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

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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

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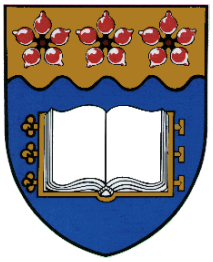

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Declaration

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

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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.