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

UNIVERSITY OF WOLLONGONG
COPYRIGHT WARNING

You may print or download ONE copy of this document for the purpose of your own research or study. The University does not authorise you to copy, communicate or otherwise make available electronically to any other person any copyright material contained on this site. You are reminded of the following:

This work is copyright. Apart from any use permitted under the Copyright Act 1968, no part of this work may be reproduced by any process, nor may any other exclusive right be exercised, without the permission of the author.

Copyright owners are entitled to take legal action against persons who infringe their copyright. A reproduction of material that is protected by copyright may be a copyright infringement. A court may impose penalties and award damages in relation to offences and infringements relating to copyright material. Higher penalties may apply, and higher damages may be awarded, for offences and infringements involving the conversion of material into digital or electronic form.

Recommended Citation


Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au
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 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

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 B₃

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 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 cis-Dihydroxylation with OsO₄ and NMO and bis-benzylation of the resultant diol 81
4.7 DDQ deprotection of the PMB ether and hydrolysis of the oxazolidinone 83
4.8 Towards the Hyacinthacine B₃ 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 B₃ 85

CHAPTER 5: TOTAL SYNTHESIS OF PURPORTED HYACINTHACINE B₇

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 B₇ 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 B₇ 100
CHAPTER 6: CONCLUSIONS

CHAPTER 7: EXPERIMENTAL SECTION

7.1 General Experimental
   7.1.1 General reaction conditions
   7.1.2 Chromatography
   7.1.3 Melting points
   7.1.4 Polarimetry
   7.1.5 Mass spectrometry
   7.1.6 Nuclear magnetic resonance spectroscopy

7.2 Experimentals for Chapters 2 and 3
   7.2.1 General method for Olefin Cross Methathesis using the Grubbs’ II catalyst
   7.2.2 General method for iodosulfonation and HI elimination
   7.2.3 General method for the Sharpless asymmetric dihydroxylation (ADH) using the AD-mix
   7.2.4 General method for the Petasis reaction
   7.2.5 General method for the synthesis of Mosher’s esters

7.3 Experimentals for Chapter 4
   7.3.1 General method for O-PMB protection
   7.3.2 Preparation of vinyl sulfone 379
   7.3.2.1 Via iodosulfonation and HI elimination using benzenesulfonyl iodide
   7.3.2.2 General method for olefin cross metathesis using the Grubb’s II catalyst under microwaves irradiation
   7.3.3 General method for the Sharpless asymmetric dihydroxylation using DHQD-IND
   7.3.4 General method for the Petasis reaction
   7.3.5 General method for the synthesis of oxazolidinones
   7.3.6 General method for ring-closing metathesis (RCM) of oxazolidinones
   7.3.7 General method for syn-dihydroxylation
7.3.8  General method for bisbenzylolation 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  148
          alcohols with L-selectride®
REFERENCES  150
# List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1.1</td>
<td>Examples of polyhydroxylated alkaloids</td>
<td>1</td>
</tr>
<tr>
<td>Figure 1.2</td>
<td>1-Deoxynorijimycin and miglitol</td>
<td>2</td>
</tr>
<tr>
<td>Figure 1.3</td>
<td>Lentiginosine and (-)-swainsonine</td>
<td>3</td>
</tr>
<tr>
<td>Figure 1.4</td>
<td>Natural hyacinthacines</td>
<td>17</td>
</tr>
<tr>
<td>Figure 2.1</td>
<td>Olefin reactivities in cross metathesis reactions</td>
<td>53</td>
</tr>
<tr>
<td>Figure 2.2</td>
<td>‟H NMR (CDCl₃) chemical shifts for H-3 in 306 and 306’</td>
<td>57</td>
</tr>
<tr>
<td>Figures 2.3a-f</td>
<td>Integration ratios of ‟H NMR peaks of H-3 in vinyl sulfones 306 and 306’</td>
<td>57</td>
</tr>
<tr>
<td>Figure 2.4</td>
<td>‟F NMR (CDCl₃, 282 MHz) spectra of the (R)-Mosher’s esters 360 and 361, respectively synthesized from the amino alcohols 353 and 354, with CF₃CH₂OH referenced at -77.8 ppm</td>
<td>64</td>
</tr>
<tr>
<td>Figure 3.1</td>
<td>‟H (300 MHz, CDCl₃) and ‟C NMR (75 MHz, CDCl₃) spectra of the indolizidine 22</td>
<td>69</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Flowers and dissected fresh bulb of the grape hyacinth (Muscari armeniacum).</td>
<td>72</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Stereochemical similarities between (-)-swainsonine (1) and hyacinthacine B₃ (104)</td>
<td>73</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Synthetic analysis for hyacinthacine B₃ (104)</td>
<td>73</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>‟F NMR (CDCl₃, 282 MHz) spectrum of the (R)-Mosher’s ester 396 with CF₃CH₂OH referenced at -77.8 ppm</td>
<td>80</td>
</tr>
<tr>
<td>Figure 4.5</td>
<td>Vicinal coupling between H-4 and H-5 of the oxazolidinone 383</td>
<td>81</td>
</tr>
<tr>
<td>Figure 4.6</td>
<td>2-D NOESY NMR (CDCl₃, 500 MHz) of diol 388</td>
<td>82</td>
</tr>
<tr>
<td>Figure 4.7</td>
<td>HF/6-31G* (SPARTAN) geometry and HOMO energy surface optimizations for 384</td>
<td>83</td>
</tr>
<tr>
<td>Figure 4.8a</td>
<td>‟H NMR (CD₃OD, 300 MHz) spectrum of synthetic 104</td>
<td>86</td>
</tr>
<tr>
<td>Figure 4.8b</td>
<td>‟C NMR (CD₃OD, 125 MHz) spectrum of synthetic 104</td>
<td>86</td>
</tr>
</tbody>
</table>
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 *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$_2$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 (7-epi-112)  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  Cossy’s first formal synthesis of (-)-swainsonine  
Scheme 1.2  Cossy’s second formal synthesis of (-)-swainsonine  
Scheme 1.3  Ham’s total synthesis of (-)-swainsonine  
Scheme 1.4  Cheng’s total synthesis of (-)-swainsonine  
Scheme 1.5  Poisson’s total synthesis of (-)-swainsonine  
Scheme 1.6  Reiser’s formal synthesis of (-)-swainsonine  
Scheme 1.7  Riera’s formal synthesis of (-)-swainsonine  
Scheme 1.8  O’Doherty’s total synthesis of (+)-swainsonine  
Scheme 1.9  Kang’s formal synthesis of (-)-swainsonine  
Scheme 1.10  Martin’s synthesis of hyacinthacine A₂  
Scheme 1.11  Goti’s synthesis of hyacinthacine A₂  
Scheme 1.12  Py’s synthesis of hyacinthacine A₂  
Scheme 1.13  Renaud’s synthesis of hyacinthacine A₁  
Scheme 1.14  Renaud’s synthesis of 3-epi-hyacinthacine A₁  
Scheme 1.15  Kaliappan’s syntheses of hyacinthacine A₃ and 5-(-)-epi-hyacinthacine A₅  
Scheme 1.16  Cao’s synthesis of hyacinthacine A₆  
Scheme 1.17  General scheme of Izquierdo’s syntheses of hyacinthacine alkaloids  
Scheme 1.18  Izquierdo’s synthesis of 7a-epi-hyacinthacine A₂  
Scheme 1.19  Izquierdo’s synthesis of 5,7a-di-epi-hyacinthacine A₃  
Scheme 1.20  Izquierdo’s synthesis of (+)-hyacinthacine A₃  
Scheme 1.21  Izquierdo’s synthesis of (+)-hyacinthacine A₂  
Scheme 1.22  Izquierdo’s synthesis of (+)-3-epi-hyacinthacine A₃  
Scheme 1.23  Izquierdo’s synthesis of (+)-3-epi-hyacinthacine A₂  
Scheme 1.24  Izquierdo’s synthesis of (-)-3-epi-hyacinthacine A₅  
Scheme 1.25  Izquierdo’s synthesis of (+)-3-epi-hyacinthacine A₅  
Scheme 1.26  Izquierdo’s synthesis of (+)-5-epi-hyacinthacine A₅  
Scheme 1.27  Izquierdo’s synthesis of (+)-5-epi-hyacinthacine A₄
Scheme 1.28 Izquierdo’s synthesis of (-)-1-epi-hyacinthacine A\textsubscript{7} and (-)-hyacinthacine A\textsubscript{7} 34
Scheme 1.29 Yoda’s synthesis of (+)-hyacinthacines B\textsubscript{1} and B\textsubscript{2} 36
Scheme 1.30 Yoda’s synthesis of hyacinthacines C\textsubscript{2} and C\textsubscript{3} and their C-5 epimers 38
Scheme 1.31 Marco’s synthesis of hyacinthacines A\textsubscript{2} 39
Scheme 1.32 Marco’s synthesis of hyacinthacine A\textsubscript{3} and 5-epi-hyacinthacine A\textsubscript{3} 40
Scheme 1.33 Chandrasekhar’s synthesis of hyacinthacine A\textsubscript{1} 41
Scheme 1.34 Delair’s synthesis of hyacinthacine A\textsubscript{1} 43
Scheme 1.35 Delair’s synthesis of hyacinthacine B\textsubscript{1} 44
Scheme 1.36 Donohoe’s synthesis of (±)-hyacinthacine A\textsubscript{1} 45
Scheme 1.37 Blechert’s synthesis of hyacinthacine A\textsubscript{2} 46
Scheme 1.38 Clapés’ syntheses of the stereoisomers of hyacinthacines A\textsubscript{1} and (-)-hyacinthacine A\textsubscript{2} 47
Scheme 1.39 Donohoe’s synthesis of (+)-hyacinthacine A\textsubscript{1} 48
Scheme 1.40 Donohoe’s syntheses of hyacinthacines A\textsubscript{6} and A\textsubscript{7} 49
Scheme 1.41 Laschat’s total synthesis of (±)-7a-epi-hyacinthacine A\textsubscript{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\textsubscript{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  
Scheme 3.3  Mechanism of the cyclization of 364 via intramolecular N-alkylation  
Scheme 3.4  Conversion of 365 to 22  
Scheme 3.5  Bates’ formal synthesis of (-)-swainsonine  

Scheme 4.1  Proposed synthesis of hyacinthacine B₁  
Scheme 4.2  O-PMB protection of (S)-4-penten-2-ol and preparation of the vinyl sulfone 379  
Scheme 4.3  Concerted [3+2] mechanism of the Os-catalyzed DH reaction postulated by Criegee  
Scheme 4.4  Stepwise [2+2] mechanism of the Os-catalyzed DH reaction postulated by Sharpless  
Scheme 4.5  Conversion of 379 to 382 via the Sharpless-Petasis sequence  
Scheme 4.6  Synthesis of (R)-Mosher’s esters 396 and 396’  
Scheme 4.7  Synthesis of the oxazolidinone 384  
Scheme 4.8  Conversion of 383 to 384 via RCM with Grubbs’ II catalyst  
Scheme 4.9  cis-DH of 384 and bisbenzylation of 385  
Scheme 4.10  O-PMB deprotection of 386 and oxazolidinone hydrolysis  
Scheme 4.11  Mesylation of 388 and concomitant cyclization  
Scheme 4.12  Global debenzylation of 384 and ion-exchange chromatography  

Scheme 5.1  Proposed synthesis of hyacinthacine B₇  
Scheme 5.2  Conversion of (R)-4-penten-2-ol to the amino alcohol 401  
Scheme 5.3  Synthesis of the oxazolidinone 402  
Scheme 5.4  RCM of 402 and cis-DH of 403  
Scheme 5.5  Conversion of 404 to 407 via protecting group manipulations  
Scheme 5.6  Mesylation-cyclization and global debenzylation  
Scheme 5.7  C-7 epimerization of 408
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$_3$OD, 300 MHz) data between natural hyacinthacine B$_3$ and synthetic 104 87
Table 4.2 Comparison of $^{13}$C NMR (100 MHz, CD$_3$OD) 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$_2$O) spectral data of natural and synthesized hyacinthacine B$_7$ (112) 95
Table 5.3 $^{13}$C NMR (100 MHz, D$_2$O) spectral data of natural and synthesized hyacinthacine B$_7$ (112) 95
Table 5.4 $^1$H NMR (500 MHz, D$_2$O) 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>[M]$^+$</td>
<td>molecular ion</td>
</tr>
<tr>
<td>$[\alpha]_D$</td>
<td>optical rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AD or ADH</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>amu</td>
<td>atomic units</td>
</tr>
<tr>
<td>b.p.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
</tr>
<tr>
<td>br.</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>$c$</td>
<td>concentration in g/100 mL</td>
</tr>
<tr>
<td>$ca.$</td>
<td>circa</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium(IV) ammonium nitrate</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>CM</td>
<td>cross metathesis</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift</td>
</tr>
<tr>
<td>DADP</td>
<td>2,5-dideoxy-2,5-imino-D-alloitol</td>
</tr>
<tr>
<td>DALDP</td>
<td>2,5-dideoxy-2,5-imino-D-altroitol</td>
</tr>
<tr>
<td>DBB</td>
<td>4,4'-ditertbutylbiphenyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>$N,N'$-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DGDP</td>
<td>2,5-dideoxy-2,5-imino-D-glucoitol</td>
</tr>
<tr>
<td>DGADP</td>
<td>2,5-dideoxy-2,5-imino-D-galactoitol</td>
</tr>
<tr>
<td>DH</td>
<td>dihydroxylation</td>
</tr>
</tbody>
</table>
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
IC₅₀   half maximal inhibitory concentration
imid. imidazole
IND   indole
i-Pr  isopropyl
J     coupling constant
m     multiplet
m     meta
M     molar
m.p.  melting point
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/z</td>
<td>mass/charge ratio</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl, methanesulfonyl</td>
</tr>
<tr>
<td>MS (as in 3 Å MS)</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>MS (as in GC-MS)</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate, trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>petrol</td>
<td>petroleum spirit b.p. 40-60 °C</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PHAL</td>
<td>phthalazine</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonate</td>
</tr>
<tr>
<td>PTSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>quant.</td>
<td>quantitative</td>
</tr>
<tr>
<td>quint.</td>
<td>quintet</td>
</tr>
<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor, retardation factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>$S_\text{N}2$</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>t-</td>
<td>tert-</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butylidimethylsilyl</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMO</td>
<td>trimethylamine N-oxide</td>
</tr>
<tr>
<td>TMP</td>
<td>tetramethylpiperidide</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl or trimethylsilane</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl, para-toluenesulfonyl</td>
</tr>
</tbody>
</table>
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-trihydroxyindolizidine 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 *Musca ria armeniacum* and was found to be a moderate inhibitor of β-galactosidase (IC$_{50}$ = 18 μM) and was a weak amylglucosidase 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 amylglucosidase 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 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 B7 was incorrect.

**Publications arising from this thesis**

