SYNTHESIS OF PIPERIDINE AND QUINOLIZIDINE ALKALOIDS

NANYANG TECHNOLOGICAL UNIVERSITY

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Without a shadow of doubt, this work would not have been possible without the unfaltering support of my husband, Heiko. These last five years have been full of challenges and obstacles that I could not have overcome alone. He is the reason I am still standing. This dissertation is dedicated to him.

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To my husband, Heiko and our two daughters, Aaliyah and Amelia,
for bringing out the best in me.

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Abstract

Natural products have been, and will continue to be, an important starting point for researchers in the quest for novel treatments for today's ailments. While these molecules often have very highly potent or specialised activities, they may not be the perfect drug candidate. Medicinal chemists aim to improve their therapeutic activity and at the same time, maximise their physicochemical properties in order to deliver effective drug molecules. Our research has focused largely on the synthesis of natural products with application to medicinal chemistry.

Herein is reported the use of *N,O*-heterocycles for the synthesis of structurally complex, biologically active molecules. Firstly, we report the use of isoxazolidines for the generation of 1,3-aminoalcohols which is an important functional moiety in substituted hydroxy piperidine and quinolizidine alkaloids. This approach has been applied to the synthesis of (-)-5-hydroxysedamine. This synthesis also features key approaches developed in our group, i.e. hydroformylation and diastereoselective dihydroxylation for the synthesis of piperidines. We believe our synthetic approach to be the most robust towards this natural product reported to date.

In the following chapter, we sought to employ isoxazolidines to the synthesis of (+)-vertine, a macrocyclic quinolizidine alkaloid which was reported to possess antimalarial activity. Our approach would enable a facile and divergent method for the synthesis of vertine and other close analogues of the natural product. This would enable structure-activity relationship (SAR) studies to investigate the key pharmacophore needed for antimalarial activity. We initiated our studies with the synthesis of (-)-lasubine I, as a proof-of-concept to investigate the tractability of our synthetic strategy.

List of Abbreviations

))	sonication
α	observed optical rotation in degrees
[α]	specific rotation [expressed without units; the units, (deg·cm^2·g^{-1}), are understood]
Ac	acetyl
acac	acetylacetonate
AD	asymmetric dihydroxylation
AIBN	2,2′-azobisisobutyronitrile
alloc	allyloxycarbonyl
anhyd	anhydrous
app	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere(s)
av	average
9-BBN	9-borabicyclo[3.3.1]nonyl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
bpy	2,2′-bipyridyl
br	broad (spectral)
Bt	benzotriazolyl
Bu, *n*-Bu	normal (primary) butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
calcd	calculated

CAN	ceric ammonium nitrate
cat	catalytic
Cbz	benzyloxycarbonyl
CI	chemical ionization
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
concd	concentrated
concn	concentration
COSY	correlation spectroscopy
*m*CPBA	*meta*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
CTAB	cetyl trimethylammonium bromide
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
d	density
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCK	dichloroketene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane

DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DPPA	diphenylphosphorazidate
dppf	1,1'-*bis*(diphenylphosphino)ferrocene
dr	diastereomer ratio
E	entgegen (*trans*)
E1	unimolecular elimination
E2	bimolecular elimination
EA	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	ethylenediamine tetraacetic acid
ee	enantiomeric excess
en	ethylene diamine
equiv.	Equivalent
ESI	electrospray ionization
Et	Ethyl
Fmoc	9-fluorenylmethoxycarbonyl
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons

Hz	Hertz
IC_{50}	half maximal inhibitory concentration
Im	imidazole
IR	infrared
J	coupling constant (in NMR spectrometry)
k	Kilo
KHMDS	potassium hexamethyldisilazane
L	litre(s)
LDA	lithium diisopropylamide
LG	leaving group
LHMDS	lithium hexamethyldisilazane, lithium *bis*(trimethylsilyl)amide
lit.	literature value
m	multiplet (spectral)
m	meta
M	molar (moles per litre)
M^+	parent molecular ion
max	maximum
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
MHz	megahertz
min	minute(s); minimum
MOM	methoxymethyl
mp	melting point
Ms	methylsulfonyl (mesyl)
MS	mass spectrometry
MSH	*O*-(mesitylsulfonyl) hydroxylamine
MTBE	methyl *tert*-butyl ether
MNBA	2-methyl-6-nitrobenzoic anhydride
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid)
MW	molecular weight
m/z	mass-to-charge ratio
N	normal (equivalents per litre)

NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
o	ortho
ORTEP	Oak Ridge Thermal Ellipsoid Plot
Oxone	potassium peroxymonosulfate
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PE	petroleum ether
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
Phth	phthaloyl
PIFA	phenyliodine *bis*(trifluoroacetate)
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PNB	*p*-nitrobenzoate
ppm	part(s) per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
PTC	phase-transfer catalysis
PTSA	*para*-toluenesulfonic acid
py	pyridine
q	quartet (spectral)

RCM	ring-closing metathesis
redox	reduction–oxidation
rel	relative
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
SAR	structure–activity relationship
SET	single electron transfer
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_N'	nucleophilic substitution with allylic rearrangement
t	triplet (spectral)
t	time
T	absolute temperature in units of kelvins (K)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMAI	tetramethylammonium iodide
TMEDA	*N,N,N′,N′*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl; tetramethylsilane
Tr	triphenylmethyl (trityl)

t_R	retention time (in chromatography)
Ts	para-toluenesulfonyl (tosyl)
TS	transition state
UV	ultraviolet
vis	visible
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)
Z	zusammen (*cis*)

Chapter 1

A REVIEW OF THE SYNTHESIS OF INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS

1.1 Introduction

Substituted indolizidine and quinolizidine alkaloids are abundantly found in Nature and have attracted a considerable amount of attention from the synthetic community. There are several reasons behind this. These alkaloids may possess interesting medicinal properties, making them excellent starting points for drug discovery programmes. Such alkaloids also possess unique structural features that provide opportunities for synthetic organic chemists as proof-of-principle exercises that bring forth novel ideas towards constructing these molecules.

This review aims to be a continuation of a series of annual reviews published by J.P. Michael[1] from 1990 to 2008 covering topics related to the isolation, structure determination, synthesis, chemical transformations and biological activity of indolizidine and quinolizidine alkaloids from microbial, plant and animal sources.[i] Given the breadth of topics covered, this review is not intended as a comprehensive treatment of each subject but rather an update on recent discoveries from June 2007 to June 2014. The review will be organised based on major alkaloid families that possess an indolizidine or quinolizidine skeleton with greater attention paid to alkaloids from plant sources. Alkaloids from animal or amphibian sources will not be covered to avoid undue length. Interesting biological activity of the alkaloids will be briefly highlighted. The review will also have a stronger focus on the synthetic routes towards these molecules. Overall, this review serves as a backdrop to our investigations into the synthesis of hydroxylated piperidine and quinolizidine alkaloids.

[i] In 2016, shortly after this review was collated, J. P. Michael published a chapter reviewing substituted indolizidine and quinolizidine alkaloids, continuing his series of reviews. See *Alkaloids: Chem Biol.* **2016,** *75,* 1-498.

1.2 Hydroxylated indolizidine alkaloids

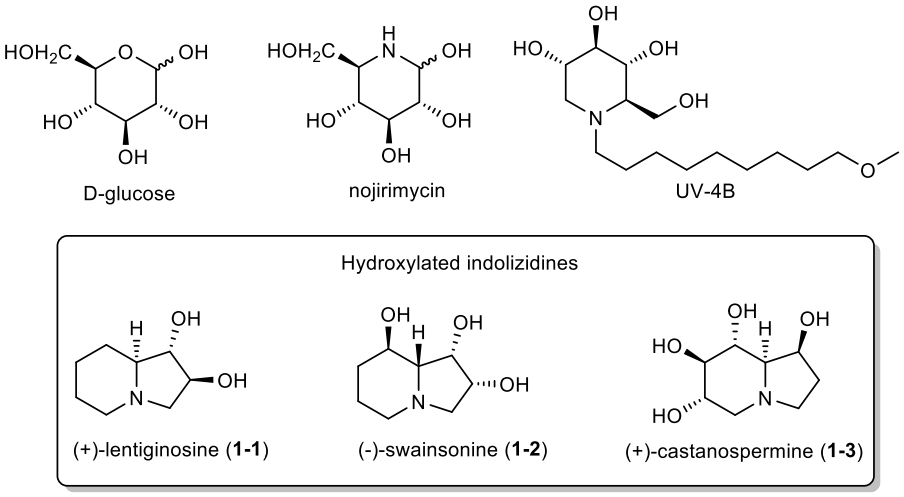


Figure 1.2-1 Structures of D-glucose and relevant iminosugars

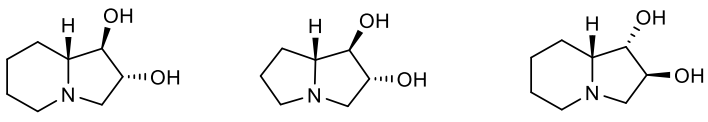
Iminosugars are defined as analogues of sugar with a nitrogen atom replacing the ring oxygen atom as illustrated by the side by side comparison of D-glucose and nojirimycin in Figure 1.2-1. In recent years, interest in iminosugars, which includes the hydroxylated indolizidines, has proceeded unabated due to recognition of their therapeutic potential as glycosidase inhibitors in various diseases such as viral infections and diabetes.[2] Most recently, iminosugar UV-4B was reported to have *in vitro* activity against all four dengue serotypes and is currently undergoing Phase 2 clinical trials for dengue treatment.[3] As a result, a vast quantity of literature has appeared during the period of this review reporting various approaches to the syntheses of iminosugars, including hydroxylated indolizidine alkaloids and their respective analogues. A majority of these approaches rely on carbohydrates as a starting point which aims to take advantage of the chiral hydroxyl centres that are in place. However, these strategies are often plagued by lengthy routes that may require multiple protection and deprotection steps. Furthermore, these tactics lack the stereochemical flexibility that is needed for the synthesis of a variety of analogues.

A number of succinct reviews have also been published recently. A general review describing recent developments in the synthesis of pyrrolidine-containing iminosugars also discusses synthetic approaches to lentiginosine (**1-1**), swainsonine (**1-2**), castanospermine

(**1-3**) and their analogues.[4] Hydroxylated indolizidine alkaloids are also highlighted in the reviews by Kim[5] and Rauter[6] that cover the various chemical strategies to the synthesis of naturally occurring iminosugars. In addition, Vankar and co-workers have published a review that covers synthesis and glycosidase inhibition activity of unnatural molecules that include those of hydroxylated indolizidines.[7]

1.2.1 Lentiginosine and related compounds

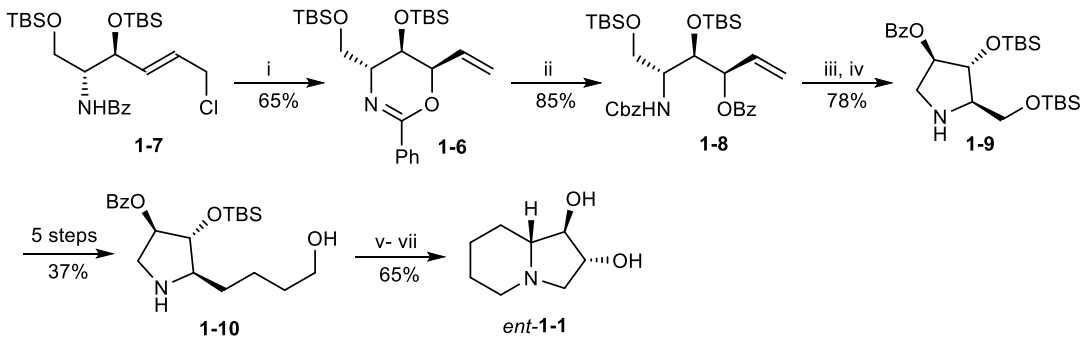
Significant biological properties as well as the various synthetic approaches to (+)-lentiginosine, **1-1**, and its analogues published since 1990 have been discussed by Brandi and co-workers in two reviews, first in 2007[8] and more recently in 2014.[9] In recent publications, Liu *et al.* showcased an asymmetric synthesis of (-)-lentiginosine (*ent*-**1-1**) by a double *aza*-Michael reaction.[10] Kim *et al.* described a synthesis of (-)-lentiginosine *via* a highly regio- and diastereoselective allylic amination using chlorosulfonyl isocyanate and later expanded it to include the synthesis of other lentiginosine analogues such as alkaloid **1-4**.[11] Sudalai *et al.* opted to synthesise (+)-lentiginosine, **1-1**, *via* an asymmetric *aza*-Cope rearrangement and a diastereoselective osmium-catalysed dihydroxylation to generate the three stereocentres.[12] Zhang and co-workers have synthesised (+)-lentiginosine and its 8a-epimer, **1-5**, using a gold-catalysed cyclisation as a key step, albeit with low diastereoselectivity.[13]



(-)-lentiginosine (*ent*-**1-1**) **1-4** **1-5**

Figure 1.2-2 Structures of lentiginosine analogues

Ham *et al.* implemented an elegant route for the synthesis of the unnatural enantiomer of (-)-lentiginosine, *ent*-**1-1**, which takes advantage of the highly diastereoselective palladium(0)-catalysed formation of *anti,syn* oxazine **1-6** from amino alcohol **1-7** (Scheme 1.2-1), which in turn could be derived from D-serine in 6 steps.[14] The diastereoselectivity of the reaction (dr 30:1) could be attributed to the bulk of the protecting group on the secondary alcohol of **1-7**. Cleavage of oxazine **1-6** with benzyl chloroformate in the presence of aqueous $NaHCO_3$ furnished carbamate **1-8** in 85% yield. Subsequent ozonolysis and intramolecular reductive amination gave pyrrolidine **1-9**. Following standard *N*-Boc protection and treatment with HF-pyridine, the resulting free primary alcohol was oxidised and the alkyl chain was extended *via* the Wittig olefination reaction following which hydrogenation with Pd/C produced alcohol **1-10**. Formation of the final product was effected by conversion of the free alcohol to the mesylate and subsequent treatment with 4M HCl-dioxane (to remove the Boc and TBS groups) followed by 1M NaOH (intramolecular cyclisation).

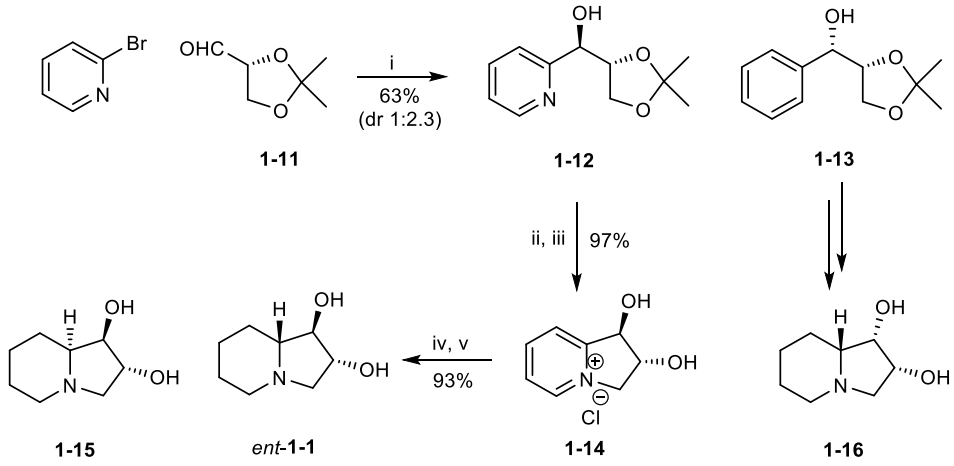


Reagents and conditions: i, $Pd(PPh_3)_4$, NaH, *n*-Bu_4NI, THF, 0 °C, 5h; ii, CbzCl, $NaHCO_3$, CH_2Cl_2:H_2O (1:1), rt, 24 h; iii, O_3, MeOH, -78 °C, then $(CH_3)_2S$; iv, 20% $Pd(OH)_2$/C, H_2 (75 psi), rt , 24 h; v, MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; vi, 4M HCl in dioxane, rt, 12 h; vii, 1M NaOH, rt, 1 h.

Scheme 1.2-1 Ham's synthesis of (-)-lentiginosine

While most synthetic strategies relied upon prior construction of either the piperidine or pyrrolidine with the requisite stereocentres, Fruit *et al.* opted to develop a pyridine-based strategy to achieve a concise synthesis of (-)-lentiginosine and several unnatural analogues (Scheme 1.2-2).[15] 2-Bromopyridine was reacted with D-mannitol derived glyceraldehyde

1-11 to give a rather low diastereomeric mixture (2.3:1) of alcohols **1-12** and **1-13** which were separable by silica gel chromatography. Acetonide cleavage of **1-12** by treatment with aqueous HCl followed by the key intramolecular cyclisation step under Mitsunobu conditions furnished pyridinium salt **1-14**. Subsequent reduction with hydrogen in the presence of PtO_2 as catalyst produced a 0.8:1 mixture of diastereomers. Subsequent treatment of each diastereomer with concentrated aqueous KOH yielded (-)-lentiginosine, *ent*-**1-1**, and its 8a-epimer, **1-15**. 1-*epi*-lentiginosine, **1-16**, was also synthesised in a similar fashion. Preparation of the 1-epimer began with alcohol **1-13** and the reduction step proceeded with high yields and diastereoselectivity.

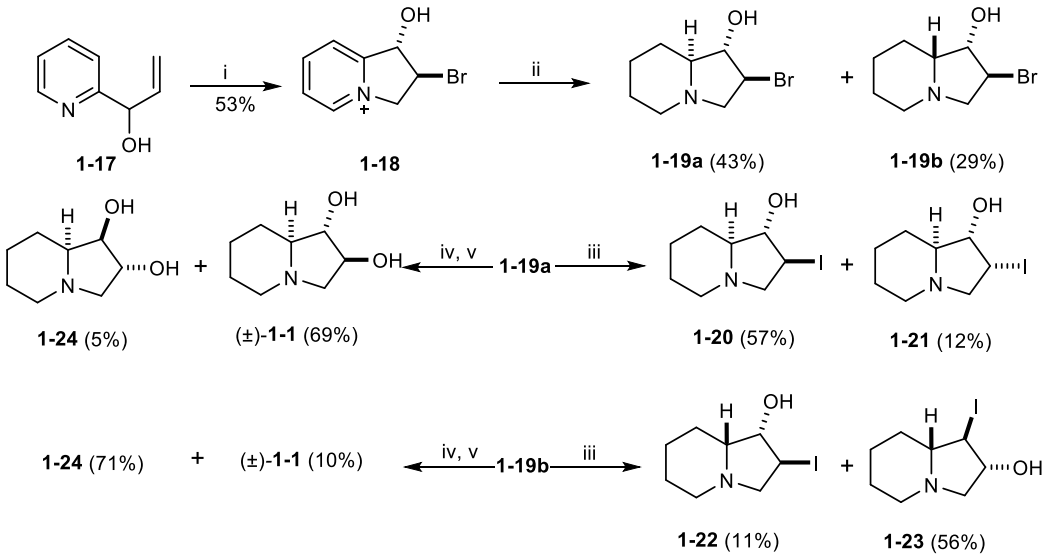


Reagents and conditions: i, *n*-BuLi, Et_2O, -78 °C to rt, overnight; ii, 2M aq. HCl, dioxane, rt, 2h; iii, PPh_3, DIAD, MeCN, 0 °C to rt, 2 h; iv, $PtO_2 \cdot H_2O$, H_2 (1 atm), EtOH, rt; v, saturated KOH, rt.

Scheme 1.2-2 Fruit's synthesis of (-)-lentiginosine, analogues 1-15 and 1-16

Brandi and co-workers also used a pyridine-based strategy to synthesise racemic lentiginosine (Scheme 1.2-3).[16] Here, pyridyl alcohol **1-17** was identified as a good starting point. Brandi reasoned that the double bond present could undergo electrophilic addition and then cyclise to form the bicyclic skeleton. Bromination of pyridyl alcohol **1-17** with NBS in aqueous THF furnished pyridinium salt **1-18** diastereoselectively with a yield of 53%. Similar to Fruit's work, the pyridinium salt was reduced by hydrogenation with catalytic amounts of PtO_2 to furnish a 0.7:1 mixture of diastereomers **1-19a** and **1-19b**. The group demonstrated that the presence of a good leaving group i.e. bromine, enabled facile

substitution to access various analogues. Indolizidine **1-19a** yielded both *cis* and *trans* iodo derivatives, **1-20** and **1-21**, while indolizidine **1-19b** yielded two regioisomers, **1-22** and **1-23** in 11 and 56% yield respectively. Treatment of **1-19a** with KOH followed by aqueous H_2SO_4 yielded racemic lentiginosine with an overall 27% yield and its diastereomer **1-24** while similar reaction with **1-19b** furnished racemic lentiginosine and **1-24** in 10 and 71% yields respectively.

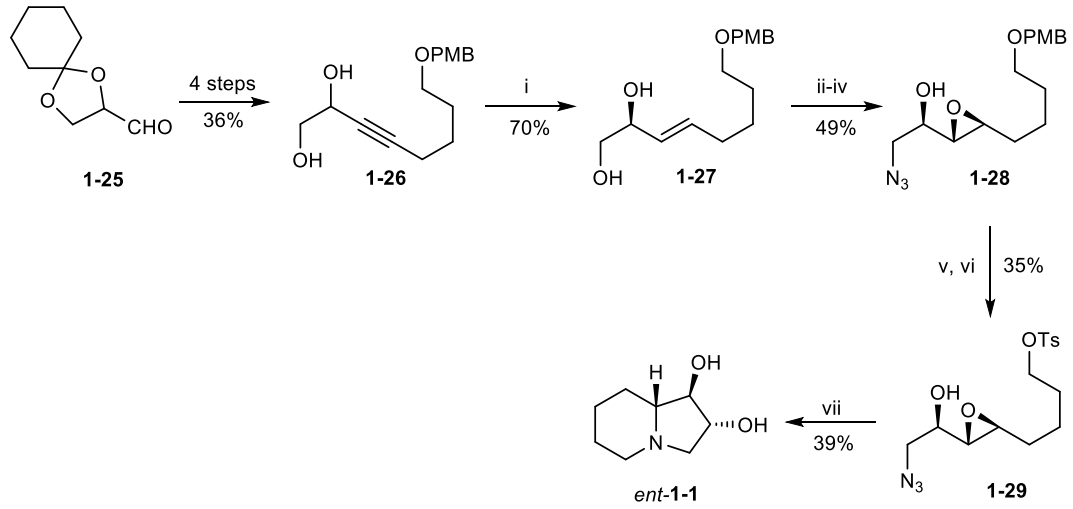


Reagents and conditions: i, NBS, THF-H_2O (9:1), 0 °C-rt, 72 h; ii, $PtO_2 \cdot H_2O$ (10 mol%), H_2 (1 atm) EtOH, rt, 6 h; iii, NaI, acetone, 70 °C, 4-5 days; iv, aqueous KOH, THF, 40 °C, 15 h; v, aqueous H_2SO_4, 100 °C, 7 h.

Scheme 1.2-3 Brandi's synthesis of (±)-lentiginosine and analogues

In 2008, Chandrasekhar *et al.* reported a straightforward one-pot construction of the indolizidine framework *via* a double cyclisation strategy to provide a concise route for the synthesis of (-)-lentiginosine (Scheme 1.2-4).[17] To this end, glyceraldehyde derivative **1-25** was converted to propargylic alcohol **1-26** over four steps and this, in turn, was reduced with $LiAlH_4$ to give allylic alcohol **1-27**. Subsequent epoxidation under Sharpless asymmetric epoxidation conditions furnished the corresponding epoxy diol in 65% yield and high enantiomeric purity. Conversely, epoxidation with *m*CPBA gave a 6:4 mixture of inseparable diastereomers. The free primary alcohol was then converted to azide **1-28** *via* displacement of the tosyl intermediate. Deprotection of the PMB group was carried out by treatment with DDQ and the resulting free primary alcohol was tosylated in preparation for

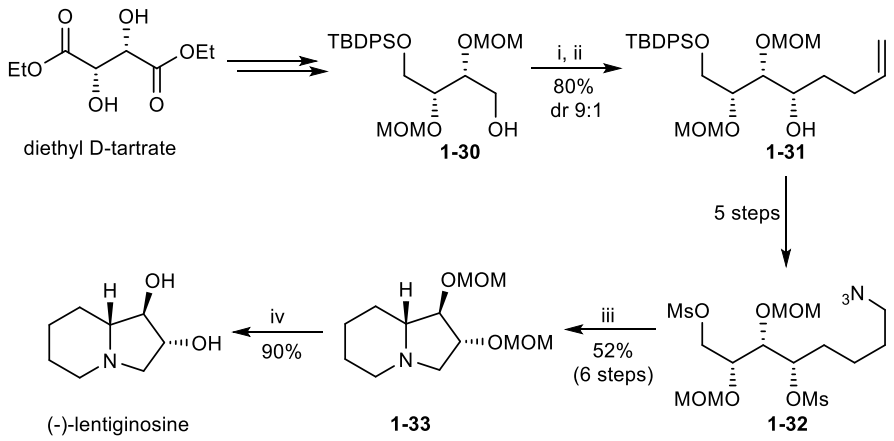
the key double cyclisation step. Reduction of azide **1-29** with Lindlar's catalyst in MeOH triggered epoxide ring opening and tosyl displacement to achieve construction of the indolizidine framework and complete the synthesis of (-)-lentiginosine.



Reagents and conditions: i, $LiAlH_4$, Et_2O 0 °C to rt, 2 h; ii, (+)-DIPT, $Ti(^iOPr)_4$, TBHP, CH_2Cl_2, -20 °C, 72 h; iii, TsCl, Et_3N, CH_2Cl_2, rt, 3 h; iv; NaN_3, DMF, 80 °C, 3 h; v, DDQ, CH_2Cl_2-H_2O (5:1), rt, 3 h; vi, TsCl, Py, 0 °C to rt, 30 min; vii, H_2 (1 atm), Lindlar's catalyst (10 mol%), MeOH, rt, 3 h, then methanolic KOH (2 drops).

Scheme 1.2-4 Chandrasekhar's synthesis of (-)-lentiginosine

More recently, Rao *et al.* adopted a similar strategy to construct both 5- and 6-membered rings of indolizidine simultaneously *via* the azide albeit using the Staudinger reaction (Scheme 1.2-5).[18] The synthesis begins with preparation of alcohol **1-30** from diethyl D-tartrate which first underwent an oxidation with Dess-Martin periodinane and the product was immediately subjected to a diastereoselective Grignard addition. This afforded a pair of diastereomers in the ratio of 9:1, favouring the desired diastereomer **1-31**. This underwent a 5 step procedure to give dimesylated azide **1-32** which was directly subjected a Staudinger protocol by treatment with triphenylphosphine in THF and H_2O to give indolizidine **1-33**. This was then treated with 6M HCl in MeOH to afford (-)-lentiginosine in 32% overall yield.



Reagents and conditions: i, DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C; ii, $H_2C{=}CHCH_2CH_2MgBr$, THF, 0 °C to rt, 5 h; iii, PPh_3, THF-H_2O, 50 °C, 16 h; iv, 6M HCl, MeOH, rt, 12 h.

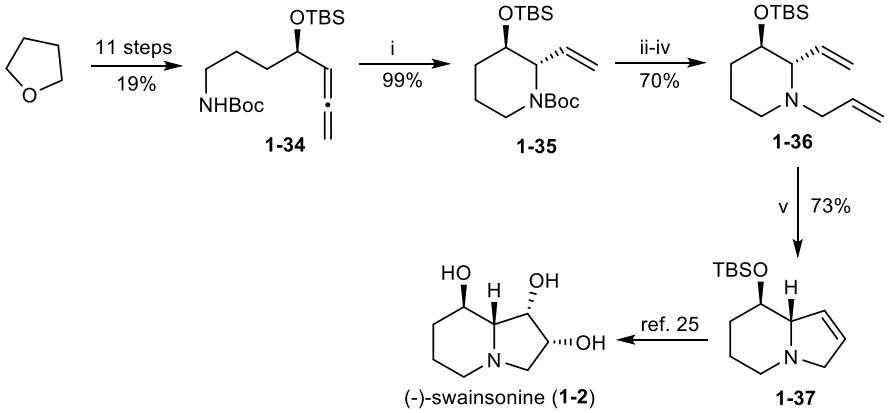
Scheme 1.2-5 Rao's synthesis of (-)-lentiginosine

1.2.2 Swainsonine and related compounds

Swainsonine has long been identified as the primary toxicant in locoweed,[19] leading to losses for livestock producers due to the diseases contracted by the animals following consumption of these plants. A study was carried out in 2006 on the toxikinetic profile of swainsonine on sheep that have been exposed to locoweed.[20] The effects of swainsonine on vascular development of doe goats was also studied.[21] Nishimura and co-workers have reported that swainsonine may enhance 5-fluorouracil chemotherapy treatment of colorectal cancer cell lines in tumors that have developed resistance.[22] Analogues of swainsonine synthesised during the period of this review include (*6R*)-C-methyl-L-swainsonine which has been found to be a more potent naringinase inhibitor than the unnatural enantiomer of swainsonine.[23]

Gold catalysed allene cyclisation has been used as a key step for the formation of the piperidine ring in bicyclic indolizidine towards a formal synthesis of (-)-swainsonine, **1-2** (Scheme 1.2-6). Here, Bates and Dewey reacted allene **1-34**,[24] itself prepared in eleven steps from THF, with gold(III) chloride in the presence of calcium carbonate and acetonitrile in dichloromethane to give the desired piperidine **1-35** as a single diastereomer in 99% yield. Subsequent *N*-Boc deprotection and allylation *via* an "alloc contraction"

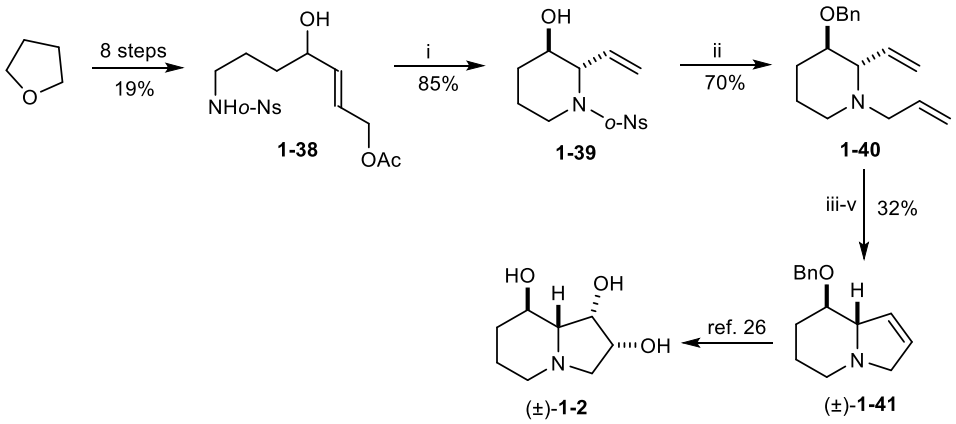
protocol delivered diene **1-36** in 83% yield. Ring closing metathesis of diene **1-36** with Grubbs second-generation catalyst in the presence of tosic acid followed by a NaOH work-up produced indolizidine **1-37**, which has previously featured in the synthetic routes reported by Blechert[25] and Pyne.[26]



Reagents and conditions: i, $AuCl_3$, $CaCO_3$, CH_2Cl_2-MeCN, rt, 1 h; ii, TFA, CH_2Cl_2, rt, 2 h; iii, AllocCl, Na_2CO_3, CH_2Cl_2, rt, 3 h; iv, $Pd(PPh_3)_4$, THF, rt, 5 h; v, Grubbs II (10 mol%), TsOH, CH_2Cl_2, reflux, 5 h.

Scheme 1.2-6 Bates' synthesis of (-)-swainsonine

Following the development of gold-catalysed allene cyclisation as a method to construct vinylpiperidines with high diastereoselectivity, Bates and co-workers investigated an alternative route that employs a palladium-catalysed Tsuji-Trost cyclisation with vinyl acetate albeit for a racemic formal synthesis of swainsonine (Scheme 1.2-7).[27] The requisite vinyl acetate **1-38**, also derived from THF in 8 steps, was treated with tetrakis(triphenylphosphine)palladium(0) and tetramethylguanidine to effect the cyclisation. This proceeded smoothly to give vinyl piperidine **1-39** in 85% yield as an inseparable 8:1 mixture of diastereomers. The minor diastereomer was removed following benzylation with Dudley's reagent to afford benzyl ether **1-40** in 70% yield. The synthesis proceeded in an analogous fashion to that carried out before to give benzyl protected **1-41**, a Pyne intermediate, in 32% yield over 3 steps. It is interesting to note in comparison to the previous synthesis, allylation was achieved in a direct fashion and ring closing metathesis proceeded with Grubbs first-generation catalyst due to the less bulky protecting group (Bn *vs* TBS protecting group in the previous synthesis).

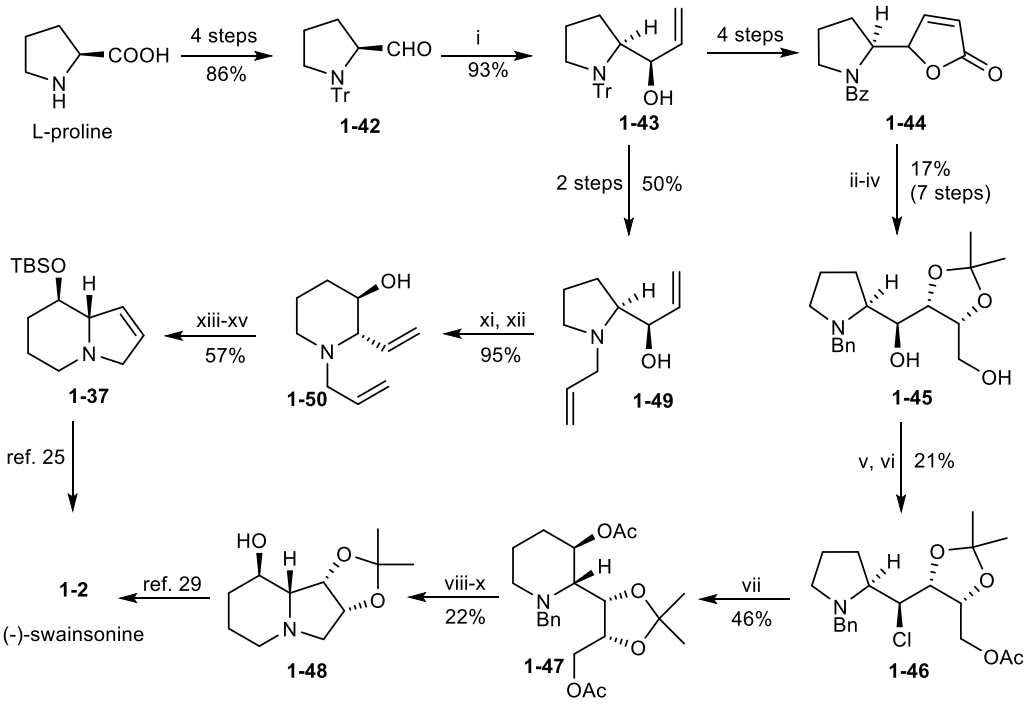


Reagents and conditions: i, $Pd(PPh_3)_4$, TMG, THF; ii, Dudley's reagent, MgO, $ClCH_2CH_2Cl$; iii, EtSH, K_2CO_3, DMF; iv, allyl Br, NaOH; v, Grubbs I, TsOH, CH_2Cl_2.

Scheme 1.2-7 Bates' synthesis of (±)-lentiginosine

In 2007, Cossy *et al.* implemented a fascinating ring expansion strategy *en route* to two formal syntheses of (-)-swainsonine (Scheme 1.2-8).[28] Both syntheses commenced with a diastereoselective Grignard addition to aldehyde **1-42** prepared over four steps from L-proline which also represents a fairly uncommon starting point for the synthesis of polyhydroxylated alkaloids. In the first strategy, the vinylic product **1-43** was converted to lactone **1-44** which was further dihydroxylated using $RuCl_3/NaIO_4$ with high diastereoselectivity and then transformed to prolinol **1-45**. A number of ring expansion protocols were attempted and it was found that chloro derivative **1-46** treated with silver acetate and irradiated with a microwave at 120 °C gave the best results with the requisite piperidine **1-47** being formed as the only product in 46% yield. Further protecting group manipulation and cyclisation under Mitsunobu conditions gave known precursor **1-48** to complete the formal synthesis of (-)-swainsonine.[29] The second route employed the ring expansion strategy at an earlier phase of the route and this enabled a more concise synthetic route to Bletchert's intermediate **1-37** to (-)-swainsonine. Bis-allylic prolinol **1-49** was prepared from prolinol **1-43** and under the ring-expansion conditions (trifluoroacetic anhydride, Et_3N, THF, reflux) and following saponification, generated piperidine **1-50** in high yield (95%) and with a diastereomeric excess greater than 95%. Various ruthenium catalysts were attempted for ring closing metathesis on silyl protected ammonium salt

derivative of **1-50** and it was found that the use of Grubbs I catalyst gave the best results and Blechert's intermediate **1-37** was formed in 82% yield. This approach to (-)-swainsonine constitutes a formal synthesis in 14 steps from L-proline with an overall yield of 14%.

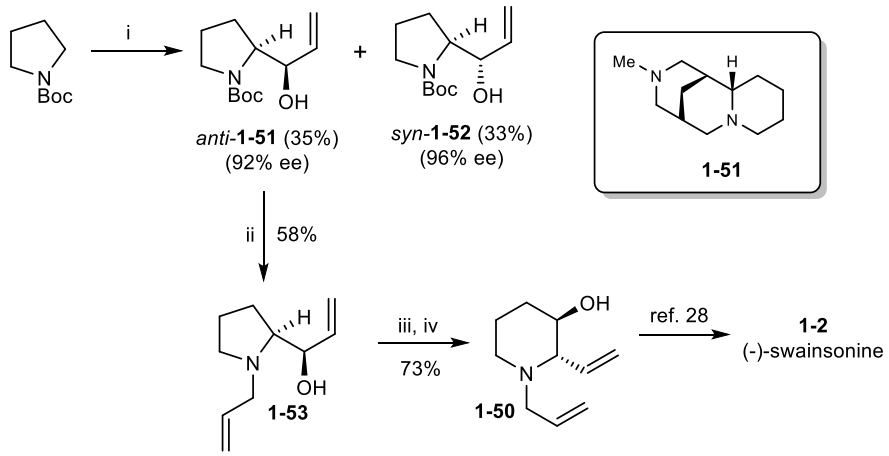


Reagents and conditions: i, vinylMgCl, Et_2O, -78 °C; ii, $RuCl_3$, $NaIO_4$, H_2SO_4, EtOAc-MeCN (1:1), H_2O, 0 °C, 1.5 min; iii, $Me_2C(OMe)_2$, PTSA, CH_2Cl_2, rt, 18 h; iv, $LiAlH_4$, THF, reflux, 2.5 h; v, AcCl, 2,4,6-collidine, CH_2Cl_2, -78 °C to rt, 3.5 h; vi, MsCl, Et_3N, THF, microwaves (100 °C), 2 h; vii, AgOAc, THF, microwaves (120 °C), 3 h; viii, NaOMe, MeOH-THF (1:4), rt, 3 h; ix, H_2 (1 atm), 5% Pd/C, EtOH, rt, 3 h; x, DEAD, PPh_3, pyridine, 0 °C, 2.5 h; xi, $(CF_3CO)_2O$, Et_3N, THF, 0 °C to reflux, 15 h; xii, 2.5 M aq. NaOH, rt, 2 h; xiii, TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h; xiv, CSA, CH_2Cl_2, 0 °C, 10 min; xv, Grubbs I (12.5 mol%), CH_2Cl_2, reflux, 6 h, then K_2CO_3.

Scheme 1.2-8 Cossy's formal syntheses of (-)-swainsonine

A similar ring expansion strategy was also employed by O'Brien *et al.* for the formal synthesis of (-)-swainsonine (Scheme 1.2-9).[30] Here, the synthesis began with an asymmetric lithiation of *N*-Boc pyrrolidine which was then treated with acrolein in the presence of (+)-sparteine surrogate **1-51** to give prolinol in a 1:1 diastereomeric ratio, both with good enantioselectivity. The desired diastereomer, *anti*-**1-52**, was then transformed to bisallylic prolinol **1-53** and subjected to the similar ring-expansion conditions used by

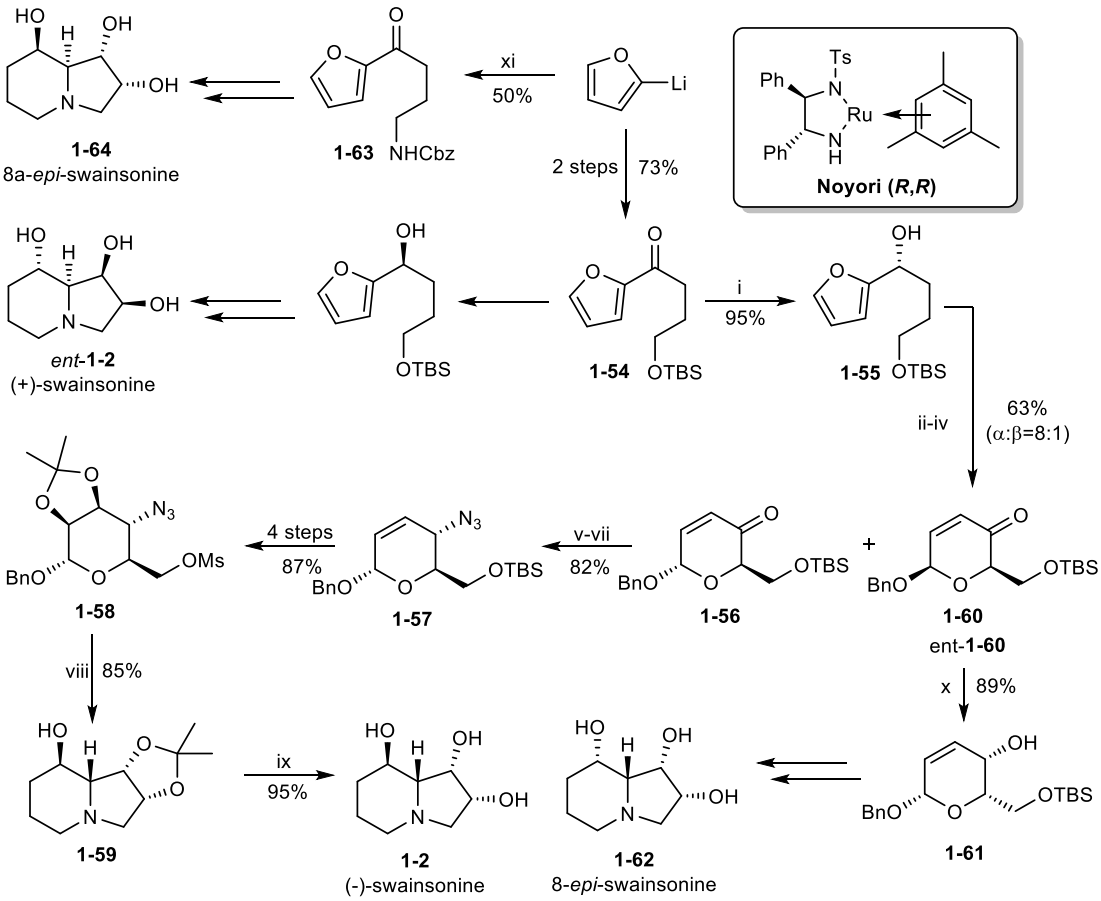
Cossy to give piperidine **1-50**.[28a] This constitutes a formal synthesis of (-)-swainsonine as the same intermediate was featured in the synthesis reported by Cossy *et al*.



Reagents and conditions: i, *s*-BuLi, **1-51**, Et_2O, -78 °C, 3 h then acrolein; ii, TFA, CH_2Cl_2, rt, 20 h , then K_2CO_3, allyl bromide, MeOH, rt, 12 h; iii, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -78 °C, 1 h, then reflux, 48 h; iv, aq. NaOH, rt, 2 h.

Scheme 1.2-9 O'Brien's formal synthesis of (-)-swainsonine

O'Doherty first presented *de novo* syntheses of both enantiomers of swainsonine in 2006 (Scheme 1.2-10).[31] The synthetic strategy relied upon several key reactions: Noyori reduction of **1-54** to **1-55**, Achmatowicz rearrrangement to form pyranone **1-56**, diastereoselective Luche reduction and azidation to afford **1-57** and dihydroxylation to form **1-58** in a selective manner. The indolizidine ring was formed *via* a one-pot reductive transformation which involved benzyl deprotection and double reductive amination (**1-58** to **1-59**). Shortly after, the method was expanded to include the syntheses of 8-*epi*- and 8a-*epi*-swainsonine.[32] Construction of the 8-epimer was executed with the enantiomeric β-anomer, *ent*-**1-60**. This then underwent an analogous route *via* pyran **1-61** to afford 8-*epi*-swainsonine, **1-62**, in 34% overall yield. Synthesis of 8a-*epi*-swainsonine on the other hand, required preparation of furan **1-63**. The synthetic route tracked very closely to that of previous work. In 2009, the group also reported a more straightforward preparation of furan **1-63**.[33] The revised synthesis provided 8a-*epi*-swainsonine, **1-64**, in 10 steps with an overall 3.8% yield, the shortest and highest yielding route to the target molecule.



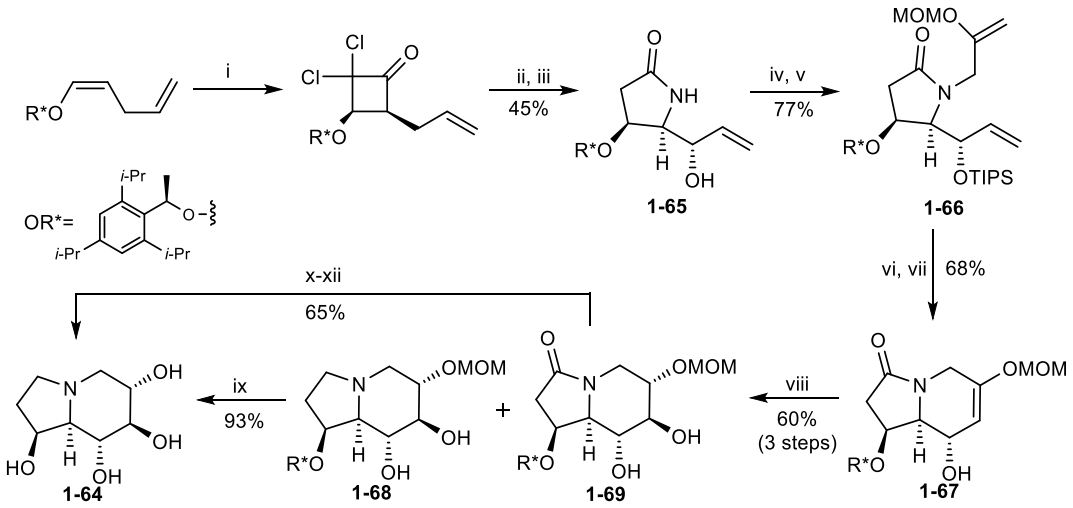
Reagents and conditions: i, Noyori (*R,R*), aq. HCO_2Na-CTAB; ii, NBS, THF-H_2O; iii, $(Boc)_2O$, -78 °C; iv, 2.5% $Pd_2(dba)_3{\cdot}CHCl_3$, 5% PPh_3, BnOH; v, $NaBH_4$, $CeCl_3$, -78 °C; vi, CH_3OCOCl, DMAP-Pyridine; vii, (Pd(allyl)Cl)$_2$-dppb (1:4), $TMSN_3$; viii, H_2, $Pd(OH)_2/C$, 7 days; ix, HCl; x, DIBAL-H; xi, pyrrolidone, *n*-BuLi, then CbzCl, -78 °C.

Scheme 1.2-10 O'Doherty's syntheses of (+) and (-)-swainsonine

1.2.3 Castanospermine and related compounds

Numerous analogues of castanospermine (**1-3**) have been synthesised along with interesting reports of their biological activity.[34] sp^2-Iminosugar derivatives of castanospermine have been prepared and analogues bearing an α-configured *N*-, *S*-, or *C*-linked pseudoanomeric group have been shown to be selective inhibitors of glucosidases.[34d] Their antiproliferative potential against breast cancer cells was also evaluated. Azetidine analogues[35] and *gem*-difluoromethylated analogues[36] of castanospermine have also been prepared. Gallos *et al.* reported a protecting group free synthesis of 1-deoxy epimers of castanospermine.[37]

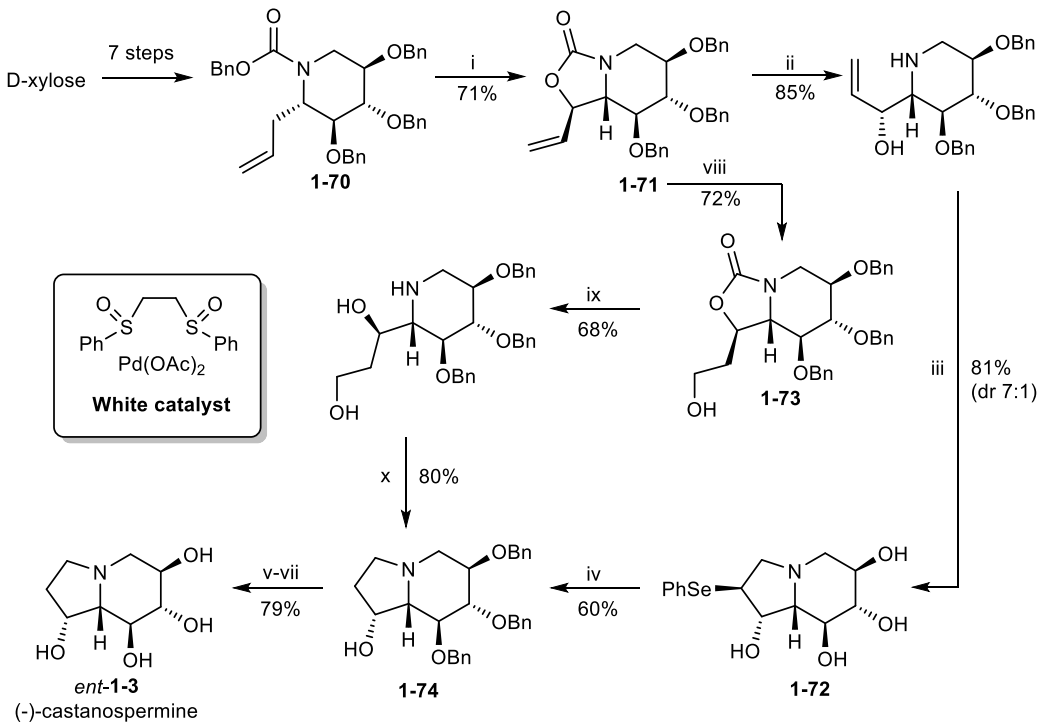
In 2006, Poisson and co-workers' synthesis of (-)-swainsonine featured a [2+2] cycloaddition of dichloroketene strategy to chiral enol ethers to gain access to γ-lactams that represent a key intermediate in the synthesis.[38] This strategy has been applied to the synthesis of (+)-castanospermine **1-3** (Scheme 1.2-11).[39] A hydroboration/oxidation strategy was also successfully developed to install the *trans-cis* hydroxyl array found in the six membered ring of (+)-castanospermine. Here, the allylic hydroxyl group in lactam **1-65** was protected as a TIPS ether and it then underwent *N*-alkylation with 3-iodo-2-(methoxymethoxy)prop-1-ene to give product **1-66**. The ensuing RCM only proved to be effective after removal of the bulky silyl protecting group and in the presence of the Grubbs II catalyst to form enol ether **1-67**. The key step involved hydroboration with excess $BH_3{\cdot}Me_2S$ complex followed by oxidation with sodium perborate. Poisson postulated that the stereoselectivity of the reaction was governed by steric shielding of the undesired face by the allylic substituent causing hydroboration to occur on the concave face of the bicyclic system. This resulted in formation of **1-68** and unreduced lactam **1-69**, both as single isomers. Indolizidines **1-68** and **1-69** were then subsequently transformed into (+)-castanospermine by final treatment with HCl in ethanol.



Reagents and conditions: i, DCK; ii, MSH, Zn/Cu, H+; iii, SeO_2; iv, TIPSOTf, AcOH; v, PTC, $ICH_2C(OMOM)CH_2$; vi, TBAF; vii, Grubbs II; viii, $BH_3{\cdot}DMS$, $NaBO_3$; ix, HCl, EtOH; x, PTSA, 2-methoxypropene; xi, $BH_3{\cdot}DMS$; xii, HCl, EtOH.

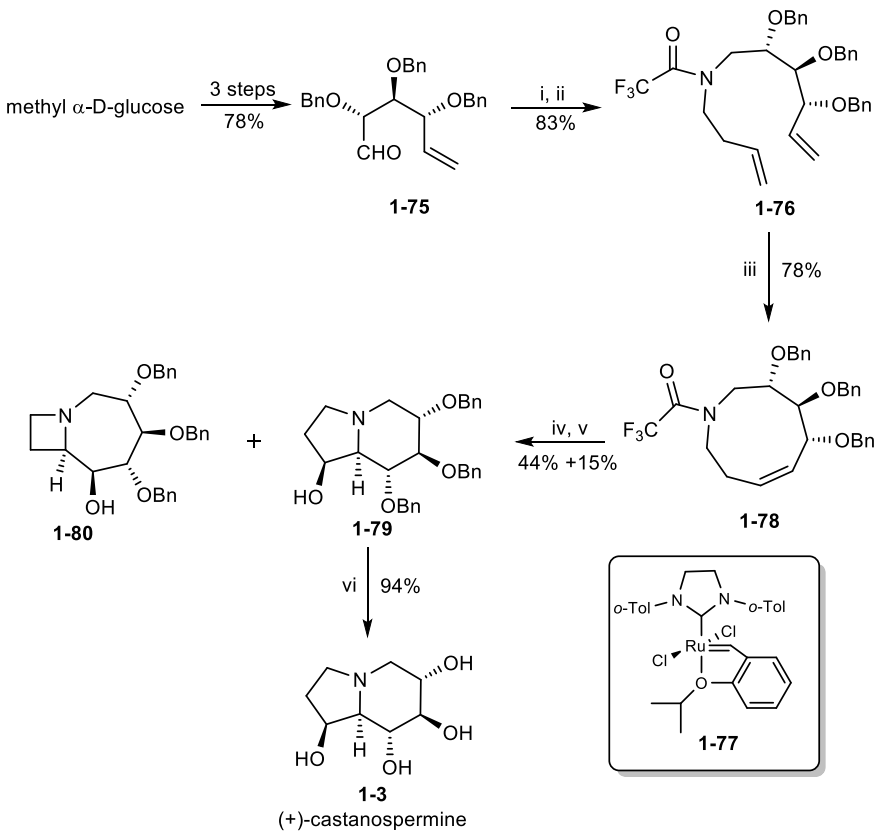
Scheme 1.2-11 Poisson's synthesis of (+)-castanospermine

Most recently, Jarosz and Malik have accomplished a synthesis of unnatural (-)-castanospermine, *ent*-**1-3** (Scheme 1.2-12), based on a palladium-mediated C-H allylic oxidation by an internal carboxybenzyl group, as exemplified in key intermediate **1-70**, obtained from D-xylose.[40] Reaction of **1-70** proceeded best with the White catalyst in the presence of $Yb(OTf)_3$ and benzoquinone to afford oxazolidinone **1-71** as a single diastereomer in 71% yield. Methanolysis followed by treatment with phenylselenyl bromide furnished the indolizidine as two diastereomers with **1-72** being the major product with a 7:1 ratio. Subsequent deselenylation and protecting group manipulations afforded the target molecule in 47% yield. In an alternative route, oxazolidinone **1-71** underwent several manipulations, including a hydroboration/oxidation procedure (**1-71** to **1-73**) and a DPPA-mediated cyclisation to construct indolizidine **1-74**.



Reagents and conditions: i, White catalyst (10 mol%), benzoquinone, $Yb(OTf)_3$, dioxane, 75 °C, 4 h; ii, KOH, MeOH, 75 °C, 12 h; iii, PhSeBr, CH_2Cl_2-pyridine, rt, 10 min; iv, $NaBH_4$, $NiCl_2.6\ H_2O$, MeOH-THF, 0 °C to rt, 2 h; v, $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 3 days; vi, Ac_2O, DMAP, pyridine, rt, 24 h; vii, MeONa, MeOH, rt, 12 h, then Amberlyst A-15; viii, catecholborane, $(Ph_3P)_3RhCl$, THF, rt, 24 h, then aq. NaOH, H_2O_2, rt, 24 h; ix, KOH, MeOH, 75 °C, 12 h; x, DPPA, Et_3N, CH_2Cl_2, rt, 12 h.

Scheme 1.2-12 Jarosz and Malik's synthesis of (-)-castanospermine

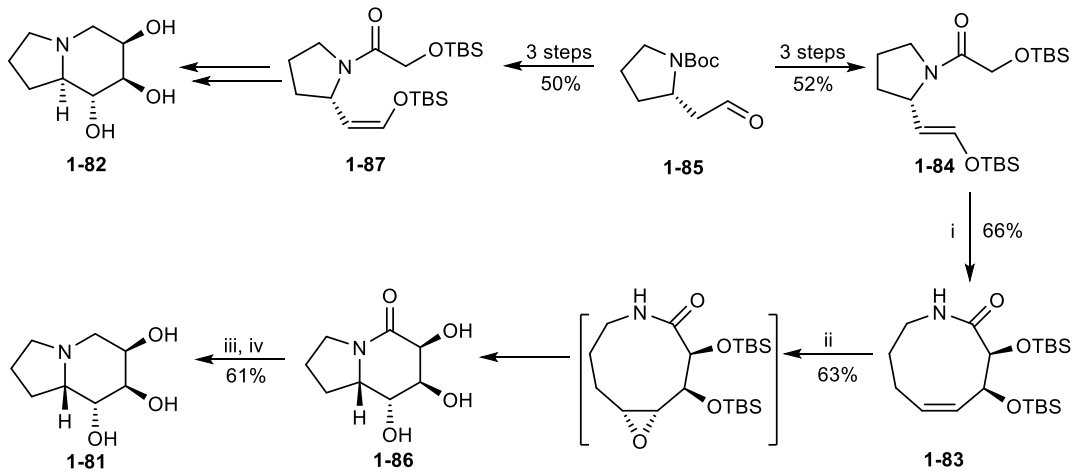


Reagents and conditions: i, homoallylamine, 4 Å MS, AcOH, $NaCNBH_3$, THF, 0 to 22 °C; ii, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0 °C; iii, Grubbs catalyst **1-77** (20 mol%), PhH, 80 °C; iv, CF_3COCH_3, Oxone, $NaHCO_3$, Na_2EDTA, MeCN-H_2O, -10 to 0 °C; v, KO*t*Bu, H_2O-Et_2O, 0 to 22 °C; vi, H_2, Pd/C, HCl, MeOH, 22 °C.

Scheme 1.2-13 Madsen's synthesis of (+)-castanospermine

While there have been numerous syntheses of (+)-castanospermine starting from D-glucose, often with unattractive protection/deprotection steps, Madsen and co-workers have developed a metathesis/transannular cyclisation strategy to form the natural product in a concise manner.[41] The synthesis began with benzyl-protected ether **1-75**, generated over three steps from methyl α-D-glucopyranoside (Scheme 1.2-13). The best conditions for the ensuing reductive amination was found to be with excess homoallyl amine and addition of $NaCNBH_3$ after careful adjustment to pH 7-8 to prevent epimerisation and direct reduction of the aldehyde. The reductive amination product was then treated with trifluoroacetic anhydride to generate trifluoroacetamide **1-76**. After several rounds of experimentation, ring closing metathesis was found to work best with slow addition of ruthenium catalyst **1-77** (10 mol%) in toluene at 80 °C. This protocol furnished cyclononene **1-78** in 78% yield. Installation of the epoxide proved to be successful with *in*

situ generated methyl(trifluoromethyl)dioxirane to afford the desired diastereomer as the major product. Treatment of the crude epoxide with KO*t*Bu in Et_2O furnished desired 5-*endo* indolizidine **1-79** and 4-*exo* byproduct **1-80** with 44% and 15% yield respectively over the two steps. Hydrogenolysis of **1-79** afforded the desired natural product in nine steps with an overall yield of 22%.



Reagents and conditions: i, LHMDS, toluene, reflux; ii, Oxone, MeOH-H_2O, 60 h, rt; iii, Ac_2O, pyridine; iv, $LiAlH_4$, THF, reflux.

Scheme 1.2-14 Suh's synthesis of castanospermine isomers 1-81 and 1-82

Similarly, Suh and co-workers have employed a substrate-controlled transannulation strategy to access the indolizidine framework from 9-membered lactams and in this case, for the synthesis of castanospermine isomers, **1-81** and **1-82** (Scheme 1.2-14).[42] Lactam **1-83** could be derived in a stereoselective manner from a microwave-assisted *aza*-Claisen rearrangement of pyrrolidine **1-84**, easily accessible from L-proline derivative **1-85**. The rearrangement reaction was predicated on studies carried out earlier by the group on stereoselective ring expansions of lactams. The group found that the geometry of the olefin of **1-84** was the key driving force for the stereochemical outcome. A boat-like transition state with the bulky silyl groups pointing in a pseudoequatorial direction will afford lactam **1-83** with the desired *cis*-relationship between the two secondary alcohol groups in deent yield (66%). The ensuing transannulation reaction was found to work best through the use of Oxone with concurrent TBS-deprotection to furnish triol **1-86**. Acetate protection and

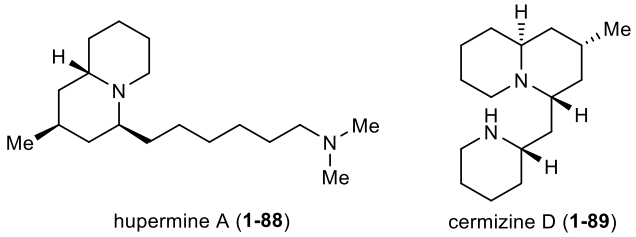
global reduction with $LiAlH_4$ produced deoxy-castanospermine derivative **1-81**. The 8a-epimer of **1-81**, indolizidine **1-82** was also prepared in a similar fashion from the (*Z*)-stereoisomer of pyrrolidine **1-84** i.e. intermediate **1-87** albeit with lower yield for the rearrrangement reaction (21%).

1.3 Plant indolizidine and quinolizidine alkaloids

1.3.1 Lycopodium alkaloids

A comprehensive review on *Lycopodium* alkaloids covering the period from 2005 to early 2012 has been published in the series The Alkaloids.[43] The review by Rinner *et al.* primarily deals with isolation of various *Lycopodium* alkaloids, their biological activities and recent developments in the total synthesis of *Lycopodium* alkaloids.

Since Rinner's review, isolation of a novel *Lycopodium* quinolizidine alkaloid, hupermine A (**1-88**) has been reported.[44] The alkaloid was found in a methanolic extract from the club moss of *Huperzia phlegmaria*. The structure and relative stereochemistry were deduced from 2D NMR spectra and NOESY correlations. The new alkaloid was weakly cytotoxic against HL-60 cells (IC_{50} 39 μM). The authors postulated that the alkaloid was generated through cleavage of the C-5 –N bond in cermizine D (**1-89**).

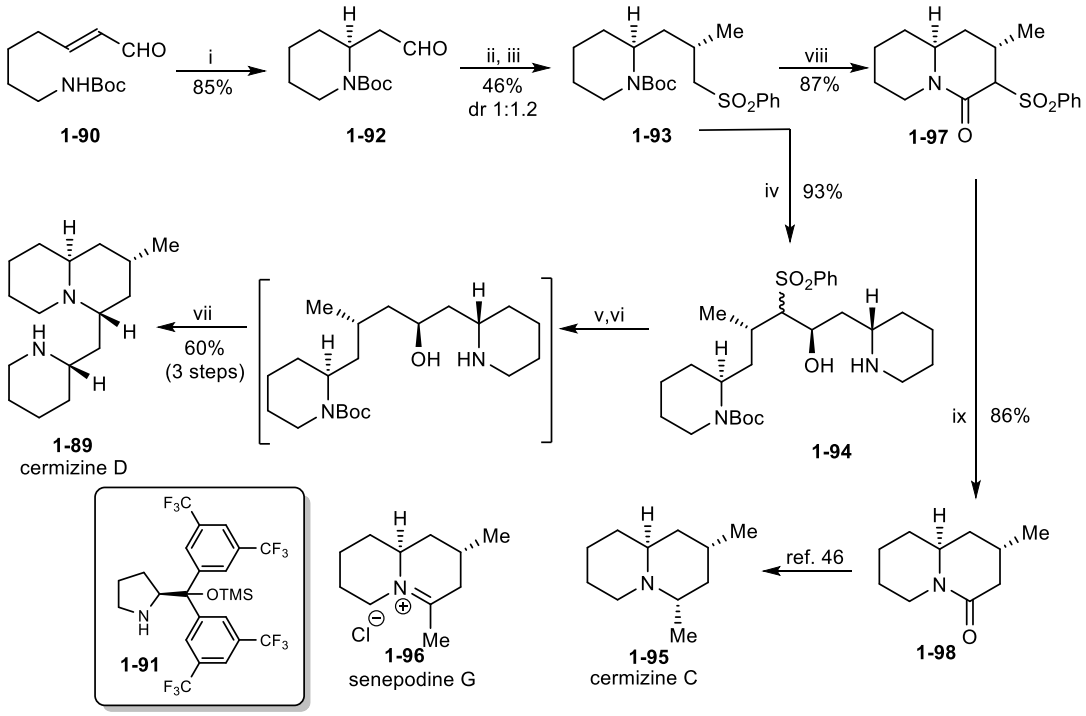


hupermine A (**1-88**) cermizine D (**1-89**)

Figure 1.3-1 Structures of hupermine A and cermizine D

Carter *et al.* have presented the most recent synthesis of cermizine D (**1-89**) *via* an organocatalytic *aza*-Michael reaction as the key step (Scheme 1.3-1).[45] In the first report, Carter disclosed the conversion of aldehyde **1-90** in the presence of proline-derived catalyst **1-91** to furnish key building block **1-92** in 85% yield and 96% ee. **1-92** could be used as a

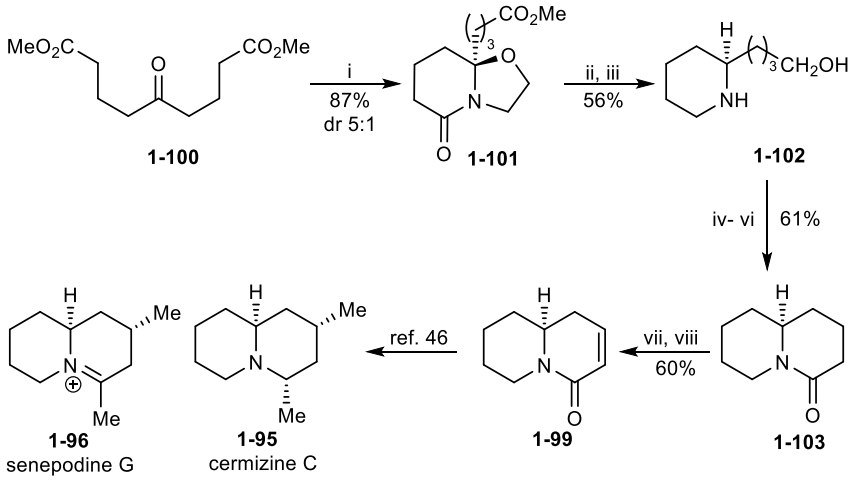
common intermediate to form two of the three piperidine rings in the natural product. **1-92** was first elaborated *via* a HWE reaction to furnish an unsaturated sulfone which subsequently underwent conjugate addition using Me_2CuLi. This gave sulfone **1-93** as an approximately 1:1 mixture of diastereomers, the main drawback of this work. Sulfone **1-93** was then coupled to the second unit of building block **1-92** and direct desulfurisation on hydroxy sulfone **1-94** was carried out. The synthesis to **1-89** was completed by deprotection of the crude product followed by cyclisation with PPh_3 and CBr_4. Experimental details were disclosed in the full paper published the year after, together with the formal synthesis of cermizine C (**1-95**) and senepodine G (**1-96**). With longer reaction times, the authors observed that the coupling reaction of **1-92** with **1-93** resulted in cyclisation product **1-97**. With this serendipitous discovery, formation of **1-97** was further optimised and subsequent Raney-Ni desulfurisation gave known intermediate **1-98**, intersecting the synthesis of both senepodine G (**1-96**) and cermizine C (**1-95**) reported by Snider and co-workers.[46]



Reagents and conditions: i, **1-91** (10 mol%), DCE-MeOH (1:3), -20 °C, 10 days; ii, $PhSO_2Me$, *n*-BuLi then $ClP(O)(OEt)_2$, THF, -78 °C, 2 h; iii, Me_2CuLi, THF, -78 °C to -20 °C, 5 h; iv, **1-92**, LDA, THF, -78 °C, 1 min; v, Raney Ni, EtOH, reflux, 15 h; vi, TMSCl, MeOH, rt, 4 h; vii, PPh_3, CBr_4, Et_3N, 0 °C to rt, 3 h; viii, LDA, THF, -78 °C, 20 min ; ix, Na/Hg, Na_2HPO_4, MeOH, 0 °C, 20 min.

Scheme 1.3-1 Carter's synthesis of cermizine C, D and senepodine G

Similarly, the formal synthesis of cermizine C and senepodine G by Amat *et al.* relied on formation of **1-99**,[47] also an intermediate in Snider and co-worker's[46] synthesis (Scheme 1.3-2). The synthesis commenced with treatment of ketodiester **1-100** with (*R*)-phenylglycinol in the presence of acetic acid to give the bicyclic lactam **1-101** as a mixture of diastereomers (dr 5:1) which were separable by column chromatography. $LiAlH_4$ reduction of the lactam and hydrogenation in the presence of $(Boc)_2O$ with $Pd(OH)_2$ as a catalyst afforded **1-102**. This was then oxidised to the acid with PDC in DMF. Subsequent deprotection with TMSCl followed by heating in refluxing xylene afforded bicyclic lactam **1-103** which was then converted to intermediate **1-99** as illustrated.

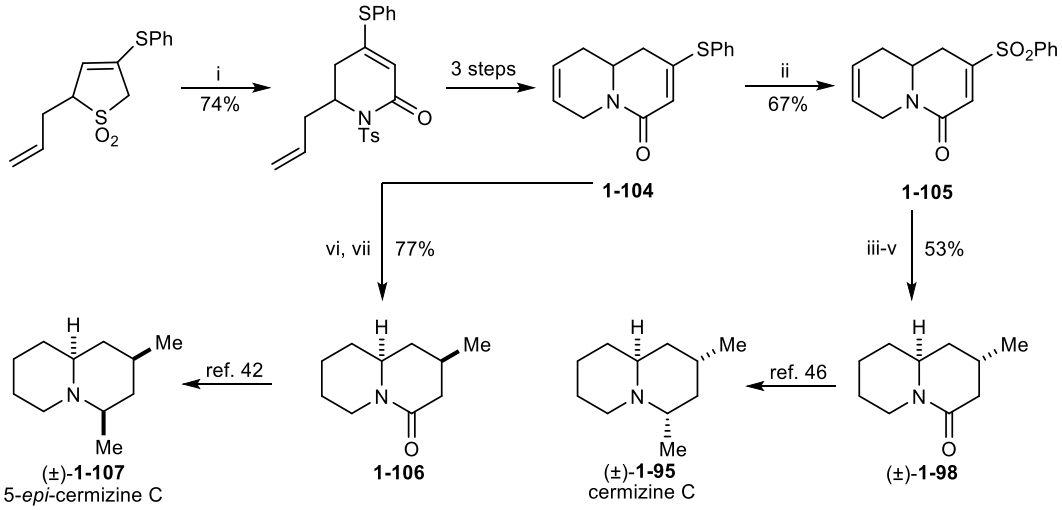


Reagents and conditions: i, (*R*)-glycinol, AcOH, toluene, reflux, 7 h; ii, $LiAlH_4$, 0 °C to rt, THF, 1 h; iii, H_2, $Pd(OH)_2/C$ (40%), Boc_2O, EtOAc, rt, 24 h; iv, PDC, DMF, rt, 24 h; v, TMSCl, NaI, MeCN, rt, 1 h; vi, xylene, reflux, 24 h; vii, *t*-BuLi, PhSeCl, THF, -78 °C, 2 h; viii, O_3, CH_2Cl_2, -78 °C to rt, 30 min.

Scheme 1.3-2 Amat's synthesis of cermizine C and senepodine G

Chou and co-workers[48] also relied on the synthesis of cermizine C by Snider and co-workers to establish their formal racemic synthesis of the natural product by a route in which the key step was an *aza*-Diels-Alder reaction to prepare quinolizidinones such as **1-104** (Scheme 1.3-3). The group has employed this strategy to construct a variety of bicyclic nitrogen structures and natural products. In this case, quinolizidinone **1-104** was oxidised with *m*CPBA to phenyl sulfone **1-105**. Desulfurisation and subsequent conjugate addition with Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$ afforded the corresponding methyl

quinolizidinone. This was reduced by catalytic hydrogenation with PtO_2 as the catalyst to give Snider's intermediate (±)-**1-98**. On the other hand, conjugate addition with Me_2CuLi on quinolizidinone **1-104** followed by hydrogenation, gave **1-106** as the major product and an intermediate towards Snider's synthesis of 5-*epi*-cermizine C (**1-107**).



Reagents and conditions: i, *p*-toluenesulfonyl isocyanate, hydroquinone, $NaHCO_3$, toluene, reflux, 4.5 h; ii, *m*CPBA (3 equiv.) CH_2Cl_2, 0 °C, 6 h; iii, 5% Na/Hg, cat. H_3PO_4, THF, reflux, 2 h; iv, MeLi, CuI, $BF_3{\cdot}Et_2O$, THF, -78 °C, 3 h; v, H_2 (1 atm), PtO_2 (15 mol%), EtOAc, rt, 11 h; vi, MeLi, CuI, $BF_3{\cdot}Et_2O$, THF, -78 °C to rt, 8 h; vii, H_2 (1 atm), PtO_2 (15 mol%), MeOH, rt, 18 h.

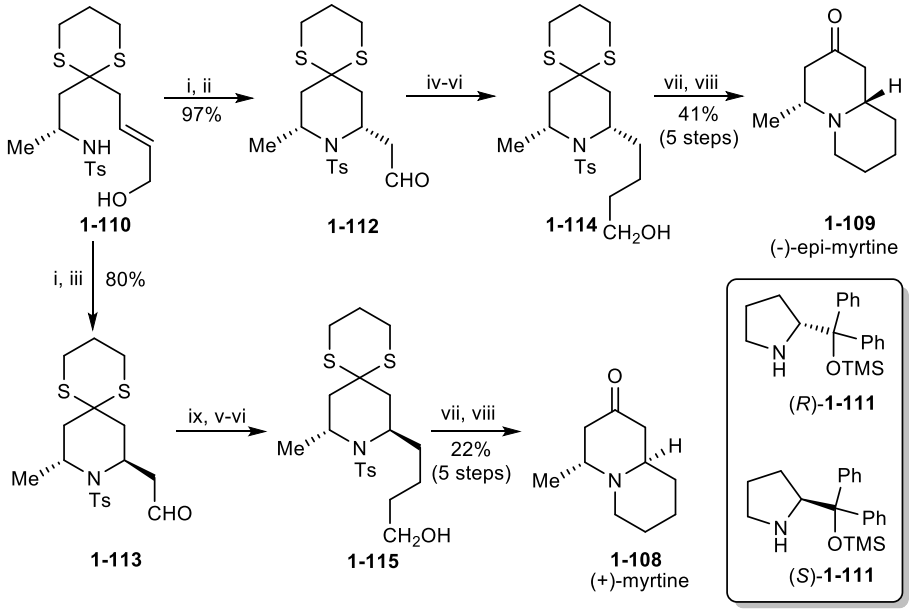
Scheme 1.3-3 Chou's formal synthesis of cermizine C and its epimer

1.3.2 (+)-Myrtine and (-)-*epi*-myrtine

Development in organocatalytic intramolecular *aza*-Michael reactions gained momentum during the period of the review with two independent groups reporting the application of the reaction to the synthesis of (+)-myrtine **1-108**, an alkaloid isolated from the blueberry tree, *Vaccinium myrtillus*.[49]

Hong and co-workers disclosed a tandem allylic oxidation/*aza*-Michael reaction to synthesise both 2,6-*trans*-and 2,6-*cis*-piperidine intermediates for construction of (+)-myrtine **1-108** and (-)-*epi*-myrtine **1-109** and respectively (Scheme 1.3-4).[50] Starting with common (*E*)-allylic alcohol substrate **1-110**, MnO_2 oxidation furnished the intermediate enal where the presence of either (*S*)- or (*R*)-pyrrolidine catalyst **1-111** greatly improved the diastereoselecivity of the reaction to form 2,6-*cis*-piperidine **1-112** (dr 20:1) or 2,6-

trans-piperidine **1-113** (dr 4:1) respectively with yields of 97% and 80% respectively. The good yields attained could be attributed to the Thorpe-Ingold effect by the 1,3-dithiane group which was essential in overcoming the poor nucleophilicity of the sulfonamide group. Intermediates **1-112** and **1-113** were elaborated to cyclisation precursors **1-114** and **1-115** *via* a Wittig reaction with pure **1-112** or Still-Gennari olefination with an inseparable mixture of **1-112** and **1-113**. This was followed by tosyl deprotection and ester reduction with $LiAlH_4$. Cyclisation occurred upon mesylation and final dithiane deprotection with *bis*(trifluoroacetoxy)iodo benzene completed the synthesis of (+)-myrtine **1-108** and its epimer **1-109**.

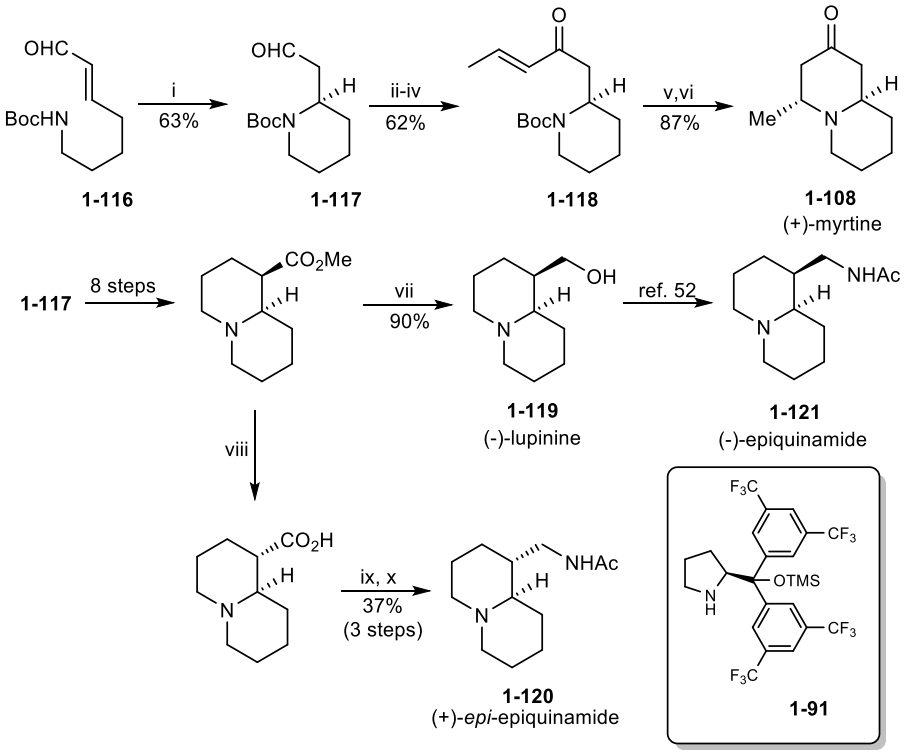


Reagents and conditions: i, MnO_2, CH_2Cl_2, 25 °C, 3 h; ii, (*S*)-**1-111**-BzOH (20 mol%), CH_2Cl_2, 0 °C, 7 h; iii, (*R*)-**1-111**-BzOH (20 mol%), CH_2Cl_2, 0 °C, 9 h; iv, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25 °C, 5 h; v, Mg (powder), MeOH, 25 °C, 20 h; vi, $LiAlH_4$, THF, -20 °C, 3 h; vii, MsCl, Et_3N, CH_2Cl_2, -78 °C, then aq. $NaHCO_3$, 25 °C, 4 h; viii, PIFA, TFA-H_2O-MeCN (1:10:10), 25 °C, 3 h; ix, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-Crown-6, THF, -78 °C, 4 h.

Scheme 1.3-4 Hong's synthesis of (+)-myrtine and (-)-*epi*-myrtine

Fustero *et al.* reported an intramolecular *aza*-Michael reaction starting from aldehyde **1-116** with proline-derived **1-91** as the catalyst to afford piperidine **1-117** with 94% ee in 63% yield (Scheme 1.3-5).[51] Chain homologation was carried out by Grignard reaction with allylmagnesium bromide, oxidation of the resulting alcohol and isomerisation of the double bond with Et_3N in MeOH to furnish intermediate **1-118**. Cleavage of the *N*-Boc

protecting group and subsequent treatment with K_2CO_3 promoted the second *aza*-Michael intramolecular cyclisation to give the desired natural product **1-108** as a single diastereomer in 87% yield over the two steps. The organocatalytic strategy was also applied to the synthesis of (-)-lupinine **1-119** and (+)-*epi*-epiquinamide **1-120**. The synthetic route to the synthesis of (-)-lupinine also constitutes a formal synthesis of (-)-epiquinamide **1-121** since this transformation has been reported earlier.[52]

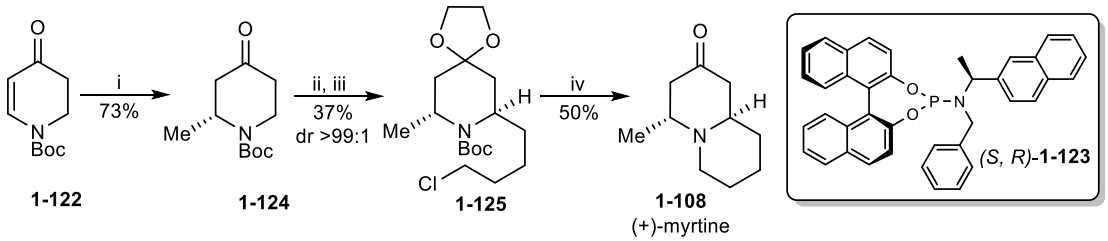


Reagents and conditions: i, **1-91** (20 mol%), $CHCl_3$, $PhCO_2H$, -50 °C, 20 h; ii, allyl-MgBr, THF, 0 °C to rt, 1h; iii, Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 5 h; iv Et_3N, MeOH, rt, 10 h; v, TFA, CH_2Cl_2, 0 °C, 1 h; vi, K_2CO_3, MeOH, 0 °C, 1 h; vii; $LiAlH_4$, THF, reflux, 3 h; viii, LiOH, THF-H_2O (4:1), 0 °C, 4 h; ix, DPPA, Et_3N, toluene, reflux, overnight; x, Ac_2O, pyridine, rt, overnight.

Scheme 1.3-5 Fustero's synthesis of (+)-myrtine, (-)-lupinine, (-)-epiquinamide and epimer

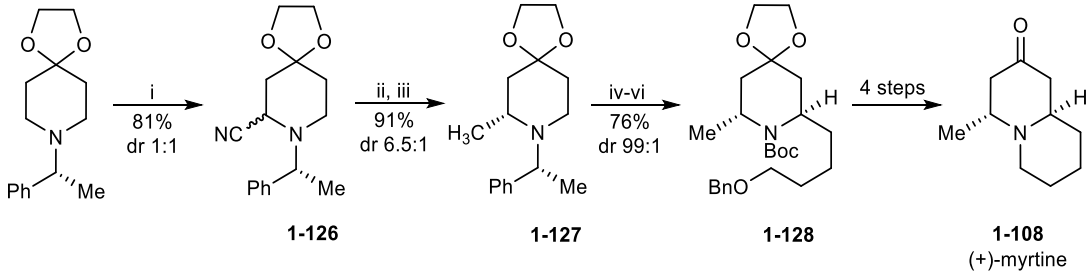
In the synthesis of (+)-myrtine **1-108** reported by Feringa and co-workers, introduction of the first stereogenic centre was carried out with a highly stereoselective copper-catalysed conjugate addition of trimethylaluminium to dehydropiperidone **1-122** in the presence of phosphoramidite ligand **1-123** (Scheme 1.3-6).[53] Careful optimisation work proved that addition of Et_2O as a co-solvent was essential to circumvent aggregation of Me_3Al and ensure formation of piperidone **1-124** with high yield and good enantioselectivity (96%

ee). After protection of the ketone, a lithiation-substitution sequence afforded 2,6-*trans*-piperidine **1-125** with high stereochemical control (dr >99:1). A one-pot reaction sequence involving ketal and *N*-Boc deprotection followed by cyclisation afforded the natural product in 50% yield.



Reagents and conditions: i, Me_3Al, $Cu(OTf)_2$ (5 mol%), (*S*,*R*)-**1-123** (10 mol%), Et_2O (10 mol%), toluene, -50 °C, 16 h; ii, PTSA, ethylene glycol, MS 3Å, toluene, reflux, 16 h; iii, *s*-BuLi, TMEDA, Et_2O, -78 °C, 3 h then CuCN.2LiCl THF, -78 °C to -50 °C, 1 h then $I(CH_2)_4Cl$, -78 °C to rt, 16 h; iv, concd. HCl, acetone, H_2O, reflux, 16 h then $NaHCO_3$, 0 °C, 16 h.

Scheme 1.3-6 Feringa's synthesis of (+)-myrtine

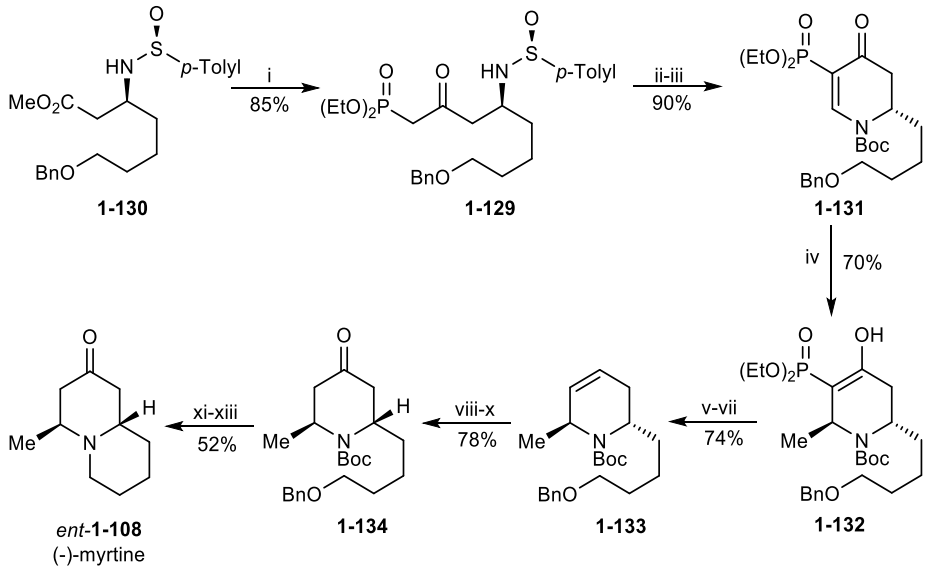


Reagents and conditions: i, NaCN, $MeOH/LiClO_4.3H_2O$ (0.2 M), glassy carbon electrode, υ= 0.05 Vs^{-1}; ii, LDA, THF, -80 °C to 0 °C, 2 h, then iodomethane, -80 °C to -10 °C; iii, $NaBH_4$, EtOH, 0 °C to 20 °C, 12 h; iv, H_2 (5 bar), 20% Pd/C, MeOH, rt, 72 h; v, $(Boc)_2O$, DIPEA, MeCN, reflux, 4 h; vi, *s*-BuLi, TMEDA, Et_2O, -80 °C to -70 °C, 2 h, then CuCN.LiCl, -80 °C to -60 °C, 2 h, then $I(CH_2)_4OBn$, -80 °C to rt, 12 h.

Scheme 1.3-7 Hurvois' synthesis of (+)-myrtine

Most recently, Hurvois and co-workers described the synthesis of (+)-myrtine **1-108** by a route commencing with electrochemical synthesis of α-amino nitrile **1-126** from the corresponding piperidinone (Scheme 1.3-7).[54] Iodomethane was added dropwise to the lithiated nitrile to introduce the methyl group. Reductive decyanation with sodium borohydride afforded **1-127** with good diastereoselectivity. The stereochemical outcome was attributed to the facial selectivity of the hydride attack. The synthesis continued with cleavage of the chiral auxiliary with 20% $Pd(OH)_2/C$ followed by *N*-Boc protection. Similar to Feringa's approach,[53] a lithiation-substitution sequence was carried out with the

N-Boc group acting as a directing group. Alkylation with the corresponding iodo compound afforded 2,6-*trans*-piperidinone **1-128** as a single diastereomer in 86% yield. After several steps involving manipulation of the *O*-benzyl group to a bromide, deprotection took place and cyclisation proceeded smoothly to afford the quinolizidine ring in 89% yield. Final acetal deprotection afforded the natural product (**1-108**) in almost quantitative yield. An analogous synthesis with *ent*-**1-127** led to synthesis of the unnatural isomer of the natural product, (-)-myrtine (*ent*-**1-108**).

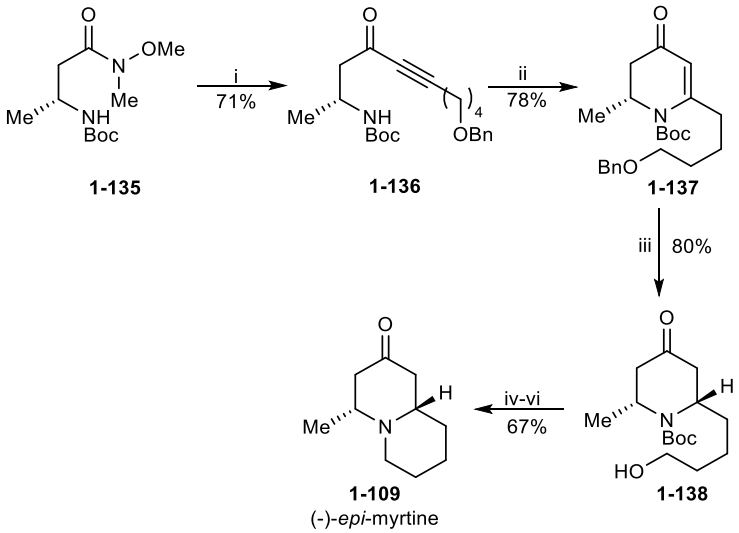


Reagents and conditions: i, $CH_3PO(OEt)_2$, *n*-BuLi, -78 °C, 2 h; ii, DMF dimethyl acetal, toluene, rt, 12 h; iii, 4N HCl, rt, 1 h; iv,$(Boc)_2O$, DMAP, Et_3N, THF, rt, 3 h; v, MeMgCl, CuI, THF, -78 °C, 2 h; vi, $NaBH_4$, MeOH, 0 °C, 30 min*;* vii, 6 N NaOH, rt, 16 h; viii, DIC, $CHCl_3$, 60 °C, 8 h; ix, $Hg(NO_3)_2$, THF-H_2O (1:2), rt, 10 min, then 6 M aq. NaOH, $NaBH_4$; x, Dess-Martin periodinane, CH_2Cl_2, rt, 2 h; xi, TFA, CH_2Cl_2, rt, 45 min; xii, H_2 (1 atm), $Pd(OH)_2$, TFA in THF, rt, 3 h; xiii, CCl_4, PPh_3, Et_3N, rt, 20 h.

Scheme 1.3-8 Davis' synthesis of (-)-myrtine

Davis and colleagues constructed the unnatural enantiomer (-)-myrtine *ent*-**1-108** using sulfinimines as a chiral auxiliary to provide access to 2, 6-*trans*-piperidines (Scheme 1.3-8).[55] The synthesis commenced with formation of phosphonate ester **1-129** *via* reaction of diethyl lithiummethylphosphonate with β-amino ester **1-130**, prepared earlier for the synthesis of another alkaloid target. The phosphonate ester was treated with DMF dimethyl acetal. The resulting enaminone was directly subjected to cyclisation under acidic conditions (4M HCl) and subsequent protection with Boc_2O afforded piperidine **1-131** in

90% yield. Conjugate addition with methyl cuprate at -78 °C afforded *trans*-piperidine **1-132** as the major product (dr 4:1) with an isolated yield of 70%. The 4-keto moiety was introduced after several steps involving manipulation to alkene **1-133** as disclosed by Pagenkopf *et al.*[56] and then oxymercuration and oxidation with Dess-Martin periodinane. Subsequent removal of the *N*- and *O*-protecting groups of ketone **1-134** afforded an intermediate which cyclised to give the natural product in 68% yield upon treatment with CCl_4 and triphenylphosphine in the presence of triethylamine.

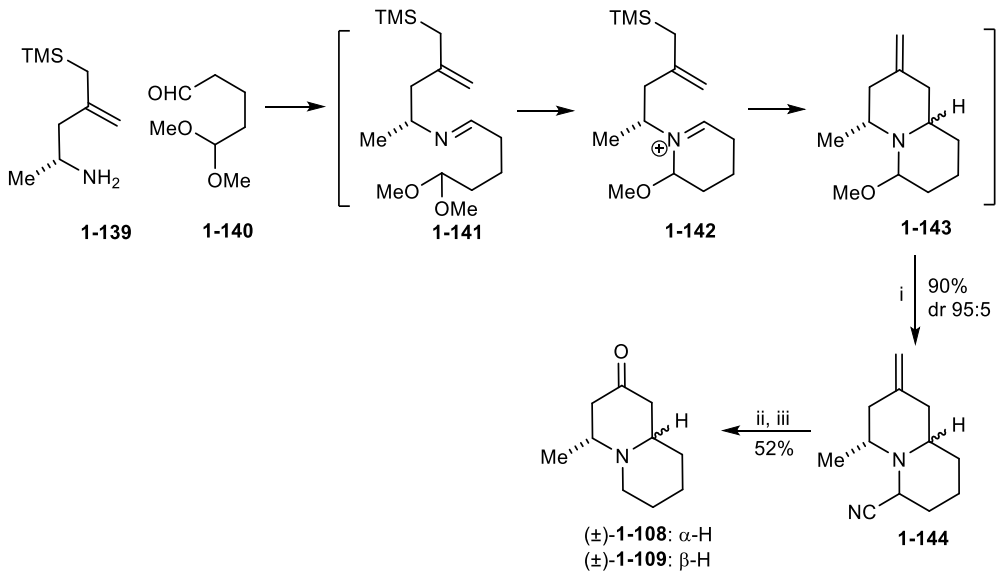


Reagents and conditions: i, $BnO(CH_2)_4C{\equiv}CH$, *n*-BuLi, THF, -78 °C to -20 °C, 3 h; ii, $Ph_3PAuCl/AgSbF_6$ (5 mol%), 1,2- $C_2H_2Cl_2$, 40 °C, 2 h; iii, H_2 (1 atm), Pd/C, MeOH, rt, 48 h; iv, CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 1 h; v, 1 M $SnCl_4$ in CH_2Cl_2, CH_2Cl_2, rt, 3h; vi, K_2CO_3, THF-H_2O (1:2), rt, 12 h.

Scheme 1.3-9 Goualt's synthesis of (-)-*epi*-myrtine

The synthesis of (-)-*epi*-myrtine **1-109** by Goualt and co-workers showcases a gold-catalysed hydroamination reaction as the key step (Scheme 1.3-9).[57] Addition of the *in situ* generated lithium acetylide to Weinreb amide **1-135** furnished cyclisation precursor **1-136** in 71% yield. Cyclisation took place with PPh_3AuSbF_6 as a catalyst generated *in situ* from a 5 mol% mixture of PPh_3AuCl and $AgSbF_6$ to selectively generate the 6-*endo*-*dig* product, dihydropyridone **1-137** in 78% yield. Hydrogenation with palladium on carbon as the catalyst afforded piperidone **1-138** as a single diastereomer in 80% yield. The synthesis was completed by standard transformations as illustrated.

Martin *et al.* conceived an iminium cascade sequence that was employed for the racemic synthesis of *epi*-myrtine starting with amino allylsilane **1-139** and monoprotected dialdehyde **1-140** under acidic conditions (Scheme 1.3-10).[58] The sequence begins with formation of imine **1-141** which then underwent the first cyclisation with an intermediate oxocarbenium ion. The second cyclisation occurs *via* addition of the allylsilane moiety to iminium ion **1-142**. Another iminium ion was generated from the *N,O*-acetal moiety in quinolizidine **1-143** which would finally be trapped by a nucleophile, in this case CN^-, *via* an axial attack to form quinolizidine **1-144** as a mixture of epimers. With the quinolizidine framework in place, the remaining steps were straightforward, entailing reduction with $NaCNBH_3$ and reduction of the exocyclic alkene to *epi*-myrtine, (±)-**1-109** as an inseperable 95:5 mixture with myrtine, (±)-**1-108**.



Reagents and conditions: i, 4 Å MS, MeCN, rt, 2 h, then TFA, -40 °C, 4 h, then aq. NaCN, CH_2Cl_2, 0 °C, 12 h; ii, $NaCNBH_3$, MeCN, rt, 24 h; iii, TFA, then O_3, CH_2Cl_2-MeOH (6:1), -78 °C, then Me_2S.

Scheme 1.3-10 Martin's synthesis of (±)-108 and (±)-109

1.3.3 Dendroprimine and related compounds

(-)-Dendroprimine (**1-145**) is an alkaloid isolated from *Dendrobium primulinum* Lindl, a member of the *Orchidaceae* family.[59] Katsumura and co-workers disclosed a tandem one-

pot sequence for the construction of substituted chiral piperidines, providing access to (-)-dendroprimine **1-145** and 5-, 7- and 5, 7-*epi*-dendroprimines **1-146**, **1-147** and **1-148**.[60]

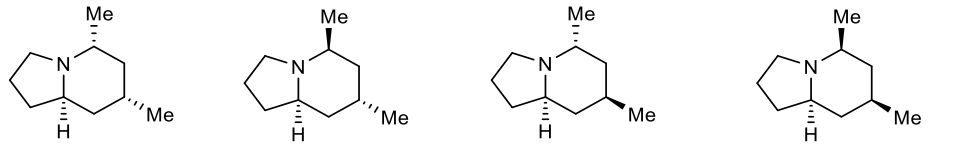
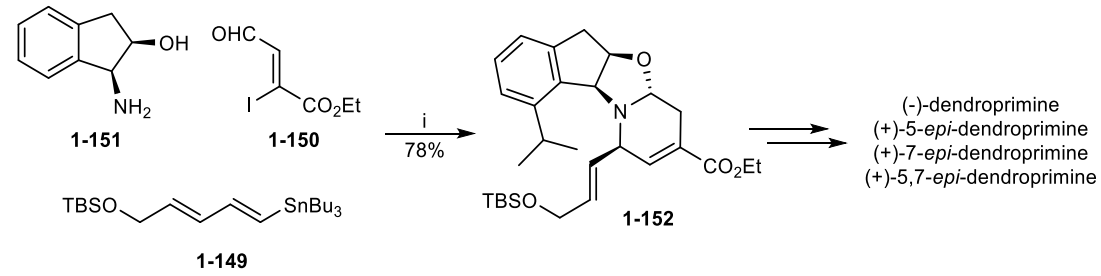


Figure 1.3-2 Structures of (-)-dendroprimine and analogues

Katsumura's tandem one-pot sequence, first reported in a 2010 communication and later expanded to a full article in 2012, consists of three steps (Scheme 1.3-11). First, a Stille-Migata coupling of vinyl stannane **1-149** with vinyl iodide **1-150** occurs in the presence of a $Pd_2(dba)_3$/TFP catalyst. This is followed by a stereoselective 6π–azaelectrocyclisation and culminates in an aminoacetal reaction between the resulting aldehyde with indanol **1-151**. The overall sequence results in formation of tetracyclic piperidine intermediate **1-152** in 78% yield and high diastereoselectivity (dr 20:1). Intermediate **1-152** was then applied to the synthesis of (-)-dendroprimine. In the 2012 full article, synthesis of its three diastereomers was also reported from the same intermediate.

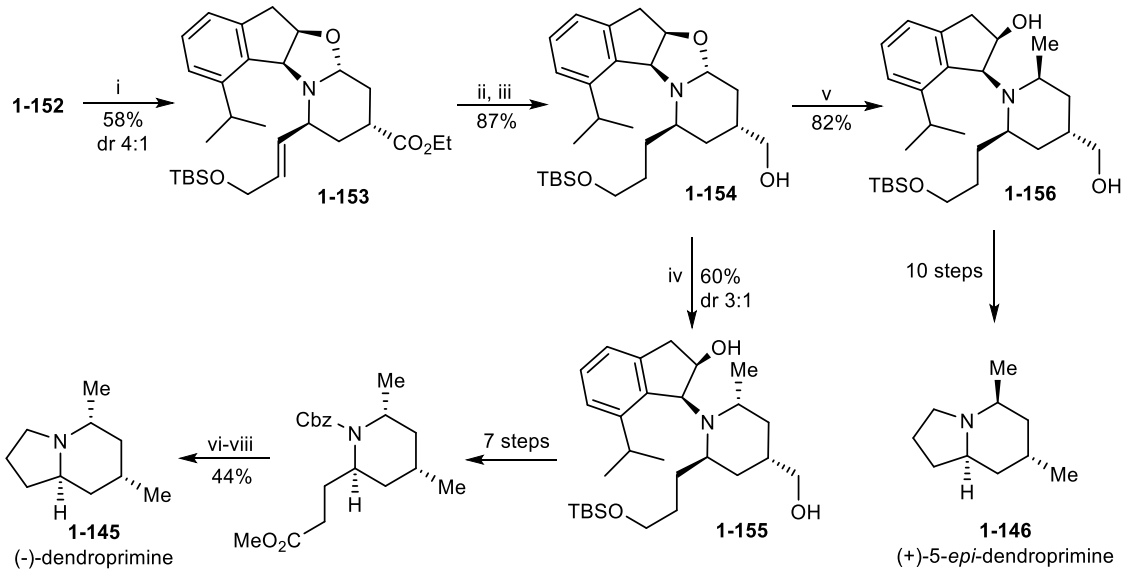


Reagents and conditions: i, $Pd_2(dba)_3$, $P(2\text{-furyl})_3$, LiCl, 4 Å MS, DMF, 80 °C, 2 h

Scheme 1.3-11 Katsumura's tandem one-pot synthesis of 1-152

In the syntheses of (-)-dendroprimine **1-145** and (+)-5-*epi*-dendroprimine **1-146**, the conjugated double bond in intermediate **1-152** was reduced with magnesium in methanol to afford ester **1-153** as a 4:1 mixture of diastereomers, which were separated by column chromatography (Scheme 1.3-12). The desired ester was reduced with Red-Al and then hydrogenated with PtO_2 as the catalyst to furnish alcohol **1-154** in 87% yield over 2 steps.

Methylation with MeMgI and CuI gave C-6 α-methyl isomer **1-155** in a 3:1 ratio of diastereomers. On the other hand, methylation with Me_3Al gave C-6 β-methyl diastereomer **1-156** as a single isomer. The synthesis continued from isomer **1-155** and **1-156** *via* the same transformations to (-)-dendroprimine and (+)-5-*epi*-dendroprimine respectively. The indane moiety was cleaved and the nitrogen was protected by a Cbz group. The hydroxymethyl group was then converted to the methyl group by Puglis' method.[61] The OTBS group was converted to a methyl ester in preparation for the cyclisation which occurred upon hydrogenation followed by heating in refluxing toluene. Finally, $LiAlH_4$ reduction of the respective diastereomers completed the syntheses of (-)-dendroprimine and (+)-5-*epi*-dendroprimine (**1-145** and **1-146**).

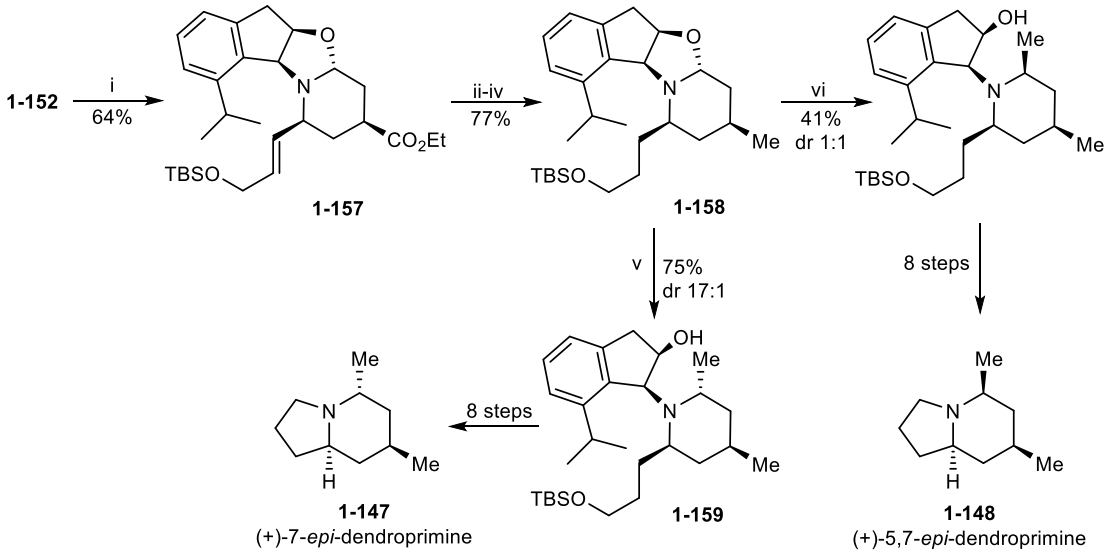


Reagents and conditions: i, Mg, MeOH, rt, 2 h; ii, Red-Al, toluene, rt; iii, H_2 (1 atm), PtO_2, THF, rt; iv, MeMgI, CuI, ether, rt; v, Me_3Al, toluene, rt, 2 h; vi, H_2 (1 atm), Pd/C, MeOH, rt; vii, toluene, reflux; viii, $LiAlH_4$, ether, reflux.

Scheme 1.3-12 Katsumura's synthesis of (-)-dendroprimine and (+)-5-*epi*-dendroprimine

In the case of (+)-7-*epi*-dendroprimine **1-147** (Scheme 1.3-13), intermediate **1-152** was reduced by hydrogenation with Raney-Ni as the catalyst to afford ester **1-157** as a single isomer in 64% yield. Red-Al reduction furnished hemiaminal **1-158** which was then converted to the methyl group by Ueno's method.[62] Methylation with Me_3Al provided C-6 α-methyl isomer **1-159** with 17:1 diastereoselectivity. Synthesis of (+)-7-*epi*-

dendroprimine was realised by means of transformations analogous to those described earlier for the syntheses of (-)-dendroprimine **1-145** and its 5-epimer **1-146**. While spectral data of (-)-dendroprimine and (+)-7-*epi*-dendroprimine **1-147** were in agreement with those reported in literature, the ^{13}C NMR spectrum of (+)-5-*epi*-dendroprimine was different from the reported data by Gelas-Mialhe.[63] The authors hypothesised that the correct structure in Gelas-Mialhe's synthesis might have been the (+)-5,7-*epi*-dendroprimine instead. To confirm this, (+)-5,7-*epi*-dendroprimine **1-148** was synthesised as illustrated and the spectral data were in good agreement with the data reported for (+)-5-*epi*-dendromine by Gelas-Mialhe and co-workers.

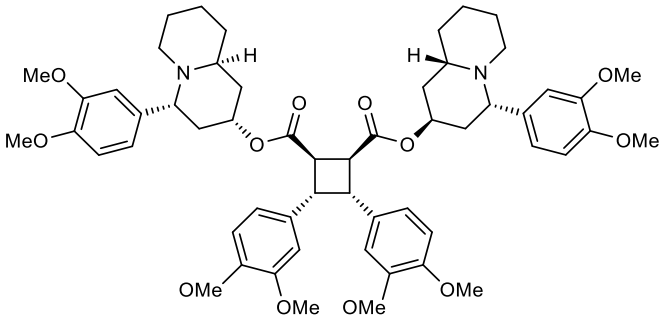


Reagents and conditions: i, H_2, W-2 Raney Ni, EtOH, rt, 2h; ii, Red-Al, toluene, rt; iii, TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 4 h; iv, Bu_3SnH, NaI, AIBN, DME, 3 h; v, Me_3Al, toluene, rt, 2 h; vi, MeMgI, ether, rt, 2 h.

Scheme 1.3-13 Katsumura's synthesis of (+)-7-*epi*-dendroprimine and (+)-5, 7-*epi*-dendroprimine

1.3.4 Lythraceae alkaloids

1.3.4.1 Isolation



1-160
(+)-sarasubine A

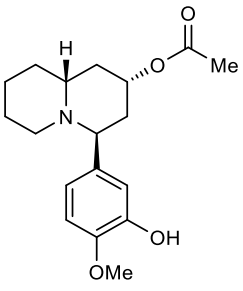
Figure 1.3-3 Structure of (+)-sarasubine A

A novel dimeric Lythraceae alkaloid with a cyclobutane ring, sarusubine A (**1-160**), was isolated from the leaves of *Lagerstroemia subcostata*.[64] The structure of the alkaloid was elucidated by NMR and other spectroscopic methods while the relative stereochemistry was determined by HMBC and NOESY correlations. Sarasubine A also showed weak anti-microbial activity against *Cryptococcus neofarmans* and *Trichophton mentagrophytes* (both MIC, 33.3 μg/ml).

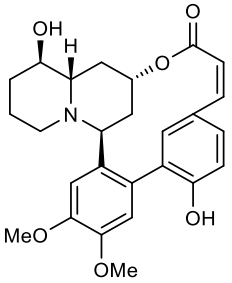
An extensive study was carried out by Rumalla and co-workers on the methanolic extracts of *Heimia salicifolia*.[65] Two new alkaloids, (2S,4S,10R)-4-(3-hydroxy-4-methoxyphenyl)-quinolizidin-2-acetate (**1-161**) and 9β-hydroxyvertine (**1-162**), were isolated along with seven known alkaloids, lythrine (**1-163**), dehydrodecodine (**1-164**), lythridine (**1-165**), vertine (**1-166**), heimidine (**1-167**), lyfoline (**1-168**) and *epi*-lyfoline (**1-169**) (Figure 1.3-4). The structures of the compounds were elucidated on the basis of one- and two-dimensional NMR spectroscopic methods while the structures of novel alkaloids **1-161**, **1-163** and **1-166** were corroborated by X-ray crystallographic data. This was the first report with complete ^{1}H and ^{13}C NMR assignments for the earlier known alkaloids. Alkaloids **1-161**, **1-163**, **1-164**, **1-166**, **1-168** and **1-169** were screened for anti-microbial and anti-malarial

activity. None of the compounds showed anti-microbial activity while **1-166** and **1-169** exhibited moderate anti-malarial activity.

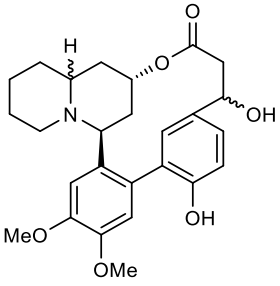
Ethanolic extracts of the aerial parts of *Lagerstroemia indica* yielded two new *Lythraceae* alkaloids, dihydrolyfoline (**1-170**) and its stereoisomer, 10-*epi*-dihydrolyfoline (**1-171**), along with lagerine (**1-172**).[66] The structures of the three alkaloids were determined using 1D and 2D NMR experiments in conjunction with the analysis of mass spectra and other spectroscopic data. This is the first report with complete ^{1}H and ^{13}C NMR assignments of natural lagerine, which further corroborates Hanaoka's[67] earlier structural reassignment.



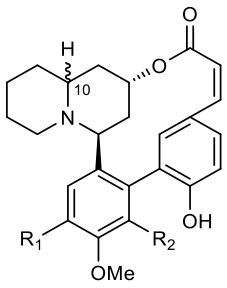
(+)-**1-161**



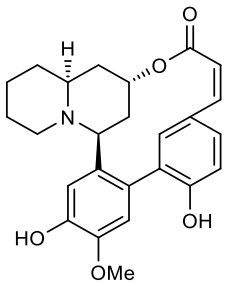
(+)-**1-162**
9β-hydroxyvertine



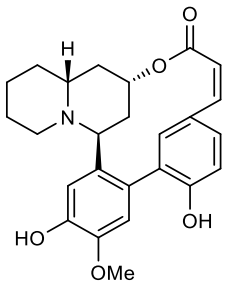
10Hα-**1-165** (lythridine)
10Hβ-**1-167** (heimidine)



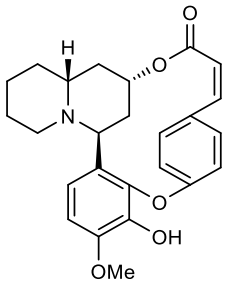
	10-H	R_1	R_2
lythrine (**1-163**)	α	OMe	H
dehydrodecodine (**1-164**)	α	H	OH
vertine (**1-166**)	β	OMe	H
lyfoline (**1-168**)	α	OH	H
epi-lyfoline (**1-169**)	α	OH	H



(-)-**1-170**
dihydrolyfoline



(-)-**1-171**
10-*epi*-dihydrolyfoline

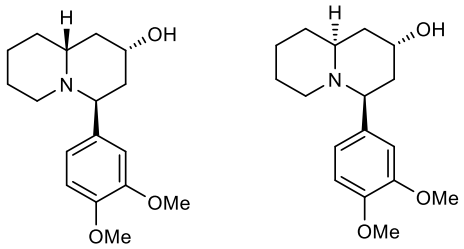


(-)-**1-172**
lagerine

Figure 1.3-4 Structures of *Lythraceae* alkaloids

1.3.4.2 Synthesis

1.3.4.2.1 Lasubines I and II

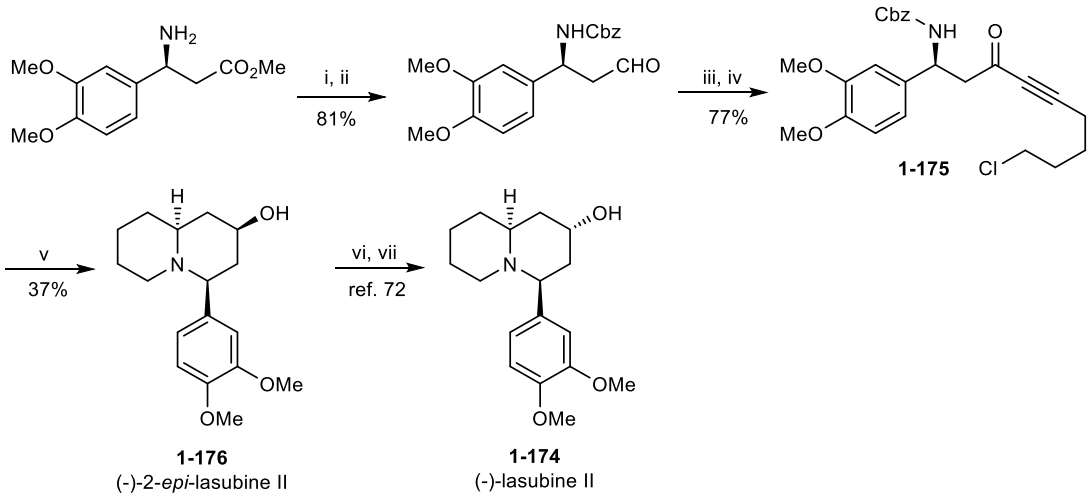


1-173 (-)-lasubine I **1-174** (-)-lasubine II

Figure 1.3-5 Structures of lasubines I and II

Within the period covered for this review, there have been numerous reports of the enantiomeric synthesis of lasubines I (**1-173**) and II (**1-174**). Two enantiomeric syntheses and one racemic syntheses of lasubine I were reported. Liao and co-workers reported a route to (-)-lasubine I featuring two sequential Roush allylboration reactions to form two stereogenic centres in the molecule.[68] Yamazaki and co-workers employed an intramolecular Michael-type addition reaction towards the synthesis of (-)-lasubine.[69] Furman and Lipner pursued a racemic synthesis of lasubine I *via* an *aza*-Diels-Alder reaction.[70] Lasubine I is a natural product that we aim to synthesise and reviews of the syntheses of lasubine I will be covered in further detail in Chapter 3. Lasubine II proved to be a more popular synthetic target during this period and will be discussed here.

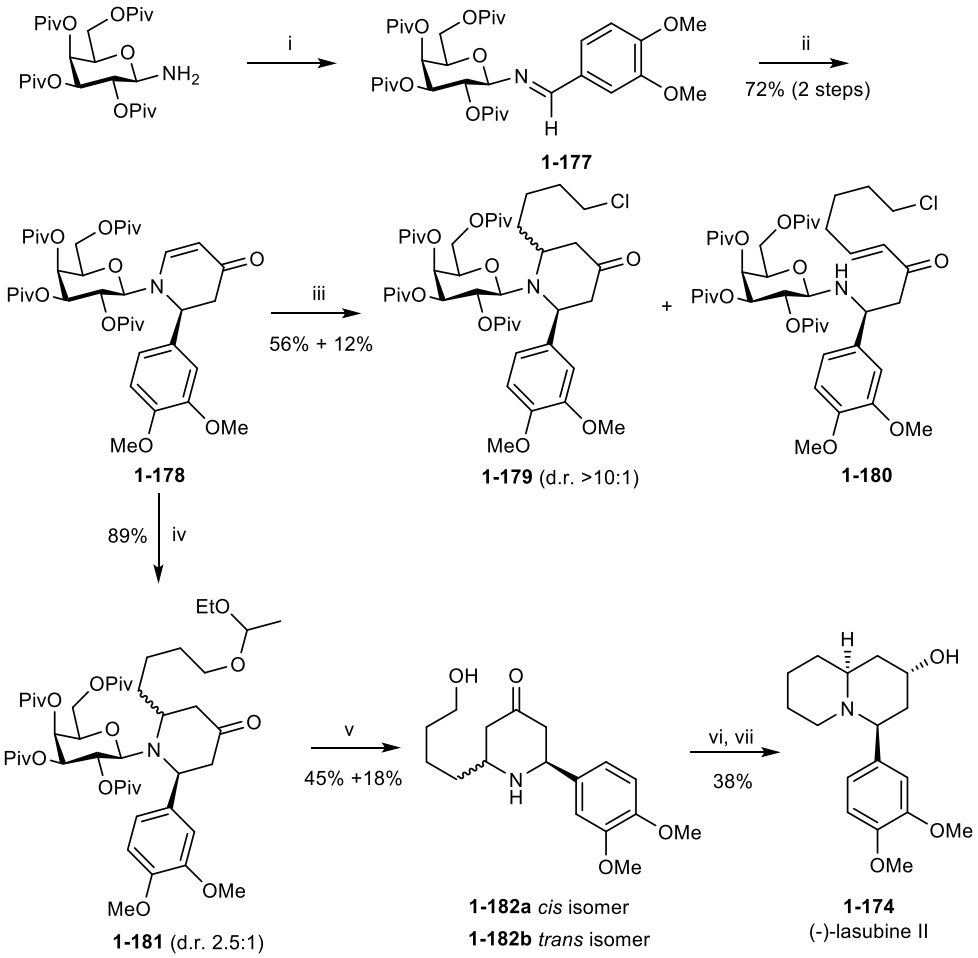
Kim *et al.*[71] have adopted a strategy similar to one published by Ma and Zhu[72] for the synthesis of (-)-lasubine II and demonstrated that removal of the Cbz protection group on the nitrogen of key precursor **1-175** triggered a sequential *endo*-type Michael addition followed by an S_N2 reaction to form the quinolizidine framework in (-)-lasubine II (**1-174**) (Scheme 1.3-14). Reduction of **1-175** was found to be most optimal with hydrogenation in refluxing methanol at atmospheric pressure in the presence of Pd/C to give (-)-2-*epi*-lasubine II **1-176** in 37% yield. **1-176** was then readily converted to the natural product *via* epimerisation of the hydroxyl group as reported earlier by Ma and Zhu.[72]



Reagents and conditions: i, CbzCl; ii, DIBAL-H; iii, $HC{\equiv}C(CH_2)_3CH_2Cl$, *n*-BuLi, $BF_3{\cdot}Et_2O$; iv, MnO_2; v, H_2 (1 atm), Pd/C, MeOH, reflux, 48 h; vi, PPh_3, DEAD, *p*-nitrobenzoic acid, THF; vii, K_2CO_3, MeOH.

Scheme 1.3-14 Kim's synthesis of (-)-lasubine II

The approach to (-)-lasubine II by Kunz *et al.*[73] commenced with formation of imine **1-177** which reacts with the Danishefsky diene to give dehydro-piperidinone **1-178** with an interesting carbohydrate auxiliary (Scheme 1.3-15). Addition of a chloro-substituted Grignard reagent in the presence of $BF_3{\cdot}Et_2O$ as the Lewis acid gave the desired 2,6-*cis*-disubstituted piperidine **1-180** with high diastereoselectivity (>10:1) albeit with by-product **1-179**, presumably formed *via* a β-elimination reaction. Conjugate addition with the alternative (1-ethoxy)ethyl- protected Grignard compound circumvented formation of a by-product analogous to **1-180** but generated the 2,6-*cis*-disubstituted piperidine **1-181** with only modest diastereoselectivity of 5:2. Cleavage of the ethoxyethyl group and the *N*-glycosidic bond afforded the free piperidinone as a mixture of diastereomers, **1-182a** and **1-182b**, which were separable by column chromatography. The major *cis* isomer **182a** was reacted with triphenylphosphine/carbon tetrachloride in the presence of triethylamine where the ring-closing *N*-alkylation afforded the piperidinone. Stereoselective reduction of the carbonyl group of with bulky LS-Selectride®, a strategy that was first employed by Comins,[74] gave the *trans*-configured lasubine II in six steps with an overall yield of 11%. This synthesis further highlights his approach to the synthesis of alkaloids by employing carbohydrates as stereodifferentiating auxiliaries.

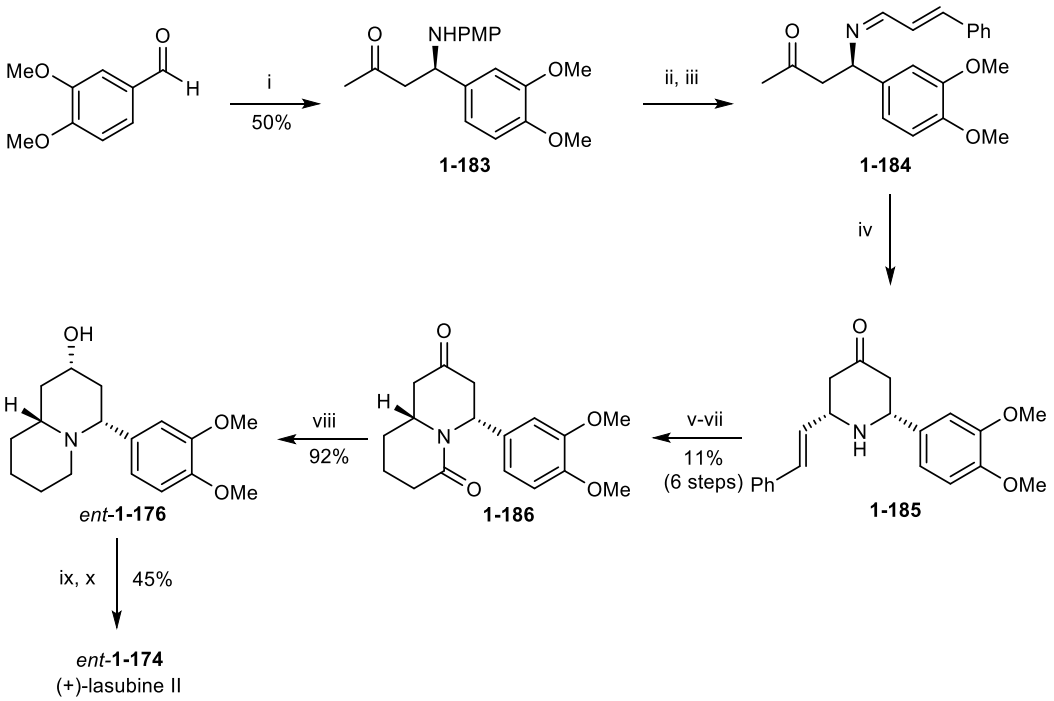


Reagents and conditions: i, veratryl aldehyde, cat. AcOH, 2-propanol, 80 °C, 30 min; ii, Danishefsky diene, $ZnCl_2$, THF, -20 °C, 36 h, then 1N HCl; iii, $Cl(CH_2)_4CuMgX_2$, $BF_3{\cdot}Et_2O$, THF, -55 °C, 18 h; iv, $EtOCH(CH_3)O(CH_2)_4CuMgX_2$, $BF_3{\cdot}Et_2O$, THF, -78 °C, 16 h; v, 1N HCl, MeOH, 20 °C, 36 h, then aq. Na_2CO_3; vi, PPh_3, CCl_4, Et_3N, MeCN, 20 °C, 48 h; vii, LS-Selectride®, THF, -78 °C, 2.5 h.

Scheme 1.3-15 Kunz's synthesis of (-)-lasubine II

Organocatalytic Mannich reactions were exploited by two groups for the synthesis of lasubine II. Proline-catalysed Mannich reaction featured in the synthesis by Rutjes and co-workers which enabled the synthesis of both enantiomers of lasubine II (Scheme 1.3-16).[75] A three-component asymmetric Mannich reaction involving acetone, *p*-anisidine and veratryl aldehyde catalysed by D-proline was carried out. This led to the formation of unnatural (+)-lasubine II while use of L-proline as the catalyst would give the natural isomer instead. While the reaction affords the respective aminoketone **1-183** with high enantioselectivity, the reaction had to be stopped after ca. 50% conversion to limit formation of the elimination byproduct. Subsequent deprotection of amine **1-183** followed

by conversion to imine **1-184** afforded the precursor for a diastereoselective Mannich cyclisation to give *cis*-disubstituted piperidone **1-185** as a single diastereomer. The stereochemical outcome of the cyclisation could be rationalised on the basis of the formation of a cationic chair-like intermediate, where both the aryl and styrenyl substituents will preferentially occupy the least hindered equatorial positions. Piperidone **1-185** was directly acylated with vinylacetic acid and subsequent treatment with the Grubbs second generation catalyst and hydrogenation led to the bicyclic compound **1-186**. $LiAlH_4$ reduction was found to be the optimal reducing agent to provide (+)-2-*epi*-lasubine II (*ent*-**1-176**) as an exclusive diastereomer which was then transformed *via* a Mitsunobu protocol put forward by Ma and co-workers.[72] **1-176** was converted *via* an identical pathway to give the natural isomer of lasubine II (**1-174**).

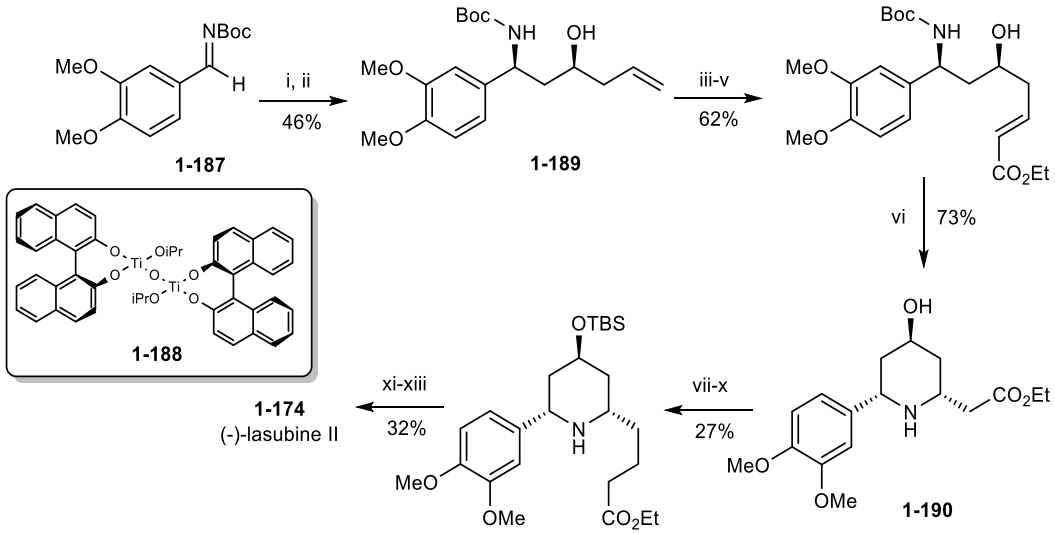


Reagents and conditions: i, *p*-anisidine, acetone, D-proline (20 mol%), DMSO, rt, 24 h; ii, 1M H_2SO_4, H_5IO_6, MeCN-H_2O (1:1), rt, 4 h, then HCl/EtOAc; iii, *trans*-cinnamaldehyde, Et_3N, DCE, rt; iv, CSA, DCE, 60 °C, 5 h; v, vinylacetic acid, DCC, DMAP, CH_2Cl_2, rt, 16 h; vi, Grubbs II (5 mol%), CH_2Cl_2, 40 °C, 2 h; vii, H_2 (1 atm), Pd/C, MeOH, rt, 16 h; viii, $LiAlH_4$, THF, 60 °C, 3 h; ix, *p*-nitrobenzoic acid, PPh_3, DEAD, THF; x, K_2CO_3, MeOH, rt.

Scheme 1.3-16 Rutjes' synthesis of (+)-lasubine II

An organocatalytic Mannich reaction also featured in the synthesis by Chandrasekhar and co-workers (Scheme 1.3-17).[76] In this case, an intramolecular proline-catalysed Mannich

reaction was carried out between acetaldehyde and *N*-Boc aldimine **1-187** to generate a β-amino aldehyde enantioselectively, which was then immediately subjected to an asymmetric Maruoka allylation using titanium complex **1-188** and allyltributylstannane to generate the 1,3-aminoalcohol **1-189** in 72% yield with 97% enantiomeric excess. The final asymmetric centre was introduced by an intramolecular *aza*-Michael addition reaction which afforded the 2,6-*cis*-isomer **1-190** as a single diastereomer in 73% yield. The synthesis of (-)-lasubine II was achieved by extension of the carbon side chain, reduction and S_N2 cyclisation.

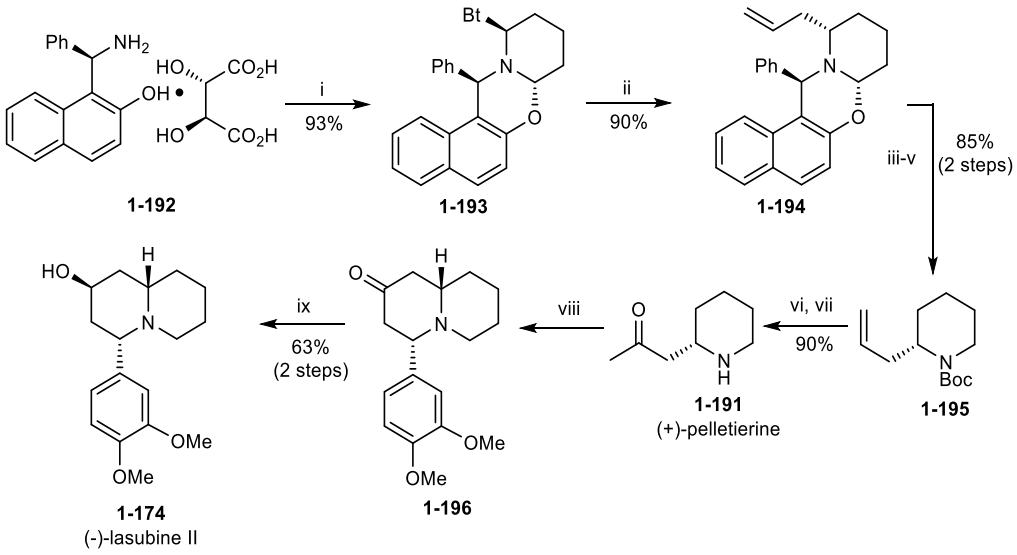


Reagents and conditions: i, CH_3CHO, L-proline (20 mol%), MeCN, 0 °C, 3 h; ii, **1-188** (10 mol%), $Bu_3SnCH_2CH{=}CH_2$, Ch_2Cl_2, -15 °C to 0 °C, 24 h; iii, OsO_4, NMO, acetone-H_2O (8:2), rt, 14 h; iv, $NaIO_4$, CH_2Cl_2-H_2O (8:2), rt, 0.5 h; v, $Ph_3P{=}CHCO_2Et$, benzene, rt, 4 h; vi, 1% HCl/*i*-PrOH, 60 °C, 4 h; vii, TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 1 h; viii, DIBAL-H, toluene, -78 °C, 2 h; ix, $Ph_3P{=}CHCO_2Et$, benzene, rt, 4 h; x, $NiCl_2$, $NaBH_4$, MeOH, 0 °C, 1 h; xi, DIBAL-H, CH_2Cl_2, 0 °C, 3 h; xii, 1M TBAF in THF, rt, 6 h; xiii, TsCl, pyridine, -20 °C to 0 °C, 8 h.

Scheme 1.3-17 Chandrasekhar's synthesis of (-)-lasubine II

In addition, several groups were interested in synthesizing enantiomers of lasubine II *via* a Mannich reaction of its biosynthetic precursor, pelletierine. The first report was put forward by Wang, Hu and co-workers[77] who established an efficient method to synthesise enantiopure 2-alkene or 2-alkyne substituted piperidines, including (+)-pelletierine (**1-191**) (Scheme 1.3-18). The (-)-tartaric acid salt of amino alcohol **1-192** was condensed with glutaraldehyde in the present of 1,2,3-benzotriazole (BtH) to give diastereopure oxazine **1-**

193, which in turn was treated with allyl trimethylsilane in the presence of $BF_3 \cdot Et_2O$ at -20 °C to give the desired alkylated product **1-194**. The piperidine could then be released *via* $LiAlH_4$ reduction followed by base-catalysed *N*-debenzylation through an *o*-quinone methide mechanism as proven by formation of the auxiliary as a racemic byproduct. Conversion of piperidine **1-195** to (-)-lasubine II ensued, first *via* a Wacker oxidation and *N*-Boc deprotection to form (+)-pelletierine (**1-191**), which in turn underwent a Mannich reaction to form a mixture of isomers of **1-196**. Under basic conditions, a one-pot isomerisation of the undesired isomer to give **1-196** as the sole isomer will occur based on an earlier observation by Pilli.[78] **1-196** was then reduced with K-Selectride® to give desired natural product, (-)-lasubine II in 40% overall yield.

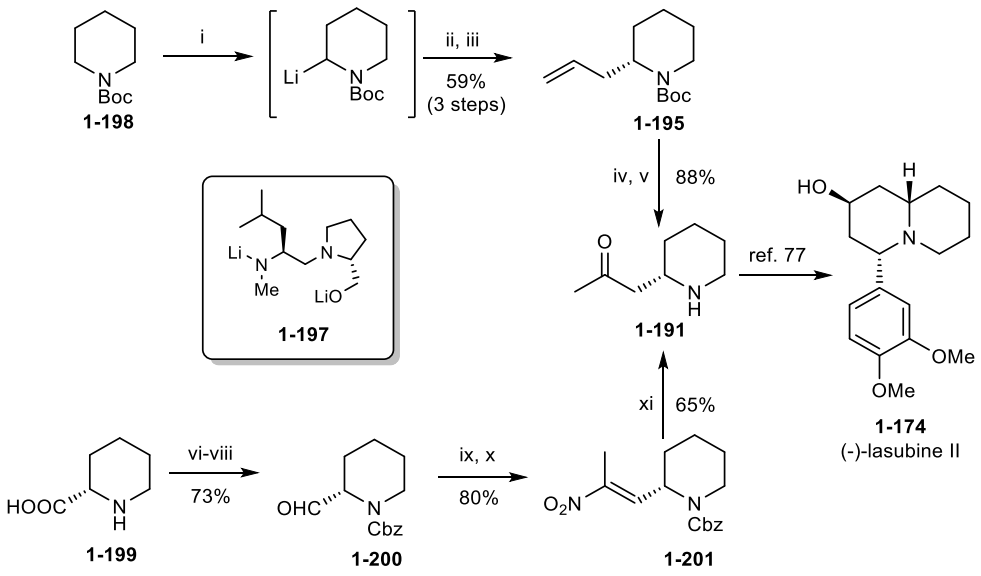


Reagents and conditions: i, $OHC(CH_2)_3CHO$, BtH, aq. K_2CO_3, CH_2Cl_2, 0 °C, 20 min; ii, $H_2C{=}CHCH_2TMS$, $BF_3 \cdot Et_2O$, CH_2Cl_2, -20 °C, 24 h; iii, $LiAlH_4$, THF, 0 °C, 0.5 h; iv, 6M NaOH, MeOH-THF, 60 °C, 1 h; v, Boc_2O, K_2CO_3, CH_2Cl_2, rt, 1h; vi, CuCl, $PdCl_2$, O_2, DMF-H_2O, rt, 10 h; vii, TFA, CH_2Cl_2, rt, 2h; viii, 3,4-dimethoxybenzaldehyde, 2M NaOH, MeOH, 60 °C, 70 h; ix, K-Selectride®, THF, -78 °C, 1 h.

Scheme 1.3-18 Wang's synthesis of (-)-lasubine II

Gawley and co-workers[79] also demonstrated another method to form of enantiopure 2-substituted piperidines (Scheme 1.3-19). Unlike Wang, Hu and co-workers' auxiliary approach,[77] a chiral ligand **1-197** was used in this case. *N*-Boc piperidine **1-198** was first deprotonated with *s*-BuLi in the presence of TMEDA. A catalytic dynamic resolution (CDR) was carried out using ligand **1-197** and then quenched with allyl bromide to give

piperidine **1-195**. From this point, the synthesis converges with the routes of Wang and Hu,[77] and thus results in a formal synthesis of (-)-lasubine II. Tilve and co-workers[80] were also interested in demonstrating a method to form enantiopure 2-substituted piperidines (Scheme 1.3-19). They chose a chiral pool strategy by beginning their synthesis with L-pipecolinic acid **1-199**. The carboxylic acid was converted to aldehyde **1-200** which was then subjected to a Henry-Nef reaction sequence. The aldehyde first underwent a Henry reaction with nitroethane to give nitro compound **1-201**. The nitro group in **1-201** was then converted to a ketone *via* the Nef reaction using $NaBH_4$ in the presence of K_2CO_3. Deprotection afforded (+)-pelletierine (**1-191**), a piperidine that has been employed as a precursor to (-)-lasubine II, thus this constitutes another formal synthesis of the natural product.

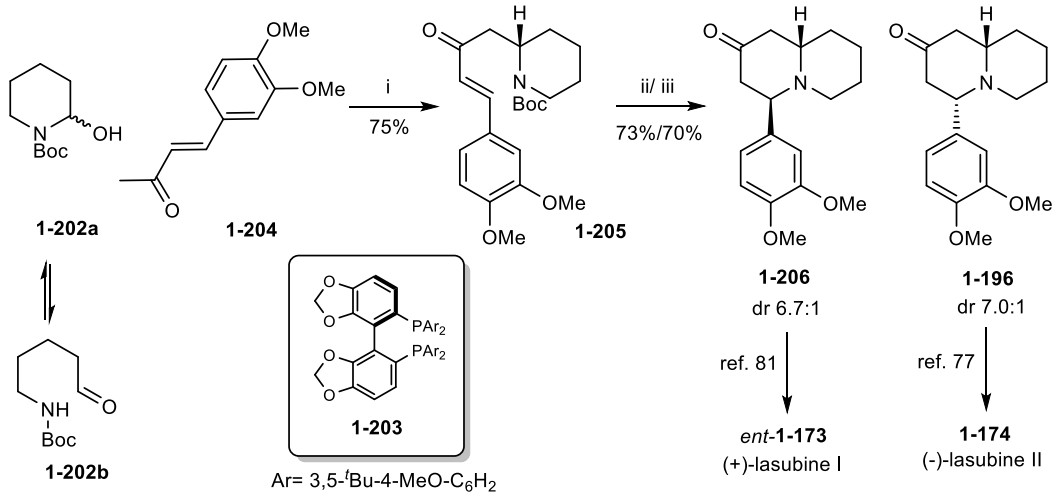


Reagents and conditions: i, *s*-BuLi, Et_2O, TMEDA, –78 °C, 3 h; ii, **1-197**, (10 mol%), –45 °C, 3 h; iii, allyl bromide, –78 °C, 10 h; iv, $PdCl_2$, CuCl (10 mol%), O_2, DMF-H_2O (10:1), rt, 10 h; v, TFA, CH_2Cl_2, 0 °C, 2 h, then NaOH; vi, $LiAlH_4$, THF, reflux, 8 h; vii, CbzCl, K_2CO_3, MeCN, 0 °C, 6 h; viii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; ix, $CH_3CH_2NO_2$, 3N KOH (0.1-0.2 mol%), 1 h, then 2 drops of concd. H_2SO_4; x, $MeSO_2Cl$, Et_3N, CH_2Cl_2; xi, $NaBH_4$, MeOH, K_2CO_3, H_2O_2, rt, 18 h.

Scheme 1.3-19 Gawley's and Tilve's formal syntheses of (-)-lasubine II

Kanai and co-workers developed an interesting cascade reaction to directly access precursors for the synthesis of alkaloids (Scheme 1.3-20).[81] Treatment of **1-202a** with 10 mol% CuO*t*Bu in the presence of the (*R*)-SEGPHOS derived ligand **1-203** triggered an

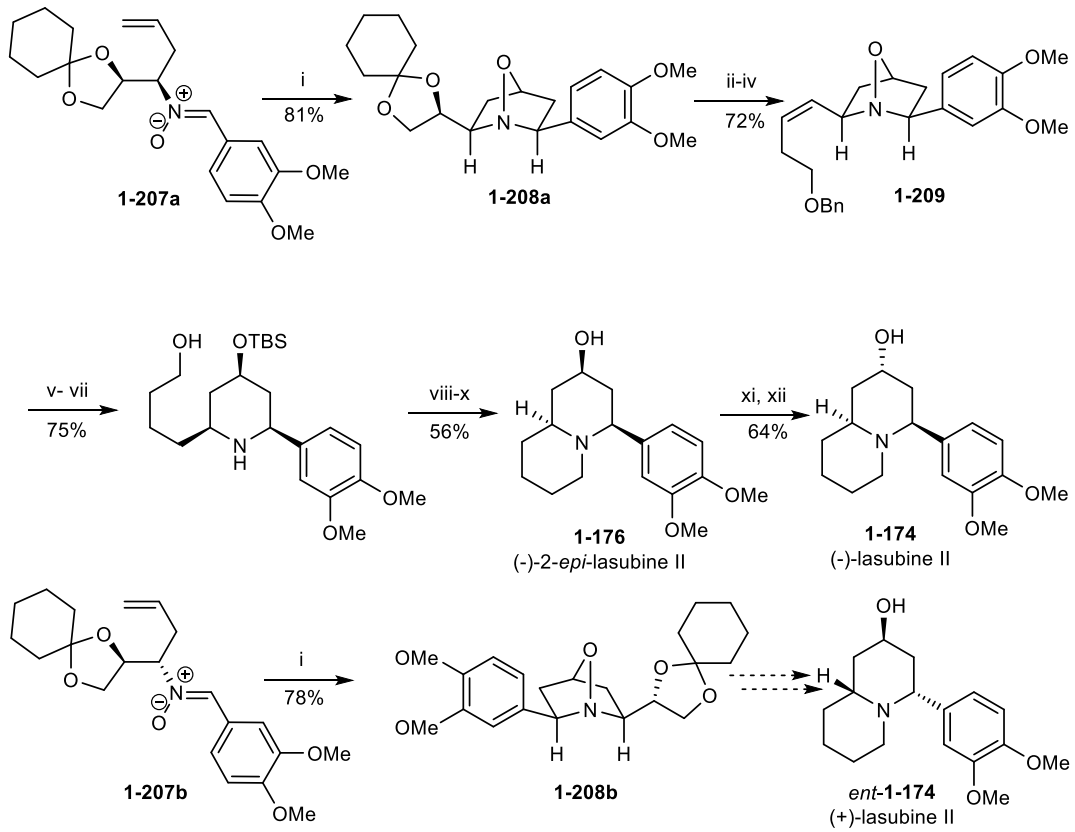
intriguing domino reaction beginning with an aldol addition between tautomer **1-202b** and **1-204**, followed by dehydration and then an enantioselective intramolecular *aza*-Michael reaction to form keto-ester **1-205** in 75% yield and 97% ee. This was readily converted to **1-206** and **1-196**, which constitutes precursors in the routes of Carretero[82] and Pilli[78] respectively and thus constitute formal syntheses of the unnatural isomer, (+)-lasubine I and natural isomer, (-)-lasubine II.



Reagents and conditions: i, CuO*t*Bu, **1-203** (10 mol%), H_2O (10 mol%), MTBE, rt, 48 h; ii, (**1-205→1-206**) TFA, CH_2Cl_2, 0 °C, 2 h then NH_4OH, MeOH, rt, 30 min; iii, (**1-205→1-196**) TFA, CH_2Cl_2, 0 °C, 2 h then NH_4OH, MeOH, rt, 48 h.

Scheme 1.3-20 Kanai's formal syntheses of (+)-lasubine I and (-)-lasubine II

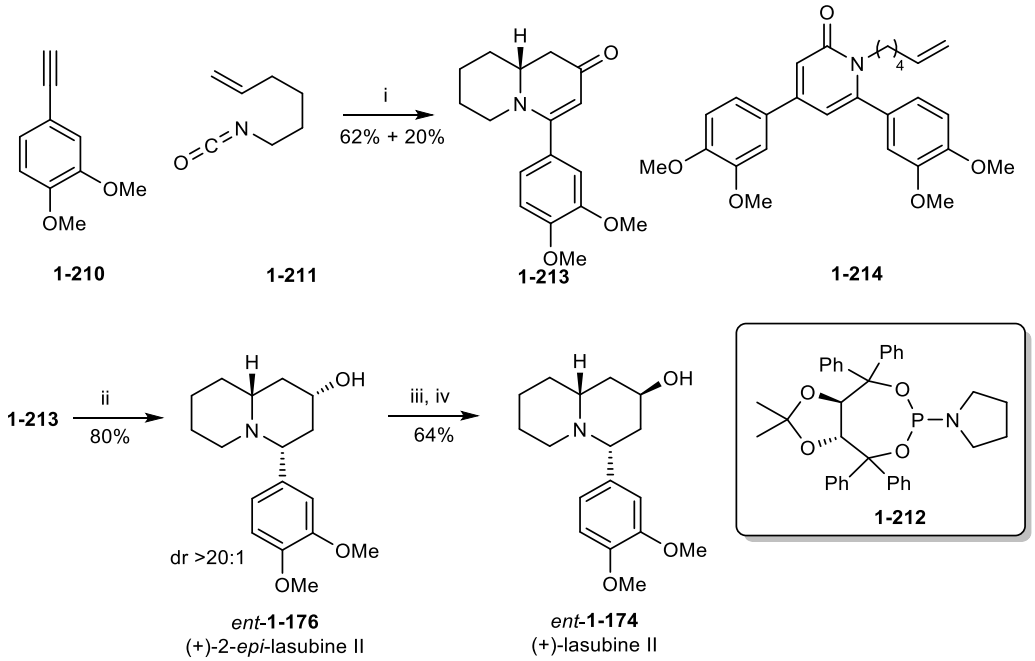
Chattopadhyay reported a method that could provide access to both enantiomers of lasubine II (Scheme 1.3-21).[83] It features an intramolecular cycloaddition of either *syn*- or *anti*-alkenylnitrone, **1-207a** or **1-207b** to furnish bicyclic ring derivative **1-208a** and **1-208b** respectively. Further transformations were carried out to homologate the side chain to furnish intermediate **1-209**, following which the *N,O* bond was cleaved with zinc in acetic acid. Hydrogenolytic removal of the benzyl group, followed by cyclisation under Mitsunobu conditions furnished (-)-2-*epi*-lasubine II (**1-176**). For the synthesis of (-)-lasubine II, the configuration of the secondary alcohol in **1-176** was first inverted by Mitsunobu reaction with 4-nitrobenzoic acid and then the corresponding ester was hydrolysed to give the natural product.



Reagents and conditions: i, toluene, reflux; ii, HCl, THF; iii, $NaIO_4$, MeCN-H_2O, rt; iv, $Br^-P^+Ph_3(CH_2)_3OBn$, *n*-BuLi, -78 °C to rt, 3 h; v, H_2 (1 atm), Pd/C, MeOH, rt; vi, Zn/AcOH, rt, 10 min; vii, TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 40 min; viii, H_2 (1 atm), $Pd(OH)_2$, MeOH, TFA, 6 h; ix, PPh_3, DEAD, THF -5 °C to rt, 4 h; x, Et_3N-HF, MeOH, rt, 3 h; xi, PPh_3, DEAD, 4-nitrobenzoic acid, toluene, rt, 3h; xii, K_2CO_3, MeOH, rt, 30 min.

Scheme 1.3-21 Chattopadhyay's synthesis of (+)-lasubine II

In 2006, Rovis *et al.* reported a novel enantioselective method to synthesise bicyclic indolizidine or quinolizidine core *via* a rhodium-catalysed [2+2+2] cycloaddition of alkenyl isocyanates and terminal alkynes (Scheme 1.3-22).[84] The authors demonstrated the utility of his method by applying it to the synthesis of (+)-lasubine II. Electron-rich acetylene **1-210** readily reacts with isocyanate **1-211** in the presence of catalytic amounts of Rh and chiral ligand **1-212** to give the vinylogous amide **1-213** in 62% yield with 98% enantiomeric excess. The reaction however, forms around 20% of pyridinone **1-214** as a side product. The synthesis was completed in a further three steps by standard transformations as illustrated.

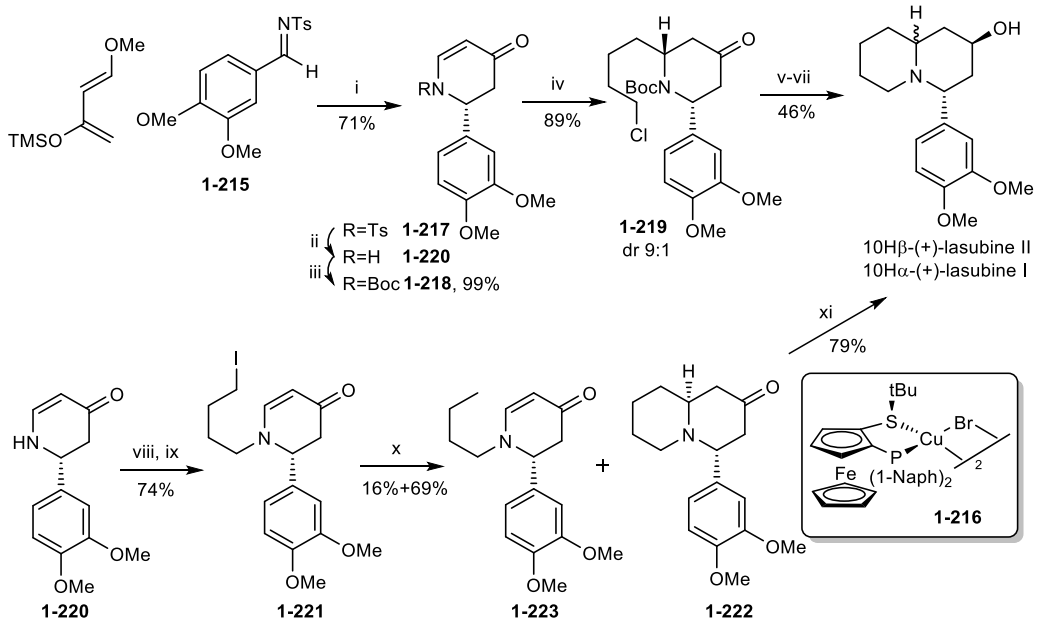


Reagents and conditions: i, $[Rh(C_2H_4)_2Cl]_2$ (5 mol%), **1-212** (10 mol%), toluene, 110 °C; ii, H_2 (1 atm), Pd/C, MeOH, rt; iii, PPh_3, DEAD, *p*-nitrobenzoic acid, rt; iv, K_2CO_3, MeOH, rt.

Scheme 1.3-22 Rovis' synthesis of (+)-lasubine II

Enantiocontrol in the synthesis of (+)-lasubines I and II by Carretero and co-workers (Scheme 1.3-23) stemmed from the key catalytic asymmetric formal *aza*-Diels-Alder reaction of *N*-sulfonyl imine **1-215** and the Danishefky diene with a Cu catalyst **1-216** to form *N*-tosyl-2,3-dihydro-pyridone **1-217** enantioselectively (94% ee).[82] This served as a common precursor for synthesis of both unnatural isomers, (+)-lasubines I and II. From the common precursor **1-217**, synthesis of (+)-lasubine II began with several steps involving manipulation of protecting groups to furnish *N*-Boc protected **1-218**, after which 1,4 addition of a Grignard reagent was carried out under conditions reported earlier by Comins.[85] A mild Boc-deprotection step was carried out on **1-219** using $SnCl_4$ in EtOAc to prevent competitive opening of the 4-piperidone ring. The resulting *N,H* piperidine cyclised smoothly upon treatment with K_2CO_3 following which, the conversion to the target alkaloid with L-Selectride® was first reported by Chalard and Remuson.[86] For the synthesis of (+)-lasubine I, *N*-alkylation was carried out with *N,H* piperidone **1-220** with 4-chloro-1-iodobutane. The chlorine group was then transformed to iodo derivative **1-221** which improved the reactivity for the radical cyclisation of the substrate. Treatment under

standard radical cyclisation conditions yielded quinolizidine **1-222**, exclusively as the *trans* isomer with small amounts of noncyclised reduced product **1-223**. The synthesis was completed as illustrated above using a transformation previously reported by Comins.[85]



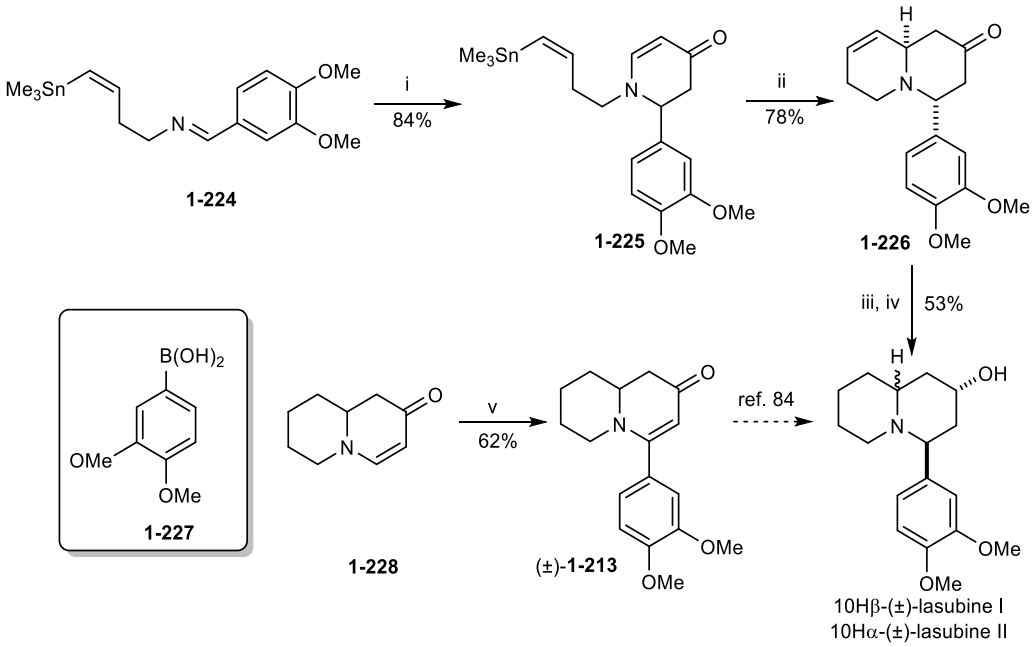
Reagents and conditions: i, **1-216** (5.1 mol%), $AgClO_4$, CH_2Cl_2, -20 °C, 12 h, then TFA; ii, actvd. Zn, THF-NH_4Cl, rt; iii, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, rt; iv, CuBr.Me_2S, $Cl(CH_2)_4MgI$, THF, -40 °C; v, $SnCl_4$, EtOAc, rt; vi, satd. K_2CO_3, CH_2Cl_2, rt; vii, L-Selectride®, THF, -78 °C; viii, $Cl(CH_2)_4I$, NaH, THF, rt; ix, NaI, acetone, Δ; x, Bu_3SnH, AIBN, benzene, Δ; xi, L-Selectride®, THF, -78 °C.

Scheme 1.3-23 Carretero's synthesis of (+)-lasubine I and II

Furman and Lipner also adopted an *aza*-Diels-Alder approach for their synthesis of racemic lasubine I (Scheme 1.3-24).[70] In the presence of $Yb(OTf)_3$, imine **1-224** reacted readily with Danishefsky's diene to form dihydropyridone **1-225** containing the vinylstannane side chain, which could undergo a Rh-catalysed cyclisation to form the bicyclic quinolizidine core **1-226** as a single diastereomer in moderate yield. Synthesis of (±)-lasubine I was completed as illustrated.

The synthesis of (±)-lasubine II by Kim and Georg was published as part of a broader study on carrying out regioselective arylation at the C6 position of cyclic enaminones using an oxidative boron-Heck reaction as the key step (Scheme 1.3-24).[87] In this case, 3,4-dimethoxyphenylboronic acid **1-227** was reacted with bicyclic enaminone **1-228** to afford

C6-arylated product (±)-**1-213** in 62% yield. The synthesis of the target alkaloid converges from compound (±)-**1-213** *via* the same transformations reported by Rovis *et al*.[84]



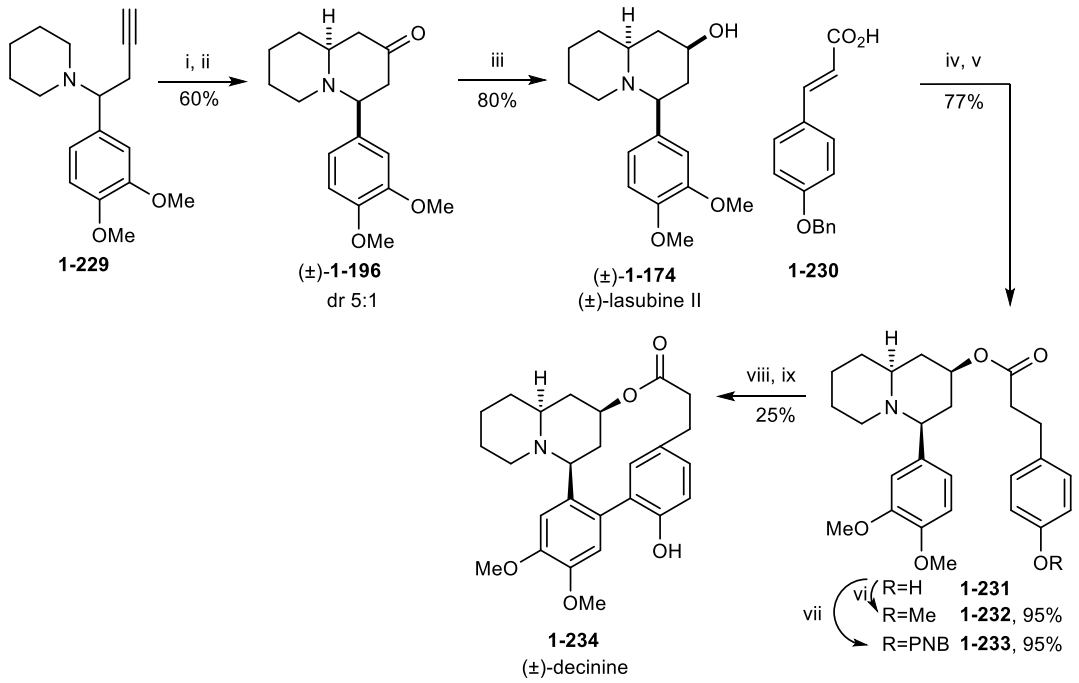
Reagents and conditions: i, Danishefsky diene, $Yb(OTf)_3$, MeCN, 20 °C, 4 h; ii, $[RhCl(cod)]_2$ (5 mol%), 1,4-dioxane, 30 °C, 4 h; iii, H_2 (1 atm), Pd/C, EtOAc, 1 h; iv, L-Selectride®, THF, -78 °C, 4 h; v, $Pd(OAc)_2$, bpy, O_2, NMP, 60 °C, 20 h.

Scheme 1.3-24 Furman's synthesis of (±)-lasubine I and Kim's formal synthesis of (±)-lasubine II

1.3.4.2.2 Macrocyclic quinolizidine alkaloids

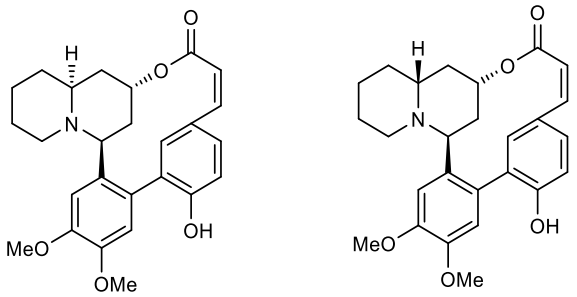
A racemic synthesis of the macrocyclic lactone quinolizidine alkaloid, decinine (**1-234**), has been reported by Tang, Chen, Yang and co-workers (Scheme 1.3-25).[88] The key step in their reaction was a biomimetic intramolecular oxidative biaryl coupling. The synthesis commenced with construction of (±)-lasubine II *via* a formal [4+2] approach involving sequential treatment of alkyne **1-229** with *m*CPBA and $Ph_3PAuNTf_2$ to form quinolizidinone (±)-**1-196**, which was then reduced with L-Selectride® to afford (±)-lasubine II in 66% yield. Phenyl acrylic acid **1-230** was then coupled with (±)-lasubine II in the presence of EDCI and DMAP. The product underwent reduction *via* hydrogenation over Pd/C to afford phenol **1-231**. Attempts to carry out the oxidative biaryl coupling on phenol **1-231** failed and the reaction proved to be successful when the free phenol was protected with either a methoxy group (**1-232**) or a PNB group (**1-233**). Oxidative biaryl

coupling reaction on **1-233** was carried out in the presence of VOF_3 with excess TFA to afford the desired product in 32% yield. Final reduction to (±)-decinine (**1-234**) was accomplished with Pd-catalysed hydrogenation in ethyl acetate.



Reagents and conditions: i, *m*CPBA, CH_2Cl_2, 0 °C, 4 Å MS; ii, $Ph_3PAuNTf_2$, CH_2Cl_2, 0 °C; iii, L-Selectride®, THF, -78 °C; iv, EDCI, DMAP, CH_2Cl_2, rt, x h; v, H_2 (1 atm), Pd/C, EtOAc, rt x h; vi, MeI, K_2CO_3, DMF; vii, PNBBr, K_2CO_3, acetone; viii, VOF_3, TFA, CH_2Cl_2, 0 °C; ix, H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, rt .

Scheme 1.3-25 Tang's synthesis of decinine



1-166
(+)-vertine

1-163
(+)-lythrine

Figure 1.3-6 Structures of (+)-vertine and (+)-lythrine

In 2010, Kündig and co-workers communicated a racemic synthesis of vertine (**1-166**) with RCM as a key macrocyclisation step.[89] Experimental details of this work have been published in a full paper detailing the synthesis of (+)-vertine (**1-166**) and its epimer, (+)-lythrine (**1-163**) (Figure 1.3-6).[90] Various macrocyclisation strategies were attempted and the synthesis will be reviewed in greater detail in Chapter 3.

1.3.5 Nuphar alkaloids

Phytochemical studies on the aerial part of the aquatic plant *Nuphar japonicum* DC have brought to light a new alkaloid, nupharic acid **1-235**, together with known alkaloids, nupharidine **1-236** and deoxynupharidine **1-237** (Figure 1.3-7).[91] The structures and relative stereochemistry were deduced from extensive analysis of 2D NMR spectra and NOESY correlations. The new alkaloid is unusual in that it lacks a furan residue that is found in the other Nuphar alkaloids identified to date. While the methanolic extracts of *Nuphar punilum* are known to show cytotoxic effects,[92] compound **1-235** did not show any cytotoxic activity against tumor cell lines, A549 and HT29, possibly due to the permeability differences with the acid present.

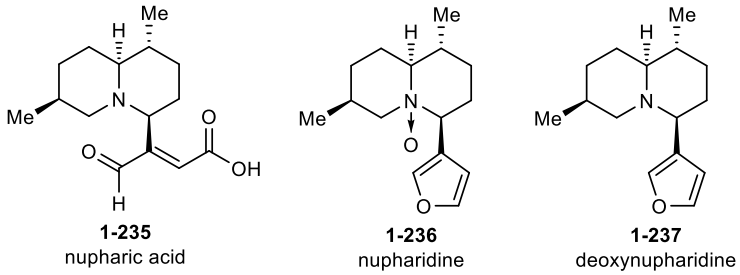
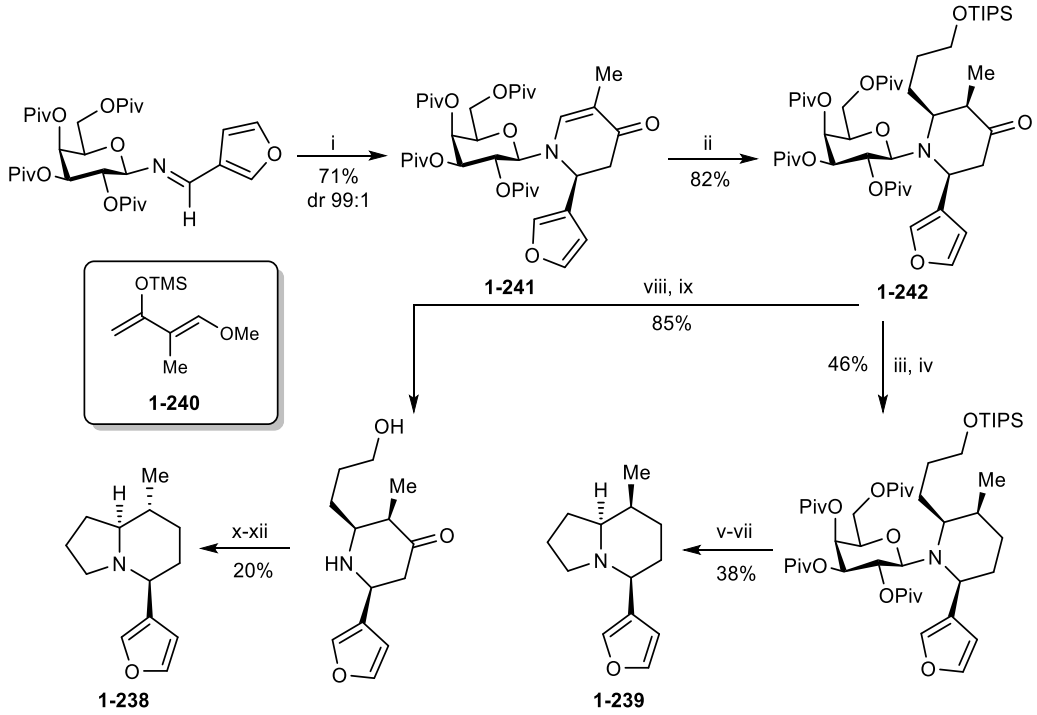


Figure 1.3-7 Structures of *Nuphar* alkaloids

Synthesis of the unnamed Nuphar alkaloid, 5-(3'furyl)-8-methylindolizidine has garnered a fair amount of interest since its isolation, as its relative and absolute configurations are still unknown. In 2009, Kunz and co-workers reported enantioselective syntheses of two diastereomers of the alkaloid **1-238** and **1-239** (Scheme 1.3-26).[93] The galactosylamine chiral auxiliary was employed to the synthesis of the alkaloids, as has been similarly exploited for the synthesis of lasubine II[73] (see Section 1.3.4.2.1) and various natural products.[94] Cyclisation with a methyl substituted Danishefsky diene **1-240** gave piperidone **1-241** with high diastereoselectivity, induced by the bulky chiral auxiliary. Conjugate addition with organocopper compound, $TIPSO(CH_3)_2Cu{\cdot}BF_3$ furnished key intermediate **1-242** in a stereoselective manner, again due to shielding by the pivaloyl carbohydrate auxiliary. Reduction of the ketone, silyl deprotection, conversion of the alcohol to the

corresponding bromide and acid cleavage gave desired indolizidine **1-238**. Changing the order and slightly modifying the above reactions furnished diastereomeric indolizidine **1-239**. It was observed that the EI mass spectrum of **1-238** matched that of the natural product, while the mass spectrum for alkaloid **1-239** had several fragments missing.

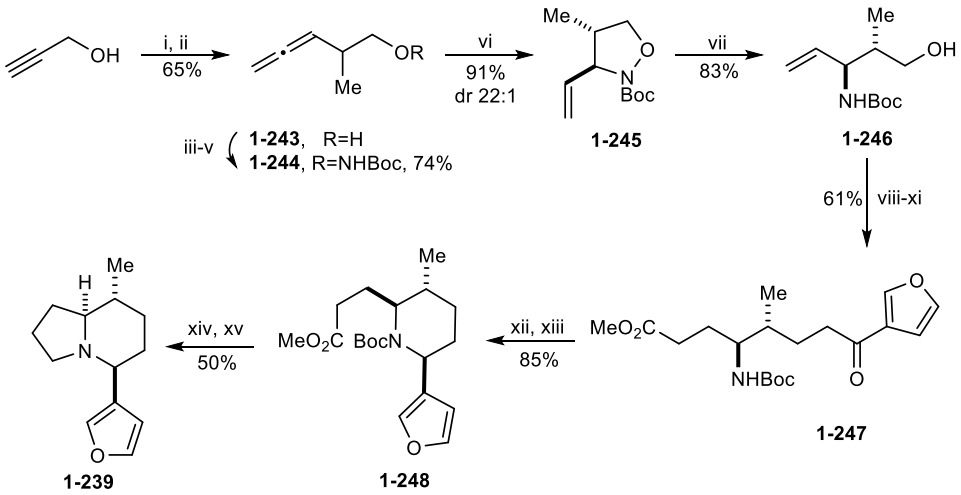


Reagents and conditions: i, $ZnCl_2$, **1-240**, THF, -78 °C to -30 °C, 72 h, then 1N HCl; ii, $TIPSO(CH_3)_2CuBr.SMe_2$, $BF_3{\cdot}Et_2O$, THF, -78 °C, 15 h; iii, LDA, THF, -78 °C, 2 h, then $5ClPyrNTf_2$, 3.5 h; iv, H_2 (1 atm), Pd/C (20 mol%), MeOH, rt, 4.5 h; v, TBAF, THF, rt, 4 h; vi, PPh_3, NCS, CH_2Cl_2, -40 °C to 25 °C, 4 h; vii, 1N HCl, MeOH, rt, 18 h, then Na_2CO_3, EtOH, reflux, 1.5 h; viii, TBAF, THF, rt, 1.5 h; ix, 1N HCl, MeOH, rt, 18 h; x, PPh_3, NBS, CH_2Cl_2, rt, 1.5 h, then Et_3N, 20 h, rt; xi, LDA, THF, -78 °C, 1 h, then $5ClPyrNTf_2$, 2 h; xii, H_2 (1 atm), Pd/C, MeOH, rt, 2 h.

Scheme 1.3-26 Kunz' syntheses of 1-238 and 1-239

Bates and co-workers reported a racemic, albeit highly diastereoselective synthesis of alkaloid **1-239** (Scheme 1.3-27).[95] The synthesis started with formation of allenic alcohol **1-243** from a Johnson-Claisen rearrangement reaction with propargyl alcohol and triethyl orthopropionate followed by $LiAlH_4$ reduction of the resulting ester. Alcohol **1-243** was transformed to *N*-Boc protected hydroxylamine **1-244** as illustrated, which then underwent a Claesson cyclisation using silver triflate in anhydrous dichloromethane with 22:1 selectivity for the desired *trans*-isoxazolidine **1-245**. It is noteworthy that the reaction was carried out with molecular sieves due to the hygroscopic nature of the silver salt. Also, the

presence of water was found to lower the diastereoselectivity of the reaction. The isomers of isoxazolidine **1-245** were separable only after formation of amino alcohol **1-246** *via* cleavage of the *N,O* bond with molybdenum hexacarbonyl. A further set of chain extension transformations were carried out on amino alcohol **1-246** to give key precursor **1-247**, *N*-Boc deprotection with TFA and subsequent $NaBH_4$ reduction of which, produced piperidine **1-248** in 85% yield as a single diastereomer. The synthesis was completed by heating **1-248** to trigger a second cyclisation and $LiAlH_4$ reduction of the resulting lactam afforded the target alkaloid **1-239** in 50% yield.

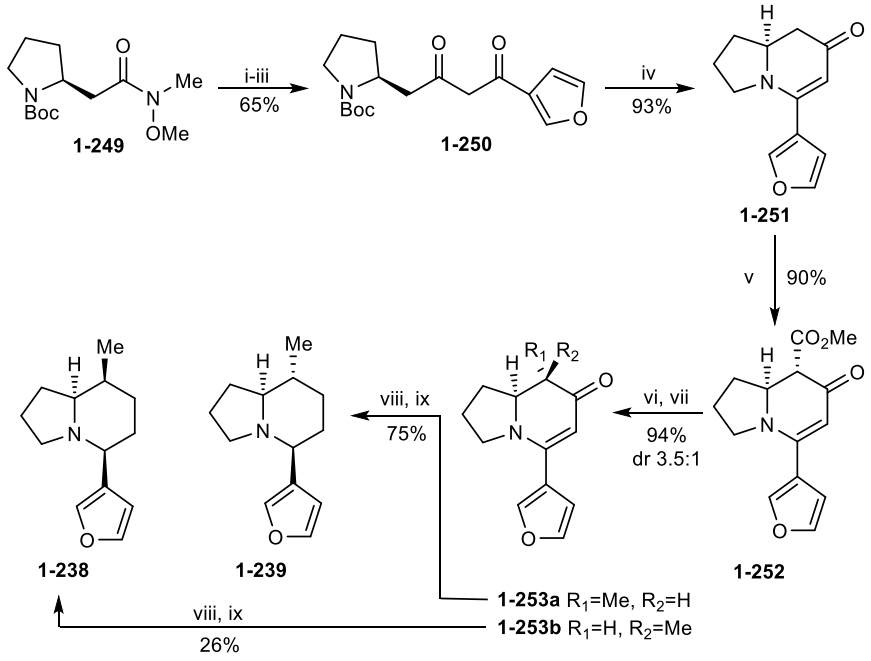


Reagents and conditions: i, $MeCH_2C(OEt)_3$, AcOH, Δ; ii, $LiAlH_4$, Et_2O; iii, PhthNOH, DIAD, PPh_3; iv, H_2NNH_2; v, Boc_2O, NaOH; vi, AgOTf (20 mol%), CH_2Cl_2, 4 Å MS; vii, $Mo(CO)_6$, $NaBH_4$, MeCN-H_2O ; viii, Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2; ix, $(EtO)_2POCH_2CO$(furyl), $Ba(OH)_2$, THF-H_2O; x, methyl acrylate, Hoveyda-Grubbs II, toluene; xi, H_2 (100 psi), $(PPh_3)_3RhCl$, toluene; xii, TFA, CH_2Cl_2; xiii, $NaBH_4$, MeOH, 0 °C; xiv, toluene, reflux; xv, $LiAlH_4$.

Scheme 1.3-27 Bates' synthesis of 1-239

Georg and Seki observed that data reported for the structure of 5-(3'furyl)-8-methylindolizidine have been inconsistent thus far and a synthetic study was initiated to unequivocally determine the structure of the natural product through an enantiopure synthesis of alkaloids **1-238** and **1-239** (Scheme 1.3-28).[96] The synthesis commenced with reaction of Weinreb amide **1-249** with MeLi, followed by an aldol reaction to introduce the furyl moiety and then oxidation to furnish diketone **1-250**. After removal of the *N*-Boc group with formic acid and then treatment with K_2CO_3 in MeOH, cyclisation proceeded

smoothly to furnish enaminone **1-251** in 93% yield. A-alkylation of the enaminone was successful using Mander's reagent. The structure of β-keto ester **1-252** was confirmed by X-ray crystal structure analysis. Alkylation with MeI introduced the methyl substituent, after which removal of the ester *via* Krapcho decarboxylation produced **1-253a** and **1-253b**, favouring formation of **1-253a** in a ratio of 3.5:1. The diastereomers were separable by column chromatography and were each subjected to treatment with Tf_2O to form the iminium enol triflate. This was reduced with $LiAlH_4$ to the corresponding triflate, which was further reduced *via* Pd-catalysed hydrogenation to afford alkaloids **1-238** and **1-239** as illustrated. Backed by X-ray crystal structure analysis, Georg and Seki were able to unambiguously validate the syntheses of the two alkaloids and shed light on the structure of the natural product, which was concluded to be **1-239**.



Reagents and conditions: i, MeLi, THF, -78 °C, 5 h; ii, *n*-Bu_2BOTf, DIPEA, Et_2O, -78 °C, then 3-furancarbaldehyde, Et_2O, 5 h, then phosphate buffer (pH=7.2), warm to 0 °C, then H_2O_2, MeOH, 1 h; iii, IBX, EtOAc, 60 °C, overnight; iv, formic acid, 0 °C to rt, 6 h, then K_2CO_3, MeOH, 0 °C to rt, overnight; v, LDA, THF, -78 °C, 1 h, then Mander's reagent, 1h; vi, NaHMDS, MeI, -78 °C, 2 h; vii, NaCN, H_2O, MW (160 °C), 1.5 h; viii, Tf_2O, CH_2Cl_2, -78 °C to rt, 3 h, then $LiAlH_4$, -78 °C to rt, 1 h; ix, H_2 (1 atm), 10% Pd/C, MeOH, overnight.

Scheme 1.3-28 Georg and Seki's syntheses of 1-238 and 1-239

This alkaloid, together with its synthetic intermediates, were tested for cytotoxicity and submitted for testing in central nervous system (CNS) receptor assays. No cytotoxicity was

observed, and the compound was found to show binding affinity to the oxytoxin receptor (Ki= 0.6 μM), sigma 1 receptor (Ki=0.23 μM) and sigma 2 receptor (Ki=1.8 μM). Oxytocin is a hormone that stimulates milk ejection and uterine contractions. Hence, binding affinity to the oxytocin receptor is an intriguing discovery given the gynecological use of castoreum (the source of the natural product) in ancient Greece.[97]

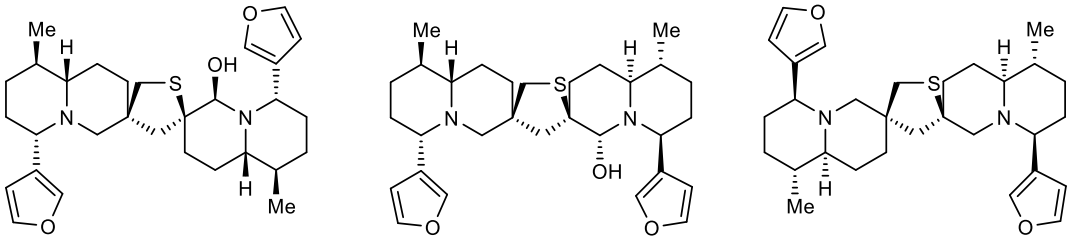
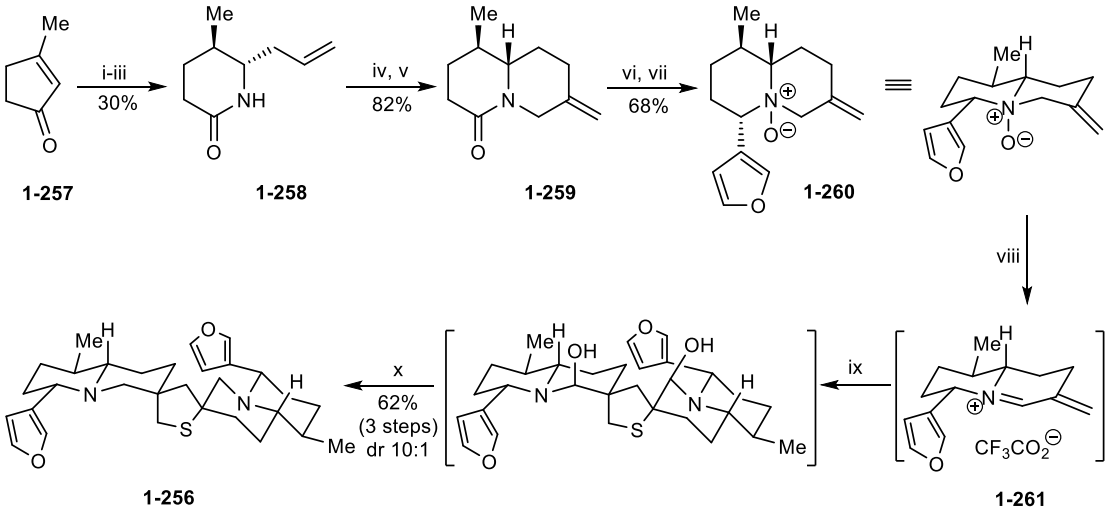


Figure 1.3-8 Structures of *Nuphar* dimers

Earlier reports on cytotoxicity of nuphar dimers toward cancer cells have spurred interest in these compounds.[92, 98] Recently, Golan-Goldhirsch and Gopas have reported that a methanolic plant extract of *N. lutea* inhibits NFκB activity which in turn induces tumour cell apoptosis.[99] The extract was also found to enhance cytotoxicity of cisplatin or etoposide towards Hodgkin lymphoma cell line (L428). Fractionated extract with strong inhibitory activity was found to contain several dimeric nupharic thioalkaloids as shown by ^{1}H and ^{13}C NMR analysis. Major components include 6-hydroxythiobinupharidine **1-254** and 6-hydroxythiobinuphlutine B **1-255**. In 2010, El-On and co-workers discovered that a partially purified plant extract of *N. lutea* containing thionuphar dimers also exhibits anti-leishmanial activity.[100] The mechanism of action was shown to be mediated through increased NO production *via* activation of NFκB (as opposed to earlier demonstration of suppression of NFκB in cancer cells). With the interesting biological profile of the nuphar dimers, it came as no surprise that a few years later, Shenvi and Jansen reported the first total synthesis of thiaspirane nuphar dimer, (-)-neothiobinupharidine **1-256** (Scheme 1.3-29) by a route involving reductive allylation of cyclopentenone **1-257** as the entry to

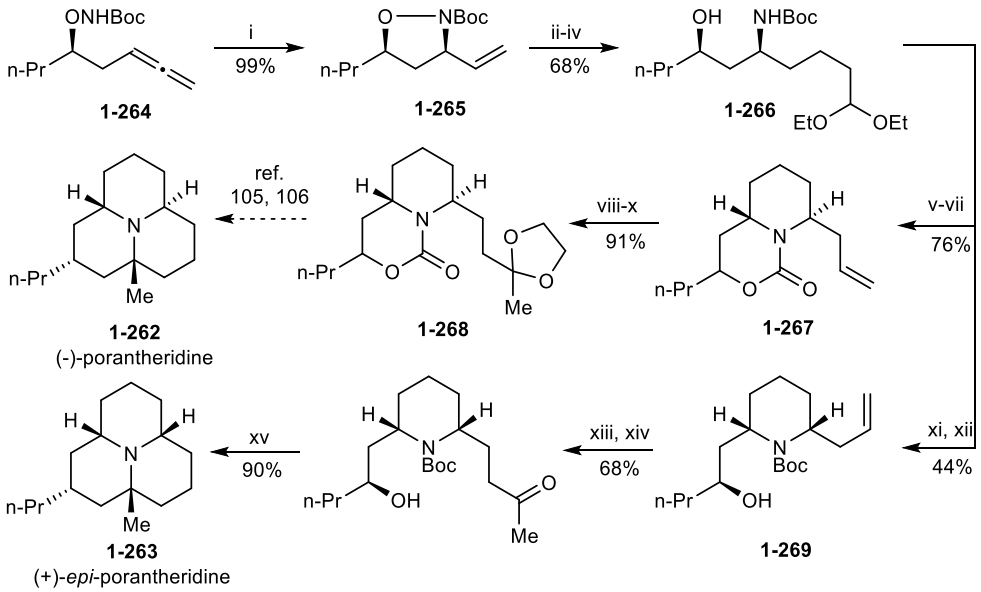
the synthesis of the quinolizidine monomer.[101] The method developed afforded the ketone with high diastereoselectivity (>10:1) and enantioselectivity (>97% ee). This ketone could be easily converted to lactam **1-258** *via* a Beckman rearrangement, which then underwent transformation to quinolizidinone **1-259** *via* an allylsilane-RCM methodology developed by Vanderwal.[102] Addition of the furyl moiety to the amide was carried out using a variation of Fowler's procedure[103] and the product was oxidised to quinolizidine *N*-oxide **1-260** in preparation for the Polonovsky elimination reaction. Treatment of the *N*-oxide with trifluoroacetic anhydride form α,β-unsaturated iminium ion **1-261** selectively. The dimerisation step was carried out by treating the monomer with 5 equivalents of Na_2S_4 in DMSO, followed by reduction with sodium borohydride to complete the synthesis of the natural product in a concise manner with an overall yield of 10%.



Reagents and conditions: i, Ph_2SiH_2, NaO*t*-Bu, *(R)-p*-Tol-BINAP, THF-pentane (1:1), -78 °C, then MeLi, LiCl, $Pd_2(dba)_3$, -78 °C to rt, overnight; ii, NaOH, $NH_2OH.HCl$, EtOH-THF-H_2O, 90 °C, 4 h; iii, TsCl, pyridine, 0 °C to rt, overnight; iv, LDA, 2-(trimethylsilyl)methylallyl iodide, THF-HMPA (1:1.5), 0 °C to rt, overnight; v, Grubbs II (2 mol%), benzene, 80 °C, 3 h, then TFA, CH_2Cl_2, 22 °C, overnight; vi, 3-furyl-Li, Et_2O, -78 °C to rt, 2 h, then $Na(OAc)_3BH$, MeOH; vii, *m*CPBA, CH_2Cl_2, 0 °C, 2 h; viii, $(CH_3CO)_2O$, CH_2Cl_2, 0 °C, 2 h; ix, $Na_2S_4 \cdot H_2O$, DMSO, 22 °C, 6 h; x, $NaBH_4$, MeOH, 22 °C, 0.5 h.

Scheme 1.3-29 Shenvi and Jansen's synthesis of (-)-neothiobinupharidine

1.3.6 Poranthera alkaloids

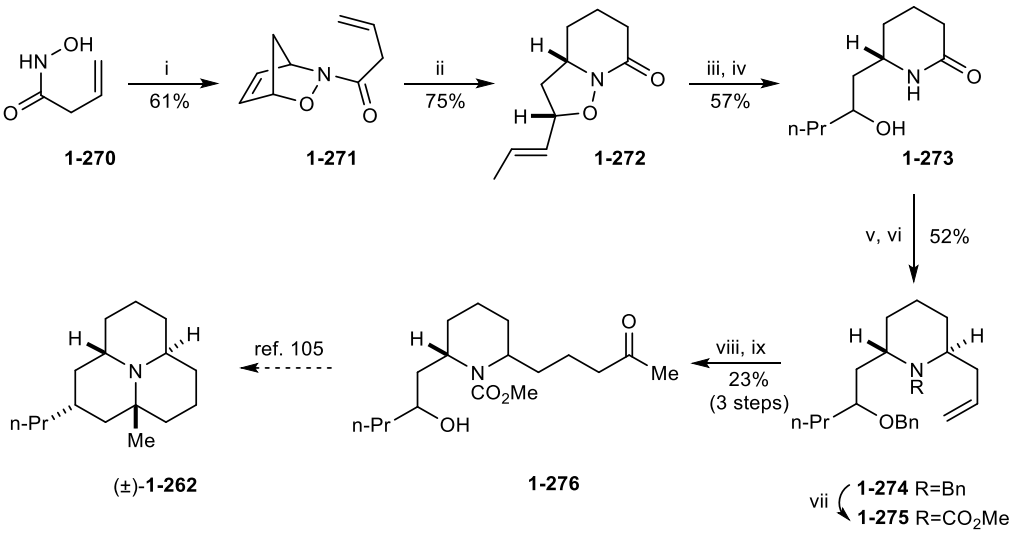


Reagents and conditions: i, $AgBF_4$, CH_2Cl_2, rt, 8 h; ii, $Mo(CO)_6$, $NaBH_4$, MeCN-H_2O (7:1), 90 °C, overnight; iii, 1,1-diethoxybut-2-ene, Grubbs II (5 mol%), CH_2Cl_2, reflux, overnight ; iv, H_2 (1 atm), 10% Pd/C, Ca_2CO_3, MeOH, rt, 3 h; v, *t*BuOK, THF, 0 °C to rt, 4 h; vi, *p*-TsOH, EtOH, rt, 4 h; vii, allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C, 0.5 h; viii, 3-buten-2-one, Grubbs II (5 mol%), CH_2Cl_2, reflux, overnight; ix, H_2 (1 atm), 10% Pd/C, MeOH, rt, 2 h; x, ethylene glycol, *p*-toluenesulfonic monohydrate, benzene, reflux, overnight; xi, PPTS, CH_2Cl_2, rt, 14 h; xii, allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C, 1 h; xiii, 3-buten-2-one, Grubbs II (5 mol%), CH_2Cl_2, reflux, overnight; xiv, H_2 (1 atm), 10% Pd/C, MeOH, rt, 2 h; xv, TFA, CH_2Cl_2, 0 °C to rt, 2 h.

Scheme 1.3-30 Bates' synthesis of (-)-porantheridine and epimer 1-263

Bates and Lu reported the formal synthesis of (-)-porantheridine **1-262** as well as a complementary synthesis of its epimer **1-263** (Scheme 1.3-30) by a route involving a silver-catalysed allene cyclisation of **1-264** to give *cis*-isoxazolidine **1-265** as the major isomer (dr 9:1).[104] Subsequent cleavage of the *N,O* bond with $Mo(Co)_6$ revealed the *syn*-aminoalcohol which underwent several transformations to intermediate **1-266**. This precursor was treated with potassium *tert*-butoxide to initate formation of the piperidine following which, treatment with *p*-TsOH triggered formation of the carbamate. This compound was then subjected to an allylation reaction using titanium tetrachloride and allyltrimethylsilane to afford **1-267** as a single isomer in 76% yield. Further chain elaboration reactions on the terminal alkene were carried out to furnish piperidine **1-268**, which was previously featured in the synthesis of the natural product by Takahata[105] and

Comins.[106] Conversely, when intermediate **1-266** was treated with mildly acidic PPTS, a bicyclic *N,O*-acetal was formed by exchange of the ethoxy groups with the alcohol and the *N*-carbamate group. This then underwent allylation using the same conditions as before to give piperidine **1-269** as a mixture of diastereomers which was found to be in the ratio of 9:1. This compound underwent similar chain elaboration reactions as earlier, and then cyclisation to *epi*-porantheridine **1-263** after removal of the *N*-Boc group with trifluoroacetic acid.



1-270 **1-271** **1-272** **1-273**

(±)-**1-262** **1-276**

Reagents and conditions: i, cyclopentadiene, $NaIO_4$, MeOH-H_2O, 0 °C, 0.5 h, then rt, 1.5 h; ii, Grubbs II (5 mol%), but-2-ene, toluene, 80 °C, 3 h; iii, H_2 (1 atm), Rh/C, EtOAc, rt; iv, $MO(CO)_6$, $NaBH_4$, MeCN-H_2O, 90 °C; v, NaH, BnBr, THF; vi, allylmagnesium bromide, THF, 45 °C, 0.5 h, then $NaBH_3CN$, AcOH, 0 °C to rt, 14 h; vii, methyl chloroformate, K_2CO_3, $CHCl_3$, 85 °C, 72 h; viii, Hoveyda-Grubbs II (15 mol%), 80 °C, hυ, 0.5 h; ix, H_2 (1 atm), $PdCl_2$, MeOH, rt, 5 h.

Scheme 1.3-31 Kouklovsky's synthesis of (±)-porantheridine

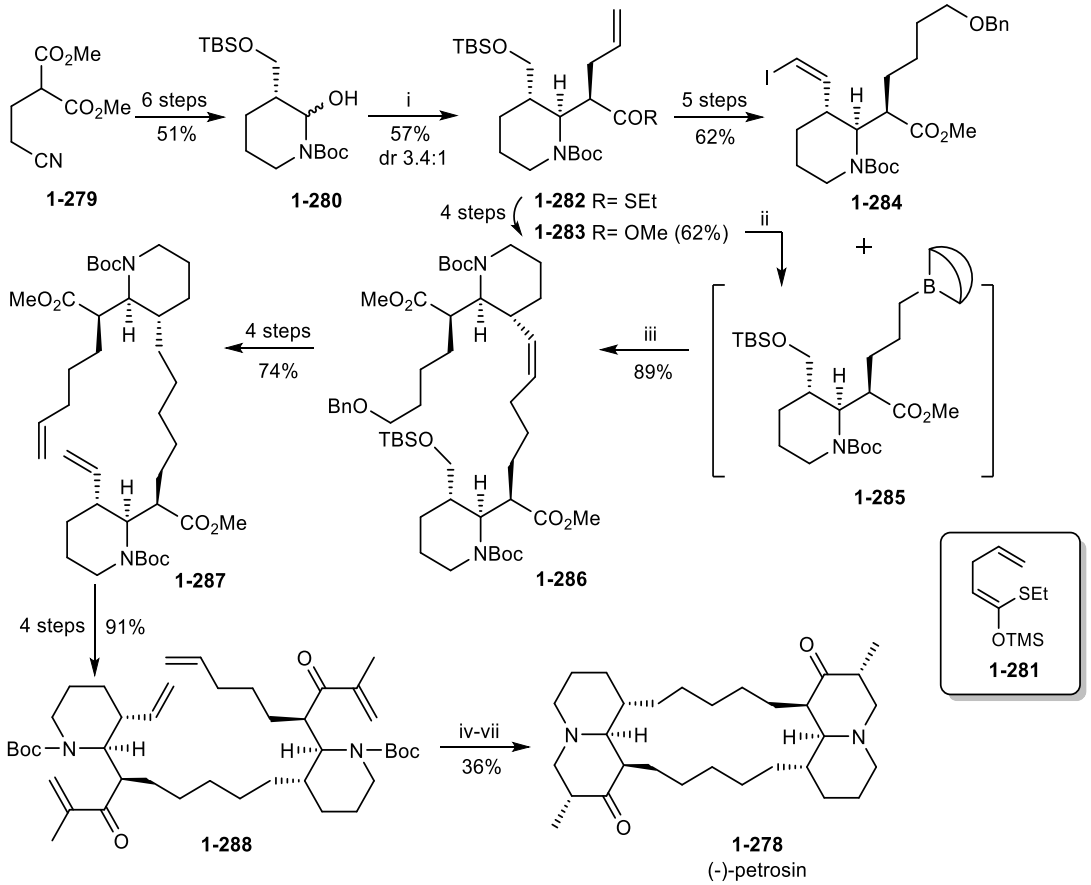
Kouklovsky and co-workers employed a sequence of reactions that include a nitroso Diels-Alder cycloaddition and a ring-rearrangement metathesis cascade to carry out a formal synthesis of racemic porantheridine, (±)-**1-262** (Scheme 1.3-31).[107] The synthesis began with oxidation of hydroxamic acid **1-270** with sodium periodate in the presence of cyclopentadiene to form the bicyclic nitroso adduct **1-271** in 61% yield which was then converted to isoxazolopiperidinone **1-272** *via* a metathesis cascade. During the cascade, the compound first underwent a ring-opening metathesis. The resulting diene underwent a ring closing metathesis on one arm to form the piperidinone backbone and a cross-metathesis

on the other arm with but-2-ene present in the reaction to form **1-272**. This compound then underwent reduction with hydrogen following which, treatment with molybdenum hexacarbonyl revealed intermediate **1-273**. Allylation and subsequent $NaBH_3CN$ reduction proved to be successful on the *O*-benzyl/*N*-benzyl derivative of **1-273** to give **1-274** as a single diastereomer in 70% yield. Unfortunately, a cross-metathesis reaction of methyl vinyl ketone with benzyl protected **1-274** failed and the reaction proved to be successful only after a protecting group swap to methyl carbamate **1-275**. The resulting alkene was reduced with H_2 in the presence of $PdCl_2$ to give **1-276**. This compound appeared in the asymmetric synthesis of the natural product by Takahata *et al.*[105] and thus this route also completes a formal synthesis of the alkaloid.

1.4 Alkaloids from marine sources

(-)-Petrosin (**1-278**), a bisquinolizidine alkaloid was isolated from the marine sponge *Petrosia seriata*[108] and exhibits anti-HIV activities.[109] In 2010, Tokuyama and co-workers reported the first enantioselective total synthesis of (+) and (-)-petrosin (Scheme 1.4-1).[110] Their synthetic route begins with a 6-step transformation of malonate **1-279** to hemiaminal **1-280** which included a lipase-mediated desymmetrisation reaction to introduce the first stereocentre. The hemiaminal underwent a Mannich reaction which was found to give the most favourable diastereoselectivity with ketene silyl acetal **1-281** (dr 3.4:1). A 4-step reaction sequence was carried out to transform thioester **1-282** to the desired methyl ester **1-283** which underwent divergent routes to furnish the two quinolizidine fragments **1-284** and **1-285**. The two fragments were then coupled *via* a Suzuki-Miyaura reaction to form intermediate **1-286** in excellent yield. Further elaboration was carried out on the alcohol groups of **302** to form *bis*-alkene **1-287**. Initial attempts at RCM with **1-288** failed and the authors postulated that prior formation of the quinolizidine rings would favour the formation of the macrocyclic ring. To form the quinolizidine, the esters in **1-288** were

manipulated to *bis*-α,β-unsaturated ketone **1-289**. The *N*-Boc groups were cleaved with zinc bromide. This set the stage for the key *aza*-Michael reaction which occurred upon treatment with wet SiO_2 in refluxing dichloroethane to give the *bis*-quinolozidine as a single isomer. The synthesis was completed by cross-metathesis and reduction of the resulting alkene by hydrogenation to afford (-)-petrosin (**1-278**). An analogous route was also employed in the synthesis of (+)-petrosin(*ent*-**1-278**).

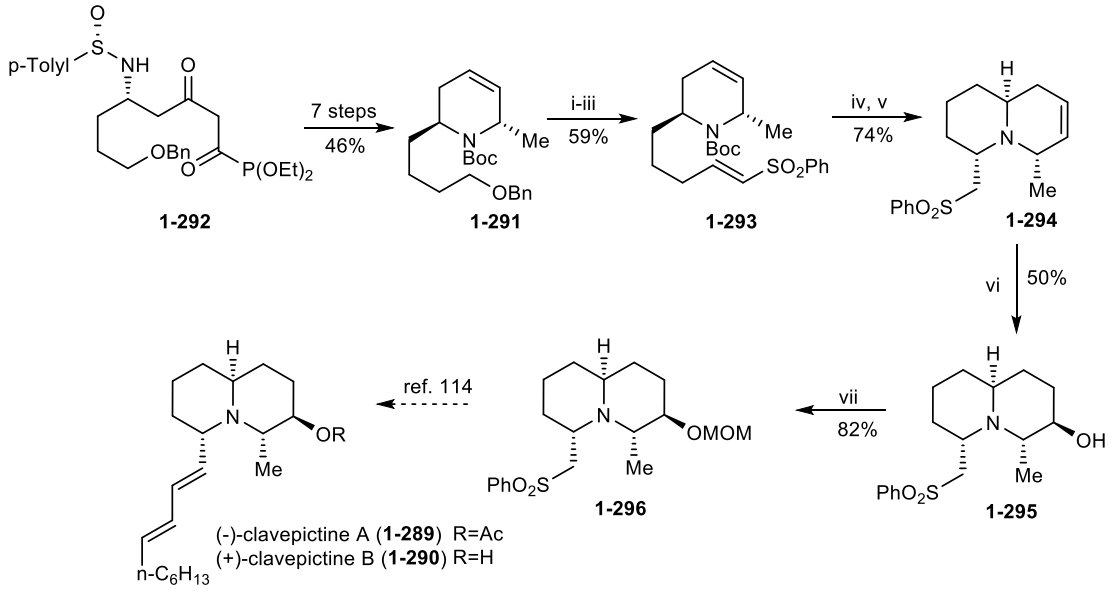


Reagents and conditions: i, **1-281**, TBSOTf, CH_2Cl_2, -78 °C; ii, $(9\text{-BBN})_2$, THF, rt; iii, $PdCl_2(dppf)\cdot CH_2Cl_2$ (5 mol%), 3 M NaOH, THF, rt; iv, $ZnBr_2$, $ClCH_2CH_2Cl$, 70 °C; v, wet SiO_2, $ClCH_2CH_2Cl$, reflux; vi, Grubbs II, *p*-quinone, toluene, reflux; H_2 (1 atm), Pd/C, Et_3N, EtOH, rt.

Scheme 1.4-1 Tokuyama's synthesis of (-)-petrosin

Clavepictines A and B, **1-289** and **1-290**, are alkaloids isolated from Bermuda tunicate *Clavelina picta*.[111] Davis and Xu reported the formal synthesis of Clavepictine A and B starting from a chiral sulfinylimine building block, a strategy that has been implemented by the group for synthesis of various alkaloids (Scheme 1.4-2).[112] Key intermediate **1-291**, derived from sulfinimine **1-292**, was utilised by the group in the synthesis of (-)-myrtine

and its preparation is described in an earlier section (see Section 1.3.2).[55, 113] This intermediate underwent several standard transformations to afford vinyl sulfone **1-293,** which underwent an intramolecular Michael cyclisation after removal of the *N*-Boc group and subsequent treatment with Cs_2CO_3, to give quinolizidine **1-294** with the desired stereochemistry, in 74% yield. Hydroboration from the less hindered face followed by H_2O_2 afforded alcohol **1-295** as a single isomer albeit with a modest yield of 50%. The regioselectivity of the borane addition may have stemmed from the positive charge held by the nitrogen group in the transition state. The alcohol was subsequently protected to furnish intermediate **1-296**, which has previously featured in the synthesis of the natural products by Toyooka and co-workers.[114]

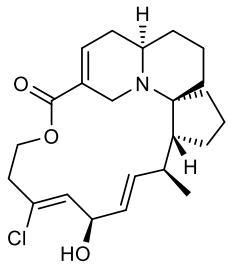


Reagents and conditions: i, Na/liq. NH_3, *t*BuOH, -78 °C, 10 min; ii, Dess-Martin periodinane, CH_2Cl_2, rt, 2 h; iii, NaH, $PhO_2SCH_2PO(OEt)_2$, THF, rt, 0.5 h; iv, TFA, CH_2Cl_2, rt, 50 min; v, Cs_2CO_3, MeOH, rt, 0.5 h; vi, BH_3·THF, THF, 0 °C, then 6N NaOH, 30% H_2O_2, 50 °C, 2 h; vii, MOMCl, DIPEA, THF, rt, 8 h.

Scheme 1.4-2 Davis' synthesis of Clavepictine A and B

Since its discovery, halichlorine **1-297** has been a popular target for synthetic chemists due to its intriguing biological activity. Recent findings on its physiological activity have been reported. Murata and co-workers investigated the effects of halichlorine on vascular contractility.[115] They conducted the studies on endothelium-denuded rat aorta and found that halichlorine inhibited L-type Ca^{2+} channels in vascular smooth muscle cells. This

inhibits intracellular Ca^{2+} influx, which results in an overall reduction in vascular contractions. Anti-atherosclerosis activity of halichlorine on endothelial cells was also investigated.[116] Studies showed that halichlorine inhibited LPS-induced NF-κB activation, which caused a reduction in the expression of adhesion molecules and monocyte adhesion to endothelial cells. This is important, as increased expression of adhesion molecules is characteristic of atherosclerosis. With respect to synthetic studies during the period covered in this review, there have been numerous contributions to the construction of the complex spirocyclic framework.[117] Work that has led to a formal synthesis of halichlorine will be reviewed.[118] Also during the period of the review, total synthesis of halichlorine has been reported by the Clive group[119] and the Arimoto and Uemera group.[120] These reports also mark a major milestone for each group with respect to the long-standing history they have shared with halichlorine and its class of marine natural products.

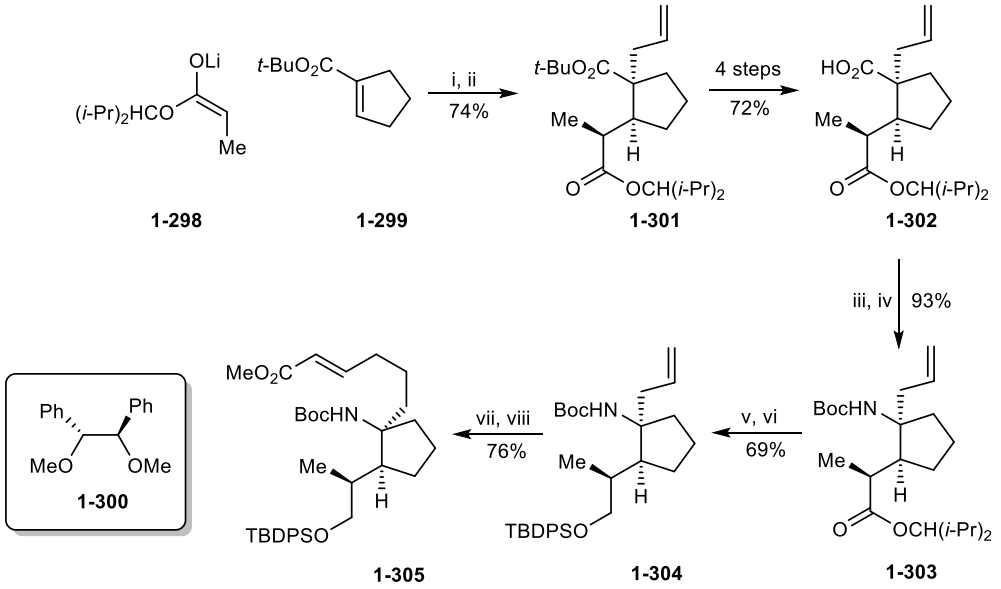


(+)-halichlorine (**1-297**)

Figure 1.4-1 Structure of (+)-halichlorine

A formal synthesis of (-)-halichlorine by Tomioka *et al.* commenced with an asymmetric conjugate addition of lithium enolate **1-298** to cyclopentene **1-299** in the presence of chiral ligand **1-300** and *i*-Pr(*c*-Hex)NLi (Scheme 1.4-3) [118a] The resulting enolate was directly subjected to a stereoselective alkylation with allylbromide to give product **1-301** with 64% ee and in 74% yield over two steps. The synthesis continued with a Curtius rearrangement on the enantiomer-enriched acid analogue **1-302** followed by a Boc protection of the resulting amine to give intermediate **1-303**. Conversion of the ester moiety to silyl alcohol **1-304** ensued which was further elongated to furnish precursor **1-305** *via* a two-step hydroboration and Suzuki-Miyaura coupling reaction sequence. The compound is

confirmed by optical rotation to be the enantiomer of Danishefsky's key intermediate[121] to natural halichlorine. Hence, the report constitutes a formal synthesis of its unnatural isomer.

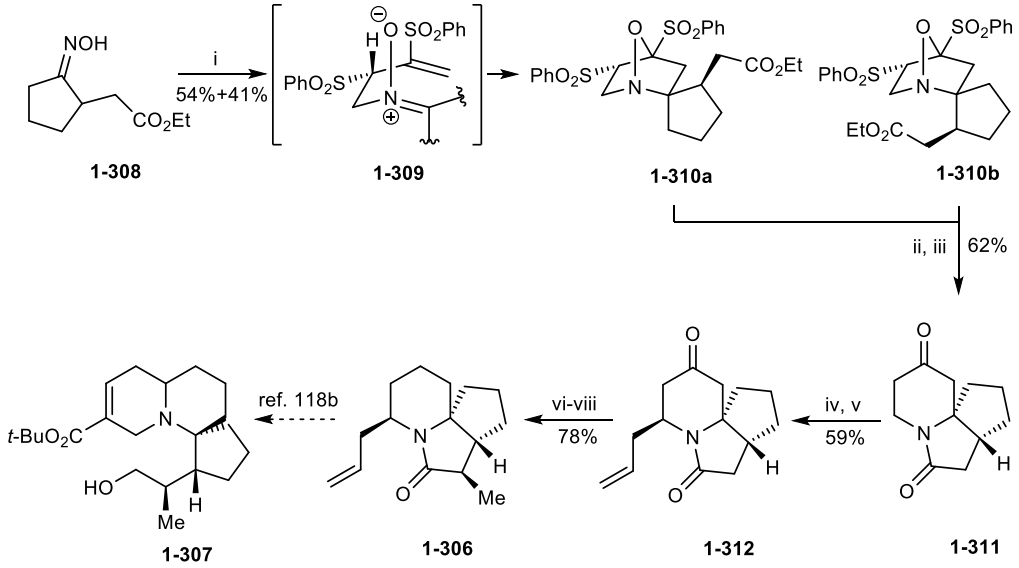


Reagents and conditions: i, **1-300**, *i*-Pr(*c*-Hex)NLi, toluene, -78 °C, 1 h; ii, allyl bromide, HMPA, -78 °C, 1 h; iii, DPPA, Et_3N, 4 Å MS, toluene, reflux, 2 h; iv, *t*BuOH, TMSCl, CH_2Cl_2, rt, 4 days; v, $NaBH_4$, DMSO, 80 °C, 2 days; vi, TBDPSCl, imidazole, DMF, rt, 2 h; vii, 9-BBN, THF, rt, 1.5 h; viii, IHC=$CHCO_2Me$, [$PdCl_2$(dppf)], $AsPh_3$, Cs_2CO_3, DMF-H_2O, rt, 3 h.

Scheme 1.4-3 Tomioka's synthesis of (-)-halichlorine

Cascade sequences proved to be a viable route to the spirocyclic core of halichlorine as demonstrated by two separate groups, namely Padwa's[118b] and Stockman's.[118c] Padwa reported the racemic preparation of the Feldman intermediate[122] **1-306** of the Danishefsky precursor[121b] **1-307** to the natural product (Scheme 1.4-4). In the first step of the cascade sequence, oxime **1-308** reacts with 2,3-*bis*-(phenylsulfonyl)-1,3-butadiene *via* a conjugate addition reaction to yield nitrone **1-309** which subsequently underwent a 1,3-dipolar cycloaddition to furnish the isoxazolidine as a mixture of two diastereomers, **1-310a** and **1-310b**. The products then underwent a stepwise reduction sequence. First, the diastereomers was treated with sodium amalgam to cleave the *N,O* bond and reveal a sulfonyl piperidone. The remaining sulfonyl group was then reduced using radical conditions (i.e. *n*-Bu_3SnH, AIBN) to furnish piperidinone **1-311**. The synthesis continued with oxidation of piperidinone **1-311** under Saegusa conditions[123] and installation of the side chain *via* conjugate addition with allyl stannane to give the desired diastereomer **1-312**

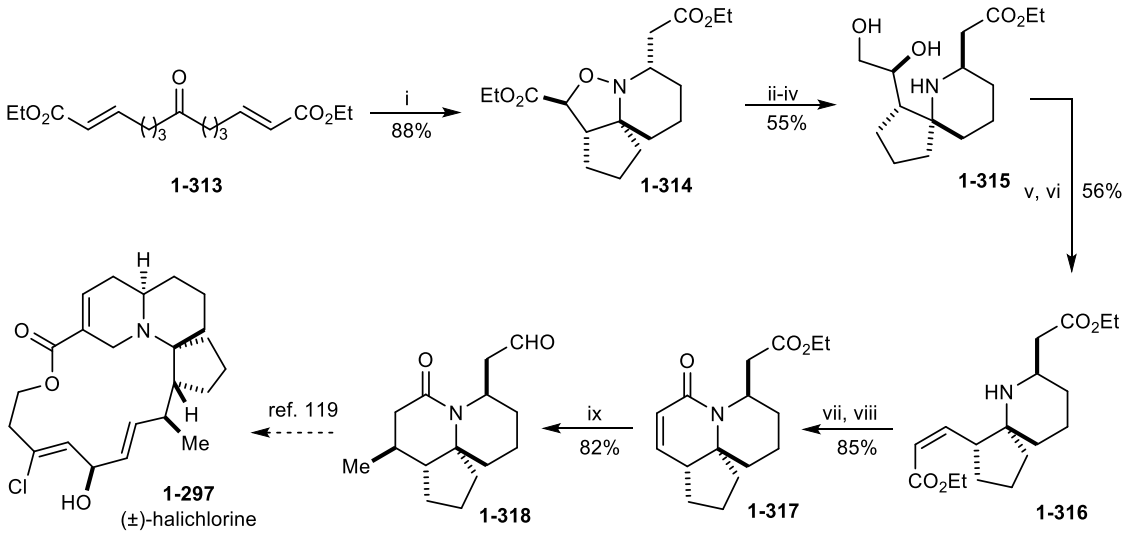
as the major product (dr 15:1). Diastereoselectivity was attributed to the approach of allyl stannane from the convex face of the tricyclic core. Treatment of the major diastereomer with 1,3-propane thiol yielded the dithiane which was converted to the advanced intermediate **1-306** by standard transformations as illustrated.



Reagents and conditions: i, 2,3-*bis*-(phenylsulfonyl)-1,3-butadiene, Δ, 24 h; ii, 5% Na/Hg, THF, rt, 12 h; iii, AIBN, *n*-Bu_3SnH, benzene, reflux, 36 h; iv, TMSOTf, Et_3N, $Pd(OAc)_2$, CH_2Cl_2, rt, 12 h; v, allyltributyltin, TMSOTf, CH_2Cl_2, 0 °C to rt, 1 h; vi, 1,3-propanedithiol, $BF_3 \cdot Et_2O$, CH_2Cl_2, rt, 12 h; vii, LDA, CH_3I, THF, -78 °C to rt, 3 h ; viii, AIBN, *n*-Bu_3SnH, benzene, reflux, 3 h.

Scheme 1.4-4 Padwa's formal synthesis of (+)-halichlorine

Stockman implemented an elegant cascade sequence which also involves a conjugate intramolecular addition of the oxime derivative of ketodiester **1-313**, followed by a 1,3-dipolar cycloaddition between the resulting nitrone and the remaining conjugate ester to afford the racemic tricyclic core **1-314** (Scheme 1.4-5).[118c] A further four steps afforded diol **1-315**, oxidative cleavage and subsequent Wittig homologation producing **1-316** in 56% yield. Formation of lactam **1-317** was successful with stoichiometric acetic acid in toluene under reflux conditions. The methyl group was introduced by addition of the Gilman reagent to **1-317** in the presence of TMSCl and triethylamine to yield the product as a single diastereomer. Reduction of the ester moiety using DIBAL-H at low temperatures furnished known aldehyde **1-318**, a late-stage intermediate [119] in Clive's synthesis of halichlorine.

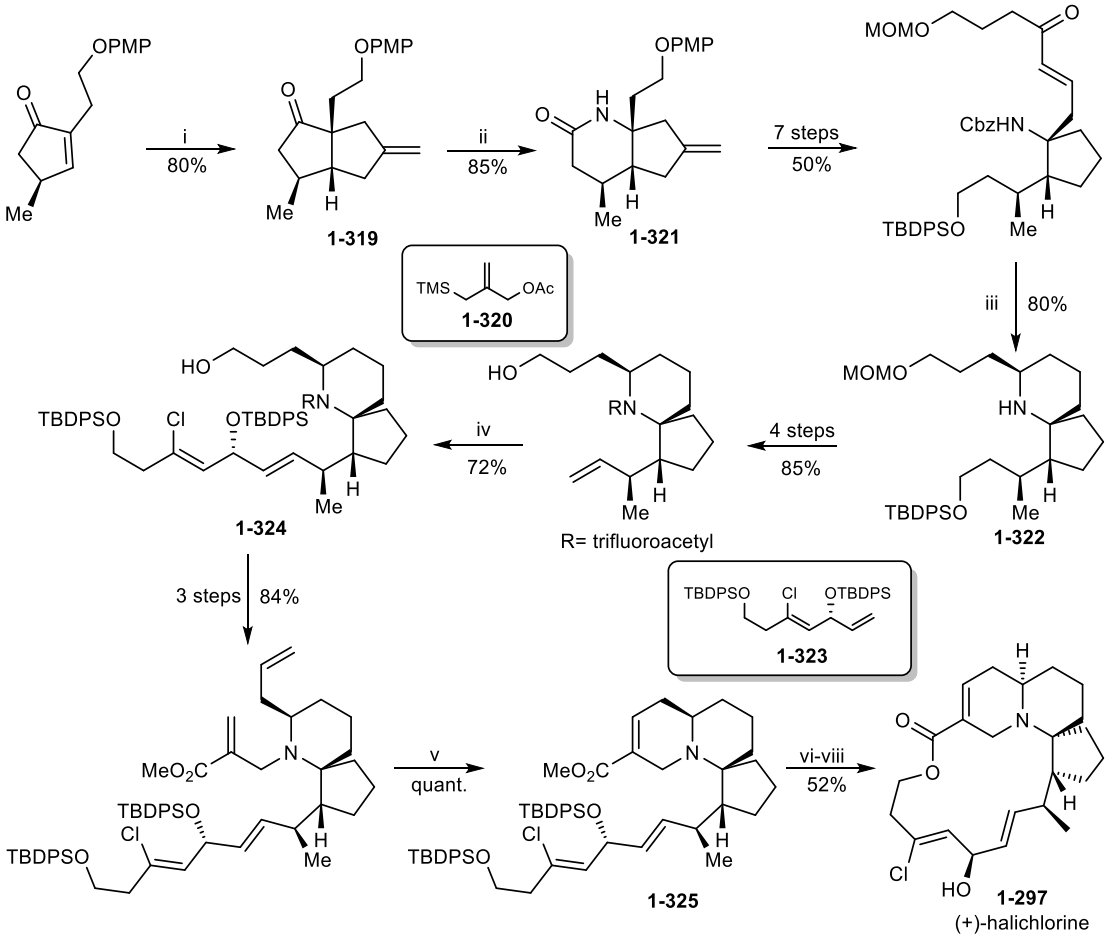


Reagents and conditions: i, NH_2OH, NaOAc, MeOH, rt, 24 h, then MeCN, reflux, 2 h; ii, $NaBH_4$, EtOH, rt, 48 h; iii, H_2 (1 atm), Pd/C, MeOH, rt, 24 h; iv, EtOH, μw, 120 °C, 12 h; v, $NaIO_4$, CH_2Cl_2-H_2O, 0 °C, 1.5 h; vi, $EtO_2CCH_2PO(OPh)_2$, NaH, THF, -78 °C, 5 h then rt, 12 h; vii, CH_3CO_2H, toluene, 110 °C, 12 h; viii, MeLi, CuI, TMSCl, Et_3N, THF, -78 °C, 5 h; ix, DIBAL-H, CH_2Cl_2, -78 °C, 0.5 h.

Scheme 1.4-5 Stockman's formal synthesis of (±)-halichlorine

The discovery of halichlorine was reported by Uemura in 1996.[124] The author, together with Arimoto and co-workers, has recently published their work on the enantioselective total synthesis of the natural product.[120] This work represents a continuation in the long-standing interest of the halichlorine family as the authors have earlier reported an asymmetric synthesis of another natural product from the same family of alkaloids.[125] In this latest report (Scheme 1.4-6), the synthesis features an elegant construction of five-membered ring **1-319** *via* a palladium-catalysed trimethylenemethane [3+2] cyclisation with alkene **1-320** as the precursor. This compound was subjected to a modified Beckmann rearrangement reaction using hindered nitrogen reagent, MSH, to give lactam **1-321** as the sole product in 85% yield. The lactam was elaborated to spirocyclic precursor **1-322** which was subjected to a one-pot four-step hydrogenation-cyclisation protocol carried out in the presence of acetic acid and $Pd(OH)_2/C$ as the catalyst. The following transformations occurred during the hydrogenation- saturation of the olefin, *N*-Cbz deprotection, amine condensation and stereoselective reduction of imine intermediate. The lower side-chain **1-323** was installed on spirocyclic core **1-322** *via* a reduced-pressure cross-metathesis to give

1-324. Following conversion of the free primary alcohol to a terminal alkene and *N*-alkylation, ring–closing metathesis reaction was carried out to form the quinolizidine skeleton of **1-325**. The synthesis was completed by removal of silyl protecting groups, ester hydrolysis and macrolactonisation under Shiina conditions.[126]

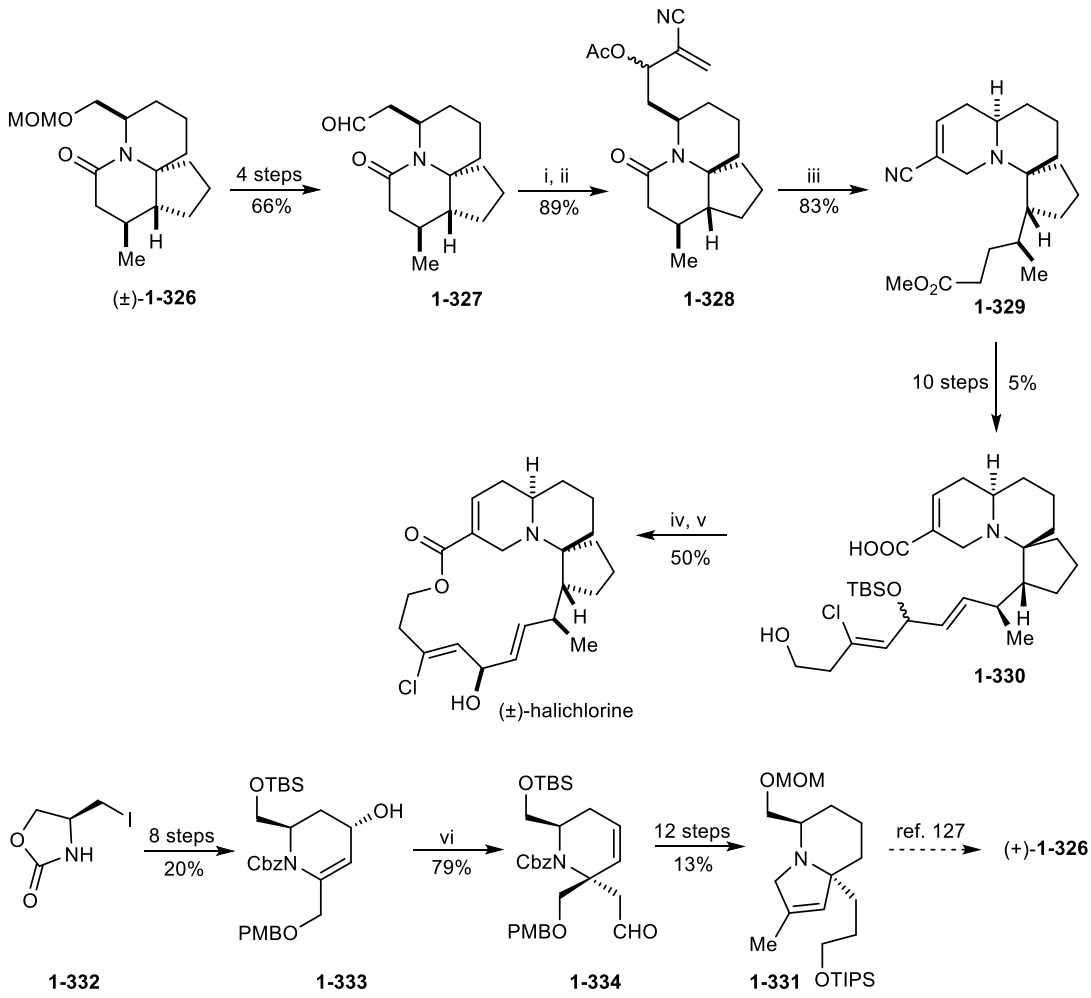


Reagents and conditions: i, **1-320**, $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, THF, reflux; ii, MSH, CH_2Cl_2, rt, 30 min then silica gel; iii, H_2 (1 atm), 5% $Pd(OH)_2/C$ (20 mol%), AcOH, EtOH, rt, 20 h; iv, **1-323**, Hoveyda-Grubbs II (28 mol%), toluene, static vacuum, 60 °C; v, Grubbs II (10 mol%), CH_2Cl_2, reflux; vi, $HF{\cdot}py_x/py$ (1:3), rt; vii, NaOH, THF, MeOH, H_2O, 50 °C; viii, MNBA, DMAP, THF, rt.

Scheme 1.4-6 Uemura's synthesis of (+)-halichlorine

In 2009, Clive and co-workers reported a total synthesis of halichlorine[119] derived from the tricyclic core **1-326** of which the synthesis had been previously disclosed in an earlier report.[127] To construct the quinolizidine framework in halichlorine, **1-326** was transformed to aldehyde **1-327** through a four step sequence (Scheme 1.4-7). The aldehyde then underwent a Baylis-Hillman reaction with acrylonitrile and the resulting alcohol was protected to afford acetate **1-328**. Upon hydrolysis of the lactam with Meerwein's salt,

spontaneous cyclisation occurred to form unsaturated nitrile **1-329**. The nitrile was converted to an acid and the lower side chain was further elongated to afford **1-330** over several steps. Macrolactonisation was accomplished using the Keck protocol and final desilylation with HF afforded halichlorine in over 46 steps. Clive also formulated a new approach to the enantiopure preparation of **1-331**, a precursor to the tricyclic core **1-326**. The new approach began with serine-derived iodide **1-332** which was manipulated to furnish piperidinol **1-333** over several steps. This underwent a Claisen-type rearrangement to afford aldehyde **1-334** which was further transformed to optically pure **1-331** and based on the transformations carried out on the racemic material, this would then constitute a formal synthesis of (+)-halichlorine.



Reagents and conditions: i, acrylonitrile, DABCO, $Sc(OTf)_3$, 5 days; ii, AcCl, pyridine, CH_2Cl_2, 0 °C to rt; iii, Me_3OBF_4, CH_2Cl_2, aq. Na_2CO_3, MeCN; iv, DMAP, DMAP·HCl, EDCI, $CHCl_3$, reflux; v, HF-pyr, THF; vi, butyl vinyl ether, $Hg(OAc)_2$, Et_3N, 110 °C, 36 h.

Scheme 1.4-7 Clive's synthesis of (±)-halichlorine

1.5 Alkaloids from bacterial metabolite

JBIR-102 **1-335**, an ester analogue of cyclizidine **1-336** was isolated from *Saccharopolyspora* sp. RL78 found in mangrove soil collected in Nosoko, Ishigaki Island, Okinawa Prefecture, Japan. Structural elucidation was carried out using 2D NMR analytical techniques. Compound **1-335** was shown to exhibit cytotoxic activities against ACC-MESO-1 and HeLa cells with IC_{50} values of 39 and 29 μM, respectively.

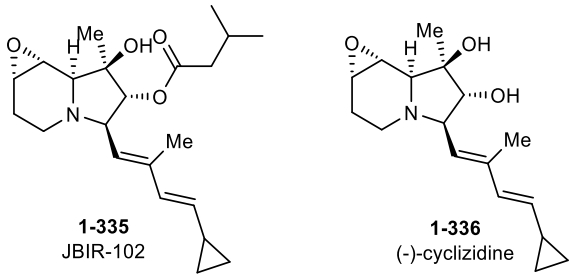
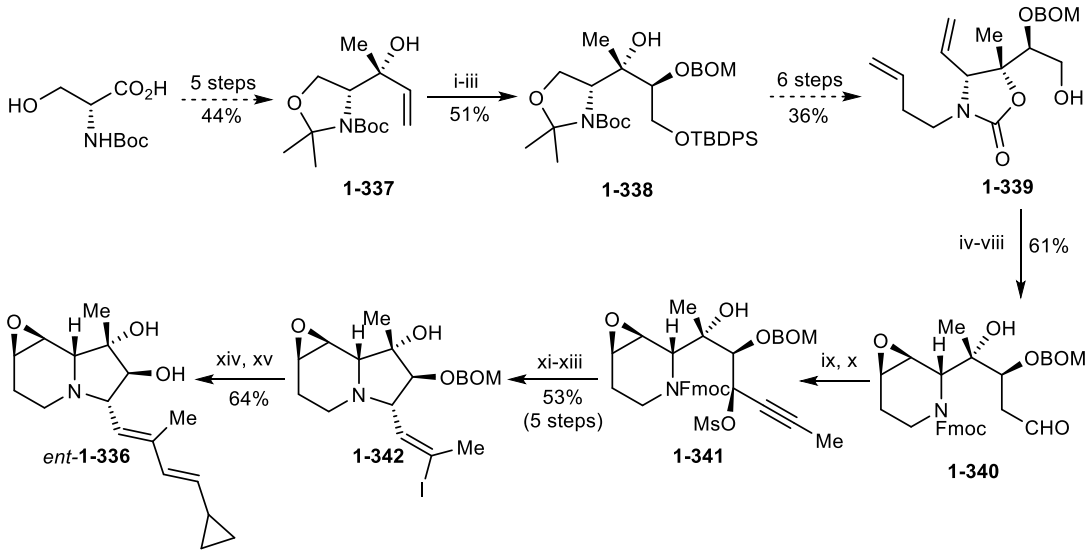


Figure 1.5-1 Structures of JBIR-102 and cyclizidine

In 2011, Hanessian and co-workers reported the first total synthesis of (+)-cyclizidine, *ent*-**1-336**, the unnatural enantiomer of the indolizidine alkaloid which was produced by a *Streptomyces* species (NCIB11649) under aerobic fementation conditions (Scheme 1.5-1).[128] Starting from *N*-Boc-D-serine, *N,O*-protected allylic alcohol **1-337** was prepared in several steps before converting it to the triol (dr >5:1) by dihydroxylation on the alkene with AD-Mix-β and then stepwise protection of the primary and secondary alcohol to give O-TBDPS/BOM derivative **1-338**. After several transformations, carbamate **1-339** underwent a ring-closing metathesis reaction following which, the carbamate was cleaved and the secondary amine was reprotected with Fmoc. The alkene formed on RCM underwent an epoxidation with Oxone in the presence of trifluoroacetone (CF_3COCH_3) with good stereoselectivity (dr >20:1) in favour of the desired diastereomer. The primary alcohol was then oxidised using Dess-Martin periodinane to give aldehyde **1-340**. Attempts to carry out a direct coupling of aldehyde **1-340** with the cylopropyl diene side chain were not successful and a stepwise approach was considered. Addition of *n*-propynylmagnesium bromide to **1-340** afforded a 3:2 mixture in favour of the desired diastereomer. The

resulting secondary alcohol was converted to afford mesylate **1-341** which was set for spontaneous cyclisation upon cleavage of the Fmoc group with piperidine. The propynyl side chain then underwent hydrostannylation to give the *E*-vinyl stannane which was treated with iodine to give vinyl iodide **1-342**. The second unit was attached *via* a Suzuki-Miyaura coupling reaction with the respective vinyl cyclopropyl boronate ester. Finally, deprotection of the BOM ether proved to be a rather delicate affair due to the various functional groups present and was effected by treatment with Freeman's reagent to give the natural product as colourless needles in an overall yield of 2.7%.



Reagents and conditions: i, AD-Mix-β, *t*BuOH-H_2O (1:1), $MeSO_2NH_2$, 0 °C, 24 h; ii, Et_3N, TBDPSCl, DMAP, CH_2Cl_2, rt, 3h; iii, BOMCl, DIPEA, TBAI, $ClCH_2CH_2Cl$, 50 °C, 12 h; iv, Grubbs II (5 mol%), CH_2Cl_2, reflux, 2 h; v, 2N KOH-EtOH (1:1), reflux, 12 h; vi, FmocCl, satd. Na_2CO_3, THF, 0 °C, 3 h; vii, Oxone, CF_3COCH_3, CH_3CN, H_2O, 0 °C, 3 h; viii, Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; ix, *n*-propynylMgBr, THF, -78 °C to rt; x, MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h; xi, piperidine, CH_3CN, rt, 12 h; xii, $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt, 0.5 h; xiii, I_2, CH_2Cl_2, 0 °C to rt; xiv, vinyl cyclopropyl boronate ester, $Pd(PPh_3)_4$, Tl_2CO_3, THF-H_2O (4:1); xv, Freeman's reagent (0.5 M in THF), THF, -78 °C, 1 h.

Scheme 1.5-1 Hanessian's synthesis of (+)-cyclizidine

1.6 Conclusion

After close to a decade of study since the last review from J. P. Michael,[1r] there has been a significant amount of work carried out in the investigations towards the synthesis of indolizidine and quinolizidine alkaloids. In the foregoing review, we have discussed a wide range of methods towards these alkaloids. While general strategies towards cyclisation of

these alkaloids remain fairly unchanged, new chemical reactions have allowed the syntheses of these alkaloids to be more facile, practical and economical. Reactions that have introduced greater stereocontrol and chemoselectivity in reactions have shortened synthetic routes and increased throughput. These new methods however, are selective to a small subset of structures, thereby reducing their breadth of application. In relation to our studies, the literature review validated our aim to carry out further investigations into the stereoselective synthesis of hydroxylated piperidine and quinolizidine alkaloids. In our work, we propose a method to access alkaloids bearing the 1,3-aminoalcohol moiety in a facile manner. The consequences of these advancements will also enable access to a wider chemical space for researchers who wish to carry out work at the interdisciplinary interface with synthetic chemistry.

Chapter 2

SYNTHESIS OF (-)-5-HYDROXYSEDAMINE

2.1 Abstract

Recent methods for the formation of 3-hydroxypiperidines *via* hydroformylation and diastereoselective dihydroxylation have been developed in our laboratory. This has proven to be an efficient route for the synthesis of pseudoconhydrine[129] and azimic acid.[130] Also, we have shown the usefulness of isoxazolidines as an intermediate for the diastereoselective formation of 1,3-aminoalcohols.[131]

In this chapter, we present the synthesis of (-)-5-hydroxysedamine, a *Sedum* alkaloid, employing tandem hydroformylation-condensation followed by a stereoselective dihydroxylation of the enamine as key steps. In addition, the synthesis will serve to highlight the tractability of *N,O*-heterocycles as intermediates in the construction of the 1,3-aminoalcohol motif commonly found in the *Sedum* alkaloids.

2.2 Introduction

The development of new synthetic methods for the construction of piperidine alkaloids has evoked a significant amount of interest from synthetic chemists. One of the reasons for this is that substituted piperidines form the skeletal framework of various natural products which often have intriguing biological activity. This is exemplified by the *Sedum* alkaloids, which have been reported to be effective in the treatment of cognitive disorders and are known to have memory-enhancing properties.[132] A characteristic feature found in many members of this alkaloid family is the 2-substituted piperidine with a hydroxy functionality in its side chain. This feature renders the molecules with a chiral 1,3-aminoalcohol moiety as illustrated in a selection of these natural products in Figure 2.2-1.

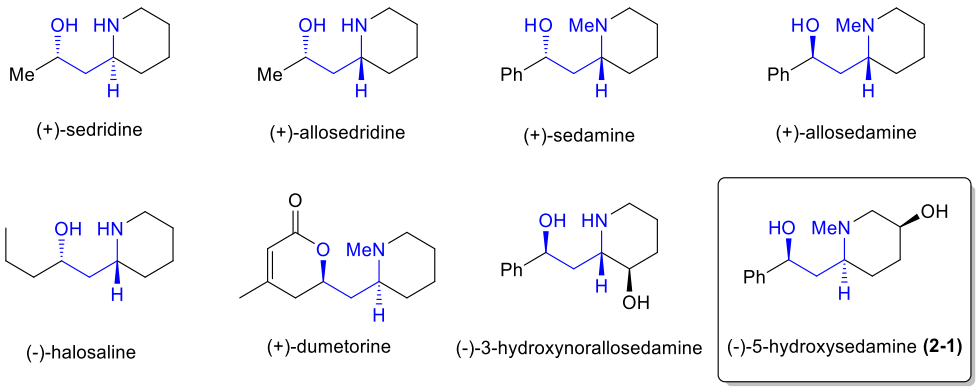
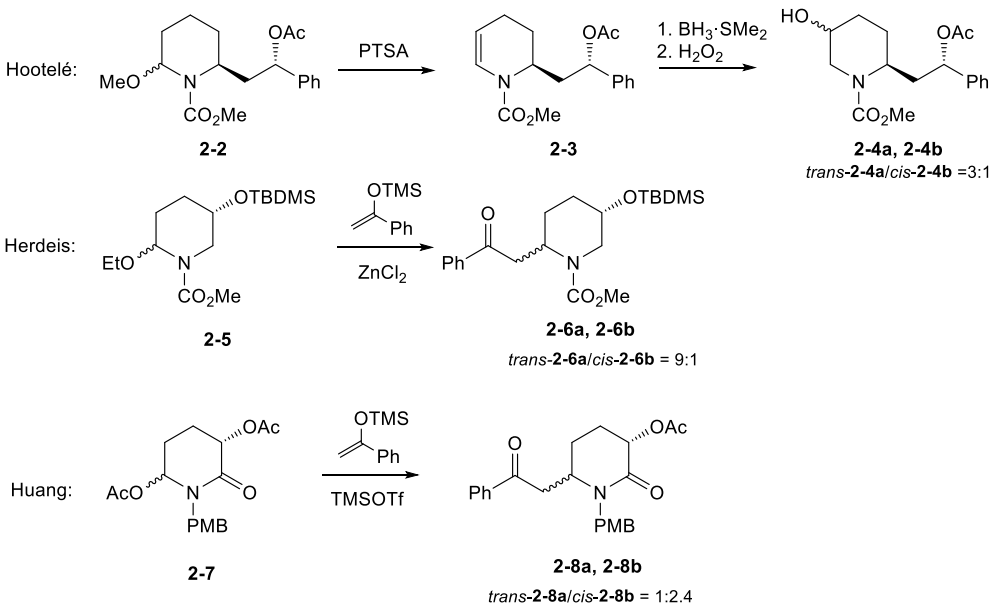


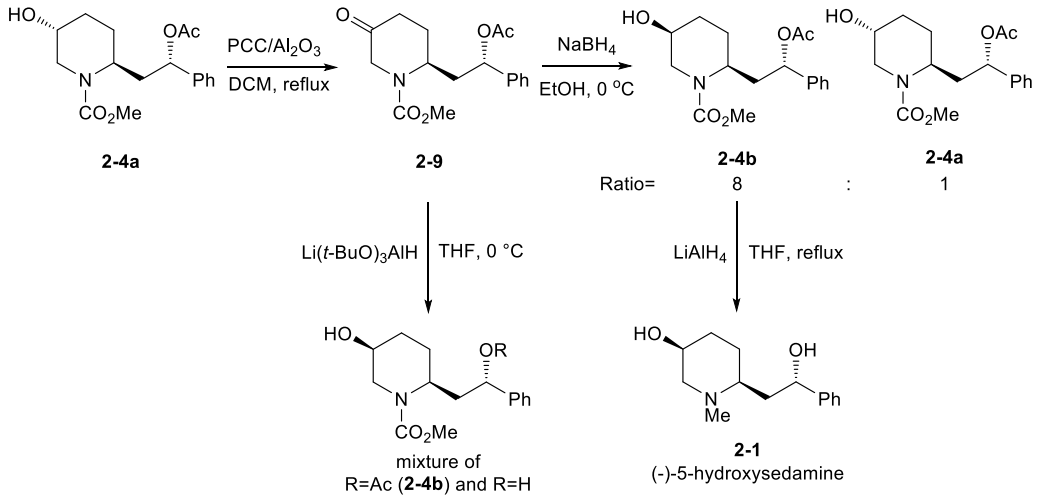
Figure 2.2-1 Structures of Sedum and related alkaloids

2.2.1 Reported syntheses of (-)-5-hydroxysedamine

(-)-5-Hydroxysedamine (**2-1**), is a hydroxylated piperidine alkaloid isolated from *Sedum acre*,[133] a perennial plant native to Europe. To the best of our knowledge, there has been no report on the biological activity of (-)-5-hydroxysedamine. Despite this, several convergent approaches to the natural product have been reported by the groups of Hootelé,[134] Herdeis[135] and Huang.[136] While there are clear differences between their syntheses, a common theme running through all three of them is the employment of a hemiaminal as a precursor to introduce the second substitution around the piperidine ring (Scheme 2.2-1).



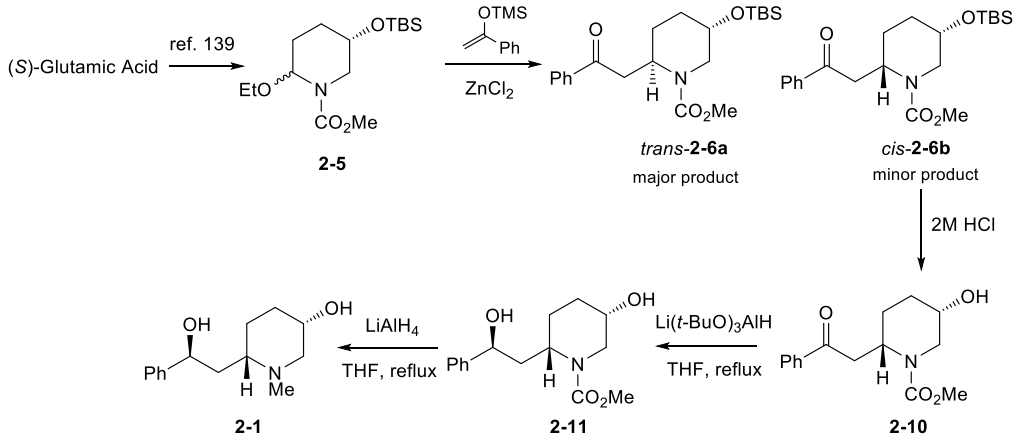
Scheme 2.2-1 Key strategies of precedent syntheses of (-)-5-hydroxysedamine



Scheme 2.2-2 Hootelé and Plehiers' synthesis of (-)-5-hydroxysedamine

Hootelé and Plehiers[134] executed this through a hydroboration-oxidation of hemiaminal **2-2**[137] to introduce the hydroxyl group in 2-hydroxypiperidine derivative **2-4a** (Scheme 2.2-1). This reaction occurred stereoselectively, with the major product being the 2,5-*trans* substituted isomer **2-4a**. Preferential attack of the borane from the less hindered side of the molecule afforded the *trans* isomer with a 2:1 selectivity ratio over the *cis* isomer.[134b] The same reaction was later reported to form the *trans* isomer with a 3:1 selectivity ratio.[134a] The isomers were separable by flash chromatography. Since (-)-5-hydroxysedamine is derived from the 2,5-*cis* substituted piperidine **2-4b** (Scheme 2.2-2), the major product **2-4a** or rather, a mixture of **2-4a** and **2-4b** was oxidised with PCC to ketopiperidine **2-9**.

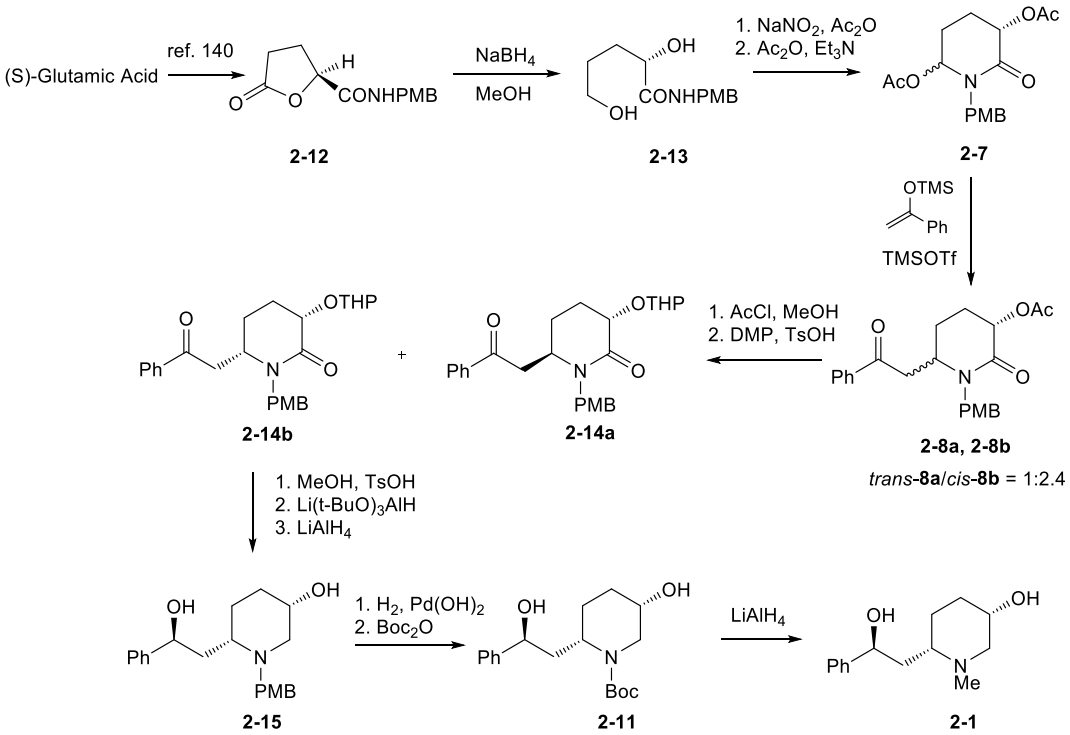
Stereoselective reduction of the ketone with $NaBH_4$ generated the desired *cis* isomer **2-4b** in a ratio of 8:1 to *trans* isomer **2-4a**. Use of lithium tri-*tert*-butoxyaluminium hydride led to exclusive formation of *cis* isomer **2-4b** with concomitant deacetylation. Carbamate **2-4b** was then further reduced with $LiAlH_4$ to give the desired natural product (**2-1**). The procedure gave the natural product with a yield of 48% from ene-carbamate **2-3**. On an interesting side note, Oppolzer attempted to replicate the hydroboration-oxidation sequence with the propyl analogue of ene-carbamate **2-3** and fell short of the ratio Hootelé claimed (6:1 in favour of the *trans* isomer).[134b] Oppolzer reported a more modest ratio of 3:1 under similar reaction conditions.[138]



Scheme 2.2-3 Herdeis' synthesis of (-)-5-hydroxysedamine

Herdeis *et al.*[135] tapped into the chiral pool in his synthesis by launching his synthesis (Scheme 2.2-3) from readily available (*S*)-glutamic acid to generate hemiaminal **2-5**.[139] Addition of a phenyl silyl enol ether in the presence of $ZnCl_2$ provided the *trans* isomer (**2-6a**) stereoselectively with a ratio of 9:1 to the *cis* isomer (**2-6b**). Herdeis postulated that preferential attack on the less hindered side of the *N*-acyliminium ion favoured the formation of the *trans* isomer. ^{1}H NMR spectroscopic data indicated that the OTBS group was in an axial orientation and was presumed to be so due to an attractive gauche effect between the nitrogen subsitutent and the β-oxygen function. Stereoselective reduction of ketone **2-10** with a bulky reducing agent (lithium tri-*tert*-butoxyaluminium hydride) resulted in the (*R*)-configurated secondary alcohol. Herdeis attributed the high

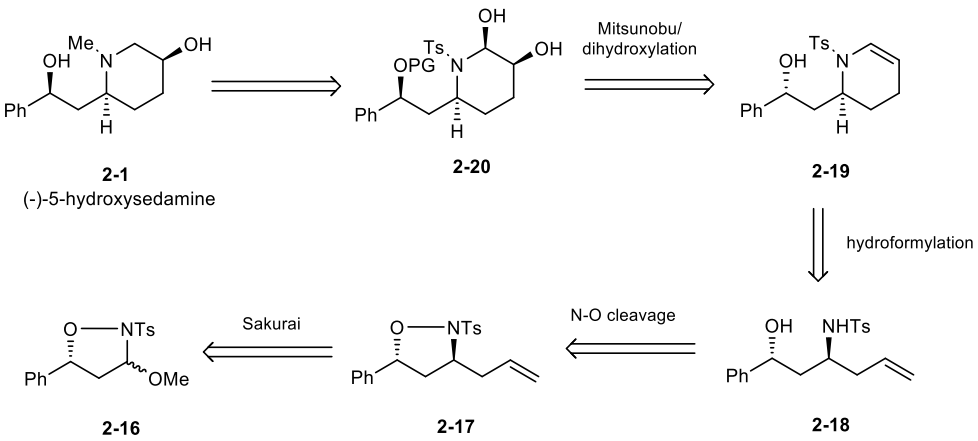
diastereoselectivity to the hydride approaching from the less hindered *si*-face of the prochiral keto group chelated with the carbonyl functionality of the carbamate by Li^+. This reasoning may seem a little counter intuitive since this forms a highly unlikely eight-membered ring chelate. Reduction of carbamate **2-11** with $LiAlH_4$ afforded (-)-5-hydroxysedamine **(2-1)** with modest yield.



Scheme 2.2-4 Huang's synthesis of (-)-5-hydroxysedamine

With the previous two methods, formation of the desired *cis*- 2,5 substituted isomer was disfavoured. In contrast, Huang *et al.*[136] proved to be successful in achieving a *cis*-diastereoselective addition to hemiaminal **2-7** (Scheme 2.2-4). The synthesis started with the same chiral building block as Herdeis's – (*S*)-glutamic acid, to form amido lactone **2-12.**[140] Reduction of amido lactone **2-12** afforded alcohol **2-13**. Chemoselective oxidation of the primary alcohol of **2-13** followed by an acetate protection provided hemiaminal **2-7** as an inconsequential 1:1 diastereomeric mixture. In the presence of TMSOTf, addition of the required phenyl silyl enol ether to hemiaminal **2-7** furnished the desired *cis*-isomer with a 2.4:1 (*cis*/*trans*) stereoselectivity, albeit as inseparable diastereomers. Separation of the isomers was only possible after a protecting group exchange to give **2-14a** and **2-14b**. The

major product was carried through to (-)-5-hydroxysedamine (**2-1**). Subsequent deprotection of alcohol **2-14b** and stereoselective reduction of the ketone under Herdeis's conditions gave a piperidinone, which was reduced with $LiAlH_4$ to give piperidine **2-15**. A second protecting group exchange and further reduction of the resulting carbamate **2-11** with $LiAlH_4$ furnished (-)-5-hydroxysedamine. Despite achieving *cis*-selectivity in the addition to hemiaminal **2-7**, the use of multiple protection and deprotection steps resulted in a rather lengthy and inefficient synthesis.



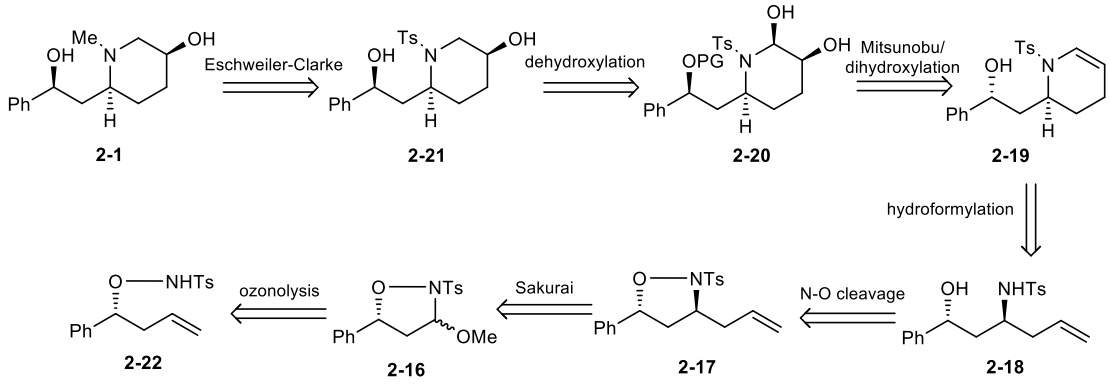
Scheme 2.2-5 Retrosynthetic strategy to (-)-5-hydroxysedamine

Overall, a simple and straightforward approach to the synthesis of (-)-5-hydroxysedamine has yet to be realised. Our objective is the development of a novel strategy (Scheme 2.2-5) that is amenable to a concise, expeditious route that also starts with cheap, readily available starting materials. In contrast to the reported syntheses of (-)-5-hydroxysedamine (**2-1**),[134-136] we envisioned the installation of the 1,3-aminoalcohol moiety prior to the construction of the piperidine framework (**2-16** to **2-17**). In addition, we have in hand, several methodologies that have been reported by our group which would enable us to accomplish the synthesis as envisaged. The first methodology will be the employment of *N,O*-heterocycle formation[141] as a useful intermediate in the stereoselective construction of 1,3-aminoalcohols. Our group has successfully applied a variation of this strategy to the synthesis of various piperidine alkaloids, including sedamine.[104, 131, 142] We will also be able to apply a second strategy that has been recently developed within the group, a tandem

hydroformylation-condensation (**2-18** to **2-19**) followed by a stereoselective dihydroxylation of enamines (**2-19** to **2-20**) as key steps in the synthesis of the piperidinol framework in (-)-5-hydroxysedamine. The tandem hydroformylation-condensation and stereoselective dihydroxylation has been implemented by our group in the synthesis of pseudoconhydrine,[129] wherein the findings will be discussed in the coming section (see Section 2.3.4.1). Herein, we discuss the results of these strategies and consequently, the success of our approach to the synthesis of (-)-5-hydroxysedamine.

2.3 Results and Discussion

2.3.1 Retrosynthetic Analysis

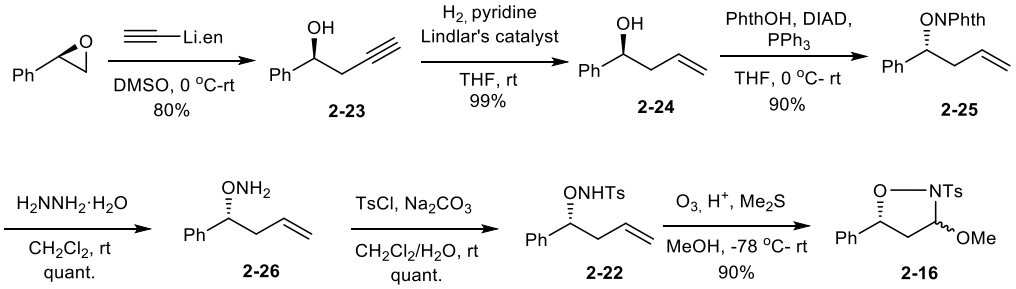


Scheme 2.3-1 Retrosynthetic analysis

Drawing from our group's successful experience of constructing pseudoconhydrine and its epimer,[129] we decided to test this method's utility towards the synthesis of **2-1** (Scheme 2.3-1). With a simple disconnection at the *N*-methyl position, **2-1** could be simplified to piperidinol **2-21**. The β-hydroxyl group in piperidinol **2-21** could be installed from a regioselective dehydroxylation of diol **2-20**, which is derived from a stereoselective dihydroxylation of enamine **2-19**. The cornerstone of the synthesis is the construction of the piperidine framework *via* a tandem hydroformylation-condensation reaction of **2-18**. This intermediate could be derived from *N,O* bond cleavage of isoxazolidine **2-17**, which in turn could be accessed from a stereoselective Sakurai reaction to 3-methoxyisoxazolidine **2-16**. This approach was predicated on the known transformation of isoxazolidines to 1,3-aminoalcohols.[104, 141, 143] A one-pot oxidative cleavage of the C=C double bond in homoallylic hydroxylamine **2-22** and spontaneous condensation of the amine carried out in methanol, would generate 3-methoxyisoxazolidine **2-16**. Hydroxylamine **2-22** could be prepared by adopting chemistry we had used to prepare analogous starting materials.[144] We chose the tosyl group as it is fairly stable under a variety of conditions. Also, the clarity of the ^{1}H-NMR spectra of the tosylates compared to the

carbamates would give us better confidence during proton assignment and structure elucidation. Thus, a concise, enantioselective strategy was conceived.

2.3.2 Synthesis of 3-methoxyisoxazolidine **2-16**



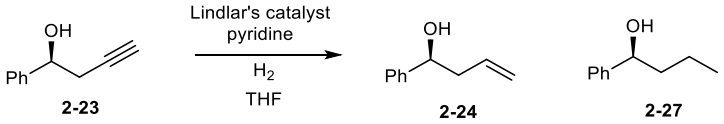
Scheme 2.3-2 Synthesis of 3-methoxyisoxazolidine 2-16

In the forward direction (Scheme 2.3-2), homoallylic alcohol **2-24** was prepared in reasonably good yield (80%) *via* a ring opening of (*R*)- styrene oxide[ii] with lithium acetylide followed by hydrogenation with Lindlar's catalyst in the presence of pyridine. While the hydrogenation was traditionally carried out with quinoline, pyridine was used, as it could be easily removed on the rotary evaporator under reduced pressure during work-up.

Initial reduction attempts of alkynol **2-23** with commercial sources of the catalyst gave inseparable mixtures of **2-24** and 'over-reduced' propyl alcohol **2-27** (Table 2.3-1). Since the role of pyridine was to further deactivate the catalyst and enhance its selectivity,[145] we were dismayed to see that not only did the reaction take a longer time (>2 h) to proceed to completion, formation of 'over-reduced' propyl alcohol **2-27** remained persistent even with increased amounts of pyridine (Table 2.3-1, Entry 3 to 6). We were finally able to resolve this issue by preparing our own batch of Lindlar's catalyst following the procedure reported by Lindlar and Dubuis.[146] Using freshly prepared catalyst in the presence of 5% w/w of pyridine, we were able to attain a clean conversion from alkynol **2-23** to the desired

[ii] (*R*)-Styrene oxide was prepared following the procedure reported in Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2002,** *124*, 1307.

homoallylic alcohol **2-24**[iii] in 99% yield. Despite taking two steps to homallylic alcohol **2-24**, this procedure proved to be superior for large-scale synthesis compared to the asymmetric allylation of benzaldehyde[147] as no purification with silica gel column chromatography was needed.



Entry	Commercial Sources of Lindlar's catalyst	Reaction Time (h)	Amount of Pyridine (% w/w)	Overall yield of **2-24**+**2-27** (%)	Ratio of **2-24**: **2-27**
1	Aldrich	2	5	99%	5:1
2	Alfa-Aesar	2	5	99%	3:1
3	Aldrich	2.5	20	95%	1:2
4	Alfa Aesar	2.5	20	97%	1:2
5	Aldrich	3.5	50	95%	1:1
6	Alfa-Aesar	3.5	50	95%	1:1

Table 2.3-1 Reduction with different sources of Lindlar's catalyst

Introduction of the hydroxylamine moiety in **2-26** was conducted *via* a Mitsunobu reaction[148] with *N*-hydroxyphthalimide as the nucleophile followed by a phthaloyl cleavage with hydrazine hydrate. Homoallylic alcohol **2-24**, in the presence of triphenylphosphine, DIAD and *N*-hydroxyphthalimide afforded *N*-phthaloyl hydroxyl amine **2-25** in excellent yield (90%). The enantiomeric excess of *N*-phthaloyl hydroxylamine **2-25** was determined to be 92% ee by chiral HPLC analysis. Cleavage of the phthaloyl group was carried out conveniently by treatment with hydrazine monohydrate at room temperature to give hydroxylamine **2-26** in quantitative yield. The free amine was subsequently reprotected as a tosylate (**2-22**) under basic conditions (Na_2CO_3) in quantitative yield.

We were able to confirm the formation of the desired tosylate by ^{1}H NMR spectroscopy (Figure 2.3-1). Appearance of signals in the aromatic range and a singlet at δ2.45 were indicative of the presence of a tosylate group. The two signals- a doublet of doublet of

[iii] Initial synthetic studies were carried out starting with racemic **2-24** which was prepared *via* a Barbier reaction with benzaldehyde and allyl bromide, using the conditions reported in Petrier, C; Luche, J.-L. *J. Org. Chem.* **1985,** *50,* 910.

triplets (ddt) at δ5.77 integrating to 1 proton (H_a) and a multiplet at δ5.00 integrating to two protons (H_b, H_c) together confirmed the presence of the terminal alkene.[iv]

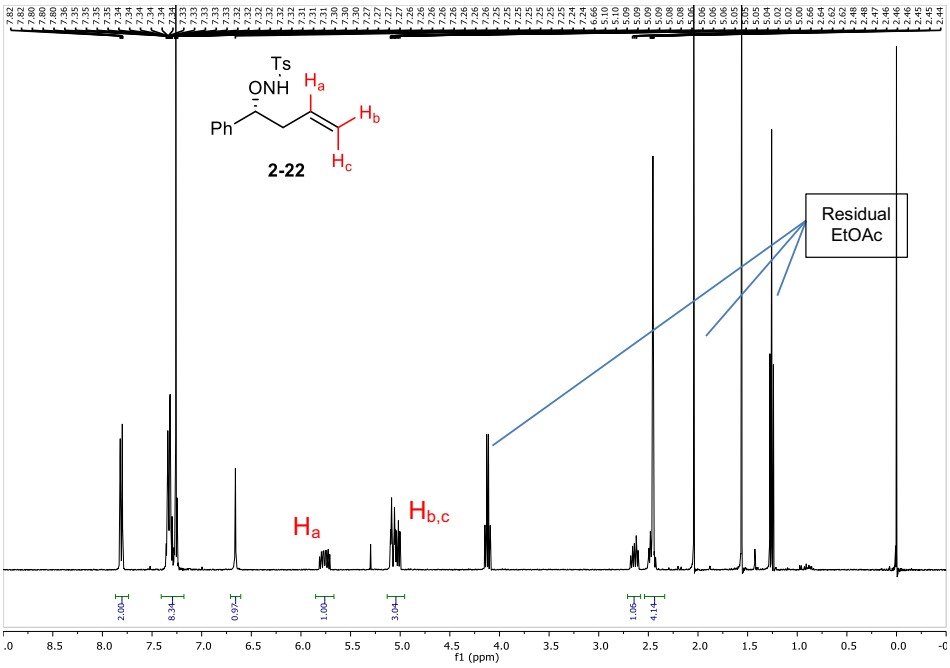


Figure 2.3-1 ^{1}H NMR spectrum of *N*-tosyl hydroxylamine 2-22

We proceeded to attempt the ozonolysis reaction with *N*-tosyl hydroxylamine **2-22** and first carried out the one-pot oxidative cleavage and formation of methoxy hemiaminal **2-16** based on a procedure reported by our group.[141] Ozonolysis of hydroxylamine **2-22** was carried out in MeOH in the presence of Amberlyst A-15. However, after Me_2S work-up, this afforded us a mixture of products, 3-methoxyisoxazolidine **2-16** (72% yield) and its 3-hydroxy counterpart (29% yield). The problem was rectified by using a homogeneous acid, TsOH, to give a clean conversion to 3-methoxyisoxazolidine **2-24** as an inconsequential 3:2 diastereomeric mixture. This may be attributed to the lower activity of heterogeneous Amberlyst A-15 in comparison to homogeneous TsOH. Formation of the 3-methoxyisoxazolidine as a mixture of isomers was confirmed by ^{1}H NMR analysis (Figure 2.3-2). Singlets at δ3.55 and δ3.54 indicated the presence of the methoxy groups while two pairs of signals (δ5.3 to δ5.7 range) corresponding to the hemiaminal proton ($H_{b/b'}$) and the

[iv] Solvent impurities were removed from all compounds prior to determination of reaction yield.

benzylic isoxazolidine proton ($H_{a/a'}$) each integrated to a ratio corresponding to approximately 3:2. With a route to isoxazolidine **2-16** secured, we initiated studies on the subsequent steps- diastereoselective allylation of the 3-methoxy derivative to form 3-allylic isoxazolidine **2-17** (i.e. Sakurai reaction) and effectively set the relative stereochemistry of the 1,3-aminoalcohol motif.

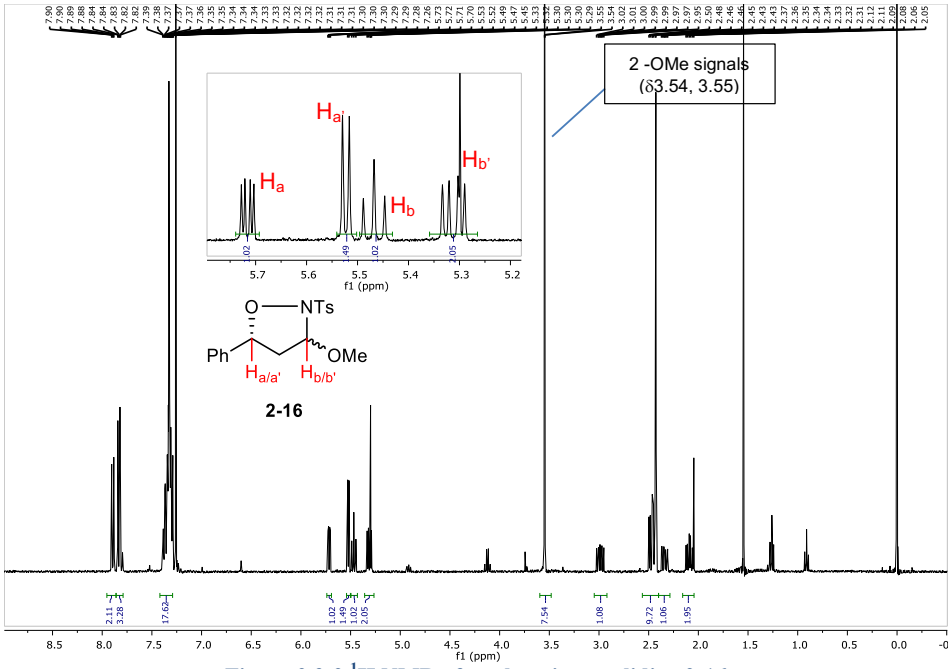
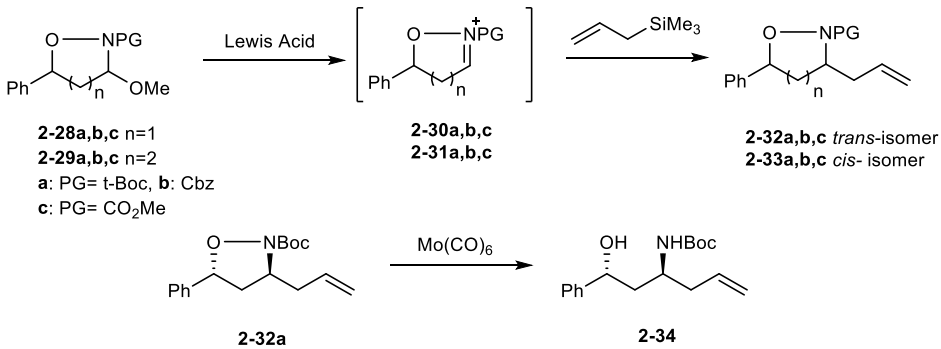


Figure 2.3-2 ^{1}H NMR of methoxyisoxazolidine 2-16

2.3.3 Installation of the 1,3-aminoalcohol motif *via* Sakurai reaction

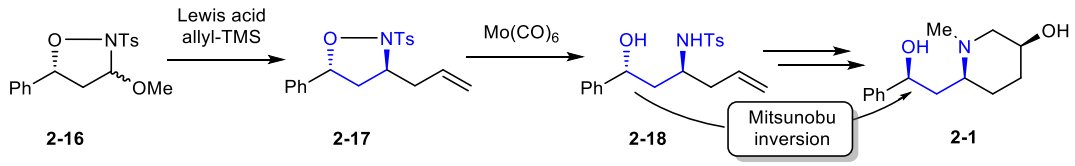


Scheme 2.3-3 Stereoselective allylation of *N,O*-heterocycles

Earlier, our group had developed a method for stereoselective allylation of 5- and 6-membered *N,O*-heterocycles (Scheme 2.3-3).[141] With $BF_3{\cdot}Et_2O$ as the Lewis acid, it was found that allylation of 5- membered isoxazolidines (**2-28a** to **c**) led to the formation of the *trans*-allylated isoxazolidines (**2-32a** to **c**) *via* iminium species **2-30a** to **c**. On the other

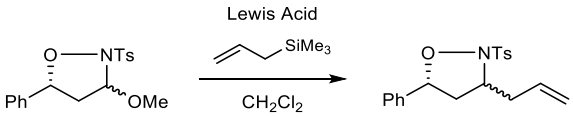
hand, allylation of 6-membered tetrahydro-1,2-oxazines (**2-29a** to **c**) led to the formation of the *cis*-allylated oxazine (**2-33a** to **c**) *via* iminium species **2-31a** to **c**. Cleavage of the *N,O* bond of the allyl isoxazolidine **2-32a** with $Mo(CO)_6$ would then reveal *anti*-1,3-aminoalcohol **2-34**. The relative configuration of the amino alcohol was confirmed by X-ray crystallographic analysis.

While the structure of (-)-5-hydroxysedamine (**2-1**) bears a *syn*-1,3-amino alcohol (Scheme 2.3-4), we were still keen to implement the above strategy to the synthesis of the natural product. Through the allylation reaction with methoxyisoxazolidine **2-16**, we would gain access to *trans*-isoxazolidine **2-17** stereoselectively, following which, cleavage of the *N,O* bond would give the *anti*-1,3-aminoalcohol. The stereochemistry of the hydroxyl group could be inverted with a Mitsunobu reaction at a later stage of the synthesis.



Scheme 2.3-4 Installation of 1,3-aminoalcohol motif in (-)-5-hydroxysedamine

2.3.3.1 *Optimisation of Sakurai reaction conditions*



Entry	Lewis Acid	Amount of allyl-TMS (equiv.)	Temperature (°C)	Reaction Time (h)	Overall yield of **2-17**+**2-35** (%)[c]	Ratio[d] of **2-17**: **2-35**
1[a]	1.2 equiv. $SnCl_4$	2.0	-78	>72 h	35	8.5:1
2[a]	1.2 equiv. $SnCl_4$	2.0	-78 to -40	48 h	40	7.2:1
3[a]	1.2 equiv. $BF_3{\cdot}Et_2O$	2.0	-78 to -40	18 h	50	7.6:1
4[a]	1.5 equiv. $BF_3{\cdot}Et_2O$	3.0	-78 to -40	18 h	63	7.5:1
5[a]	2.0 equiv. $BF_3{\cdot}Et_2O$	3.0	-78 to rt	5 h	72	8.0:1
6[b]	2.0 equiv. $BF_3{\cdot}Et_2O$	3.0	-78 to rt	5 h	68	7.5:1

[a] Reaction was carried out with the racemate [b] Reaction was carried out with the optically active form [c] Isolated yields [d] Determined by isolated yield

Table 2.3-2 Optimisation of Sakurai reaction conditions

Due to the initial unavailability of $BF_3{\cdot}Et_2O$, preliminary studies on the Sakurai reaction were carried out with 1.0 M $SnCl_4$ in dichloromethane. Isoxazolidine **2-16** was first subjected to conditions (Entry 1, Table 2.3-2) reported by our group.[141] However, the

reaction proved to be sluggish and required long reaction times (> 72 h). Allylation of isoxazolidine **2-16** with 1.0 M $SnCl_4$ at a higher temperature showed improvement in yields as well as accelerated reaction times. The allylation reaction generated **2-17** as a mixture of diastereomers with *cis* to *trans* ratios ranging between 1:7 and 1:8.

We then decided to attempt the reaction with $BF_3 \cdot Et_2O$ and were pleased to see slightly improved yields at -40 °C. Modifying the reaction stoichiometry and gradually warming the reaction from -78 °C to room temperature instead of leaving it to stir at a constant low temperature turned out to be necessary to coax this process into giving good yields consistently on a multigram scale.

We postulated that the electron withdrawing tosyl group, in comparison to the carbamate, has a stronger destabilizing effect on the iminium ion precursor which is formed in the rate-determining step. At higher temperatures, the increase in energy drove the formation of the iminium ion precursor, leading to higher yields. In addition, the shorter reaction span needed with higher temperatures, possibly boosted yields by circumventing product decomposition. Interestingly, the ratio of the *cis* to *trans* isomer remained relatively consistent. Addition occurred on the less hindered side of the iminium ion. The stereochemistry of the major isomer was confirmed by X-ray crystallography of racemate **2-17** (Figure 2.3-3). We were satisfied with the results of the allylation reaction and sought to continue the synthesis.

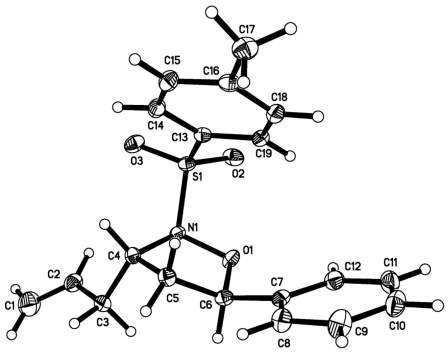
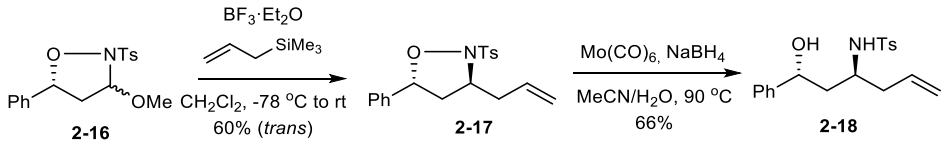


Figure 2.3-3 X-ray crystal structure of (±)-2-17

2.3.3.2 *Reductive cleavage of the N,O bond in isoxazolidine* **2-17**



Scheme 2.3-5 Synthesis of 1,3-aminoalcohol 2-18

There have been various reported procedures for the reductive cleavage of isoxazolidines. These procedures include hydrogenation with Raney-Ni[149] or Pd,[150] reduction with Zn in AcOH[151] or $LiAlH_4$.[152] Hydrogenation reactions are incompatible due to the presence of the alkene in **2-17**. Reduction with zinc on the other hand, proved to only work with unprotected amines. The rest of the procedures are rather harsh and may cause unwanted side reactions. Cicchi[143a] originally reported a mild procedure to reduce the *N,O* bond with $Mo(CO)_6$ in wet acetonitrile under reflux conditions. Miller and co-workers[143b] built on this and found that addition of $NaBH_4$ simplified the work-up of this reaction hence, improving yields of the isolated product. We were able to achieve a clean reduction of **2-17** with $Mo(CO)_6$ in the presence of $NaBH_4$, to give the *anti*-1,3-aminoalcohol **2-18** with a yield of 66% (Scheme 2.3-5). Cleavage of *N,O* bond in isoxazolidine **2-17** to form 1,3-aminoalcohol **2-18** was confirmed by NMR spectroscopic data. Comparison of ^{13}C spectra of isoxazolidine **2-17** and 1,3-aminoalcohol **2-18** (Figure 2.3-4) indicated a clear upfield shift of the signals corresponding to the carbons attached to the oxygen (δ82.9 to δ70.0) and the nitrogen (δ61.1 to δ50.5). This indicated a change in the electronegativity in the atoms attached to the carbons where the oxygen and nitrogen have been reduced following cleavage of the *N,O* bond.

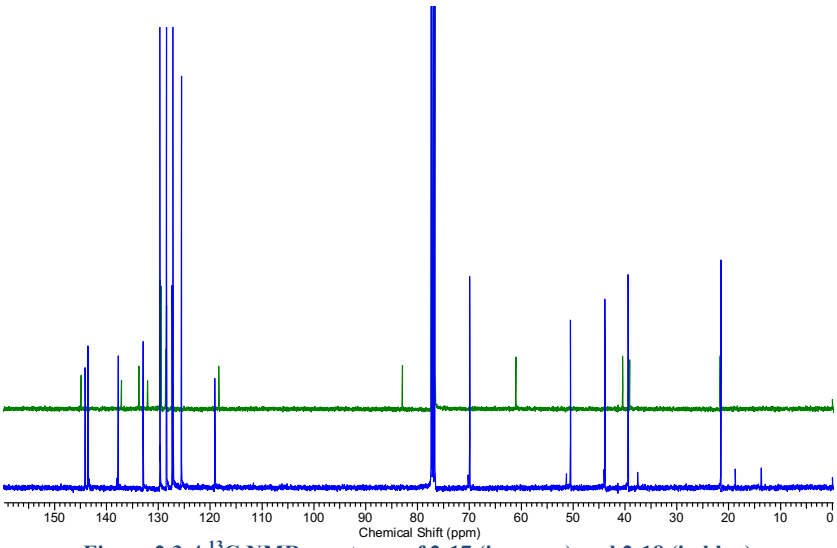
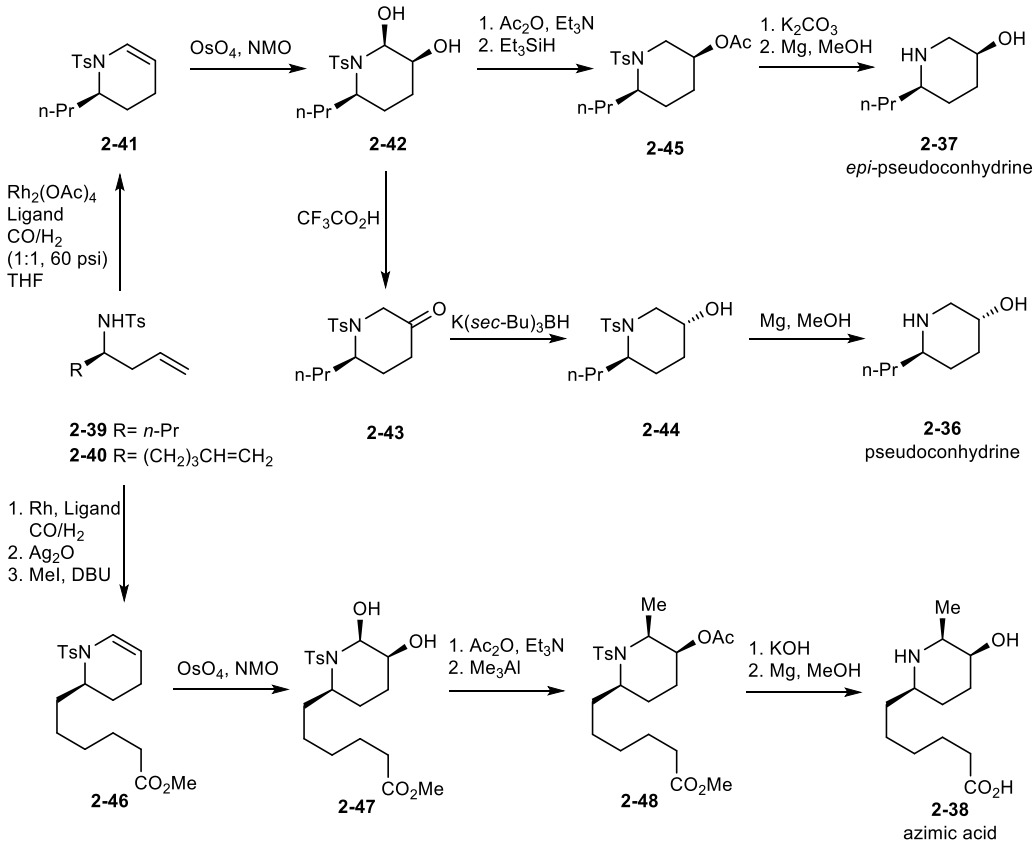


Figure 2.3-4 ^{13}C NMR spectrum of 2-17 (in green) and 2-18 (in blue)

Due to the toxic nature of $Mo(CO)_6$, we also sought to find a more environmental-friendly reducing agent. We became interested in investigating titanium(III) chloride as a 'greener' alternative. The formation of non-toxic by-products (NH_4Cl and TiO_2) rendered this reagent attractive. Furthermore, titanium trichloride ($TiCl_3$) was able to reduce nitrosamines to amines[153] hence, by extension, we postulated that the reduction of the *N,O* bond in isoxazolidines could occur in a similar manner. We proceeded to attempt the *N,O* cleavage reaction in the presence of $TiCl_3$ under various acidic and basic conditions. As we experienced no success in cleaving the *N,O* bond under these conditions, we decided to return to our original protocol for *N,O* bond cleavage with $Mo(CO)_6$. With the 1,3-aminoalcohol in hand, we initiated our investigation on hydroformylation conditions towards **2-19**.

2.3.4 Installation of the 2,5-*cis* substitution motif *via* hydroformylation

2.3.4.1 Synthesis of pseudoconhydrine, its epimer and azimic acid



Scheme 2.3-6 Synthesis of pseudoconhydrine, its epimer and azimic acid

Hydroformylation is a reaction that in essence, generates aldehydes from alkenes and has been historically used in the synthesis of bulk chemicals. In recent years however, it has garnered greater traction from academic groups for the synthesis of complex natural products. The key advantage of employing hydroformylation is that it offers an atom efficient access to aldehydes often under neutral conditions. The reaction is highly chemoselective and is tolerant to other functional groups. The starting materials of hydroformylation reactions, alkenes, are fairly robust and could be carried through many standard synthetic transformations without protection.

Our group has successfully incorporated tandem hydroformylation-condensation as the key step to form several natural products; pseudoconhydrine (**2-36**), its epimer (**2-37**) as well as azimic acid (**2-38**) starting from tosyl-protected amines **2-39** or **2-40** (Scheme 2.3-6).

The alkenes underwent a hydroformylation-condensation reaction to form a cyclic enamine. In the case of pseudoconhydrine and its epimer, an Upjohn dihydroxylation reaction was carried out across the double bond in enamine **2-41** to give diol **2-42** with an all-*cis* stereochemistry as the major isomer, with a ratio of 7:1. The experimental result corroborated with DFT calculations which predicted a *cis*/*trans* ratio of 6:1 at room temperature. The transition state of the all-*cis* product featured a Gibbs free energy of activation of 57.0 kJ mol^{-1}. This was lower than the transition state of the *trans*-propyl product (61.4 kJ mol^{-1}). The transition state of the all-*cis* product showed the osmium tetroxide moiety interacting with the tosyl group as shown below. The following reasons were put forward to explain the calculated transition state. Electrostatic attraction directed the partially positive tolyl group towards the negatively polarised oxygen atoms on osmium while electrostatic repulsion between the latter and the sulfonyl oxygens directed the sulfonyl fragment away from the osmium tetroxide moiety. Another factor present was hydrophobic interactions, driven by a combined influence of repulsion from water molecules and attraction between the two lipophilic groups, the pseudo axial propyl group and the tolyl group. To sum it up, the above factors led to a lower-energy all-*cis* transiton state which favoured the formation of the desired all-*cis* isomer as the major product.

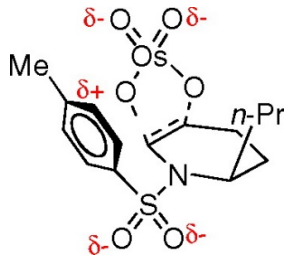
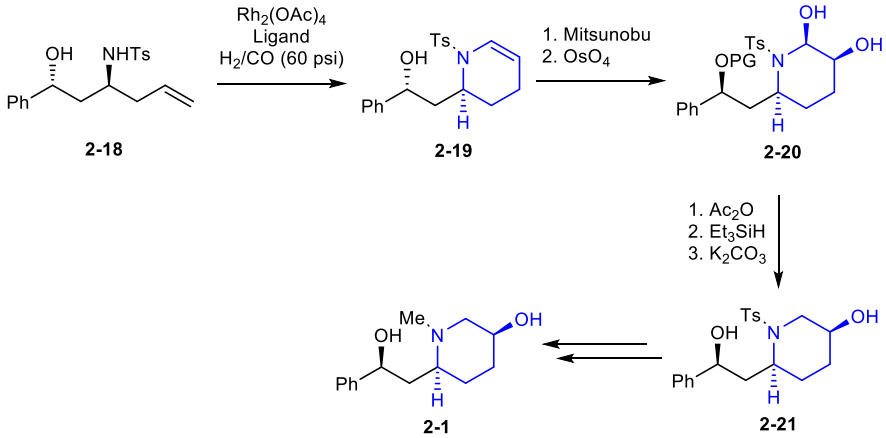


Figure 2.3-5 Proposed transition state of the dihydroxylation reaction

Subsequent treatment of **2-42** with trifluoroacetic acid led to ketopiperidine **2-43** following which, reduction with K-Selectride® gave 2,5-*trans* isomer **2-44** which was subsequently transformed to pseudoconhydrine (**2-36**). The 2,5-*cis* isomer was stereoselectively generated *via* a regioselective dehydroxylation of the acetate derivative of diol **2-42** to give **2-45**. Subsequent deprotection steps led to the formation of *epi*-pseudoconhydrine (**2-37**).

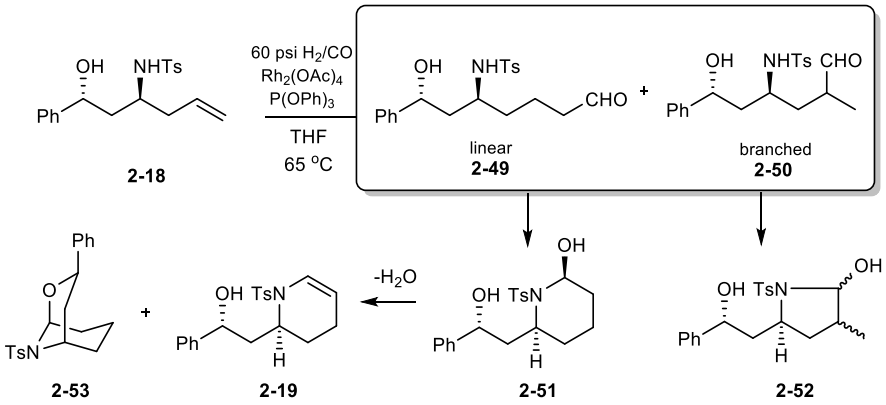
In the case of azimic acid (**2-38**), the terminal aldehyde formed after hydroformylation was subsequently converted to methyl ester **2-46**. Drawing parallels with the synthetic route to *epi*-pseudoconhydrine, dihydroxylation led to formation of diol **2-47** which was protected as a diacetate and subsequently methylated to give the all-*cis* product **2-48**. Further transformations led to the desired natural product.

Like *epi*-pseudoconhydrine and azimic acid, (-)-5-hydroxysedamine also contains a 2-substituent, 5-hydroxy *cis* substitution motif on the piperidine. We hypothesised that it would be fitting to adopt a similar strategy to derive the natural product. Since the method favoured the formation of the 2,5-*cis* isomer, it would be superior to the strategies found in previous reports to (-)-5-hydroxysedamine (see Section 2.2.1) wherein the *cis* isomer was the disfavoured product. As described earlier in our retrosynthetic strategy (see Section 2.3.1), we hypothesised that the hydroxypiperidine motif in (-)-5-hydroxysedamine (Scheme 2.3-7) would be derived from **2-21**. This was constructed *via* intermediate **2-20** which arose from a dihydroxylation of cyclic enamine **2-19**, synthesised from hydroformylation of 1,3-aminoalcohol **2-18**.



Scheme 2.3-7 Installation of 2,5-*cis* substitution motif

2.3.4.2 *Hydroformylation of 1,3-aminoalcohol* ***2-18***



Scheme 2.3-8 Tandem hydroformylation-condensation reaction of 2-18

Hydroformylation of alkene **2-18** was first carried out using $Rh_2(OAc)_4$ (1 mol%) in THF under a mixture of CO and H_2 (30 psi of each gas) with triphenyl phosphite as the ligand. The reaction mixture was heated to 65 °C and left to stir for 22 hours. Hydroformylation of alkene **2-18** faces two competitive pathways which would form either the linear isomer **2-49** or the branched isomer **2-50**. The linear isomer **2-49** led to the formation of the 6-membered hemiaminal **2-51**, following which, elimination of water gave desired cyclic enamine **2-19**. A competing pathway is the formation of the branched isomer **2-50**. This led to the 5-membered product **2-52**, which was isolated as mixtures of isomers.

We were able to isolate cleanly both products, hemiaminal **2-51** and **2-19**, the structures of which were confirmed by ^{1}H NMR spectroscopy. Side by side comparisons of the two spectra proved useful for structural confirmation. While most of the diagnostic signals appeared within the same region, a key difference was noted with respect to proton H_a. In hemiaminal **2-51** (Figure 2.3-6), proton H_a appeared as a broad singlet at δ5.56 while in enamine **2-19** (Figure 2.3-7), proton H_a appeared as a doublet further downfield at δ6.66. This shift corresponded to the structural difference between a hemiaminal and an enamine. Another observation would be the appearance of a signal at δ5.12 which corresponded to alkene proton H_b in cyclic enamine **2-19**.

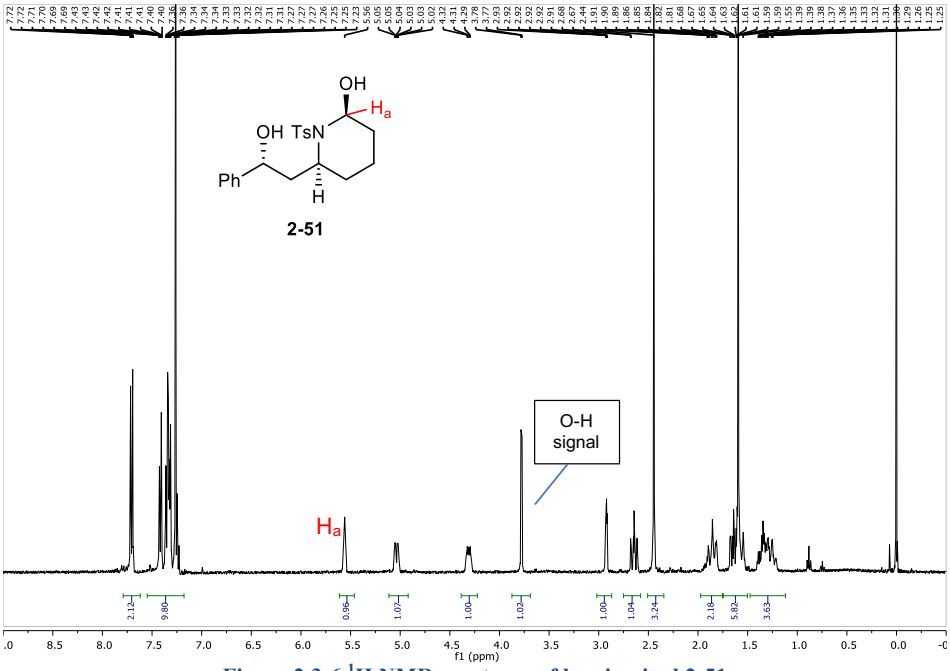


Figure 2.3-6 ^{1}H NMR spectrum of hemiaminal 2-51

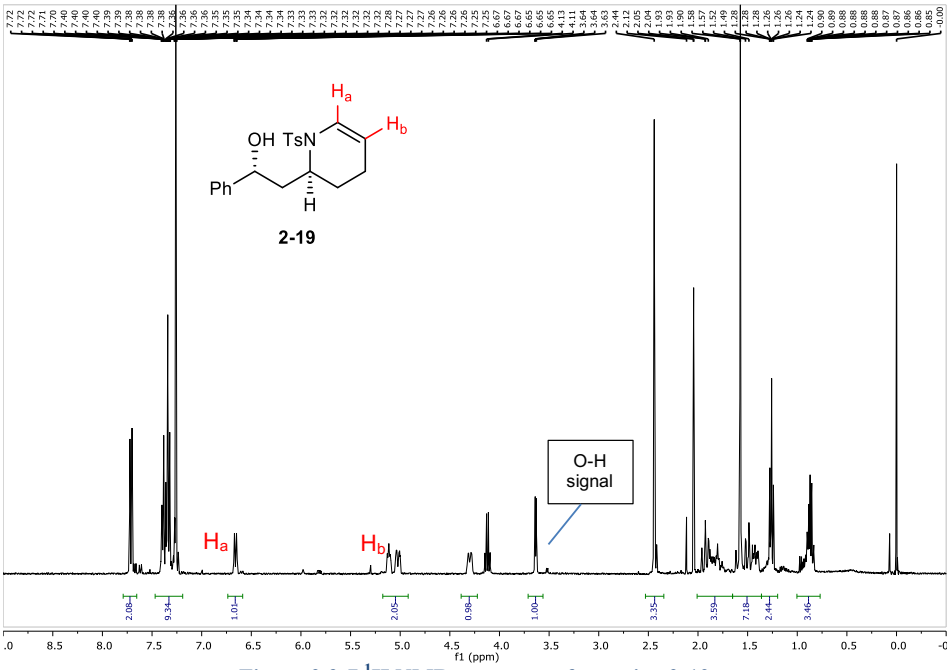


Figure 2.3-7 ^{1}H NMR spectrum of enamine 2-19

Interestingly, another side product isolated from silica chromatography was assigned a structure of bicyclic aminal **2-53** based on ^{1}H NMR analysis. A broad singlet at δ5.74, similar to H_a in **2-51** was highly indicative of the presence of a hemiaminal. The O-H signal, which was present in the spectra of **2-19** and **2-51**, was not observed. Also, the rest of the signals were very similar to **2-51** with the exception of the aromatic region, which has visibly changed indicating that the phenyl group was in a different magnetic environment.

In addition, we were able to isolate an X-ray crystal of **2-53**, hence confirming the structure of the side product. Having identified the various products formed during the reaction, we proceeded to carry out optimisation work to improve the yields for the formation of the desired ene-sulfonamide **2-19**.

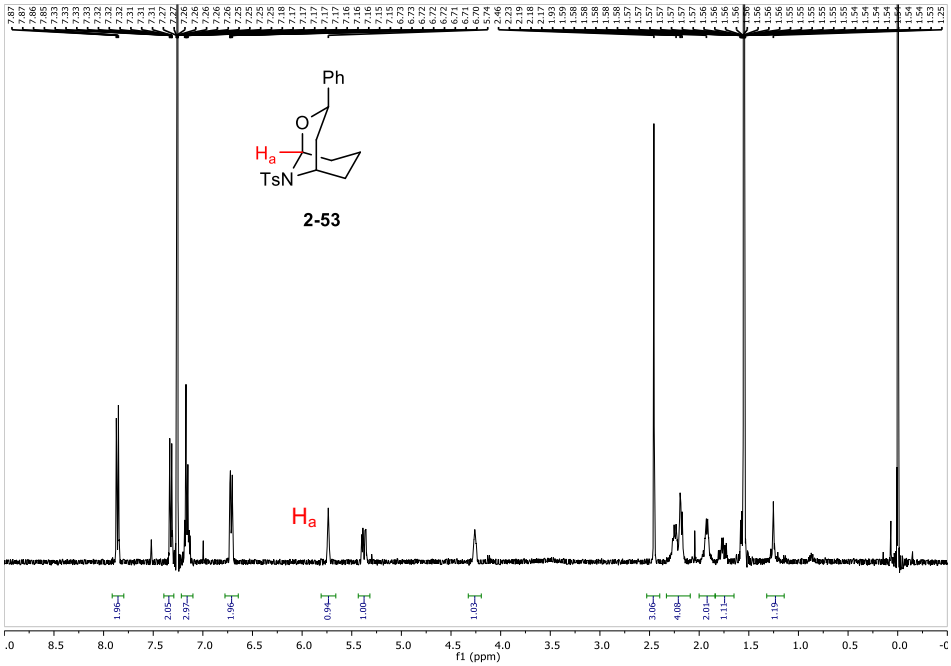


Figure 2.3-8 1H NMR spectrum of bicyclic aminal 2-53

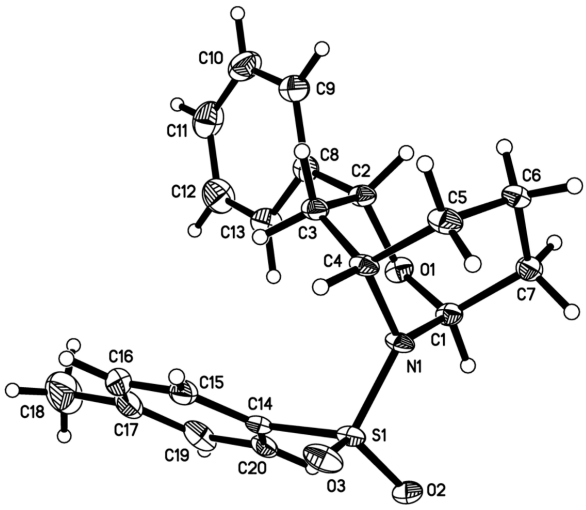
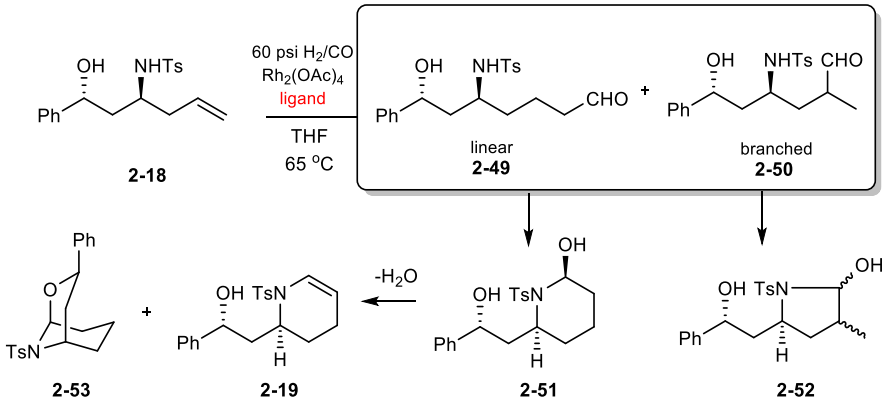


Figure 2.3-9 X-ray crystal structure of bicyclic aminal 2-53

2.3.4.3 *Optimisation of hydroformylation reaction conditions*



Entry	Ligand	Ligand to metal ratio	Yield[b] of **2-19** (%)	Yield[b] of **2-53** (%)	Yield[b] of **2-51** (%)	Yield[b] of **2-52** (%)
1[a]	$P(OPh)_3$	3:1	2	0	35	29
2[a]	$P(OPh)_3$	10:1	19	0	27	18
3[a]	$P(OPh)_3$	20:1	48	18	0	23
4[a]	BIPHEPHOS	1:1	75	12	0	0

[a] Reaction was carried out with racemic material [b] Isolated yields

Table 2.3-3 Hydroformylation reaction with varying ligands

With increased loadings of triphenyl phosphite, while keeping all the other variables constant (Entry 1 to 3, Table 2.3-3), we observed formation of greater amounts of the desired linear ene-sulfonamide **2-19** with yields varying between 2% and 48% and suppressed the formation of five-membered branch isomer **2-52**. We also observed that higher ligand to metal ratios drove the formation of ene-sulfonamide **2-19** from *N,O*-acetal **2-51**. Unfortunately, we also observed formation of bicyclic aminal **2-53** with higher loadings of triphenyl phosphite.

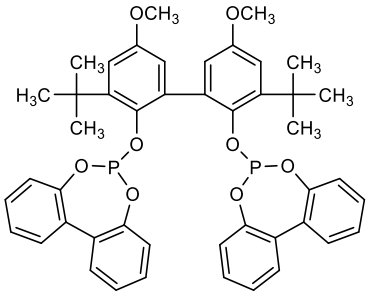
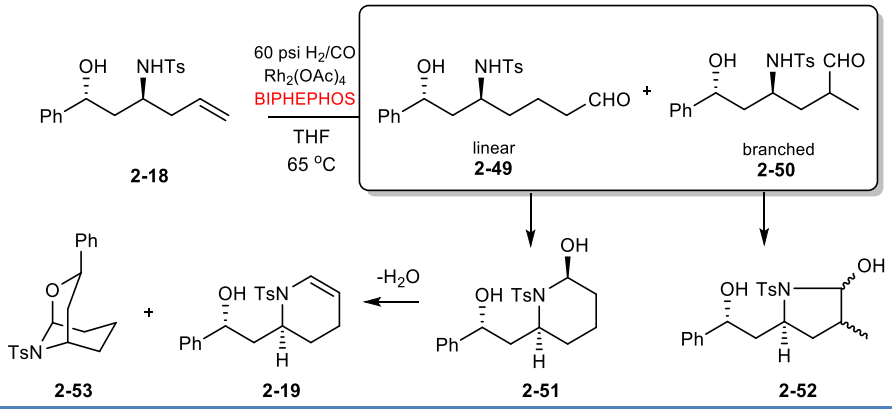


Figure 2.3-10 Structure of BIPHEPHOS

We first sought to limit the formation of the branched isomer through the use the use of a bulkier ligand, BIPHEPHOS[154] (Entry 4, Table 2.3-3). BIPHEPHOS (Figure 2.3-10) has been used as a ligand for the hydroformylation of propene on industrial scale to give the highest linear to branched ratio (n: iso) of product. This gave us 100% selectivity for the

linear isomer as well as formation of the ene-sulfonamide with reasonable yield (75%) albeit with only one other side product, bicyclic aminal **2-53** (12% yield). Presence of the linear ene-sulfonamide precursor, *N,O*-acetal **2-51** was not detected even with low metal to ligand ratios for BIPHEPHOS. Pleased with the results obtained with BIPHEPHOS, we chose to adopt the same conditions towards the synthesis of the optically active form of the natural product.

2.3.4.4 Reproducibility of results with optimised hydroformylation conditions



Entry	Commercial Sources of BIPHEPHOS	Lot No.	Yield[c] of **2-19** (%)	Yield[c] of **2-53** (%)	Yield[c] of **2-51** (%)	Yield[c] of **2-52** (%)
1[a]	STREM	20660000	5	7	45	11
2[b]	STREM	20660000	8	6	44	18
3[a]	Aldrich	MKBP2384V	10	12	43	18
4[b]	Aldrich	MKBP2384V	12	10	47	20
5[a]	STREM	229272500	6	8	42	20
6[b]	STREM	229272500	6	7	44	18

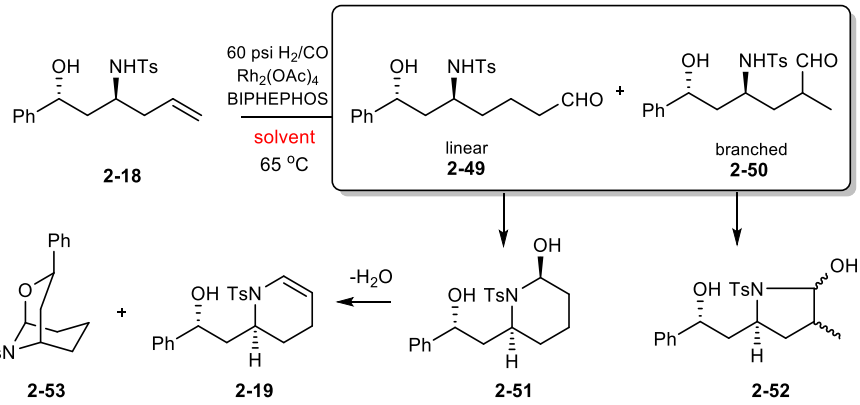
[a] Reaction was carried out with racemic material [b] Reaction was carried out with optically active material
[c] Isolated yields

Table 2.3-4 Hydroformylation reaction with different sources of BIPHEPHOS

Unfortunately, while performing the hydroformylation reaction on optically active material, we were unable to replicate the earlier results obtained while using a brand new bottle of BIPHEPHOS from STREM. We were dismayed to observe the formation of **2-51** as the major product instead of the desired ene-sulfonamide **2-19**. We then carried out the reaction, keeping all parameters constant except with a second brand new bottle of BIPHEPHOS from Aldrich and STREM, with both racemic and optically active material to check for anomalous results. From the catalyst screening we carried out (Table 2.3-4), we found that it further corroborated our latest results and confirmed that our original yields

were indeed an aberration and no longer reproducible. Unfortunately, we were unable to carry out further investigation to the cause of the change in yields since there was no more catalyst left in the old bottle of catalyst.

Unperturbed by our findings, we sought to investigate if a change in solvent would favour the formation of ene-sulfonamide **2-19**. We carried out the hydroformylation reaction with BIPHEPHOS and $Rh_2(OAc)_4$ in toluene (Table 2.3-5) and were pleasantly surprised to find that dehydration of hemiaminal **2-51** proceeded to completion to give a mixture of the bicyclic acetal and ene-sulfonamide **2-19**. However, the yield of ene-sulfonamide **2-19** was rather sub-obtimal (45 to 55% isolated yield) with a significant amount of bicyclic acetal produced. We chose to circumvent this problem by carrying out the hydroformylation reaction with a protecting group on the secondary alcohol to inhibit the formation of bicyclic aminal **2-53**.

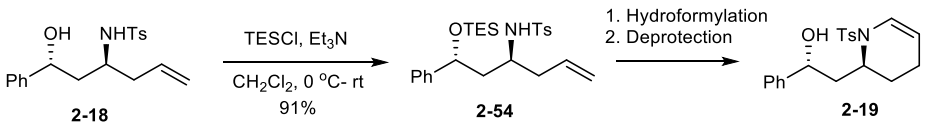


Entry	Source of BIPHEPHOS	Solvent	Yield[b] of **2-19** (%)	Yield[b] of **2-53** (%)	Yield[b] of **2-51** (%)	Yield[b] of **2-52** (%)
1[a]	STREM	THF	5	7	45	11
2[a]	STREM	Toluene	46	35	0	0
3[b]	STREM	THF	6	7	44	18
4[b]	STREM	Toluene	55	27	0	0

[a] Reaction was carried out with optically active material [b] Racemic material

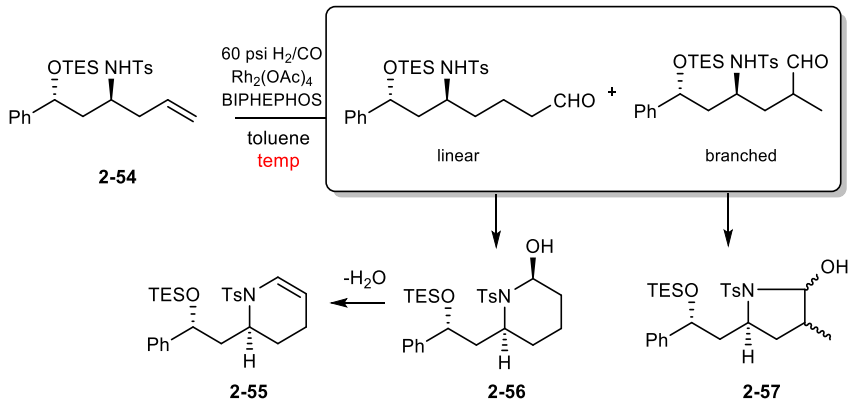
Table 2.3-5 Hydroformylation conditions with varying solvents

2.3.4.4.1 Silyl-protection of β-substituted secondary alcohol



Scheme 2.3-9 Protection of secondary alcohol with TES group

In our initial studies, we carried out protection of secondary alcohol **2-18** with the ubiquitous TBS group. However, steric hindrance around the secondary alcohol precluded the completion of the reaction with the bulky TBS group. Since the TMS group is known to be highly labile in the presence of an acid or a base,[155] protection of the secondary alcohol with a TES group proved to be the most viable strategy (Scheme 2.3-9). *O*-Triethylsilyl alcohol **2-54** was formed in excellent yield (91%) from 1,3-aminoalcohol **2-18** in the presence of triethylamine. With the protected alcohol in hand, we proceeded to perform the hydroformylation.

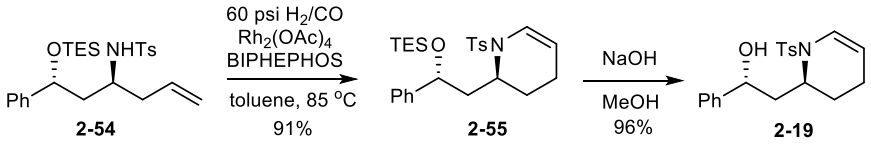


Entry	Catalyst	Ligand	Temperature (°C)	Yield[b] of **2-55** (%)	Yield[b] of **2-56** (%)	Yield[b] of **2-57** (%)
1[a]	$Rh_2(OAc)_4$	BIPHEPHOS	65	30	58	0
2[a]	$Rh_2(OAc)_4$	BIPHEPHOS	85	91	0	0

[a] Reaction was carried out with optically active material [b] Isolated yields

Table 2.3-6 Hydroformylation of silyl protected alcohol 2-43

Hydroformylation of *O*-silyl protected alcohol **2-54** (Table 2.3-6) was initially carried out under the optimised conditions in toluene with the free secondary alcohol **2-18**. The reaction was carried out with BIPHEPHOS and $Rh_2(OAc)_4$ at 65 °C with 60 psi H_2/CO and left to stir for 22 hours. The reaction proceeded smoothly to give the desired ene-sulfonamide **2-55** in 30% yield albeit mostly as hemiaminal **2-56** (58% yield). Encouraged by the results we carried out the reaction at a higher temperature (85 °C) and found clean conversion to the desired ene-sulfonamide **2-55** with 91% yield. Formation of five-membered ring product, **2-57**, was not observed.



Scheme 2.3-10 Formation of enamine 2-19 from TES-protected alcohol 2-54

Deprotection of the alcohol could not be carried out under acidic conditions since we anticipated that it would promote cyclisation to undesired bicyclic aminal **2-53**. *O*-silyl alcohol **2-55** was treated with NaOH in MeOH to give free alcohol **2-19** in 96 % yield with an overall yield of 79% over the 3 steps (Scheme 2.3-10). This was significantly higher than the 55% yield obtained while carrying out the hydroformylation with unprotected secondary alcohol **2-18**. While protecting groups typically should be avoided in total synthesis, its use in this case is justified since the overall yield over the 3 steps is higher than that obtained without the use of protecting groups.

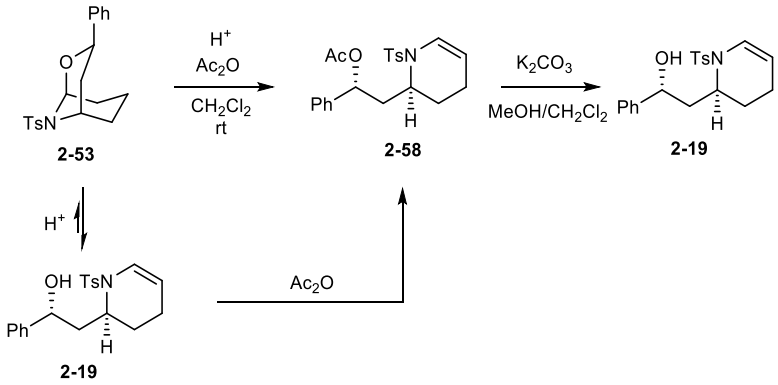
2.3.4.5 Preliminary mechanistic studies on the dehydration pathway

We proposed two mechanistic explanations for the formation of the ene-sulfonamide from *N,O*-acetal **2-51**, that the dehydration is caused by either $P(OPh)_3$ or the acetate. Since higher loadings of the $P(OPh)_3$ drove the dehydyration of hemiaminal **2-51**, we initially proposed a $P(OPh)_3$-mediated dehydration. We tested this hypothesis by carrying out a preliminary reaction of **2-51** with $P(OPh)_3$ at 65 °C and at atmospheric pressure. Unfortunately, the results were inconclusive. We obtained an inseparable mixture of products which precluded its identification.

We were also interested in testing whether the acetic acid formed from the acetate ligand in $Rh_2(OAc)_4$ was responsible for the dehydration of heminaminal **2-51**. We designed a negative control experiment with $Rh(CO)_2(acac)$ as the metal catalyst and BIPHEPHOS as the ligand. Dehydration of hemiaminal **2-51** was not inhibited, as proven by the formation of ene-sulfonamide **2-19**. Contrary to our hypothesis, we observed an increase in the formation of the bicyclic aminal **2-53**.

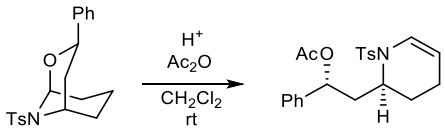
Gratifyingly, dehydration of hemiaminal **2-51** proceeded smoothly to give a mixture of the bicyclic acetal and ene-sulfonamide **2-19** after being resubjected through the optimised hydroformylation conditions.[v] Based on the results in hand, we came to a conclusion that there may be a complex synergistic effect between the various factors which causes the dehydration of hemiaminal **2-51**.

*2.3.4.6 Conversion of bicyclic aminal **2-53** to ene-sulfonamide **2-19***



Scheme 2.3-11 Trapping alcohol 2-19 as acetate 2-56

We were also interested in investigating the possibility of converting bicyclic aminal **2-53** to ene-sulfonamide **2-19**. In the presence of an acid, the formation of the two compounds was in equilibrium with each other. We speculated that, by trapping the secondary alcohol of the ring opened product as an acetate, we would be able to gradually 'shift' the equilibrium to the ring-opened form, ene-sulfonamide **2-19** (Scheme 2.3-11).



Entry[a]	Acid	Yield of **2-58** (%)
1	Amberlyst A-15	70[b]
2	$BiCl_3$	Partial conversion observed by TLC, product not isolated.
3	$La(OTf)_3$	Formation of **2-56** not observed by TLC
4	$Yb(OTf)_3$	
5	$Sc(OTf)_3$	
6	$Y(OTf)_3$	
7	$Nd(OTf)_3$	
8	$In(OTf)_3$	

[a] Reaction was carried out with optically active material [b] Isolated yields

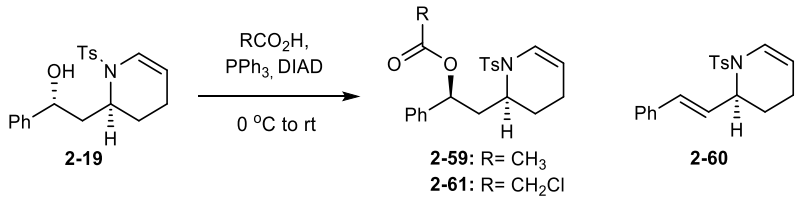
Table 2.3-7 Ring opening of bicyclic aminal 2-53

[v] Reaction was subjected to 60 psi H_2/CO, 1 mol% $Rh_2(OAc)_4$ and 1 mol% BIPHEPHOS in toluene at 65 °C for 22 hours.

We screened several Lewis acids as well as an ion exchange resin, Amberlyst A-15. Formation of the acetate was observed with Amberlyst A-15 and $BiCl_3$, but worked best with Amberlyst A-15 to furnish acetate **2-58** in 70% yield. Methanolysis with K_2CO_3 at room temperature yielded ene-sulfonamide **2-19** in quantitative yield.

2.3.5 Synthesis of (-)-5-hydroxysedamine

*2.3.5.1 Mitsunobu inversion of benzylic alcohol **2-19***



2-19 **2-59:** R= CH_3 **2-61:** R= CH_2Cl **2-60**

Entry	Nucleophile	Solvent	Yield[c] of **2-59**/**2-61** (%)	Yield[c] of **2-60** (%)	Recovered **2-19**, Yield[c] (%)
1[a]	CH_3CO_2H	THF	37	30	Yes, 16%
2[a]	$ClCH_2CO_2H$	THF	50	31	No
3[a]	$ClCH_2CO_2H$	Toluene	82	18	No
4[b]	$ClCH_2CO_2H$	Toluene	70	17	No

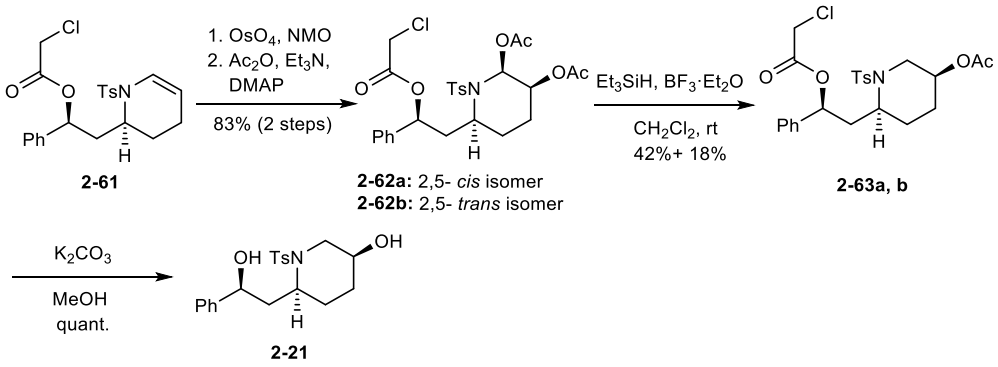
[a] Reaction was carried out with the racemate [b] Reaction was carried out with the optically active form
[c] Isolated yield

Table 2.3-8 Mitsunobu reaction conditions with varying nucleophile

With ene-sulfonamide **2-19** in hand, we attempted the Mitsunobu reaction[148](Table 2.3-8) with acetic acid as the nucleophile. The reaction was sluggish with some **2-19** recovered. The desired product **2-59** was isolated in an almost 1:1 ratio with the eliminated product **2-60**. Based on Bessodes's work[156] with carrying out the Mitsunobu reaction on sterically hindered secondary alcohols, we carried out an investigation of different nucleophiles with varying pK_a. The optimum condition was with chloroacetic acid (pK_a = 2.86) as the nucleophile[vi] with the reaction being carried out in toluene. This gave us chloroacetate ester **2-61** with the desired *cis*-1,3-aminoalcohol motif in 80% yield.

[vi] We found that acids (i.e. dichloroacetic acid and trichloroacetic acid) with lower pK_a values led to decomposition of starting material.

2.3.5.2 *Formation of hydroxypiperidine* ***2-21***



Scheme 2.3-12 Synthesis of hydroxypiperidine 2-21

As discussed earlier in the synthesis of *epi*-pseudoconhydrine (Section 2.3.4.1), we had shown that dihydroxylation of the alkene under the modified Upjohn condition[157] would occur in a stereoselective manner to give us the *cis* isomer as the major product. Similarly, dihydroxylation of **2-61** gave the diols as inseparable isomers. The major isomer assigned as the *cis* product based on previous work. The diol mixture was immediately converted to diacetate **2-62** with a yield of 83% over the two steps (Scheme 2.3-12). The ratio of products (*cis* to *trans* ratio = 5:1) was determined by measuring the integration of ^{1}H NMR signals of isomeric protons H_a and $H_{a'}$ (Figure 2.3-11).

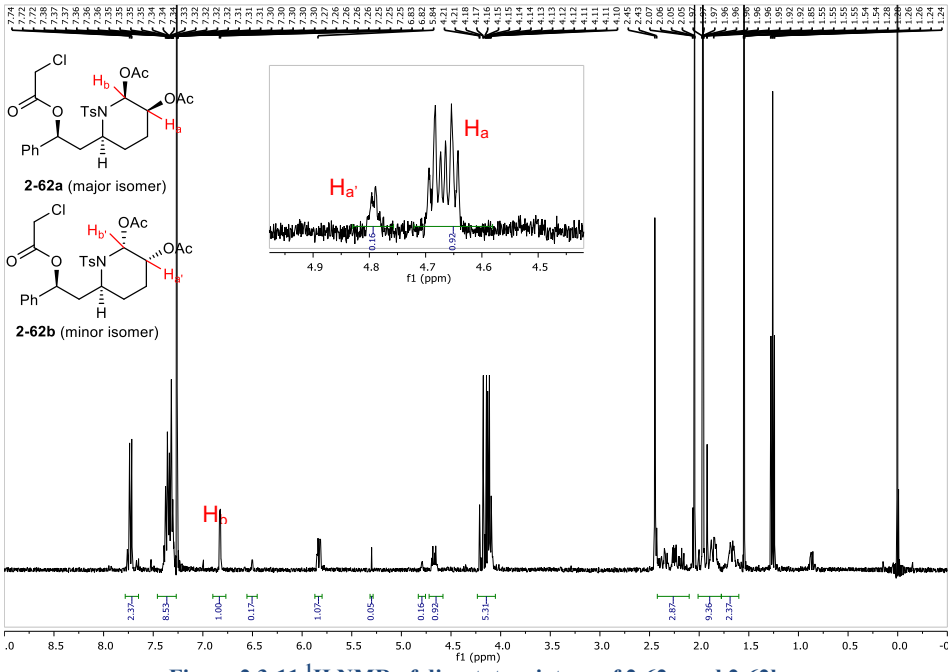


Figure 2.3-11 ^{1}H NMR of diacetate mixture of 2-62a and 2-62b

While the ratio of products was slightly lower than that obtained for *epi*-pseudoconhydrine (6:1), we were pleased with our result given the increased complexity of the chain substituent. The inseparable diacetate isomers of **2-62** were then subjected to Kursanov's reduction conditions[158] with triethylsilane and trifluoroacetic acid to remove the acetoxy group alpha to the nitrogen. At this step, separation of the two isomers was successful. Structural confirmation of the product **2-63a** was carried out by ^{1}H NMR analysis. Due to the loss of the acetate group, hemiaminal proton H_b (major isomer) which was previously observed at δ6.49 in diacetate **2-62a** (Figure 2.3-11) experienced a downfield shift. The singlet corresponding to the acetate peaks at δ1.96 also integrated to 3 protons for one acetate group instead of 6 protons for two acetate groups Figure 2.3-12.

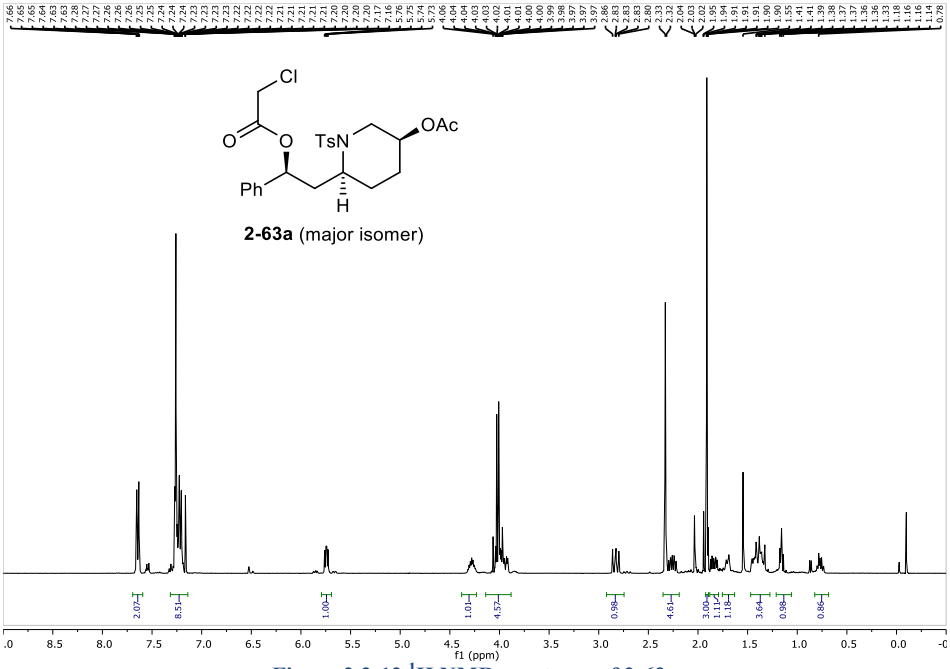
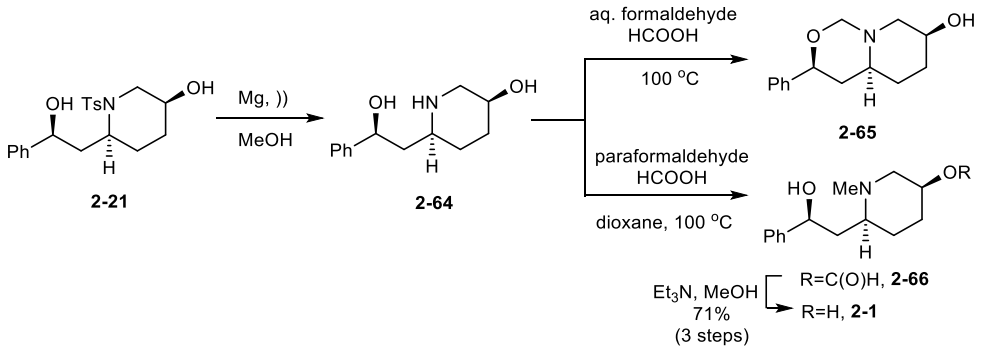


Figure 2.3-12 ^{1}H NMR spectrum of 2-63a

Methanolysis of the remaining ester groups on the major isomer gave hydroxypiperidine **2-21** in reasonable yield (42% yield over 2 steps). We continued with the synthesis to the natural product and investigated the tosyl deprotection and introduction of the methyl substituent on the piperidine nitrogen *via* the Eschweiler-Clarke reaction.

2.3.5.3 *Final steps: Installation of N-methyl substituent*



Scheme 2.3-13 Synthesis of (-)-5-hydroxysedamine

Tosyl deprotection of hydroxypiperidine **2-21** proved to be uneventful. Under Carpino's conditions,[159] the hydroxypiperidine was sonicated with Mg turnings in anhydrous methanol to give the free amine (**2-64**). The product was used in the following reaction without further purification.

We first carried out the *N*-methylation *via* the Eschweiler-Clarke reaction with Farkas' conditions[160] (Scheme 2.3-13) using aqueous formaldehyde and formic acid. We were dismayed to find the formation of *N,O*-acetal **2-65**, caused by the nucleophilic attack of the alcohol on the iminium ion precursor. We were also surprised that the *N,O*-acetal did not undergo further reduction. Gratifyingly, the Eschweiler-Clarke reaction carried out under non-aqueous conditions with paraformaldehyde and formic acid in dioxane proceeded to give us a mixture of the desired natural product **2-1** with formate ester **2-66** in a 1:1 ratio. Subsequent treatment of formate ester **2-66** with methanolic triethylamine gave the natural product. The Eschweiler-Clarke reaction with paraformaldehyde and formic acid proved to be amenable to the synthesis of **2-1** to give the natural product in 71% yield from piperidinol **2-21**. Spectroscopic data and optical rotation were in excellent agreement with that reported.[133-137]

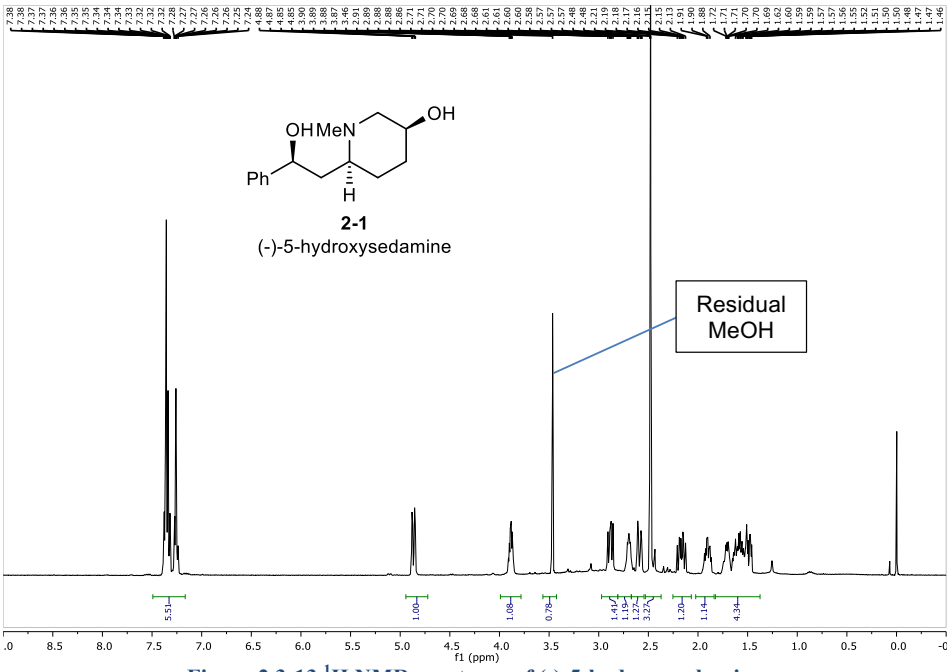


Figure 2.3-13 ^{1}H NMR spectrum of (-)-5-hydroxysedamine

2.4 Conclusion

We have described a novel synthetic route to the synthesis of (-)-5-hydroxysedamine. The synthesis of the natural product was completed with an overall yield of 4.5% over 16 steps, starting from homoallylic alcohol **2-24**.

From our work, the Sakurai reaction has emerged as a feasible solution to the stereoselective formation of 1,3-aminoalcohols. Another key feature of the synthesis is the application of tandem hydroformylation-condensation and stereoselective dihydroxylation in the formation of the 2,5-*cis*-substituted piperidine motif.

It is hoped that lessons learned from this synthesis, especially the Sakurai reaction, could be applied to syntheses of vertine and its family of quinolizidine alkaloids.

Chapter 3

TOWARDS THE SYNTHESIS OF (+)-VERTINE AND ITS ANALOGUES FOR SAR STUDIES AGAINST *PLASMODIUM FALCIPARUM*

3.1 Abstract

Malaria, a vector borne disease, is the leading cause of death in tropical and subtropical regions[161] and has been a major impediment to development in these regions. Reports of resistance[162] to the current line of treatment for malaria presents an urgent need for efficacious drugs with novel modes of action.

In this chapter, we propose a route for the synthesis of (+)-vertine (also known as cryogenine),[163] a member of the *Lythraceae* family of alkaloids and also a moderately active antimalarial natural product.[65] Planned Structure - Activity Relationship (SAR) studies around the molecule would require a strategy which provided facile access to a variety of synthetic analogues. Synthesis of these compounds will also serve to highlight chemistry that has been developed in our laboratory, namely the Sakurai reaction with isoxazolidines. This reaction was implemented successfully in the synthesis of (-)-5-hydroxysedamine (see Chapter 2). Our studies towards the synthesis of (+)-vertine led to formal syntheses of close members of the *Lythraceae* family, (+)-lasubine II and subcosine II.[141]

3.2 Introduction

3.2.1 Malaria

Malaria is an infectious disease caused by protozoan parasites of the genus *Plasmodium* of which five species affect humans (*P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi*).[164] It is predominant in tropical and subtropical regions, occurring in parts of the Americas, Asia and Africa. Each year, there are over 220 million cases of malaria.[161] Malaria is the cause of death for nearly one million people a year, the majority of whom are infants and pregnant women in sub-Saharan Africa.[164d, 165] Economically, direct costs of malaria have been estimated to be at more than 12 billion US dollars a year.[166]

3.2.1.1 Transmission

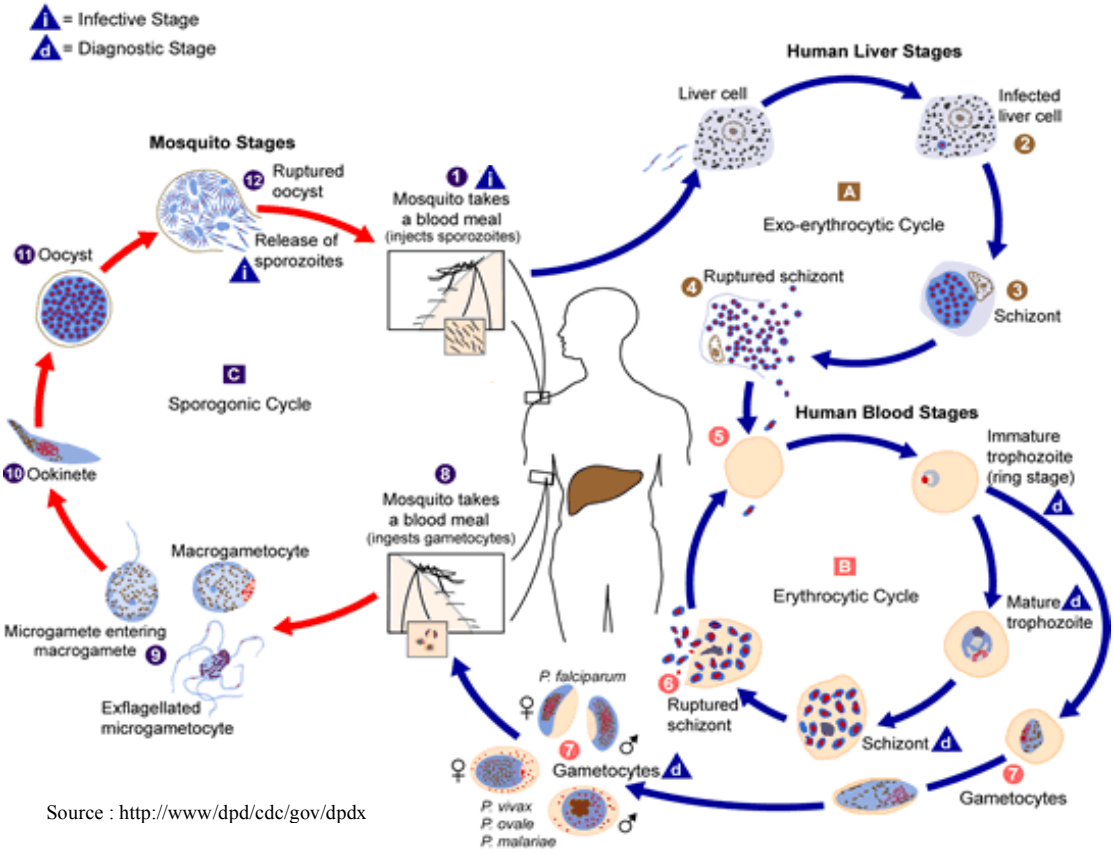


Figure 3.2-1 Life cycle of Plasmodium parasite in humans and mosquitoes

Malaria parasites are transmitted to humans by infected female mosquitoes of the *Anopheles* genus.[167] Young mosquitoes first ingest the malaria parasite by feeding on an infected human carrier (Figure 3.2-1).[167b] The infected *Anopheles* mosquitoes carry *Plasmodium* sporozoites in their salivary glands, which will be transmitted to another human host when the mosquito feeds (Step 1). Malaria in humans develops *via* two phases: an exoerythrocytic (Cycle A) and an erythrocytic (Cycle B) phase. The exoerythrocytic phase involves infection of the liver, whereas the erythrocytic phase involves infection of the erythrocytes, or red blood cells. When the infected mosquito takes a blood meal from a human, sporozoites in the mosquito's saliva enter the bloodstream and migrate to the liver.[168] Within 30 minutes of introduction into the human host, the sporozoites infect the liver cells (Step 2),[169] multiplying asexually for a period of 6 – 15 days (Step 3). Once in the liver, these organisms differentiate to yield thousands of merozoites,[167a, 170] which, following the rupture of their host cells (Step 4), escape into the blood,[171] thus beginning the erythrocytic stage of the life cycle.[172] It is important to note that in certain strains of *Plasmodium* (*P. vivax* and *P. ovale*), the parasite may persist in its dormant form, or hypnozoite,[173] in the liver and could cause a relapse several weeks or even years later.[164c, 174] In the erythrocyctic stage, or in the bloodstream, merozoites will infect healthy red blood cells (Step 5).[172b] The ring stage trophozoites mature into schizonts, which upon rupture releases tens of thousands of merozoites (Step 6) that will infect more red blood cells, leading to illness and complications.[172a] A few of the merozoites develop into sexual forms of the parasite, known as male and female gametocytes (Step 7).[175]

Once ingested by the *Anopheles* mosquito (Step 8), the parasite gametocytes taken up in the blood will fuse in the mosquito gut (Step 9). This produces an ookinete (Step 10) that penetrates the gut lining and produces an oocyst (Step 11) in the gut wall.[167a] When the oocyst ruptures, it releases sporozoites (Step 12) that migrate through the mosquito's body to the salivary glands, where they are then ready to infect a new human host.[167b]

3.2.1.2 Symptoms

Symptoms of malaria[176] include fever, headache, muscle aches, and chills. Nausea, vomiting, and diarrhoea may also occur. Malaria may cause anemia due to the loss of red blood cells. Symptoms usually appear in the erythrocytic stage of the infection, which starts between 10 and 15 days after the mosquito bite. If not treated, malaria could quickly become life-threatening by disrupting the blood supply to vital organs. Infection with one type of malaria, *Plasmodium falciparum*, if not promptly treated, may cause kidney failure, seizures, mental confusion, coma (cerebral malaria), and eventually, death.[177] As the malaria parasite is found in red blood cells of an infected person, malaria could also be transmitted through blood transfusion, organ transplant, or the shared use of needles or syringes contaminated with blood.[178] Malaria may also be transmitted from a mother to her unborn infant before or during delivery.[179]

3.2.1.3 Treatment

Currently, artemisinin-based combination therapy (ACT)[180] is the recommended form of treatment for infection with *P. falciparum*.[181] Artemisinin (**3-1**) is isolated from the plant *Artemisia annua*, or sweet wormwood.[182] Structurally, artemisinin is a sesquiterpene lactone containing a unique peroxide bridge. It has been used in traditional Chinese medicine to treat fever for over 2000 years. Artemisinin and its derivatives are potent medicines known for their ability to rapidly reduce the number of *Plasmodium* parasites in the blood of patients with malaria.[183] However, due to its short half-life, artemisinin is used in combination with another drug to effectively eliminate the remaining parasites and prevent recrudescence.[184]

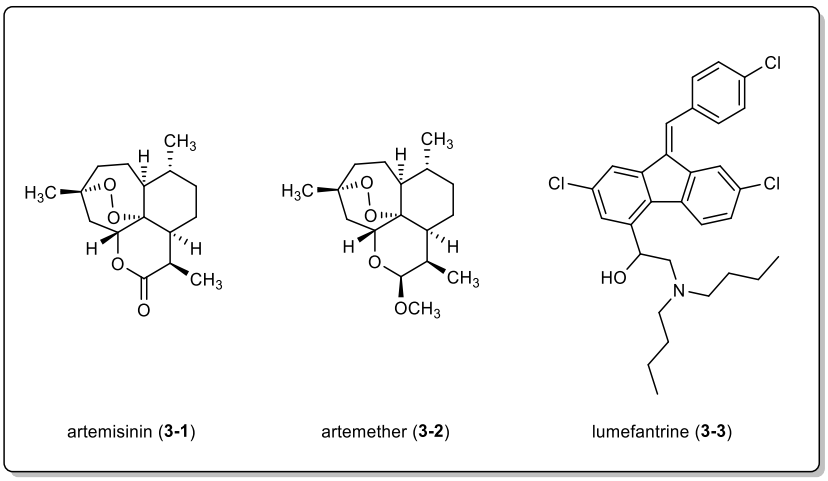


Figure 3.2-2 Anti-malarial compounds

Coartem, a highly effective ACT, is a combination of artemether (**3-2**), a semi-synthetic derivative of artemisinin and lumefantrine (**3-3**). Coartem remains the gold standard for ACTs because lumefantrine has never been used as monotherapy.[185] Hence, there has been no opportunity for the development of drug resistance against it. Coartem is commonly used in many African countries as first line of treatment against *P. falciparum*.[181]

3.2.1.4 Malaria and Drug Resistance

The malaria parasite is capable of becoming resistant to the action of anti-malaria drugs. This is due to small changes in the parasite DNA (point mutations).[186] Resistance to antimalarial medicines has been a recurring problem over the years. Resistance of *P. falciparum* to previous generations of medicines, such as chloroquine and sulfadoxine-pyrimethamine (SP), became prevalent in the 1970s and 1980s.[187] Resistance occurred as a result of several factors, including over prescription or lack of patient adherence to prescribed antimalarial regimens.

In recent years, parasite resistance to artemisinin has been detected in four countries of the Greater Mekong sub-region: Cambodia, Myanmar, Thailand and Vietnam.[162] While there are plenty of factors that contribute to the emergence and spread of resistance, the use of oral artemisinins as a monotherapy is thought to be an important driver.[161] When treated

with an oral artemisinin-based monotherapy, patients may prematurely discontinue treatment following the rapid disappearance of malaria symptoms. However, such patients could still have persistent parasites in their bloodstream. Without a second drug given as part of a combination, these resistant parasites survive and could infect another mosquito, which in turn transmits the parasite to another human.

If resistance to artemisinins develops and spreads to other large geographical areas, the consequences to public health would be devastating since an alternative antimalarial medicine is not available.[188] Despite the ongoing efforts in malaria research, there are significant gaps for medicines to block transmission and in preventing recrudescence.[189] Thus, there is an urgent need for the discovery of novel and highly efficacious antimalarial drugs.

3.2.2 (+)-Vertine and the *Lythraceae* alkaloids

2-Hydroxy-4-phenylquinolizidine represents a structural motif found in the skeletal framework of the *Lythraceae* alkaloids. In 1962, Ferris *et al.*[163, 190] first reported the isolation of several phenylquinolizidine alkaloids, including vertine (**1-166**), from *Decodon Verticillatus*, a flowering plant belonging to the *Lythraceae* family (Figure 3.2-3). Isolation and partial characterisation of alkaloid **1-166** from *Heimia myrtifolia* and *Heimia salicifolia* was also reported by Raffauf and co-workers.[191] Schwarting and co-workers examined *Heimia salicifolia*[192] and found that vertine induced dramatic hypothermia in rabbits and rats after parenteral administration.[193] Based on this observation, alkaloid **1-166** was also named cryogenine.

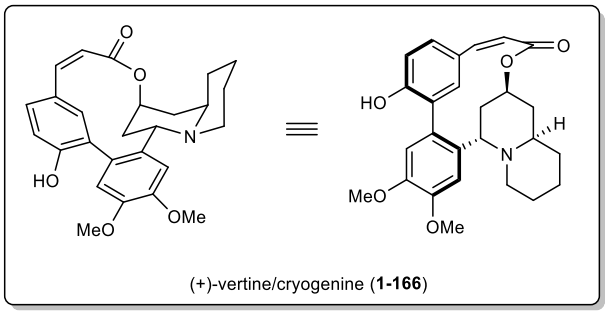


Figure 3.2-3 Structure of (+)-vertine

3.2.2.1 Biological Activity

The aerial parts of *Heimia Salicifolia* have been widely used by Central American and Mexican shamans as an antipyretic, antisyphilitic and general tonic.[194] It has also been indicated that the plant could be used as an insect repellant,[195] as a diuretic or as a laxative.[194] Perhaps more interesting, is the controversial folkloric usage of *Heimia Salicifolia* for its ability to induce psychotomimetic activity after administration as a decoction with alcohol or other intoxicants. This is based on a publication by J. B. Calderón[196] who noted that the plant was said to possess a 'curious and unique physiological action' such as a 'pleasant drunkenness… all objects appear yellow and the sounds of bells, human voices or any other reach their ears as if coming from a long distance.' However, there has been no clinical and/or experimental data to prove the psychotomimetic or psychodysleptic effects of the plant or its isolated alkaloids.[193]

(+)-Vertine (**1-166**), one of the major alkaloids isolated from *Heimia Salicifolia*, has been shown to exhibit ataractic, anti-pyretic, anti-inflammatory and anti-spasmodic properties.[193] Of greater importance is the antimalarial properties exhibited by vertine (**1-166**). As mentioned in Section 1.3.4.1, Khan and co-workers[65] reported modest antimalarial activity of **1-166** against *Plasmodium falciparum* with an IC_{50} value of 4.76 µg/ml for both chloroquine sensitive (D6) and chloroquine resistant (W2) clones, as compared to the positive control chloroquine with IC_{50} values of 13 and 115 ng/ml and artemisinin with IC_{50} values of 12 and 6 ng/ml for D6 and W2 clones respectively. *Epi*-lyfoline (**1-169**),

with a different methoxy pattern substitution to vertine, exhibited a slight increase in potency with an IC_{50} value of 2.8 μg/ml for both D6 and W2 clones.

3.2.2.2 Structural conformation

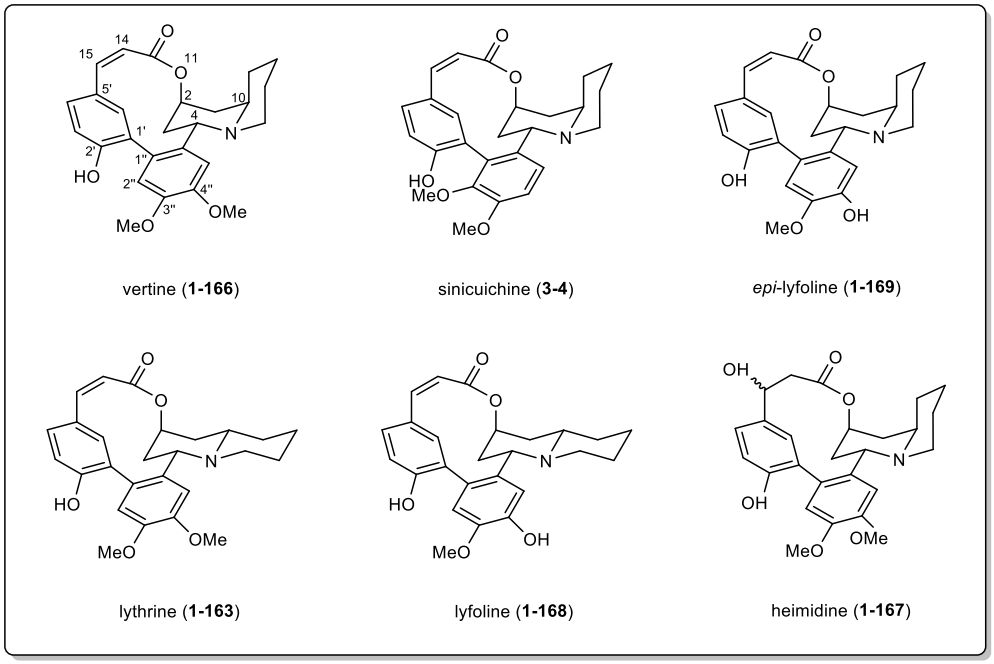


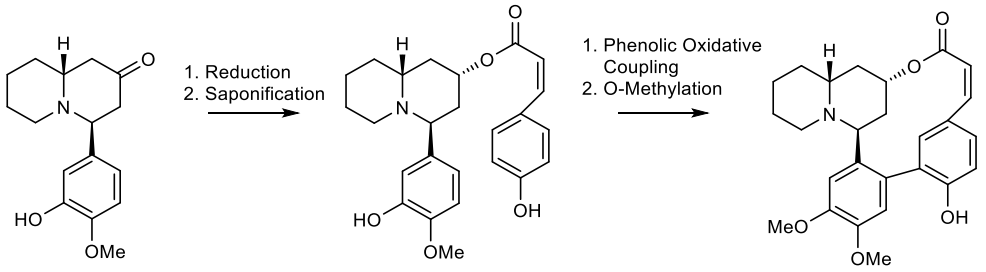
Figure 3.2-4 Structures of selected *Lythraceae* alkaloids

A majority of the *Lythraceae* alkaloids (Figure 3.2-4) are characterised by a 12-membered α,β-unsaturated macrolactone ring which includes a biphenyl motif and a quinolizidine ring.[193] Substitution on the quinolizidine ring is found at C-2 with an axially oriented oxygen group and a second substitution at C-4 by an equatorially oriented aromatic ring. It is also interesting to note that the biphenyl motif of these alkaloids is non-planar, hence inducing a chiral aryl-aryl axis. These alkaloids differ in several ways, namely, the stereochemistry at the bridgehead carbon of the quinolizidine ring, oxidation pattern around the biphenyl motif and lastly, substitution at the cinnamoyl functionality.

The configuration at the bridgehead carbon of the bicyclic quinolizidine, C-10, will affect conformation of the two rings with respect to each other as exemplified by *cis*-fused vertine (**1-166**) and *trans*-fused lythrine (**1-163**). The oxygenation pattern of the phenyl rings may also vary. For instance, sinicuichine (**3-4**) bears methoxy groups at C-2" and C-3" which is

different from the dimethoxy substitution in vertine (**1-166**). Both lyfoline (**1-168**) and *epi*-lyfoline (**1-169**) have a free hydroxyl group instead of a methoxy substitution at C-4" as observed in the corresponding alkaloids, lythrine (**1-163**) and vertine (**1-166**). The alkaloids may also differ in the substitution at the cinnamoyl ester functionality, C-14 and C-15. For example, in heimidine (**1-167**), the double bond has been hydrated.

3.2.2.3 Biosynthesis

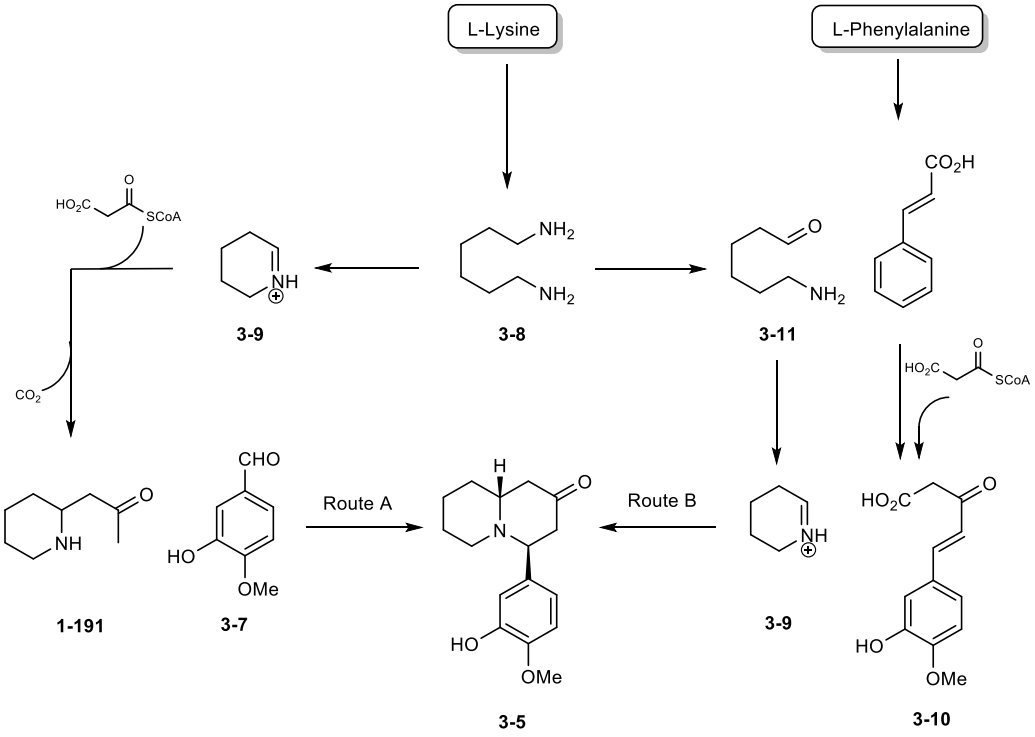


Scheme 3.2-1 Biosynthetic pathway of vertine

Since their discovery, a number of proposals have been put forward to describe the biosynthesis of the *Lythraceous* biphenylquinolizidine lactones alkaloids.[197] These proposals agree on the second half of the synthetic pathway (Scheme 3.2-1). Phenylquinolizidinone **3-5** is reduced to the respective phenylquinolizidinol, which in turn undergoes esterification with the corresponding cinnamoyl moiety, for example, *p*-coumaric acid, which is derived from phenylalanine *via* cinnamic acid. Oxidative phenolic coupling of the two aryl units in **3-6** will provide the macrocyclic framework of these alkaloids.

However, the proposals differ in the mode of biosynthesis of quinolizidine framework in phenylquinolizidinone **3-5**. Ferris *et al.* [197a] postulated that **3-5** may arise from a Mannich reaction (Route A, Scheme 3.2-2) of pelletierine (**1-191**) with a corresponding C_6-C_1 unit (**3-7**). Pelletierine is in turn derived from lysine *via* an intermediate, cadaverine (**3-8**), to form Δ^1-piperideine **3-9**. Condensation of **3-9** with malonyl-CoA will ultimately give rise to pelletierine (**1-191**). Later, Spenser and co-workers[197d] suggested that the

phenylquinolizidine ring may arise from lysine and a C_6-C_4 equivalent (**3-10**) derived from phenylalanine (Route B, Scheme 3.2-2). **3-10** may arise from the biotransformation of phenylalanine to cinnamic acid followed by chain extension with an acetyl or malonyl CoA. Condensation of **3-11** will form Δ^1-piperideine (**3-9**) and this in turn will undergo a Michael addition with **3-10** to give the corresponding phenylquinolizidinone ring framework.

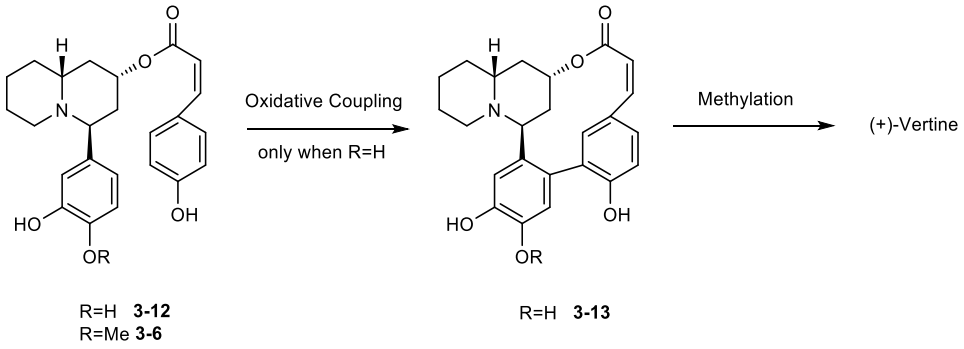


Scheme 3.2-2 Proposed biosynthetic pathway

Spenser and co-workers[197d] also carried out radioactive labelling experiments to validate the pelletierine hypothesis (Route A, Scheme 3.2-2). While they found that ^{14}C-labelled lysine, cadaverine and Δ^1-piperideine were utilised in the biotransformation to decodine and decinine, they did not observe the incorporation of ^{14}C-labelled pelletierine. Hence, pelletierine (Route A, Scheme 3.2-2) does not serve as a precursor for the formation of the phenylquinolizidinone **3-5**. This has also been validated by the work carried out by two other groups separately.[197f, 198]

Herbert and co-workers later further demonstrated that mono-methylated phenols do not participate in alkaloid biosynthesis (Scheme 3.2-3). Oxidative phenolic coupling proceeded

with dihydroxyquinolizidine **3-12** to yield the biphenyl system in **3-13**. Contrary to this, methylated phenol **3-6** was not incorporated into the formation of vertine.[vii]



Scheme 3.2-3 Phenolic Oxidative Coupling in vertine biosynthesis

3.2.3 Aim of this work

Natural products have long been recognised as a source for leads structures for the discovery of novel therapeutic agents. An early example of the therapeutic potential of natural products would be the synthesis of the anti-inflammatory agent, acetylsalicylic acid, commonly known as aspirin, which was derived from a natural product, salicin.[199] Another well-known example and the most famous to date would be Alexander Fleming's discovery of penicillin, a β-lactam antibiotic, from the fungus, *Penicillium notatum,* in 1929.[200] His ground-breaking discovery has far-reaching effects as even today, β-lactams remain at the forefront of antimicrobial chemotherapy.

Today, natural products continue to provide a diverse source of structures as lead compounds for drug discovery.[201] An analysis carried out by Newman and Cragg[202] on the sources of new drugs between 1981 and 2006 found that 50% were natural products or derived from natural products. A famous example is Paclitaxel (Taxol®), a natural product isolated from the Pacific Yew tree that has been successfully developed for treatment of various cancers.[203] Current commercial evidence also supports the case for natural

[vii] To that end, the proposed biosynthetic pathway to vertine and other *Lythraceae* alkaloids may serve to provide valuable hints or starting points for the design of our own synthetic strategy.

products. The sale of Lipitor, a drug derived from a natural product as a lead compound, exceeded US$ 125 billion since it was approved in 1996.[204] In the academic field of research, notable groups like Danishefsky's,[205] Nicolaou's[206] and Schreiber's[207] have successfully showcased the awesome potential of the synergy between synthetic organic chemistry and medicinal chemistry to the design of natural product-based drug candidates.

Natural products have also been a source of therapeutic agents for malaria and we believe that will continue to be of importance. With the reported anti-malarial activity of vertine (**1-166**) and *epi*-lyfoline (**1-169**), we were interested in beginning structure-activity relationship (SAR) studies on vertine and gain access to novel analogues with greater potency and fewer deleterious properties. We were optimistic that the natural product might serve as a valuable lead compound, from which more active analogues could be developed through chemical synthesis with our planned synthetic route. We planned to synthesize vertine, closely-related natural products from the *Lythraceae* family and a small array of synthetic analogues, to further investigate the minimum pharmacophore required for anti-malarial activity.

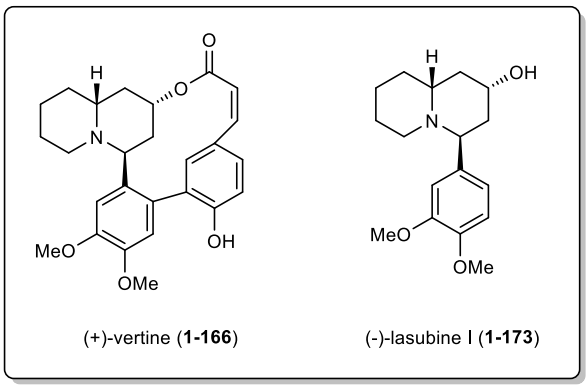
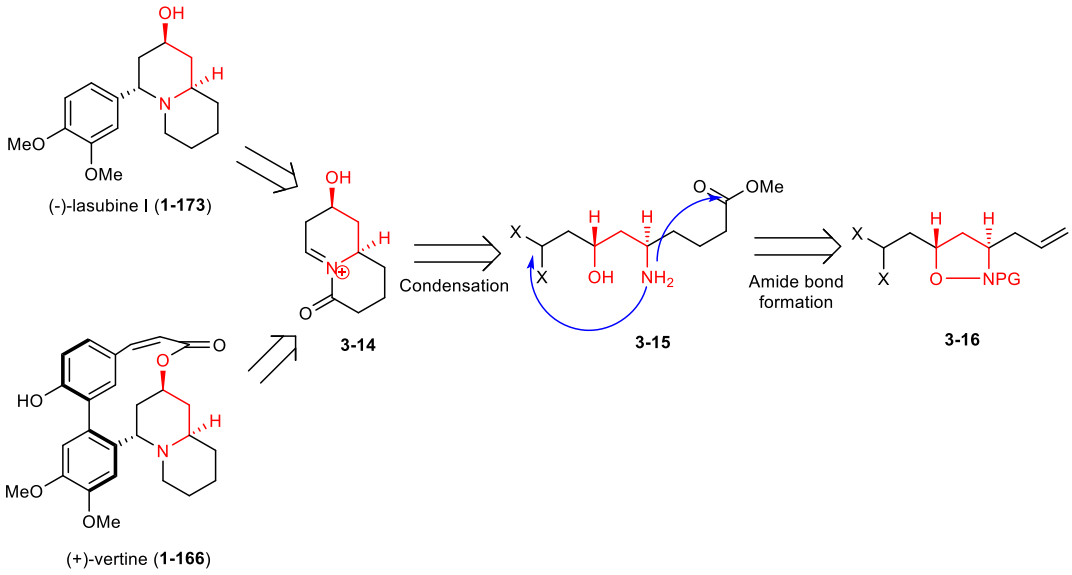


Figure 3.2-5 Structure of (-)-lasubine I and (+)-vertine

We began our synthetic study with the synthesis of (-)-lasubine I (**1-173**), a simplified analogue of (+)-vertine (**1-166**) as a form of proof-of-concept to first test the robustness of our retrosynthetic strategy. We would then be able to build upon the method developed for lasubine I and continue with the synthesis of the macrolactone framework on the quinolizidine ring to give vertine. The final aim was to carry out small perturbations or

variations on the synthetic method to facilitate access to closely-related *Lythraceae* alkaloids or synthetic analogues.

It is important to note that unlike prior reported syntheses of vertine and lasubine I, our synthetic strategy will employ a late-stage installation of the aryl group *via N*-acyliminium ion chemistry. The key reason behind our strategy would be to provide a facile and divergent route to the synthesis of the planned synthetic analogues. Our synthetic strategy would also provide us with routes to otherwise 'inaccessible' compounds that cannot be derived from modification of the natural product itself. This feature of our synthetic strategy would greatly enhance our capabilities to investigate the pharmacophoric space around the natural product which, to our knowledge, has never been carried out on this class of alkaloids.



Scheme 3.2-4 Proposed retrosynthetic strategy to vertine and lasubine

The synthesis of lasubine I (**1-173**), vertine (**1-166**) and its analogues (natural or synthetic) would require the construction of a key intermediate, hydroxyquinolizidinone **3-14** or its epimer (Scheme 3.2-4). Synthesis of the key intermediate **3-14** will be predicated on the formation of *anti*-1,3-aminoalcohol **3-15** which in turn could arise from isoxazolidine **3-16**. Formation of *trans*-substituted isoxazolidine **3-16** will take advantage of a method developed earlier in our laboratory[141]- Sakurai reaction with methoxyisoxazolidines and

allyltrimethylsilane in the presence of a Lewis acid.[viii] The formidable synthetic challenge posed in the synthesis of vertine would be the formation of the macrocycle. The difficulty faced by Kündig in the synthesis of the rigid biaryl-containing macrocycle is a testament of this.[89-90]

Herein, we propose a number of routes to obtain the macrocycle based on different disconnections, including those that have not been explored by Kündig. The disconnection strategies include a biomimetically-inspired phenolic oxidative coupling between the biphenyl groups and an intramolecular cyclisation *via* the iminium ion with a biphenyl moiety. It is important to note that these strategies also present novel methods for the formation of macrocycles. To the best of our knowledge, formation of macrocycles in a stereocontrolled manner with *N*-acyliminium ion chemistry has never been reported.

[viii] Construction of *anti*-1,3-aminoalcohols *via* the Sakurai reaction and *N,O* cleavage has been successfully applied earlier to the synthesis of (-)-5-hydroxysedamine (refer to Chapter 2).

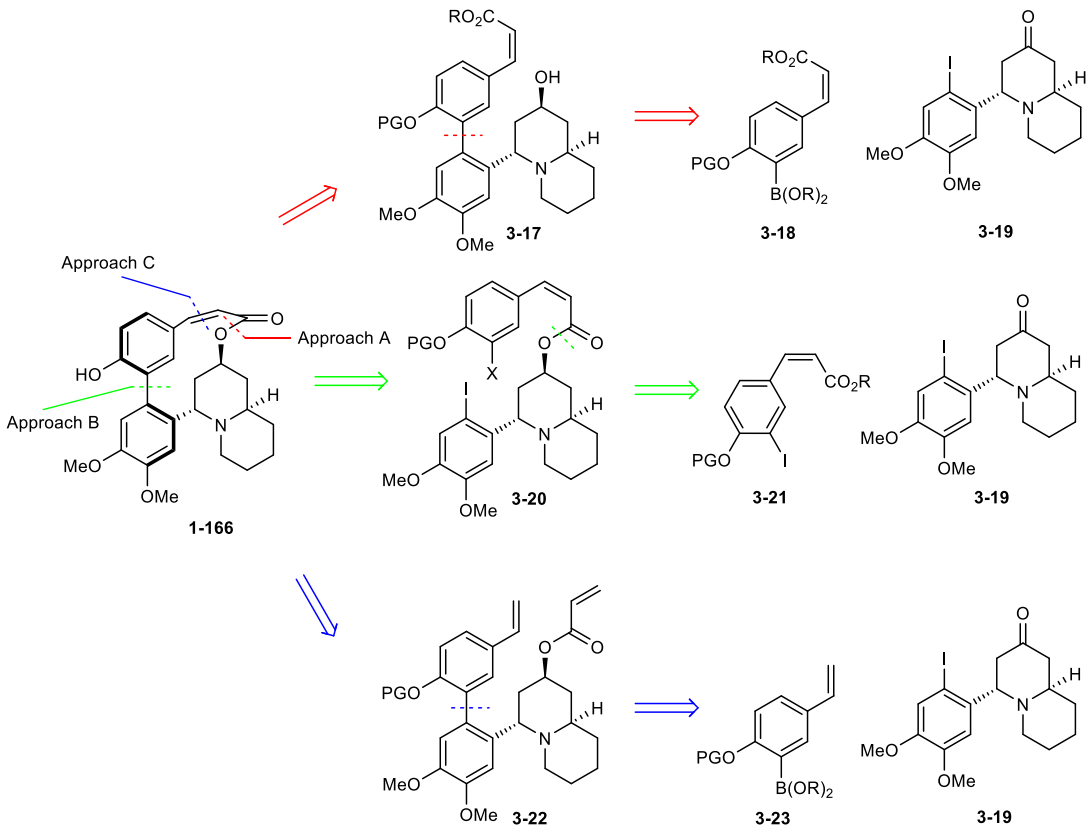
3.3 Retrosynthetic Strategy

3.3.1 Synthetic Strategy to (+)-vertine

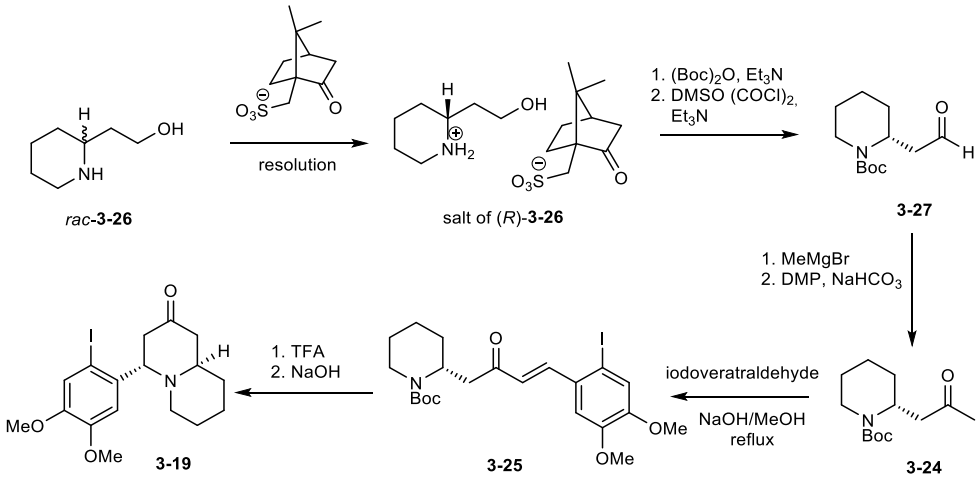
3.3.1.1 Prior syntheses of vertine

The synthesis of vertine (**1-166**) has been reported by Kündig, both in racemic[89] and enantiomeric forms.[90] Several disconnections were investigated for the formation of the macrolactone ring (Scheme 3.3-1). The first approach (Approach A) involved ring closure *via* lactonisation of intermediate **3-17**, derived from a Suzuki-Miyaura coupling[208] of **3-18** and phenylquinolizidinone **3-19**. Another approach (Approach B) that was considered was an aryl-aryl cross coupling with intermediate **3-20**, derived from esterification with the alcohol derivative of phenylquinolizidinone **3-19** and the corresponding α,β-unsaturated ester **3-21**. The final approach (Approach C) consisted of a ring-closing metathesis (RCM) as a key step for the formation of the macrolactone. Intermediate **3-22** may be derived *via* a route analogous to the first approach whereby boronate ester **3-23** is coupled with phenylquinolizidinone **3-19**.

The common intermediate for the above three approaches; phenylquinolizidinone **3-19**, (Scheme 3.3-2) was accessible *via* a stepwise aldol condensation of *N*-Boc protected-(*R*)-pelletierine **3-24** with iodoveratraldehyde to form **3-25**. Cyclisation *via* a Michael addition gave rise to *cis*-phenylquinolizidinone **3-19** as the major product in 69% yield over the two steps. Enantiopure pelletierine derivative **3-24** was prepared starting from racemic 3-piperidineethanol **3-26** by a resolution with (*S*)-10-camphorsulfonic acid according to a procedure reported by Hou.[209] *N*-Boc protection of enantiopure piperidine **3-26** and Swern oxidation of the primary alcohol furnished aldehyde **3-27** which in turn underwent a Grignard addition with MeMgBr. Subsequent oxidation with Dess-Martin periodinane (DMP) yielded pelletierine derivative **3-24** in 81% yield over the four steps.



Scheme 3.3-1 Kündig's macrocycle disconnection strategies



Scheme 3.3-2 Synthesis of Kündig's key intermediate

While the synthesis of key intermediate **3-19** proved to be relatively facile, lactonisation *via* a transesterification reaction with various Lewis acids did not yield the desired outcome (Approach A, Scheme 3.3-1). Other strategies investigated such as a stepwise deprotection and lactonisation or macrolactonisation with a trimethylsilyl ether as a protecting group also proved to be unsuccessful.

Studies were then initiated on the aryl-aryl cross coupling reaction (Approach B, Scheme 3.3-1) as a key step for macrocyclisation. Unfortunately, esterification of *Z*-acrylic acid **3-21** with the alcohol derivative of phenylquinolizidinone **3-19** led to isomerisation around the double bond to give the *E*-isomer under all conditions attempted. Furthermore, aryl-aryl cross coupling of **3-20** under Stille conditions[210] resulted in decomposition of the starting material. Since the route proved to be untenable, Kündig proceeded to investigate his final approach- ring closure *via* RCM.

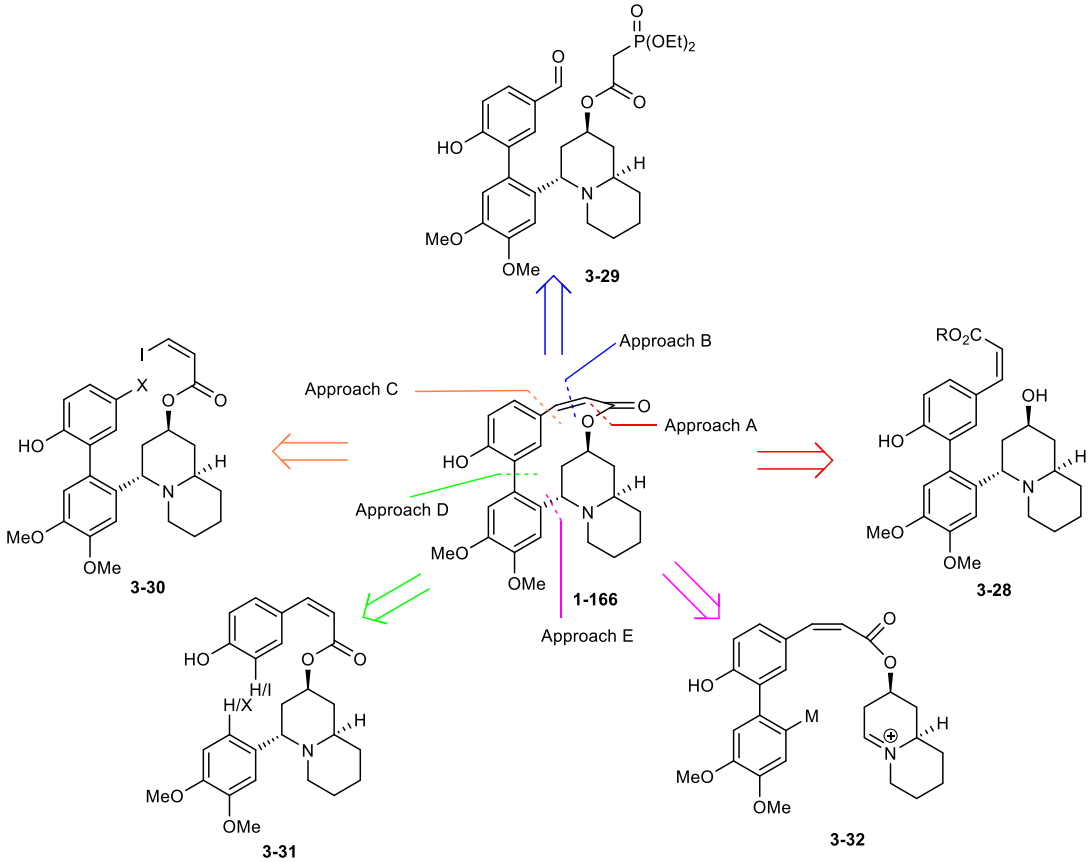
While the first two approaches proved to be intractable for the synthesis of vertine, Kündig attained success with his final approach (Approach C, Scheme 3.3-1) and by extension, showcased the utility of RCM reactions as a strategy for ring closure, despite the lack of literature precedents for the formation of *Z*-alkenes α to the carbonyl moiety. The RCM reaction of **3-22** with Hoveyda-Grubbs II as a catalyst in refluxing toluene proved to be the best conditions to afford (+)-vertine with an overall yield of 4.4% over 16 steps, starting from (*R*)-3-piperidineethanol.

3.3.1.2 Retrosynthetic approach to vertine

In Kündig's synthesis of (+)-vertine,[90] investigations were carried out on more 'conspicuous' disconnection strategies for macrocyclisations. We were interested in initiating studies (Scheme 3.3-3) on disconnections at other junctions of the 13-membered ring, as well as further investigating the strategies that failed in Kündig's hands.

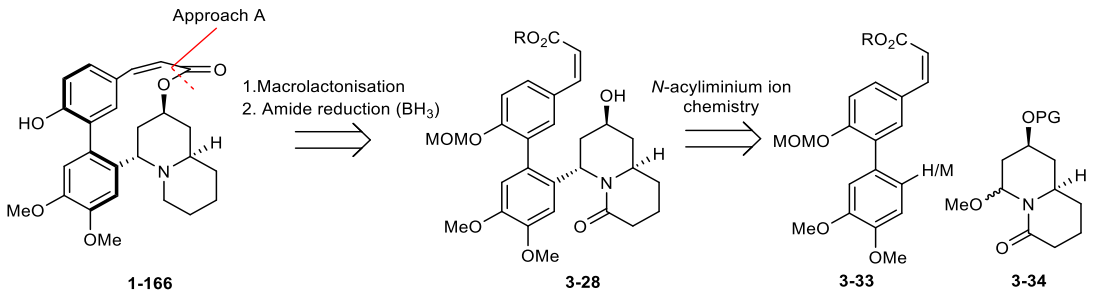
Contrary to Kündig's approach, we intended to firstly construct the hydroxyquinolizidine skeletal framework independent of the C-4 phenyl moiety. Coupling of the biphenyl rings to the quinolizidine framework in the later stages of the synthesis would also facilitate introduction of a variety of aromatic rings with different substitution patterns for future SAR studies. Based on precedent work carried out by Kündig, we decided to choose a

methoxymethyl ether (MOM) protecting group for the phenol present in vertine. Herein, we propose several scenarios for macrocyclisation.



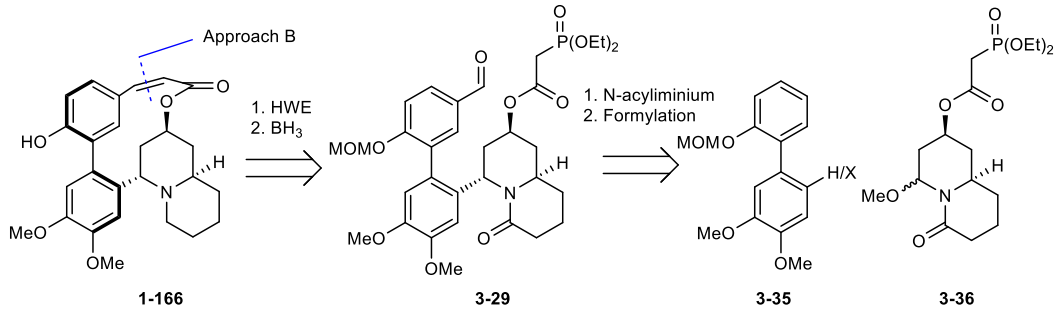
Scheme 3.3-3 Proposed disconnection strategies

Approach A involves a macrolactonisation of intermediate **3-28**. Approach B will be predicated on cyclisation *via* the Horner-Wadsworth-Emmons olefination with intermediate **3-29**. Approaches C and D could arise from a coupling reaction with intermediate **3-30** and **3-31** respectively. Approach E is predicated on *N*-acyliminium ion chemistry *via* **3-32**.



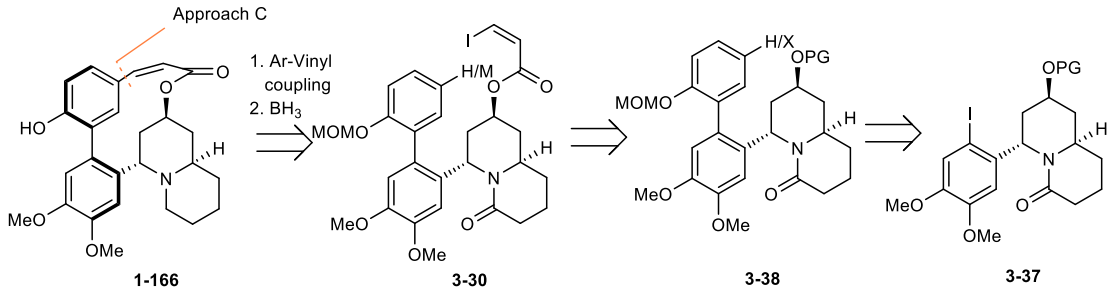
Scheme 3.3-4 Retrosynthetic strategy (Approach A)

The first approach would employ macrolactonisation (Approach A, Scheme 3.3-4) as the ring-closing step. This strategy has been applied by Kündig and co-workers but proved to be unsuccessful in their hands. Kündig reported decomposition during attempts at cyclisation *via* "acid activation" with the Mukaiyama[211] and Corey-Nicolaou reagents.[212] The use of HBTU led to complex mixtures and difficult purifications. Lactonisation has been a popular method for ring closure of macrolactones and there have been a plethora of reported strategies and reagents.[213] Hence, we believe this presents an opportunity for further investigation. The intermediate for lactonisation (**3-28**) could be obtained from coupling of biphenyl fragment **3-33** and hydroxyquinolizidinone **3-34** *via* *N*-acyliminium ion chemistry. All our strategies would launch from the common key intermediate, hydroxyquinolizidinone **3-34**. Reduction of the amide would have to be done at the end of the synthesis with BH_3.[214] We predict that the electron poor α,β–unsaturated lactone in the natural product would not be susceptible to reduction with electrophilic BH_3.



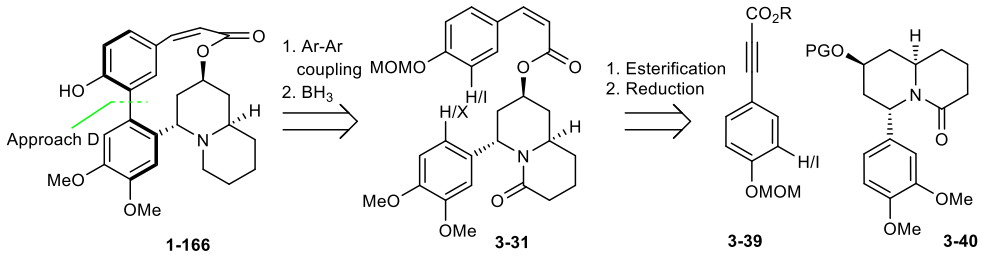
Scheme 3.3-5 Retrosynthetic strategy (Approach B)

A disconnection across the vinyl bond was also considered. Kündig earlier demonstrated success using RCM as a ring closing step at this juncture. We perceived that this posed to us a possibility for ring closure *via* another method for double bond formation- Horner-Wadsworth-Emmons (HWE) olefination (Approach B, Scheme 3.3-5).[215] Aldehyde **3-29** could be accessed *via* coupling of biphenyl fragment **3-35** and hydroxyqunolizidinone **3-36**, employing a route analogous to that described in Approach A followed by a Vilsmeier formylation.[216] Esterification of common intermediate **3-34** with a phosphonoacetate would result in the precursor (**3-36**) needed for cyclisation.



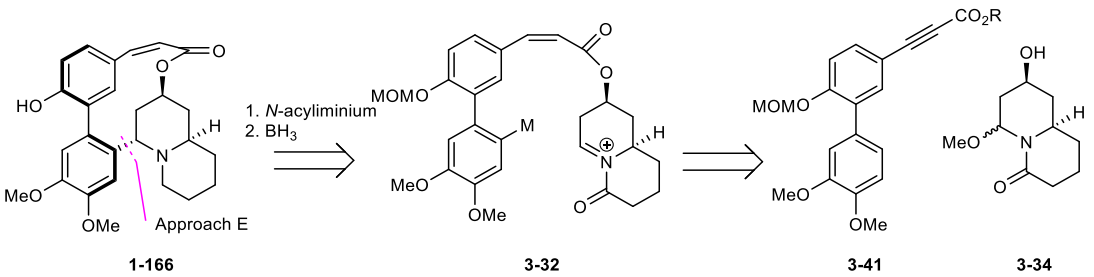
Scheme 3.3-6 Retrosynthetic strategy (Approach C)

Ring closure at the aryl-vinyl bond (Approach C, Scheme 3.3-6) presents to us a novel disconnection strategy. This could arise from a coupling between α,β-unsaturated iodoester **3-30** with a metal-activated biphenyl fragment. Alternatively, coupling between the aryl-vinyl bond may arise based on the method reported by Rawal.[217] Coupling of the common intermediate, hydroxyquinolizidinone **3-34** and the requisite aryl fragment, followed by iodination would form **3-37**. Aryl-aryl coupling would give **3-38** followed by esterification with iodoacrylic acid would give cyclisation precursor **3-30**.



Scheme 3.3-7 Retrosynthetic strategy (Approach D)

Aryl-aryl coupling on **3-31** as a strategy for ring closure (Approach D, Scheme 3.3-7) could also be carried out as a method for macrocyclisation. Inspired by the biosynthetic synthesis of vertine (**1-166**), we considered the possibility of employing a phenolic oxidative coupling as the key step for ring closure. Kündig also investigated aryl-aryl cross coupling as a strategy for ring closure. Unfortunately, esterification proved to be problematic due to isomerisation of the double bond. Furthermore, cross coupling under Stille conditions[210] led to decomposition of the starting material. We intended to circumvent the isomerisation issue by carrying out an esterification with alkyne **3-39** to quinolizidinone **3-40**. The *E*-isomer in **3-31** could arise from a stereoselective reduction of the acetylenic bond. Aryl-aryl cross-coupling could arise from a Friedel-Crafts type reaction.



1-166 3-32 3-41 3-34

Scheme 3.3-8 Retrosynthetic strategy (Approach E)

Lastly, we envisioned bond formation between the biphenyl group and the quinolizidine ring utilizing *N*-acyliminium chemistry (Approach E, Scheme 3.3-8), as a key step for ring closure. Construction of the α,β-unsaturated ester could arise from esterification with common key intermediate **3-34** with the corresponding acetylenic acid **3-41** derived from a Sonogashira coupling with a propiolic acid to the biphenyl fragment. Buchwald has reported the selective Sonogashira reaction of propiolic acid with aryl chlorides.[218] The resulting acetylenic ester could then be reduced stereoselectively to the *Z*-alkene **3-32** by hydrogenation.

In summary, we have proposed several novel disconnection strategies (i.e. *N*-acyliminium ion chemistry, phenolic oxidative coupling, aryl-vinyl coupling, HWE olefination) and a re-investigation of strategy attempted by Kündig (i.e. Macrolactonisation).

3.3.2 Future SAR studies

We intended to initiate SAR studies first with an investigation to find the minimum pharmacophore needed for the anti-malarial activity of vertine (**1-166**). Synthesis of truncated molecules or natural products related to vertine (**1-166**) will prove to be useful in this study. Figure 3.3-1 shows structures of several proposed synthetic analogues (**3-42** to **3-47**). Synthesis of key intermediate, hydroxyquinolizidinone **3-34** should present a facile route to the synthesis of these analogues.

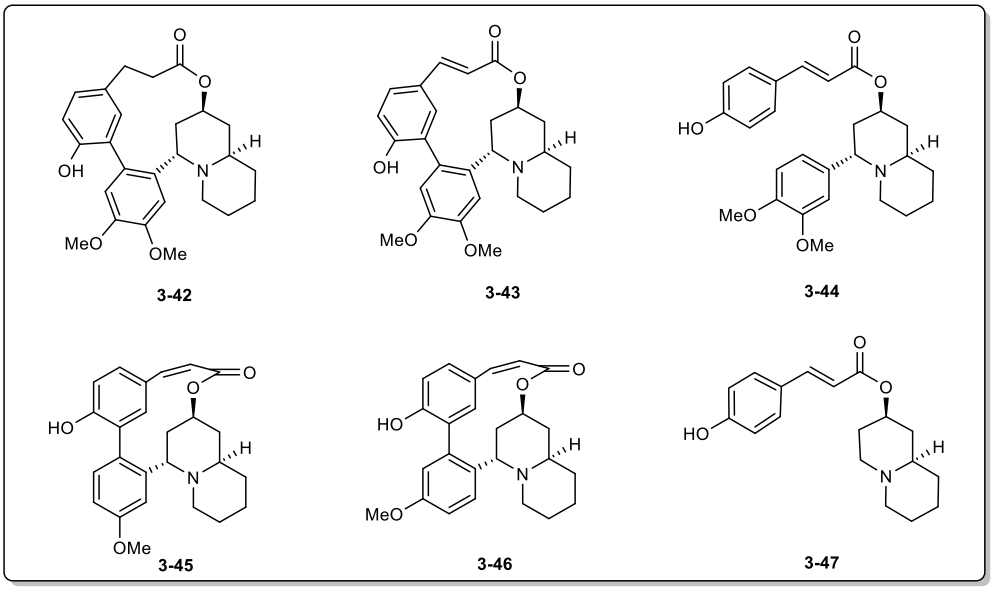


Figure 3.3-1 Structures of proposed analogues

An investigation into functional group tolerance around the biphenyl ring with various electron withdrawing and electron donating groups would also be desirable. We intended to carry out synthesis of a small array of analogues (~10-15 analogues) by taking advantage of the facilities available for parallel synthesis. We also intended to address structural or physicochemical liabilities currently present in the natural product. Lactones tend to be unstable hydrolytically under physiological conditions. They are prone to cleavage and could be converted to inactive hydrolysates. A strategy to overcome this liability would be by enhancing metabolic stability with fluorine substitution as postulated by Miao and co-workers.[219]

The phenol in vertine for instance would be highly prone to oxidation to form a quinone, a highly toxic pharmacophore.[220] Synthesis of analogues that would circumvent these liabilities would be highly desirable. Also, the presence of a Michael acceptor in vertine poses a liability. Michael acceptors are very reactive species due to the possibility of nonselective alkylation various cellular macromolecules. Such modification may induce mutations, which are cytotoxic and carcinogenic.[221] Synthesis of analogues without the Michael acceptor would be useful for the investigation. Basic amine groups may also pose a human ether-a-go-go (hERG) liability[222] and vertine (**1-166**) should be tested for this.

Hence, synthesis of alternative analogues that increase metabolic stability and enhance the safety features of the molecule without loss of activity would be one of the goals of this SAR study.

3.3.3 Synthetic strategy to (-)-lasubine I

(-)-Lasubine I (**1-173**) was first isolated from the leaves of *Lagerstroemia subcostata* Koehne (Japanese name: Shima-sarusuberi) by Fuji *et al.* in 1978 along with three other closely related alkaloids, (-)-lasubine II (**1-174**), (+)-subcosine I (**3-48**) and (+)-subcosine II (**3-49**).[223] Similar to vertine, these alkaloids belong to the *Lythraceae* family. To the best of our knowledge, biological activity concerning lasubine I/II and subcosine I/II have yet to be published. However, there are many biologically important and structurally intriguing alkaloids that possess the quinolizidine skeleton.[1h] This has conspired to make lasubine I (**1-173**) and its related alkaloids attractive targets for total synthesis.

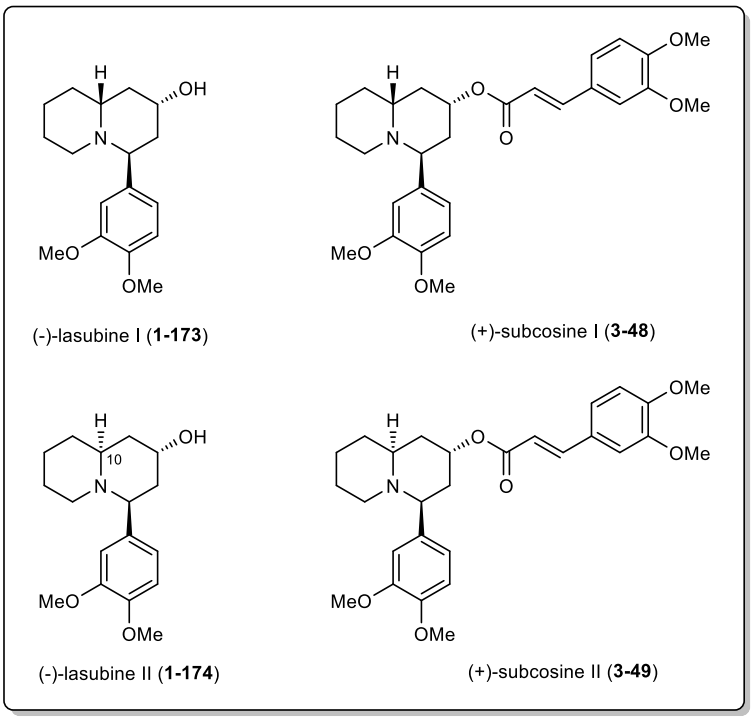


Figure 3.3-2 Structures of lasubine I, II and subcosine I, II

Structurally, lasubine I (**1-173**) features a 2,4-substituted *cis*-fused quinolizidine ring system. Due to the difference in stereochemistry of lasubine II (**1-174**) at C-10, this

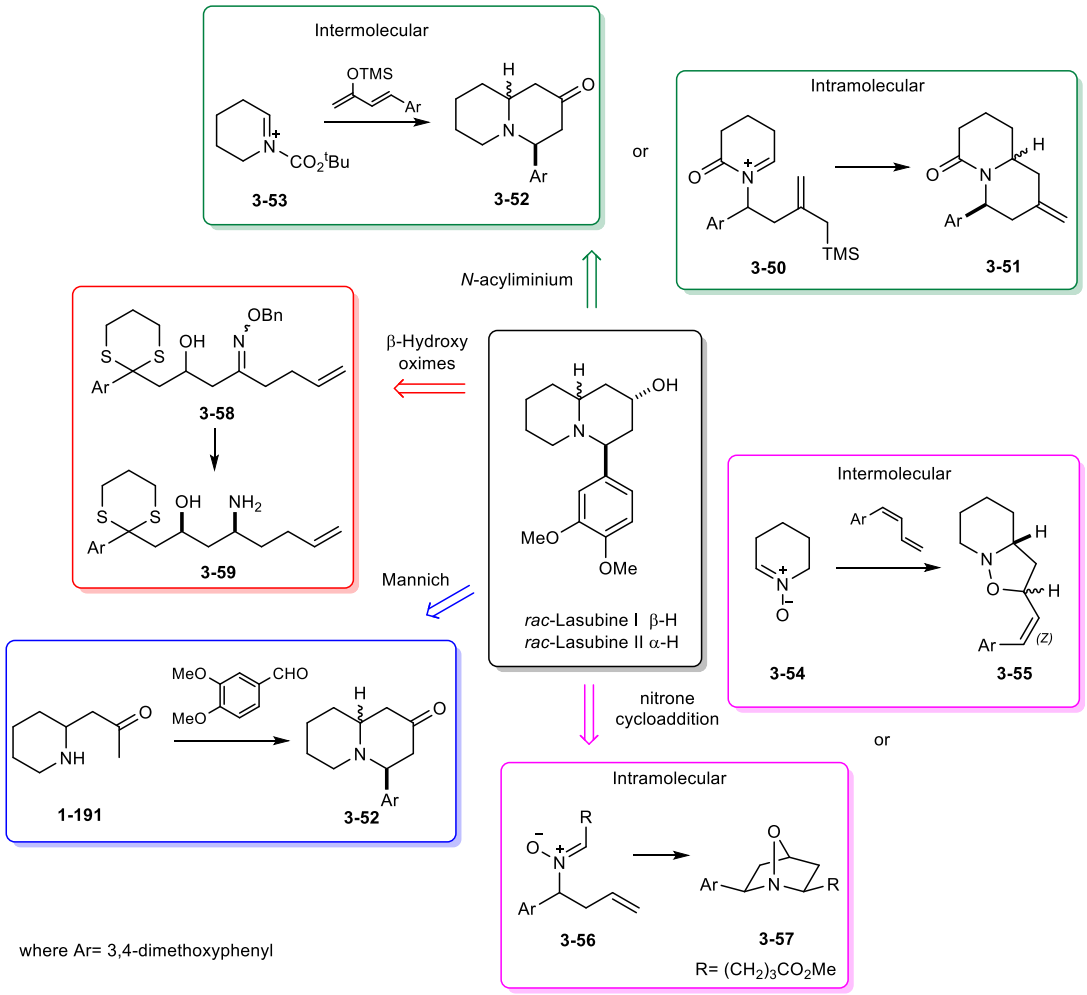
generates a *trans*-fused quinolizidine ring instead. Both **1-173** and **1-174** are characterised by substitution at C-2 with a hydroxyl group and at C-4 by a 3,4-dimethoxyphenyl moiety. Subcosine I (**3-48**) and II (**3-49**) are esters of lasubine I (**1-173**) and lasubine II (**1-174**) respectively with a 3,4-dimethoxycinnamoyl moiety.

3.3.3.1 Prior syntheses of lasubine I

To date, there have been numerous reports of the synthesis of lasubine I and II, both in racemic[224, 74, 78, 225] and enantiomeric forms,[68, 71-72, 75-77, 79, 83-86, 226] establishing these simple alkaloids as hallmark synthetic targets for the development of methods for the construction of *N*-heterocycles.

Scheme 3.3-9 summarises routes reported to racemic forms of lasubine I and II. A common general synthetic design for racemic lasubine I or II involves *N*-acyliminium ion chemistry either in an intramolecular fashion[224d, 224f] or an intermolecular fashion.[78, 225d] An intramolecular *N*-acyliminium ion cyclisation is exemplified by Remuson's work[224f] where hydroxylactam **3-50** was treated with trifluoroacetic acid to generate the iminium ion which underwent cyclisation with the allylsilyl side-chain to give quinolizidine **3-51**. Conversely, Pilli and co-workers employed an intermolecular *N*-acyliminium ion strategy. Quinolizidinone **3-52** was prepared *via* addition of 3-((trimethylsilyl)oxy) 1,3-dienes to cyclic *N*-acyliminium ion **3-53**. A popular strategy involves nitrone cycloadditions, in an intermolecular fashion as demonstrated by Kibayashi *et al.* (**3-54** to **3-55**),[224a-c] and in an intramolecular fashion (**3-56** to **3-57**) as demonstrated by Hoffmann *et al*.[225c] Narasaka and co-workers[225a, 225b] utilised highly stereoselective preparations of β-aminoalcohols (**3-58**) from β-hydroxy oximes (**3-59**). A more concise approach to racemic lasubine I and II was based on the use of the Mannich reaction of pelletierine (**1-191**) with 3,4-subsituted dimethoxybenzaldehyde. Overall, these routes are based on early introduction of the aryl group. This would mean that the synthesis of an analogue with a varying aryl group would

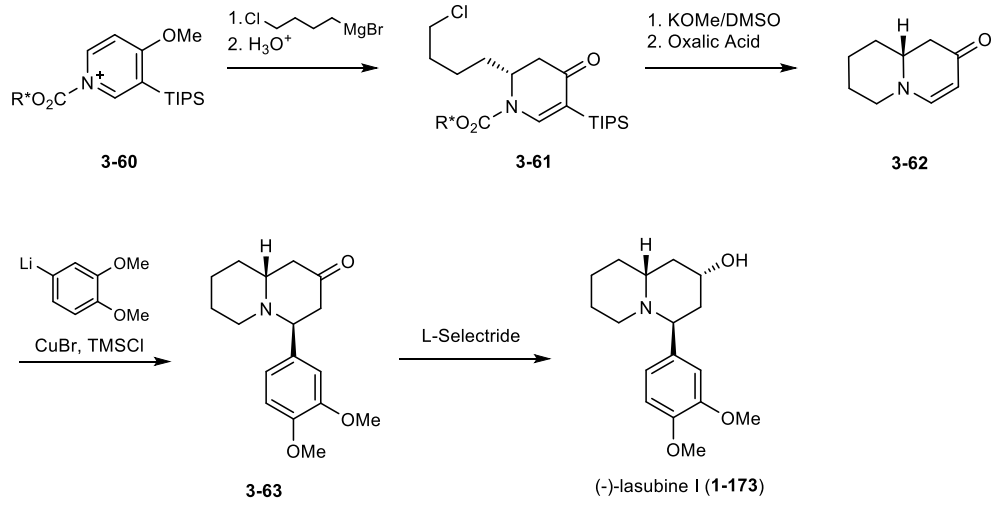
have to be carried out from the beginning. We believe a route that could diverge to a variety of analogues from one common intermediate would be ideal.



Scheme 3.3-9 Prior synthetic strategies to racemic lasubine I and II

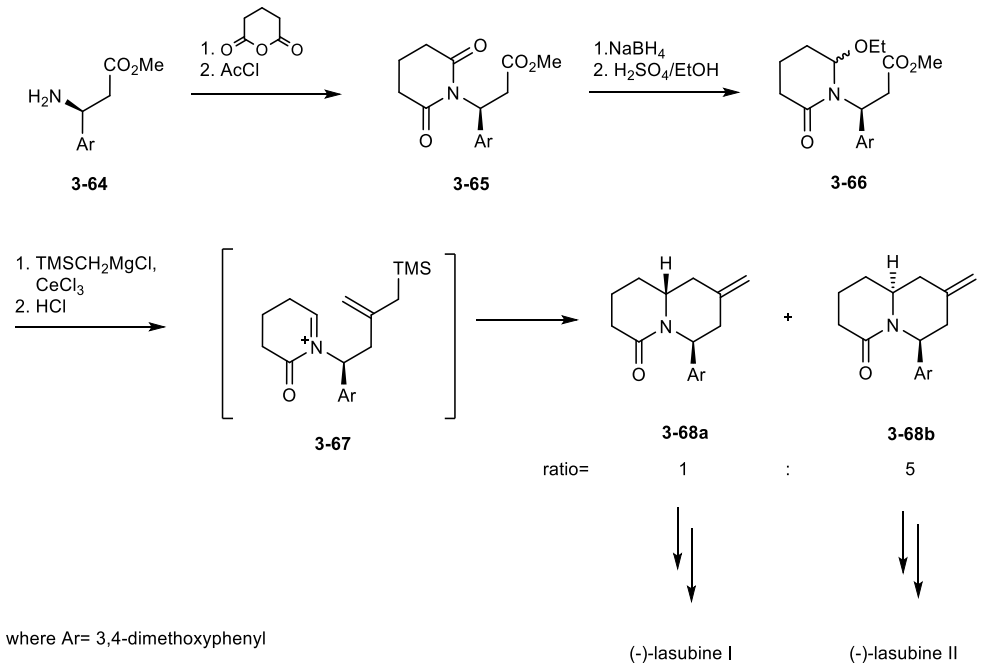
Six enantiopure preparations of lasubine I (**1-173**) have been reported to date.[68, 85-86, 226a-c] The first asymmetric synthesis of lasubine I, reported by Comins,[85] was based upon a diastereoselective addition to a chiral pyridinium salt to form dihydropyridones. Remuson[86] built upon his strategy for racemic lasubine I and II,[86] by carrying out an intramolecular cyclisation of *N*-acyliminium ion with an allylsilane starting with a chiral β-amino ester with decent stereoselectivity. The key step in Kündig's approach, took advantage of the planar chirality imparted by the chromium tricarbonyl moiety to induce a diastereoselective *aza*-Diels–Alder cycloaddition followed by an intramolecular radical cyclisation reaction.[226a] Davis and co-workers[226b] employed a hydroxy-directed reduction of an imine

to form enantiopure lasubine I. Liao's syntheses[68] employed two sequential asymmetric Roush allylborations to form the acyclic precursor in an enantioselective manner. The last reported synthesis was from the Kibayashi group and involved the stereoselective formation of a bicyclic lactone with the desired *trans*-2, 6-piperidine skeleton in place.[226c]



Scheme 3.3-10 Comins' synthesis of (-)-lasubine I

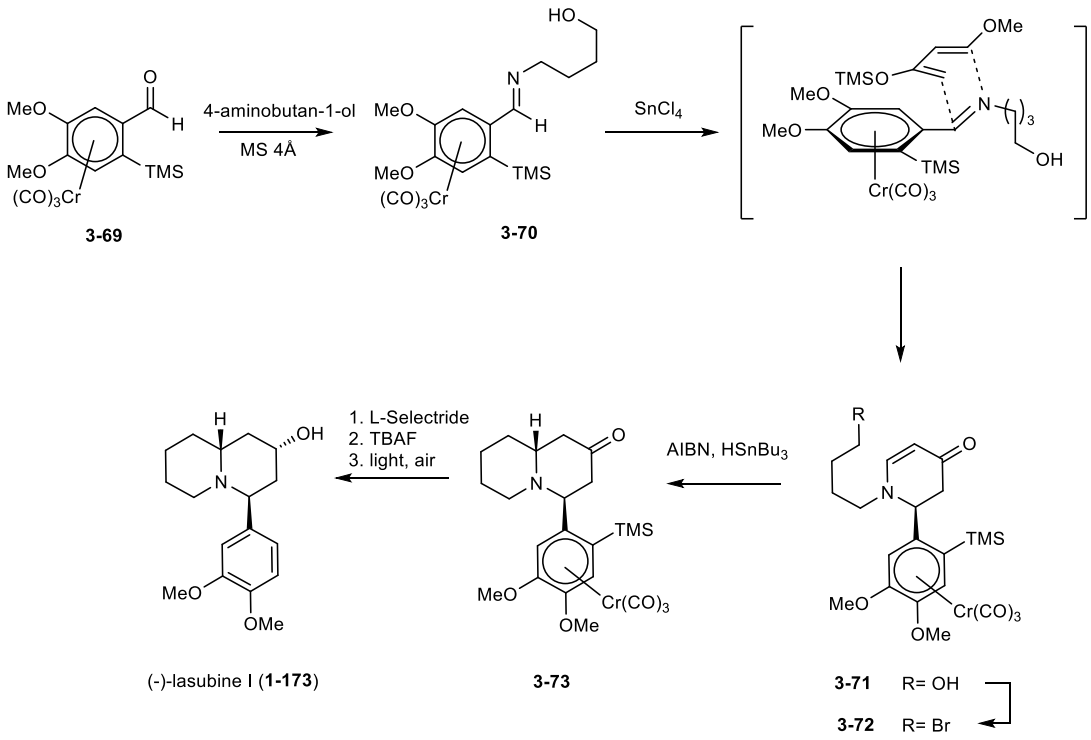
Comins' synthetic strategy (Scheme 3.3-10) began with the reaction of chiral 1-acylpyridinium salt **3-60** with a Grignard reagent gave dihydropyridone **3-61** in 77% yield and 86% de.[85] Configuration at C-2 of the major diastereomer **3-61** was assigned based on results disclosed in an earlier paper.[227] Subsequent removal of the chiral auxiliary and cyclisation was effected with KOMe in DMSO to give quinolizidine **3-62**. This was used as a building block for lasubine I. The 3,4-dimethoxyphenyl moiety in lasubine I was introduced *via* an axial 1,4-addition to the enone of **3-62** with 53% yield. Stereoselective reduction of **3-63** with L-Selectride® gave lasubine I with an overall yield of 27% over 4 steps. While Comins' route involved late stage introduction of the aryl group, the diastereoselectivity of the reaction to form dihydropyridone **3-61** is not very high.



Scheme 3.3-11 Remuson's synthesis of (-)-lasubine I and II

Remuson and co-workers[86] adapted their earlier work featuring an intramolecular *N*-acyliminium ion cyclisation for an asymmetric version, by starting with β-amino ester **3-64**[ix] in the syntheses of lasubine I and II (Scheme 3.3-11). Synthesis of the quinolizidine ring system began with synthesis of **3-65**. Ethoxylactam **3-66** was first treated with $CeCl_3$ and trimethylsilylmethylmagnesium chloride, followed by hydrolysis with 1 N HCl. This induced cyclisation *via* intermediate **3-67** to form methylenequinolizidinones **3-68a** and **3-68b** in a 1:5 ratio, with a yield of 60%. Minor diastereomer **3-68a** was then carried forward towards the synthesis of lasubine I *via* manipulations on the methylene moiety to the alcohol with an overall yield of 7% over 6 steps.

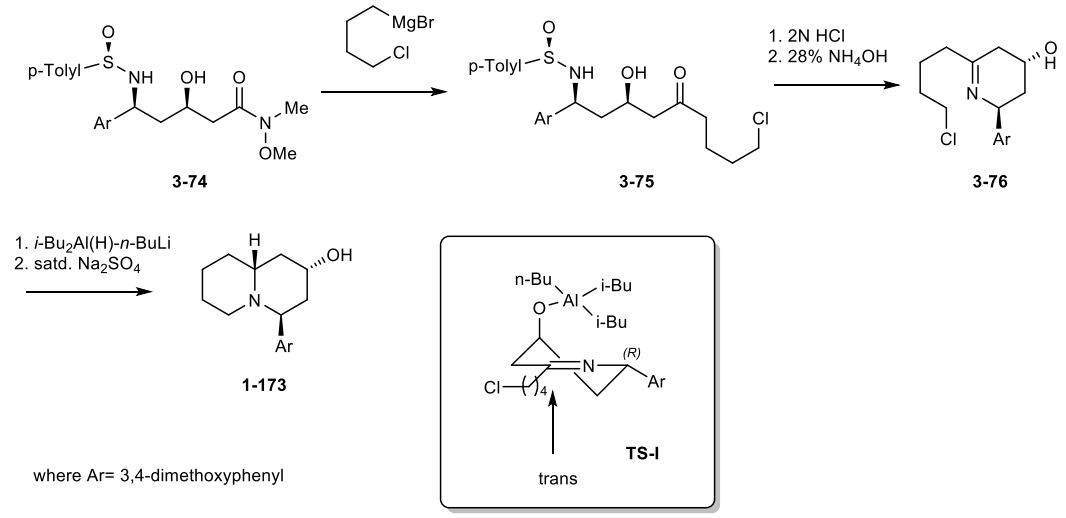
[ix] (*S*)-β-Amino ester **3-64** was prepared according to procedure outlined in Davies *et al. Tetrahedron: Asymmetry* **1991,** *2*, 183. Conjugate addition of a chiral auxiliary, (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, to methyl 3,4-dimethoxyphenylcinnamate occurred with excellent diasteroselectivity (>92% de). Subsequent debenzylation with Pearlman's catalyst and hydrogen gave the desired amino ester **3-64**.



Scheme 3.3-12 Kündig's synthesis of (-)-lasubine I

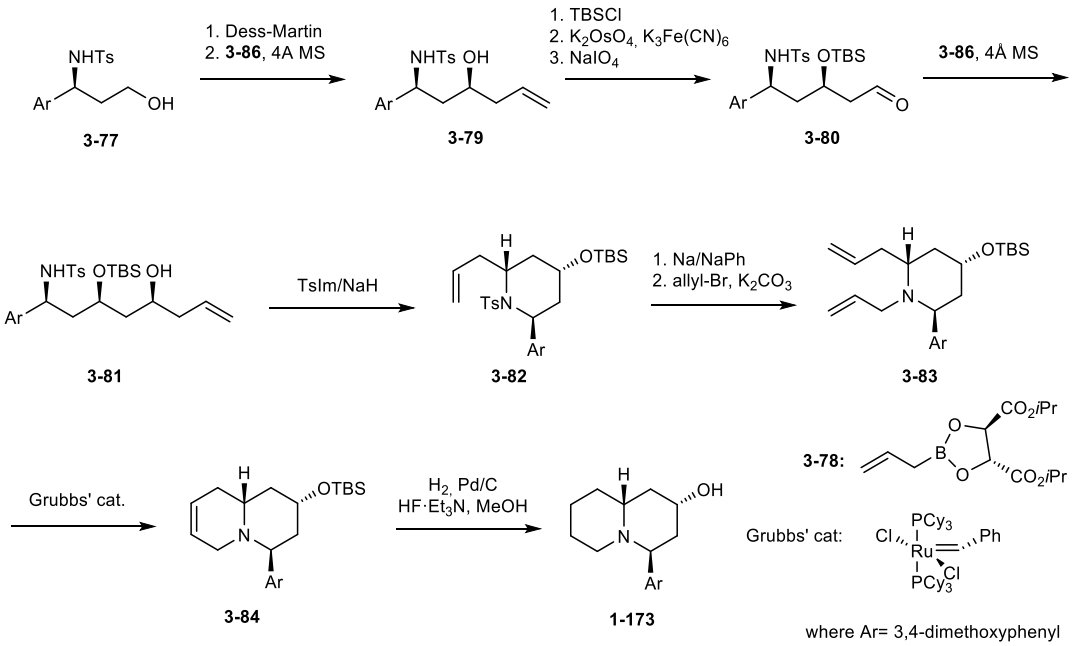
The highlight of Kündig and Ratni's synthesis of lasubine I (Scheme 3.3-12) entails a diastereoselective *aza*-Diels-Alder cyclisation followed by an intramolecular radical cyclisation reaction.[226a] High diastereoselectivity is attributed to the presence of a planar chiral arene $Cr(CO)_3$ complex that acts as a stereodirecting group for both key reactions. Chromium complex **3-69** may be prepared from the corresponding aldehyde followed by a resolution with L-valinol *via* imine formation. Alternatively, complex **3-69** may be prepared following a procedure described by Alexakis and co-workers,[228] albeit with modest yield (35%). Conversion of the aldehyde complex **3-69** to imine complex **3-70** proved to be facile. An *aza*-Diels-Alder reaction was then carried out with Danishefsky's diene in the presence of $SnCl_4$ to afford **3-71** as a single diastereomer with modest yield (48%). The presence of the chromium complex blocks approach of the diene to the imine *re*-face. Beckwith *et al.* first reported intramolecular radical cyclisation proceeded with modest diastereoselectivity (*trans*: *cis* ratio = 3:1) with phenyl substituted dihydropyridinones.[224e] However, Kündig demonstrated that with a $Cr(CO)_3$-complexed arene, diastereoselectivity is improved for the same transformation. The reaction with **3-72**

gave ketone **3-73** as a single diastereomer in 90% yield. L-Selectride® reduction of the ketone afforded the alcohol as a single diastereomer. Subsequent desilylation and decomplexation gave enantiopure lasubine I in 28% yield over 8 steps.



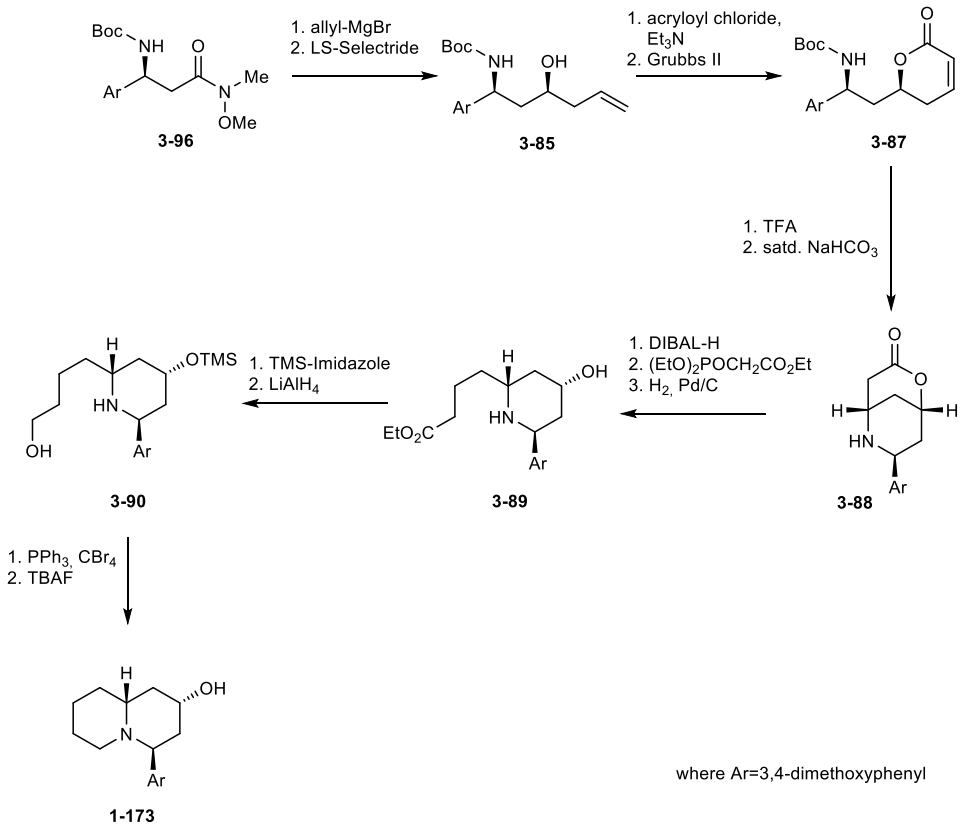
Scheme 3.3-13 Davis' synthesis of (-)-lasubine I

Davis and co-workers[226b] were interested in demonstrating the utility of their method, hydroxyl-directed reduction of 1,3-dehydropiperidines (Scheme 3.3-13). Davis observed that reduction of imine **3-74** occurs stereoselectively to give the *trans* product in the presence of the "ate" complex, i-Bu_2Al(H)-*n*-BuLi, which was prepared by adding *n*-BuLi to DIBAL-H. It was suggested, as shown in **TS-1** that the increased steric bulk of the alkoxy aluminum species would favour the approach of the hydride reagent from the opposite face, leading to the *trans* configuration found in (-)-lasubine I (**1-173**). Following their method, lasubine I was synthesised as a single diastereomer in 60% yield over 4 steps where Weinreb amide **3-75** was converted to imine **3-74** *via* ketone **3-76**.



Scheme 3.3-14 Liao's synthesis of (-)-lasubine I

·Liao's synthesis (Scheme 3.3-14) of lasubine I features two sequential and highly stereoselective Roush allylborations for the formation of two stereogenic centres. S_N2 cyclisation and ring-closing metathesis reactions were employed for the construction of the quinolizidine ring system.[68] The synthesis started with alcohol **3-77** which was formed stereoselectively *via* Evans' chiral auxiliary acetamide. Alcohol **3-77** was oxidised to the aldehyde with Dess-Martin periodinane and then subjected to the first asymmetric Roush allylboration by treatment with (*R,R*)-diisopropyl tartrate allyl boronate **3-78** under standard conditions to form allylic alcohol **3-79**. TBS protection of the alcohol and oxidative cleavage of the terminal alkene gave aldehyde **3-80** which was subjected to a second asymmetric Roush allylboration resulting in formation of allylic alcohol **3-81**. S_N2 cyclisation was brought about by conversion of alcohol **3-81** to the corresponding tosylate to spontaneously form **3-82**. Detosylation and *N*-allylation afforded the ring-closing metathesis precursor **3-83** in 78% yield. The final key step was the ring-closing metathesis with Grubbs catalyst to give rise to the bicyclic product **3-84**. Pd-catalysed hydrogenation in HF/Et_3N and MeOH afforded lasubine I (**1-173**) with an overall yield of 8.8%.



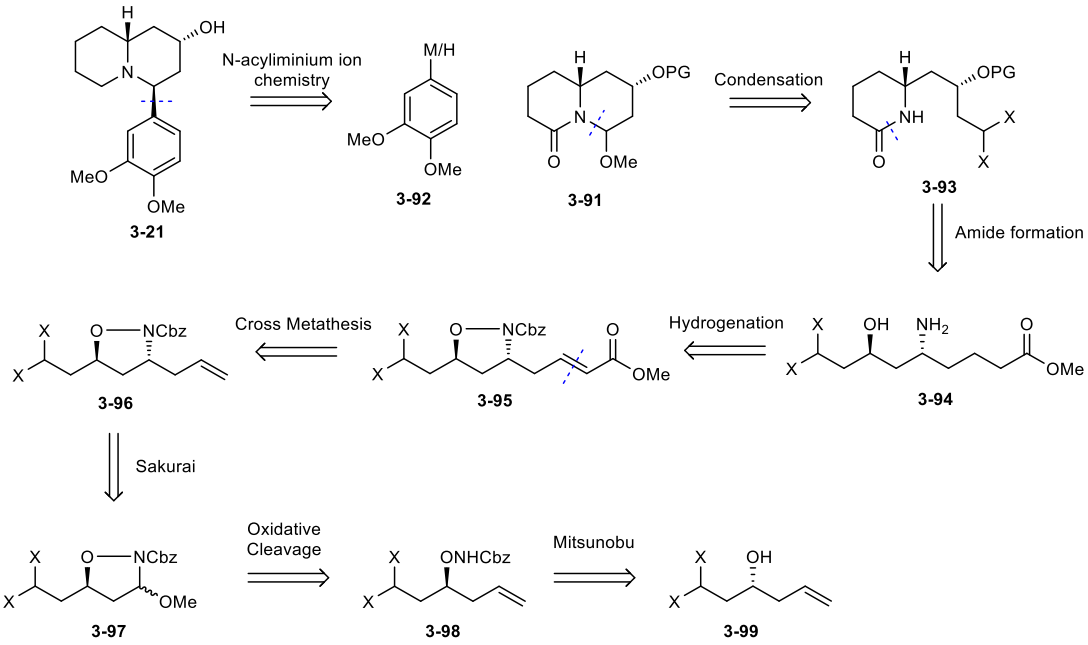
Scheme 3.3-15 Kibayashi's synthesis of (-)-lasubine I

The most recent synthesis of (-)-lasubine I was reported by Kibayashi and co-workers in 2009.[226c] The synthesis (Scheme 3.3-15) started with preparation of *N*-Boc protected aminoalcohol **3-85** (an intermediate analogous to Liao's *N*-tosyl protected **3-79**) from an allylation reaction with the corresponding Weinreb amide **3-86**. The key steps involve the formation of α,β-unsaturated lactone **3-87** formed *via* ring closing metathesis followed by an intramolecular Michael-type addition to form the first six-membered piperidine ring in **3-88**. This was then converted to ester **3-89** *via* a HWE reaction. The second cyclisation was realised *via* an S_N2 reaction of alcohol **3-90** to form lasubine I with an overall yield of 25% over 12 steps.

Despite the fairly diverse approaches reported toward the natural product (**1-173**), all the syntheses reported, with the exception of Comins', involve introduction of the 3,4-dimethoxyphenyl moiety early on in the synthesis. This renders these approaches impractical, especially for structure-activity relationhip (SAR) studies where synthesis of

structurally-diverse compounds from a common building block is of primary importance. Our strategy would serve to fulfil the need for a concise synthetic method to facilitate access to the natural product and its analogues with good yield and diastereoselectivity.

3.3.3.2 Retrosynthetic approach to lasubine I



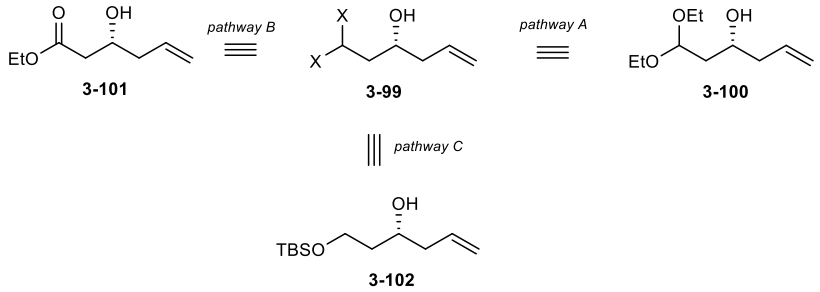
Scheme 3.3-16 Proposed retrosynthetic strategy

Our proposed retrosynthetic strategy is shown above in Scheme 3.3-16. With a disconnection at the carbon-phenyl bond, we envisioned that a late stage installation of the phenyl moiety could be achieved *via* the common intermediate, *N*-acyliminium derivative of **3-91**, either with a metal-activated aryl fragment or with a Friedel-Crafts type reagent (**3-92**). This reaction draws similarities to the Pictet–Spengler reaction with *N*-acyliminium ions.[229] We identified that the quinolizidinone framework in **3-91** could arise from lactam **3-93** *via* condensation of the amine to an acetal-like moiety or a masked aldehyde. Lactam **3-93** could be spontaneously formed *via* amine **3-94** which would be revealed during an *in situ* carboxybenzyl (Cbz) deprotection[230] and reductive *N,O* bond cleavage of isoxazolidine **3-95** with hydrogen and a suitable heterogenous catalyst.[149-150] Synthesis of cyclisation precursor **3-95**, prior to cross-metathesis with methyl acrylate,[231] would be predicated on the synthesis of *trans*-substituted allylic isoxazolidines **3-96** *via* the Sakurai reaction with

methoxyisoxazolidine **3-97**.[141] This in turn, could be accessed from a one-pot oxidative cleavage of homoallylic hydroxylamine **3-98** and condensation of the amine, carried out in methanol. Hydroxylamine **3-98** could be prepared from homoallylic alcohol **3-99** by adopting chemistry we had used to prepare analogous starting materials.[141, 147a] For the synthesis of **3-99**, we considered several functional groups which would serve as robust starting points for the synthesis which will be discussed in further detail in the following section.

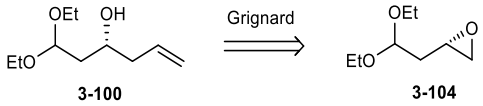
3.4 Results and Discussion

3.4.1 Determination of key starting precursor



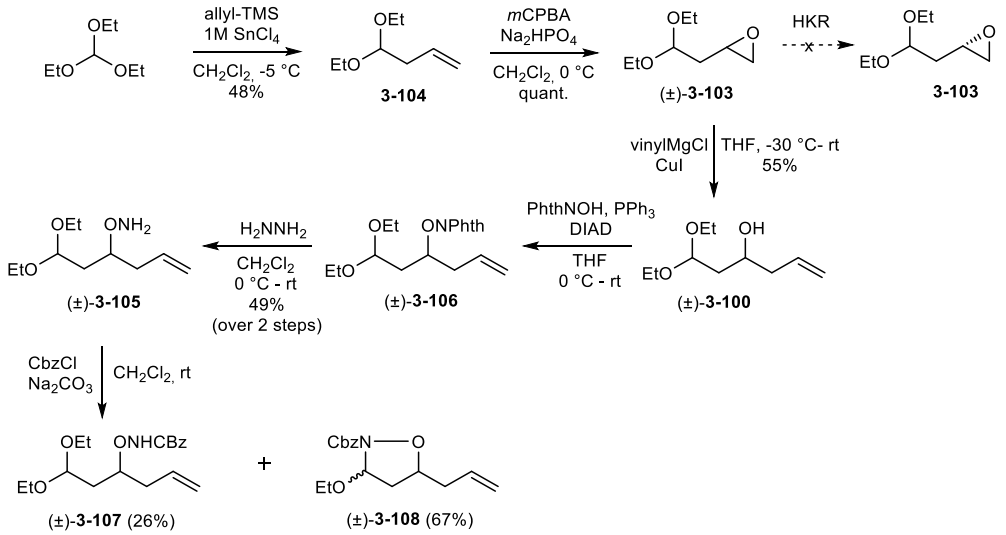
Scheme 3.4-1 Summary of Pathway A, B and C

A crucial prerequisite of alcohol **3-99** is a robust synthetic equivalent, meaning a functional group that would remain unreactive through most of the synthesis and could be easily converted to an aldehyde or an acetal for the key cyclisation step. We investigated three leads- acetal **3-100**, ester **3-101** and silyl ether **3-102** (Scheme 3.4-1), whereupon the functional groups would have a dual role as starting points for the synthesis as well as a robust precursor for the aldehyde functionality needed in the formation of **3-91**. The merits and drawbacks of the pertinent leads will be discussed in further detail in this section.



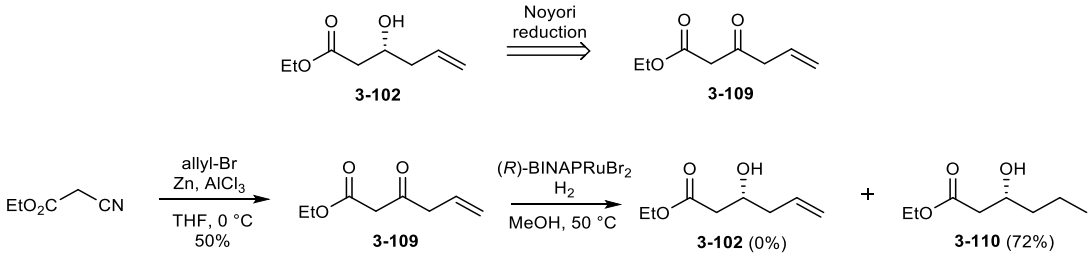
Scheme 3.4-2 Retrosynthetic strategy (Pathway A)

Our attention was first drawn to acetal **3-100** as it was the most obvious choice being the requisite functional group needed for the key cyclisation from **3-93** to **3-91**. We envisioned that acetal **3-100** could be derived from a ring opening of epoxide **3-103** with a suitable Grignard reagent.



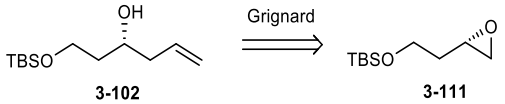
Scheme 3.4-3 Outcome of Pathway A

Racemic epoxide (±)-**3-103** could be synthesised from an allylation reaction of triethylorthoformate,[232] followed by *m*CPBA oxidation of the terminal alkene of **3-104**. On the contrary, we also recognised potential shortcomings of synthesizing epoxide **3-103** in an enantiopure manner. A survey of the literature came up empty handed with no reported procedure of deriving **3-103** enantioselectively. The optimisation process to discover a reaction for this purpose would have proven to be a non-trivial process, making this pathway highly undesirable. Nevertheless, we pursued our synthetic route with the racemic form of **3-100**. Formation of hydroxylamine **3-105** from phthalimide derivative **3-106** proceeded smoothly with a yield of 49% over the 2 steps. In our attempt to protect the hydroxylamine with a Cbz group, we observed the formation of desired Cbz-protected hydroxylamine **3-107** as well as condensation of the amine onto the ethyl acetal to form isoxazolidine **3-108** in fairly large amounts. This was surprising given the absence of acid in the reaction or work-up. With this result, we reached a conclusion about the intractability of this route and chose to abandon Pathway A.



Scheme 3.4-4 Synthetic strategy (Pathway B)

The second functional group we considered was ester **3-101,** which we envisioned could arise from ethyl cyanoacetate *via* a Barbier-type reaction reported by Lee and Lin,[233] followed by a Noyori reduction[234] of allylic β-ketoester **3-109**. Much to our dismay, formation of **3-109** proved to be unamenable to large-scale synthesis. In our hands at scales of above 10 grams, we were unable to mitigate the risks from the uneven evolution of heat in the flask, which led to safety concerns. Furthermore, our attempts at the Noyori reduction under conditions reported by Genet[235] revealed the formation of over-reduced alkane **3-110** as the major product, which led us to quickly abandon this pathway.

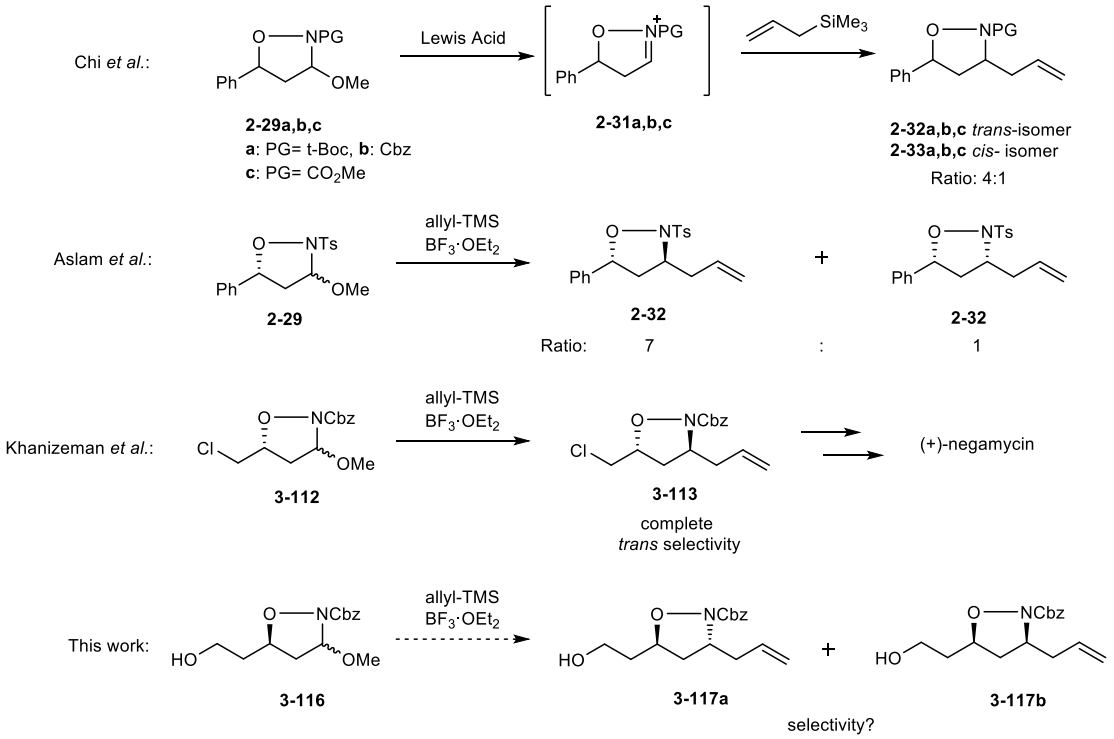


Scheme 3.4-5 Synthetic strategy (Pathway C)

Due to the lack of success faced with ester **3-101** and acetal **3-100**, we turned our attention to the synthesis of TBS –protected silyl ether **3-102**. Unlike the lack of precedence with the formation of enantiopure ethyl acetal **3-103**, Hydrolytic Kinetic Resolution (HKR) of epoxide **3-111** had been reported by several groups.[236] While starting with the TBS-protected alcohol meant an additional oxidation step in the overall synthetic route, we were increasingly attracted to this route, due to a recent success in our group with an analogous Sakurai reaction, also a key step in this proposed synthetic route to (-)-lasubine I (Scheme 3.4-6).

In the previous chapter, the Sakurai reaction with a phenyl group substituent on the isoxazolidine ring yielded in favour of the *trans* isomer with a ratio of 7:1. Earlier reports of the same reaction (see Section 2.3.3) with varying protecting groups proceeded with

similarly modest stereoselectivity (*trans* to *cis* ratio = 4:1). In more recent work carried out by another group member, Nisha Khanizeman, we were pleasantly surprised to find that the allylation of chlorine substituted isoxazolidine **3-112** under the same conditions gave the desired *trans* isomer **3-113** as a single isomer.[237] This ultimately led to the total synthesis of (+)-negamycin.



Scheme 3.4-6 Stereochemical outcome of Sakurai allylation reactions

The gratifying stereochemical outcome obtained in the Sakurai reaction was attributed to the electrostatic attraction between the electronegative chlorine atom (δ-) and the positively charged iminium ion intermediate (Figure 3.4-1) resulting in an effective shielding of one face. The experimental results were later corroborated with *in silico* calculations. The lowest energy conformation has the chlorine atom hovering over the isoxazolidine ring, thereby blocking one face from nucleophilic attack. This conformation was also found to be 2.9 kcal mol^{-1} lower in energy than the next lowest conformation. Analogous calculations with an ethyl side chain were also carried out. The lowest energy conformation placed the CH_3 terminus in free space, pointing away from the isoxazolidine ring. Energy differences with other conformations were within 1 kcal mol^{-1}.

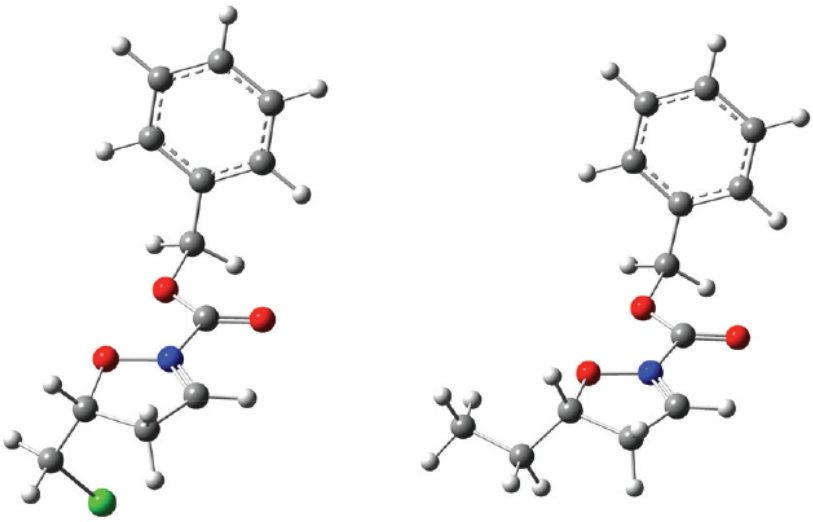
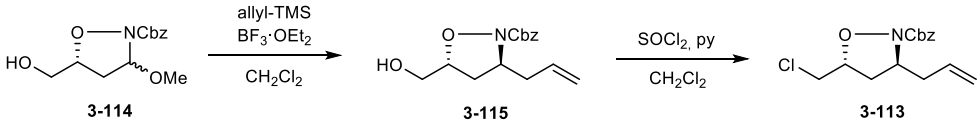


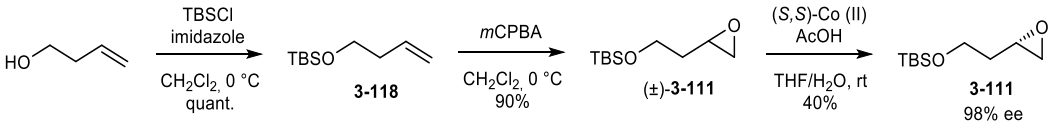
Figure 3.4-1 Lowest energy conformations of iminium ion intermediate with chloro and ethyl substituents



3-114 **3-115** **3-113**

Scheme 3.4-7 Conversion of hydroxymethyl to chloromethyl isoxazolidine

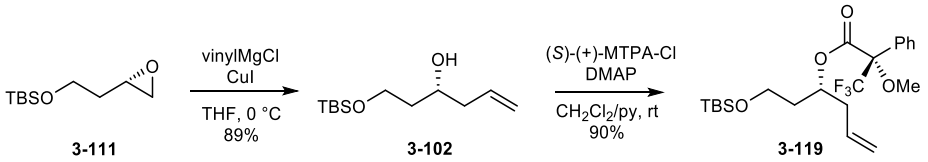
The hypothesis was then extended to include other electronegative functional groups and as such, hydroxymethyl isoxazolidine **3-114** was prepared.[237] Treatment of **3-114** with allyltrimethylsilane under the same conditions as the conversion from **3-112** to **3-113**, gave the *trans*-isoxazolidine **3-115** as a single isomer. The formation of the *trans* isomer was confirmed by conversion of **3-115** to **3-113** with thionyl chloride and pyridine. With this result in hand, we were interested to find out if the stereoselectivity of this reaction would be retained with a single carbon extension on the side chain, that is, would allylation of methoxy isoxazolidine **3-116** result in formation allyl isoxazolidine **3-117a** exclusively.



Scheme 3.4-8 Synthesis of enantiopure epoxide 3-111

Synthesis of the requisite TBS protected epoxide **3-111** began with TBS protection of commercially available alcohol buten-1-ol followed by an *m*CPBA epoxidation on the terminal alkene of **3-118** to give racemic epoxide (±)-**3-111** in 90% yield over the two steps. Following the HKR procedure reported by Paterson and co-workers,[236b] we were able to

generate epoxide **3-111** enantioselectively with 40% yield at 99% ee. We found that the high enantioselectivity could only be obtained with purified epoxide (±)-**3-111**. HKR with the crude epoxide led to reaction outcomes with only 50% ee. The % ee was confirmed with formation of Mosher's ester[x] from silyl ether **3-102** from samples of purified and crude epoxide as shown in Figure 3.4-2 and Figure 3.4-3 respectively. A possible reason for the difference in purity of the epoxides could be the presence of trace amounts of *meta*-chlorobenzoic acid found in the crude sample of racemic epoxide **3-111** may have deactivated the Co-OAc salen catalyst needed for HKR..



Scheme 3.4-9 Synthesis of Mosher's ester derivative of silyl ether 3-102

To form silyl ether **3-102**, the epoxide underwent a ring-opening reaction with vinyl magnesium chloride, catalysed by copper iodide. The reaction proved to be very facile and proceeded with good yield. Alcohol **3-102** was then treated with Mosher's acid chloride with catalytic amounts of DMAP in pyridine (Scheme 3.4-9). The ^{1}H NMR spectrum of ester **3-119** derived from HKR of crude epoxide (Figure 3.4-2) indicated the presence of the two diastereomers as could be seen by the two –OMe singlet peaks at δ3.54 and δ3.56. Two set of signals at the δ5.5- 6.0 range, corresponding to the internal alkene proton are also clearly visible. This is in contrast to the ^{1}H NMR spectrum of ester **3-119** derived from HKR of purified epoxide **3-111 (**Figure 3.4-3**)**. Only one –OMe singlet at δ3.54 was present and only one set of signal corresponding to the allylic proton at δ5.65 (doublet of doublet of triplets) was visible.

[x] Mosher's ester was used as it offered a simple method to determine ee in the absence of a UV-active chromaphore at λ=254 nm.

With a viable route to silyl ether **3-102** in an enantiopure fashion, we turned our attention to the formation of isoxazolidine **3-116**, the precursor for the key Sakurai allylation reaction.

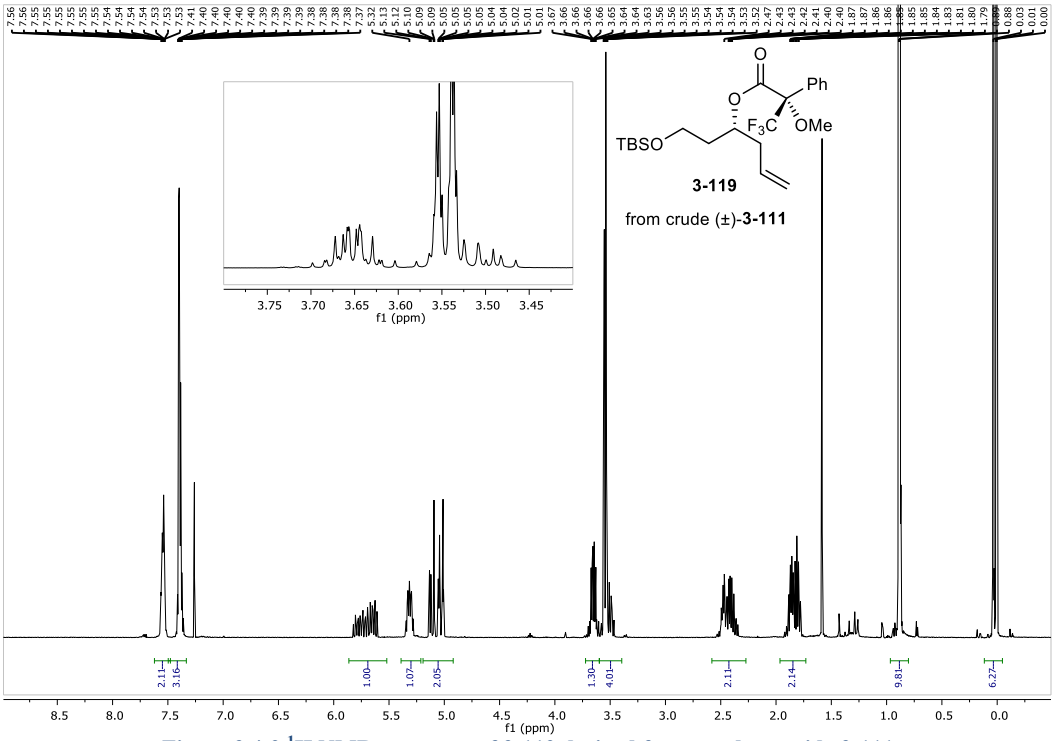


Figure 3.4-2 ^{1}H NMR spectrum of 3-119 derived from crude epoxide 3-111

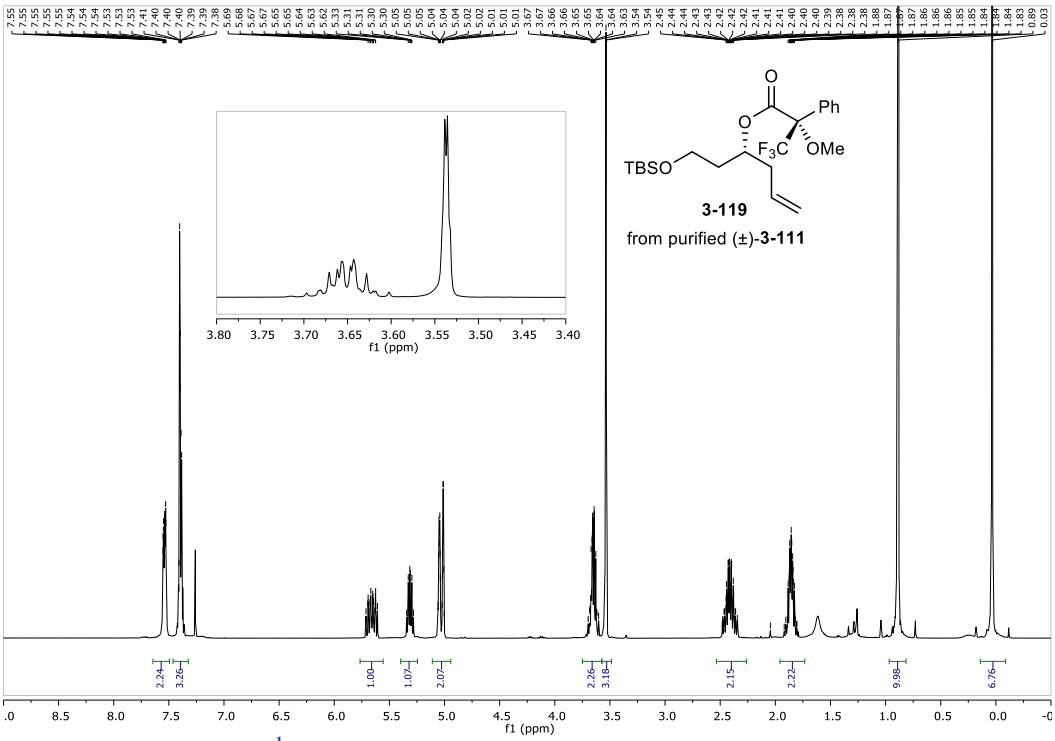
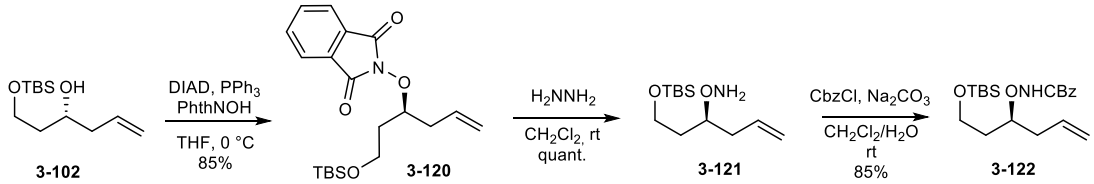


Figure 3.4-3 ^{1}H NMR spectrum of 3-119 derived from purified epoxide 3-111

3.4.2 Sakurai allylation reaction and preparation of its key intermediate 3-116



Scheme 3.4-10 Synthesis of *N*-Cbz protected hydroxylamine 3-122

Alcohol **3-102** was subjected to a similar protocol as discussed in detail in the previous chapter. Mitsunobu reaction with *N*-hydroxyphthalimide (**3-102** to **3-120**) and phthaloyl cleavage (**3-120** to **3-121**) followed by protection of the amine (**3-121** to **3-122**).[147a, 238] Protection of the amine was carried out with a Cbz group as it could be easily removed during a global hydrogenation carried out in the final stage of the synthesis. The above sequence proceeded smoothly with an overall yield of 73% over the three steps. (Scheme 3.4-10)

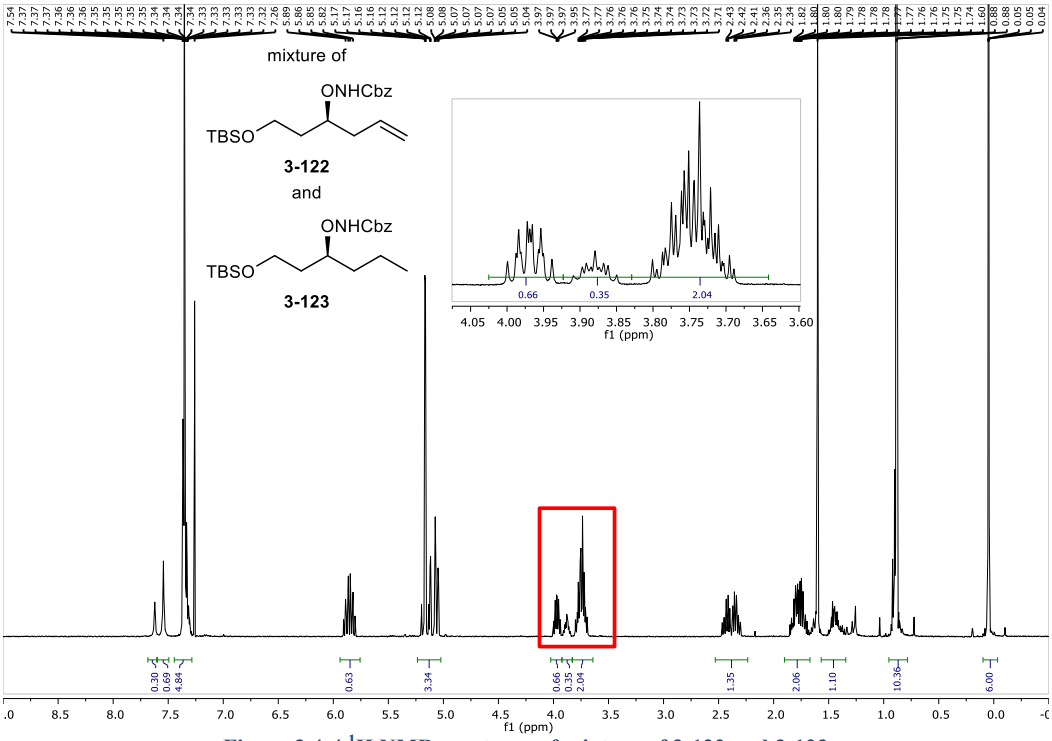


Figure 3.4-4 ^{1}H NMR spectrum of mixture of 3-122 and 3-123

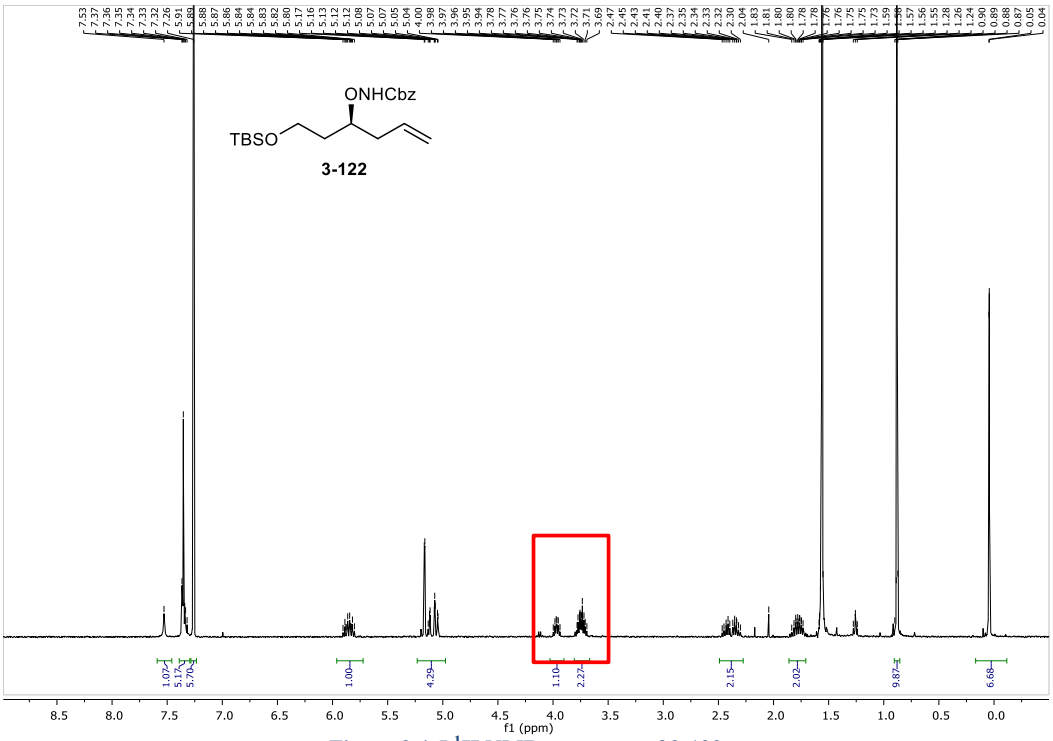


Figure 3.4-5 ^{1}H NMR spectrum of 3-122

It is worth noting that during phthaloyl cleavage on small scale, we observed reduction of the alkene to form alkane **3-123** by hydrazine hydrate, which proved to be difficult to remove from desired alkene **3-122**. Presence of the alkane was visible upon Cbz protection, as could be seen by the presence of additional peaks in the ^{1}H NMR spectrum above in the δ3.65 to δ4.00 range (Figure 3.4-4). Formation of this undesirable side product however, was easily circumvented simply be carrying out the reaction on a larger scale, to furnish the desired Cbz protected hydroxylamine as a single product resulting in a cleaner ^{1}H NMR spectrum (Figure 3.4-5).

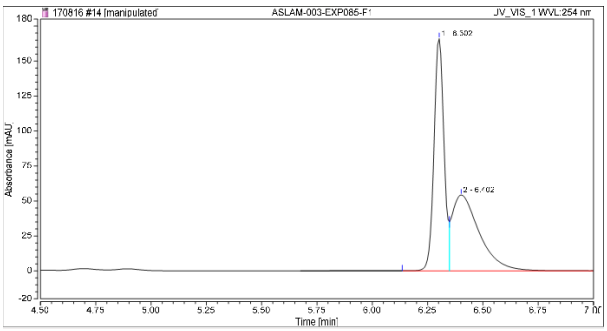


Figure 3.4-6 HPLC trace with racemic sample of 3-122

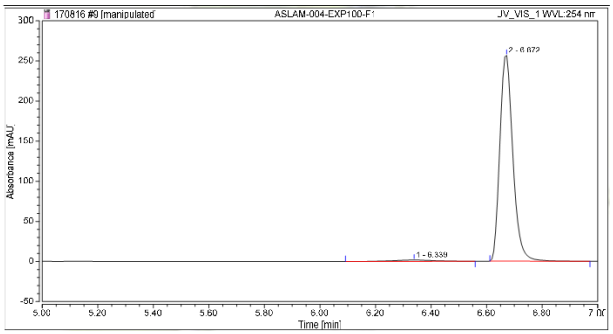
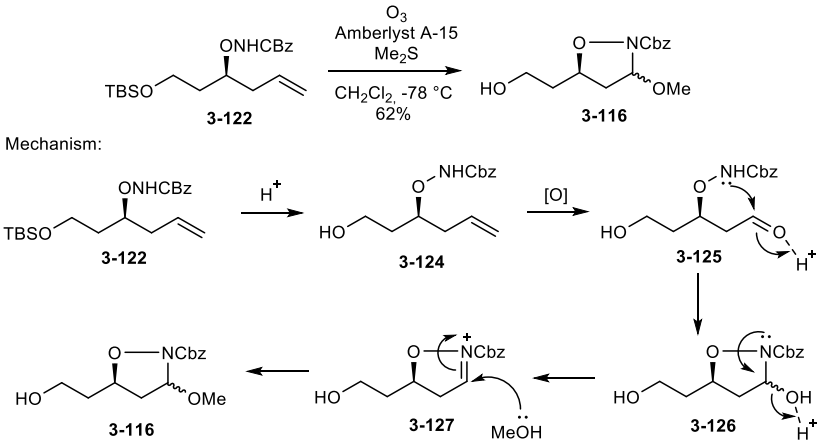


Figure 3.4-7 HPLC trace with enantiopure sample of 3-122

To ensure that enantiopurity of the hydroxylamine was preserved following inversion of the stereocentre during the Mitsunobu reaction with *N*-hydroxyphthalimide (**3-102** to **3-120**), a normal phase chiral high performance liquid chromatography analytical method was developed to determine enantiomeric purity of single enantiomer samples of Cbz-protected hydroxylamine **3-122**.[xi] A Chiralcel® OD-3 column (150 × 4.6 mm I.D.) maintained at room temperature was used in the method. Samples were analysed with an isocratic elution using *n*-Hexane/IPA (90:10, v/v) as the mobile phase, with a detection wavelength of 254 nm. Desired separation of the two enantiomers from the racemic mixture was achieved in <7 minutes, as can be seen in the chromatogram above (Figure 3.4-6). By measuring the ratios of the area under both peaks found in the enantiopure sample, we were heartened to see that the high enantiomeric purity of **3-122** (>98% ee) was preserved (Figure 3.4-7).



Scheme 3.4-11 Ozonolysis reaction and mechanism

[xi] Method was developed for hydroxylamine **3-122** as samples of phthalimide derivative **3-120** were found to be unstable with the chiral chromatographic columns available under standard conditions for chiral HPLC separation.

With *N*-Cbz-protected hydroxylamine **3-122** in hand, ozonolysis in methanol was attempted with Amberlyst A-15 chosen as the acid catalyst for cyclisation. Under these acidic conditions, loss of the TBS ether group was observed to form **3-124**. Oxidative cleavage of the terminal alkene to the corresponding aldehyde (**3-125**) and subsequent condensation of the amine gave hydroxy isoxazolidine **3-126**. Methanolic exchange *via* iminium **3-127** afforded methoxy isoxazolidine **3-116** as an inconsequential mixture of diastereomers in the ratio of 2:1 in 62% yield.

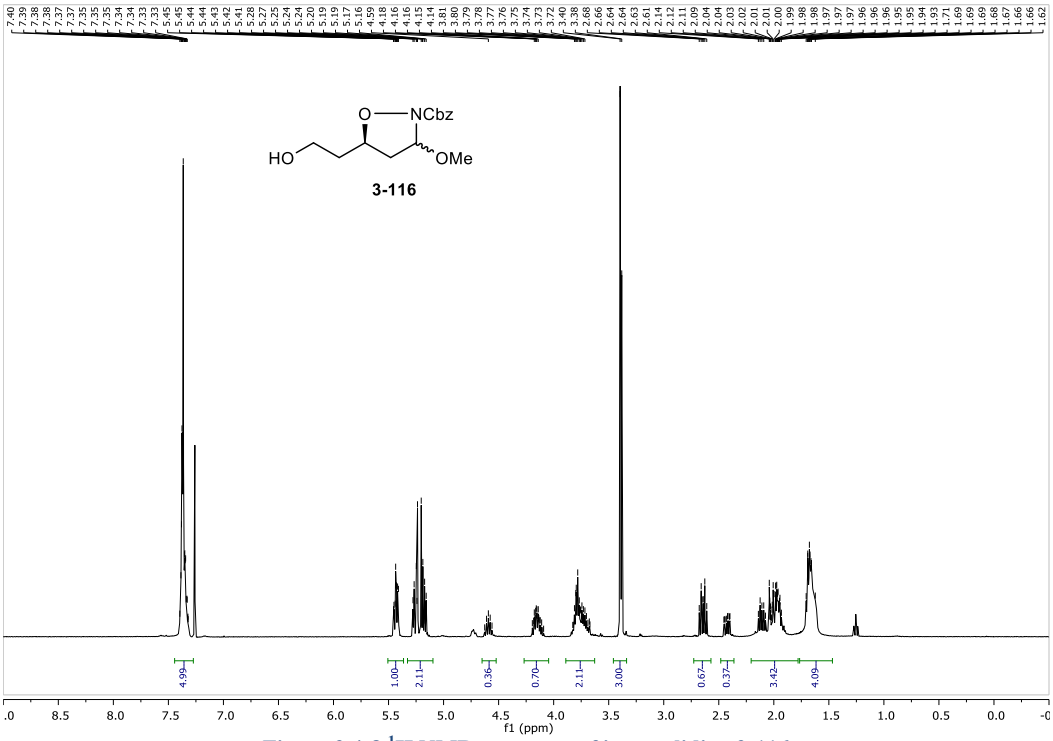
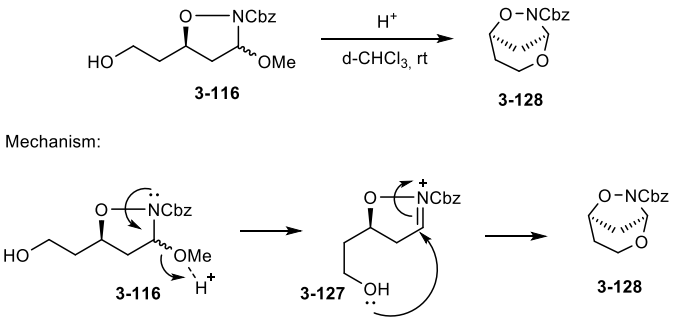


Figure 3.4-8 ^{1}H NMR spectrum of isoxazolidine 3-116

The ^{1}H NMR spectrum shows two singlets, characteristic of a mixture of two methoxy products at δ3.40 and δ3.38 ppm. In the course of our work, we discovered that NMR samples dissolved in acidic $CDCl_3$ led to formation of a new compound as observed by ^{1}H NMR spectroscopy. Formation of this interesting product was not observed in samples that were dissolved in $CDCl_3$ which had been passed through basic alumina prior to usage. ^{1}H NMR spectrum of the new compound indicated absence of –OMe signals which allowed us to assign the new product the structure of acetal **3-128**. We postulated that

methoxyisoazolidine **3-116** undergoes a second cyclisation to from acetal **3-128** as shown in Scheme 3.4-12.[xii]



Scheme 3.4-12 Formation of acetal 3-128 from 3-116

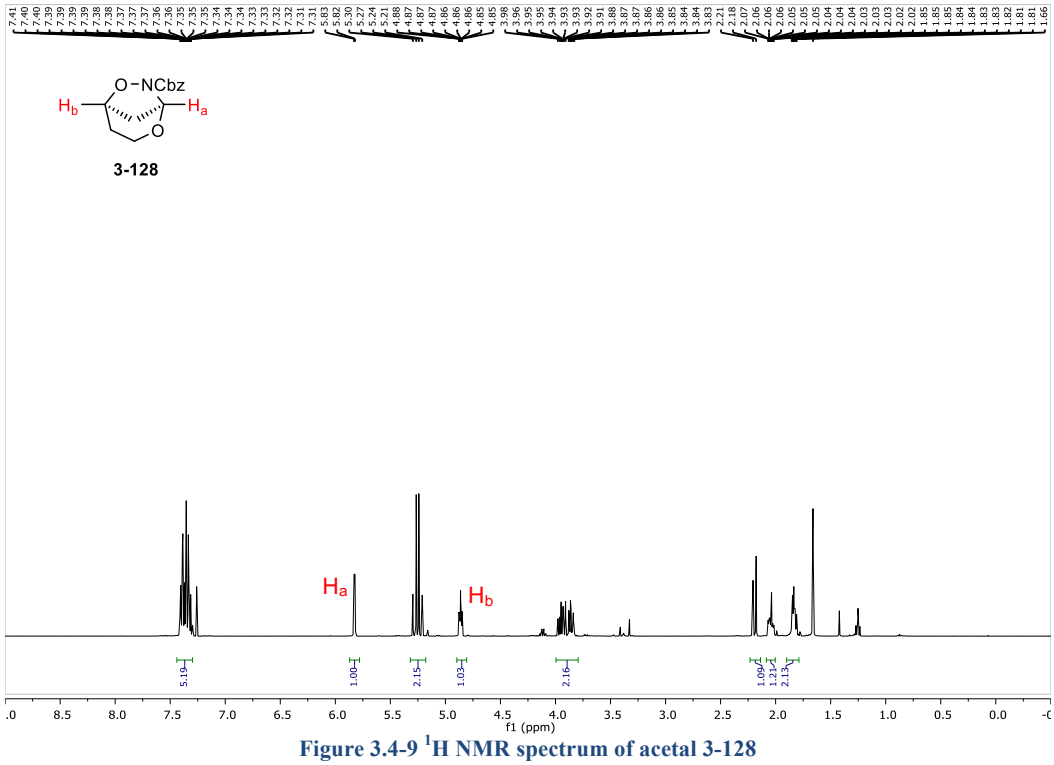


Figure 3.4-9 ^{1}H NMR spectrum of acetal 3-128

We were also able to confirm our characterisation of acetal **3-128** by IR spectroscopy. Comparison of the IR spectra of methoxy isoxazolidine **3-116** and acetal **3-128** provided further proof of our assignment. The broad -OH stretch observed at 3426 cm^{-1} in methoxy isoxazolidine **3-116** (Figure 3.4-11) was clearly absent in the IR spectrum of acetal **3-128** (Figure 3.4-10).

[xii] Even if only acetal **3-128** was obtained, the synthesis would not be affected because it would give the same iminium ion under Lewis acidic conditions.

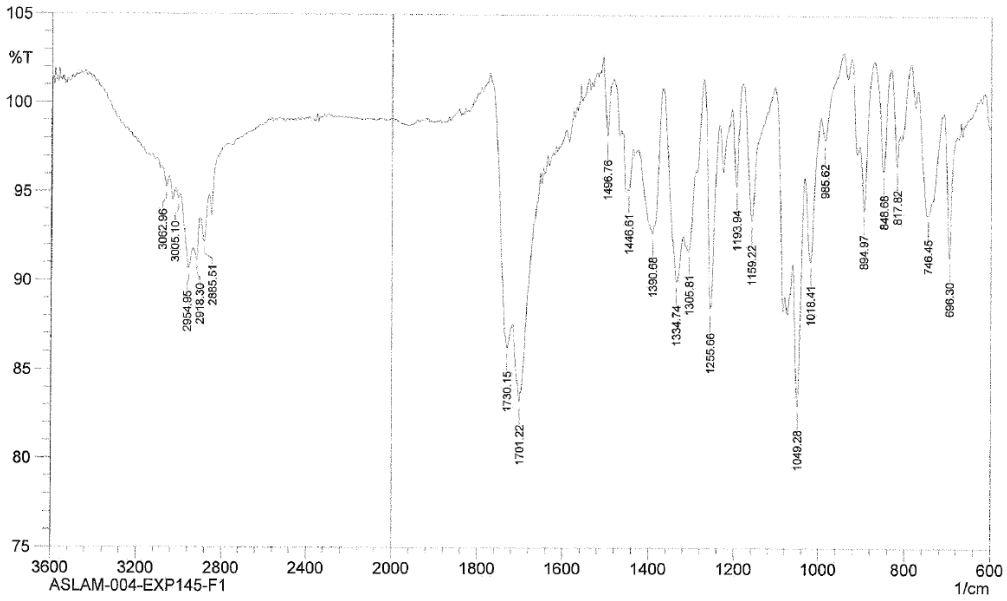


Figure 3.4-10 IR spectrum of acetal 3-128

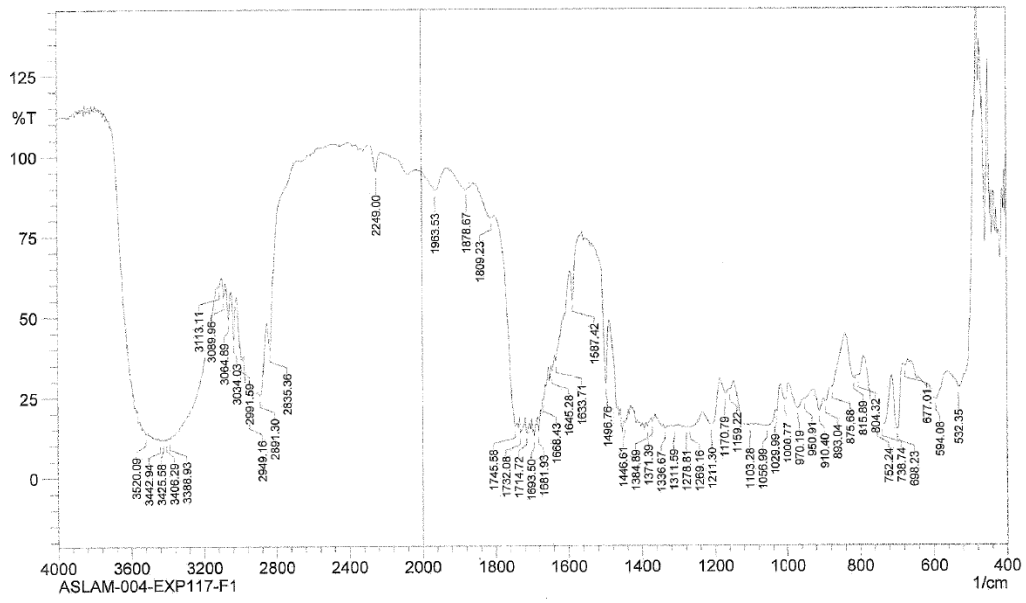
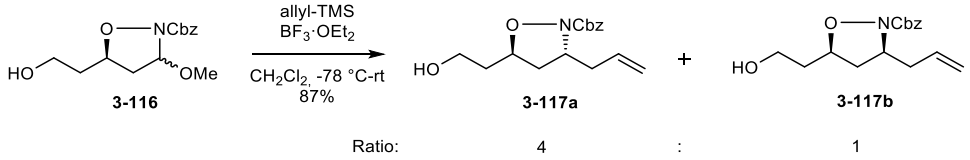


Figure 3.4-11 IR spectrum of methoxyisoxazolidine 3-116

While we reasoned that the acidic nature of $CDCl_3$ could have plausibly triggered the cyclisation, we were surprised to see that the cyclisation was not observed when methoxyisoxazolidine **3-116** was treated with acidic Amberlyst A-15 in analytical grade $CHCl_3$. Another interesting observation was that the cyclisation only occurred with $CDCl_3$ obtained from Aldrich. Conversion of methoxy isoxazolidine **3-116** to acetal **3-128** was not observed in samples dissolved with $CDCl_3$ sourced from Cambridge Isotope for instance. This led us to conclude that there may be a more complex array of factors involved which

may have caused this phenomenon. Nevertheless, we continued to investigate the next step in our synthetic route, the Sakurai allylation reaction.



Scheme 3.4-13 Sakurai allylation reaction with methoxyisoxazolidine 3-116

The reaction was carried out by addition of allyltrimethylsilane to methoxy isoxazolidine **3-116** at -78 °C in the presence of boron trifluoride diethyl etherate as the requisite Lewis acid (Scheme 3.4-13). We were slightly disappointed but rather unsurprised to find a mixture of the *trans* isomer (**3-117a**) to *cis* isomer (**3-117b**) in the ratio of 4:1. At this stage, the major isomer was assigned to be *trans* product **3-117a** based on past experimental outcomes of this well-studied reaction. While the stereoselectivity of this reaction was modest at best, we were satisfied that it was consistent with our findings thus far.

The explanation behind this result is two-fold. The longer side chain resulted in a weakened electrostatic attraction between electronegative OH group and δ+ charge on the iminium ion species which in turn led to a less effective shielding of the undesired face of the isoxazolidine to nucleophilic attack. Another contributing factor to the weaker electrostatic attraction would be the higher degree of rotational freedom introduced by the longer side chain which would lead to increased number of conformations with a lower energy barrier between each conformation. Hence, there would be a greater likelihood of the electronegative hydroxyl group pointing away from the iminium ion species in the isoxazolidine ring. This is unlike the case of chloromethyl isoxazolidine **3-112** and hydroxymethyl isoxazolidine **3-114**, where the electronegative group hovers above the isoxazolidine ring. *In silico* modelling of iminium intermediates of hydroxymethyl isoxazolidine **3-114** and hydroxyethyl isoxazolidine **3-116** were carried out to illustrate this difference in position of the hydroxyl group in the respective lowest energy conformation states (Figure 3.4-12).

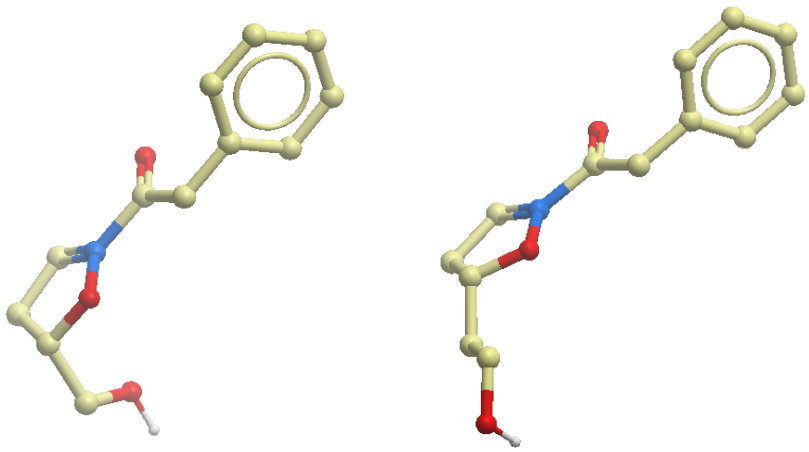
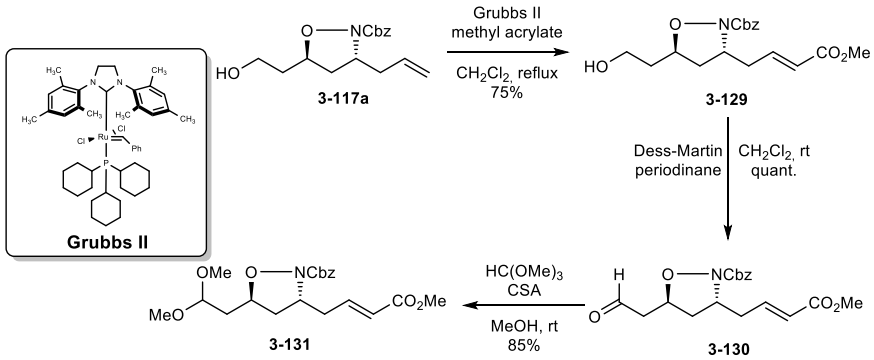


Figure 3.4-12 Lowest energy conformation of iminium intermediates of hydroxymethyl and hydroxyethyl isoxazolidines 3-114 and 3-116

Separation of the isomers proved to be a non-trivial process. We were able to obtain reasonable yields of the *trans* isomer cleanly after several rounds of silica chromatography to comfortably continue the investigation of the following steps.

3.4.3 Preparation of global hydrogenation precursor **3-131**



Scheme 3.4-14 Synthesis of methoxy acetal 3-131

With the successful isolation of Sakurai product **3-117a**, we continued the synthesis by carrying out a cross-metathesis with methyl acrylate using Grubbs II [239] as the catalyst (Scheme 3.4-14).

The cross-metathesis reaction acts by the redistribution of alkene bonds. The widely accepted mechanism, which was originally proposed by Hérison and Chauvin,[240] proceeds by a [2+2] cycloaddition of an alkene to a metal alkylidene to form a metallocyclobutane intermediate, which subsequently undergoes a [2+2] cycloreversion to generate ethylene

and a substrate-loaded metal carbene. This intermediate reacts with the second olefin in the same fashion to release the product and regenerate the catalyst. The second-generation Grubbs catalyst features a saturated *N*-heterocyclic carbene and is more reactive in cross-metathesis than the original version.

With a low catalytic loading of 5 mol%, the reaction proceeded cleanly to generate *trans* alkene **3-129** in 75% yield. We were confident of the formation of the *trans* alkene by investigation of the coupling constants of the diagnostic peaks found in the ^{1}H NMR spectrum. The coupling constant between the two protons found on the alkene (H_a and H_b) was found to be 15.7 Hz which was consistent with that of a *trans* vicinal interaction (Figure 3.4-13).

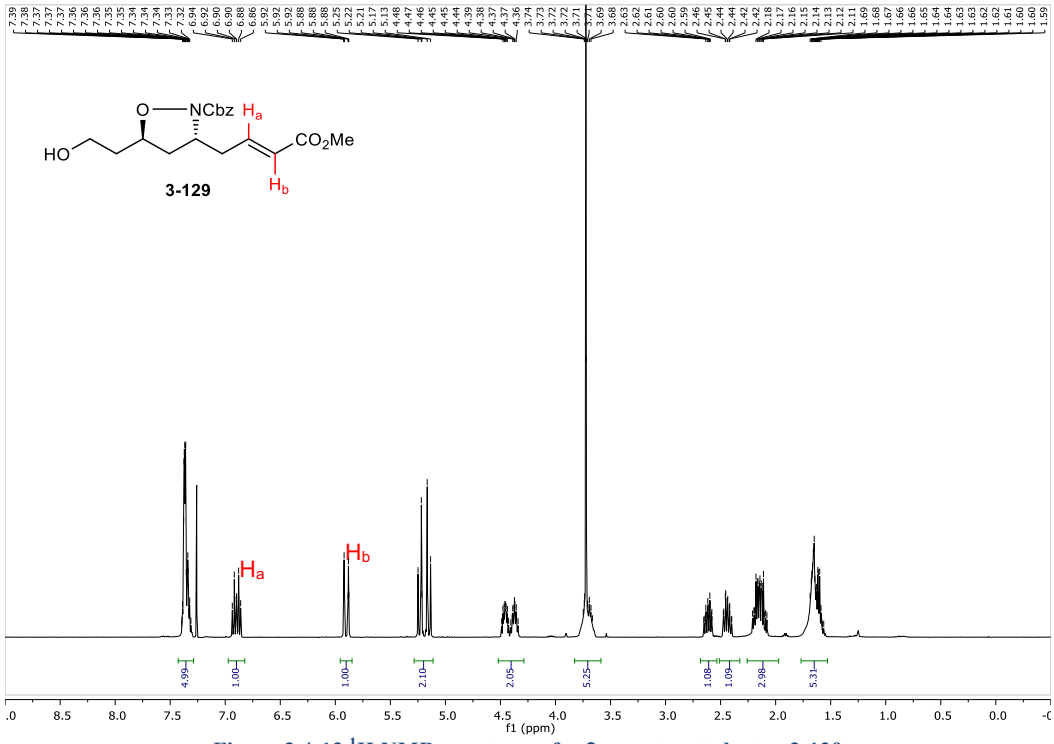
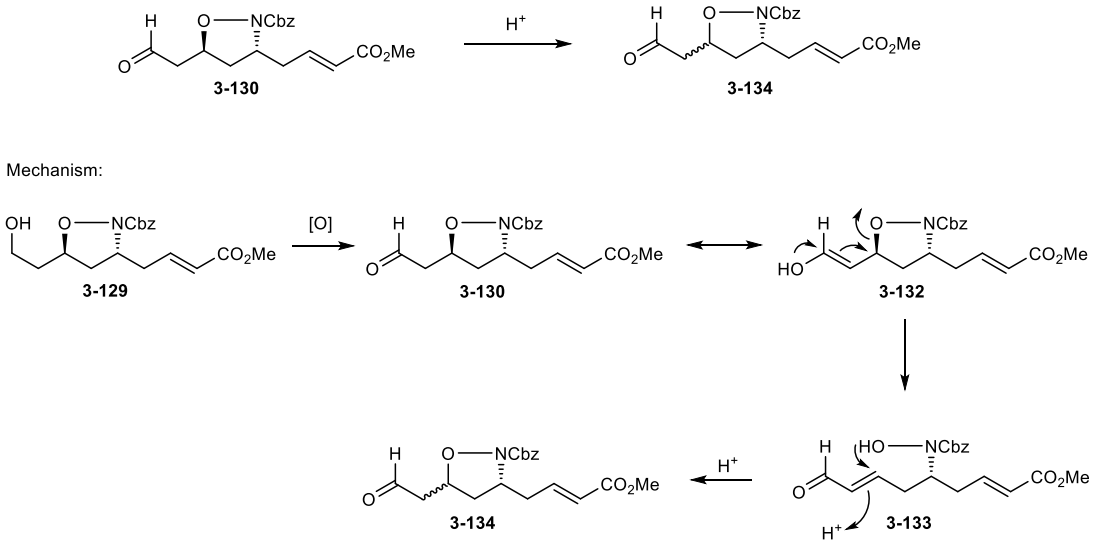


Figure 3.4-13 ^{1}H NMR spectrum of α,β- unsaturated ester 3-129

The terminal alcohol in **3-129** was then oxidised with the commercially available oxidant, Dess-Martin periodinane, to give the desired aldehyde **3-130** in excellent yield. A straightforward work-up with aqueous sodium bicarbonate and sodium thiosulfate was carried out to remove excess periodinane to furnish the aldehyde fairly cleanly. The product was then used in the subsequent reaction immediately. Further purification of the aldehyde

by silica chromatography was found to result in epimerisation of the product through a retro Michael mechanism. Aldehyde **3-130** could tautomerise to enol **3-132** which then proceeds to form intermediate **3-133**. This led to formation of mixtures epimers in **3-134**. Prolonged storage of the aldehyde would also lead to similar degradation of the compound.

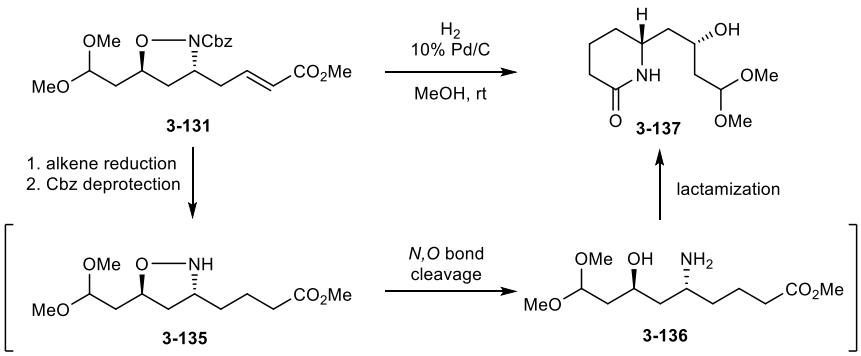


Scheme 3.4-15 Epimerisation of aldehyde 3-130 to 3-134

We then turned our attention to the formation of methyl acetal **3-131**. We first attempted to do so with trimethyl orthoformate and Amberlyst A-15[xiii] as the catalyst. While this reaction worked well on small scale, the reaction proved to be sluggish on scale-up causing undesirable epimerisation on the oxygen stereocentre of the isoxazolidine as a result of extended reaction time (Scheme 3.4-15). We were able to overcome this issue by utilizing an acid with a higher pK_a, camphor sulfonic acid. (pK_a = 1.2). We postulated that the homogeneous nature of the acid shortened the reaction time needed for the complete consumption of precursor **3-130** and the weaker acid strength prevented epimerisation. The reaction gave methoxy acetal **3-131** without any epimerisation and in excellent yield (85%).

[xiii] Amberlyst A-15 is a strongly acidic, sulfonic acid polymeric resin. Measuring pK_a values of solid acids is difficult. An estimated pK_a of C_6H_5-SO_3H= -6.5 based on Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*, Wiley-Interscience: New York, 1985; Ch. 1.

3.4.4 Global hydrogenation and cyclisation reaction



Scheme 3.4-16 Global hydrogenation of 3-131

We first attempted hydrogenation of methoxy acetal **3-131** with 10% Pd/C in methanol at room temperature and pressure (Scheme 3.4-16). The reaction could be done in flow using the H-cube reactor and by batch method in a round bottomed flask with a H_2 balloon. While both methods gave the desired product with the same yield (92% yield), hydrogenation carried out with the H-cube reactor took a shorted amount of time (<4h in flow vs >8 h by batch). The product isolated from both reactions was found to be identical whereby the Cbz group was removed, alkene bond was reduced (**3-135**) and the *N,O* bond of the isoxazolidine was cleaved (**3-136**). This ultimately led to the formation of lactam **3-137** in quantitative yield. Through analysis of NMR spectroscopic data, we confirmed the formation of lactam **3-137**. An absence of peaks in the aromatic and the alkenyl regions of the ^{1}H NMR spectrum confirmed reduction of the double bond and removal of the Cbz group. Downfield shift of the signal corresponding to the carbonyl carbon from δ166.5 to δ172.1 in the ^{13}C NMR spectrum correlated with a conversion of the ester in **3-131** to a lactam in **3-137**. All the other signals found in the ^{13}C spectrum were in the expected range and clearly support the reported structure. Hence, we could unequivocally confirm formation of the lactam.

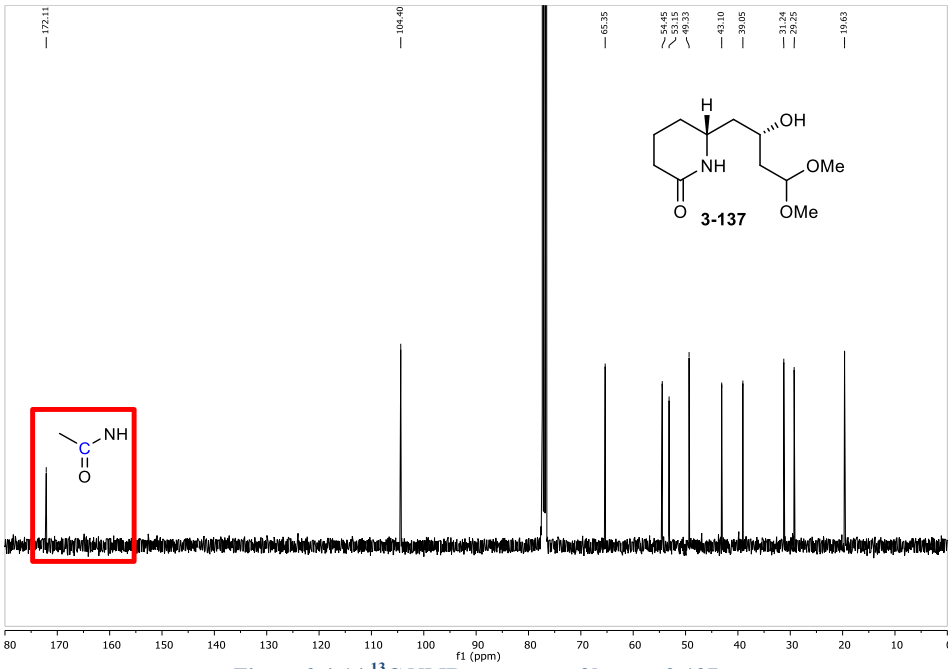


Figure 3.4-14 ^{13}C NMR spectrum of lactam 3-137

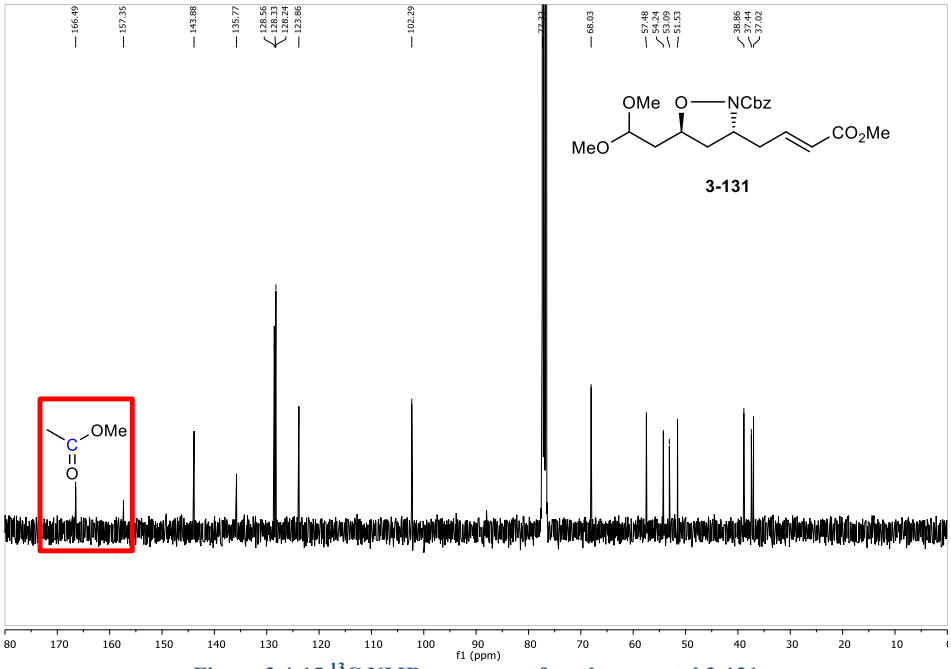


Figure 3.4-15 ^{13}C NMR spectrum of methoxy acetal 3-131

Pleased with the result, we turned our attention to exploring conditions necessary for the formation of quinolizidine **3-34**. The transformation was first carried out in acetonitrile in the presence of Amberlyst A-15. Much to our dismay, this did not lead to the formation of the desired quinolizidine **3-34** but to a complex mixture of products instead. We were however, able to isolate trace amounts of quinolizidine **3-138**, the structure of which was assigned by examination of ^{1}H NMR spectroscopic data (Figure 3.4-16). Signals found at

δ7.44 and δ5.33 ppm correspond to a double bond connected to strongly electron withdrawing group like the lactam found in **3-138**. Presence of the methoxy group is represented by the singlet peak at δ3.37 ppm. The stereochemistry of the methoxy group was not determined.

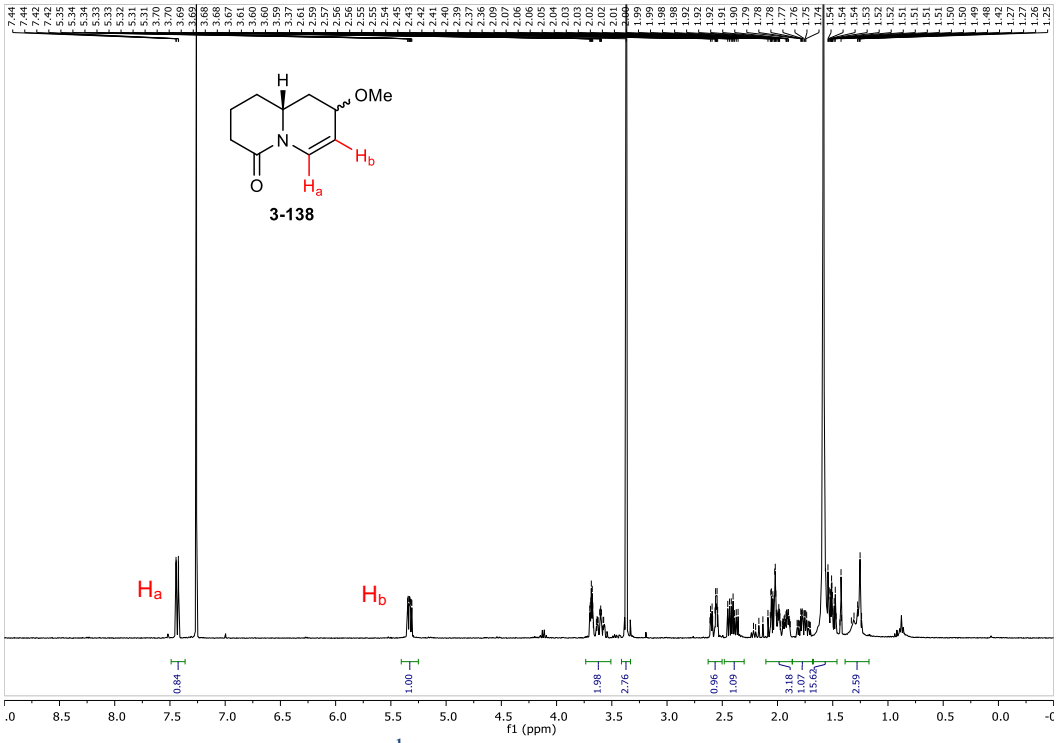
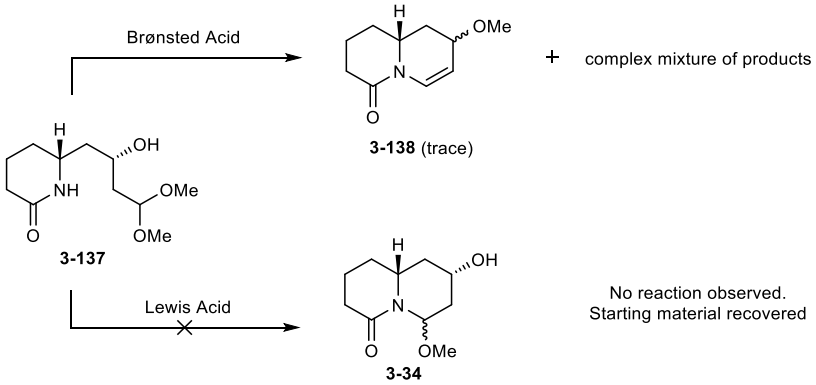


Figure 3.4-16 ^{1}H NMR spectrum of quinolizidine 3-138

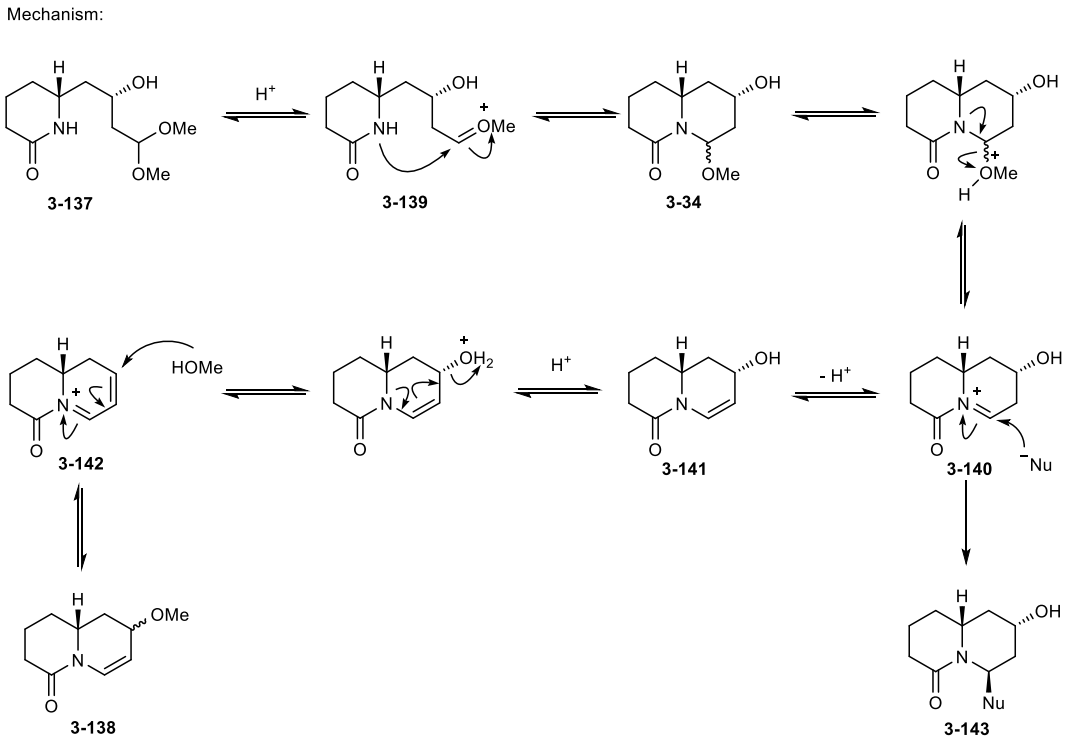


Scheme 3.4-17 Reaction of methoxy acetal 3-137 with Bronsted and Lewis acids

Other protic acids such as acetic acid, *p*-toluenesulfonic acid and trifluoroacetic acid were also explored. For each of the protic acids, we observed formation of quinolizidine **3-138** (Scheme 3.4-17). Lactam **3-137** was also treated with a range of Lewis acids including $BF_3{\cdot}Et_2O$, $TiCl(Oi\text{-}Pr)_3$, BCl_3, and $TiCl_4$. Interestingly, we did not observe any cyclisation

and recovered only starting material, lactam **3-137**, even with longer reaction times and higher reaction temperatures.

The reaction was further investigated in CD_3CN and monitored by ^1H NMR spectroscopy. In the presence of TFA, diagnostic peaks that corresponded to side product **3-138** appeared almost instantaneously which suggested that elimination of the secondary alcohol is kinetically favoured.



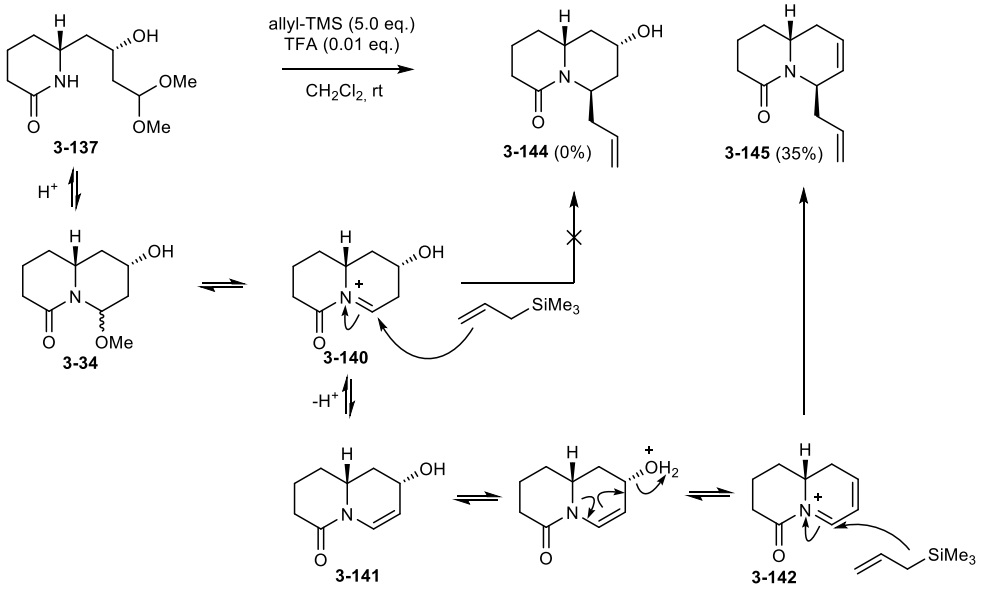
Scheme 3.4-18 Proposed mechanism for formation of 3-138

We proposed a mechanism for the formation of product **3-138**. Cyclisation *via* intermediate **3-139** occurred spontaneously to generate the desired acetal quinolizidine **3-34** which proved to be susceptible to elimination of the hydroxyl group under acidic conditions. Iminium intermediate **3-140** could tautomerise to enamine **3-141**. Under acidic conditions, the hydroxyl group is eliminated to form **3-142**. This could undergo a nucleophilic attack with a methoxy anion to form side product **3-138**. With the elimination of the secondary alcohol proving to be problematic, several alternative strategies were pursued.

We initially sought to overcome this problem by carrying out the cyclisation in the presence of a suitable nucleophile that would be able to sequester the desired methoxy quinolizidine

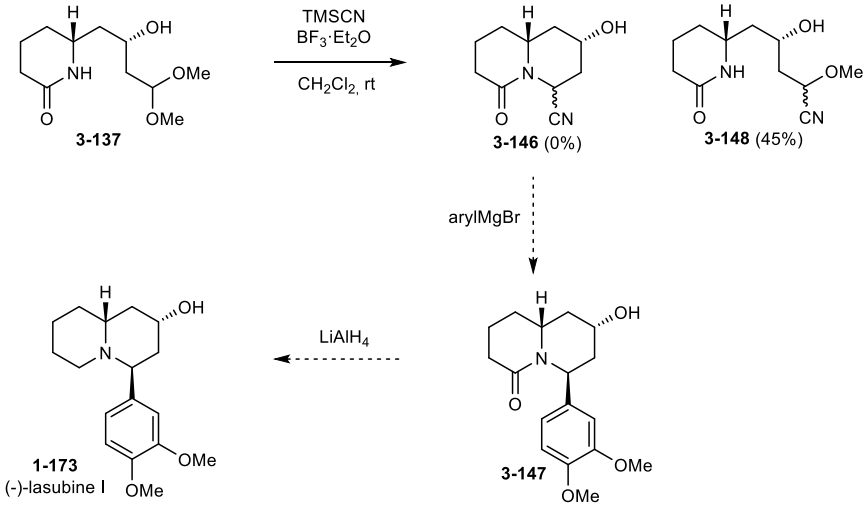
3-34 generated *in situ* and thereby inhibit elimination of the alcohol. Preferential axial attack by the nucleophile with iminium intermediate **3-140** would give quinolizidine **3-143** with the desired stereoconfiguration.

We chose to first attempt this with an excess amount of allyltrimethylsilane as the trapping reagent in the presence of trifluoroacetic acid. Interestingly, we hoped to isolate **3-144** but we observed the formation of **3-145** instead, indicating that elimination preceded nucleophilic attack.



Scheme 3.4-19 Allylation reaction of 3-137

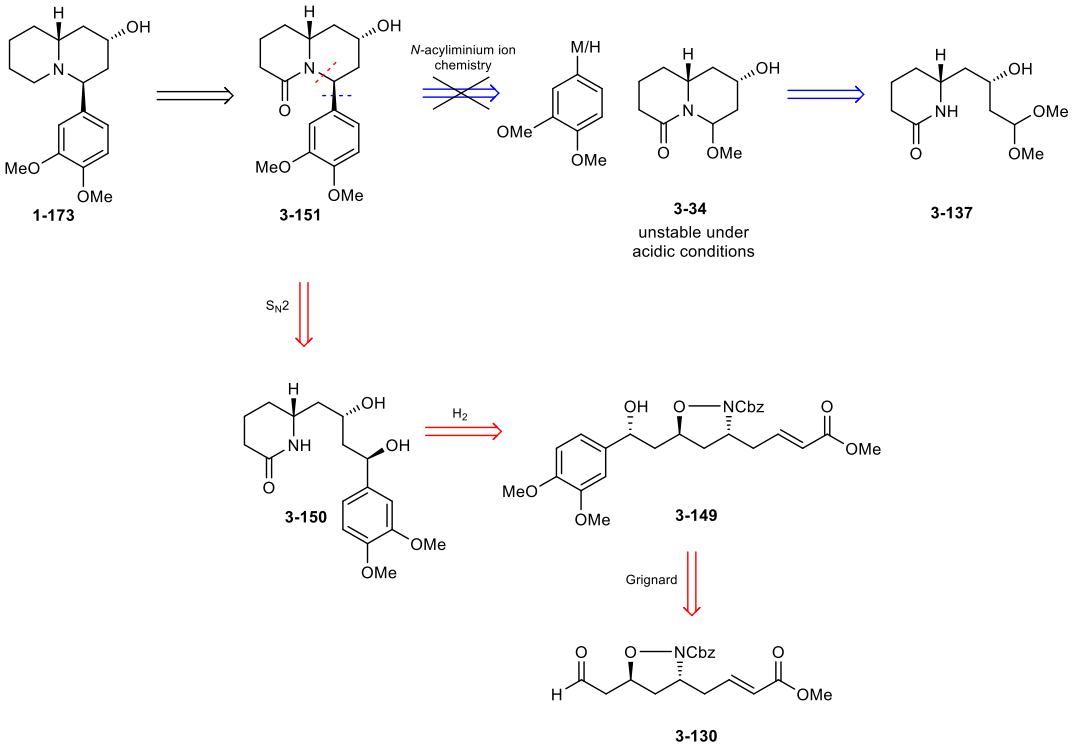
Another cyclisation strategy attempted was the *in situ* conversion of methoxy quinolizidine **3-34** to cyano quinolizidine **3-146** which may be rendered unsusceptible to elimination with the absence of a protic acid source. Treatment with an aryl Grignard reagent would then effect formation of quinolizidine **3-147** and subsequent reduction would give the desired natural product, (-)-lasubine I. Lactam **3-137** was treated with TMSCN in the presence of $BF_3 \cdot Et_2O$. Unfortunately, this proved to be unsuccessful in effecting cyclisation. This led instead, to the formation of cyanomethoxy derivative **3-148** as a mixture of isomers. In the absence of $BF_3 \cdot Et_2O$, no reaction was observed and starting material was recovered.



Scheme 3.4-20 Attempted conversion of 3-137 to 3-146

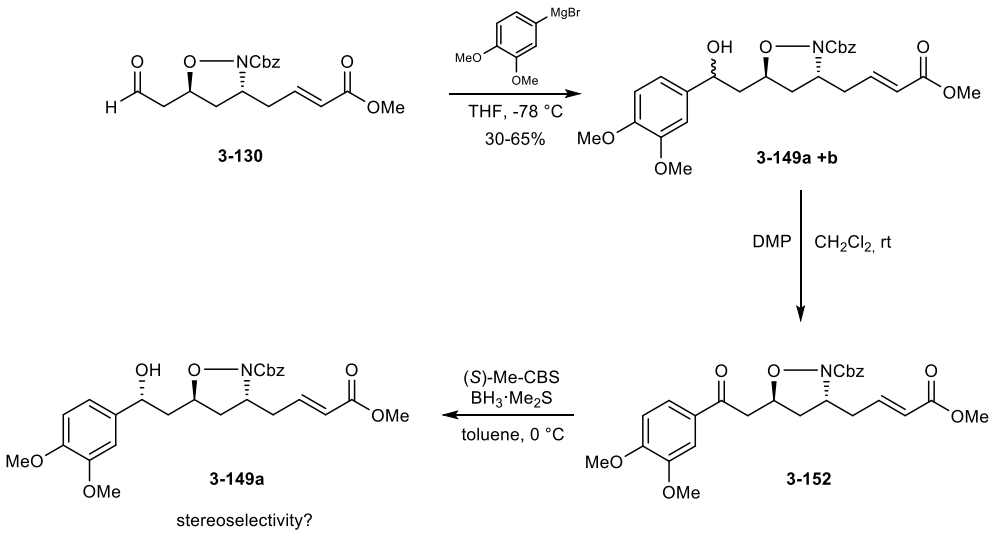
We chose not to protect the secondary alcohol, as we were certain that doing so would make it a better leaving group or at least, would not make it a worse leave group than the free alcohol, leading to a faster rate of elimination. Hence, with the above two strategies proving to be unsuccessful at mitigating the elimination of the secondary alcohol and no other viable strategy forward, we chose to abandon this route.

3.4.5 Revised synthetic strategy to (-)-lasubine I



Scheme 3.4-21 Revised synthetic strategy to lasubine I

Since we were not able to isolate quinolizidine **3-34**, we decided to introduce the aryl group at an earlier stage *via* a Grignard addition to aldehyde **3-130** (Scheme 3.4-21). While we were uncertain of the stereoselectivity of the Grignard reaction, we hypothesised that oxidation of the Grignard product **3-149** to the corresponding ketone, followed by asymmetric reduction with a suitable catalyst, would provide access to the desired alcohol. Global hydrogenation would then furnish us with diol **3-150** and we would be able to effect cyclisation by a nucleophilic displacement reaction. Subsequent reduction of lactam **3-151** would give us the desired natural product.



Scheme 3.4-22 Synthesis of desired alcohol 3-149a

We first examined conditions for addition of the requisite Grignard reagent, 3,4-dimethoxyphenyl magnesium bromide to aldehyde **3-130** (Scheme 3.4-22). Treatment of the aldehyde with excess of the Grignard reagent -78 °C, produced the desired alcohol as a diastereomeric mixture. The diastereomeric ratio and reaction yield had an inverse relation to the scale at which the reaction was carried out. Diastereomeric ratios were better in small scale experiments (approx. 2:1) but were consistently found to be poorer (1:1) on larger scale reactions as could be seen by integration of the diagnostic peaks in the ^{1}H NMR spectra (Figure 3.4-17 and Figure 3.4-18). The reaction yield was also significantly higher on small scale (~65%) but yields on large scale reactions ranged between 30 to 40%. We suspect that purity of the aldehyde (earlier found to be susceptible to epimerisation) and

the amounts of acidic by-product from the previous Dess-Martin oxidation (**3-129** to **3-130**) present may have had implications on the reaction outcome.

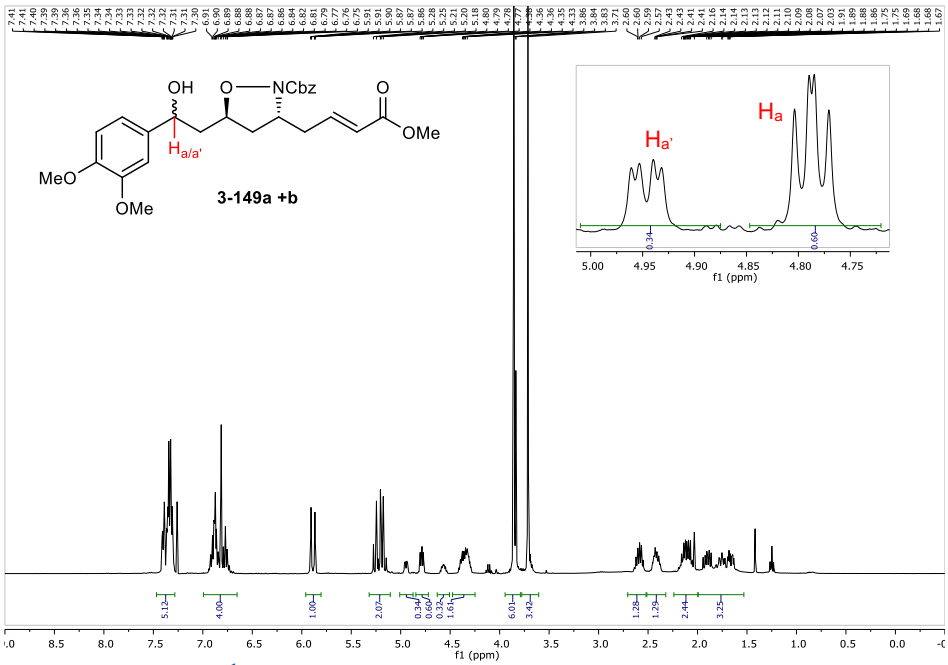


Figure 3.4-17 ^{1}H NMR of Grignard addition product on a small reaction scale

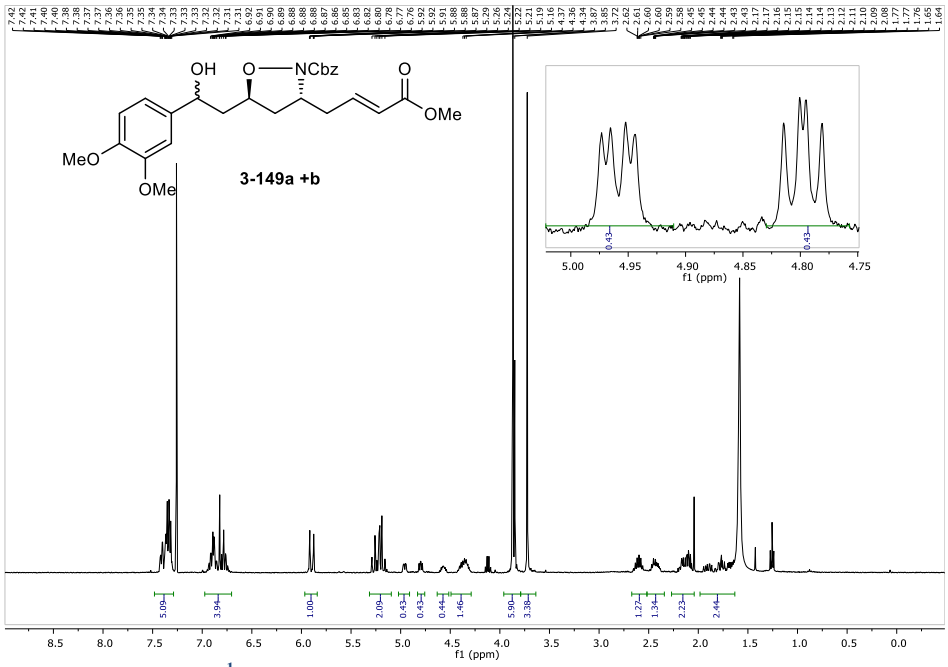


Figure 3.4-18 ^{1}H NMR of Grignard addition product on a larger reaction scale

Subsequent oxidation of the secondary alcohol with Dess-Martin periodinane to the ketone proved to be facile and furnished ketone **3-152** in 80% yield. With the ketone in hand, we turned our attention to the asymmetric reduction to the desired alcohol. We opted to do this

with the Corey-Bakshi-Shibata (CBS) reduction, where an achiral ketone is reduced enantioselectively in the presence of a chiral oxazaborolidine-borane complex.[241]

The reaction was first attempted using (*S*)-Methyl-CBS oxazoborolidine as a chiral catalyst and $BH_3 \cdot Me_2S$ as a hydride source. No reaction was observed at temperatures below 0 °C. An excess amount of BH_3 was also required to drive the reaction to completion. Interestingly, we observed that both (*R*) and (*S*) catalyst favoured formation of the same isomer with similar stereoselectivity ratios obtained. This could be seen clearly by comparison of ^1H NMR spectra of the alcohols generated from reactions with both chiral ligands (Figure 3.4-19 and Figure 3.4-20). The ratio of the two isomers were measured based on the integrals of two diagnostic peaks at δ4.00 and δ4.95 ppm. In both spectra, the ratio of the integrals of the two peaks were approximately 7:1 and in favour of the same isomer. The same reaction was also attempted with different chiral oxazoborolidine ligands ((*S*)-butyl-CBS, (*S*)-*o*-tolyl-CBS) and borane adducts (catecholborane, $BH_3 \cdot NHMe_2$), at different reaction times, varying temperatures with very little change to the stereoselectivity.

This proved that the catalyst effected very little stereocontrol over the substrate. Ketone reduction was also carried out with $BH_3 \cdot Me_2S$ in the absence of chiral catalyst. The reaction favoured the formation of the same isomer with the same ratio of stereoisomers obtained. We postulated that stereoselectivity was more likely substrate controlled and the catalyst had very little or no effect to the outcome.

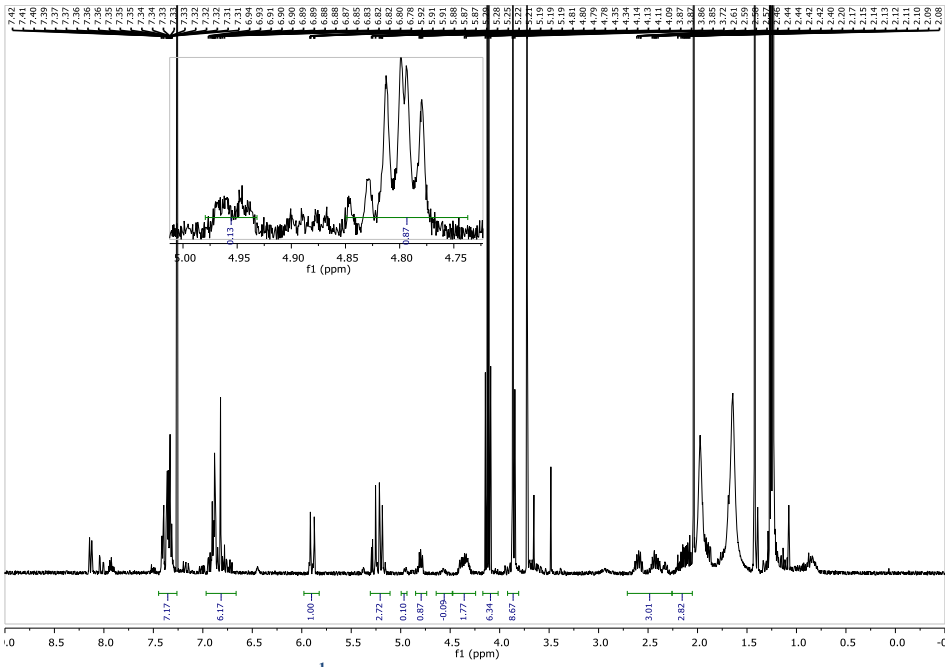


Figure 3.4-19 ^{1}H NMR of 3-149a+b with (*S*)-Me-CBS ligand

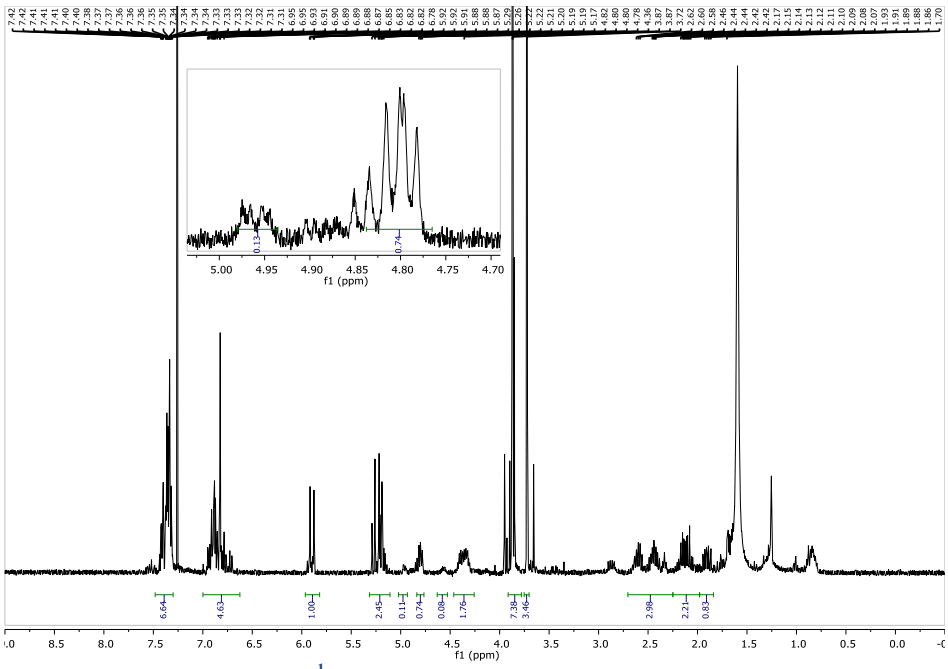
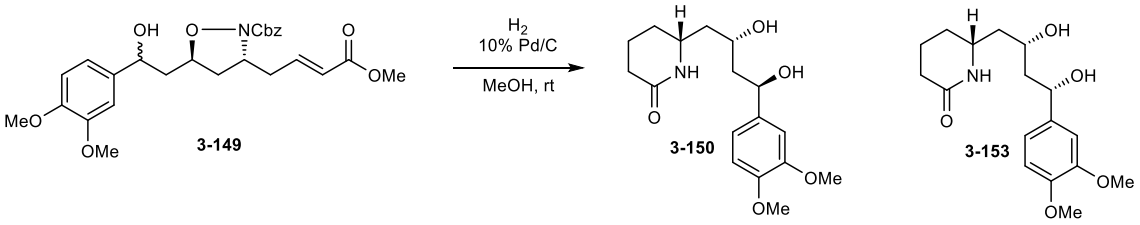


Figure 3.4-20 ^{1}H NMR of 3-149a+b with (*R*)-Me-CBS ligand

At this stage, we were unable to ascertain whether the CBS reduction favoured the 1,3- *syn* diol or the 1,3-*anti* diol. While we were disheartened by the low stereoselectivity attained thus far, we proceeded to carry out the global hydrogenation of the 2:1 mixture of alcohols obtained after Grignard addition.



Scheme 3.4-23 Global hydrogenation of 3-149

Global hydrogenation of the alcohol proceeded as expected to form lactams **3-150** and **3-153**, with an overall yield of 75%. We were fortunate to be able to separate the two lactams cleanly and obtain a crystal structure of the minor stereoisomer. A definitive confirmation of the stereochemical assignments came from the X-ray structure of compound, whose ORTEP view is shown in Figure 3.4-21. In the structure below, O3 and O2 are pointing in opposite directions. With this information in hand, we were able to assign the minor isomer as 1,3-*anti*-diol.

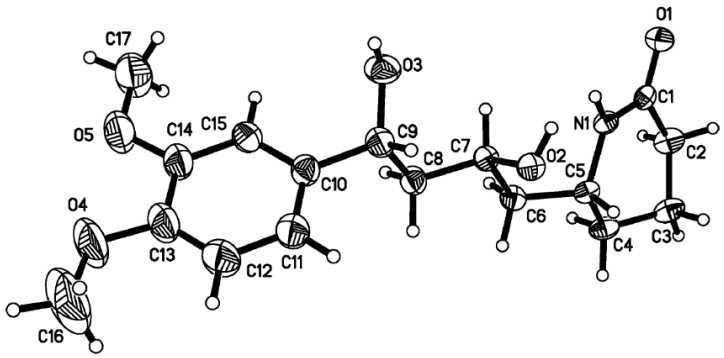
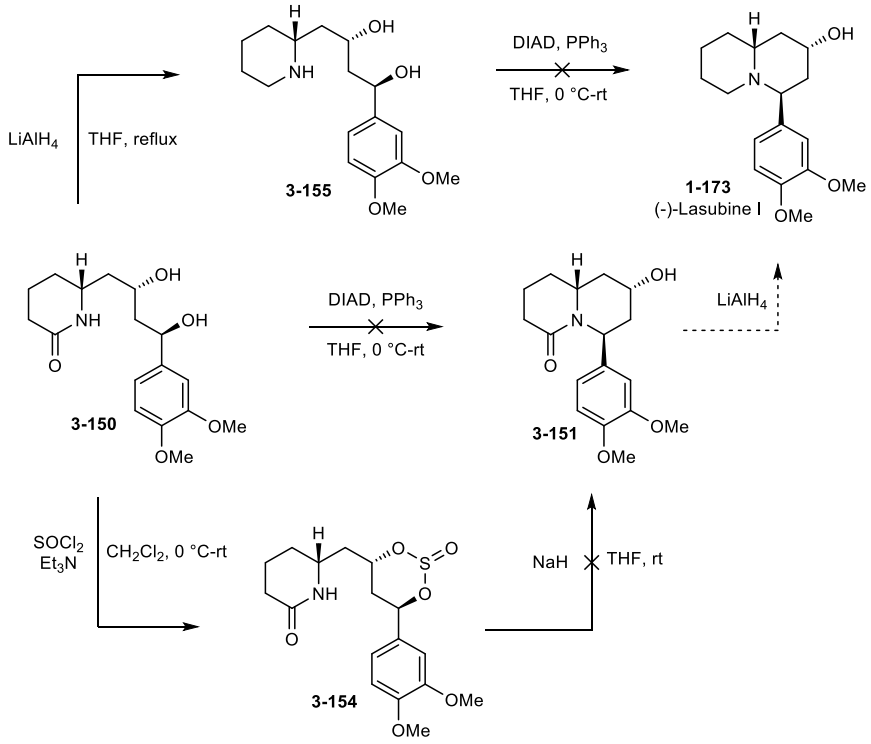


Figure 3.4-21 X-ray crystal structure of minor isomer from hydrogenation of 3-149

Despite the rather disappointing relevation, we continued to pursue the synthetic route with the minor isomer **3-150** and proceeded to investigate the cyclisation *via* a Mitsunobu reaction (Scheme 3.4-24).[242] We were dismayed to find that lactam **3-150** was unreactive and sought to activate the secondary benzylic alcohol in **3-150** by forming cyclic sulfite **3-154** and then carrying out the cyclisation in the presence of an appropriate base. While we were successful at forming the desired cyclic sulfite following conditions reported by Sharpless,[243] we were unable to effect cyclisation and the lactam remained unreactive when treated with NaH.

Motivated by a report by Saha and co-workers[85] on a successful Mitsunobu cyclisation with an amine in their synthesis of (-)-lasubine II, we decided to attempt the Mitsunobu reaction with corresponding amine **3-155**. Lactam **3-150** was first reduced with excess $LiAlH_4$ to afford the amine in quantitative yield. Mitsunobu reaction with amine **3-155** failed to give the desired product, and instead resulted in formation of a complex mixture of products, which we were not able to characterise.



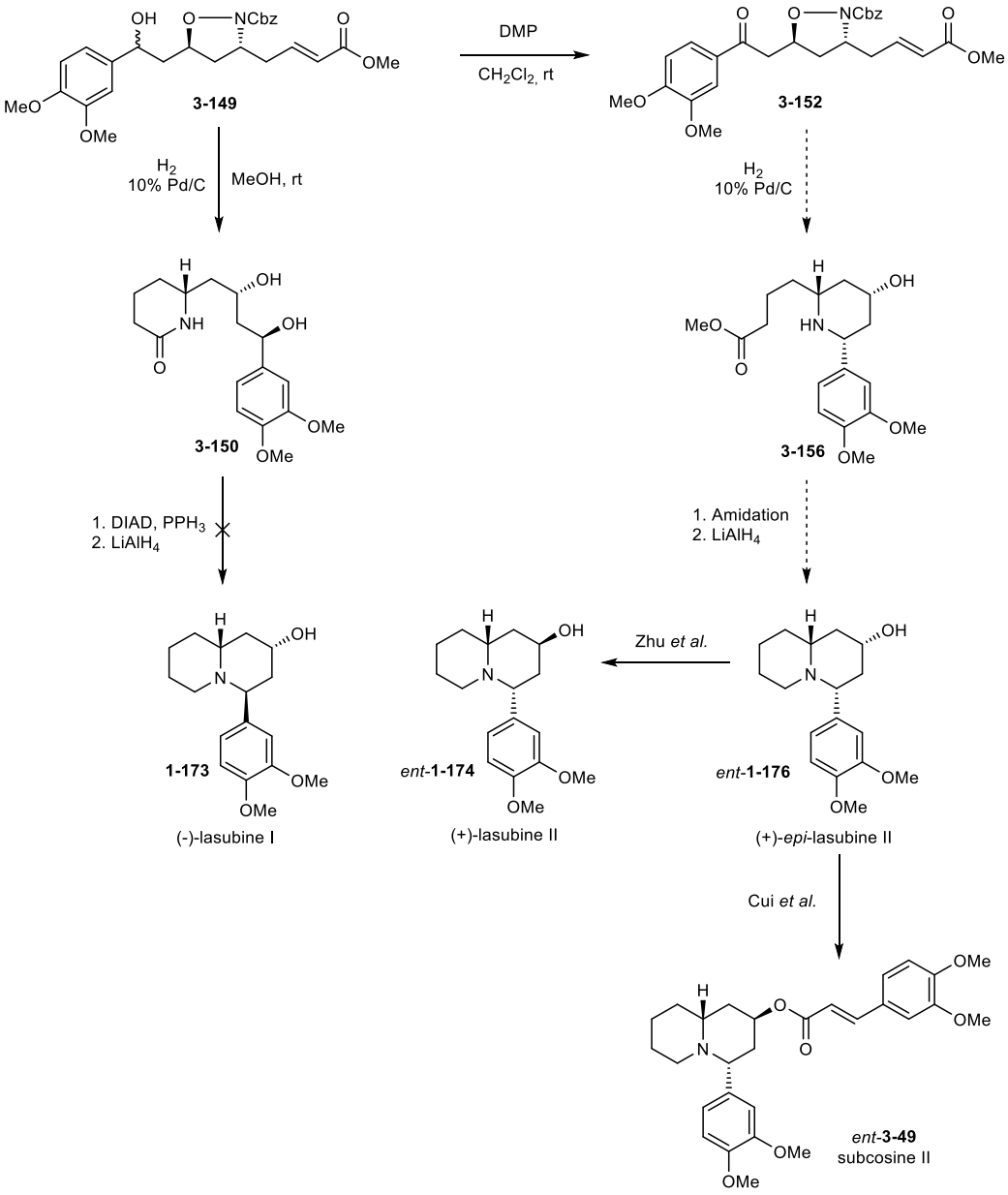
Scheme 3.4-24 Attempted cyclisation of 3-150

3.4.6 Formal syntheses of lasubine II and subcosine II

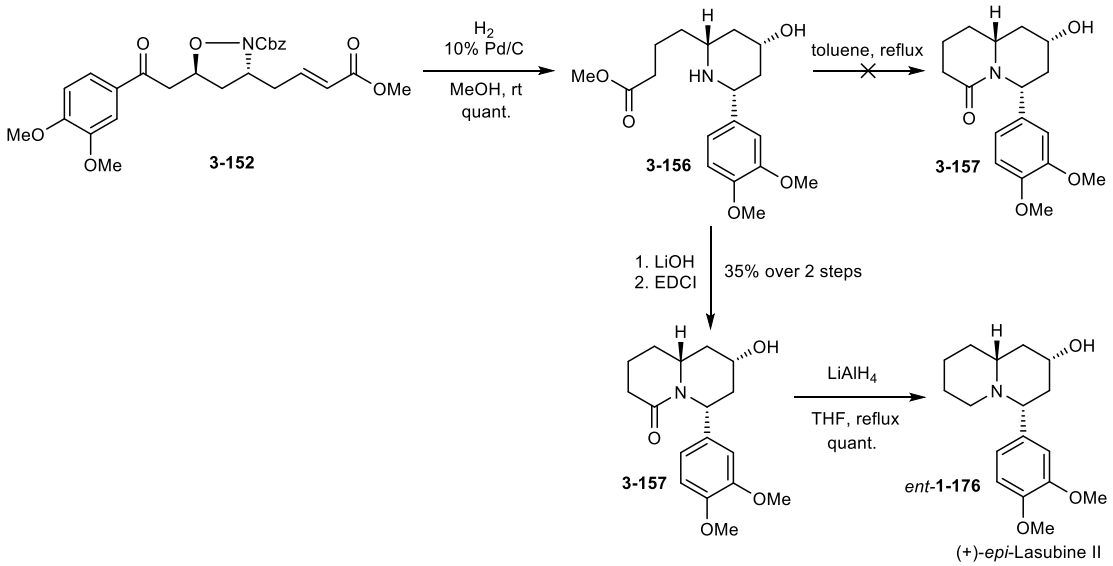
With no viable route to (-)-lasubine I (**1-173**), we opted to pursue another member of the *Lythraceae* family, lasubine II. The unnatural isomer, (+)-lasubine II, *ent*-**1-174** differs only slightly from (-)-lasubine I (**1-173**) as shown in Scheme 3.4-25. We envisioned access to (+)-lasubine II could be achieved *via* the synthesis of (+)-*epi*-lasubine II (*ent*-**1-176**), a known intermediate. Mitsunobu inversion of the secondary alcohol in *ent*-**1-176** following a protocol first reported by Zhu and Ma[72] would lead us to a formal synthesis of (+)-

lasubine II and by further extension, (-)-subcosine II (*ent*-**3-49**), following a procedure reported by Cui *et al*.[244]

Retrosynthetic analysis of (+)-*epi*-lasubine II leads us to piperidine **3-156** as a suitable precursor. We envisioned the latter compound may be formed *via* hydrogenation reduction of ketone **3-152**, an intermediate which we had successfully synthesised earlier in our investigations towards (-)-lasubine I. In theory, the stereochemical outcome of the hydrogenation should be dictated by the axial attack of the nucleophile on the imine generated *in situ*.



Scheme 3.4-25 Proposed synthetic strategy to (+)-lasubine II and subcosine II



Scheme 3.4-26 Synthesis of (+)-*epi*-lasubine II

With this plan in mind, we set out to carry out the hydrogenation reaction. This was effected by passing a solution of ketone **3-152** through the H-cube reactor with 10% Pd/C as the catalyst at a rate of 1.0 ml/min (Scheme 3.4-26), yielding ester **3-156** in quantitative yield. We were pleased to confirm that the stereochemical outcome was as predicted by analysis of the ^{1}H NMR spectrum where the coupling constants of the benzylic proton were found to be 11.4 and 2.4 Hz. These values correspond to a proton that is in an axial position based on the Karplus equation. Hence, the aromatic group was in a *cis* relation to the –OH group.

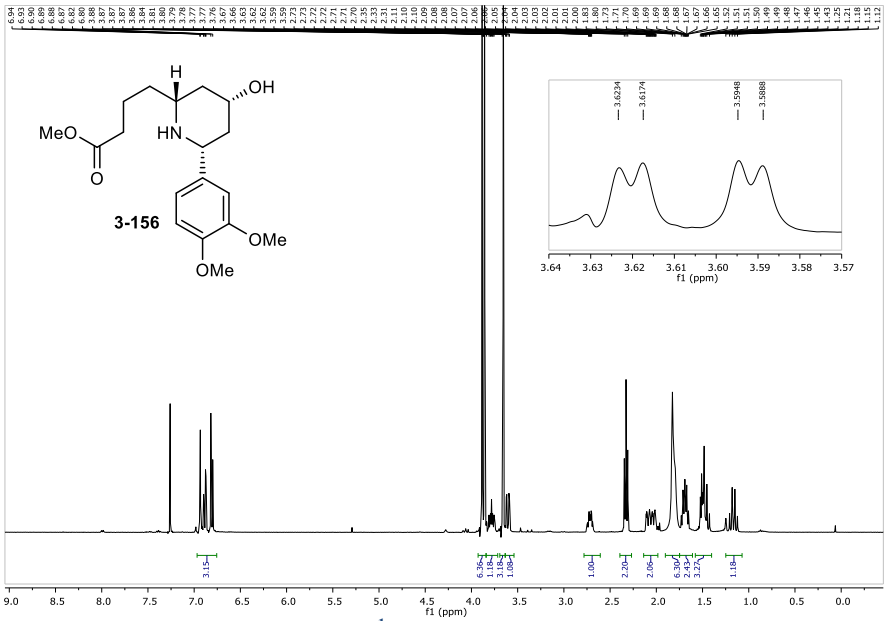


Figure 3.4-22 ^{1}H NMR spectrum of 3-156

Subsequently, we attempted to form the lactam by heating a solution of ester **3-156** in refluxing toluene. This did not effect cyclisation, no reaction was observed and piperidine **3-156** was recovered.[xiv] We were however, able to effect lactamisation *via* a two-step procedure. Ester **3-156** was converted to form the carboxylate with LiOH in aqueous methanol following which amidation in the presence of EDCI gave lactam **3-177** with an overall yield of 35%. Subsequent $LiAlH_4$ reduction in THF under reflux conditions gave the desired (+)-*epi*-lasubine II in good yield. Comparison of ^{1}H, ^{13}C NMR data and specific rotation were in good agreement with reported values,[75] hence confirming the identity of the final compound isolated.

3.5 Conclusion

While we were not successful in the synthesis of (-)-lasubine I, we were able to access (+)-*epi*-lasubine II, bringing about the formal syntheses of (+)-lasubine II and subcosine II. The synthesis was completed in 14 steps, starting from TBS protected epoxide **3-111**.

From this work, we were also able to further validate the Sakurai reaction as a method to gain access to 1,3-aminoalcohols in a stereoselective manner and showcase the reaction for the synthesis of a natural product.

Despite the setbacks, the synthetic route still fulfils our initial profile for a divergent synthesis and could be applied to the synthesis of analogues of the natural product. The work presented would serve as a backdrop for future studies towards the synthesis of the macrocycle, (+)-vertine and its analogues presented earlier. This would enable medicinal chemistry studies to investigate its activity against *Plasmodium falciparum*.

[xiv] A similar experience was encountered in our group for the synthesis of Nuphar alkaloids where cyclisation of the 6-membered ring could not be effected through heating.

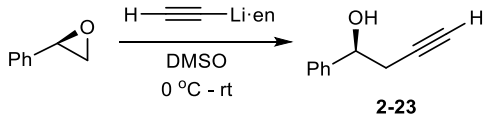
Chapter 4

EXPERIMENTAL

4.1 General Methods

Unless otherwise indicated, all starting materials were obtained from commercial suppliers and were used without further purification. Each reaction with air- and moisture-sensitive components was carried out under a nitrogen atmosphere unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was performed on Merck DC precoated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualisation was performed with a 254 nm UV lamp, or staining with ammonium molybdate or potassium permanganate solution. Flash column chromatography was performed using silica gel 60 (particle size 0.040-0.063) purchased from Merck. All melting points were measured on a Stanford Research Systems OptiMelt apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1030 polarimeter using a 10 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL 400 MHz or JEOL 396 MHz spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ^{1}H, δ 77.0 for ^{13}C) where possible or alternatively to $SiMe_4$ (δ = 0.00 ppm) as internal standard. Coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). IR spectra were obtained on a Jasco FT/IR-4100 spectrometer or Shimadzu IR Prestige-21 spectrometer and are reported in frequency of absorption (cm^{-1}). Low resolution mass spectra were obtained on a Waters Acquity UPLC PDA with ZQ2000 system. High-resolution mass spectra (HRMS) were acquired on a Waters Q-ToF Premier mass spectrometer in positive ion mode.

(S)-1-phenylbut-3-yn-1-ol (**2-23**)



2-23

To a stirred mixture of lithium acetylide-ethylenediamine complex (12.90 g, 140.0 mmol) in anhydrous DMSO (80 mL) cooled to 0 °C in an ice-water bath was added (*R*)-styrene oxide[xv] (11.4 mL, 100.0 mmol) dropwise *via* an addition funnel. Once addition was complete, the reaction mixture was warmed slowly to room temperature and left to stir for a further 2 hours. Once reaction was determined to be complete by TLC analysis, the reaction mixture was poured into 200 mL of iced water and extracted with Et_2O (5 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give desired alkyne **2-23** (11.72 g, 80%) as a yellow oil that was used in the subsequent reaction without further purification.

R_f 0.27 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -12.1 (*c* 0.14, CH_2Cl_2); {lit.[xvi] $[\alpha]_D^{28}$ -12.1 (*c* 1.5, MeOH)}

ν_{max} (neat) 3404, 3296, 3062, 3032, 2910, 1635, 1494, 1454, 1201, 1082, 1014 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.27-7.42 (5H, m), 4.87 (1H, t, *J* 6.3 Hz), 2.64 (2H, dd, *J* 6.3, 2.5 Hz), 2.37 (1H, br s), 2.07 (1H, t, *J* 2.5 Hz);

δ_C (100 MHz $CDCl_3$): 142.4, 128.5, 128.0, 125.7, 80.6, 72.3, 71.0, 29.4;

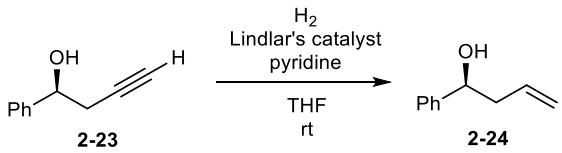
MS (ESI +ve) *m/z* 129.5 (M^+-OH, 100);

HRMS (ESI) *m/z* calculated for $C_{10}H_{11}O$ $[M+H]^+$ 147.0810, found 147.0800.

[xv] (*R*)-Styrene oxide was prepared following the procedure reported in Jacobsen, E.N. *et al. J. Am. Chem. Soc.* **2002,** *124*, 1307.
[xvi] Usanov, D. L.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2010,** *49,* 8169.

The data were consistent with those reported in the literature.[xvii]

(S)-1-phenylbut-3-en-1-ol (**2-24**)



To a stirred solution of alkyne **2-23** (1.30 g, 8.9 mmol) in anhydrous THF (30 mL) was added pyridine (65 mg) and Lindlar's catalyst[xviii] (65 mg). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. Once the reaction was complete as determined by TLC analysis, reaction mixture was filtered through a pad of Celite and washed with EtOAc (2 x 5 mL). The filtrate was concentrated *in vacuo* to give desired homoallylic alcohol **2-24** (1.27 g, 100%) in quantitative yield as a clear oil that was used in the subsequent reaction without further purification.

R_f 0.33 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -64.1 (*c* 0.12, CH_2Cl_2); {lit.[xix] $[\alpha]_D^{20}$ -63.2 (*c* 0.95, $CHCl_3$)}

ν_{max} (neat) 3404, 3074, 3030, 2904, 1641, 1492, 1454, 1197, 1047, 1001 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.26-7.42 (5H, m), 5.81 (1H, ddt, *J* 17.2, 10.1, 7.0 Hz), 5.08-5.23 (2H, m), 4.74 (1H, t, *J* 5.3 Hz), 2.38-2.64 (2H, m), 2.03 (1H, br s);

δ_C (100 MHz $CDCl_3$): 143.8, 134.4, 128.3, 127.5, 125.8, 118.3, 73.3, 43.7;

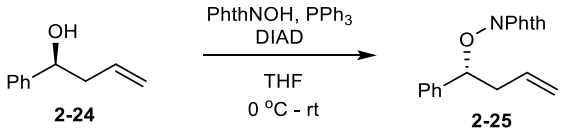
MS (ESI +ve) *m/z* 131.5 (M^+-OH, 100);

HRMS (ESI) *m/z* calculated for $C_{10}H_{13}O$ $[M+H]^+$ 149.0966, found 149.0971.

[xvii]. Sandgren, V. *et al. Bioorg. Med. Chem.* **2012,** *20,* 4377.
[xviii] Lindlar's catalyst was prepared following the procedure reported in Lindlar, H.; Dubuis, R. *Organic Syntheses;* Wiley & Sons: New York, 1973; Collect. Vol. 5. pp 880.
[xix] Hessler, F. *et al. Eur. J. Org. Chem.* **2014,** 2543

The data were consistent with those reported in the literature.[xx]

(R)-2-((1-phenylbut-3-en-1-yl)oxy)isoindoline-1,3-dione (**2-25**)



A stirred mixture of homoallylic alcohol **2-24** (8.00 g, 54.0 mmol), PPh_3 (17.00 g, 64.8 mmol) and *N*-hydroxyphthalimide (10.57 g, 64.8 mmol) in anhydrous THF (100 mL) was cooled to 0 °C in an ice-water bath. A solution of DIAD (12.8 mL, 64.8 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at 0 °C for 1 hour and then left to stir at room temperature overnight. The mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, absorbed onto silica and purified by flash chromatography with gradual elution (5 to 20% Ethyl Acetate/Hexane) to give desired *N*-hydroxyphthalimide **2-25** derivative as a colourless solid (14.23 g, 90%).

Mp 85-86 °C;

R_f 0.35 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +197.1 (c 0.11, CH_2Cl_2);

ν_{max} (nujol) 3404, 1728, 1643, 698 cm^{-1};

δ_H (396 MHz, $CDCl_3$): 7.59-7.78 (4H, m), 7.46 (2H, dd, *J* 7.5, 2.0 Hz), 7.26-7.39 (3H, m), 5.78 (1H, ddt, *J* 17.0, 10.3, 7.0 Hz), 5.39 (1H, t, *J* 7.0 Hz), 4.99-5.22 (2H, m), 2.95 (1H, dt, *J* 14.3, 7.0 Hz), 2.72 (1H, dt, *J* 14.3, 7.0 Hz);

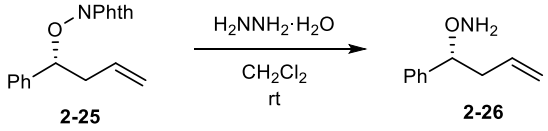
δ_C (100 MHz, $CDCl_3$): 163.6, 137.4, 134.2, 133.0, 129.1, 128.8, 128.3, 128.1, 123.3, 118.0, 88.3, 39.2;

[xx] List, B. *et al. Angew. Chem.* **2016,** *128,* 13394.

MS (ESI +ve) *m/z* 131.5 (M^+-$C_8H_4NO_3$, 100);

HRMS (ESI) *m/z* calculated for $C_{18}H_{16}O$ $[M+H]^+$ 294.1130, found 294.1128.

(R)-O-(1-phenylbut-3-en-1-yl)hydroxylamine (**2-26**)



Hydrazine monohydrate (8.6 mL, 177.2 mmol) was added dropwise to a stirred solution of *N*-hydroxyphthalimide **2-25** (13.00 g, 44.3 mmol) in CH_2Cl_2 (350 mL) at room temperature. The mixture was stirred for 2 hours, then filtered through a pad of Celite, washing with Et_2O (100 mL). The filtrate was concentrated *in vacuo* to give desired hydroxylamine **2-26** (7.41 g, 100%) as a clear oil that was used without further purification.

R_f 0.15 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +68.3 (c 0.13, CH_2Cl_2);

ν_{max} (neat) 3420, 3317, 3075, 3030, 2905, 1641, 1585, 1454, 1184 cm^{-1};

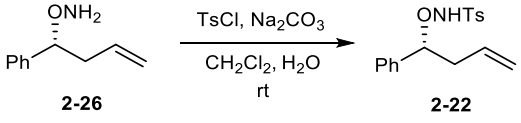
δ_H (400 MHz, $CDCl_3$): 7.27-7.41 (5H, m), 5.76 (1H, ddt, *J* 17.0, 10.1, 7.0 Hz), 5.24 (2H, br s.), 4.99-5.13 (2H, m), 4.56 (1H, t, *J* 7.0 Hz), 2.59 (1H, dt, *J* 14.0, 7.0 Hz), 2.42 (1H, dt, *J* 14.0, 7.0 Hz);

δ_C (100 MHz, $CDCl_3$): 141.3, 134.4, 128.4, 127.8, 126.7, 117.0, 86.6, 40.5;

MS (ESI -ve) m/z 163.4 (M^-, 100);

HRMS (ESI) m/z calculated for $C_{10}H_{14}O$ $[M+H]^+$ 164.1075, found 164.1075.

(R)-4-methyl-N-((1-phenylbut-3-en-1-yl)oxy)benzenesulfonamide (**2-22**)



Anhydrous sodium carbonate (4.88 g, 46.0 mmol) and tosyl chloride (8.77 g, 46.0 mmol) were added sequentially to a stirred solution of hydroxylamine **2-26** (5.00 g, 30.6 mmol) in CH_2Cl_2 (50 mL) and water (50 mL) at room temperature. The mixture was stirred overnight. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5 to 20% Ethyl Acetate/Hexane) to give desired *N*-tosyl hydroxylamine **2-22** (9.48 g, 98%) as a clear oil.

R_f 0.32 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +102.8 (c 0.34, CH_2Cl_2);

ν_{max} (neat) 3435, 3225, 3066, 3032, 2924, 1714, 1643, 1597, 1454, 1339, 1183 cm^{-1};

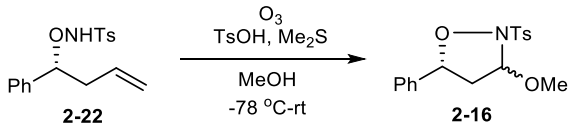
δ_H (400 MHz, $CDCl_3$): 7.82 (2H, d, *J* 8.2 Hz), 7.23-7.40 (7H, m), 6.67 (1H, s), 5.77 (1H, ddt, *J* 17.2, 9.9, 7.0 Hz), 4.98-5.15 (3H, m), 2.65 (1H, dt, *J* 14.8, 7.0 Hz), 2.41-2.54 (4H, m);

δ_C (100 MHz, $CDCl_3$) 144.8, 139.6, 133.8, 133.7, 129.6, 128.7, 128.4, 128.3, 127.1, 117.6, 88.0, 39.6, 21.7;

MS (ESI +ve) m/z 131.5 (M^+-$C_7H_8NO_3S$, 100), 148.6 (M+-$C_7H_7NO_2S$, 10);

HRMS (ESI) m/z calculated for $C_{17}H_{20}NO_3S$ $[M+H]^+$ 318.1164, found 318.1185.

(5R)-3-methoxy-5-phenyl-2-tosylisoxazolidine (**2-16**)



p-Toluenesulfonic acid monohydrate (230 mg, 1.2 mmol) was added to a solution of *N*-tosyl hydroxylamine **2-22** (7.66 g, 24.1 mmol) in MeOH (100 mL). The mixture was cooled to -78 °C and a stream of O_3/O_2 was passed through the mixture until the solution turned

blue in colour. The flask was then purged with O_2 until the blue colour dissipated. Me_2S (2.4 mL, 28.9 mmol) was added and the reaction mixture was warmed to room temperature and stirred for a further 48 h. The reaction solvent was removed with a rotary evaporator and the residue was taken up in CH_2Cl_2 (100 mL) and washed with water (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography with gradual elution (5 to 25% Ethyl Acetate/Hexane) to give methoxy isoxazolidine **2-16** (7.22 g, 90%) as a mixture of diastereomers (ratio = 1.5:1) and as a clear oil.

R_f 0.38, 0.33 (20% Ethyl Acetate/Hexane);

ν_{max} (neat) 3500, 2957, 1635, 1597, 1456, 1368, 1333, 1224, 1183 cm^{-1};

Minor diastereomer:

δ_H (400 MHz, $CDCl_3$): 7.89 (2H, d, *J* 8.2 Hz), 7.22-7.44 (7H, m), 5.71 (1H, dd, *J* 6.8, 2.7 Hz), 5.46 (1H, t, *J* 8.2 Hz), 3.54 (3H, s), 2.98 (1H, ddd, *J* 13.4, 8.2, 6.8 Hz), 2.42 (3H, s), 2.33 (1H, ddd, *J* 13.4, 8.2, 2.7 Hz);

δ_C (100 MHz, $CDCl_3$): 145.1, 137.6, 133.6, 129.7, 129.0, 128.7, 128.6, 127.5, 91.7, 84.7, 56.6, 44.0, 21.7;

Major diastereomer:

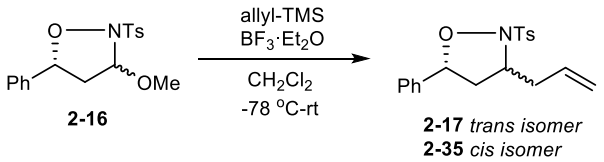
δ_H (400 MHz, $CDCl_3$): 7.82 (2H, d, *J* 8.2 Hz), 7.22-7.44 (7H, m), 5.51 (1H, d, *J* 5.2 Hz), 5.30 (1H, dd, *J* 12.0, 5.2 Hz), 3.54 (3H, s), 2.40-2.50 (4H, m), 2.08 (1H, ddd, *J* 12.0, 5.2 Hz);

δ_C (100 MHz, $CDCl_3$): 145.2, 136.4, 132.6, 129.6, 129.4, 128.8, 128.5, 127.4, 91.9, 83.2, 55.7, 43.0, 21.7.

MS (ESI +ve) m/z 302.9 (M^+-OCH_3, 28);

HRMS (ESI) m/z calculated for $C_{17}H_{19}NO_4SNa$ $[M+Na]^+$ 356.0932, found 356.0930.

(3S,5R)-3-allyl-5-phenyl-2-tosylisoxazolidine (**2-17**) and *(3R,5R)-3-allyl-5-phenyl-2-tosylisoxazolidine* (**2-35**)



2-16

2-17 *trans isomer*
2-35 *cis isomer*

$BF_3{\cdot}Et_2O$ (4.4 mL, 36.0 mmol) was added to a stirred solution of methoxy isoxazolidine **2-16** (6.0 g, 18.0 mmol) and allyltrimethylsilane (11.4 mL, 72.0 mmol) in anhydrous CH_2Cl_2 (60 mL) at -78 °C. Once addition was complete, the reaction mixture was gradually warmed to room temperature and left to stir until the reaction was shown to be complete by TLC analysis. The reaction mixture was cooled to -78 °C and quenched with Et_3N (2.5 mL, 18.0 mmol). The mixture was allowed to warm to room temperature and was diluted with water (100 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5 to 25% Ethyl Acetate/Hexane) to give the *trans* isomer **2-17** (3.73 g, 60%) as a crystalline solid and the *cis* isomer **2-35** (517 mg, 8%) as a pale yellow oil.

Trans diastereomer **2-17**:

Mp 72-77 °C;

R_f 0.40 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{21}$ +85.7 (*c* 0.25, CH_2Cl_2);

ν_{max} (neat) 3439, 2922, 2852, 1636, 1456, 1377 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.80 (2H, d, *J* 8.2 Hz), 7.23-7.37 (7H, m), 5.90 (1H, ddt, *J* 17.1, 10.1, 7.0 Hz), 5.13-5.25 (3H, m), 4.39 (1H, q, *J* 7.0 Hz), 2.63 (1H, dt, *J* 14.2, 6.4 Hz), 2.39-2.48 (4H, m), 2.29-2.38 (1H, m), 2.19 (1H, td, *J* 11.8, 8.0 Hz);

δ_C (100 MHz $CDCl_3$): 144.9, 137.1, 133.7, 132.1, 129.6, 129.5, 128.5, 128.4, 127.2, 118.3, 82.9, 61.1, 40.5, 39.1, 21.7;

MS (ESI +ve) *m/z*, 345.0 (M^++H, 100), 367.0 (M^++Na, 10);

HRMS (ESI) *m/z* calculated for $C_{19}H_{22}NO_3S$ $[M+H]^+$ 344.1320, found 344.1311.

Cis diastereomer **2-35**:

R_f 0.46 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{21}$ -68.0 (*c* 0.20, CH_2Cl_2);

ν_{max} (film) 3065, 2981, 2852, 1598, 1357, 1332 cm^{-1};

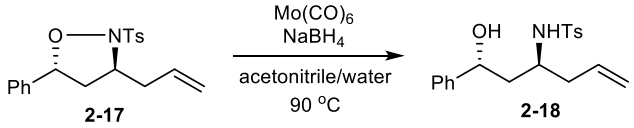
δ_H (400 MHz $CDCl_3$): 7.90 (2H, d, *J* 8.2 Hz), 7.27-7.41 (7H, m), 5.89 (1H, ddt, *J* 17.2, 10.2, 6.9 Hz), 5.13-5.21 (3H, m), 4.45 (1H, qd, *J* 7.5, 5.5 Hz), 2.64-2.83 (2H, m), 2.42-2.55 (4H, m), 2.08 (1H, ddd, *J* 12.5, 10.2, 7.5 Hz);

δ_C (100 MHz $CDCl_3$): 144.9, 136.9, 133.7, 133.2, 129.7, 129.2, 128.6, 128.5, 127.8, 126.8, 118.2, 83.2, 60.0, 42.4, 40.4, 21.7;

MS (ESI +ve) *m/z*, 345.0 (M^++H, 100), 240.8 (40), 173.6 (64), 155.5 (70);

HRMS (ESI) *m/z* calculated for $C_{19}H_{22}NO_3S$ $[M+H]^+$ 344.1320, found 344.1319.

N-((1R,3S)-1-hydroxy-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (**2-18**)



$Mo(CO)_6$ (692 mg, 2.6 mmol) was added to a solution of isoxazolidine **2-17** (3.01 g, 8.7 mmol) in acetonitrile (28 mL) and water (4 mL). The mixture was stirred at room temperature for 15 minutes, and $NaBH_4$ (758 mg, 13.1 mmol) was added in one portion. The reaction mixture was heated to 90 °C and left to stir overnight. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with Et_2O (20 mL) and the resulting mixture was filtered through a pad of Celite and washed with Et_2O (2 x 20 mL). The filtrate was concentrated *in vacuo*. The crude product was

purified by flash column chromatography with gradual elution (5 to 30% Ethyl Acetate/Hexane) to give desired 1,3-aminoalcohol **2-18** (1.98 g, 66%) as a colourless solid.

Mp 92-93 °C;

R_f 0.13 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{21}$ +30.6 (*c* 0.12, CH_2Cl_2);

ν_{max} (nujol) 3446, 1638, 1597, 1317, 1155 cm^{-1};

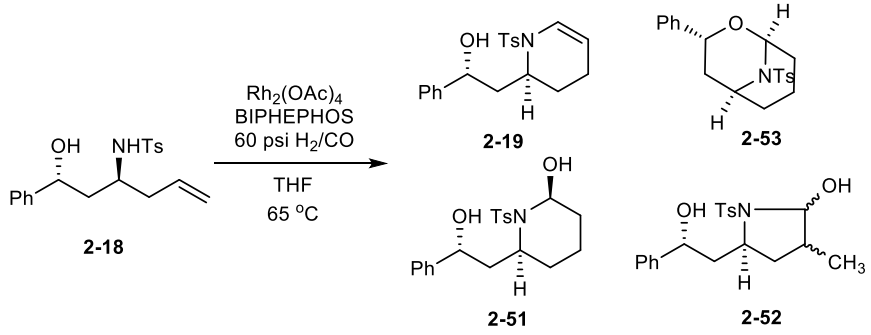
δ_H (396 MHz $CDCl_3$): 7.70-7.91 (2H, m), 7.11-7.45 (7H, m), 5.40-5.54 (1H, m), 4.71-5.07 (4H, m), 3.61-3.72 (1H, m), 2.87 (1H, br s.), 2.45 (3H, s), 1.97-2.18 (2H, m), 1.70-1.82 (1H, m), 1.54-1.68 (1H, m);

δ_C (100 MHz $CDCl_3$): 144.1, 143.5, 137.7, 132.9, 129.7, 128.4, 127.3, 127.2, 125.5, 119.1, 70.0, 50.5, 43.9, 39.4, 21.5;

MS (ESI -ve) *m/z*, 345.0 (M^--H, 100);

HRMS (ESI) *m/z* calculated for $C_{19}H_{24}NO_3S$ $[M+H]^+$ 346.1477, found 346.1468.

(R)-1-phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethanol (**2-19**)*, (1S,3S,5S)-3-phenyl-9-tosyl-2-oxa-9-azabicyclo[3.3.1]nonane* (**2-53**)*, (2S,6S)-6-((R)-2-hydroxy-2-phenylethyl)-1-tosylpip- eridin-2-ol* (**2-51**) *by hydroformylation*



In a Fisher-Porter tube, amino alcohol **2-18** (100 mg, 0.29 mmol), $Rh_2(OAc)_4$ (1 mg, 0.03 mmol) and BIPHEPHOS (5 mg, 0.06 mmol) were dissolved in anhydrous THF (5 mL). The reaction mixture was purged with H_2/CO (1:1) three times and then charged with H_2 (30 psi) and CO (30 psi). The reaction mixture was heated to 65 °C and left to stir for 22 hours. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography with gradual elution (5 to 35% Ethyl Acetate/Hexane) to give several products, the desired ene-sulfonamide **2-19** (5 mg, 5%), bicyclic aminal **2-53** (7 mg, 7%), hydroxypiperidinol **2-51** (49 mg, 45%) and an inseparable mixture of isomers of hydroxypyrrolidine **2-52** (12 mg, 11%).

Ene-sulfonamide **2-19**:

Mp 117-119 °C;

R_f 0.24 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -213.7 (*c* 0.35, CH_2Cl_2);

ν_{max} (film) 3443, 1645, 1597, 1338, 1163, 1101, 922 cm^{-1};

δ_H (396 MHz $CDCl_3$): 7.71 (2H, d, *J* 8.6 Hz), 7.23-7.42 (7H, m), 6.66 (1H, d, *J* 8.2 Hz), 5.12 (1H, app t, *J* 5.9 Hz), 5.02 (1H, br d, *J* 11.0 Hz), 4.30 (1H, br d, *J* 11.0 Hz), 3.63 (1H, d, *J* 4.5 Hz), 2.44 (3H, s), 1.73-1.98 (3H, m), 1.37-1.53 (1H, m), 0.80-0.99 (2H, m);

δ_C (100 MHz $CDCl_3$): 144.2, 143.8, 135.1, 129.8, 128.3, 127.2, 127.1, 125.7, 123.1, 110.9, 69.2, 49.7, 41.6, 23.8, 21.6, 17.5;

MS (ESI +ve) *m/z* 381.0 (M^++Na, 10), 341.0 (M^+-OH, 100);

HRMS (ESI) *m/z* calculated for $C_{20}H_{24}NO_3S$ $[M+H]^+$ 358.1477, found 358.1461.

Bicyclic aminal ***2-53***:

Mp 138-142 °C;

R_f 0.31 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +3.83 (*c* 0.37, CH_2Cl_2);

ν_{max} (film) 2921, 1704, 1643, 1598, 1347, 1163 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.86 (2H, d, *J* 8.2 Hz), 7.33 (2H, d, *J* 8.2 Hz), 7.12-7.20 (3H, m), 6.72 (2H, dd, *J* 7.5, 2.1 Hz), 5.74 (1H, m), 5.38 (1H, dd, *J* 12.4, 4.1 Hz), 4.26 (1H, m), 2.46 (3H, s), 2.13-2.33 (4H, m), 1.87-1.99 (2H, m), 1.77 (1H, td, *J* 12.8, 5.9 Hz), 1.17-1.26 (1H, m);

δ_C (100 MHz $CDCl_3$): 143.3, 142.6, 138.7, 129.8, 128.1, 127.9, 127.6, 125.6, 79.0, 73.2, 47.6, 35.6, 30.7, 30.3, 21.5, 20.2;

MS (ESI +ve) *m/z* 381.0 (M^++Na, 10), 341.0 (40), 254.8 (100), 236.8 (58);

HRMS (ESI) *m/z* calculated for $C_{20}H_2NO_3S$ $[M+H]^+$ 358.1477, found 358.1493.

Hydroxypiperidinol **2-51**:

Mp 139-140 °C;

R_f 0.13 (20% Ethyl Acetate/Hexane);

ν_{max} (film) 3519, 2947, 1598, 1491, 1325, 1158 cm^{-1};

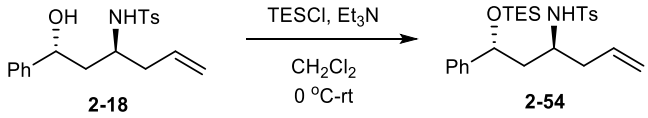
δ_H (396 MHz $CDCl_3$): 7.68-7.74 (2H, m), 7.39-7.45 (2H, m), 7.21-7.30 (5H, m), 5.53-5.5.59 (1H, m), 4.99-5.08 (1H, m), 4.25-4.37 (1H, m), 3.78 (1H, d, *J* 4.1 Hz), 2.92 (1H, br s), 2.64 (1H, ddd, *J* 14.0, 11.6, 2.5 Hz), 2.44 (3H, s), 1.79-1.98 (2H, m), 1.52-1.69 (4H, m), 1.16-1.44 (2H, m);

δ_C (100 MHz $CDCl_3$): 144.3, 143.7, 137.7, 130.0, 128.3, 126.9, 126.5, 125.6, 69.9, 69.8, 50.0, 45.2, 30.1, 28.8, 21.5, 13.1;

MS (ESI +ve) *m/z* 399.0 (M^+ +Na, 18), 341.0 (26), 254.8 (100), 236.8 (44), 155.5 (40);

HRMS (ESI) *m/z* calculated for $C_{20}H_{26}NO_4S$ $[M+H]^+$ 376.1583, found 376.1578.

4-methyl-N-((1R,3S)-1-phenyl-1-((triethylsilyl)oxy)hex-5-en-3-yl)benzenesulfonamide (**2-54**)



Et_3N (380 μL, 4.1 mmol) was added dropwise to a solution of amino alcohol **2-18** (1.00 g, 2.9 mmol) and chlorotriethylsilane (420 μL, 3.5 mmol) in CH_2Cl_2 (15 mL), cooled to 0 °C in an ice-water bath. Once addition was complete, the reaction mixture was warmed to room temperature and left to stir overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous NH_4Cl (20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% Ethyl Acetate/Hexane) to give desired *O*-silyl alcohol **2-54** (1.22 g, 91%) as a clear oil.

R_f 0.43 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +28.7 (*c* 0.25, CH_2Cl_2);

ν_{max} (film) 3284, 2954, 2911, 2876, 1454, 1415, 1329, 1160, 1092 cm^{-1};

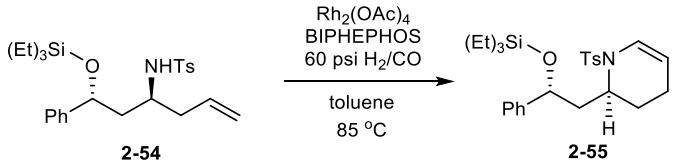
δ_H (396 MHz $CDCl_3$): 7.72 (2H, d, *J* 8.2 Hz), 7.29 (2H, d, *J* 8.2 Hz), 7.18-7.23 (3H, m), 7.03-7.09 (2H, m), 5.51-5.69 (2H, m), 4.93-5.07 (2H, m), 4.87 (1H, dd, *J* 7.7, 4.1 Hz), 3.28-3.38 (1H, m), 2.44 (3H, s), 2.18-2.38 (2H, m), 1.58-1.79 (2H, m), 0.83-0.92 (9H, m), 0.42-0.60 (6H, m);

δ_C (100 MHz $CDCl_3$): 143.9, 143.1, 138.2, 133.8, 129.6, 128.2, 127.4, 127.2, 125.7, 118.2, 73.0, 51.2, 42.8, 38.9, 21.5, 6.7, 4.7;

MS (ESI -ve) *m/z* 459.1 (M^--H, 88), 345.0 (30), 171.6 (44), 117.3 (100);

HRMS (ESI) *m/z* calculated for $C_{25}H_{38}NO_3SSi$ $[M+H]^+$ 460.2342, found 460.2328.

(S)-2-((R)-2-phenyl-2-((triethylsilyl)oxy)ethyl)-1-tosyl-1,2,3,4-tetrahydropyridine (**2-55**)



In a Fisher-Porter tube, silyl ether **2-54** (500 mg, 1.1 mmol), $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) and BIPHEPHOS (17 mg, 0.02 mmol) were dissolved in anhydrous toluene (20 mL). The reaction mixture was purged with H_2/CO (1:1) three times and then charged with H_2 (30 psi) and CO (30 psi). The reaction mixture was heated to 85 °C and left to stir for 22 hours. The reaction mixture was allowed to cool to room temperature, the pressure was vented and then the reaction mixture concentrated *in vacuo*. The crude residue was purified by flash column chromatography with gradual elution (5 to 15% Ethyl Acetate/Hexane) to give the desired ene-sulfonamide **2-55** (466 mg, 91%) as a clear oil.

R_f 0.58 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -218.8 (*c* 0.18, CH_2Cl_2);

ν_{max} (film) 2952, 2912, 2875, 1643, 1449, 1358, 1166, 1095 cm^{-1};

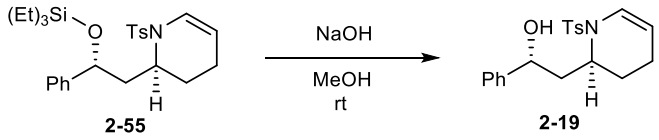
δ_H (396 MHz $CDCl_3$): 7.64 (2H, d, *J* 8.2 Hz), 7.20-7.34 (7H, m), 6.58 (1H, d, *J* 8.2 Hz), 4.99-5.05 (1H, m), 4.96 (1H, dd, *J* 9.1, 3.2 Hz), 4.12 (1H, m), 2.42 (3H, s), 1.61-1.94 (5H, m), 1.39-1.53 (1H, m), 0.85-0.92 (9H, m), 0.37-0.73 (6H, m);

δ_C (100 MHz $CDCl_3$): 145.5, 143.3, 136.0, 129.6, 128.1, 127.2, 127.0, 126.0, 123.7, 110.0, 72.3, 50.6, 44.1, 24.2, 21.5, 17.3, 6.9, 4.9;

MS (ESI -ve) *m/z* 341.0 (M^--$OC_6H_{15}Si$, 100), 236.8 (95);

HRMS (ESI) *m/z* calculated for $C_{26}H_{38}NO_3SSi$ $[M+H]^+$ 472.2342, found 472.2397.

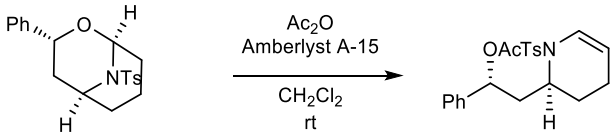
(R)-1-phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethanol (**2-19**) *by desilylation*



2-55 **2-19**

A solution of ene-sulfonamide **2-55** (465 mg, 0.99 mmol) in 10% solution of NaOH in methanol (10 mL) was left to stir at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% Ethyl Acetate/Hexane) to give desired alcohol **2-19** (340 mg, 96%) as a colourless solid, identical to that described above

(S)-1-phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethyl acetate (**2-58**)



2-53 **2-58**

To a solution of bicyclic aminal **2-53** (289 mg, 0.81 mmol) in CH_2Cl_2 (10 mL) was added Amberlyst-A15 (12 mg) and Ac_2O (120 μL, 1.2 mmol). The reaction mixture was left to stir at room temperature overnight. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 to 20% Ethyl Acetate/Hexane) to give desired acetate **2-58** (224 mg, 70%) as a colourless powder.

Mp 171-175 °C

R_f 0.27 (20% Ethyl Acetate/Hexane)

$[\alpha]_D^{22}$ -169 (*c* 0.11, CH_2Cl_2)

ν_{max} (nujol) 3422, 2361, 1738, 1647, 1597, 1365, 1337, 1231, 1161 cm^{-1}

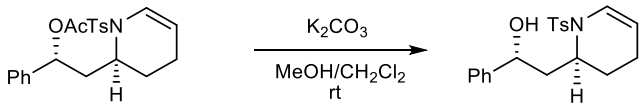
δ_H (396 MHz $CDCl_3$): 7.62 (2H, d, *J* 8.2 Hz), 7.35 (4H,m), 7.28-7.31 (3H, m), 6.60 (1H, d, *J* 9.0 Hz), 5.82 (1H, dd, *J* 9.0, 4.5 Hz), 4.95-5.20 (1H, m), 4.10 (1H, dd, *J* 7.7, 3.6 Hz), 2.42 (3H, s), 2.08-2.25 (3H, s), 1.76-2.05 (4H, m), 1.40-1.52 (1H, m), 0.83-0.98 (1H, m)

δ_C (100 MHz $CDCl_3$): 170.1, 143.4, 140.6, 135.8, 129.6, 128.5, 127.9, 127.1, 126.5, 123.5, 109.9, 72.9, 49.5, 38.2, 23.3, 21.5, 21.2, 17.3

MS (ESI +ve) *m/z* 340.1 (M^+-OAc, 30)

HRMS (ESI) *m/z* calculated for $C_{22}H_{26}NO_4S$ $[M+H]^+$ 400.1583, found 400.1592.

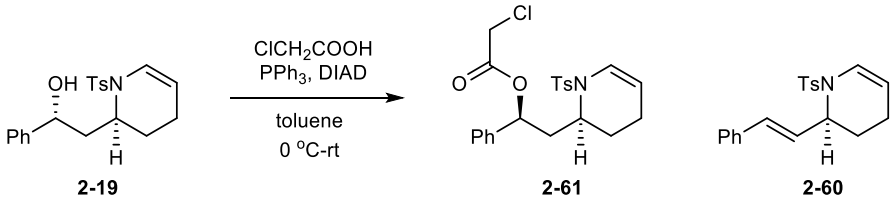
(R)-1-phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethanol (**2-19**) *by saponification*



2-58 **2-19**

K_2CO_3 (21 mg, 0.15 mmol) was added to a solution of the acetate protected piperidinol **2-58** (50 mg, 0.13 mmol) in MeOH (5 mL) and CH_2Cl_2 (2 mL). The reaction mixture was left to stir at room temperature for 2 hours or until the reaction was complete as indicated by TLC analysis. The reaction mixture was concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (5 mL) and washed with water (3 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired alcohol **2-19** (46 mg, 100%) as a colourless solid, identical to that described above.

(S)-1-phenyl-2-((S)-1-tosyl-1,2,3,4-tetrahydropyridin-2-yl)ethyl 2-chloroacetate (**2-61**) *and (S,E)-2-styryl-1-tosyl-1,2,3,4-tetrahydropyridine* (**2-60**)



2-19 **2-61** **2-60**

DIAD (710 μL, 3.57 mmol) was added dropwise to a solution of the ene-sulfonamide **2-19** (639 mg, 1.79 mmol), PPh_3 (939 mg, 3.57 mmol) and chloroacetic acid (338 mg, 3.57 mmol) in toluene at 0 °C. Reaction mixture was left to stir at 0 °C for 1 hour and then allowed to warm to room temperature and left to stir overnight. Once the reaction was determined to be complete by TLC analysis, the reaction mixture was concentrated *in vacuo*. The crude product was dissolved in CH_2Cl_2 and absorbed onto silica, then purified by flash column chromatography with gradual elution (5 to 15% Ethyl Acetate/Hexane) to give desired acetate **2-61** (540 mg, 70%) as a clear oil and the undesired alkene **2-60** (100 mg, 17%) as a colourless powder.

Acetate **2-61***:*

R_f 0.32 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -221.2 (*c* 0.14, CH_2Cl_2);

ν_{max} (film) 2961, 2926, 1759, 1644, 1340, 1165 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.63 (2H, d, *J* 8.2 Hz), 7.23-7.44 (7H, m), 6.62 (1H, d, *J* 7.8 Hz), 5.94 (1H, dd, *J* 9.1, 4.6 Hz), 4.98-5.10 (1H, m), 3.96-4.21 (3H, m), 2.29-2.49 (4H, m), 1.77-1.97 (3H, m), 1.55 (1H, m), 0.82-1.00 (1H, m);

δ_C (100 MHz $CDCl_3$): 166.6, 143.5, 139.4, 135.8, 129.7, 128.6, 128.5, 126.9, 126.8, 123.6, 109.1, 75.4, 49.8, 41.1, 38.3, 22.8, 21.5, 17.1;

MS (ESI +ve) *m/z* 236.8 (100), 341.0 (M^+-$C_2H_2O_2{}^{35}Cl$, 90), 435.0 (M^++H, 23), 437.0 (M^++H, 8), 457.0 (M^++Na, 23), 459.0 (M+2$^+$+Na, 8);

HRMS (ESI) *m/z* calculated for $C_{22}H_{25}NO_4S^{35}Cl$ $[M+H]^+$ 434.1193, found 434.1189.

Alkene **2-60***:*

Mp 108-110 °C;

R_f 0.45 (20% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -188.1 (*c* 0.09, CH_2Cl_2);

ν_{max} (film) 2927, 2193, 2021, 1648, 1596, 1494, 1359, 1339, 1163, 1098 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.68 (2H, d, *J* 7.8 Hz), 7.17-7.32 (7H, m), 6.73 (1H, d, *J* 8.2 Hz), 6.48 (1H, d, *J* 15.9 Hz), 5.93 (1H, dd, *J* 15.9, 5.7 Hz), 5.02 (1H, t, *J* 6.9 Hz), 4.74 (1H, m), 2.36 (3H, s), 1.69-2.09 (4H, m), 1.31-1.47 (2H, m);

δ_C (100 MHz $CDCl_3$): 143.4, 136.5, 136.4, 131.4, 129.6, 128.4, 127.5, 127.1, 126.4, 126.2, 123.7, 108.2, 54.4, 25.5, 21.5, 17.5;

MS (ESI +ve) *m/z* 341.0 (M^++H, 30), 169.7 (45), 143.6 (100);

HRMS (ESI) *m/z* calculated for $C_{20}H_{22}NO_2S$ $[M+H]^+$ 340.1371, found 340.1336.

(2S,3S,6S)-6-((S)-2-(2-chloroacetoxy)-2-phenylethyl)-1-tosylpiperidine-2,3-diyl diacetate (**2-62a**) *and (2R,3R,6S)-6-((S)-2-(2-chloroacetoxy)-2-phenylethyl)-1-tosylpiperidine-2,3-diyl diacetate* (**2-62b**) *as an inseparable mixture*

2-61

2-62a *2,5- cis isomer*
2-62b *2,5- trans isomer*

$MeSO_2NH_2$ (166 mg, 1.74 mmol) was added to a solution of ene-sulfonamide **2-61** (250 mg, 0.58 mmol) in THF (18 mL). When the $MeSO_2NH_2$ had completely dissolved, NMO (410 μL of a 50% aqueous solution, 1.74 mmol), H_2O (2 mL) and $K_2OsO_4.2H_2O$ (21 mg, 0.06 mmol) were added. Reaction mixture was left to stir at room temperature for 48 hours. The reaction mixture was taken up in EtOAc (30 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the diol (271 mg, 0.58 mmol) as a mixture of diastereomers (ratio= 4.6:1) that was used in the subsequent reaction without further purification.

Ac_2O (120 μL, 1.28 mmol), Et_3N (210 μL, 1.45 mmol) and DMAP (1 mg, 0.01 mmol) were added to the solution of the crude diol in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was left to stir at room temperature for 3 hours or until the reaction was determined to be complete by TLC analysis. The reaction mixture was quenched with saturated aqueous NH_4Cl (15 mL) and diluted with CH_2Cl_2 (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (25% Ethyl Acetate/Hexane) to give the desired diacetates **2-62a** and **2-62b** (268 mg, 83%) as a crystalline solid and as a mixture of inseparable diastereomers (ratio= 4.6:1).

Mp 135-140 °C;

R_f 0.27 (40% Ethyl Acetate/Hexane);

ν_{max} (film) 2952, 2373, 2364, 1747, 1362, 1240, 1165 cm^{-1};

Major diastereomer **2-62a**:

δ_H (396 MHz $CDCl_3$): 7.72 (2H, d, *J* 8.6 Hz), 7.27-7.40 (7H, m), 6.82 (1H, d, *J* 3.6 Hz), 5.82 (1H, dd, *J* 10.4, 3.6 Hz), 4.66 (1H, dt, *J* 11.9, 4.2 Hz), 3.98-4.26 (3H, m), 2.44 (3H,

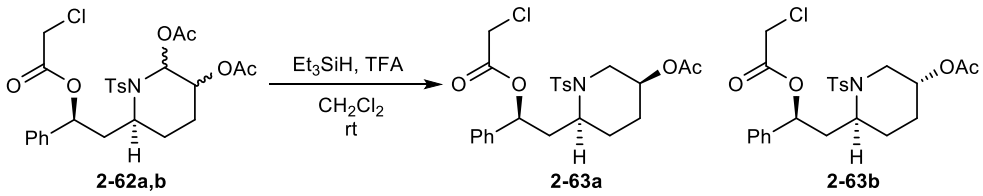
s), 2.29-2.41 (1H, m), 2.12-2.28 (1H, m), 1.96 (3H, s), 1.95 (3H, s), 1.78-1.89 (2H, m), 1.59-1.71 (2H, m);

δ_C (100 MHz $CDCl_3$): 169.8, 168.9, 166.9, 144.1, 139.1, 137.2, 129.9, 128.8, 128.6, 127.3, 126.4, 75.8, 75.4, 69.4, 48.9, 41.0, 39.6, 26.0, 21.6, 21.0, 20.7, 19.0;

MS (ESI +ve) *m/z* 575.1, (M^++Na, 14) 577.1 (M^++Na, 3), 493.0, 495.0 (M^+-$C_2H_3O_2$, 44), 399.0 (M^+-$C_4H_5O_4{}^{35}Cl$, 100), 351.0 (45), 294.9 (90);

HRMS (ESI) *m/z* calculated for $C_{26}H_{30}NO_8S^{35}Cl$ $[M+H]^+$ 552.1459, found 552.1474.

(S)-2-((2S,5S)-5-acetoxy-1-tosylpiperidin-2-yl)-1-phenylethyl 2-chloroacetate (**2-63a**) and *(S)-2-((2S,5R)-5-acetoxy-1-tosylpiperidin-2-yl)-1-phenylethyl 2-chloroacetate* (**2-63b**)



Et_3SiH (580 μL, 3.63 mmol) and trifluoroacetic acid (30 μL, 0.36 mmol) were added to a solution of the mixture of diacetates, **2-62a** and **2-62b** (200 mg, 0.36 mmol), in anhydrous CH_2Cl_2 (10 mL). The reaction mixture was left to stir at room temperature overnight or until reaction was complete as indicated by TLC analysis. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (5 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 to 20% Ethyl Acetate/Hexane) to give the two isomers as clear oils: major isomer **2-63a** (75 mg, 42%), minor isomer **2-63b** (33 mg, 18%).

Major isomer **2-63a**:

R_f 0.36 (40% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -44.5 (*c* 0.38, CH_2Cl_2);

ν_{max} (film) 3449, 2594, 1759, 1732, 1597, 1494, 1454, 1342, 1242, 1161 cm^{-1};

δ_H (396 MHz $CDCl_3$): 7.67 (2H, d, *J* 8.2 Hz), 7.21-7.32 (7H, m), 5.77 (1H, dd, *J* 8.6 and 5.0 Hz), 4.31 (1H, tt, *J* 10.3, 4.9 Hz), 3.89-4.13 (4H, m), 2.86 (1H, dd, *J* 14.0, 11.3 Hz), 2.36 (3H, s), 2.24-2.33 (1H, m), 1.94 (3H, s), 1.87 (1H, ddd, *J* 14.5, 6.8, 5.0 Hz), 1.69-1.79 (1H, m), 1.34-1.45 (3H, m);

δ_C (100 MHz $CDCl_3$): 169.9, 166.6, 143.6, 139.0, 137.9, 129.9, 128.7, 128.6, 127.0, 126.7, 76.0, 67.4, 49.1, 43.3, 41.1, 36.3, 26.1, 24.5, 21.5, 21.0;

MS (ESI +ve) *m/z* 399.0 (M^+-$C_2H_2O_2{}^{35}Cl$, 15), 296.9 (100) 236.8 (15);

HRMS (ESI) *m/z* calculated for $C_{24}H_{29}NO_6S^{35}Cl$ $[M+H]^+$ 494.1404, found 494.1397.

Minor isomer **2-63b**:

R_f 0.40 (40% Ethyl Acetate/Hexane);

$[\alpha]_D^{21}$ -87.33 (*c* 0.21, CH_2Cl_2);

ν_{max} (film) 2962, 1758, 1347, 1213, 1163 cm^{-1};

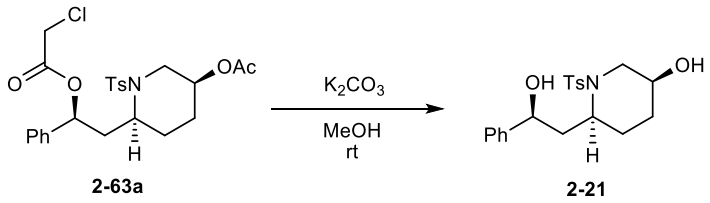
δ_H (396 MHz $CDCl_3$): 7.64 (2H, d, *J* 8.2 Hz), 7.28-7.45 (7H, m), 6.62 (1H, s), 5.95 (1H, dd, *J* 8.6, 5.0 Hz), 4.16 (1H, d, *J* 16.0 Hz), 4.05 (1H, d, *J* 12.0 Hz), 3.91-4.00 (1H, m), 2.36-2.48 (4H, m), 2.10-2.29 (4H, m), 1.82-1.96 (2H, m), 1.51 (1H, dd, *J* 13.8, 6.6 Hz), 0.80-1.00 (3H, m);

δ_C (100 MHz $CDCl_3$): 169.5, 166.5, 143.9, 139.1, 137.0, 135.0, 129.8, 128.6, 128.5, 127.1, 126.8, 115.9, 75.4, 49.6, 41.1, 37.9, 22.5, 21.5, 20.7, 20.4;

MS (ESI +ve) *m/z* 399.0 (M^+-$C_2H_2O_2{}^{35}Cl$, 100), 357.0 (36), 294.9 (42);

HRMS (ESI) *m/z* calculated for $C_{24}H_{29}NO_6S^{35}Cl$ $[M+H]^+$ 494.1404, found 494.1409.

(3S,6S)-6-((S)-2-hydroxy-2-phenylethyl)-1-tosylpiperidin-3-ol (**2-21**)



2-63a **2-21**

K_2CO_3 (31 mg, 0.23 mmol) was added to a stirred solution of the acetate protected piperidinol **2-63a** (45 mg, 0.09 mmol) in MeOH (5 mL). The reaction mixture was left to stir at room temperature for 2 hours or until reaction was complete as indicated by TLC analysis. The reaction mixture was concentrated *in vacuo*. The residue was taken up in EtOAc (5 mL) and washed with water (3 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **2-21** as a colourless oil (34 mg, 100%), which was used without further purification.

R_f 0.06 (40% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -56.2 (*c* 0.10, CH_2Cl_2);

ν_{max} (film) 3451, 2925, 2854, 1598, 1454, 1330, 1154 cm^{-1};

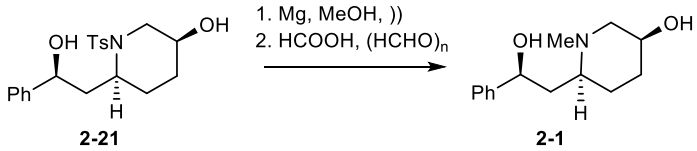
δ_H (400 MHz $CDCl_3$): 7.73 (2H, d, *J* 8.2 Hz), 7.26-7.37 (7H, m), 4.71 (1H, dd, *J* 8.9, 4.3 Hz), 4.20-4.30 (1H, m), 3.92 (1H, ddd, *J* 14.0, 4.3, 0.9 Hz), 3.36-3.54 (1H, m), 2.77 (1H, dd, *J* 13.7, 11.0 Hz), 2.42 (3H, s), 2.27 (1H, d, *J* 5.5 Hz), 1.93-2.03 (1H, m), 1.75-1.90 (2H, m), 1.30-1.51 (3H, m);

δ_C (100 MHz $CDCl_3$): 144.2, 143.4, 137.9, 129.8, 128.6, 127.7, 127.1, 125.8, 72.3, 66.1, 49.6, 46.6, 38.9, 28.2, 26.5, 21.5;

MS (ESI +ve) *m/z* 399.0 (M^++Na, 10), 254.8 (100), 114.3 (68);

HRMS (ESI) *m/z* calculated for $C_{20}H_{25}NO_4SNa$ $[M+Na]^+$ 398.1402, found 398.1430.

(-)-5-hydroxysedamine (**2-1**)



Activated Mg turnings (24 mg, 1.00 mmol) were added in 5 mg portions every hour to a solution of the *N*-tosylpiperidinol **2-21** (19 mg, 0.05 mmol) in anhydrous MeOH (4 mL), as the mixture was being sonicated in an ultrasonic cleaning bath. Once the reaction was complete as determined by TLC analysis, the reaction mixture was acidified with 2M HCl and washed with CH_2Cl_2 (5 mL). The aqueous layer was neutralised with 2M NaOH and extracted with CH_2Cl_2 (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the piperidinol as a pale yellow oil which was used in the subsequent reaction without further purification.

To a solution of the piperidinol (11 mg, 0.05 mmol) dissolved in dioxane (3 mL), was added formic acid (20 μL, 0.50 mmol) and paraformaldehyde (15 mg, 0.50 mmol). The reaction mixture was heated to 100 °C and left to stir overnight. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The crude residue was re-dissolved in MeOH (5 mL) and Et_3N (110 μL, 0.80 mmol) was added. The resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash column chromatography (10% MeOH/Chloroform with 1% Et_3N) to give the desired piperidine **2-1** as a yellow oil (8 mg, 71%).

R_f 0.04 (10% MeOH/$CHCl_3$ with 1% Et_3N);

$[\alpha]_D^{23}$ -55.3 (*c* 0.15, MeOH) {lit.[xxi] $[\alpha]_D^{22}$ -40 (*c* 0.3, MeOH), lit.[xxii] $[\alpha]_D^{20}$ -53 (*c* 0.3, MeOH), lit.[xxiii] $[\alpha]_D^{20}$ -51 (*c* 2.5 MeOH), lit.[xxiv] $[\alpha]_D^{23}$ -53.4 (*c* 0.5, MeOH)};

ν_{max} (film) 3343, 2934, 2802, 1600, 1451, 1253, 1058 cm^{-1};

δ_H (396 MHz $CDCl_3$): 7.19-7.43 (5H, m), 4.87 (1H, dd, *J* 10.4, 2.3 Hz), 3.88 (1H, tt, *J* 7.5, 3.6 Hz), 2.88 (1H, dd, *J* 12.7, 7.7 Hz), 2.66-2.74 (1H, m), 2.59 (1H, dd, *J* 12.7, 3.6 Hz), 2.48 (3H, s), 2.17 (1H, ddd, *J* 14.2, 10.3, 8.2 Hz), 1.91 (1H, ddt, *J* 13.4, 8.9, 4.5 Hz), 1.67-1.76 (1H, m), 1.53-1.66 (2H, m), 1.49 (1H, ddd, *J* 14.2, 5.5, 2.8 Hz);

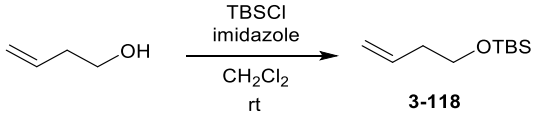
δ_C (100 MHz $CDCl_3$): 145.0, 128.2, 127.2, 125.4, 73.3, 63.6, 59.7, 57.5, 42.4, 39.6, 30.1, 24.0;

MS (ESI +ve) *m/z* 236.9 (M^+ +H, 80), 114.4 (100);

HRMS (ESI) *m/z* calculated for $C_{14}H_{22}NO_2$ $[M+H]^+$ 236.1651, found 236.1642.

[xxi] Ibebekebomangwa, W.; Hootelé, C. *Tetrahedron* **1987,** *43*, 935.
[xxii] Plehiers, M.; Hootelé, C. *Can. J. Chem.* **1996,** *74*, 2444.
[xxiii] Herdeis, C.; Held, W. A.; Kirfel, A.; Schwabenlander, F. *Liebigs Ann. Chem.* **1995,** 1295.
[xxiv] Liu, G.; Meng, J.; Feng, C. G.; Huang, P. Q. *Tetrahedron: Asymmetry* **2008,** *19*, 1297.

(but-3-en-1-yloxy)(tert-butyl)dimethylsilane (**3-118**)



To a solution of 3-buten-1-ol (25.0 mL, 290.5 mmol) in CH_2Cl_2 (300 mL) was added imidazole (21.76 g, 319.6 mmol) and *t*-butyldimethylsilyl chloride (TBSCl) (48.16 g, 319.6 mmol). The reaction mixture was left to stir at room temperature overnight. Saturated aqueous NH_4Cl (2 × 100 mL) was added to the reaction mixture and the organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by vacuum distillation (1 mbar, 50 °C) to give the desired TBS protected alcohol **3-118** as a colourless oil (54.20 g, 99%).

R_f 0.79 (10% Ethyl Acetate/Hexane);

ν_{max} (neat) 3078, 2955, 2877, 2342, 1830, 1641, 1464, 1383, 1256, 1099 cm^{-1};

δ_H (400 MHz $CDCl_3$): 5.82 (1H, ddt, *J* 17.1, 10.2, 6.8 Hz), 5.14-4.94 (2H, m), 3.66 (2H, t, *J* 6.8 Hz), 2.29 (1H, dt, *J* 6.8, 1.3 Hz), 2.26 (1H, dt, *J* 6.8, 1.3 Hz), 0.89 (9H, s), 0.05 (6H, s);

δ_C (101 MHz $CDCl_3$): 135.4, 116.2, 62.8, 37.5, 26.0, 18.4, -5.3;

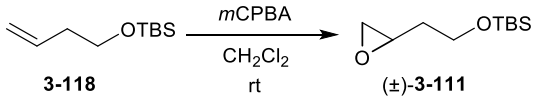
MS (ESI +ve) *m/z* 109.2 (90), 129.2 (M^+-*t*-Bu, 40), 156.3 (M^+-C_2H_6, 86);

HRMS (ESI) *m/z* calculated for $C_{10}H_{23}OSi$ $[M+H]^+$ 187.1518, found 187.1517.

The data were consistent with those reported in the literature.[xxv]

[xxv] Paterson, I.; Haslett, G. W. *Org. Lett.* **2013,** *15,* 1338.

tert-butyldimethyl(2-(oxiran-2-yl)ethoxy)silane ((±)-**3-111**)



3-Chloroperbenzoic acid (*m*CPBA) (77%, 51.95 g, 231.8 mmol) was added portionwise to a stirred solution of silyl alcohol **3-118** (36.00 g, 193.2 mmol) in CH_2Cl_2 (300 mL). The reaction mixture was left to stir at room temperature overnight. The white precipitate was first removed by filtration through a pad of Celite. The filtrate was washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and Na_2SO_3 (2 × 100 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting at 5% Ethyl Acetate/Hexane to give the desired epoxide **3-111** (35.20 g, 92%).

R_f 0.56 (10% Ethyl Acetate/Hexane);

ν_{max} (neat) 2953, 2928, 2857, 1472, 1387, 1256, 1103 cm^{-1};

δ_H (400 MHz $CDCl_3$): 3.87-3.68 (2H, m), 3.05 (1H, dddd, *J* 6.6, 5.1, 4.0, 2.8 Hz), 2.78 (1H, app t, *J* 4.0 Hz), 2.52 (1H, dd, *J* 5.1, 2.8 Hz), 1.90 - 1.65 (2H, m), 0.90 (9H, s), 0.06 (6H, s);

δ_C (101 MHz $CDCl_3$): 60.0, 50.0, 47.2, 35.9, 25.9, 18.3, -5.4;

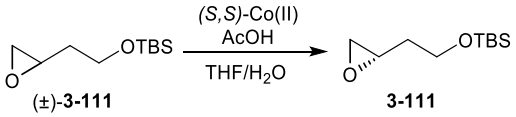
MS (ESI +ve) *m/z* 109.2 (90), 145.3 (M^+-*t*-Bu, 40);

HRMS (ESI) *m/z* calculated for $C_{10}H_{23}O_2Si$ $[M+H]^+$ 203.1467, found 203.1460.

The data were consistent with those reported in the literature.[xxvi]

[xxvi] Ficini, J. *et al. Heterocycles* **1987,** *25,* 329.

(S)-tert-butyldimethyl(2-(oxiran-2-yl)ethoxy)silane (**3-111**)



To a mixture of (*S*,*S*)-(+)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamino-cobalt(II) (894 mg, 1.5 mmol), racemic epoxide **3-111** (59.95 g, 296.2 mmol), acetic acid (339 μL, 5.9 mmol) and THF (2.9 mL) at 0 °C, was added water (2.9 mL, 162.9 mmol) in one portion. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was purified by flash column chromatography (2 to 5% Ethyl Acetate/Hexane) to provide chiral epoxide **3-111** (24.02 g, 101 mmol, 40 %) as a yellowish oil. The absolute configuration and enantiopurity of epoxide **3-111** was determined as >95:5 er based upon ^{1}H NMR analysis of the corresponding Mosher's ester derivative **3-119**.

R_f 0.56 (10% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -13.5 (*c* 1.05, $CHCl_3$) {lit.[xxvii] $[\alpha]_D^{26}$ –12.8 (c 2.11, $CHCl_3$)};

ν_{max} (neat) 2953, 2928, 2857, 1472, 1387, 1256, 1103 cm^{-1};

δ_H (400 MHz $CDCl_3$): 3.87-3.68 (2H, m), 3.05 (1H, dddd, *J* 6.6, 5.1, 4.0, 2.8 Hz), 2.78 (1H, t, *J* 5.1 Hz), 2.52 (1H, dd, *J* 5.1, 2.8 Hz), 1.90 - 1.65 (2H, m), 0.90 (9H, s), 0.06 (6H, s);

δ_C (101 MHz $CDCl_3$): 60.0, 50.0, 47.2, 35.9, 25.9, 18.3, -5.4;

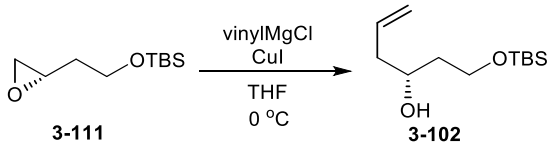
MS (ESI +ve) *m/z* 109.2 (90), 145.3 (M^+-*t*-Bu, 40);

HRMS (ESI) *m/z* calculated for $C_{10}H_{23}O_2Si$ $[M+H]^+$ 203.1467, found 203.1460.

[xxvii] Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471.

The data were consistent with those reported in the literature.[xxviii]

(R)-1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-ol (**3-102**)



To a solution of resolved chiral epoxide **3-111** (24.02 g, 118.7 mmol) and CuI (4.53 g, 23.8 mmol) in THF (200 mL) at –78 °C, was added vinyl magnesium chloride (111.3 mL, 178.1 mmol of a 1.6M in THF solution) in a dropwise fashion. After addition was complete, the reaction mixture was warmed slowly to room temperature and stirred until the reaction was shown to be complete by TLC analysis. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 mL) and the insoluble copper salts were removed by filtration. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Ethyl Acetate/Hexane) to yield allylic silyl ether **3-102** as a yellow oil (24.35 g, 89%).

R_f 0.36 (10% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ +8.8 (*c* 1.07, $CHCl_3$); {lit.[xxix] $[\alpha]_D^{20}$ +9.0 (c 0.95, $CHCl_3$)}

ν_{max} (neat) 3447, 2930, 2859, 1827, 1641, 1471, 1256, 1090 cm^{-1};

δ_H (400 MHz $CDCl_3$): 5.85 (1H, ddt, *J* 17.3, 10.2, 7.1 Hz), 5.19-5.00 (2H, m), 3.98-3.71 (3H, m), 3.35 (1H, d, *J* 2.4 Hz), 2.39-2.10 (2H, m), 1.76-1.63 (2H, m), 0.90 (9H, s), 0.08 (6H, s);

[xxviii] McGowan, M. A.; Stevenson, C. P.; Schiffler, M. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010,** *49,* 6147.
[xxix] Kobayashi, K.; Fujii, Y.; Hirayama, Y.; S. Kobayashi, S.; Hayakawa, I.; Kigoshi, H. *Org. Lett.* **2012,** *14,* 1290.

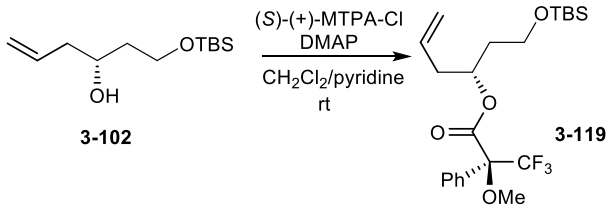
δ_C (101 MHz $CDCl_3$): 135.0, 117.3, 71.2, 62.6, 42.0, 37.8, 25.9, 18.1, -5.5, -5.6;

MS (ESI +ve) *m/z* 130.1 (20), 156.1 (80), 213.2 (M^+-OH, 30), 231.2 (M^++H, 100);

HRMS (ESI) *m/z* calculated for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 231.1780, found 231.1770.

The data were consistent with those reported in the literature.[xxx]

(R)-1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**3-119**)



To a stirred solution of allylic silyl ether **3-102** (20.0 mg, 86.8 μmol) and a catalytic amount of 4-DMAP in CH_2Cl_2 (0.5 mL) and pyridine (0.5 mL) at room temperature was added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*S*)-(+)-MTPA-Cl) (24.1 mg, 95.5 μmol). The mixture was stirred for 1.5 hours at room temperature, then diluted with CH_2Cl_2 (10 mL) and washed sequentially with solutions of saturated aqueous NH_4Cl (5 mL), 1M HCl (2 × 5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Ethyl Acetate/Hexane) to provide (*R*)-Mosher's ester **3-119** as a colourless oil (35.0 mg, 90%).

R_f 0.51 (10% Ethyl Acetate/Hexane);

$[\alpha]_D^{22}$ -3.2 (*c* 1.55, $CHCl_3$); {lit.[xxxi] $[\alpha]_D^{25}$ -2 (c 1.0, $CHCl_3$)}

ν_{max} (neat) 3447, 2953, 2857, 1746, 1258, 1169, 1099 cm^{-1};

[xxx] Dittoo, A.; Brandt, D.; Bellosta, V.; Cossy, J. *Tetrahedron* **2015,** *71,* 5835.
[xxxi] Pilli, R. A. *et al. Tetrahedron* **2014,** *70,* 6467.

δ_H (400 MHz $CDCl_3$): 7.64-7.49 (2H, m), 7.46-7.32 (3H, m), 5.66 (1H, ddt, *J* 17.5, 9.8, 7.4 Hz), 5.40-5.25 (1H, m), 5.11-4.94 (2H, m), 3.75-3.57 (2H, m), 3.54 (3H, s), 2.53-2.26 (2H, m), 1.96-1.73 (2H, m), 0.89 (9H, s), 0.03 (6H, s).

δ_C (101 MHz $CDCl_3$): 166.0, 132.7, 132.3, 129.5, 128.3, 127.5, 123.4 (q, J_{C-F} 288.4 Hz), 118.4, 84.6 (q, J_{C-F} 27.7 Hz), 73.8, 59.0, 55.3, 38.3, 36.3, 25.9, 18.2, -5.4;

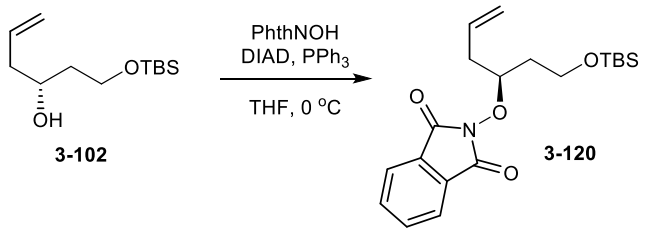
δ_F (376 MHz $CDCl_3$):-71.4;

MS (ESI +ve) *m/z* 123.1 (40), 156.1 (100), 213.2 (M^+-$C_{10}H_8F_3O_3$, 40), 447.2 (M^++H, 25), 469.1 (M^++Na, 25), 510.1 (M^++MeCN+Na, 10)

HRMS (ESI) *m/z* calculated for $C_{22}H_{34}F_3O_4Si$ $[M+H]^+$ 447.2178, found 447.2176.

The data were consistent with those reported in the literature.[xxxii]

(S)-2-((1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)oxy)isoindoline-1,3-dione (**3-120**)



A stirred mixture of silyl ether **3-102** (17.66 g, 76.6 mmol), PPh_3 (24.13 g, 92.0 mmol) and *N*-hydroxyphthalimide (15.00 g, 92.0 mmol) in anhydrous THF (400 mL) was cooled to 0 °C in an ice-water bath. Once cooled, diazopropyl azodicarboxylate (DIAD) (18.1 mL, 92.0 mmol) was added in a dropwise fashion. The mixture was stirred at 0 °C for 1 hour and then left to stir at room temperature overnight. The mixture was concentrated *in vacuo* and the residue was absorbed onto silica and purified by flash chromatography

[xxxii] Pilli, R. A. *et al. Tetrahedron* **2014,** *70,* 6467.

with gradual elution (5-10% Ethyl Acetate/Hexane) to give desired *N*-hydroxyphthalimide **3-120** derivative as a colourless oil (21.63 g, 75%).

R_f 0.54 (10% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ +29.5 (*c* 1.15, $CHCl_3$);

ν_{max} (neat) 3509, 2953, 2854, 1790, 1743, 1468, 1373, 1256, 1188, 1096 cm^{-1};

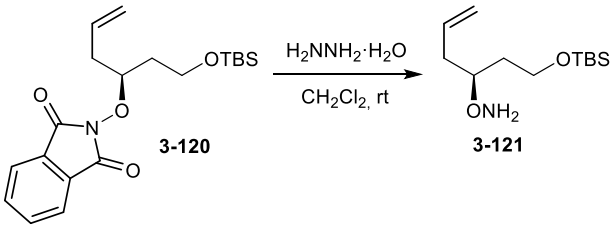
δ_H (400 MHz, $CDCl_3$): 7.89-7.68 (4H, m), 5.93 (ddt, 1H, *J* 17.1, 10.2, 6.9 Hz), 5.20-5.03 (2H, m), 4.51-4.40 (1H, m), 3.94-3.75 (2H, m), 2.63-2.40 (2H, m), 2.06-1.80 (2H, m), 0.87 (9H, s), 0.05 (6H, s);

δ_C (101 MHz, $CDCl_3$): 164.2, 134.4, 133.4, 129.1, 123.4, 117.8, 84.9, 59.5, 37.6, 35.7, 25.9, 18.2, -5.4;

MS (ESI +ve) *m/z* 164.0 (16), 244.3 (M^+-$C_8H_3O_2$, 30), 376.5 (M^++H, 100), 398.5 (M^++Na, 42);

HRMS (ESI) *m/z* calculated for $C_{20}H_{30}NO_4Si$ $[M+H]^+$ 376.1944, found 376.1943.

(S)-O-(1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)hydroxylamine (**3-121**)



Hydrazine monohydrate (5.6 mL, 116.1 mmol) was added dropwise to a stirred solution of *N*-hydroxyphthalimide **3-120** (21.63 g, 57.6 mmol) in CH_2Cl_2 (400 mL) at room temperature. The mixture was stirred for 2 hours, and then filtered through a pad of Celite, washing with Et_2O (2 × 100 mL). The filtrate was concentrated *in vacuo* to give desired hydroxylamine **3-121** (12.10 g, 86%) as a clear oil that was used in the subsequent reaction without further purification.

R_f 0.35 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ +27.7 (c 1.21, $CHCl_3$);

ν_{max} (neat) 3316, 3075, 2953, 2857, 1639, 1586, 1256, 1092 cm^{-1};

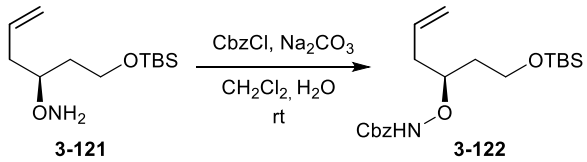
δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddt, *J* 17.2, 10.2, 7.1 Hz), 5.22 (2H, br s), 5.15-5.01 (2H, m), 3.82-3.62 (3H, m), 2.47-2.23 (2H, m), 1.86-1.62 (2H, m), 0.90 (9H, s), 0.06 (6H, s);

δ_C (101 MHz, $CDCl_3$): 135.0, 116.8, 80.3, 60.0, 37.5, 35.7, 26.0., 18.3, -5.3;

MS (ESI +ve) m/z 114.2 (100), 246.5 (M^++H, 70);

HRMS (ESI) m/z calculated for $C_{12}H_{28}NO_2Si$ $[M+H]^+$ 246.1889, found 246.1881.

Benzyl (S)-((1-((tert-butyldimethylsilyl)oxy)hex-5-en-3-yl)oxy)carbamate (**3-122**)



3-121 **3-122**

Anhydrous sodium carbonate (7.74 g, 73.7 mmol) and benzyl chloroformate (8.2 mL, 73.7 mmol) were added sequentially to a stirred solution of hydroxylamine **3-121** (12.00 g, 48.9 mmol) in CH_2Cl_2 (300 mL) and water (300 mL) at room temperature. The mixture was stirred overnight. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5-20% Ethyl Acetate/Hexane) to give desired *N*-benzyloxycarbonyl hydroxylamine **3-122** (15.00 g, 81%) as a clear oil.

R_f 0.73 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ +22.0 (*c* 1.16, $CHCl_3$);

ν_{max} 3445, 3285, 2953, 2855, 1732, 1495, 1254, 1096 (neat) cm^{-1};

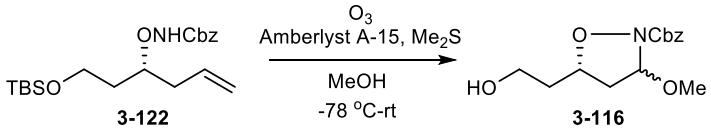
δ_H (400 MHz, $CDCl_3$): 7.52 (1H, br s), 7.39-7.29 (5H, m), 5.85 (1H, ddt, *J* 17.2, 10.3, 7.0 Hz), 5.23-4.98 (4H, m), 4.03-3.90 (1H, m), 3.81-3.67 (2H, m), 2.49-2.28 (2H, m), 1.86-1.71 (2H, m), 0.88 (9H, s), 0.04 (6H, s);

δ_C (101 MHz, $CDCl_3$): 157.4, 135.7, 134.4, 128.5, 128.3, 128.3, 117.3, 82.9, 67.4, 59.9, 37.5, 35.4, 25.9, 18.2, -5.4;

MS (ESI +ve) *m/z* 171.3 (40), 204.3 (90), 380.5 (M^++H, 100), 402.6 (M^++Na, 64);

HRMS (ESI) m/z calculated for $C_{20}H_{34}NO_4Si$ $[M+H]^+$ 380.2257, found 380.2256.

Benzyl (5R)-5-(2-hydroxyethyl)-3-methoxyisoxazolidine-2-carboxylate (**3-116**)



Amberlyst A-15 (865.8 mg, 5.0 mmol) was added to a solution of *N*-benzyloxycarbonyl hydroxylamine (**3-122**) (38.17 g, 100.5. mmol) in MeOH (500 mL). The mixture was cooled to -78 °C and a stream of O_3/O_2 was passed through the mixture until the solution turned blue in colour. The flask was then purged with O_2 until the blue colour dissipated. Me_2S (8.9 mL, 121.2 mmol) was added and the reaction mixture was warmed to room temperature and stirred for a further 24 h. The reaction solvent was removed with a rotary evaporator and the residue was taken up in CH_2Cl_2 (300 mL) and washed with water (2 x 100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography with gradual elution (25-50% Ethyl Acetate/Hexane) to give methoxy isoxazolidine **3-116** (22.08 g, 78%) as a mixture of inconsequential diastereomers (ratio = 1.5:1) and as a clear oil.

R_f 0.23 (% Ethyl Acetate/Hexane);

ν_{max} 3520, 2950, 1746, 1497, 1270, 1057 (neat) cm^{-1};

Minor diastereomer:

δ_H (400 MHz, $CDCl_3$): 7.44-7.27 (5H, m), 5.51-5.36 (1H, m), 5.33-5.10 (2H, m), 4.65-4.52 (1H, m), 3.89-3.63 (2H, m), 3.38 (3H, s), 2.43 (1H, ddd, *J* 13.1, 7.0, 1.7 Hz), 2.21-1.78 (3H, m);

δ_C (101 MHz, $CDCl_3$): 156.6, 135.5, 128.6, 128.4, 128.0, 89.9, 79.5, 68.3, 60.0, 55.8, 41.1, 35.2;

Major diastereomer:

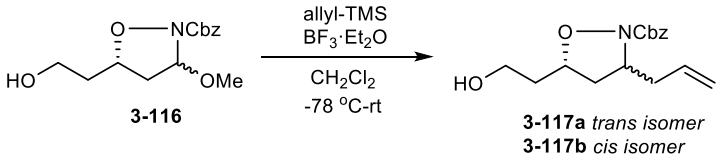
δ_H (400 MHz, $CDCl_3$): 7.44 -7.27 (5H, m), 5.51-5.36 (1H, m), 5.33-5.10 (2H, m), 4.27-4.05 (1H, m), 3.89-3.63 (2H, m), 3.40 (3H, s), 2.64 (1H, dt, *J* 13.1, 7.1 Hz), 2.21 – 1.78 (3H, m);

δ_C (101 MHz, $CDCl_3$): 157.4, 135.6, 135.5, 128.6, 128.4, 128.0, 91.8, 80.6, 68.2, 59.6, 56.2, 41.5, 35.2;

MS (ESI +ve) *m/z* 206.1 (100), 304.1 (M^++Na, 40);

HRMS (ESI) m/z calculated for $C_{14}H_{20}NO_5$ $[M+H]^+$ 282.1341, found 282.1340.

benzyl (3R,5S)-3-allyl-5-(2-hydroxyethyl)isoxazolidine-2-carboxylate (**3-117a**) *and benzyl (3S,5S)-3-allyl-5-(2-hydroxyethyl)isoxazolidine-2-carboxylate* (**3-117b**)



3-116

3-117a *trans isomer*
3-117b *cis isomer*

$BF_3 \cdot Et_2O$ (6.1 mL, 49.8 mmol) was added to a stirred solution of methoxy isoxazolidine **3-116** (7.00 g, 24.9 mmol) and allyltrimethylsilane (15.8 mL, 99.5 mmol) in anhydrous CH_2Cl_2 (100 mL) at -78 °C. Once addition was complete, the reaction mixture was gradually warmed to room temperature and left to stir until the reaction was shown to be complete by TLC analysis. The reaction mixture was cooled to -78 °C and quenched with Et_3N (3.5 mL, 25.0 mmol). The mixture was allowed to warm to room temperature and was

diluted with water (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (25 to 50% Ethyl Acetate/Hexane) to give the *trans* isomer **3-117a** (3.81 g, 52%) as a colourless oil, *cis* isomer **3-117b** (725 mg, 10%) as a pale yellow oil and a remaining 1:1 mixture of both isomers (1.84 g, 25%) which was not separated.

Trans diastereomer **3-117a**:

R_f 0.35 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -51.8 (*c* 1.40, $CHCl_3$);

ν_{max} (neat) 3428, 2949, 2887, 1713, 1455, 1337, 1088 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.49-7.30 (5H, m), 5.77 (1H, ddt, *J* 17.2, 10.2, 7.1 Hz), 5.38-4.96 (4H, m), 4.45 (1H, ddt, *J* 9.1, 7.1, 4.5 Hz), 4.36-4.24 (1H, m), 3.85-3.57 (2H, m), 2.48 (1H, dddt, *J* 14.1, 7.1, 5.8, 1.3 Hz), 2.34-2.14 (2H, m), 2.06 (1H, ddd, *J* 12.6, 8.3, 4.6 Hz), 1.72-1.51 (2H, m).

δ_C (101 MHz $CDCl_3$): 157.4, 135.8, 133.8, 128.6, 128.4, 118.0, 79.4, 68.0, 60.2, 58.1, 39.1, 38.8, 36.2;

MS (ESI +ve) *m/z* 248.4 (M+-C_2H_5O, 100), 292.4 (M^++H, 30), 314.3 (M^++Na, 20);

HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549, found 292.1556.

Cis diastereomer **3-117b**:

R_f 0.35 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ +66.2 (*c* 1.22, $CHCl_3$)

ν_{max} (neat) 3416, 2945, 1730, 1454, 1337, 1074 cm^{-1};

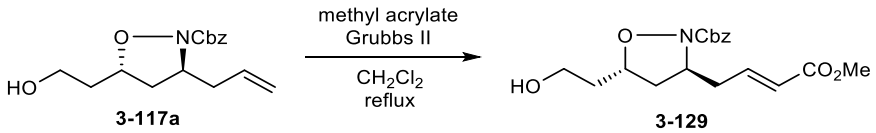
δ_H (400 MHz $CDCl_3$): 7.43-7.28 (5H, m), 5.77 (1H, ddt, *J* 17.2, 10.2, 7.0 Hz), 5.23 (1H, d, *J* 12.3 Hz), 5.16 (1H, d, *J* 12.3 Hz), 5.14-5.02 (2H, m), 4.34-4.23 (1H, m), 4.03 (1H, app dq, *J* 10.0, 6.2 Hz), 3.87-3.67 (2H, m), 2.54-2.41 (2H, m), 2.36-2.25 (1H, m), 1.92 (2H, app q, *J* 6.0 Hz), 1.76-1.56 (1H, m);

δ_C (101 MHz $CDCl_3$): 158.4, 135.9, 134.0, 128.6, 128.3, 127.9, 117.8, 80.3, 67.8, 59.9, 59.7, 40.0, 39.9, 35.3;

MS (ESI +ve) *m/z* 248.4 (M+-C_2H_5O, 100), 292.4 (M^++H, 32), 314.3 (M^++Na, 16);

HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549, found 292.1548.

benzyl (3R,5S)-5-(2-hydroxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2-carboxylate (**3-129**)



To a stirred solution of allyl isoxazolidine **3-117a** (5.50 g, 18.9 mmol) and methyl acrylate (5.1 mL, 57.0 mmol) in CH_2Cl_2 (250 mL) heated at reflux, was added a solution of Grubbs II catalyst (242 mg, 285 μmol) in CH_2Cl_2 (5 mL), dropwise over a period of 3 hours. The reaction mixture was then left to stir at the same temperature overnight. The reaction mixture was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The residue was absorbed onto silica gel and purified by flash column chromatography with gradual elution (50 to 70% Ethyl Acetate/Hexane) to give desired α,β- unsaturated ester **3-129** (4.99 g, 75%) as a clear oil.

R_f 0.22 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -44.3 (*c* 2.38, $CHCl_3$);

ν_{max} (neat) 3443, 2951, 2889, 1715, 1454, 1337, 1215, 1086 cm^{-1};

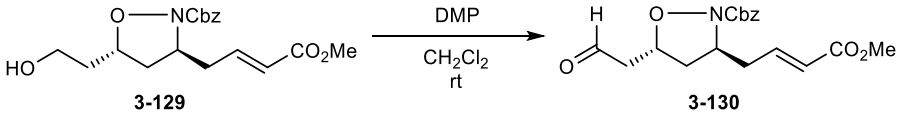
δ_H (400 MHz $CDCl_3$): 7.43-7.29 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.3 Hz), 5.90 (1H, dt, *J* 15.7, 1.5 Hz), 5.23 (1H, d, *J* 12.1 Hz), 5.15 (1H, d, *J* 12.1 Hz), 4.46 (1H, ddt, *J* 9.1, 7.0, 4.6 Hz), 4.41-4.32 (1H, m), 3.83-3.59 (5H, m), 2.62 (1H, dddd, *J* 14.5, 7.2, 6.1, 1.5 Hz), 2.44 (1H, dtd, *J* 14.5, 7.2, 1.5 Hz), 2.26-1.97 (2H, m), 1.77-1.53 (2H, m).;

δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 143.8, 135.6, 128.6, 128.5, 128.4, 123.9, 79.3, 68.1, 60.1, 57.5, 51.5, 39.1, 37.4, 36.1;

MS (ESI +ve) *m/z* 306.4 (M^+-C_2H_5O, 100), 350.5 (M^++H, 10);

HRMS (ESI) *m/z* calculated for $C_{18}H_{24}NO_6$ $[M+H]^+$ 350.1604, found 350.1602.

benzyl (3R,5S)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)-5-(2-oxoethyl)isoxazolidine-2-carboxylate (**3-130**)



3-129 **3-130**

Dess-Martin periodinane (DMP) (3.71 g, 8.8 mmol) was added in one portion at room temperature to a solution of alcohol **3-129** (2.04 g, 5.8 mmol, 1.0 eq) in CH_2Cl_2 (30 mL). The reaction was stirred for 4 hours and a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (30 mL) was added. The slurry was stirred until all solids were dissolved to form a clear biphasic mixture. The aqueous layer was extracted three times with Et_2O (3 x 15 mL) and the combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired aldehyde **3-130** as a clear oil (99%) which was used in the subsequent reaction without further purification.

R_f 0.38 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -43.8 (*c* 1.48, $CHCl_3$);

ν_{max} (neat) 3507, 2951, 1715, 1697, 1454, 1337, 1074 cm^{-1};

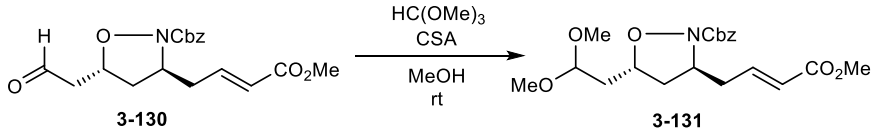
δ_H (400 MHz $CDCl_3$): 9.65 (1H, t, *J* 1.3 Hz), 7.42-7.31 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.2 Hz), 5.91 (1H, dt, *J* 15.7, 1.5 Hz), 5.24 (1H, d, *J* 12.1 Hz), 5.16 (1H, d, *J* 12.1 Hz), 4.78-4.66 (1H, m), 4.45-4.34 (1H, m), 3.73 (3H, s), 2.74 (1H, ddd, *J* 17.5, 7.1, 1.3 Hz), 2.62 (1H, dddd, *J* 14.8, 7.1, 6.1, 1.3 Hz), 2.51-2.37 (2H, m), 2.27 (1H, ddd, *J* 12.8, 7.1, 4.2 Hz), 2.09 (1H, ddd, *J* 12.8, 8.3, 5.0 Hz);

δ_C (101 MHz $CDCl_3$): 198.9, 166.4, 157.5, 143.6, 135.6, 128.6, 128.5, 128.4, 124.0, 75.3, 68.2, 57.7, 51.6, 47.2, 38.8, 37.3;

MS (ESI +ve) *m/z* 304.2 (M^+-C_2H_5O, 100), 370.1 (M^++Na, 5);

HRMS (ESI) *m/z* calculated for $C_{18}H_{22}NO_6$ $[M+H]^+$ 348.1447, found 348.1451.

benzyl (3R,5S)-5-(2,2-dimethoxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2-carboxylate (**3-131**)



3-130 **3-131**

(±)-Camphorsulfonic acid (CSA) (6.7 mg, 28.7 μmol) was added to a solution of aldehyde **3-130** (200 mg, 576 μmol) and trimethyl orthoformate (9.4 μL, 86.3 μmol) in dry MeOH (5 mL). The mixture was left to stir at room temperature overnight. The reaction was neutralised with Et_3N (0.1 mL) and the solvents removed under reduced pressure. The residue was redissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ (2 x 5 mL) The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography with gradual elution (40 to 60% Ethyl Acetate/Hexane) to give diacetal **3-131** as a colourless oil (190 mg, 85%).

R_f 0.45 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{23}$ -26.9 (*c* 0.67, $CHCl_3$);

ν_{max} (neat) 2953, 1738, 1722, 1697, 1454, 1337, 1275, 1125 cm^{-1};

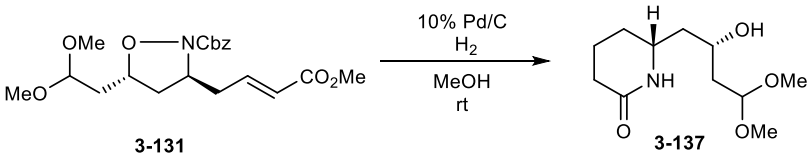
δ_H (400 MHz $CDCl_3$): 7.44-7.30 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.3 Hz), 5.90 (1H, dt, *J* 15.7, 1.5 Hz), 5.21 (1H, d, *J* 12.1 Hz), 5.17 (1H, d, *J* 12.1 Hz), 4.52 (1H, dd, *J* 7.8, 3.6 Hz), 4.46-4.29 (2H, m), 3.73 (3H, s), 3.34 (3H, s), 3.21 (3H, s), 2.62 (1H, dddd, *J* 14.7, 7.4, 6.0, 1.6 Hz), 2.43 (1H, dtd, *J* 14.7, 7.4, 1.6 Hz), 2.19-2.10 (2H, m), 1.77 (1H, ddd, *J* 14.2, 8.9, 3.6 Hz), 1.59 (1H, m).;

δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 143.9, 135.8, 128.6, 128.3, 128.2, 123.9, 102.3, 68.0, 57.5, 54.2, 53.1, 51.5, 38.9, 37.4, 37.0;

MS (ESI +ve) *m/z* 318.2 (M^+-$C_3H_7O_2$, 100), 416.2 (M^++Na, 10);

HRMS (ESI) *m/z* calculated for $C_{20}H_{28}NO_7$ $[M+H]^+$ 394.1866, found 394.1885.

(R)-6-((S)-2-hydroxy-4,4-dimethoxybutyl)piperidin-2-one (**3-137**)



3-131 **3-137**

In a round-bottomed flask, acetal **3-131** was dissolved (180 mg, 458 μmol) in MeOH (100 mL). The sample inlet line and outlet line were both placed in the reaction solution. A 30 mm column of 10% Pd/C was inserted into the H-Cube reactor. The pressure was set to 1 bar, the flow rate of the HPLC pump was set to 1.0 mL/min, and the temperature to 25 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction was started by pressing the "start" button on the touch screen control. The reaction mixture was continuously passed through the instrument, until the starting material was shown to be completely consumed by TLC analysis. The column was washed with MeOH (10 mL in 10 min) to remove any substrate still adsorbed to the catalyst. The reaction mixture was then evaporated *in vacuo* and the resulting residue was purified by flash column

chromatography (10% Methanol/Ethyl Acetate) to give the desired lactam **3-137** as a colourless oil (105 mg, 99%)

R_f 0.25 (10% Methanol/Ethyl Acetate);

$[\alpha]_D^{23}$ -33.8 (*c* 0.51, $CHCl_3$);

ν_{max} (neat) 3443, 2951, 1632, 1126, 1053 cm^{-1};

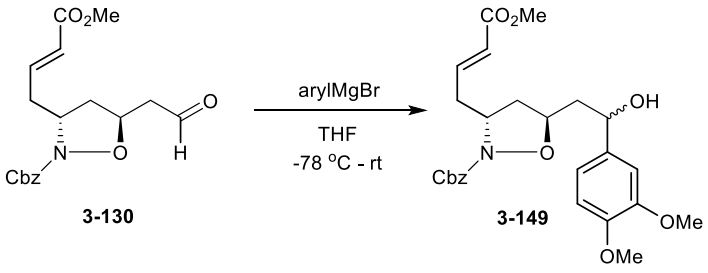
δ_H (400 MHz $CDCl_3$): 6.52 (1H, br s), 4.55 (1H, dd, *J* 6.7, 3.9 Hz), 4.10-3.90 (1H, m), 3.75-3.61 (1H, m), 3.44 (1H, br s), 3.40 (3H, s), 3.36 (3H, s), 2.42-2.22 (2H, m), 1.93-1.81 (3H, m), 1.79-1.51 (m, 4H), 1.47-1.35 (m, 1H);

δ_C (101 MHz $CDCl_3$): 172.1, 104.4, 65.4, 54.5, 53.2, 49.3, 43.1, 39.1, 31.2, 29.3, 19.6;

MS (ESI +ve) *m/z* 168.2 (M+-$C_2H_7O_2$, 100), 200.3 (M^+-OCH_3, 26), 232.40 (M^++H, 34), 254.3 (M^++Na, 10);

HRMS (ESI) *m/z* calculated for $C_{11}H_{22}NO_4$ $[M+H]^+$ 232.1549, found 232.1547.

benzyl (3R,5S)-5-((R)-2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2-carboxylate and benzyl (3R,5S)-5-((S)-2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2-carboxylate (**3-149**)



To a solution of aldehyde **3-130** (80.0 mg, 230 μmol) in anhydrous THF (5 mL) cooled to -78 °C was added the Grignard reagent, 3,4-dimethoxyphenyl magnesium bromide (1.4 mL, 690 μmol of a 0.5 M in THF solution) in a dropwise fashion. The reaction mixture was

allowed to stir at the same temperature for a further 1 hour and then allowed to warm slowly to room temperature. Progress of the reaction was monitored closely by TLC analysis based on the disappearance of the starting material The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 ×10 mL) The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography to give the alcohol **3-149** as a 2:1 mixture of diastereomers (73 mg, 65%).

R_f 0.35 (50% Ethyl Acetate/Hexane);

ν_{max} (neat) 3520, 2952, 2837, 1732, 1714, 1514, 1444, 1337, 1028 cm^{-1};

Major diastereomer (**3-149a**):

δ_H (400 MHz $CDCl_3$): 7.48 -7.29 (5H, m), 6.96-6.71 (4H, m), 5.89 (1H, dt, *J* 15.7, 1.4 Hz), 5.27 (1H, d, *J* 12.1 Hz), 5.20 (1H, d, *J* 12.1 Hz), 4.79 (1H, dd, *J* 7.8, 5.5 Hz), 4.45-4.27 (2H, m), 3.87 (6H, s), 3.72 (3H, s), 2.59 (1H, dddd, *J* 14.9, 7.4, 6.3, 1.5 Hz), 2.42 (1H, dtd, *J* 14.5, 7.1, 1.5 Hz), 2.24-2.03 (2H, m), 1.90 (1H, ddd, *J* 14.5, 10.1, 7.8 Hz), 1.66 (1H, ddd, *J* 14.5, 5.7, 3.8 Hz);

δ_C (101 MHz $CDCl_3$): 166.4, 157.7, 149.1, 148.5, 143.7, 136.7, 135.6, 128.6, 128.5, 128.4, 123.9, 118.1, 111.1, 109.1, 79.7, 72.4, 68.3, 57.5, 56.0, 55.9, 51.5, 43.2, 39.2, 37.4;

Minor diastereomer (**3-149b**):

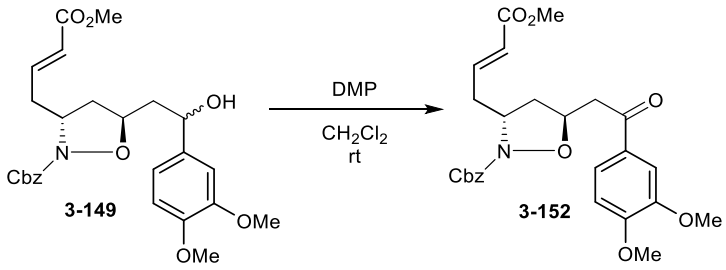
δ_H (400 MHz $CDCl_3$): 7.47 -7.27 (5H, m), 7.02-6.61 (4H, m), 5.88 (1H, dd, *J* 15.7, 1.6 Hz), 5.32-5.10 (2H, m), 4.95 (1H, dd, *J* 8.6, 3.3 Hz), 4.64-4.50 (1H, m), 4.47-4.24 (1H, m), 3.85 (s, 6H), 3.71 (s, 3H), 2.68-2.53 (m, 1H), 2.51-2.33 (m, 1H), 2.20-2.05 (m, 1H), 1.83-1.71 (m, 2H);

δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 149.1, 148.4, 143.8, 136.9, 135.7, 128.6, 128.4, 128.1, 123.9, 117.6, 111.1, 108.9, 77.9, 70.8, 68.1, 57.6, 56.0, 55.9, 51.6, 42.5, 39.1, 37.5;

MS (ESI +ve) *m/z* 424.2 (100), 508.2 (M^++Na, 14);

HRMS (ESI) *m/z* calculated for $C_{26}H_{32}NO_8$ $[M+H]^+$ 486.2128, found 486.2111.

benzyl (3R,5S)-5-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2-carboxylate (**3-152**)



Dess-Martin periodinane (DMP) (288 mg, 679 μmol) was added in one portion at room temperature to a solution of alcohol **3-149** (220 mg, 453 μmol) in CH_2Cl_2 (10 mL). The reaction was stirred for 4 hours and a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (10 mL) was added. The slurry was stirred until all solids were dissolved to form a clear biphasic mixture. The aqueous layer was extracted three times with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (50 to 70% Ethyl Acetate/Hexane) to give the desired ketone **3-152** as a yellow oil (140 mg, 64%).

R_f 0.56 (50% Ethyl Acetate/Hexane);

$[\alpha]_D^{24}$ -38.9 (*c* 0.27, $CHCl_3$);

ν_{max} (neat) 3362, 2931, 2855, 1732, 1643, 1514, 1261 cm^{-1};

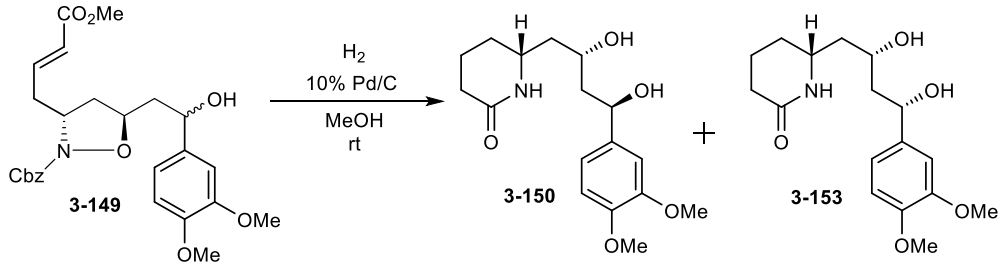
δ_H (400 MHz $CDCl_3$): 7.44 (1H, d, *J* 2.0 Hz), 7.40-7.28 (6H, m), 6.92 (1H, dt, *J* 15.7, 7.2 Hz), 6.82 (1H, d, *J* 8.4 Hz), 5.92 (1H, dt, *J* 15.7, 1.5 Hz), 5.21 (1H, d, *J* 12.1 Hz, 1H), 5.15 (1H, d, *J* 12.1 Hz), 4.91-4.78 (1H, m), 4.48-4.33 (1H, m), 3.95 (3H, s), 3.90 (3H, s), 3.73 (3H, s), 3.45 (1H, dd, *J* 17.0, 4.9 Hz), 2.87 (1H, dd, *J* 17.0, 8.5 Hz), 2.73-2.59 (1H, m), 2.47 (1H, dtd, *J* 14.6, 7.3, 1.5 Hz), 2.37 (1H, ddd, *J* 12.8, 7.0, 4.0 Hz), 2.17 (1H, ddd, *J* 12.8, 8.3, 5.2 Hz);

δ_C (101 MHz $CDCl_3$): 195.3, 166.5, 157.4, 153.7, 149.2, 143.8, 135.8, 129.7, 128.6, 128.3, 128.2, 123.9, 122.9, 110.0, 109.9, 68.0, 57.8, 56.1, 56.0, 51.5, 41.8, 39.0, 37.3;

MS (ESI +ve) *m/z* 440.2 (40), 484.2 (M^++H, 100), 506.1 (M^++Na, 10);

HRMS (ESI) *m/z* calculated for $C_{26}H_{30}NO_8$ $[M+H]^+$ 484.1971, found 484.1977.

(R)-6-((2S,4R)-4-(3,4-dimethoxyphenyl)-2,4-dihydroxybutyl)piperidin-2-one (**3-150**) *and (R)-6-((2R,4R)-4-(3,4-dimethoxyphenyl)-2,4-dihydroxybutyl)piperidin-2-one* (**3-153**)



In a round bottomed flask, acetal **3-149** (240 mg, 742 μmol) was dissolved in MeOH (150 mL). The sample inlet line and outlet line were both placed in the reaction solution. A 30 mm column of 10% Pd/C was inserted into the HCube reactor. The pressure was set to 1 bar, the flow rate of the HPLC pump was set to 1.0 mL/min, and the temperature to 25 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction was started by pressing the "start" button on the touch screen control. The reaction mixture was continuously cycled through the instrument, until the starting material was shown to be completely consumed by TLC analysis. The column was washed with MeOH (10 mL in

10 min) to remove any substrate still adsorbed to the catalyst. The reaction mixture was then evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (10% Methanol/Dichloromethane) to give the desired *anti*-1,3-diol **3-150** as a colourless crystalline solid (47.5 mg, 20%) and undesired *syn*-1,3-diol **3-153** as a colorless oil (95.5 mg, 38%).

Anti-1,3-diol **3-150**:

R_f 0.25 (10% Methanol/Dichloromethane);

Mp 119.1 °C

$[\alpha]_D^{21}$ +10.2 (*c* 0.23, $CHCl_3$)

ν_{max} (neat) 3362, 2943, 1614, 1516, 1262, 1140, 1024 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.30 (1H, br s), 6.93 (1H, d, *J* 2.0 Hz), 6.89 (1H, dd, *J* 8.2, 2.0 Hz), 6.83 (1H, d, *J* 8.2 Hz), 4.98 (1H, dd, *J* 9.0, 3.1 Hz), 4.31 (1H, br s), 4.25-4.15 (1H, m), 3.94-3.80 (7H, m), 3.78-3.63 (1H, m), 2.49-2.16 (2H, m), 1.95-1.49 (7H, m), 1.48-1.32 (1H, m).

δ_C (101 MHz $CDCl_3$): 173.2, 149.1, 148.3, 137.4, 117.6, 111.2, 109.0, 70.8, 65.0, 56.0, 55.9, 49.5, 45.7, 43.1, 31.1, 29.0, 19.4;

MS (ESI +ve) *m/z* 112.1 (10), 306.1 (80), 324.2 (M^++H, 36), 647.4 ($2M^+$+H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{26}NO_5$ $[M+H]^+$ 324.1811, found 324.1815.

Syn-1,3-diol **3-153**:

R_f 0.27 (10% Methanol/Dichloromethane);

$[\alpha]_D^{21}$ -35.5 (*c* 1.30, $CHCl_3$);

ν_{max} (neat) 3304, 2945, 1643, 1514, 1265, 1139, 1026 cm^{-1};

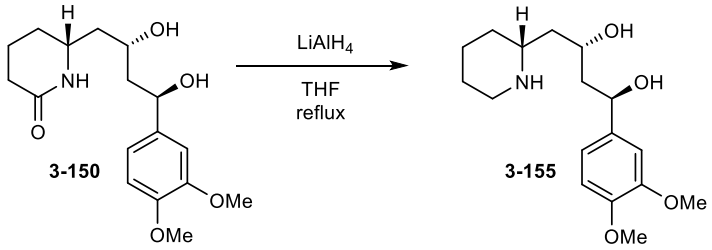
δ_H (400 MHz $CDCl_3$): 7.09 (1H, br s), 6.93 (1H, d, *J* 1.9 Hz), 6.92-6.79 (2H, m), 4.96-4.83 (1H, m), 4.48 (1H, br s), 4.23 (1H, m), 3.90 (3H, s), 3.87 (3H, s), 3.82 (1H,br s), 3.77-3.60 (1H, m), 2.44-2.19 (2H, m), 1.98 (1H, dt, *J* 14.4, 10.2 Hz), 1.93-1.77 (2H, m), 1.78-1.51 (4H, m), 1.49-1.33 (1H, m);

δ_C (101 MHz $CDCl_3$): 172.6, 149.2, 148.6, 137.2, 117.7, 111.1, 108.8, 75.2, 69.4, 56.0, 55.9, 49.3, 45.1, 43.2, 31.1, 29.2, 19.6.;

MS (ESI +ve) *m/z* 112.1 (24), 306.1 (100), 324.2 (M^++H, 46), 647.4 ($2M^+$+H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{26}NO_5$ $[M+H]^+$ 324.1811, found 324.1817.

(1R,3S)-1-(3,4-dimethoxyphenyl)-4-((R)-piperidin-2-yl)butane-1,3-diol (**3-155**)



To a solution of diol **3-150** (25.0 mg, 77.3 μmol) in anhydrous THF (5 mL) was added a 1.0 M solution of $LiAlH_4$ in THF (0.4 mL, 387 μmol). The mixture was heated to reflux and stirred for 6 hours under a N_2 atmosphere. The reaction was quenched by adding H_2O (0.5 mL). The resulting mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* to give the desired piperidine **3-155** as a colourless oil (15.5 mg, 65%).

R_f 0.10 (10% Methanol/Dichloromethane);

$[\alpha]_D^{23}$ +8.4 (*c* 0.46, $CHCl_3$,);

ν_{max} (neat) 3361, 2926, 2855, 1631, 1516, 1456, 1261, 1026 cm^{-1};

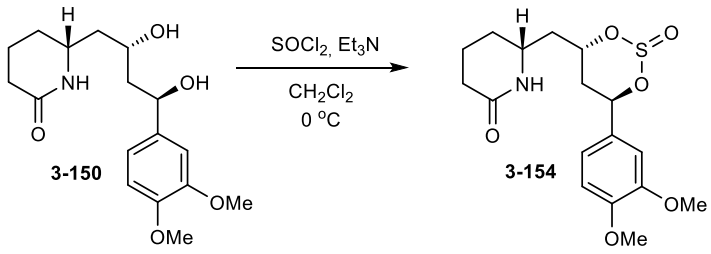
δ_H (400 MHz $CDCl_3$): 7.00 (1H, d, *J* 1.9 Hz), 6.94-6.72 (2H, m), 4.93 (1H, dd, *J* 10.2, 2.4 Hz), 4.40-4.17 (1H, m, 1H), 3.90 (3H, s), 3.87 (3H, s), 3.08-3.02 (1H, m), 3.00-2.85 (1H, m), 2.70-2.44 (1H, m), 2.01-1.21 (m, 8H);

δ_C (101 MHz $CDCl_3$): 149.0, 148.1, 137.8, 117.8, 111.0, 109.0, 74.7, 70.9, 56.0, 55.9, 54.9, 46.7, 46.4, 41.7, 31.5, 26.2, 24.5;

MS (ESI +ve) *m/z* 292.1 (26), 310.2 (M^++H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{28}NO_4$ $[M+H]^+$ 310.2018, found 310.2024.

(6R)-6-(((4S,6R)-6-(3,4-dimethoxyphenyl)-2-oxido-1,3,2-dioxathian-4-yl)methyl)piperidin-2-one (**3-154**)



To a solution of diol **3-150** (80.0 mg, 247 μmol) and trimethylamine (140 μL, 990 μmol) in CH_2Cl_2 (5 mL) cooled in an ice-water bath was added a solution of thionyl chloride (27 μL, 371 μmol) in CH_2Cl_2 (2 mL) in a dropwise fashion over a period of 10 minutes. Stirring was continued for 5 min at 0 °C and the reaction was monitored closely by thin layer chromatography. The reaction mixture was diluted with cold Et_2O (10 mL) and washed with cold water (2 x 5 mL) and brine (10 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10% Methanol/Dichloromethane) to give the desired sulfite **3-154** as a 1:1 mixture of diastereomers (20.0 mg, 22%).

R_f 0.15 (10% Methanol/Dichloromethane);

ν_{max} (neat) 3381, 2951, 2878, 1643, 151, 1337, 1265, 1169, 1024 cm^{-1};

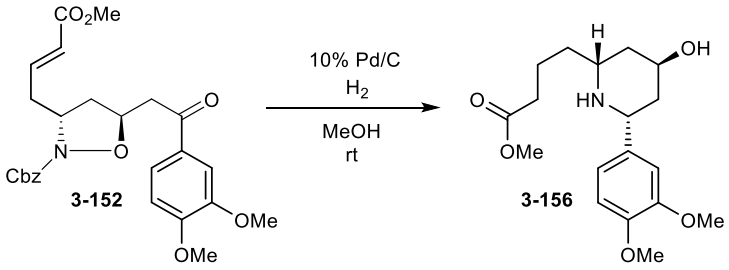
δ_H (400 MHz $CDCl_3$): 7.08-6.76 (3H, m), 6.23 (1H, br s), 4.98-4.72 (1H, m), 4.59-4.39 (1H, m), 3.91 (3H, s),3.89 (3H, s), 3.74 (1H, s), 3.09-2.77 (1H, m), 2.72-2.49 (1H, m), 2.49-2.22 (2H, m), 2.22-1.69 (5H, m), 1.58 (1H, m);

δ_C (101 MHz $CDCl_3$): 172.3, 150.3, 149.5, 121.6, 121.4, 121.2, 120.7, 111.8, 111.6, 111.5, 75.5, 62.4, 60.1, 56.1, 56.0, 49.8, 49.6, 43.2, 42.9, 36.2, 35.4, 31.3, 28.6, 19.0;

MS (ESI +ve) *m/z* 168.1 (14), 306.1 (14), 370.1 (M^++H, 30), 739.3 ($2M^+$+H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{24}NO_6S$ $[M+H]^+$ 370.1324, found 370.1342.

Methyl 4-((2R,4S,6R)-6-(3,4-dimethoxyphenyl)-4-hydroxypiperidin-2-yl)butanoate (**3-156**)



In a round-bottomed flask, ketone **3-152** was dissolved (240 mg, 496 μmol) in MeOH (100 mL). The sample inlet line and outlet line were both placed in the reaction solution. A 30 mm column of 10% Pd/C was inserted into the HCube reactor. The pressure was set to 1 bar, the flow rate of the HPLC pump was set to 1.0 mL/min, and the temperature to 25 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction was started by pressing the "start" button on the touch screen control. The reaction mixture was continuously passed through the instrument, until the starting material was shown to be completely consumed by TLC analysis. The column was washed with MeOH (10 mL in 10 min) to remove any substrate still adsorbed to the catalyst. The reaction mixture was

then evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (10% Methanol/Dichloromethane) to give the desired piperidine **3-156** as a brown oil (155 mg, 92%)

R_f 0.20 (10% Methanol/Dichloromethane);

$[\alpha]_D^{24}$ +28.1 (*c* 1.03, $CHCl_3$);

ν_{max} (neat) 3420, 2943, 1730, 1518, 1264, 1026 cm^{-1};

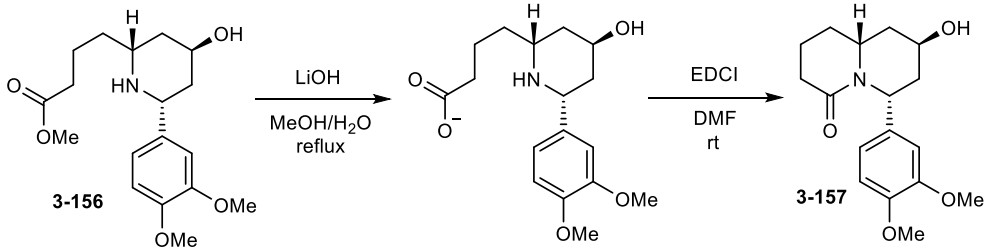
δ_H (400 MHz $CDCl_3$): 6.94 (1H, d, *J* 2.0 Hz), 6.89 (1H, dd, *J* 8.2, 2.0 Hz), 6.81 (1H, d, *J* 8.2 Hz), 3.88 (3H, s), 3.86 (3H, s), 3.78 (1H, tt, *J* 11.0, 4.5 Hz), 3.66 (3H, s), 3.61 (1H, dd, *J* 11.5, 2.3 Hz), 2.72 (1H, dtd, *J* 11.1, 6.3, 2.3 Hz), 2.33 (2H, app t, *J* 7.4 Hz), 2.17-1.99 (2H, m), 1.76-1.61 (2H, m), 1.59-1.38 (3H, m), 1.16 (1H, app q, *J* 11.3 Hz).;

δ_C (101 MHz $CDCl_3$): 174.0, 149.0, 148.5, 135.2, 119.1, 111.1, 110.4, 69.1, 59.6, 56.0, 55.9, 55.2, 51.6, 42.8, 40.6, 35.4, 33.8, 21.1;

MS (ESI +ve) *m/z* 338.2 (M^++H. 100);

HRMS (ESI) *m/z* calculated for $C_{18}H_{28}NO_5$ $[M+H]^+$ 338.1967, found 338.1980.

(6R,8S,9aR)-6-(3,4-dimethoxyphenyl)-8-hydroxyoctahydro-4H-quinolizin-4-one (**3-157**)



LiOH (6.1 mg, 255 μmol) and H_2O (5.0 μL, 277 μmol) were added to a solution of ester **3-156** (78.0 mg, 231 μmol) in MeOH (5 mL). The mixture was heated under reflux conditions overnight. The mixture was then cooled to room temperature and the volatiles were

removed *in vacuo*. The residue was re-dissolved in DMF (3 mL) and EDCI·HCl (66.5 mg, 347 μmol) was added. The reaction mixture was left to stir at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with silica (10% Methanol/Dichloromethane) to give quinolizidinone **3-157** as a yellow oil (52.0 mg, 74%).

R_f 0.10 (10% Methanol/Dichloromethane);

$[\alpha]_D^{24}$ +56.5 (*c* 0.34, $CHCl_3$);

ν_{max} (neat) 3443, 2930, 1614, 1516, 1445, 1254, 1142, 1024 cm^{-1};

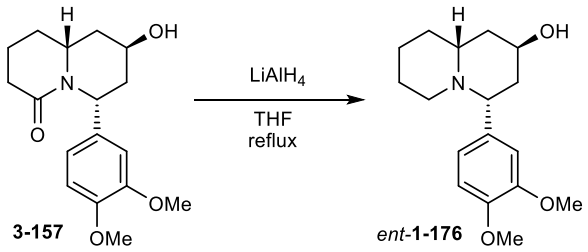
δ_H (400 MHz $CDCl_3$): 6.88-6.70 (3H, m), 5.30 (1H, t, *J* 4.6 Hz), 4.15-3.98 (1H, m), 3.85 (3H, s), 3.83 (3H, s), 3.45 (1H, ddt, *J* 13.2, 10.6, 2.8 Hz), 2.57-2.27 (4H, m), 2.21 (1H, ddd, *J* 13.9, 8.3, 2.4 Hz), 2.03-1.92 (2H, m), 1.88-1.73 (1H, m), 1.72-1.51 (2H, m).;

δ_C (101 MHz $CDCl_3$): 170.7, 149.1, 147.7, 135.2, 117.4, 111.4, 109.4, 65.4, 55.9, 55.8, 53.1, 52.9, 39.9, 37.7, 32.5, 31.0, 20.4;

MS (ESI +ve) *m/z* 150.1 (10), 168.1 (40), 306.1 (M^++H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{24}NO_4$ $[M+H]^+$ 306.1705, found 306.1700.

(+)-2-epi-lasubine II (*ent*-**1-176**)



To a solution of quinolizidinone **3-157** (25.0 mg, 81.9 μmol) in anhydrous THF (5 mL) was added 1.0 M solution of $LiAlH_4$ in THF (0.2 mL, 205 μmol). The mixture was heated to reflux and stirred for 6 hours under an inert atmosphere. The reaction was quenched by adding H_2O (0.5 mL). The resulting mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and purified by flash chromatography (10% Methanol/Dichloromethane) to give the desired piperidine *ent*-**1-176** as a pale yellow oil (21.5 mg, 90%)

R_f 0.20 (10% Methanol/Dichloromethane);

$[\alpha]_D^{24}$ +65.0 (*c* 0.78, $CHCl_3$) {lit.[xxxiii] $[\alpha]_D^{20}$ +57 (*c* 0.46, MeOH)};

ν_{max} (neat) 3345, 2932, 2853, 1514, 1454, 1263, 1030 cm^{-1};

δ_H (400 MHz $CDCl_3$): 7.10-6.44 (3H, m), 3.88 (3H, s), 3.86 (3H, s), 3.78-3.66 (1H, m), 2.92 (1H, dd, *J* 11.6, 2.7 Hz), 2.72-2.65 (1H, m), 2.13-1.76 (3H, m), 1.76-1.33 (7H, m), 1.33-1.15 (2H, m);

δ_C (101 MHz $CDCl_3$): 148.0, 136.5, 120.5-119.0 (br, 2C), 112.0-109.0 (br, 2C), 68.4, 68.3, 61.0, 56.0, 55.9, 52.9, 45.1, 42.7, 33.6, 26.0, 24.6;

MS (ESI +ve) *m/z* 292.1 (M^++H, 100);

HRMS (ESI) *m/z* calculated for $C_{17}H_{26}NO_3$ $[M+H]^+$ 292.1913, found 292.1914.

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