2010

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

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

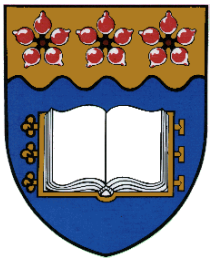
A thesis submitted in fulfillment of the requirements

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

Acknowledgement

I must first express my utmost gratitude towards my supervisor and mentor, Prof. Stephen Pyne. Without his invaluable support, guidance, dedication and encouragement throughout the course of my postgraduate studies, this degree would never have been completed.

I would like to thank the University of Wollongong for financial support in the form of an International Student Tuition Scholarship and a University Postgraduate Award (UPA) Scholarship.

A big thank-you to the support staff at the School of Chemistry, in particular Dr. Wilford Lie for help in NMR analysis (even on Sundays), Dr. Thitima Urathamakul, Larry Hick (RIP), Karin Maxwell and Dr. John Korth for acquiring hi-res mass spectra of my compounds just in time for publication.

To present and past members of the Pyne Group—Dr. Thunwadee Ritthiwigrom, Dr. Arife Yazici, Dr. Pitchaya Mungkornasawakul, Dr. Thanapat Sastraruji, Dr. Theeraphan Machan, Kwankamol Sastraruji, Morwenna Baird, Dr. Minyan Tang, Dr. Steve Taylor, Dr. Andrew Davis, Dr. Ian Morgan and others—thank you for sharing with me *the* best working environment. I have enjoyed working side by side with you and shall always remember the friendship, companionship and laughter (and birthday cakes) we have all shared.

To my friends in Hong Kong, the US, Australia, Thailand and other parts of the world, especially the MLC, AW, BY, JL, MO, JW, the PC Group, IY and KL—thanks for keeping my sanity in check when I felt stressed, baffled and burnt out. You all mean so much to me.

To my family—first my brother, Gerard—bro, thanks for always looking out for me. To my parents, Charles and Grace—every little thing you have done for me has shaped the person I am today. Through the years you have demonstrated to me the very essence of unconditional love. Thanks for instilling in me the desire for knowledge, a hopeful attitude and the strength to carry on when things seem to go awry.

Above all, to the Lord Almighty—thank You for letting me learn about Your creations from a molecular perspective. May I continue to serve You in Your Laboratory of Life.

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-*anti* 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 *N*-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 B_3 72
4.1 Overview of synthetic plan 72
4.2 Vinyl sulfone synthesis *via* 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 chrial 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 *cis*-Dihydroxylation with OsO_4 and NMO and bis-benzylation of the resultant diol 81
4.7 DDQ deproection 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 *via O*-mesylation and S_N2 displacement 84
4.8.2 Global debenzylation 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 B_7 89
5.1 Synthetic plan 91
5.2 From (*R*)-4-penten-2-ol to the *anti* 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 *O*-PMB protection 124

7.3.2 Prepration of vinyl sulfone **379** 125

7.3.2.1 *Via* 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 *syn*-dihydroxylation 130

7.3.8 General nethod 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	^{1}H NMR ($CDCl_3$) chemical shifts for H-3 in **306** and **306′**	57
Figures 2.3a-f	Integration ratios of ^{1}H 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 (*R*)-Mosher's esters **360** and **361**, respectively synthesized from the amino alcohols **353** and **354**, with CF_3CH_2OH referenced at -77.8 ppm	64
Figure 3.1	^{1}H (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 (*Muscari armeniacum*).	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 (*R*)-Mosher's ester **396** with CF_3CH_2OH 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	^{1}H 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_3OD, 300 MHz) spectrum of synthetic **104**	87
Figure 5.1	Flowers and fresh bulb of *Scilla socialis*	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_2O, 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_2O) NMR spectrum of **409** (7-*epi*-**112**)	99
Figure 5.7	NOESY NMR (500 MHz, D_2O) spectrum of supposedly 'natural hyacinthacine B_7' sent to us by Prof. Kato	101

List of Schemes

Scheme 1.1	Cossy's first formal synthesis of (-)-swainsonine	
Scheme 1.2	Cossy'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-*epi*-hyacinthacine A_1	24
Scheme 1.15	Kaliappan's syntheses of hyacinthacine A_3 and 5-(-)-*epi*-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-*epi*-hyacinthacine A_2	29
Scheme 1.19	Izquierdo's synthesis of 5,7a-di-*epi*-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-*epi*-hyacinthacine A_3	31
Scheme 1.23	Izquierdo's synthesis of (+)-3-*epi*-hyacinthacine A_2	31
Scheme 1.24	Izquierdo's synthesis of (-)-3-*epi*-hyacinthacine A_5	32
Scheme 1.25	Izquierdo's synthesis of (+)-3-*epi*-hyacinthacine A_5	32
Scheme 1.26	Izquierdo's synthesis of (+)-5-*epi*-hyacinthacine A_5	33
Scheme 1.27	Izquierdo's synthesis of (+)-5-*epi*-hyacinthacine A_4	33

Scheme 1.28	Izquierdo's synthesis of (-)-1-*epi*-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 hyacinathacine A_3 and 5-*epi*-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-*epi*-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 $PhSO_2I$	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** *via* intramolecular *N*-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	*O*-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** *via* the Sharpless-Petasis sequence	79
Scheme 4.6	Synthesis of (*R*)-Mosher's esters 396 and 396'	79
Scheme 4.7	Synthesis of the oxazolidinone **384**	80
Scheme 4.8	Conversion of **383** to **384** *via* RCM with Grubbs' II catalyst	81
Scheme 4.9	*cis*-DH of **384** and bisbenzylation of **385**	82
Scheme 4.10	*O*-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 (*R*)-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 *cis*-DH of **403**	93
Scheme 5.5	Conversion of **404** to **407** *via* protecting group manipulations	94
Scheme 5.6	Mesylation-cyclization and gobal 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 ^{1}H 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 ^{1}H NMR spectral data between hyacinthacines B_3 (**104**) and B_3 (**112**) isolated from natural sources	90
Table 5.2	^{1}H 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	^{1}H 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
$[\alpha]_D$	optical rotation
Ac	acetyl
AD or ADH	asymmetric dihydroxylation
amu	atomic units
b.p.	boiling point
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
Bu	butyl
c	concentration in g/100 mL
ca.	*circa*
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	*N*,*N*'-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	*N*,*N*-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-Pr	isopropyl
J	coupling constant
m	multiplet
m	*meta*
M	molar
m.p.	melting point

m/*z*	mass/charge ratio
m-CPBA	*meta*-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	*N*-bromosuccinimide
NMO	4-methylmorpholine *N*-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 ^{o}C
Ph	phenyl
PHAL	phthalazine
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
PTSA	para-toluenesulfonic acid
q	quartet
quant.	quantitative
quint.	quintet
RCM	ring-closing metathesis
R_f	retention factor, retardation factor
rt	room temperature
s	singlet
S_N2	bimolecular nucleophilic substitution
t	triplet

t-	*tert*-
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMO	trimethylamine *N*-oxide
TMP	tetramethylpiperidide
TMS	trimethylsilyl or trimethylsilane
TPAP	tetrapropylammonium perruthenate
Ts	tosyl, *para*-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 μM) TOWARDS BOTH GOLGI MANNOSIDASE II AND LYSOSOMAL α-d-MANNOSIDASE. THE POLYHYDROXYLATED PYRROLIZIDINE ALKALOID HYACINTHACINE B_3** 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 μM) AND WAS A WEAK AMYLOGLUCOSIDASE INHIBITOR (IC_{50} = 51 μM). HYACINTHACINE B_7** 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 polyhdroxylated indolizildine 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 B_3 **104** and the purported structure of hyacinthacine B_7 **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 B_3. In an analogous fashion, the reported structure of hyacinthacine B_7 **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 B_7 was incorrect.

Publications arising from this thesis

1. Au, Christopher W.G.; Nash, Robert, J.; Pyne, Stephen G. 'Synthesis of hyacinthacine B_3 and purported hyacinthacine B_7' *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**, *8*0, 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.