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Synthesis of 1,2-anti amino alcohols and their applications in the asymmetric synthesis of polyhydroxylated indolizidine and pyrrolizidine alkaloids

Christopher Wai Gee Au
University of Wollongong

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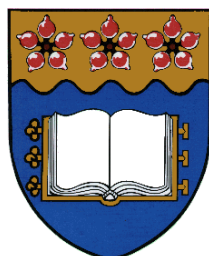
Synthesis of 1,2-*anti* Amino Alcohols and Their Applications in the Asymmetric Synthesis of Polyhydroxylated Indolizidine and Pyrrolizidine Alkaloids

A thesis submitted in fulfillment of the requirements
for the award of the degree of

DOCTOR OF PHILOSOPHY

from

UNIVERSITY OF WOLLONGONG



Christopher Wai Gee Au

B.S. (*California*)

School of Chemistry

March, 2010

Declaration

I, Christopher Wai Gee Au, declare that this thesis, submitted in fulfillment of the requirements for the award of Doctor of Philosophy, in the School of Chemistry, University of Wollongong, is wholly my own work unless reference is provided. This document has not been submitted for qualifications at any other academic institution.

Christopher Wai Gee Au

March, 2010

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Table of Contents

Declaration	i
Acknowledgement	ii
Table of Contents	iii
List of Figures	vii
List of Schemes	ix
List of Tables	xii
List of Abbreviations	xiii
Abstract	xvii
Publications arising from this thesis	xviii
CHAPTER 1: INTRODUCTION	1
1.1 Glycosidase enzymes and glycosidase inhibitors	1
1.2 Polyhydroxylated indolizidines	2
1.2.1 Total and formal syntheses of swainsonine since 2005	3
1.2.2 Synthesis of other swainsonine analogues since 2005	16
1.3 Polyhydroxylated pyrrolizidine alkaloids	16
1.3.1 Hyacinthacines	17
1.3.2 Total syntheses of hyacinthacines	20
1.4 Aims of project	51
CHAPTER 2: SYNTHESIS OF 1,2-<i>anti</i> AMINO ALCOHOLS	52
2.1 Synthesis of vinyl sulfones	52
2.1.1 Grubbs cross metathesis reaction	53
2.1.2 CAN-mediated radical reaction	54
2.1.3 Iodosulfonation-dehydroiodination with benzenesulfonyl iodide	58
2.2 Sharpless asymmetric dihydroxylation (ADH) and Petasis borono- Mannich reaction	59

CHAPTER 3: A FORMAL SYNTHESIS OF (-)-SWAINSONINE	
3.1	Preparing for the first cyclization 66
3.1.1	Protecting group manipulations 67
3.1.2	Cyclization by intramolecular <i>N</i> -alkylation 67
3.2	Utilizing Lewis-acid assisted RCM to construct the ‘B-ring’ 68
3.3	A formal synthesis complete 68
CHAPTER 4: TOTAL SYNTHESIS OF HYACINTHACINE B₃ 72	
4.1	Overview of synthetic plan 72
4.2	Vinyl sulfone synthesis <i>via</i> a cross-metathesis reaction 75
4.3	The Sharpless-Petasis sequence revisited 76
4.3.1	Dihydroxylation of 379 using AD-mix 76
4.3.2	Dihydroxylation of 379 using the DHQD-IND chiral ligand 78
4.3.3	The Petasis reaction using a chiral allyl amine 79
4.4	Oxazolidinone synthesis with triphosgene 80
4.5	Formation of the A-ring by RCM with Grubbs’ II catalyst 81
4.6	<i>cis</i> -Dihydroxylation with OsO ₄ and NMO and bis-benylation of the resultant diol 81
4.7	DDQ deprotection of the PMB ether and hydrolysis of the oxazolidinone 83
4.8	Towards the Hyacinthacine B ₃ 84
4.8.1	Nucleophilic cyclization of the B-ring <i>via</i> <i>O</i> -mesylation and S _N 2 displacement 84
4.8.2	Global debenylation and purification by basic ion-exchange chromatography 85
4.8.3	Comparing spectral data with natural hyacinthacine B ₃ 85
CHAPTER 5: TOTAL SYNTHESIS OF PURPORTED HYACINTHACINE B₇ 89	
5.1	Synthetic plan 91
5.2	From (<i>R</i>)-4-penten-2-ol to the <i>anti</i> amino alcohol 401 92
5.3	Towards the purported structure of hyacinthacine B ₇ 92
5.4	Comparison of spectral data with the natural product 94
5.5	Synthesis of the C-7 epimer of the pyrrolizidine 112 97
5.6	Further comparison of 112 and 409 with natural hyacinthacine B ₇ 100

CHAPTER 6: CONCLUSIONS	102
CHAPTER 7: EXPERIMENTAL SECTION	104
7.1 General Experimental	104
7.1.1 General reaction conditions	104
7.1.2 Chromatography	104
7.1.3 Melting points	105
7.1.4 Polarimetry	105
7.1.5 Mass spectrometry	105
7.1.6 Nuclear magnetic resonance spectroscopy	105
7.2 Experimentals for Chapters 2 and 3	106
7.2.1 General method for Olefin Cross Methathesis using the Grubbs' II catalyst	106
7.2.2 General method for iodosulfonation and HI elimination	106
7.2.3 General method for the Sharpless asymmetric dihydroxylation (ADH) using the AD-mix	108
7.2.4 General method for the Petasis reaction	108
7.2.5 General method for the synthesis of Mosher's esters	119
7.3 Experimentals for Chapter 4	124
7.3.1 General method for <i>O</i> -PMB protection	124
7.3.2 Preparation of vinyl sulfone 379	125
7.3.2.1 <i>Via</i> iodosulfonation and HI elimination using benzenesulfonyl iodide	125
7.3.2.2 General method for olefin cross metathesis using the Grubb's II catalyst under microwaves irradiation	125
7.3.3 General method for the Sharpless asymmetric dihydroxylation using DHQD-IND	126
7.3.4 General method for the Petasis reaction	126
7.3.5 General method for the synthesis of oxazolidinones	128
7.3.6 General method for ring-closing metathesis (RCM) of oxazolidinones	129
7.3.7 General method for <i>syn</i> -dihydroxylation	130

7.3.8	General method for bisbenzylation of secondary diols	131
7.3.9	General method for PMB deprotection using DDQ	133
7.3.10	General method for hydrolysis of oxazolidinones	134
7.3.11	General method for mesylation-cyclization	135
7.3.12	General method for hydrogenolysis of benzyl ethers	136
7.4	Experimentals for Chapter 5	137
7.4.1	General method for Swern oxidation	148
7.4.2	General method for the reduction of ketones to secondary alcohols with L-selectride [®]	148
REFERENCES		150

List of Figures

Figure 1.1	Examples of polyhydroxylated alkaloids	1
Figure 1.2	1-Deoxynorijimycin and miglitol	2
Figure 1.3	Lentiginosine and (-)-swainsonine	3
Figure 1.4	Natural hyacinthacines	17
Figure 2.1	Olefin reactivities in cross metathesis reactions	53
Figure 2.2	^1H NMR (CDCl_3) chemical shifts for H-3 in 306 and 306'	57
Figures 2.3a-f	Integration ratios of ^1H NMR peaks of H-3 in vinyl sulfones 306 and 306'	57
Figure 2.4	^{19}F NMR (CDCl_3 , 282 MHz) spectra of the (<i>R</i>)-Mosher's esters 360 and 361 , respectively synthesized from the amino alcohols 353 and 354 , with $\text{CF}_3\text{CH}_2\text{OH}$ referenced at -77.8 ppm	64
Figure 3.1	^1H (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) spectra of the indolizidine 22	69
Figure 4.1	Flowers and dissected fresh bulb of the grape hyacinth (<i>Muscari armeniacum</i>).	72
Figure 4.2	Stereochemical similarities between (-)-swainsonine (1) and hyacinthacine B ₃ (104)	73
Figure 4.3	Synthetic analysis for hyacinthacine B ₃ (104)	73
Figure 4.4	^{19}F NMR (CDCl_3 , 282 MHz) spectrum of the (<i>R</i>)-Mosher's ester 396 with $\text{CF}_3\text{CH}_2\text{OH}$ referenced at -77.8 ppm	80
Figure 4.5	Vicinal coupling between H-4 and H-5 of the oxazolidinone 383	81
Figure 4.6	2-D NOESY NMR (CDCl_3 , 500 MHz) of diol 388	82
Figure 4.7	HF/6-31G* (SPARTAN) geometry and HOMO energy surface optimizations for 384	83
Figure 4.8a	^1H NMR (CD_3OD , 300 MHz) spectrum of synthetic 104	86
Figure 4.8b	^{13}C NMR (CD_3OD , 125 MHz) spectrum of synthetic 104	86

Figure 4.9	2-D NOESY NMR (CD ₃ OD, 300 MHz) spectrum of synthetic 104	87
Figure 5.1	Flowers and fresh bulb of <i>Scilla socialis</i>	89
Figure 5.2	Proposed structure of the hyacinthacine B ₇ (112) and reported NOESY correlations	92
Figure 5.3	2-D NOESY NMR spectrum (D ₂ O, 500 MHz) of synthetic 112	96
Figure 5.4	HF/6-31G* optimized structure (Spartan) and NOESY correlations of compound 112	97
Figure 5.5	The purported structure of the hyacinthacine B ₇ (112) and its C-7 epimer (409)	97
Figure 5.6	NOESY (500 MHz, D ₂ O) NMR spectrum of 409 (<i>7-epi-112</i>)	99
Figure 5.7	NOESY NMR (500 MHz, D ₂ O) spectrum of supposedly ‘natural hyacinthacine B ₇ ’ sent to us by Prof. Kato	101

List of Schemes

Scheme 1.1	Cosy's first formal synthesis of (-)-swainsonine	
Scheme 1.2	Cosy's second formal synthesis of (-)-swainsonine	6
Scheme 1.3	Ham's total synthesis of (-)-swainsonine	7
Scheme 1.4	Cheng's total synthesis of (-)-swainsonine	8
Scheme 1.5	Poisson's total synthesis of (-)-swainsonine	10
Scheme 1.6	Reiser's formal synthesis of (-)-swainsonine	12
Scheme 1.7	Riera's formal synthesis of (-)-swainsonine	13
Scheme 1.8	O'Doherty's total synthesis of (+)-swainsonine	15
Scheme 1.9	Kang's formal synthesis of (-)-swainsonine	16
Scheme 1.10	Martin's synthesis of hyacinthacine A ₂	21
Scheme 1.11	Goti's synthesis of hyacinthacine A ₂	22
Scheme 1.12	Py's synthesis of hyacinthacine A ₂	22
Scheme 1.13	Renaud's synthesis of hyacinthacine A ₁	23
Scheme 1.14	Renaud's synthesis of 3- <i>epi</i> -hyacinthacine A ₁	24
Scheme 1.15	Kaliappan's syntheses of hyacinthacine A ₃ and 5-(-)- <i>epi</i> -hyacinthacine A ₅	25
Scheme 1.16	Cao's synthesis of hyacinthacine A ₆	26
Scheme 1.17	General scheme of Izquierdo's syntheses of hyacinthacine alkaloids	27
Scheme 1.18	Izquierdo's synthesis of 7a- <i>epi</i> -hyacinthacine A ₂	29
Scheme 1.19	Izquierdo's synthesis of 5,7a-di- <i>epi</i> -hyacinthacine A ₃	29
Scheme 1.20	Izquierdo's synthesis of (+)-hyacinthacine A ₃	30
Scheme 1.21	Izquierdo's synthesis of (+)-hyacinthacine A ₂	30
Scheme 1.22	Izquierdo's synthesis of (+)-3- <i>epi</i> -hyacinthacine A ₃	31
Scheme 1.23	Izquierdo's synthesis of (+)-3- <i>epi</i> -hyacinthacine A ₂	31
Scheme 1.24	Izquierdo's synthesis of (-)-3- <i>epi</i> -hyacinthacine A ₅	32
Scheme 1.25	Izquierdo's synthesis of (+)-3- <i>epi</i> -hyacinthacine A ₅	32
Scheme 1.26	Izquierdo's synthesis of (+)-5- <i>epi</i> -hyacinthacine A ₅	33
Scheme 1.27	Izquierdo's synthesis of (+)-5- <i>epi</i> -hyacinthacine A ₄	33

Scheme 1.28	Izquierdo's synthesis of (-)-1- <i>epi</i> -hyacinthacine A ₇ and (-)-hyacinthacine A ₇	34
Scheme 1.29	Yoda's synthesis of (+)-hyacinthacines B ₁ and B ₂	36
Scheme 1.30	Yoda's synthesis of hyacinthacines C ₂ and C ₃ and their C-5 epimers	38
Scheme 1.31	Marco's synthesis of hyacinthacines A ₂	39
Scheme 1.32	Marco's synthesis of hyacinthacine A ₃ and 5- <i>epi</i> -hyacinthacine A ₃	40
Scheme 1.33	Chandrasekhar's synthesis of hyacinthacine A ₁	41
Scheme 1.34	Delair's synthesis of hyacinthacine A ₁	43
Scheme 1.35	Delair's synthesis of hyacinthacine B ₁	44
Scheme 1.36	Donohoe's synthesis of (±)-hyacinthacine A ₁	45
Scheme 1.37	Blechert's synthesis of hyacinthacine A ₂	46
Scheme 1.38	Clapés' syntheses of the stereoisomers of hyacinthacines A ₁ and (-)-hyacinthacine A ₂	47
Scheme 1.39	Donohoe's synthesis of (+)-hyacinthacine A ₁	48
Scheme 1.40	Donohoe's syntheses of hyacinthacines A ₆ and A ₇	49
Scheme 1.41	Laschat's total synthesis of (±)-7a- <i>epi</i> -hyacinthacine A ₁	50
Scheme 1.42	General scheme for the planned project	51
Scheme 2.1	Synthesis of the vinyl sulfones 306 and 308	52
Scheme 2.2	Cross metathesis using a ruthenium catalyst	53
Scheme 2.3	Synthesis of the vinyl sulfone 309 via a CAN-mediated reaction	54
Scheme 2.4	Mechanism of the CAN-mediated synthesis of 309	55
Scheme 2.5	Synthesis of the vinyl sulfone 306 via a CAN-mediated reaction	56
Scheme 2.6	Iodosulfonation-dehydroiodination with benzenesulfonyl iodide	58
Scheme 2.7	Synthesis of the vinyl sulfone 306 using PhSO ₂ I	58
Scheme 2.8	Synthesis of α-hydroxy aldehydes 323 and 325 via Sharpless ADH	59
Scheme 2.9	An example of the Petasis borono-Mannich reaction	60
Scheme 2.10	Our speculation of the mechanism of the Petasis reaction	60
Scheme 2.11	Sharpless ADH reactions of vinyl sulfones 306 and 308	61
Scheme 2.12	The Sharpless-Petasis sequence	63
Scheme 2.13	Synthesis of Mosher's esters	64
Scheme 2.14	Synthesis of the oxazolidinone 362	65
Scheme 3.1	Proposed synthesis of compound 22	66

Scheme 3.2	Conversion of 353 to 364	67
Scheme 3.3	Mechanism of the cyclization of 364 <i>via</i> intramolecular <i>N</i> -alkylation	68
Scheme 3.4	Conversion of 365 to 22	68
Scheme 3.5	Bates' formal synthesis of (-)-swainsonine	70
Scheme 4.1	Proposed synthesis of hyacinthacine B ₃	75
Scheme 4.2	<i>O</i> -PMB protection of (S)-4-penten-2-ol and preparation of the vinyl sulfone 379	76
Scheme 4.3	Concerted [3+2] mechanism of the Os-catalyzed DH reaction postulated by Criegee	77
Scheme 4.4	Stepwise [2+2] mechanism of the Os-catalyzed DH reaction postulated by Sharpless	77
Scheme 4.5	Conversion of 379 to 382 <i>via</i> the Sharpless-Petasis sequence	79
Scheme 4.6	Synthesis of (<i>R</i>)-Mosher's esters 396 and 396'	79
Scheme 4.7	Synthesis of the oxazolidinone 384	80
Scheme 4.8	Conversion of 383 to 384 <i>via</i> RCM with Grubbs' II catalyst	81
Scheme 4.9	<i>cis</i> -DH of 384 and bisbenzylation of 385	82
Scheme 4.10	<i>O</i> -PMB deprotection of 386 and oxazolidinone hydrolysis	84
Scheme 4.11	Mesylation of 388 and concomitant cyclization	85
Scheme 4.12	Global debenzylation of 384 and ion-exchange chromatography	85
Scheme 5.1	Proposed synthesis of hyacinthacine B ₇	91
Scheme 5.2	Conversion of (<i>R</i>)-4-penten-2-ol to the amino alcohol 401	92
Scheme 5.3	Synthesis of the oxazolidinone 402	93
Scheme 5.4	RCM of 402 and <i>cis</i> -DH of 403	93
Scheme 5.5	Conversion of 404 to 407 <i>via</i> protecting group manipulations	94
Scheme 5.6	Mesylation-cyclization and global debenzylation	94
Scheme 5.7	C-7 epimerization of 408	98

List of Tables

Table 1.1.	Protected polyhydroxypyrrolidine precursors and the respective products in Izquierdo's syntheses of hyacinthacines	28
Table 2.1	Summary of CM reactions	54
Table 2.2	Summary of different methods used to synthesize the vinyl sulfone 306	56
Table 2.3	Summary of the Sharpless-Petasis sequence shown in Scheme 2.12	53
Table 4.1	Comparison of ^1H NMR (CD_3OD , 300 MHz) data between natural hyacinthacine B_3 and synthetic 104	87
Table 4.2	Comparison of ^{13}C NMR (100 MHz, CD_3OD) data between natural hyacinthacine B_3 and synthetic 104	88
Table 5.1	Comparison of ^1H NMR spectral data between hyacinthacines B_3 (104) and B_3 (112) isolated from natural sources	90
Table 5.2	^1H NMR (500 MHz, D_2O) spectral data of natural and synthesized hyacinthacine B_7 (112)	95
Table 5.3	^{13}C NMR (100 MHz, D_2O) spectral data of natural and synthesized hyacinthacine B_7 (112)	95
Table 5.4	^1H NMR (500 MHz, D_2O) spectral data of natural hyacinthacine B_7 and the synthetic compounds 112 and 409	99
Table 5.5	Biological assays of the synthetic pyrrolizidines 112 and 409 at 1000 μM in comparison with natural hyacinthacine B_7	100

List of Abbreviations

[M] ⁺	molecular ion
[α] _D	optical rotation
Ac	acetyl
AD or ADH	asymmetric dihydroxylation
amu	atomic units
b.p.	boiling point
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
br.	broad
Bu	butyl
<i>c</i>	concentration in g/100 mL
<i>ca.</i>	<i>circa</i>
CAN	cerium(IV) ammonium nitrate
cat.	catalyst
Cbz	carboxybenzyl
CM	cross metathesis
COSY	correlation spectroscopy
CSA	camphor sulfonic acid
d	doublet
δ	chemical shift
DADP	2,5-dideoxy-2,5-imino-D-alloitol
DALDP	2,5-dideoxy-2,5-imino-D-altroitol
DBB	4,4'-ditertbutylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DGDP	2,5-dideoxy-2,5-imino-D-glucoitol
DGADP	2,5-dideoxy-2,5-imino-D-galactoitol
DH	dihydroxylation

DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDP	2,5-dideoxy-2,5-imino-D-mannitol
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv.	equivalents
ESIMS	electrospray ionization mass spectrometry
Et	ethyl
FAB	fast atom bombardment
GC	gas chromatography
HF	Hartree-Fock
HMBC	heteronuclear multiple bond coherence
HOMO	highest occupied molecular orbital
HRESIMS	high resolution electrospray ionization mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	2-iodoxybenzoic acid
IC ₅₀	half maximal inhibitory concentration
imid.	imidazole
IND	indole
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constant
m	multiplet
<i>m</i>	<i>meta</i>
M	molar
m.p.	melting point

<i>m/z</i>	mass/charge ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
mol	mole
MOM	methoxymethyl
Ms	mesyl, methanesulfonyl
MS (as in 3 Å MS)	molecular sieves
MS (as in GC-MS)	mass spectrometry
NBS	<i>N</i> -bromosuccinimide
NMO	4-methylmorpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
OTf	triflate, trifluoromethanesulfonate
Pd/C	palladium on carbon
petrol	petroleum spirit b.p. 40-60 °C
Ph	phenyl
PHAL	phthalazine
Piv	pivaloyl
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
PTSA	<i>para</i> -toluenesulfonic acid
q	quartet
quant.	quantitative
quint.	quintet
RCM	ring-closing metathesis
<i>R_f</i>	retention factor, retardation factor
rt	room temperature
s	singlet
S _N 2	bimolecular nucleophilic substitution
t	triplet

<i>t</i> -	<i>tert</i> -
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMO	trimethylamine <i>N</i> -oxide
TMP	tetramethylpiperidide
TMS	trimethylsilyl or trimethylsilane
TPAP	tetrapropylammonium perruthenate
Ts	tosyl, <i>para</i> -toluenesulfonyl

Abstract

POLYHYDROXYLATED ALKALOIDS—NATURAL HETEROCYCLES THAT CONTAIN ONE OR MORE BASIC NITROGEN ATOMS AND VARIOUS NUMBERS OF HYDROXY SUBSTITUENTS—ARE A CLASS OF ORGANIC COMPOUNDS THAT HAS ATTRACTED MUCH ATTENTION DUE TO THEIR INHIBITORY ACTIVITIES AGAINST GLYCOSIDASE ENZYMES. THE 1,2,8-TRIHYDROXY-INDOLIZIDINE ALKALOID (-)-SWAINSONINE 1 WAS FIRST ISOLATED IN 1973 FROM THE FUNGUS *RHIZOCTONIA LEGUMINICOLA* AND EXHIBITED HIGH INHIBITORY ACTIVITIES ($IC_{50} = 0.2 \mu M$) TOWARDS BOTH GOLGI MANNOSIDASE II AND LYSOSOMAL α -D-MANNOSIDASE. THE POLYHYDROXYLATED PYRROLIZIDINE ALKALOID HYACINTHACINE B₃ 104 WAS ISOLATED FROM FRESH BULBS OF THE HYACINTHACEAE PLANT *MUSCARI ARMENIACUM* AND WAS FOUND TO BE A MODERATE INHIBITOR OF β -GALACTOSIDASE ($IC_{50} = 18 \mu M$) AND WAS A WEAK AMYLOGLUCOSIDASE INHIBITOR ($IC_{50} = 51 \mu M$). HYACINTHACINE B₇ 112, REPORTED TO BE THE C-7 EPIMER OF 104, WAS ISOLATED FROM THE BULBS OF *SCILLA SOCIALIS* AND EXHIBITED WEAK INHIBITORY ACTIVITY TOWARDS AN AMYLOGLUCOSIDASE ENZYME.

The main focus of this study was to examine the utility of 1,2-*anti* amino alcohols in the development of a general strategy towards synthesizing polyhydroxylated indolizidine and pyrrolizidine alkaloids. Chiral α -hydroxy aldehydes generated *in situ* by the Sharpless asymmetric dihydroxylation (ADH) reaction of vinyl sulfones underwent a borono-Mannich reaction with β -styrenyl boronic acid and primary amines to give 1,2-*anti* amino alcohols in high enantiomeric purities (83-95% ee). The *anti* amino alcohol **353**, synthesized *via* the Sharpless-Petasis sequence from 4-penten-1-ol, was converted into indolizidine **22** in an additional four synthetic steps. This represented a formal synthesis of (-)-**1** in ten-steps and 7.7% overall yield from commercially available starting material.

The utility 1,2-*anti* amino alcohols in alkaloid synthesis was further exemplified in the total syntheses of hyacinthacine B₃ **104** and the purported structure of hyacinthacine B₇ **112**. Starting from (*S*)-4-penten-2-ol, the *anti* amino alcohol **382** was synthesized *via* the Sharpless-Petasis sequence and was converted to **104** in a total 13 steps and 5.6% overall yield. This total synthesis confirms the structure of hyacinthacine B₃. In an analogous fashion, the reported structure of hyacinthacine B₇ **112** was synthesized in 13 synthetic steps from (*R*)-4-penten-2-ol (**397**) and 3.4% overall yield. However, the NMR data of our synthetic **112** did

not agree with those of the natural product. Further spectroscopic studies have confirmed the structure and stereochemical configuration of our synthetic **112** and concluded that the reported structure of hyacinthacine B₇ was incorrect.

Publications arising from this thesis

1. Au, Christopher W.G.; Nash, Robert, J.; Pyne, Stephen G. 'Synthesis of hyacinthacine B₃ and purported hyacinthacine B₇' *Chem. Commun.*, **2010**, 46, 713-715.
2. Pyne, Stephen G.; Au, Christopher W.G.; Davis, Andrew S.; Morgan, Ian R.; Ritthiwigrom, Thunwadee; Yazici, Arife. 'Exploiting the borono-Mannich reaction in bioactive alkaloid synthesis' *Pure Appl. Chem.*, **2008**, 80, 751-762.
3. Au, Christopher W.G.; Pyne, Stephen G. 'Asymmetric synthesis of *anti*-1,2-amino alcohols *via* the Borono-Mannich reaction: a formal synthesis of (-)-swainsonine' *J. Org. Chem.*, **2006**, 71, 7097-7099.