolved in anhydrous THF (50 mL) and cooled to -20 °C. To this solution was added diisopropyl azodicarboxylate (5.8 mL, 29.70 mmol) as a solution in anhydrous THF (5 mL) dropwise and the temperature maintained at -20 °C. Upon complete addition the reaction was warmed to room temperature for 4-6 hours. The solvent was removed *in vacuo* to afford the crude product, which was purified by column chromatography using 15% EtOAc/Hexane as an eluant to afford the title compound (**1.26**) as a colourless solid (4.3 g, 98%).

Mp = 70-71°C

^1H NMR (400MHz, CDCl_3) δ 7.85-7.73 (4H, m, ArH), 5.92 (1H, ddt, J = 17.2, 10.2, 7.0 Hz, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.22 (1H, dd, J = 17.2, 1.5 Hz, $\text{CH}_2\text{CH}=\text{CHH}$), 5.16 (1H, dd, J = 10.0, 1.4 Hz, $\text{CH}_2\text{CH}=\text{CHH}$), 4.42 (1H, m, CH), 3.73 (2H, dd, J = 4.6, 0.9 Hz,

ClCH₂), 2.69 (1H, ddd, *J* = 14.6, 6.5, 6.0 Hz, CHH), 2.60 (1H, ddd, *J* = 14.6, 6.4, 6.0 Hz, CHH).

¹³C NMR (100 MHz, CDCl₃) δ 163.7, 134.6, 131.8, 128.7, 123.6, 118.9 (CH₂), 86.0, 43.4(CH₂), 34.9 (CH₂)

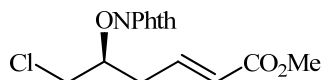
IR ν_{max} 1790, 1732, 1612, 1188 cm⁻¹

MS (ESI) *m/z* 289 ([M (³⁵Cl)+Na]⁺)

MS (ESI-TOF, HR) *m/z* [M (³⁵Cl)+H]⁺ calcd for C₁₃H₁₃³⁵ClNO₃: 266.0584; found: 266.0580

[α]_D^{22.4} -2.7 (*c* 0.8, CHCl₃)

Synthesis of chloro-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylloxy)-hex-2-enoic acid methyl ester (**1.23**)



Compound (**1.26**) (0.27 g, 1.04 mmol) and methyl acrylate (0.37 mL, 4.15 mmol) were dissolved in anhydrous CH₂Cl₂ (5 mL). To the mixture was added Grubbs (II) (0.17 g, 0.20 mmol) in one portion and was warmed to reflux for 4 hours. Subsequently, the solvent was evaporated and the crude product was purified by column chromatography using 30% EtOAc/Hexane as an eluent to afford the title compound (**1.23**) as a colourless solid (0.29 g, 86%)

Mp = 78-80 °C

^1H NMR (400 MHz, CDCl_3) δ 7.84-7.73 (4H, m, ArH), 7.05 (1H, dt, $J = 16.0, 7.3$ Hz, CH=CH), 6.04 (1H, d, $J = 16.0$, CH=CH), 4.46 (1H, m, CH), 3.74 (2H, dd, $J = 12.0, 4.1$ Hz, CH_2), 3.69 (3H, s, OCH_3), 2.87 (1H, m, CH_2), 2.75 (1H, m, CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 163.6, 141.9, 134.7, 128.6, 124.6, 123.7, 85.2, 60.3, 51.5, 43.2 (CH_2), 33.3 (CH_2)

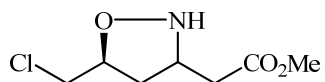
IR ν_{max} 3028, 2953, 1738, 1714, 1661, 1373 cm^{-1}

MS (ESI) m/z 323 [$\text{M} (^{35}\text{Cl})$] $^+$

MS (ESI-TOF, HR) m/z [$\text{M} (^{35}\text{Cl})+\text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{15}^{35}\text{ClNO}_5$: 324.0639; found: 324.0634

$[\alpha]_{\text{D}}^{22.3} +24.9$ (c 1.0, CHCl_3)

Synthesis of (5-chloromethyl-isoxazolidin-3-yl)-acetic acid methyl ester (**1.22**)



To a solution of compound (**1.23**) (0.26 g, 0.79 mmol) in CH_2Cl_2 (5 mL) was added hydrazine monohydrate (0.15 mL, 4.76 mmol) at 0 °C and the reaction was warmed to room temperature for 1 hour. The white precipitate was formed and filtered through Celite. The solvent was removed *in vacuo* to yield the title product (**1.22**) as a colourless oil (racemic mixture) (0.13 g, 89%)

^1H NMR (500 MHz, CDCl_3) δ 4.77 (1H, br s, NH), 4.41 (1H, ddd, $J = 11.9, 10.2, 5.3$ Hz, CHO), 4.29 (1H, ddd, $J = 12.6, 7.7, 5.0$ Hz, CHH), 3.90 (1H, ddd, $J = 13.8, 6.9, 2.2$ Hz, CHH), 3.85 (1H, ddd, $J = 5.1, 3.7, 2.2$ Hz, CHH), 3.70 (3H, s, OCH_3), 3.67 (1H, dd, $J = 11.5, 6.5$ Hz, CHH), 3.66 (1H, dd, $J = 5.1, 3.7$ Hz, CHH), 3.62 (1H, dd, $J = 6.2, 4.7$ Hz, CHH), 3.58 (1H, dd, $J = 11.5, 4.5$ Hz, CHH), 2.70 (1H, dd, $J = 16.2, 7.0$ Hz, CHH), 2.65 (1H, dd, $J = 16.1, 6.9$ Hz, CHH), 2.60 (1H, ddd, $J = 14.2, 7.8, 7.8$ Hz, CHH), 2.53 (1H, dd, $J = 16.2, 6.6$ Hz, CHH), 2.47 (1H, dd, $J = 16.1, 6.9$ Hz, CHH), 2.34 (1H, ddd, $J = 13.0, 7.5, 5.6$ Hz, CHH), 2.16 (1H, ddd, $J = 12.9, 8.7, 4.6$ Hz, CHH), 1.81 (1H, ddd, $J = 12.9, 7.1, 7.1$ Hz, CHH)

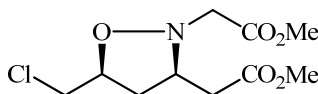
^{13}C NMR (125 MHz, CDCl_3) δ 171.6, 80.9, 79.1, 57.3, 57.1, 51.9, 46.1, 45.4 (CH_2), 38.9 (CH_2), 38.6 (CH_2)

IR ν_{max} 3224, 2953, 1732, 1202 cm^{-1}

MS (ESI) m/z 194 $[\text{M} (^{35}\text{Cl})+\text{H}]^+$

MS (ESI-TOF, HR) m/z $[\text{M} (^{35}\text{Cl})+\text{H}]^+$ calcd for $\text{C}_7\text{H}_{13}^{35}\text{ClNO}_3$: 194.0584; found: 194.0580.

Synthesis of (5-chloromethyl-2-methoxycarbonylmethyl-isoxazolidin-3-yl)-acetic acid methyl ester (1.28a)



Compound (**1.22**) (0.37 g, 1.91 mmol) and NaHCO₃ (0.18 g, 2.10 mmol) were dissolved in DMF (10 mL); methyl bromoacetate (0.2 mL, 2.10 mmol) was added and the reaction mixture was heated to 60 °C for 12 hours. Upon completion the reaction was quenched with H₂O (25 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic extract was washed with brine, dried with anhydrous MgSO₄. The solvent was removed *in vacuo* to afford the crude product, which was purified by column chromatography using 50% EtOAc/Hexane as an eluent to afford major product (**1.28a**) (0.30 g, 60% yield) as a colorless oil, followed by the minor product (**1.28b**) (0.10 g, 20% yield) as a colourless oil, (a/b = 3:1, isolated yield).

Less polar diastereomer (major product) (**1.28a**)

¹H NMR (400 MHz, CDCl₃) δ 4.32 (1H, qt, *J* = 12.0, 4.0, 1.3 Hz, CHO), 3.69 (3H, s, OCH₃), 3.67 (1H, d, *J* = 8 Hz, CHHN), 3.62 (3H, s, OCH₃), 3.62 (1H, dd, *J* = 12.0, 8.0 Hz, CHH), 3.58 (1H, d, *J* = 8.0 Hz, CHHN), 3.48 (1H, m, CHN), 3.45 (1H, dd, *J* = 12.0, 8.0 Hz, CHH), 2.68 (1H, dt, *J* = 12.0, 8.0 Hz, CHH), 2.66 (1H, dd, *J* = 12.0, 8.0 Hz, CHH), 2.47 (1H, dd, *J* = 12.0, 8.0 Hz, CHH), 1.88 (1H, dt, *J* = 12.0, 8.0 Hz, CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 171.5, 169.0, 76.4, 62.2, 57.9 (CH₂), 45.0 (CH₂), 38.7 (CH₂), 38.3 (CH₂)

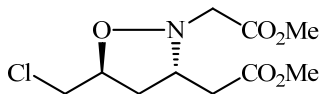
IR ν_{max} 2955, 1737, 1438, 1382, 1201, 1013, 798 cm⁻¹

MS (ESI) *m/z* 265 [M (³⁵Cl)]⁺, 156 (36%)

MS (ESI-TOF, HR) *m/z* [M (³⁵Cl)+H]⁺ calcd for C₁₀H₁₇³⁵ClNO₅: 266.0795; found: 266.0789

[α]_D^{22.1} +57.0 (*c* 0.4, CHCl₃)

Synthesis of dimethyl 2,2'-((3*S*,5*S*)-5-(chloromethyl)isoxazolidine-2,3-diyl)diacetate (1.28b)



More polar diastereomer (minor product) (**1.28b**)

^1H NMR (400 MHz, CDCl_3) δ 4.30 (1H, q, *CHO*), 3.69 (3H, s, *OCH*₃), 3.63 (3H, s, *OCH*₃), 3.63 (1H, d, $J = 16.0$ Hz, *CHHN*), 3.54 (1H, dd, $J = 12.0, 8.0$ Hz, *CHH*), 3.52 (1H, d, $J = 16.0$ Hz, *CHHN*), 3.46 (1H, dd, $J = 12.0, 4.0$ Hz, *CHH*), 3.38 (1H, m, *CHN*), 2.59 (1H, dd, $J = 16.0, 8.0$ Hz, *CHH*), 2.46 (1H, dd, $J = 16.0, 8.0$ Hz, *CHH*), 2.40 (1H, dt, $J = 12.0, 8.0, 1.3$ Hz, *CHH*), 2.17 (1H, dt, $J = 12.0, 8.0$ Hz, *CHH*)

^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 169.2, 76.6, 61.9, 58.5 (CH_2), 45.2 (CH_2), 38.2 (CH_2), 37.3 (CH_2)

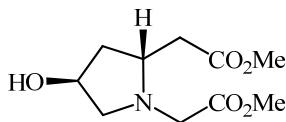
IR ν_{max} 2955, 1737, 1438, 1382, 1201, 1013, 798 cm^{-1}

MS (ESI) m/z 265 [$\text{M} (^{35}\text{Cl})+\text{H}$]⁺, 156 (35%)

MS (ESI-TOF, HR) m/z [$\text{M} (^{35}\text{Cl})+\text{H}$]⁺ calcd for $\text{C}_{10}\text{H}_{17}^{35}\text{ClNO}_5$: 266.0785; found: 266.0789

$[\alpha]_{\text{D}}^{22.4} -77.8$ (c 0.7, CHCl_3)

Synthesis of (4-hydroxy-1-methoxycarbonylmethyl-pyrrolidin-2-yl)-acetic acid methyl ester (1.21)



Compound (**1.28a**) (3.6 mg, 0.13 mmol), CaCO₃ (1.5 mg, 0.15 mmol) and Pd/C (3.6 mg, 10% w/w) were dissolved in sealed tube in MeOH (2 mL). The reaction tube was connected to the high pressure Parr hydrogenation apparatus and pressurized with 100 psi of hydrogen. The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a Celite pad and the residue washed with MeOH. The filtrates were collected and the solvent was removed *in vacuo* to yield the title compound (**1.21**) as colourless oil (3.2 mg, 96%).

¹H NMR (400 MHz, CD₃OD) δ 4.89 (1H, brs CHOH), 4.46 (1H, apparent brs, CHOH), 4.27 (1H, d, *J* = 17.4 Hz, CHH), 3.99 (1H, d, *J* = 17 Hz, CHH), 3.91 (1H, apparent brs, CHN), 3.79 (3H, s, OCH₃), 3.76 (1H, dd, *J* = 12.8, 4.6 Hz, CHH), 3.70 (3H, s, OCH₃), 3.65 (1H, d, *J* = 11.0 Hz, CHH), 3.31 (1H, apparent brs, CHH), 3.05 (1H, d, *J* = 12.0 Hz, CHH), 2.99 (1H, dd, *J* = 17.0, 5.5 Hz, CHH), 2.75 (1H, dd, *J* = 17.0, 6.9 Hz, CHH)

¹³C NMR (100 MHz, CDCl₃) δ 173.0, 170.9, 70.3, 64.1(CH₂), 57.5(CH₂), 53.2, 52.7 (2C), 41.5(CH₂), 37.5(CH₂)

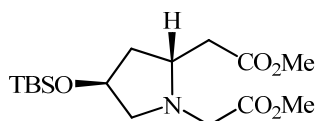
IR ν_{max} 3434, 2954, 1732, 1437, 1381, 1202, 1167 cm⁻¹

LRMS (ESI) *m/z* 232 (M+H)⁺

MS (ESI-TOF, HR) m/z (M+H)⁺ calcd for C₁₀H₁₈NO₅: 232.1185; found: 232.1184

$[\alpha]_D^{22.2} +36.9$ (*c* 0.4, CHCl₃)

Synthesis of [4-(*tert*-butyl-dimethyl-silanyloxy)-1-methoxycarbonylmethyl-pyrrolidin-2-yl]-acetic acid methyl ester (1.30**)**



A solution of compound (**1.21**) (0.10 g, 0.43 mmol) and imidazole (0.29 g, 4.32 mmol) in DMF (10 mL) was treated with TBSCl (0.52 g, 3.46 mmol) and DMAP (0.03g, 0.04 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was treated with 3% NaOH (10 mL) and then extracted with EtOAc (3×30 mL). The organic extracts were washed with brine, dried with anhydrous MgSO₄ and the solvent was removed *in vacuo* to afford the crude product, which was purified by column chromatography (hexane-EtOAc, 1:1) to give the title compound (**1.30**) (0.16 g, 92%). as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 4.33 (1H, qt, *J* = 5.5, 1.4 Hz, CHO), 3.69 (3H, s, OCH₃), 3.64 (3H, s, OCH₃), 3.53 (1H, d, *J* = 16.9 Hz, CHHN), 3.39 (1H, dd, *J* = 10.0, 5.9 Hz, CHH), 3.24 (1H, d, *J* = 16.9 Hz, CHHN), 3.22 (1H, m CHN), 2.58 (1H, dd, *J* = 15.1, 4.6 Hz, CHH), 2.38 (1H, dd, *J* = 9.6, 5.0 Hz, CHH), 2.30 (1H, dd, *J* = 15.6, 8.6

Hz, CHH), 1.95 (1H, m, CHH), 1.77 (1H, dt, $J = 13.3, 7.3$ Hz, CHH), 0.84 (9H, s, $3 \times \text{CH}_3$), 0.01 (6H, s, $2 \times \text{CH}_3$)

^{13}C NMR (100 MHz, CDCl_3) δ 172.2, 171.4, 70.2, 63.0 (CH_2), 59.0 (CH_2), 55.4, 51.6, 51.5, 41.4 (CH_2), 39.4 (CH_2), 25.7, 25.6, 1.1, -3.0, -4.8

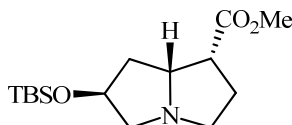
IR ν_{max} 2953, 2930, 2856, 1740, 1171, 837 cm^{-1}

MS (ESI) m/z 346 ($\text{M}+\text{H}^+$)

MS (ESI-TOF, HR) m/z ($\text{M}+\text{H}^+$)⁺ calcd for $\text{C}_{16}\text{H}_{32}\text{NO}_5\text{Si}$: 346.2050; found: 346.2051

$[\alpha]_{\text{D}}^{22.2} +38.1$ (c 1.0, CHCl_3)

Synthesis of 6-(*tert*-butyl-dimethyl-silyloxy)-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (**1.48**)



Compound (**1.30**) (7.9 mg, 0.23 mmol) in dry THF (2 mL) was treated with a 1.0 M solution of KHMDS in THF (0.27 mL, 0.27 mmol) under nitrogen. The mixture was stirred for 30 minutes. Subsequently, it was diluted with CH_2Cl_2 (10 mL), washed with brine, dried and evaporated. The crude product was dissolved in MeOH (2 mL), cooled to 0 °C under argon and treated with NaBH_4 (1.9 mg, 0.05 mmol). The mixture was stirred for 0.5-1 hour, then filtered through Celite and evaporated. To the residue

and triethylamine (0.1 mL, 0.68 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added methanesulfonylchloride (0.03 mL, 0.34 mmol,) and the mixture was stirred at this temperature for 30 minutes. The reaction mixture was warmed to room temperature for 1 hour. Upon completion the reaction was quenched with H₂O (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3×20 mL) and the combined organic extracts was washed with brine, dried with anhydrous MgSO₄ and the solvent removed *in vacuo* to afford the crude product, using crude product for the next step. The crude product and PtO₂ (3.6 mg, 0.02 mmol) were taken in sealed tube in MeOH (2 mL). The reaction tube was connected to the high pressure Parr hydrogenation apparatus and pressurized with 100 psi of hydrogen gas. The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a Celite pad and the residue washed with MeOH (3×10 mL). The filtrates were collected and the solvent was removed *in vacuo* to yield the title compound (**1.48**) as a colourless oil (2.4 mg, 25% yield over 4 steps)

¹H NMR (400 MHz, CDCl₃) δ 4.32 (1H, quint, *J* = 8.0 Hz, CHO), 3.72 (1H, m, CHN), 3.70 (3H, s, OCH₃), 3.17 (1H, dd, *J* = 12.0, 8.0 Hz, CHH), 3.11 (1H, q, *J* = 8.0 Hz, CHCO₂CH₃), 2.95 (2H, m, CH₂), 2.51 (1H, dd, *J* = 8.0, 8.0 Hz, CHH), 2.24 (1H, m, CHH), 1.90 (1H, appear quint, CHH), 1.85(1H, m, CHH), 1.47 (1H, m, CHH), 0.85 (9H, s, 3×CH₃), 0.05 (6H, s, 2×CH₃)

¹³C NMR (100 MHz, CDCl₃) δ 173.5(CO), 72.7, 63.6, 62.4 (CH₂), 53.9 (CH₂), 51.5, 47.6, 37.8 (CH₂), 26.0 (CH₂), 25.7, 18.0, -0.04, -10.0

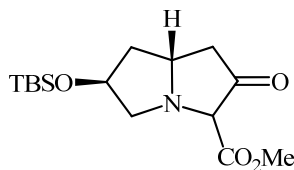
IR ν_{max} 2930, 2857, 1737, 1640, 1438, 838 cm⁻¹

MS (ESI) *m/z* 300 (M+H)⁺

MS (ESI-TOF, HR) m/z (M+H)⁺ calcd for C₁₅H₃₀NO₃Si: 300.1995; found: 300.2019

$[\alpha]_D^{22.2} +5.2$ (c 0.4, CHCl₃)

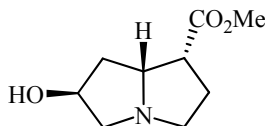
6-(*tert*-butyl-dimethyl-silyloxy)-2-oxo-hexahydro-pyrrolizine-3-carboxylic acid methyl ester (1.44)



¹H NMR (400 MHz, CDCl₃) δ 4.55 (1H, m, CHO), 4.10 (1H, m, CHN), 3.78 (3H, s, OCH₃), 3.57 (1H, s, COCHN), 3.21 (1H, dd, J = 12.5, 2.8 Hz, CHH), 3.06 (1H, dd, J = 12.5, 5.6 Hz, CHH), 2.82 (1H, dd., J = 10.9, 8.1 Hz, CHH), 2.40 (1H, dd, J = 19.0, 2.9 Hz, CHH), 2.00 (1H, dd, J = 5.9, 1.7 Hz, CHH), 1.55 (1H, dt, J = 10.9, 5.6 Hz, CHH), 0.86 (9H, s, 3×CH₃), 0.05 (6H, s, 2×CH₃)

¹³C NMR (100 MHz, CDCl₃) δ 208.5, 168.6, 73.8 (CH₂), 73.0, 64.2 (CH₂), 58.8, 52.7, 41.7 (CH₂), 41.6 (CH₂), 25.8, 18.0, -4.8, -10.0

Synthesis of 6-hydroxy-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (1.20)



To a solution of compound (**1.48**) (0.02 g, 0.06 mmol) and Amberlyst-A 26(F) (0.06 g, 4 mequiv/g) was vigorously stirred in THF:MeOH (9:1); (2 mL) and heated to 50-60 °C for 48 hours. The resin was filtered off and the solvent was removed *in vacuo* to afford the title product (**1.20**) as a colourless oil (8.0 mg, 65%)

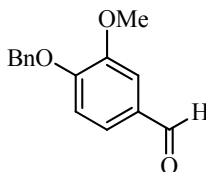
^1H NMR (400 MHz, CDCl_3) δ 4.52 (1H, m, CHO), 3.99 (1H, m, CH), 3.73 (3H, s, OCH_3), 3.41 (1H, dd, $J = 8.4, 8.2$ Hz, CH), 3.26 (1H, d, $J = 11.2$ Hz, CH), 2.80 (1H, dd, $J = 11.2, 4.3$ Hz, CH), 2.22-2.04 (4H, m, $2 \times \text{CH}_2$), 1.64 (1H, m, CHH), 1.49 (1H, m, CHH)

^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 74.5, 68.6, 64.0, 62.9, 52.1, 41.3, 31.8, 31.6

IR ν_{max} 3287, 3120, 2923, 2885, 1726, 1438, 1376, 1213 cm^{-1}

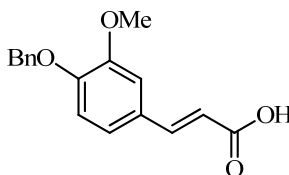
MS (ESI-TOF, HR) m/z ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_9\text{H}_{16}\text{NO}_3$: 186.1130; found: 186.1125.

$[\alpha]_{\text{D}}^{21.0}$ -33.7 (c 0.1, CHCl_3)

Synthesis of 4-(benzyloxy)-3-methoxybenzaldehyde (1.53)¹⁶⁵

To a solution of vanillin (**1.52**) (5.0 g, 32.8 mmol) in acetone (20 mL) under nitrogen was added K_2CO_3 (5.5 g, 39.4 mmol) and BnBr (4.3 mL, 36.1 mmol). The mixture was refluxed until completion (TLC), filtered through Celite, and concentrated *in vacuo* to provide the benzylated vanillin (**1.53**) as a colourless oil (7.4 g, 93%). The 1H NMR analysis was consistent with data reported in the literature.¹⁶⁵

1H NMR (400 MHz, $CDCl_3$) δ 9.87 (1H, s, CHO), 7.74-6.84 (8H, m, ArH), 5.20 (2H, s, CH_2Ar), 3.83 (3H, s, OCH_3)

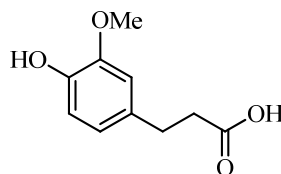
Synthesis of (*E*)-3-(4-(benzyloxy)-3-methoxyphenyl)acrylic acid (1.54)¹⁶⁶

To a solution of malonic acid (4.5 g, 42.7 mmol) in anhydrous pyridine (10 mL), aldehyde (**1.53**) (8.0 g, 32.8 mmol) and piperidine (10 mL) were added, and the solution

was refluxed for 1.5 h. Carbon dioxide evolution has ended by this time. The solution was cooled to rt, poured into a mixture of ice, 40 mL of conc. HCl and 130 mL of H₂O, precipitating the acid as a colourless solid. The solid was collected by filtration and washed with ice water. The product was crystallized from EtOH and dried *in vacuo* to give the title compound (**1.54**) (7.4 g, 79%) as colourless needles. The ¹H NMR analysis data were consistent with those reported in the literature.¹⁶⁶

¹H NMR (400 MHz, CDCl₃) δ 7.70 (1H, d, *J* = 15.9, CH=CH), 7.74-6.84 (8H, m, ArH), 6.29 (1H, d, *J* = 15.9 Hz, CH=CH), 5.20 (2H, s, CH₂Ar), 3.92 (3H, s, OCH₃)

Synthesis of 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (**1.55**)⁵⁰

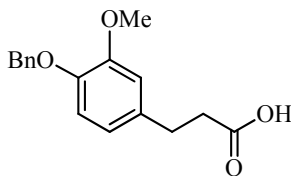


To a solution of carboxylic acid (**1.54**) (7.4 g, 26.0 mmol) in EtOAc (50 mL) under nitrogen at rt was added 10% Pd/C (0.3 g, 2.60 mmol) and the solution was placed under an atmosphere of H₂ (1 atm). The mixture was stirred at rt until completion (TLC), filtered through Celite and concentrated *in vacuo* to provide the dihydroferulic acid (**1.55**) (4.9 g, 85%) as a colourless solid. All of the spectroscopic data were consistent with those reported in the literature.⁵⁰

^1H NMR (400 MHz, CDCl_3) δ 6.80-6.60 (3H, m, ArH), 3.83 (3H, s, OCH_3), 2.83 (2H, t, $J = 7.3$ Hz, CH_2CH_2), 2.56 (2H, t, $J = 7.3$ Hz, CH_2CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ 177.2 (CO), 149.0, 146.0, 134.0, 121.9, 116.4, 113.3, 56.6, 37.3, 31.9

Synthesis of 3-(4-(benzyloxy)-3-methoxyphenyl)propanoic acid (**1.56**)^{50,14}

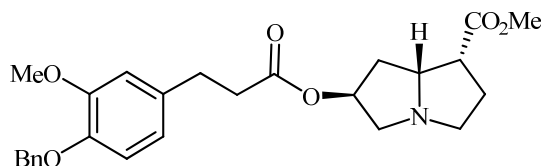


To a solution of the dihydroferulic acid (**1.55**) (0.7 g, 3.46 mmol) in acetone-MeCN (1:1, 20 mL) under nitrogen was added K_2CO_3 (1.6 g, 3.81 mmol) and BnBr (1.2 mL, 3.81 mmol). The mixture was refluxed until completion (TLC), filtered through Celite, and concentrated *in vacuo* to provide crude dibenzylated dihydroferulic acid. To a solution of the crude acid in MeOH- H_2O (1:1, 20 mL) was added KOH (1.0 g, 17.8 mmol) and the solution was stirred at 70 °C until completion of the reaction. The mixture was then cooled to rt and washed with CHCl_3 (3×25 mL). The aqueous layer was neutralized with conc. HCl until pH 2 and extracted with CHCl_3 (5×25 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (hexane-EtOAc, 3:7) to give the carboxylic acid (**1.56**) (0.77 g, 78%) as a colourless solid. All spectroscopic data were consistent with those reported in the literature.^{50,14}

^1H NMR (400 MHz, CDCl_3) δ 12.0 (1H, OH), 7.44-7.29 (5H, m, ArH), 6.64-6.83 (3H, m, ArH), 5.12 (2H, s, ArCH₂), 3.87 (3H, s, OCH₃), 2.86 (2H, t, $J = 7.0$ Hz, CH₂CH₂), 2.56 (2H, t, $J = 7.0$ Hz, CH₂CH₂)

^{13}C NMR (100 MHz, CDCl_3) δ 177.1, 151.3, 148.2, 139.2, 136.2, 129.7, 129.1, 129.0, 121.8, 116.4, 114.2, 72.8, 56.8, 37.1, 31

Synthesis of 6-[3-(4-benzyloxy-3-methoxy-phenyl)-propionyloxy]-hexahydro-pyrrolizine-1-carboxylic acid methyl ester (1.57)



To a solution of compound (**1.20**) (4.0 mg, 0.02 mmol), 3-(*p*-benzyloxy-*m*-methoxy-phenyl)propanoic acid (8.0 mg, 0.02 mmol) DMAP (4.0 mg, 0.02 mmol) and EDCI (8.0 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred at 0 °C for 1 hour and warmed to room temperature for 12 hours. Upon completion the reaction was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extract was washed with brine, dried with anhydrous MgSO_4 and the solvent was removed *in vacuo* to afford the crude product, which was purified by column chromatography using 0-20% MeOH/ CH_2Cl_2 as eluent to afford the title compound (**1.57**) (6.0 mg, 68%) as a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.44-7.29 (5H, m, ArH), 6.64-6.83 (3H, m, ArH), 5.38 (1H, m, CHO), 5.12 (2H, s, ArCH₂), 3.87 (3H, s, OCH₃), 3.85 (1H, m, CH), 3.72 (3H, s, OCH₃), 3.36-3.21 (2H, m, CH₂), 2.92 (1H, m, CH), 2.86 (2H, t, $J = 7.0$ Hz, CH₂), 2.59 (2H, m, CH₂), 2.26-2.21 (1H, m, CH), 2.20-2.05, (2H, m, CH₂), 2.02-1.97 (1H, m, CH), 1.68-1.59 (1H, m, CH), 1.53-1.45 (1H, m, CH)

^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 173.6, 149.5, 137.3, 133.5, 128.4, 127.7, 127.2, 120.1, 114.2, 112.1, 76.6, 71.1, 68.1, 64.5, 60.3, 55.9, 53.6, 51.7, 46.6, 38.7, 36.0, 34.2, 30.5, 29.6, 27.0

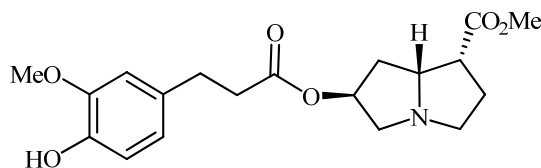
IR ν_{max} 2922, 2852, 1734, 1458, 1261, 748 cm^{-1}

MS (ESI) m/z 454 (M+H)⁺

MS (ESI-TOF, HR) m/z (M+H)⁺ calcd for C₂₆H₃₂NO₆: 454.2230; found: 454.2233

$[\alpha]_{\text{D}}^{21.1} -6.0$ (c 0.3, CHCl_3)

Synthesis of 6-[3-(4-hydroxy-3-methoxy-phenyl)-propionyloxy]-hexahydro-pyrolizine-1-carboxylic acid methyl ester (amphorogynine C)¹³



To a solution of compound (**1.57**) (4.0 mg, 0.08×10^{-4} mol) in EtOAc (2 mL) under nitrogen at rt was added 10% Pd/C (2.0 mg, 0.01 mmol) and the solution was placed under an atmosphere of H₂ (1 atm). The mixture vigorously stirred at rt in a hydrogen atmosphere for 12 hours. The reaction mixture was filtered through a pad of Celite and the residue was washed with EtOAc (3 × 10 mL). The filtrates were collected and the solvent was removed *in vacuo* to yield amphorogynine C (2.0 mg, 90%).

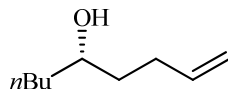
¹H NMR (400 MHz, CDCl₃) δ 6.87-6.69 (3H, m, ArH), 5.37 (1H, m, CHO), 3.87 (3H, s, OCH₃), 3.85 (1H, m, CH), 3.72 (3H, s, OCH₃), 3.48 (2H, m, CH₂), 3.21 (1H, m, CH), 2.97-2.80 (4H, m, 2 × CH₂), 2.64 (2H, t, *J* = 7.0 Hz, CH₂), 2.12 (2H, m, CH₂), 1.90 (1H, m, CH₂), 1.69~1.50 (1H, m, CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 146.9, 132.1, 120.9, 114.2, 111.0, 77.2, 64.0, 60.0, 55.8, 55.8, 52.0, 46.6, 36.3, 35.1, 30.7, 26.4

$[\alpha]_D^{21.0}$ -4.4 (*c* 0.1, CHCl₃)

4.3 Experimental Section for Chapter 2

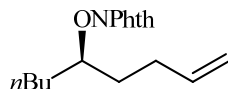
Synthesis of (*S*)-non-1-en-5-ol (**2.39**)^{18d}



Allyl bromide (3.00 g, 30.0 mmol) was added dropwise to a suspension of Mg turnings (2.92 g, 0.12 mol) in anhydrous ether. The mixture was stirred for 1.5 hour and the resulting ether solution was transferred by cannula to a new flask. (*S*)-Hex-1-ene-oxide (**2.36**) (6.5 mL, 74.9 mmol) was added slowly allowing the ether to reflux. The mixture was stirred for 1 hour and saturated aqueous NH₄Cl (20 mL) was added. The mixture was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine (3×10 mL) and dried (MgSO₄), filtered and concentrated under reduced pressure, to give the alcohol (**2.39**) (4.29 g, 89% yield) as a colourless oil, which was used without purification. All spectral data were consistent with those reported in the literature.^{18d}

¹H NMR (300MHz, CDCl₃); δ 0.91 (3H, t, *J* = 6.9 Hz, CH₃), 1.32-1.56 (8H, m, 4×CH₂), 2.12-2.21 (2H, m, CH₂), 3.61-3.64 (1H, m, OCH), 4.97 (1H, ddt, *J* = 10.1, 2.2, 1.2 Hz, CHH), 5.05 (1H, ddt, *J* = 17.2, 1.8, 1.6 Hz, CHH), 5.84 (1H, ddt, *J* = 17.1, 10.2, 6.7 Hz, CH)

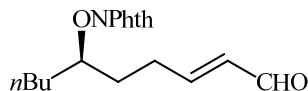
¹³C NMR (75 MHz, CDCl₃); δ 138.7, 114.7, 71.5, 37.2, 36.5, 30.1, 27.8, 22.7, 14.0

Synthesis of (*R*)-2-(non-1-en-5-yloxy)isoindoline-1,3-dione (2.35**)^{18d}**

The alcohol (**2.39**) (3.60 g, 25.3 mmol), PhthNOH (4.53 g, 27.8 mmol), and Ph₃P (7.95 g, 30.3 mmol) were dissolved in toluene (100 mL). DIAD (7.35 mL, 37.9 mmol) was added dropwise to the mixture at 0 °C and the mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:EtOAc, 9:1) to afford the phthalimide (**2.35**) (6.96 g, 96% yield) as a colorless oil that solidified during refrigeration. All spectral data were consistent with those reported in the literature.^{18d}

¹H NMR (300MHz, CDCl₃); δ 0.94 (3H, t, *J* = 7.2 Hz, CH₃), 1.34-1.55 (4H, m, 2×CH₂), 1.68-1.85 (4H, m, 2×CH₂), 2.22-2.44 (2H, m, CH₂), 4.28 (1H, quint, *J* = 5.9 Hz, OCH), 5.01 (1H, ddt, *J* = 10.2, 1.9, 1.2 Hz, CHH), 5.10 (1H, ddt, 17.2, 1.8, 1.6 Hz, CHH), 5.88 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, CH), 7.73-7.85 (4H, m, ArH)

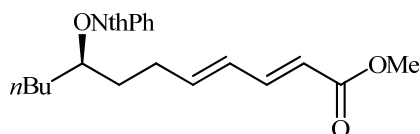
¹³C NMR (75 MHz, CDCl₃); δ 164.3, 138.0, 134.4, 129.0, 123.4, 114.9, 87.6, 32.1, 31.6, 29.1, 27.0, 22.7, 14.0

Synthesis of (*R,E*)-6-(1,3-dioxoisindolin-2-yloxy)dec-2-enal (2.40**)^{18d}**

The alkene (**2.35**) (0.71 g, 2.49 mmol) and Grubb's II catalyst (0.42 g, 0.49 mmol) were dissolved in dichloromethane, Crotonaldehyde (0.82 mL, 9.94 mmol) as a solution of dichloromethane (2 mL) was added and the mixture was heated at reflux for 2 hour under N₂. The solvent was evaporated and the residue was purified by flash chromatography (hexane:EtOAc, 9:1) to afford the aldehyde (**2.40**) (0.81 g, 91% yield) as a colorless oil. All spectral data were consistent with those reported in the literature.^{18d}

¹H NMR (300MHz, CDCl₃); δ 0.88 (3H, t, *J* = 7.2 Hz, CH₃), 1.19-1.55 (4H, m, 2×CH₂), 1.57-1.72 (2H, m, CH₂), 1.75-1.90 (2H, m, CH₂), 2.52-2.75 (2H, m, CH₂), 4.22 (1H, quint, *J* = 5.7 Hz, OCH₂), 6.16 (1H, dd, *J* = 15.7, 7.9 Hz, CH), 6.93 (1H, dt, *J* = 15.6, 6.7 Hz, CH), 7.71-7.81 (4H, m, ArH), 9.48 (1H, d, *J* = 7.9 Hz, CH)

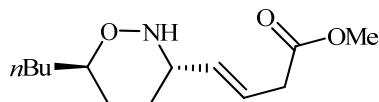
¹³C NMR (75 MHz, CDCl₃); δ 194.1, 164.3, 158.1, 134.5, 133.1, 128.8, 123.4, 87.2, 32.0, 30.5, 27.9, 27.0, 22.6, 13.9

Synthesis of (*R,2E,4E*)-methyl 8-(1,3-dioxoisindolin-2-yloxy)dodeca-2,4-dienoate (2.32)^{18d}

One pot method: The alkene (**2.35**) (0.71 g, 2.49 mmol) and Grubb's II catalyst (0.42 g, 0.49 mmol) were dissolved in CH₂Cl₂. Crotonaldehyde (0.82 mL, 9.94 mmol) was added and the mixture was heated at reflux for 2 hours under N₂. The volatiles were evaporated and the residue was taken up in CH₂Cl₂ (20 mL). Methyl (triphenylphosphoranylidene) acetate (0.70 g, 1.84 mmol) was added and the mixture was stirred at room temperature under N₂ overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane:EtOAc, 3:1) to afford the ester (**2.32**) (0.81, 93% yield) as a colourless oil. All spectral data were consistent with those reported in the literature.^{18d}

¹H NMR (300MHz, CDCl₃); δ 0.88 (3H, t, *J* = 7.2 Hz, CH₃), 1.26-1.50 (4H, m, 2×CH₂), 1.63-1.84 (4H, m, 2×CH₂), 2.40-2.56 (2H, m, CH₂), 3.72 (3H, s, OCH₃), 4.23 (1H, quint, *J* = 5.6 Hz, OCH), 5.81 (1H, d, *J* = 15.8 Hz, =CH), 6.12-6.31 (2H, m, 2×=CH), 7.22-7.30 (1H, m, =CH), 7.74-7.78 (4H, m, ArH)

¹³C NMR (75 MHz, CDCl₃); δ 167.7, 164.4, 145.1, 143.6, 134.5, 129.0, 128.9, 123.5, 119.1, 87.5, 51.4, 32.2, 31.5, 28.3, 27.1, 22.7, 14.0

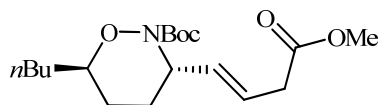
Synthesis of (*E*)-methyl 4-((3*S*,6*R*)-6-butylmorpholin-3-yl)but-3-enoate (2.33**)^{18d}**

The diethyl ester (**2.32**) (0.3 g, 0.85 mmol) was dissolved in CH₂Cl₂ (10 mL) and hydrazine monohydrate (0.4 mL, 8.53 mmol) was added. The mixture was stirred at room temperature for 10 hours. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (hexane:EtOAc, 95:5) to afford the oxazine (**2.33**) (0.19 g, 93% yield) as a colourless oil. All spectral data were consistent with those reported in the literature.^{18d}

¹H NMR (300MHz, CDCl₃); δ 0.89 (3H, t, *J* = 6.7 Hz, CH₃), 1.26-1.89 (10H, m, 5×CH₂), 3.06 (2H, d, *J* = 7.0 Hz, CH₂), 3.50-3.55 (2H, m, NH, CH), 3.68 (3H, s, OCH₃), 5.43 (1H, dd, *J* = 15.6, 7.0 Hz, CH), 5.78 (1H, dt, *J* = 15.4, 7.0 Hz, CH)

¹³C NMR (75 MHz, CDCl₃); δ 171.8, 132.5, 125.1, 79.4, 59.5, 51.8, 37.7 (CH₂), 34.5 (CH₂), 30.5 (CH₂), 30.2 (CH₂), 27.6 (CH₂), 22.7 (CH₂), 14.0

Synthesis of (3*S*,6*R*)-*tert*-butyl 6-butyl-3-((*E*)-4-methoxy-4-oxobut-1-enyl)morpholine-2-carboxylate (2.45)



To a solution of amine (**2.33**) (0.93 g, 3.93 mmol), triethylamine (0.98 mL, 7.08 mmol) and DMAP (0.04 g, 0.39 mmol) in dry dichloromethane (10mL), (Boc)₂O (1.29 g, 5.90 mmol) was added at 0 °C and the mixture was allowed to warm at room temperature and was then stirred for 12 hours. The resulting solution was washed with saturated aqueous NH₄Cl (20 mL), the aqueous layer was extracted with CH₂Cl₂ (50 mL) and the organic layer was dried over anhydrous MgSO₄. The solvent was subsequently evaporated off and the residue was chromatographed on a silica gel column with (hexane/EtOAc, 4:1) as the eluent to give the title product (**2.45**) (0.13 g, 98% yield) as a colourless oil.

¹H NMR (400MHz, CDCl₃); δ 0.87 (3H, t, *J* = 6.8 Hz, CH₃), 1.20-1.60 (8H, m, 4×CH₂), 1.44 (9H, s, *t*Bu), 1.83-2.01 (4H, m, 2×CH₂), 3.05 (2H, dd, *J* = 6.8, 4.1 Hz, CH₂CO₂CH₃), 3.63 (3H, s, OCH₃), 3.89 (1H, m, CHO), 4.41 (1H, t, *J* = 5.5 Hz, CHN), 5.74 (2H, m, CH=CH)

¹³C NMR (100 MHz, CDCl₃); δ 172.0, 155.8, 131.8, 123.5, 79.8, 77.5, 57.1, 51.8, 37.7 (CH₂), 31.6 (CH₂), 28.4 (CH₂), 28.0 (CH₂), 25.5 (CH₂), 24.6 (CH₂), 22.7 (CH₂), 14.1

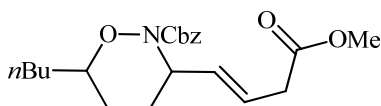
IR (NaCl) ν_{max}: 3425, 2954, 1735, 1165 cm⁻¹

MS (ESI) *m/z* 364 (M+Na)⁺

HRMS m/z ($M+Na$)⁺ calcd for C₁₈H₃₁NO₅Na 364.2100, found 364.2109

$[\alpha]_D^{21} = -0.5$ (c 1.6, CHCl₃)

Synthesis of (*E*)-benzyl 6-butyl-3-(4-methoxy-4-oxobut-1-en-1-yl)-1,2-oxazinane-2-carboxylate (2.52**)**



To a solution tetrahydro-1,2-oxazine (**2.33**) (0.33 g, 1.36 mmol) in CH₂Cl₂:H₂O (1:1) 10 mL and NaHCO₃ (0.13 g, 1.64 mmol) was added CbzCl (0.27 g, 1.64 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3×15mL). The organic layer and extracts were combined, dried, and evaporated to give the crude product, which was chromatographed on silica gel column with (hexane/EtOAc, 3:1) as the eluent to give the title product (**2.52**) (0.42 g, 82% yield) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 7.43-7.29 (5H, m, ArH), 5.77 (2H, dddd, $J = 15.2, 15.1, 8.3, 6.4$ Hz, CH=CH), 5.15 (2H, d, $J = 12.3$ Hz, CH₂Ph), 4.53 (1H, m, CH), 3.95 (1H, m, CH), 3.67 (3H, s, OCH₃), 3.08 (2H, m, CH₂CO₂CH₃), 1.99 (2H, m, CH₂), 1.82 (1H, m, CH₂), 1.62 (1H, m, CH₂), 1.54-1.23 (6H, m, 3×CH₂), 0.82 (3H, t, $J = 7.0$ Hz, CH₃)

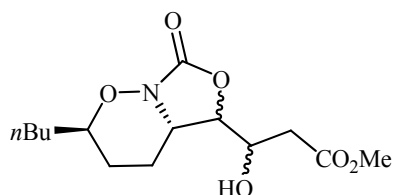
¹³C NMR (125 MHz, CDCl₃); δ 171.8, 155.5, 131.3, 131.3, 129.3, 128.8, 128.8, 128.3, 128.1, 124.0, 80.2, 73.4, 67.3, 57.1, 51.7, 37.5, 31.3, 27.9, 25.0, 24.4, 22.5, 13.9

IR (NaCl) ν_{max} : 2953, 2871, 1735, 1699, 1276, 1251, 1153 cm^{-1}

MS (ESI) m/z 376 (M+H)⁺, 332 (45%)

HRMS m/z (M+Na)⁺ calcd for C₂₁H₂₉NO₅Na 398.1981, found 398.1943

Synthesis of methyl 3-((2*R*,4*a*S)-2-butyl-7-oxohexahydrooxazolo[3,4-*b*][1,2]oxazin-5-yl)-3-hydroxypropanoate (2.47)



Trifluoroacetic anhydride (0.1 mL, 0.54 mmol) was added dropwise to a stirred mixture of UHP (0.17 g, 1.80 mmol) and tetrahydro-1,2-oxazine (**2.45**) (0.05 g, 0.18 mmol) in dichloromethane (50 mL) at room temperature. After 3 days the reaction mixture was quenched with saturated aqueous NaHCO₃ (20 mL), the aqueous layer was extracted with dichloromethane (50 mL) and the combined organic layers were dried over anhydrous MgSO₄. The solvent was subsequently evaporated off and the residue was chromatographed on a silica gel column with (hexane/EtOAc, 4:1) as the eluent to give the title product (**2.47**) (4.0 mg, 18% yield) as a colourless solid.

Mp = 95-97°C

^1H NMR (400MHz, CDCl_3); δ 4.25 (1H, q, $J = 5.9$ Hz, CHOH , minor), 4.16 (1H, dt, $J = 8.2, 2.2$ Hz, CHOCO , minor), 4.09 (1H, dt, $J = 8.2, 2.2$ Hz, CHOCO , major), 3.98 (1H, m, CH , minor), 3.94 (1H, m, CH , major), 3.90 (1H, q, $J = 8.2$ Hz, CHOH , major), 3.77 (1H, m, $\text{CH}_2\text{CHOCH}_2$), 3.73 (3H, s, OCH_3 , minor), 3.71 (3H, s, OCH_3 , major), 2.80 (1H, dd, $J = 17.4, 2.7$ Hz, CHHCO_2Me), 2.52 (1H, dd, $J = 17.4, 8.7$ Hz, CHHCO_2Me), 1.98-1.79 (2H, m, CH_2), 1.68-1.52 (2H, m, CH_2), 1.47-1.27 (6H, m, $3\times\text{CH}_2$)

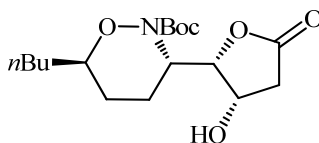
^{13}C NMR (100 MHz, CDCl_3); δ 173.0 (minor), 172.7 (major), 155.4 (minor), 154.5 (major), 81.5 (major), 80.5 (minor), 79.3 (major), 75.3 (minor), 67.3 (major), 65.2 (minor), 56.2 (minor), 54.8 (major), 52.2, 37.4 (minor), 37.0 (major), 33.7 (minor), 33.6 (major), 28.2 (major), 27.8 (minor), 27.3, 27.0, 22.6 (major), 21.2 (minor), 13.9

IR (NaCl) ν_{max} : 3451, 2955, 2932, 2871, 1774, 1438, 1063 cm^{-1}

MS (ESI) m/z 302 ($\text{M}+\text{H}$) $^+$

HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_6$ 302.1604, found 302.1610

Synthesis of (3*S*,6*R*)-*tert*-butyl 6-butyl-3-((2*S*,3*S*)-3-hydroxy-5-oxotetrahydrofuran-2-yl) morpholine-2-carboxylate (2.54b**)**



To a mixture of NMO (0.25 mL, 2.45 mmol), MeSO₂NH₂ (0.07 g, 0.81 mmol), (DHQD)₂PHAL (0.06 g, 0.08 mmol) and K₂O₈S₄·2H₂O (0.003 g, 0.08 mmol) in acetone:H₂O (9:1) at room temperature was added olefin (**2.45**) (0.27 g, 0.81 mmol) in one portion. The reaction mixture was stirred for 12 hours and then quenched with solid Na₂SO₃. Stirring was continued for an additional 1 hour, and the solution was extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated. Silica gel column chromatography of the crude product (EtOAc:hexane, 1:1) gave compound (**2.54b**) (0.168 g, 60% yield) as a colorless solid, followed by (**2.54a**) (0.042 g, 12% yield) as a colorless solid, (**2.54a/2.54b** = 1:10, isolated yield).

Mp = 146-147 °C

¹H NMR (400MHz, CDCl₃); δ 0.90 (1H, t, *J* = 6.8 Hz, CH₃), 1.29-1.58 (6H, m, 3×CH₂), 1.50 (9H, s, *t*Bu), 1.76-1.89 (2H, m, CH₂), 1.92-2.28 (2H, m, CH₂), 2.47 (1H, dd, *J* = 17.7, 4.1 Hz, CHHCO), 2.76 (1H, dd, *J* = 17.8, 6.4 Hz, CHHCO), 4.00 (1H, m, CH₂CHOCH₂), 4.12 (1H, brs, OH), 4.49 (1H, q, *J* = 6.8 Hz, CHN), 4.55 (1H, m, CHOH), 4.70 (1H, t, *J* = 5.9 Hz, CHO)

^{13}C NMR (100 MHz, CDCl_3); δ 174.4, 155.8, 82.2, 81.9, 81.4, 68.1, 53.3, 38.0 (CH_2), 32.8 (CH_2), 28.2, 27.9 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 20.6 (CH_2), 14.0

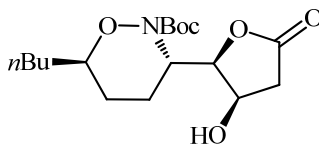
IR (NaCl) ν_{max} : 3417, 2939, 1774, 1666, 1427 cm^{-1}

MS (ESI) m/z 366 ($\text{M}+\text{Na}^+$)

HRMS m/z ($\text{M}+\text{Na}^+$)⁺ calcd for $\text{C}_{17}\text{H}_{29}\text{NO}_6\text{Na}$ 366.1893, found 366.1895

$[\alpha]_{\text{D}}^{21} = -8.13$ (c 0.51, CH_2Cl_2)

(3*S*,6*R*)-*tert*-Butyl 6-butyl-3-((2*R*,3*R*)-3-hydroxy-5-oxotetrahydrofuran-2-yl)morpholine-2-carboxylate (2.54a)



Mp = 124-126 °C

^1H NMR (400MHz, CDCl_3); δ 0.92 (1H, t, $J = 6.4$ Hz, CH_3), 1.30-1.45 (4H, m, $2\times\text{CH}_2$), 1.46 (9H, s, $t\text{Bu}$), 1.84 (2H, m, CH_2), 2.02 (1H, m, CH_2), 2.14 (1H, m, CH_2), 2.59 (1H, d, $J = 17.4$ Hz, CH_2), 2.72 (1H, ddd, $J = 17.4, 5.0, 2.3$ Hz, CH_2), 4.01 (1H, m, CHN), 4.31 (1H, m, CHO), 4.41 (1H, m, CH_2), 4.51 (1H, dd, $J = 10.5, 2.7$ Hz, CH_2), 4.70 (1H, brs, OH)

^{13}C NMR (100 MHz, CDCl_3); δ 175.3, 156.0, 82.9, 81.7, 81.6, 67.3, 50.9, 38.2 (CH_2), 32.0 (CH_2), 28.2, 28.0 (CH_2), 24.5 (CH_2), 22.6 (CH_2), 20.6 (CH_2), 14.0

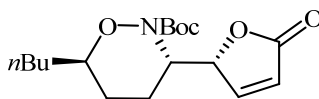
IR (NaCl) ν_{max} : 3417, 2931, 1782, 1643, 1435, 1165 cm^{-1}

MS (ESI) m/z 343 (M^+)

HRMS m/z ($M+Na$)⁺ calcd for $C_{17}H_{29}NO_6Na$ 366.1893, found 366.1903

$[\alpha]_D^{22} = -75.8$ (c 0.58, CH_2Cl_2)

Synthesis of (3*S*,6*R*)-*tert*-butyl 6-butyl-3-((*R*)-5-oxo-2,5-dihydrofuran-2-yl)morpholine-2-carboxylate (2.64**)**



To a stirred solution of alcohol (**2.54a**) (0.08 g, 2.40 mmol) in CH_2Cl_2 (5 mL) were added methanesulfonylchloride (0.3 mL, 3.60 mmol) and triethylamine (1.0 mL, 7.21 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was chromatographed on Silica gel (EtOAc/Hexane, 3:7) to give the butenolide (**2.64**) (0.24 g, 95% yield) as a colorless oil.

1H NMR (400MHz, $CDCl_3$); 0.90 (3H, t, $J = 6.8$ Hz, CH_3), 1.30-1.57 (6H, m, $3 \times CH_2$), 1.60 (9H, s, tBu), 1.70-1.86 (2H, m, CH_2), 1.96-2.11 (2H, m, CH_2), 3.75 (1H, m, CHN), 3.91 (1H, m, CHO), 5.40 (1H, dt, $J = 8.7, 1.8$ Hz, $CHOCH=CH$), 6.11 (1H, dd, $J = 5.9, 1.8$ Hz, $CHCH=CH$), 7.51 (1H, dd, $J = 5.9, 1.3$ Hz, $CH=CHCO$)

^{13}C NMR (100 MHz, $CDCl_3$); δ 172.7, 155.7, 154.7, 121.4, 82.0, 81.8, 80.9, 59.2, 32.4 (CH_2), 28.2, 27.9 (CH_2), 26.3 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 13.9

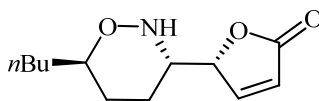
IR (NaCl) ν_{max} : 3425, 2931, 1759, 1689, 1396, 1172 cm^{-1}

MS (ESI) m/z 348 ($\text{M}+\text{Na}$)⁺

HRMS m/z ($\text{M}+\text{Na}$)⁺ calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_5\text{Na}$ 348.1787, found 348.1780

$[\alpha]_{\text{D}}^{22} = -109.4$ (c 0.83, CH_2Cl_2)

Synthesis of (*R*)-5-((3*S*,6*R*)-6-butylmorpholin-3-yl)furan-2(5*H*)-one (**2.65**)



A solution of butenolide (**2.64**) (0.06 g, 0.20 mmol) in 10 mL of CH_2Cl_2 at 0 °C was treated with trifluoroacetic acid (0.06 mL, 0.40 mmol) and stirred for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure, methanol saturated with ammonia (5 mL) was added, and the mixture was again concentrated. The crude product was purified by silica gel (triethylamine-deactivated) chromatography with EtOAc to give the title compound (**2.65**) (0.04 g, 96% yield) as a colourless oil.

^1H NMR (400MHz, CDCl_3); 0.81 (3H, t, $J = 6.9$ Hz, CH_3), 1.20-1.43 (8H, m, $4 \times \text{CH}_2$), 1.70 (2H, m, $2 \times \text{CH}_2$), 3.32 (1H, m, CHN), 3.37 (1H, m, CHO), 4.80 (1H, brs, NH), 4.99 (1H, dd, $J = 3.6, 1.8$ Hz, CHO), 6.09 (1H, dt, $J = 5.9, 1.4$ Hz, $\text{CH}=\text{CHCO}$), 7.45 (1H, d, $J = 5.9$ Hz, $\text{CH}=\text{CHCO}$)

^{13}C NMR (100 MHz, CDCl_3); δ 172.3, 153.5, 121.9, 83.2, 80.5, 58.4, 34.1 (CH_2), 29.6 (CH_2), 27.2 (CH_2), 24.0 (CH_2), 22.4 (CH_2), 13.7

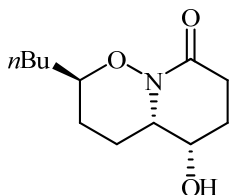
IR (NaCl) ν_{max} : 3425, 2931, 2862, 1751, 1651, 1458, 1342, 1165, 1095, 817 cm^{-1}

MS (ESI) m/z 226 ($\text{M}+\text{H}$) $^+$

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_3\text{Na}$ 248.1263, found 248.1263

$[\alpha]_{\text{D}}^{22} = -120.1$ (c 0.27, CH_2Cl_2)

Synthesis of 2-butyl-5-hydroxyhexahydropyrido[1,2-*b*][1,2]oxazin-8(2*H*)-one (2.67)



A solution of butenolide (**2.65**) (0.02 g, 0.08 mmol) and CaCO_3 (0.01 g, 0.08 mmol) in 2 mL of MeOH was hydrogenated over PtO_2 (2.0 mg) under H_2 overnight. After filtering off the catalyst, the MeOH was evaporated under reduced pressure, and the crude product was purified by flash column chromatography using NEt_3 deactivated silica gel (5% in $\text{MeOH}/\text{CH}_2\text{Cl}_2 = 0.5:9.5$) to give the bicyclic lactam (**2.67**) (0.02 g, 82% yield) as a colourless amorphous.

^1H NMR (400MHz, CDCl_3); δ 3.84 (1H, quint, $J = 3.6$ Hz, $\text{CH}_2\text{CHOCH}_2$), 3.72 (1H, m, CH), 3.60 (1H, dt, $J = 7.1, 3.4$ Hz, CH), 2.66 (1H, ddd, $J = 14.4, 8.8, 5.5$ Hz, CH_2),

2.35 (1H, dt, $J = 12.2, 5.6$ Hz, CH_2), 2.15 (1H, brs, OH), 2.04-1.92 (2H, m, CH_2), 1.84 (2H, m, CH_2), 1.75-1.50 (2H, m, CH_2), 1.48-1.28 (6H, m, $3 \times \text{CH}_2$), 0.90 (3H, t, $J = 3.2$ Hz, CH_3)

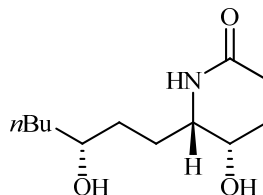
^{13}C NMR (100 MHz, CDCl_3); δ 81.9, 70.1, 64.7, 33.7, 30.0, 29.0, 28.2, 27.1, 26.5, 22.6, 13.9

IR (NaCl) ν_{max} : 3369, 2932, 2871, 1640, 1455, 1070, 955 cm^{-1}

MS (ESI) m/z 228 ($\text{M}+\text{H}$) $^+$

HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{12}\text{H}_{22}\text{NO}_3$ 228.1600, found 228.1607

Synthesis of (5*S*,6*S*)-5-hydroxy-6-((*R*)-3-hydroxyheptyl)piperidin-2-one (2.34)



A solution of butenolide (**2.65**) (0.02 g, 0.08 mmol) and CaCO_3 (0.01 g, 0.08 mmol) in 2 mL of MeOH was hydrogenated over pre-reduced Adam's catalyst PtO_2 (2.0 mg) in a Parr apparatus at 100 psi of H_2 overnight. After filtering off the catalyst, the MeOH was evaporated under reduced pressure, and the crude product was purified by flash column chromatography using NEt_3 deactivated silica gel (10% MeOH/ CH_2Cl_2) to give the amide (**2.34**) (0.02 g, 95% yield) as a colourless oil.

^1H NMR (400MHz, CDCl_3); δ 0.90 (3H, t, $J = 6.8$ Hz, CH_3), 1.28-1.50 (4H, m, $2\times\text{CH}_2$), 1.60 (2H, m, CH_2), 1.72-1.90 (2H, m, CH_2), 1.99 (1H, m, CH_2), 2.33 (1H, dt, $J = 18.8, 6.8$ Hz, CH_2), 2.5 (1H, dt, $J = 18.8, 6.8$ Hz, CH_2), 3.30 (1H, m, CH), 3.59 (1H, m, CH), 3.71 (1H, quint, $J = 5.5$ Hz, CH), 6.80 (1H, s, NH).

^{13}C NMR (100 MHz, CDCl_3); δ 172.2, 71.5, 67.5, 58.8, 37.4 (CH_2), 32.3 (CH_2), 30.1 (CH_2), 28.0 (CH_2), 27.8 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 14.0

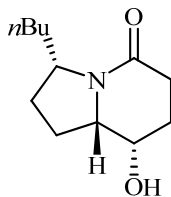
IR (NaCl) ν_{max} : 3417, 2121, 1635, 1473, 1265, 1033, 740 cm^{-1}

MS (ESI) m/z 230 ($\text{M}+\text{H}^+$)

HRMS m/z ($\text{M}+\text{Na}^+$)⁺ calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_3\text{Na}$ 252.1576, found 252.1581

$[\alpha]_{\text{D}}^{22} = -34.0$ (c 0.97, CHCl_3)

Synthesis of (3*S*,8*S*,8*a**S*)-3-butyl-8-hydroxyhexahydroindolizin-5(1*H*)-one (2.70)



To a solution of amide (**2.34**) (0.03 g, 0.13 mmol) in dry THF (2 mL) at -78 °C was added a 1.6 M of $n\text{BuLi}$ in hexane (0.1 mL, 0.16 mmol) under a nitrogen atmosphere. After stirring for 30 min, a solution of TsCl (0.03 g, 0.17 mmol) in dry THF (1 mL) was added. The mixture was stirred for 30 min and allowed to warm to room temperature during 1 hour. The reaction was quenched with saturated ammonium chloride (5 mL) and the mixture was poured into EtOAc (10 mL). The layers were separated, the

aqueous phase was extracted with EtOAc (3×30 mL), and the combined organic fractions were washed with brine (2×20 mL). The organic layer was dried with MgSO₄, filtered, and the solvent was removed *in vacuo*. The crude product obtained was purified by column chromatography on silica gel using MeOH/CH₂Cl₂ (1:9) as eluent to afford the title compound (**2.70**) (0.02 g, 52% yield) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 0.88 (3H, t, *J* = 6.9 Hz, CH₃), 1.10-1.36 (6H, m, 3×CH₂), 1.52-1.78 (2H, m, CH₂), 1.81 (1H, m, CHH), 1.94 (1H, m, CHH), 2.12 (1H, m, CHH), 2.15 (1H, m, CHH), 2.44 (1H, dd, *J* = 9.7, 7.4 Hz, CHH), 2.48 (1H, dd, *J* = 7.9, 3.6 Hz, CHH), 3.27 (1H, m, CH), 3.64 (1H, m, CH), 3.97 (1H, apparent t, CH).

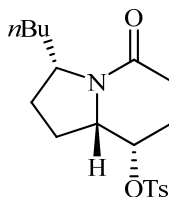
¹³C NMR (100 MHz, CDCl₃); δ 171.6, 72.0, 64.4, 57.8, 32.2, 30.7, 30.6, 29.1, 28.7, 27.6, 22.6, 14.0

IR (NaCl) ν_{max}: 3417, 1635, 1458, 1257, 1087 cm⁻¹

MS (ESI) *m/z* 212 (M+H)⁺

HRMS *m/z* (M+H)⁺ calcd for C₁₂H₂₂NO₂ 212.1651, found 212.1653

[α]_D²² = -3.38 (*c* 0.18, CH₂Cl₂)

3-Butyl-5-oxooctahydroindolizin-8-yl 4-methylbenzenesulfonate (2.71)

^1H NMR (400MHz, CDCl_3); δ 7.80 (2H, d, $J = 8.2$ Hz, ArH), 7.36 (2H, d, $J = 8.2$ Hz, ArH), 4.40 (1H, m, CH), 3.95 (1H, m, CH), 3.47 (1H, m, CH), 2.46 (3H, s, ArCH₃), 2.49-2.30 (2H, m, CH₂), 2.06 (2H, m, CH₂), 1.91-1.69 (4H, m, 2 \times CH₂), 1.52-1.06 (6H, m, 3 \times CH₂), 0.87 (3H, t, $J = 6.9$ Hz, CH₃)

^{13}C NMR (100 MHz, CDCl_3); δ 168.4, 145.1, 133.9, 129.9, 127.7, 80.2, 61.5, 57.7, 32.5, 30.2, 29.1, 28.7, 27.9, 27.4, 22.6, 21.6, 14.0

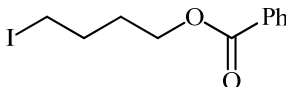
IR (NaCl) ν_{max} : 2927, 1649, 1447, 1414, 1190 cm^{-1}

MS (ESI) m/z 366 (M+H)⁺

HRMS m/z (M+H)⁺ calcd for C₁₉H₂₈NO₄S 366.1759, found 366.1758

4.4 Experimental Section for Chapter 3

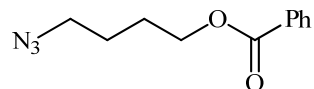
Synthesis of benzoic acid 4-iodo-butyl ester (**3.53**)¹⁶⁷



To a solution of NaI (55.3 g, 0.37 mol) in reagent grade THF (30 mL) and reagent grade acetonitrile (15 mL), with external cooling (~10-15 °C), benzoyl chloride (42.8 mL, 0.37 mol) was added in one portion. The reaction was stirred in the absence of light overnight. The reaction mixture was then diluted with water (approx. 100 mL). The organic layer was washed with saturated aqueous NaHSO₃ (50 mL), saturated aqueous Na₂CO₃ (50 mL) and dried over MgSO₄. The solvent was then removed *in vacuo* to give the title compound (**2.53**) as colourless oil (113.1 g, 90% yield). All spectral data were consistent with those reported in the literature.¹⁶⁷

¹H NMR (400 MHz, CDCl₃) δ 8.01 (2H, m, ArH), 7.53 (1H, t, *J* = 7.3 Hz, ArH), 7.43 (2H, t, *J* = 7.8 Hz, ArH), 4.34 (2H, t, *J* = 6.4 Hz, OCH₂), 3.24 (2H, t, *J* = 6.8 Hz, CH₂I), 1.99-1.88 (4H, m, CH₂)

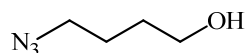
¹³C NMR (100 MHz, CDCl₃) δ 166.5, 132.9, 130.1, 129.5, 128.3, 63.7, 30.0 29.6, 5.9

Synthesis of 4-azidobutyl benzoate (3.50)¹⁶⁷

Sodium azide (35.8 g, 0.56 mol) was added portionwise to a solution of 4-iodobutyl benzoate (**3.53**) (111.5 g, 0.37 mol), in reagent grade DMF (300 mL) with external cooling (~10-15 °C) and in the absence of light. The reaction mixture was allowed to stir overnight, and then diluted with ether (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was further extracted with ether (3×100 mL) and the combined organic layers were concentrated *in vacuo*. The concentrate was then taken into hexane (100 mL), washed with water (50 mL), brine (30 mL) and dried over MgSO₄. The solvent was then removed *in vacuo* to give the title compound (**3.50**) as a colourless oil (85.2 g, quantitative). All spectral data were consistent with those reported in the literature.¹⁶⁷

¹H NMR (400 MHz, CDCl₃) δ 8.01 (2H, dd, *J* = 8.2, 0.9 Hz, ArH), 7.53 (1H, t, *J* = 7.3, Hz, ArH), 7.43 (2H, t, *J* = 7.8 Hz, ArH), 4.34 (2H, t, *J* = 6.4 Hz, OCH₂), 3.34 (2H, t, *J* = 6.8 Hz, CH₂N₃), 1.99-1.88 (4H, m, CH₂)

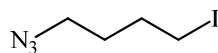
¹³C NMR (100 MHz, CDCl₃) δ 166.5, 132.9, 130.1, 129.5 (2C), 128.3 (2C), 63.7, 51.0, 26.0, 25.6

Synthesis of 4-azidobutanol (3.55)^{167b}

Lithium hydroxide (19.6 g, 0.47 mol) was added to a solution of 4-azidobutyl benzoate (**3.54**) (85.2, 0.39 mol) in reagent grade THF (100 mL), water (80 mL), and methanol (20 mL). The reaction mixture was left to stir overnight. The reaction was then diluted with water (50 mL) and ether (50 mL). The layers were then separated and the aqueous layer was further extracted with ether (3×50 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was then removed *in vacuo* to give the title compound (**3.55**) as a pale yellow oil (42.7 g, 95%). All spectral data were consistent with those reported in the literature.^{167b}

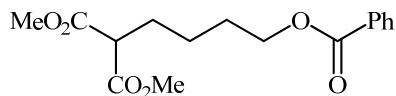
¹H NMR (400 MHz, CDCl₃) 3.65 (2H, t, *J* = 6.0 Hz, CH₂OH), 3.31 (2H, t, *J* = 6.4 Hz, CH₂N₃), 1.88 (1H, s, OH), 1.72-1.56 (4H, m, CH₂

¹³C NMR (100 MHz, CDCl₃) δ 62.1, 51.3, 29.7, 25.3

Synthesis of 5-azidobutyl-1-iodide (3.56)¹⁶⁸

To a solution of 5-azidobutanol (**3.55**) (6.7 g, 0.06 mol) in a 1:1 mixture of acetonitrile and tetrahydrofuran (10 mL) at 0 °C was sequentially added imidazole (10.3 g, 0.015 mol), triphenylphosphine (19.8 g, 0.08 mol), and iodine (22.0 g, 0.09 mol). The reaction was stirred for 20 min, subsequently it was quenched with aqueous saturated Na₂S₂O₃ (50 mL). The aqueous layer was extracted with ethyl acetate (3×50 mL), and the combined organic layers were washed with water, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification by flash chromatography (4:1) hexane/ethyl acetate) afforded the 5-azidobutyl-1-iodide (**3.56**) (6.0 g, 71%) as clear oil that was used immediately in the next reaction. The ¹H NMR spectroscopic data were consistent with those reported in the literature.¹⁶⁸

¹H NMR (400 MHz, CDCl₃) 3.34 (2H, t, *J* = 6.4 Hz, CH₂N₃), 3.25 (2H, t, *J* = 6.8 Hz, CH₂I), 1.72-1.56 (4H, m, CH₂)

Synthesis of 2-(4-benzoyloxy-butyl)-malonic acid dimethyl ester (3.62)

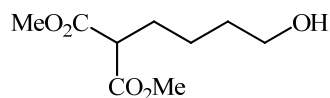
To a 50 mL THF solution of KO^tBu (14.8 g, 0.27 mol) added a THF solution of dimethyl malonate (30 mL, 0.55 mol) slowly at 0 °C. After stirring the reaction mixture at the same temperature for 5 minute, a 20 mL solution of benzoic acid 4-iodo-butyl ester (**3.53**) (26.6 g, 0.18 mol) in THF was added dropwise, and stirred for another 3-4 days. Upon completion the reaction was quenched with saturated aqueous NH₄Cl. The layers were separated and the aqueous layer was extracted with EtOAc and the combined organic extracts was washed with brine, anhydrous MgSO₄ and the solvent removed *in vacuo* to afford the crude product, which was distilled to remove the excess of dimethyl malonate (50 °C at 4 mmHg) to provide the title compound (**3.62**) as a colourless oil (57.0 g, 94%)

¹H NMR (400 MHz, CDCl₃) δ 7.99 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.51 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.39 (2H, t, *J* = 7.8 Hz, Ar*H*)
¹³C NMR (100 MHz, CDCl₃) δ 169.5, 166.3, 132.7, 130.1, 129.3, 128.1, 64.3 (CH₂), 52.3 51.3, 28.3 (CH₂), 28.2 (CH₂), 23.7 (CH₂)

IR (NaCl) ν_{max}: 2954, 1732, 1715, 1451, 1435, 1270, 1152, 1115, 710 cm⁻¹

MS (ESI) *m/z* 309 (M+H)⁺, 187 (30%)

HRMS *m/z* (M+Na)⁺ calcd for C₁₆H₂₀O₆Na 331.1158, found 331.1172

Synthesis of 2-(4-hydroxy-butyl)-malonic acid dimethyl ester (3.63)

Potassium carbonate (11.3 g, 82.1 mmol), was added to a solution of 2-(4-benzoyloxy-butyl)-malonic acid dimethyl ester (**3.62**) (23.0 g, 74.6 mmol), in reagent grade MeOH (50 mL). The reaction was left to stir for 1 hour at room temperature. The reaction was then diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (50 mL) and dried over MgSO₄. The solvent was then removed *in vacuo* to give the title compound (**3.63**) as pale yellow oil (14.5 g, 95%).

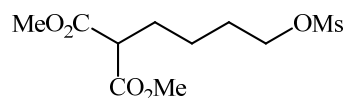
¹H NMR (400MHz, CDCl₃); δ 3.70 (6H, s, 2×OCH₃), 3.59 (2H, t, *J* = 6.4 Hz, CH₂OH), 3.34 (1H, t, *J* = 7.8 Hz, COCHCO), 1.88 (2H, m, CH₂), 1.54 (2H, m, CH₂), 1.36 (2H, m, CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 169.7, 62.1 (CH₂), 52.4, 51.5, 32.0 (CH₂), 28.4 (CH₂), 23.4 (CH₂)

IR (NaCl) ν_{max}: 3381, 2954, 2867, 1729, 1435, 1343, 1198, 1150, 1055, 1033 cm⁻¹

MS (ESI) *m/z* 205 (M+H)⁺, 187 (70%), 173 (100%), 83 (21%)

HRMS *m/z* (M+H)⁺ calcd for C₉H₁₇O₅ 205.0362, found 205.0345

Synthesis of 2-(4-methanesulfonyloxy-butyl)-malonic acid dimethyl ester (3.64)

To a stirred solution of alcohol (**3.63**) (15.2 g, 0.75 mol) in THF, triethylamine (6.36 mL, 0.14 mol) was added. After cooling the mixture to 0 °C and dropwise addition of methanesulfonyl chloride (20.8 mL, 0.82 mol), the reaction mixture was stirred for 1 hour at room temperature. Then, a mixture of water and ice (100 mL) were added and stirred until the ice was melted. The aqueous layer was separated and extracted with ether (3×100 mL). The combined organic layers were washed once with water (100 mL), once with aqueous 2N HCl (50 mL), once with saturated aqueous NaHCO₃ (50 mL), brine, dried (MgSO₄), and evaporated to give the crude product which was then purified by flash column chromatography (EtOAc/hexane 1:5) to give the title compound (**3.64**) (17.9 g, 82%) as a yellowish oil.

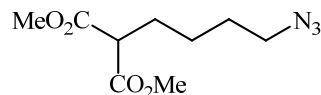
¹H NMR (400MHz, CDCl₃); δ 4.16 (2H, t, *J* = 6.4 Hz, CH₂), 3.67 (6H, s, 2×OCH₃), 3.31 (1H, t, *J* = 7.8 Hz, COCHCO), 2.95 (3H, s, CH₃), 1.87 (2H, m, CH₂), 1.72 (2H, m, CH₂), 1.39 (2H, m, CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 169.4, 69.3 (CH₂), 52.3, 51.5, 37.1, 28.5 (CH₂), 27.9 (CH₂), 23.1 (CH₂)

IR (NaCl) ν_{max}: 1729, 1347, 1242, 1222, 1168, 939 cm⁻¹

MS (ESI) *m/z* 283 (M+H)⁺, 187 (27%), 173 (12%)

HRMS *m/z* (M+Na)⁺ calcd for C₁₀H₁₈O₇SNa 305.0671, found 305.0695

Synthesis of 2-(4-azido-butyl)-malonic acid dimethyl ester (3.61)

Sodium azide (11.6 g, 0.18 mol) was added portionwise to a solution of mesylated compound (**3.64**) (16.9 g, 59.7 mmol), in reagent grade DMF (10 mL) with external cooling (~10-15 °C) and in the absence of light. The reaction mixture was allowed to stir overnight, and then diluted with ether (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was further extracted with ether, the combined organic layers were concentrated *in vacuo* to afford product then purified by flash column chromatography (EtOAc/Hexane 1:5) to give the title compound (**3.61**) (12.8 g, 94%) as a colourless oil.

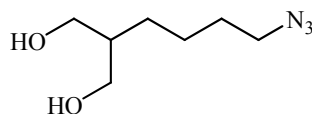
^1H NMR (400MHz, CDCl_3); δ 3.72 (6H, s, $2\times\text{OCH}_3$), 3.34 (1H, t, $J = 7.3$ Hz, COCHCO), 3.26 (2H, t, $J = 6.9$ Hz, CH_2N_3), 1.90 (2H, m, CH_2), 1.59 (2H, m, CH_2), 1.39 (2H, m, CH_2)

^{13}C NMR (100 MHz, CDCl_3) δ 169.4, 52.2, 51.2, 50.7 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 24.2 (CH_2)

IR (NaCl) ν_{max} : 2092, 1731, 1435, 1250, 1197, 1149, 1012 cm^{-1}

MS (ESI) m/z 202 (26%), 138 (12%)

HRMS m/z ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_9\text{H}_{16}\text{N}_3\text{O}_4$ 230.0849, found 230.0847

Synthesis of 2-(4-azido-butyl)-propane-1,3-diol (3.50)

To a suspension of LiCl (0.5 g, 11.9 mmol) and NaBH₄ (9.3 g, 0.24 mol) in THF (10 mL) and EtOH (10 mL) was added ester (**3.61**) (13.7 g, 59.7 mmol) at 20-30 °C during 1 hour. Conc. HCl (7.5 mL) was added below 20 °C and the mixture was stirred at room temperature for 1 hour. After filtration, the filtrate was concentrate *in vacuo*. The residue was dissolved in EtOAc (50 mL) and the solution was washed with 7.5% aqueous NaHCO₃ (50 mL). The organic layer was separated and the aqueous layer was further extracted with EtOAc (3× 50 mL), and the organic layer were concentrated *in vacuo* to afford the title diol (**3.50**) (8.6 g, 83%) as a colourless oil.

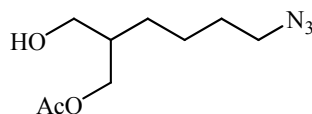
¹H NMR (400MHz, CDCl₃); δ 3.73 (2H, m, CH₂), 3.59 (2H, m, CH₂), 3.47 (1H, brs, OH), 3.25 (2H, m, CH₂), 1.68 (1H, brs, OH), 1.56 (2H, m, CH₂), 1.39 (2H, m, CH₂), 1.25 (2H, m, CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 65.6 (CH₂), 65.4 (CH₂), 51.3 (CH₂), 41.8, 29.1 (CH₂), 27.3 (CH₂), 24.3 (CH₂)

IR (NaCl) ν_{max}: 3333, 2934, 2865, 2091, 1257, 1030 cm⁻¹

MS (ESI) *m/z* 174 (M+H)⁺, 146 (50%), 138 (45%), 128 (25%), 110 (25%)

HRMS *m/z* (M+Na)⁺ calcd for C₇H₁₅N₃O₂Na 196.1059, found 196.1062

Synthesis of acetic acid 6-azido-2-hydroxymethyl-hexyl ester (3.65)

Concentrated H₂SO₄ (2.5 mL, 0.47 mmol) was added to a mixture of diol (**3.50**) (8.1 g, 46.6 mmol) and triethylorthoacetate (12.8 mL, 69.9 mmol) in dry THF (50 mL). The reaction was allowed to stir for 2 hours and the mixture was then poured into an ice-cold solution of 5% NaHCO₃ (50 mL). The product was extracted with CH₂Cl₂ (3×30 mL), washed with saturated aqueous NaCl (50 mL), and dried over anhydrous Na₂SO₄. The solvent was evaporated *in vacuo* to give the crude product, which was dissolved in 80% aqueous acetic acid (10 mL) and left for 1 hour at room temperature. The solution was evaporated to dryness and the residue was co-evaporated three times with water to afford the title compound (**3.65**) as a colorless oil (8.9 g, 89%).

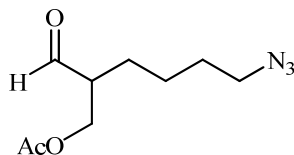
¹H NMR (400MHz, CDCl₃); δ 4.07 (2H, ddd, *J* = 15.1, 11.4, 5.0 Hz, CH₂O), 3.50 (2H, ddd, *J* = 16.4, 11.0, 4.6 Hz, CH₂O), 3.22 (2H, t, *J* = 6.8 Hz, CH₂N₃), 2.46 (1H, brs, OH), 2.01 (3H, s, COCH₃), 1.75 (1H, m, CH₂CHCH₂), 1.55 (2H, m, CH₂), 1.42-1.35 (4H, m, 2×CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 171.5, 64.3 (CH₂), 62.1 (CH₂), 51.0 (CH₂), 40.1, 28.8 (CH₂), 27.2 (CH₂), 23.9 (CH₂), 20.7

IR (NaCl) ν_{max}: 3420, 2933, 2866, 2092, 1735, 1459, 1366, 1236, 1033 cm⁻¹

MS (ESI) *m/z* 216 (M+H)⁺, 188 (100%), 128 (50%), 110 (32%)

HRMS *m/z* (M+Na)⁺ calcd for C₉H₁₇N₃O₃Na 238.1151, found 238.1168

Synthesis of acetic acid 6-azido-2-formyl-hexyl ester (3.67)

Alcohol (**3.65**) (0.12 g, 55.8 mmol), was added to a solution of IBX (0.22 g, 78.1 mmol), in reagent grade DMSO (5 mL) with external cooling (~10-15 °C). On complete consumption of starting material by TLC analysis, the mixture was diluted with water (10 mL) and filtered through a thick pad of Celite, washing through with EtOAc (3×25 mL). The aqueous layer was separated, saturated with NaCl (20 mL) and extracted with EtOAc (3× 50 mL). Subsequently the solvent was evaporated *in vacuo* to give the title compound (**3.67**) (0.1 g, 50% yield) as a colourless oil.

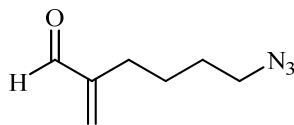
^1H NMR (400MHz, CDCl_3); δ 9.68 (1H, s, CHO), 4.32 (2H, d, $J = 6.4$ Hz, CH_2OAc), 3.29 (2H, t, $J = 6.9$ Hz, CH_2N_3), 2.61 (1H, m, CH), 2.05 (3H, s, COCH_3), 1.8-1.4 (6H, m, $3\times\text{CH}_2$)

^{13}C NMR (100 MHz, CDCl_3) δ 201.7, 62.1, 51.1, 50.9, 44.4, 28.9, 25.3, 24.1, 20.8

IR (NaCl) ν_{max} : 2092, 1729, 1227, 1038 cm^{-1}

MS (ESI) m/z 236 ($\text{M}+\text{Na}$) $^+$

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_9\text{H}_{15}\text{N}_3\text{O}_3\text{Na}$ 236.0954, found 236.0959

Synthesis of 6-azido-2-methylene-hexanal (3.48)

Aldehyde (**3.67**) (0.1 g, 44.8 mmol) was treated with triethylamine (0.1 mL, 49.3 mmol) in DMSO:CH₂Cl₂ (1:1) (10 mL). The reaction mixture was allowed to stir for 3-4 hours, and then diluted with CH₂Cl₂ (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was further extracted with CH₂Cl₂ (3×20 mL). The combined organic layers were concentrated *in vacuo* to afford the crude product, which was then purified by flash column chromatography (EtOAc/hexane 1:5) to give the title compound (**3.48**) (0.07 g, 93%) as a colourless oil.

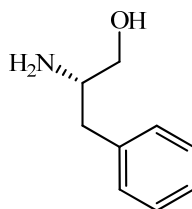
¹H NMR (400MHz, CDCl₃); δ 9.51 (1H, s, CHO), 6.24 (1H, s, CHH), 6.00 (1H, s, CHH), 3.25 (2H, t, *J* = 6.4 Hz, CH₂N₃), 2.24 (2H, t, *J* = 7.4 Hz, CH₂C=C), 1.50 (4H, m, 2×CH₂)

¹³C NMR (100 MHz, CDCl₃) δ 194.4, 149.5, 134.2 (CH₂), 51.0 (CH₂), 28.3 (CH₂), 27.2 (CH₂), 24.8 (CH₂)

IR (NaCl) ν_{\max} : 3374, 2941, 2867, 2090, 1736, 1687, 1456, 1239, 1041, 949 cm⁻¹

MS (ESI) *m/z* 154 (M+H)⁺

HRMS *m/z* (M+H)⁺ calcd for C₇H₁₂N₃O 154.0980, found 154.0974

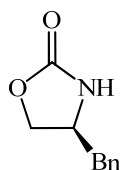
Synthesis of (*S*)-phenylalaninol (3.92**)^{122,134a}**

Under, nitrogen, to a suspension of NaBH₄ (6.1 g, 0.16 mol) in anhydrous THF (100 mL), cooled to 0 °C was added dropwise with vigorous mechanical stirring. BF₃·OEt₂ (39.6 mL, 0.32 mol). Careful temperature monitoring was mandatory to keep the reaction temperature below 5 °C. (*S*)-Phenylalanine (**3.91**) (13.2 g, 0.08 mol) was added in portion at 0 °C. After completion of the addition and the ending of gas evolution, the mixture was stirred at room temperature overnight. The reaction was quenched with methanol (50 mL) and evaporated *in vacuo*. 12 N NaOH (80 mL) was added and stirred for 1 hour and subsequently filtration through Celite gave the crude mixture. The resulting slurry was extracted with four 50 mL portions of CHCl₃. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give the (*S*)-phenylalaninol (**3.92**) (5.1 g, 74 %) as a colourless solid. All spectral data were consistent with those reported in the literature.^{122,134b}

¹H NMR (400MHz, CDCl₃); δ 7.30 (2H, t, *J* = 7.8 Hz, ArH), 7.23 (1H, t, *J* = 7.3 Hz, ArH), 7.18 (2H, d, *J* = 6.9 Hz, ArH), 3.62 (1H, dd, *J* = 11.0, 4.1 Hz, CHHOH), 3.37 (1H, dd, *J* = 10.9, 7.3 Hz, CHHOH), 3.11 (1H, m, CH₂CHCH₂), 2.78 (1H, dd, *J* = 13.7, 5.4 Hz, CHHPh), 2.51 (1H, dd, *J* = 8.6, 8.6 Hz, CHHPh)

^{13}C NMR (100 MHz, CDCl_3) δ 138.6, 129.1 (2CH), 128.4 (2CH), 126.3 (CH), 66.0 (CH₂), 54.1, 40.6 (CH₂)

Synthesis of (*S*)-4-benzyloxazolidin-2-one (3.93**)^{122,134b}**

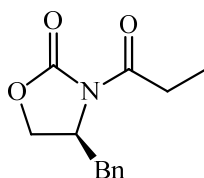


(*S*)-Phenylalaninol (**3.92**) (5.1 g, 0.04 mol), dry K_2CO_3 (0.5 g, 3.69 mmol) and diethyl carbonate (8.6 mL, 0.07 mol) were mixed. With stirring, the mixture was heated to 135 °C in a distillation apparatus; the remaining solid amino alcohol dissolved within 5 min. Distilling EtOH (10 mL) was collected over a period of 2 h. Then, the mixture was allowed to cool to room temperature and CH_2Cl_2 (20 mL) was added. The organic layer was washed with H_2O (50 mL) and dried (Na_2SO_4). After removal of the solvent a colourless oil was obtained, which crystallized from EtOAc/hexane (3:2) to give the oxazolidinone (**3.93**) (4.6 g, 77%) as colourless crystals. All spectral data were consistent with those reported in the literature.^{122,134b}

^1H NMR (500MHz, CDCl_3); δ 7.34 (2H, t, $J = 7.1$ Hz, ArH), 7.27 (1H, t, $J = 7.4$ Hz, ArH), 7.18 (2H, d, $J = 7.2$ Hz), 5.46 (1H, brs, NH), 4.46 (1H, t, $J = 8.3$ Hz, CHHOCO), 4.16 (1H, t, $J = 5.5$ Hz, CHHOCO), 4.10 (1H, m, CH_2CHCH_2), 2.88 (2H, d, $J = 6.7$ Hz, CH_2Ph)

^{13}C NMR (100 MHz, CDCl_3) δ 159.7 (OCO), 135.7, 128.8 (2CH), 128.6 (2CH), 126.8 (CH), 69.2 (OCH_2), 53.4 (CH), 40.9 (CH_2)

Synthesis of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (3.49**)^{122,134b}**

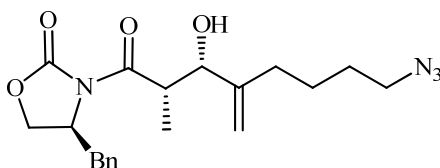


A solution of (*S*)-4-phenylmethyl-2-oxazolidinone (**3.93**) (3.8 g, 214 mmol) in anhydrous THF (20 mL) under N_2 , was cooled to $-78\text{ }^\circ\text{C}$. *n*BuLi (1.6 M in hexane) (16 mL, 257 mmol) was added dropwise to the reaction mixture. After 20 minutes, propionyl chloride (2.6 mL, 300 mmol) was added dropwise. After 2.5 hours the reaction mixture was allowed to warm to room temperature and was quenched with saturated aqueous NH_4Cl (20 mL). The majority of the THF was removed *in vacuo*. CH_2Cl_2 (50 mL) was added and this solution was washed with 10% aqueous NaOH (30 mL). This aqueous layer was extracted again with CH_2Cl_2 (2 \times 25 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated *in vacuo* to yield the title compound (**3.49**) (5.0 g, 88%) as a colourless solid. All spectral data were consistent with those reported in the literature.^{122,134b}

^1H NMR (400MHz, CDCl_3); δ 7.33 (2H, t, $J = 7.3$ Hz, ArH), 7.25 (1H, t, $J = 7.3$ Hz, ArH), 7.18 (2H, d, $J = 7.3$ Hz, ArH), 4.64 (1H, m, CH_2CHCH_2), 4.15 (2H, t, $J = 7.8$

Hz, OCH₂CH), 3.26 (1H, dd, $J = 13.7, 3.6$ Hz, CHHPH), 2.93 (2H, q, $J = 7.8$ Hz, CH₂CH₃), 2.75 (1H, dd, $J = 13.7, 9.6$ Hz, CHHPH), 1.18 (3H, t, $J = 7.7$ Hz, CH₂CH₃)
¹³C NMR (400MHz, CDCl₃); δ 173.8 (COCH₃), 153.3 (OCO), 135.1, 129.2, 128.7, 127.1, 66.0(OCH₂), 54.9(CH), 37.6(CH₂), 28.9(CH₂), 8.1(CH₃)
 $[\alpha]_D^{21} = +55.6$ (c 1.27, CHCl₃)

Synthesis of (S)-3-((2S,3S)-8-azido-3-hydroxy-2-methyl-4-methyleneoctanoyl)-4-benzyloxazolidin-2-one (3.47)



To a dry round bottomed flask under nitrogen was added a solution of oxazolidinone (**3.49**) (0.15 g, 0.65 mmol) in CH₂Cl₂ (10 mL). The solution was cooled to 0 °C. Titanium (IV) chloride (0.7 mL, 0.72 mmol) was added dropwise and the solution allowed to stir for 5 minutes. To the yellow slurry or suspension was added diisopropylethylamine (0.3 mL, 1.76 mmol). The dark red titanium enolate was stirred for 20 minutes at 0 °C, and then was cooled to -78 °C. Aldehyde (**3.48**) (0.1 g, 0.62 mmol) was added dropwise. The resulting mixture was stirred for one hour at -78 °C and then was warmed to 0 °C. The reaction was quenched with saturated aqueous NH₄Cl (20 mL), and the layers were extracted with CH₂Cl₂ (2×20 mL). The organic layers were combined and dried with anhydrous Na₂SO₄, filtered and concentrated. The resulting resi-

due was purified by flash column chromatography (EtOAc/hexane 1:3) to give the title compound (**3.47**) (0.19 g, 75%) as a colourless oil.

^1H NMR (400MHz, CDCl_3); δ 7.36-7.28 (4H, m, ArH), 7.20 (1H, d, $J = 6.8$ Hz, ArH), 5.22 (1H, s, C=CHH), 4.72 (1H, m, CH_2CHCH_2), 4.44 (1H, brs, OH), 4.23 (1H, dd, $J = 9.1, 7.8$ Hz, CH_2O), 4.22 (1H, d, $J = 2.7$ Hz, CHOH), 3.96 (1H, ddd, $J = 9.6, 6.8, 2.7$ Hz, CH_2O), 3.29 (2H, t, $J = 6.4$ Hz, CH_2N_3), 2.91 (1H, d, $J = 2.7$ Hz, CH), 2.79 (1H, dd, $J = 13.7, 13.2$ Hz, CH), 2.04 (1H, m, CHCH₃), 1.60 (6H, m, $3 \times \text{CH}_2$), 1.20 (3H, d, $J = 6.8$ Hz, CH₃)

^{13}C NMR (100 MHz, CDCl_3) δ 177.0, 152.9, 147.3, 134.9, 129.3, 128.9, 127.4, 111.0 (CH₂), 72.8, 66.2 (CH₂), 55.1, 51.2 (CH₂), 40.2, 37.7 (CH₂), 32.1 (CH₂), 28.5 (CH₂), 24.9 (CH₂), 10.0

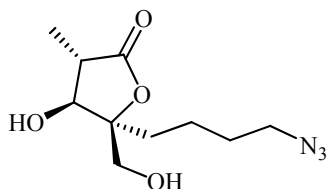
IR (NaCl) ν_{max} : 3507, 2938, 2095, 1775, 1697, 1454, 1384, 1209, 1108, 906, 702 cm^{-1}

MS (ESI) m/z 359 (M+H)⁺, 341 (100%)

HRMS m/z (M+H)⁺ calcd for $\text{C}_{19}\text{H}_{27}\text{N}_4\text{O}_3$ 359.2083, found 359.2083

$[\alpha]_{\text{D}}^{23} = +42.49$ (c 1.32, CH_2Cl_2)

Synthesis of (3*S*,4*S*,5*S*)-5-(4-azidobutyl)-4-hydroxy-5-(hydroxymethyl)-3-methyl-dihydrofuran-2(3*H*)-one (3.46)



Vanadyl acetyl acetonate (2.0 mg, 0.04 mmol) was added in one portion to a stirred solution of alkene (**3.47**) (0.11 g, 0.27 mmol) in anhydrous toluene (5 mL) under nitrogen at room temperature. After 5 minutes, *t*BuOOH (0.1 mL, 0.29 mmol, 70% in water) was added in one portion and the reaction mixture stirred for one hour at room temperature before additional of water (1 mL). The reaction mixture was then stirred at room temperature overnight, before removal of solvent *in vacuo* to afford a crude product that was purified by column chromatography (2 % MeOH/CH₂Cl₂) to afford the lactone (**3.46**) (0.04 g, 66%) as a colourless amorphous.

¹H NMR (400MHz, CDCl₃); δ 3.93 (1H, d, *J* = 12.3 Hz, CHO), 3.82 (2H, dd, *J* = 11.8 Hz, CH₂OH), 3.64 (2H, brs, 2×OH), 3.30 (2H, t, *J* = 6.8 Hz, CH₂N₃), 2.88 (1H, quint, *J* = 6.9 Hz, CHCH₃), 1.80-1.60 (4H, m, 2×CH₂), 1.47 (2H, m, CCH₂), 1.30 (3H, d, *J* = 7.3 Hz, CHCH₃)

¹³C NMR (100 MHz, CDCl₃) δ 177.7 (CO), 87.4, 80.4 (CH), 64.4 (CH₂), 50.9 (CH₂), 44.0 (CH), 35.0 (CH₂), 28.9 (CH₂), 20.2 (CH₂), 13.8 (CH₃)

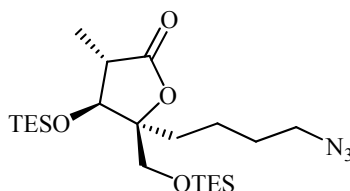
IR (NaCl) ν_{max}: 3417, 2938, 2096, 1755, 1456, 1249, 1213, 1053, 944, 704 cm⁻¹

MS (ESI) *m/z* 244 (M+H)⁺

HRMS m/z (M+H)⁺ calcd for C₁₀H₁₈N₃O₄ 244.1297, found 244.1297

$[\alpha]_D^{23} = +1.34$ (c 0.3, CH₂Cl₂)

Synthesis of (3*S*,4*S*,5*S*)-5-(4-azidobutyl)-3-methyl-4-(triethylsilyloxy)-5-((triethylsilyloxy)methyl)dihydrofuran-2(3*H*)-one (3.110)



Triethylamine (0.2 mL, 1.36 mmol) and triethyl silyl chloride (0.12 g, 0.81 mmol) were added to a solution of diol (**3.46**) (0.07 g, 0.27 mmol) in dry CH₂Cl₂ (10 mL) at room temperature. After stirring at room temperature overnight, the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL) and the mixture was extracted with CH₂Cl₂ (2×20 mL). The combined organic phases were washed with water, brine, and then dried (MgSO₄). The solvent was removed under reduced pressure, to give crude TES protected product which was then purified by flash column chromatography (EtOAc/hexane 1:4) to give the title compound (**3.110**) (0.12 g, 93%) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 3.90 (2H, t, $J = 10.0$ Hz, CH₂OSi), 3.59 (1H, d, $J = 10.6$ Hz, CHO), 3.27 (2H, t, $J = 6.7$ Hz, CH₂N₃), 2.96 (1H, quint, $J = 7.4$ Hz, CHCH₃), 1.66-1.41 (6H, m, 2×CH₂), 1.23 (3H, d, $J = 7.3$ Hz, CH₃CH), 0.97 (9H, t, $J = 8.0$ Hz,

$3\times\text{CH}_3$), 0.93 (9H, t, $J = 7.9$ Hz, $3\times\text{CH}_3$), 0.62 (6H, q, $J = 7.7$ Hz, $3\times\text{CH}_2$), 0.57 (6H, q, $J = 7.7$ Hz, $3\times\text{CH}_2$)

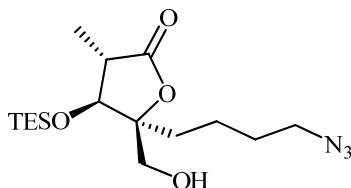
^{13}C NMR (125MHz, CDCl_3) δ 177.1, 86.2, 80.3, 64.0 (CH_2), 51.1 (CH_2), 43.3, 33.9 (CH_2), 29.1 (CH_2), 20.5 (CH_2), 14.4, 6.7, 6.6, 5.1 (CH_2), 4.2 (CH_2)

IR (NaCl) ν_{max} : 2956, 2917, 2877, 2850, 2097, 1770, 1647, 1458, 1264, 1111 cm^{-1}

MS (ESI) m/z 472 ($\text{M}+\text{H}$)⁺, 426 (15%)

HRMS m/z ($\text{M}+\text{Na}$)⁺ calcd for $\text{C}_{22}\text{H}_{45}\text{N}_3\text{O}_4\text{Si}_2\text{Na}$ 494.2870, found 494.2846

Synthesis of (3*S*,4*S*,5*S*)-5-(4-azidobutyl)-5-(hydroxymethyl)-3-methyl-4-(triethylsilyloxy)dihydrofuran-2(3*H*)-one (3.111)



To solution of TES protected alcohol (**3.110**) (0.09 g, 0.02 mmol) in MeOH (5 mL) was added PPTS (0.05 g, 0.02 mmol) in one portion. The resulting mixture was stirred vigorously for 2 hours. Brine (5 mL) was added to the reaction mixture and the solvent was removed *in vacuo*. The resulting residue was diluted with EtOAc (20 mL) and added to a separating funnel containing brine (20 mL). The aqueous layer was extracted with EtOAc (2 \times 20 mL). The organic layers were combined and dried with anhydrous Na_2SO_4 , filtered and concentrated. The resulting residue was purified by flash

column chromatography (EtOAc/hexane 1:4) to give the title compound (**3.111**) (0.06 g, 92%) as a clear oil.

^1H NMR (400MHz, CDCl_3); δ 3.99 (1H, d, $J = 8.5$ Hz, CHO), 3.82 (1H, dd, $J = 12.4$, 6.2 Hz, CHHOH), 3.72 (1H, dd, $J = 8.0$ Hz, CHHOH), 3.29 (2H, t, $J = 6.7$ Hz, CH_2N_3), 2.81 (1H, quint, $J = 7.4$ Hz, CHCH_3), 2.30 (1H, t, $J = 6.6$ Hz, CH_2C), 1.81 (1H, m, CH_2C), 1.65-1.43 (4H, m, $2 \times \text{CH}_2$), 1.31 (3H, d, $J = 7.3$ Hz, CH_3CH), 0.92 (9H, t, $J = 8.0$ Hz, $3 \times \text{CH}_3$), 0.66 (6H, q, $J = 7.8$ Hz, $2 \times \text{CH}_2$)

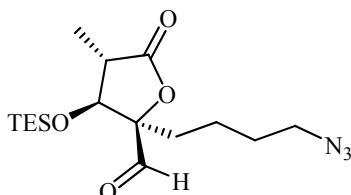
^{13}C NMR (100 MHz, CDCl_3) δ 176.0, 86.2, 81.2, 64.8 (CH_2), 51.0 (CH_2), 43.6, 34.4 (CH_2), 28.9 (CH_2), 20.2 (CH_2), 14.1, 6.6, 4.9 (CH_2)

IR (NaCl) ν_{max} : 3460, 2956, 2878, 2096, 1775, 1458, 1245, 1137, 1009 cm^{-1}

MS (ESI) m/z 358 ($\text{M}+\text{H}$) $^+$, 330 (60%), 312 (15%), 244 (15%), 216 (15%), 198 (15%)

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_{16}\text{H}_{31}\text{N}_3\text{O}_4\text{SiNa}$ 380.2006, found 380.1982

Synthesis of (2*R*,3*S*,4*S*)-2-(4-azidobutyl)-4-methyl-5-oxo-3-(triethylsilyloxy) tetrahydrofuran-2-carbaldehyde (3.115)



Dess-Martin periodinane (0.19 g, 0.46 mmol), was added to a mixture of the alcohol (**3.111**) (0.07 g, 0.21 mmol) and NaHCO₃ (0.05 g, 0.62 mmol), in dry dichloromethane (10 mL) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature. The reaction was monitored by TLC to ensure the complete oxidation. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Hexane 1:4) to give the title compound (**3.115**) (0.07 g, 98%) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 9.61 (1H, s, HC=O), 4.03 (1H, d, *J* = 7.9 Hz, CHO), 3.27 (2H, t, *J* = 6.7 Hz, CH₂N₃), 2.61 (1H, quint, *J* = 7.5 Hz, CHCH₃), 2.26 (1H, m, CHHCH₂), 1.64 (1H, m, CHHCH₂), 1.61 (2H, quint, *J* = 7.1 Hz, CH₂CH₂N₃), 1.48 (1H, m, CHHCH₂C), 1.36 (1H, m, CHHCH₂C), 1.30 (3H, d, *J* = 7.3 Hz, CH₃CH), 0.95 (9H, t, *J* = 7.9 Hz, 3×CH₃CH₂Si), 0.62 (6H, q, *J* = 7.9 Hz, 3×CH₃CH₂Si)

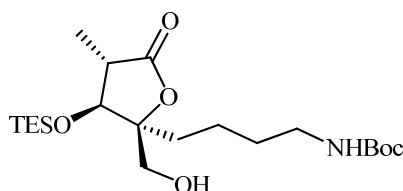
¹³C NMR (100 MHz, CDCl₃) δ 199.9 (CO), 177.4 (CO), 86.2, 81.2, 51.0 (CH₂), 43.6, 34.4 (CH₂), 28.9 (CH₂), 20.2 (CH₂), 14.1, 6.6, 4.9 (CH₂)

IR (NaCl) ν_{max}: 2093, 1790, 1740, 1227 cm⁻¹

MS (ESI) *m/z* 356 (M+H)⁺

HRMS m/z ($M+Na$)⁺ calcd for C₁₆H₂₉N₃O₄SiNa 378.1893, found 378.1895

Synthesis of *tert*-butyl 4-((2*S*,3*S*,4*S*)-2-(hydroxymethyl)-4-methyl-5-oxo-3-(triethylsilyloxy)tetrahydrofuran-2-yl)butylcarbamate (3.117**)**



The alcohol (**3.111**) (0.06 g, 0.17 mmol) was dissolved in EtOAc (10 mL), di-*tert*-butyl dicarbonate (0.05 g, 0.21 mmol) and 10% Pd-C (0.01 g, 0.02 mmol) were added, and the mixture vigorously stirred in a hydrogen atmosphere for 12 hours. The catalyst was then filtered (Celite) and the filtrate evaporated. The residue was purified by flash chromatography on silica gel with EtOAc/hexane (1:4) to give *N*-Boc protected product (**3.117**) (0.07 g, 88%) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 4.54 (1H, brs, *NHBoc*), 3.99 (1H, d, $J = 8.4$ Hz, *CHO*), 3.81 (1H, dd, $J = 12.6, 7.3$ Hz, *CHHOH*), 3.71 (1H, dd, $J = 12.2, 7.4$ Hz, *CHHOH*), 3.11 (2H, brs, *CH₂NHBoc*), 2.81 (1H, quint, $J = 7.3$ Hz, *CHCH₃*), 2.36 (1H, m, C *CHHCH₂*), 1.79 (1H, m, C *CHHCH₂*), 1.58-1.38 (4H, m, *CH₂CH₂*), 1.43, (9H, s, 3×*CH₃*), 1.30 (3H, d, $J = 7.3$ Hz, *CH₃CH*), 0.98 (9H, t, $J = 7.9$ Hz, 3×*CH₃CH₂Si*), 0.65 (6H, q, $J = 7.9$ Hz, 3×*CH₃CH₂Si*)

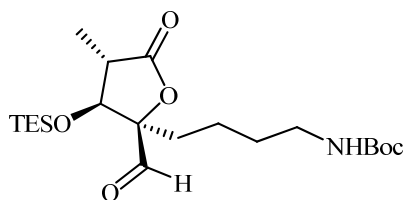
^{13}C NMR (100 MHz, CDCl_3) δ 176.6 (CO), 146.7 (CO), 86.7, 85.1, 80.8, 66.0 (CH_2), 44.7, 39.9 (CH_2), 34.6 (CH_2), 30.3 (CH_2), 28.3 (CH_3), 27.3 (CH_3), 19.9 (CH_2), 14.2, 6.5, 4.0 (CH_2)

IR (NaCl) ν_{max} : 3410, 2938, 2877, 1770, 1688, 1518, 1458, 1370, 1117, 1068 cm^{-1}

MS (ESI) m/z 454 ($\text{M}+\text{Na}$) $^+$

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_{21}\text{H}_{41}\text{NO}_6\text{SiNa}$ 454.2593, found 454.2601

Synthesis of *tert*-butyl 4-((2*R*,3*S*,4*S*)-2-formyl-4-methyl-5-oxo-3-(triethylsilyloxy)tetrahydrofuran-2-yl)butylcarbamate (3.118)



Dess-Martin periodinane (0.14 g, 0.33 mmol), was added to a mixture of alcohol (**3.117**) (0.07 g, 0.15 mmol) and NaHCO_3 (0.04 g, 0.45 mmol), in dry dichloromethane (10 mL) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature. The reaction was monitored by TLC to ensure complete oxidation of alcohol. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 1:4) to give the title compound (**3.118**) (0.06 g, 85%) as a colourless oil.

^1H NMR (500MHz, CDCl_3); δ 9.61 (1H, s, $\text{HC}=\text{O}$), 4.52 (1H, brs, NHBoc), 4.02 (1H, d, $J = 7.9$ Hz, CHO), 3.11 (2H, m, CH_2NHBoc), 2.80 (1H, quint, $J = 7.5$ Hz, CHCH_3),

2.30 (1H, m, CCHHCH₂), 1.80 (1H, m, CCHHCH₂), 1.58-1.38 (4H, m, CH₂CH₂), 1.43, (9H, s, 3×CH₃), 1.30 (3H, d, *J* = 7.3 Hz, CH₃CH), 0.98 (9H, t, *J* = 7.9 Hz, 3×CH₃CH₂Si), 0.65 (6H, q, *J* = 7.9 Hz, 3×CH₃CH₂Si)

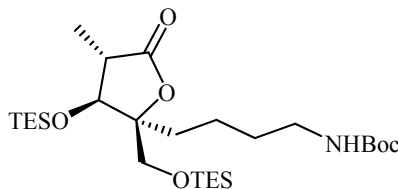
¹³C NMR (100 MHz, CDCl₃) δ 199.0, 175.7, 152.6, 88.6, 82.2, 45.6 (CH₂), 43.1, 32.6 (CH₂), 29.0 (CH₂), 28.0, 20.4 (CH₂), 13.4, 6.5, 4.7 (CH₂)

IR (NaCl) ν_{max}: 2956, 2877, 1770, 1740, 1688, 1427, 1127 cm⁻¹

MS (ESI) *m/z* 452 (M+Na)⁺

HRMS *m/z* (M+Na)⁺ calcd for C₂₁H₃₉NO₆SiNa 452.1893, found 452.1895

Synthesis of *tert*-butyl 4-((2*S*,3*S*,4*S*)-4-methyl-5-oxo-3-(triethylsilyloxy)-2-((triethylsilyloxy)methyl)tetrahydrofuran-2-yl)butylcarbamate (3.133)



Azide (**3.110**) (0.05 g, 0.11 mmol) was dissolved in EtOAc (10 mL), di-*tert*-butyl dicarbonate (0.03 g, 0.13 mmol) and 10% Pd-C (0.02 g, 0.01 mmol) were added, and the mixture vigorously stirred in a hydrogen atmosphere for 12 hours. The catalyst was then filtered (Celite) and the filtrate evaporated. The residue was purified by flash chromatography on silica gel with EtOAc/hexane (1:4) to give the *N*-Boc protected product (**3.133**) (0.04 g, 72%) as a colourless oil.

^1H NMR (500MHz, CDCl_3); δ 4.51 (1H, brs, NHBoc), 3.88 (2H, dd, $J = 10.0, 10.0$ Hz, CH_2O), 3.52 (1H, d, $J = 10.6$ Hz, CHO), 3.10 (2H, m, CH_2NHBoc), 2.96 (1H, quint, $J = 7.4$ Hz, CHCH_3), 1.63 (1H, m, CCHHCH_2), 1.50-1.32 (5H, m, $\text{CHHCH}_2\text{CH}_2$), 1.43 (9H, s, $3\times\text{CH}_3$), 1.23 (3H, d, $J = 7.4$ Hz, CH_3CH), 0.96 (9H, t, $J = 8.0$ Hz, $3\times\text{CH}_3\text{CH}_2\text{Si}$), 0.93 (9H, t, $J = 7.9$ Hz, $3\times\text{CH}_3\text{CH}_2\text{Si}$), 0.62 (6H, q, $J = 7.7$ Hz, $3\times\text{CH}_3\text{CH}_2\text{Si}$), 0.57 (6H, q, $J = 7.7$ Hz, $3\times\text{CH}_3\text{CH}_2\text{Si}$)

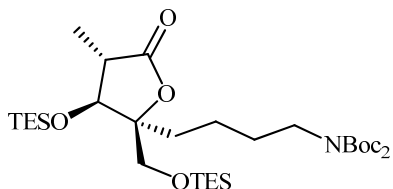
^{13}C NMR (125MHz, CDCl_3) δ 177.3, 158.1, 154.9, 146.7, 106.4, 86.2, 80.4, 64.0 (CH_2), 45.7 (CH_2), 44.1 (CH_2), 43.3, 39.1 (CH_2), 28.3, 20.6 (CH_2), 14.3, 8.7, 6.4, 5.7 (CH_2), 4.1

IR (NaCl) ν_{max} : 2956, 2877, 1770, 1688, 1518, 1458, 1370, 1264, 1117, 1068 cm^{-1}

MS (ESI) m/z 546 ($\text{M}+\text{H}$) $^+$

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_{27}\text{H}_{55}\text{NO}_6\text{Si}_2\text{Na}$ 568.3486, found 568.3490

Synthesis of di-*tert*-butyl 4-((2*S*,3*S*,4*S*)-4-methyl-5-oxo-3-(triethylsilyloxy)-2-((triethylsilyloxy)methyl)tetrahydrofuran-2-yl)butylcarbamate (3.134)



To a stirred solution of *N*-Boc- γ -butyrolactone (**3.133**) (0.04 g, 0.09 mmol) in acetonitrile (5 mL) at room temperature, di-*tert*-butyl dicarbonate (0.03 g, 0.11 mmol) was added in one portion. The mixture was stirred at room temperature for 24 hours. After

the reaction was complete (TLC; hexane/EtOAc, 70:30), the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1:3) to yield the title compound (**3.134**) (0.04 g, 71%) as a colourless oil.

^1H NMR (500MHz, CDCl_3); δ 3.88 (2H, t, $J = 9.6$ Hz, CH_2OH), 3.57 (1H, d, $J = 11.0$ Hz, CHO), 3.54 (2H, t, $J = 6.8$ Hz, CH_2N), 2.97 (1H, quint, $J = 7.4$ Hz, CHCH_3), 1.62-1.35 (6H, m, $3\times\text{CH}_2$), 1.49 (18H, s, $6\times\text{CH}_3$), 1.23 (3H, d, $J = 6.7$ Hz, CH_3CH), 0.96 (9H, t, $J = 7.4$ Hz, $3\times\text{CH}_3$), 0.93 (9H, t, $J = 7.8$ Hz, $3\times\text{CH}_3$), 0.62 (6H, t, $J = 7.5$ Hz, $3\times\text{CH}_2$), 0.56 (6H, t, $J = 7.7$ Hz, $3\times\text{CH}_2$)

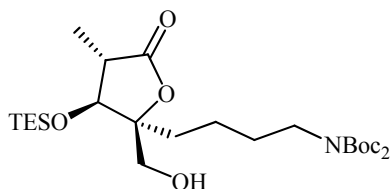
^{13}C NMR (125 MHz, CDCl_3) δ 177.2, 152.6, 86.3, 82.1, 80.3, 64.1 (CH_2), 46.0 (CH_2), 43.3, 34.1(CH_2), 29.3 (CH_2), 28.0, 20.5 (CH_2), 14.4, 6.7, 6.6, 5.0 (CH_2), 4.1 (CH_2)

IR (NaCl) ν_{max} : 2956, 2877, 1782, 1696, 1457, 1367, 1243, 1135, 1015, 812, 745 cm^{-1}

MS (ESI) m/z 668 ($\text{M}+\text{Na}$) $^+$

HRMS m/z ($\text{M}+\text{Na}$) $^+$ calcd for $\text{C}_{32}\text{H}_{63}\text{NO}_8\text{Si}_2\text{Na}$ 668.4014, found 668.4016

Synthesis of di-*tert*-butyl 4-((2*S*,3*S*,4*S*)-2-(hydroxymethyl)-4-methyl-5-oxo-3-(triethylsilyloxy)tetrahydrofuran-2-yl)butylcarbamate (3.135)



To solution of bis-TES protected alcohol (**3.134**) (0.05 g, 0.08 mmol) in MeOH (5 mL) was added PPTS (0.02 g, 0.09 mmol) in one portion. The resulting mixture was stirred vigorously for 2 hours. Brine (5 mL) was added to the reaction mixture and the solvent was removed *in vacuo*. The resulting residue was diluted with EtOAc (20 mL) and added to a separating funnel containing brine (20 mL). The aqueous layer was extracted with EtOAc (2×20 mL). The organic layers were combined and dried with anhydrous Na₂SO₄, filtered and concentrated. The resulting residue was purified by flash column chromatography (EtOAc/hexane 1:4) to give the title compound (**3.135**) (0.03 g, 93%) as a colourless oil.

¹H NMR (500MHz, CDCl₃); δ 3.98 (1H, d, *J* = 8.3 Hz, CHO), 3.80 (1H, dd, *J* = 12.4, 5.9 Hz, CH₂OH), 3.69 (1H, dd, *J* = 12.4, 8.4 Hz, CH₂OH), 3.54 (2H, t, *J* = 7.3 Hz, CH₂N), 2.80 (1H, quint, *J* = 7.4 Hz, CHCH₃), 2.31 (1H, dd, *J* = 8.4, 6.0 Hz, CH₂C), 1.78 (1H, m, CH₂C), 1.65 (1H, brs, CH₂OH), 1.61-1.34 (4H, m, 2×CH₂), 1.48 (18H, s, 6×CH₃), 1.29 (3H, d, *J* = 7.3 Hz, CH₃CH), 0.97 (9H, t, *J* = 8.0 Hz, 3×CH₃), 0.64 (6H, q, *J* = 7.8 Hz, 2×CH₂)

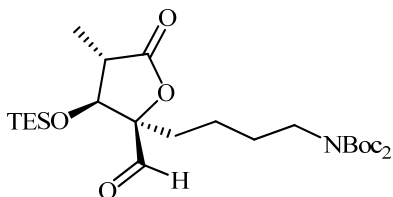
^{13}C NMR (125 MHz, CDCl_3) δ 176.1, 152.6, 86.5, 82.1, 81.1, 65.1 (CH_2), 45.9 (CH_2), 43.7, 34.6 (CH_2), 29.1 (CH_2), 28.0, 20.2 (CH_2), 14.2, 6.6, 4.8 (CH_2)

IR (NaCl) ν_{max} : 3417, 2957, 1780, 1696, 1458, 1367, 1246, 1134, 1007, 856, 746 cm^{-1}

MS (ESI) m/z 554 ($\text{M}+\text{Na}^+$)

HRMS m/z ($\text{M}+\text{Na}^+$)⁺ calcd for $\text{C}_{26}\text{H}_{49}\text{NO}_8\text{SiNa}$ 554.3122, found 554.3125

Synthesis of di-*tert*-butyl 4-((2*R*,3*S*,4*S*)-2-formyl-4-methyl-5-oxo-3-(triethylsilyloxy)tetrahydrofuran-2-yl)butylcarbamate (3.136)



Dess-Martin periodinane (0.039 g, 0.094 mmol), was added to a mixture of alcohol (**3.135**) (0.03 g, 0.05 mmol) and NaHCO_3 (0.01 g, 0.01 mmol), in dry dichloromethane (5 mL) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature. The reaction was monitored by TLC to ensure complete oxidation of alcohol. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane 1:4) to give the title compound (**3.136**) (0.02 g, 71%) as a colourless oil.

^1H NMR (500MHz, CDCl_3); δ 9.60 (1H, s, $\text{O}=\text{CH}$), 4.02 (1H, d, $J = 7.9$ Hz, CHO), 3.54 (2H, t, $J = 7.6$ Hz, CH_2N), 2.59 (1H, quint, $J = 7.6$ Hz, CHCH_3), 2.27 (1H, dddd,

$J = 11.8, 11.7, 4.7, 4.6$ Hz, CH_2C), 1.70 (1H, dddd, $J = 11.8, 11.8, 4.7, 4.6$ Hz, CH_2C),
1.62-1.38 (2H, m, $2 \times \text{CH}_2$), 1.48 (18H, s, $9 \times \text{CH}_3$), 1.29 (3H, d, $J = 7.3$ Hz, CH_3CH),
0.95 (9H, t, $J = 8.0$ Hz, $3 \times \text{CH}_3$), 0.61 (6H, q, $J = 7.8$ Hz, $3 \times \text{CH}_2$)

^{13}C NMR (125 MHz, CDCl_3) δ 199.0, 175.7, 152.6, 88.6, 82.2, 45.6 (CH_2), 43.1, 32.6
(CH_2), 29.0 (CH_2), 28.0, 20.4 (CH_2), 13.4, 6.5, 4.7 (CH_2)

IR (NaCl) ν_{max} : 2958, 2878, 1790, 1740, 1694, 1457, 1367, 1127 cm^{-1}

MS (ESI) m/z 552 ($\text{M}+\text{Na}$)⁺

HRMS m/z ($\text{M}+\text{Na}$)⁺ calcd for $\text{C}_{26}\text{H}_{47}\text{NO}_8\text{Na}$ 552.2965, found 552.2969

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