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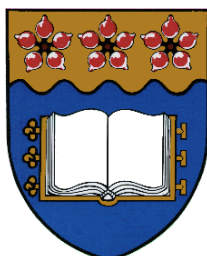
# **Synthesis of 1,2-*anti* Amino Alcohols and Their Applications in the Asymmetric Synthesis of Polyhydroxylated Indolizidine and Pyrrolizidine Alkaloids**

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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## *List of Abbreviations*

[M] <sup>+</sup>	molecular ion
[α] <sub>D</sub>	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 <sub>50</sub>	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

$m/z$	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
$R_f$	retention factor, retardation factor
rt	room temperature
s	singlet
S <sub>N</sub> 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  $\alpha$ -D-MANNOSIDASE. THE POLYHYDROXYLATED PYRROLIZIDINE ALKALOID HYACINTHACINE **B<sub>3</sub> 104** WAS ISOLATED FROM FRESH BULBS OF THE HYACINTHACEAE PLANT *MUSCARI ARMENIACUM* AND WAS FOUND TO BE A MODERATE INHIBITOR OF  $\beta$ -GALACTOSIDASE ( $IC_{50} = 18 \mu M$ ) AND WAS A WEAK AMYLOGLucosidase INHIBITOR ( $IC_{50} = 51 \mu M$ ). HYACINTHACINE **B<sub>7</sub> 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  $\alpha$ -hydroxy aldehydes generated *in situ* by the Sharpless asymmetric dihydroxylation (ADH) reaction of vinyl sulfones underwent a borono-Mannich reaction with  $\beta$ -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<sub>3</sub> 104** and the purported structure of hyacinthacine **B<sub>7</sub> 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<sub>3</sub>**. In an analogous fashion, the reported structure of hyacinthacine **B<sub>7</sub> 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<sub>7</sub> was incorrect.

### ***Publications arising from this thesis***

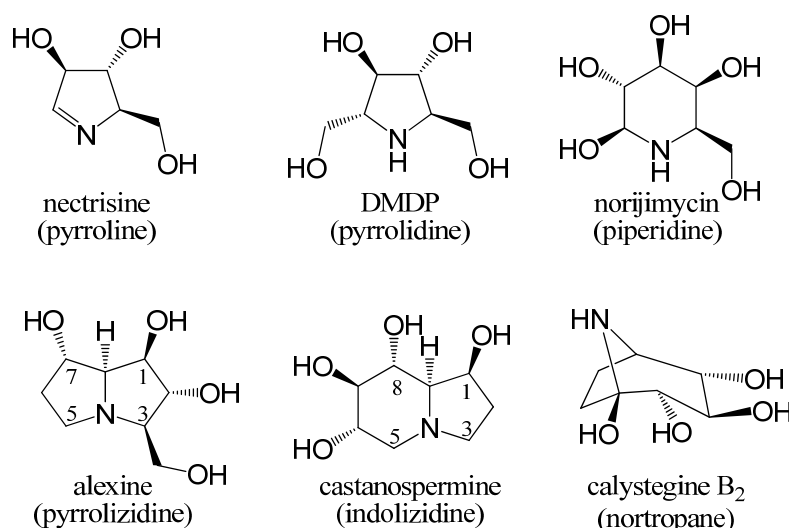
1. Au, Christopher W.G.; Nash, Robert, J.; Pyne, Stephen G. 'Synthesis of hyacinthacine B<sub>3</sub> and purported hyacinthacine B<sub>7</sub>' *Chem. Commun.*, **2010**, 46, 713-715.
2. Pyne, Stephen G.; Au, Christopher W.G.; Davis, Andrew S.; Morgan, Ian R.; Ritthiwigrom, Thunwadee; Yazici, Arife. '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.

# CHAPTER 1: INTRODUCTION

This thesis reports on the development of a new synthetic strategy for the synthesis of the polyhydroxylated indolizidine alkaloid, swainsonine and the polyhydroxylated pyrrolizidine alkaloids hyacinthacine B<sub>3</sub> and hyacinthacine B<sub>7</sub>. Before a more detailed discussion of the aims of this project are given, it seems appropriate to first briefly review polyhydroxylated alkaloids in terms of their structures and biological activities as glycosidase enzyme inhibitors and to discuss the previous syntheses of swainsonine and the hyacinthacine alkaloids.

## 1.1 Glycosidase enzymes and glycosidase inhibitors

Glycosidases are enzymes that are commonly found in biological systems with functions in the catabolism of complex carbohydrates, the transportation of glycoproteins, anti-microbial defense mechanisms and pathogenesis. As a result of the many biological functions of glycosidase enzymes, compounds that exhibit inhibitory activities towards these enzymes may therefore alter the course of one or more important biological processes.

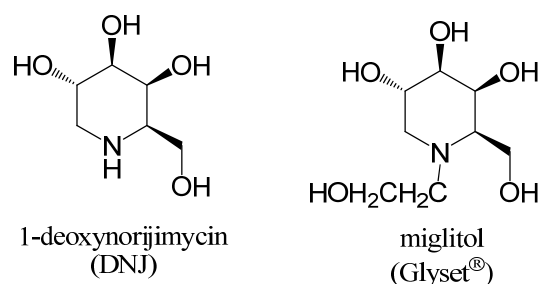


**Figure 1.1** Examples of polyhydroxylated alkaloids.

An example of organic compounds that have attracted much attention to their glycosidase inhibitory activities is the polyhydroxylated alkaloids, natural heterocycles that contain one or more basic nitrogen atoms and various numbers of hydroxy substituents. Classified

by their ring structures, polyhydroxylated alkaloids include pyrrolines, pyrrolidines, piperidines, pyrrolizidines, indolizidines and nortropanes (Figure 1.1).

An example of a polyhydroxylated alkaloid that led to the development of a therapeutic agent is the piperidine alkaloid 1-deoxynojirimycin (DNJ, Figure 1.2) which was isolated from mulberry leaves (*Morus* spp.). The hydroxy and hydroxymethyl substituents of DNJ were determined by structure elucidation studies to have the a D-*gluco* configuration, and DNJ was found to be a strong inhibitor of digestive  $\alpha$ -glycosidases<sup>1</sup>. These findings offered an explanation for the usage of mulberry leaves as a remedy for diabetes in traditional Chinese medicine.<sup>2</sup> The biological activities of DNJ also sparked interests in synthesizing *N*-substituted DNJ compounds, including miglitol (Figure 1.2), which has been marketed as the diabetic drug Glyset<sup>®</sup>.<sup>2</sup>



**Figure 1.2** 1-Deoxynojirimycin and miglitol.

Due to their glycosidase inhibitory activities, polyhydroxylated alkaloids are also studied for potential applications as anti-viral, anti-cancer and anti-metastasis drugs, and as therapeutic agents for autoimmune and lysosomal storage disorders.<sup>2,3</sup>

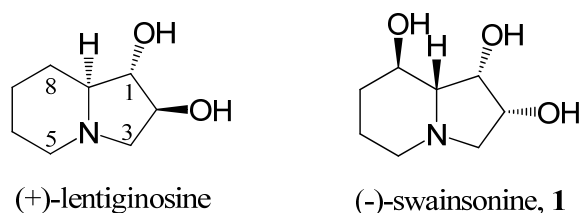
## 1.2 Polyhydroxylated indolizidines

Indolizidine alkaloids are identified by their 1-aza-bicyclo[4.3.0]octane core structure. Examples of polyhydroxylated indolizidine alkaloids isolated from Nature include castanospermine (Figure 1.1)<sup>4</sup> and its three epimers (6-*epi*-<sup>5</sup>, 6,7-*epi*-<sup>6</sup> and 7-deoxy-6-*epi*-castanospermine<sup>7</sup>) from the legume *Castanospermum australe* and lentiginosine (Figure 1.3) and 2-*epi*-lentiginosine<sup>8</sup> from *Astragalus lentiginosus*.

(-)-Swainsonine (**1**), a 1,2,8-trihydroxy-indolizidine alkaloid, was first isolated by Broquist *et al.* in 1973 from the fungus *Rhizoctonia leguminicola*.<sup>9</sup> Since then the



isolation of (-)-swainsonine has been reported from the Australian legume *Swainsona canescens*<sup>10</sup> and other plants and fungi (Fig 1.3).<sup>11-14,3</sup>



**Figure 1.3** Lentiginosine and (-)-swainsonine.

Investigations on the biological activities of (-)-swainsonine have focused on its inhibition of glycosidases. In an account published in 2000, Nash *et al.* thoroughly reviewed the biological and clinical testing of (-)-swainsonine, amongst other indolizidine and pyrrolizidine alkaloids, as anti-cancer, anti-diabetic and anti-viral agents and immune stimulant.<sup>3</sup> In an *in vitro* study, (-)-swainsonine exhibited high inhibitory activities ( $IC_{50} = 0.2 \mu M$ ) towards both Golgi mannosidase II and lysosomal  $\alpha$ -D-mannosidase but had no effect on Golgi mannosidases IA and IB.<sup>15</sup> This result suggests that while (-)-swainsonine may be used as a potential anti-metastasis agent due to its selective mannosidase inhibition, adverse effects such as interference with normal lysosomal processing are also expected.

### 1.2.1 Total and formal syntheses of swainsonine since 2005

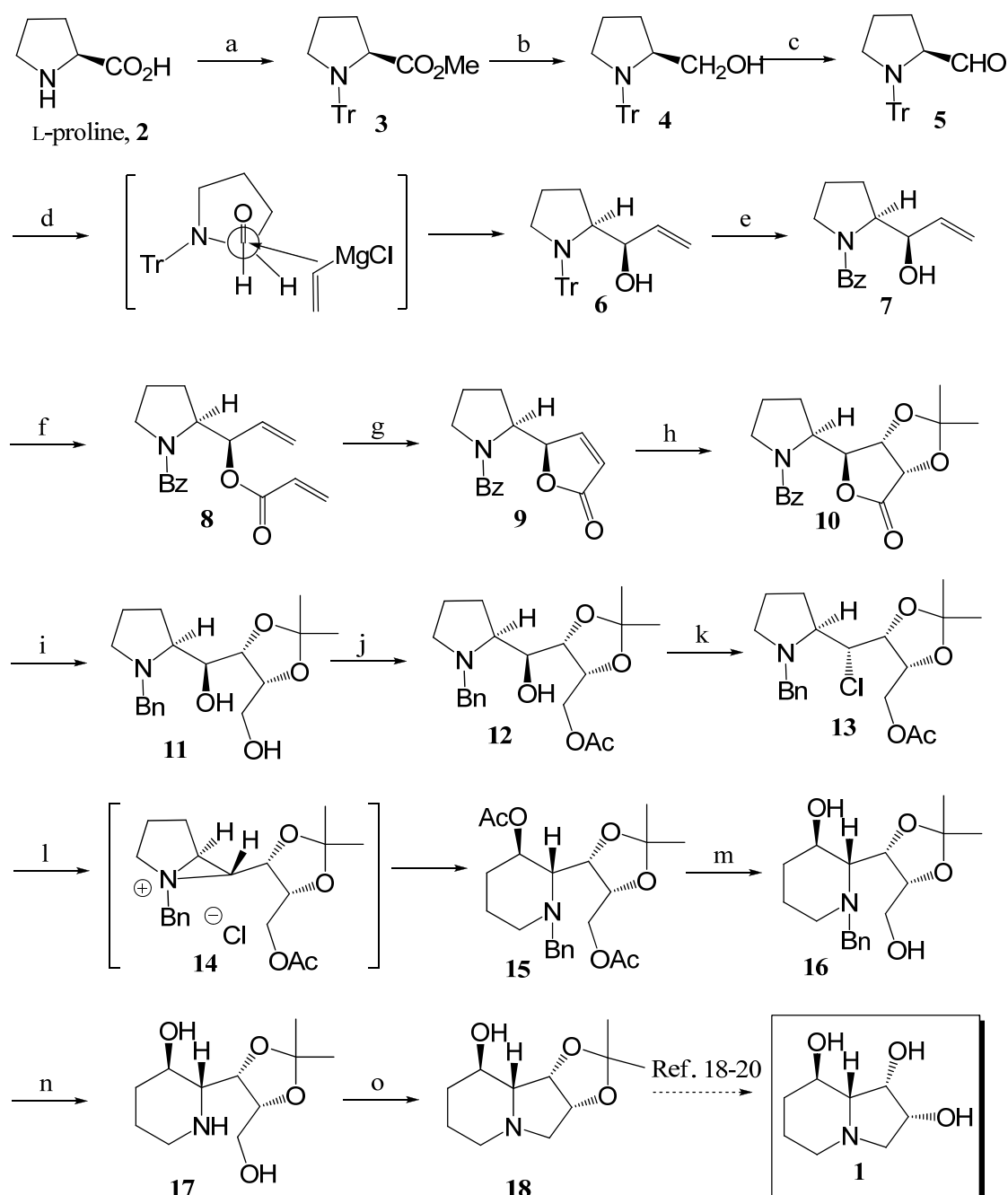
The interesting biological activities of swainsonine have sparked interests in developing strategies to the total synthesis of (+)- and (-)-swainsonine and swainsonine analogues. In 2005, Pyne published a review on the synthesis of swainsonine and analogues from 2000 to 2005.<sup>16</sup> The syntheses of (+)- and (-)-swainsonine from 2005 will be discussed in this section. These syntheses can be grouped into three general categories: (1) syntheses from ‘chiral pool’ precursors, including amino acids and a sugar derivative; (2) using a chiral auxiliary; and (3) from non-chiral precursors, utilizing diastereoselective synthesis and asymmetric catalysis.

### 1.2.1.1 Syntheses from ‘chiral pool’ precursors

#### *From Amino Acids*

In 2007, Cossy *et al.* reported two formal syntheses of **1** from L-proline **2**.<sup>17</sup> In the first synthesis, esterification and *N*-alkylation of L-proline gave amino ester **3**. Reduction with  $\text{LiAlH}_4$  followed by Swern oxidation of **4** gave *N*-tritylprolinal **5**, which then underwent a Grignard reaction with vinylmagnesium chloride to give *N*-tritylprolinol **6** with a high diastereomeric ratio (98:2) in favor of the Felkin-Ahn diastereoisomeric product. A detritylation-benzoylation sequence gave pyrrolidine **7**, which then coupled with acryloyl chloride to afford diene **8**. After the ring-closing metathesis (RCM) reaction of **8** with Grubbs' II catalyst that gave the lactone **9**, the diastereoselective dihydroxylation of **9** with  $\text{RuCl}_3$  and  $\text{NaIO}_4$  followed by the protection of the resulting diol as an acetal gave acetone **10**. Reduction of the lactone and benzoate groups in **10** gave diol **11**, which was selectively protected at the primary hydroxyl position to give prolinol **12**. Upon treatment with mesyl chloride and microwave irradiation, **12** was converted to chloro compound **13**, which underwent a ring-expansion reaction with silver acetate to give piperidine **15** *via* the aziridinium intermediate **14**. Deprotection of the diacetate in **15** followed by *N*-debenzylation gave **17**. Cyclization under Mitsunobu reaction conditions then afforded indolizidine **18**, which had previously<sup>18-20</sup> been converted to **1** *via* an acid-catalyzed removal of the acetal protecting group (Scheme 1.1).

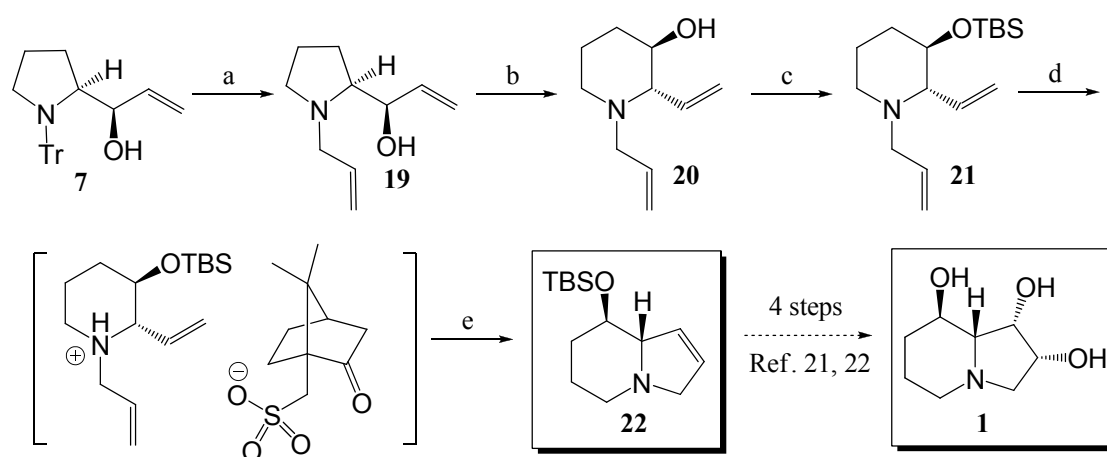
Scheme 1.1



*Reagents and conditions:* (a) (i)  $\text{SOCl}_2$ , MeOH; (ii)  $\text{Ph}_3\text{CCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CHCl}_3$ , 90%, 2 steps; (b)  $\text{LiAlH}_4$ , THF, 98%; (c)  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ;  $\text{CH}_2\text{Cl}_2$ , 95%; (d)  $\text{CH}_2=\text{CHMgCl}$ ,  $\text{Et}_2\text{O}$ , 93%; (e) (i) 5M HCl,  $\text{Et}_2\text{O}$ ; (ii) NaOH, then  $\text{PhCOCl}$ , 68%, 2 steps; (f) acryloyl chloride, DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 65%; (g) Grubbs II cat., toluene, 80 °C; (h) (i) cat.  $\text{RuCl}_3$ ,  $\text{NaIO}_4$  (1.5 equiv.), cat.  $\text{H}_2\text{SO}_4$ ,  $\text{EtOAc}/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ; (ii)  $\text{MeC(OMe)}_2$ , APTS,  $\text{CH}_2\text{Cl}_2$ , 41%, 3 steps; (i)  $\text{LiAlH}_4$ , THF, reflux, 94%; (j)  $\text{AcCl}$ , 2,4,6-collidine,  $\text{CH}_2\text{Cl}_2$ , 88%; (k)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ , THF, microwaves, 100 °C; 24%; (l)  $\text{AgOAc}$ , THF, microwaves, 120 °C 46%; (m) NaOMe, MeOH, THF, 83%; (n)  $\text{H}_2$ , Pd/C, EtOH; (o) DEAD,  $\text{PPh}_3$ , pyridine, 27%, 2 steps.

The second formal synthesis of **1** by Cossy, *et al.*<sup>17</sup> followed the same route from L-proline **2** to *N*-tritylprolinol **6**. Replacement of the *N*-trityl protecting group with an *N*-allyl group was achieved in two steps and was followed by a diastereoselective ring expansion reaction to give piperidinol **20** with a 95% diastereomeric excess which was subsequently protected as a TBS ether. In preparation for the RCM of **21** with Grubbs' I catalyst, the amino moiety of **21** was deactivated with CSA to form a piperidinyl salt. The RCM reaction gave the known indoline **22**, which had previously been converted to (-)-swainsoine in four steps (Scheme 1.2).<sup>21,22</sup>

**Scheme 1.2**

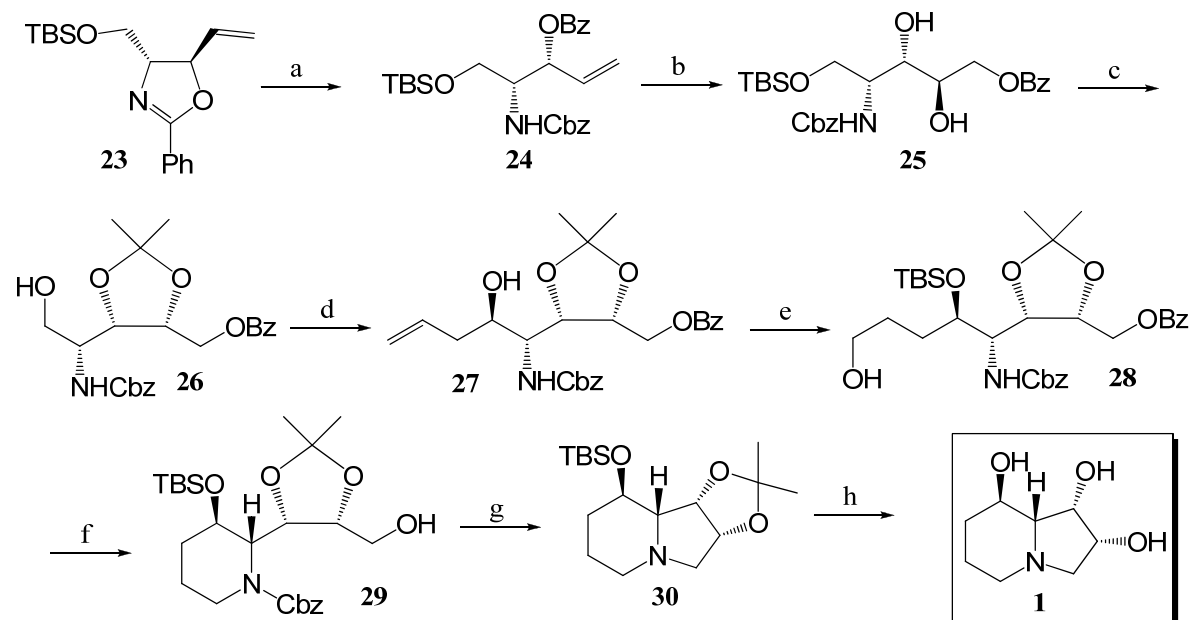


*Reagents and conditions:* (a) (i) HCl, Et<sub>2</sub>O; (ii) allylbromide, K<sub>2</sub>CO<sub>3</sub>, toluene, 50%, 2 steps; (b) (CF<sub>3</sub>CO)<sub>2</sub>O, Et<sub>3</sub>N, THF, reflux, then NaOH, 95%; (c) TBSCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 70%; (d) CSA, CH<sub>2</sub>Cl<sub>2</sub>; (e) Grubbs I cat., CH<sub>2</sub>Cl<sub>2</sub>, reflux, then K<sub>2</sub>CO<sub>3</sub>, 82%, 2 steps.

In 2009, Ham *et al.* reported a total synthesis of (-)-swainsonine from the D-serine-derived *trans*-oxazoline **23** in 13 steps.<sup>23</sup> The treatment of **23** with CbzCl resulted in the opening of the oxazoline ring to afford the carbamate **24**. Dihydroxylation of the terminal olefin in **24** with osmium tetroxide and NMO proceeded with high diastereoselectivity (9:1). Treatment of the resultant diol with saturated Na<sub>2</sub>SO<sub>3</sub> triggered a migration of the secondary benzoyl group to the primary position. Protection of the diol **25** as an acetal was followed by desilylation to give the primary alcohol **26**. Oxidation of **26** and then reaction of the resulting aldehyde with allyltrimethylsilane and TiCl<sub>4</sub> afforded the *anti*-amino alcohol **27** with an *anti/syn* ratio of 15:1. Protection of **27** as a TBS ether and subsequent hydroboration by BH<sub>3</sub>-SMe<sub>2</sub> gave the alcohol **28**, which then underwent a mesylation-cyclization sequence to form the piperidine ring and a hydrolysis reaction of the primary benzoyl ester to give **29**. After mesylation of the free hydroxy group in **29**,

hydrogenolysis with  $\text{Pd}(\text{OH})_2$  gave indolizidine **30**, which after acid hydrolysis was converted to **1** (Scheme 1.3).

**Scheme 1.3**

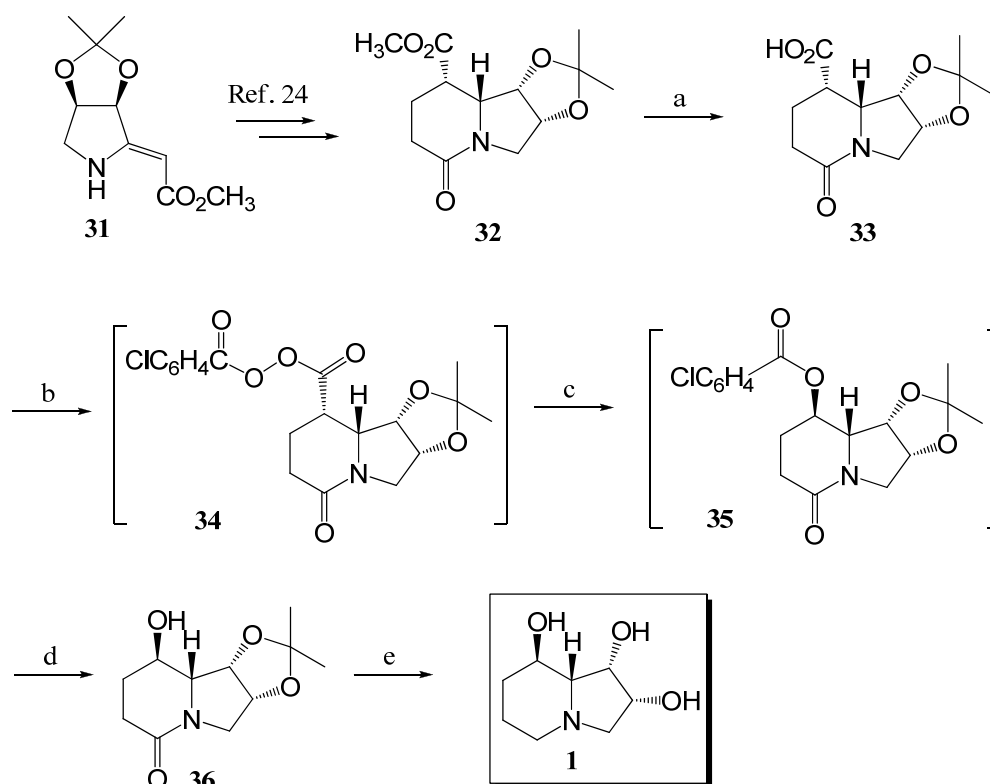


*Reagents and conditions:* (a)  $\text{CbzCl}$ ,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{H}_2\text{O}$ ,  $0\text{ }^\circ\text{C}$  to rt, 8 h, 96%; (b)  $\text{OsO}_4$ ,  $\text{NMO}$ , acetone: $\text{H}_2\text{O}$  then sat.  $\text{Na}_2\text{SO}_3$ ,  $0\text{ }^\circ\text{C}$ , 10 h, 89%; (c) (i)  $\text{DMP}$ ,  $\text{PPTS}$ , acetone,  $40\text{ }^\circ\text{C}$ , 8 h; (ii)  $\text{HF}$ , pyridine,  $\text{THF}$ ,  $0\text{ }^\circ\text{C}$  to rt, 3 h, 78%, 2 steps; (d) (i)  $\text{DMP}$ ; (ii)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_2=\text{CHCH}_2\text{Si}(\text{CH}_3)_3$ ,  $-78\text{ }^\circ\text{C}$ , 24 h, 83%, 2 steps; (e) (i)  $\text{TBSOTf}$ , 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ; (ii)  $\text{BH}_3\text{-SMe}_2$ ,  $\text{THF}$ ,  $0\text{ }^\circ\text{C}$  to rt, 70%, 2 steps; (f) (i)  $\text{MsCl}$ ,  $\text{TEA}$ ,  $\text{CH}_2\text{Cl}_2$ ; (ii)  $\text{NaH}$ ,  $\text{THF}$  then 2 N  $\text{NaOH}$ , 76%, 2 steps; (g) (i)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (ii)  $\text{Pd}(\text{OH})_2/\text{C}$ ,  $\text{H}_2$ ,  $\text{MeOH}$ , 84%, 2 steps; (h) 6 N  $\text{HCl}$  then Dowex-50WX8, 82%.

### From a sugar derivative

In 2008, Cheng *et al.* reported the total synthesis of (-)-swainsonine (**1**) and 7-alkyl swainsonines from enamino ester **31**, which was synthesized from the sugar derivative D-erythronic acid  $\gamma$ -lactone.<sup>24</sup> In the total synthesis of **1**, the enamino ester **31** was first converted to the indolizidone **32** in two steps under previously optimized conditions.<sup>25</sup> After basic hydrolysis, the resultant acid **33** was subjected to oxidative conditions with *m*-CPBA and DCC to give the unstable diacyl peroxide intermediate **34**, which was converted to the indolizidinone ester **35** *via* thermolytic rearrangement. After the basic hydrolysis of **35** to give 8-hydroxyindolizidinone **36**, borane reduction followed by acidic hydrolysis afforded **1** in a total of five steps from **32** (Scheme 1.4).

Scheme 1.4



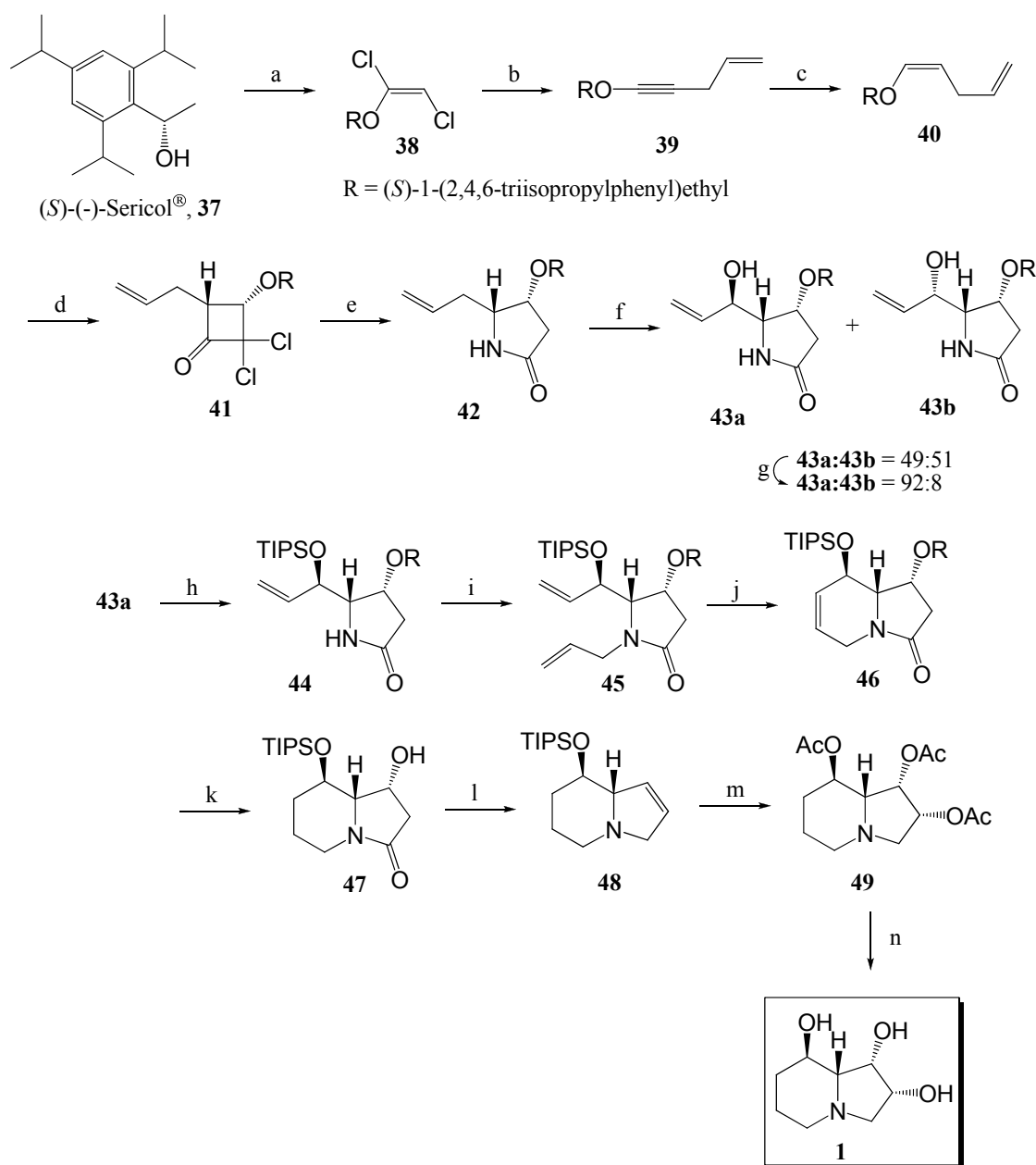
Reagents and conditions: (a) NaOH, EtOH, 89%; (b) DCC, *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (c) Toluene, reflux; (d) NaOH, MeOH, rt, 49%, 3 steps; (e) BH<sub>3</sub>-THF then HCl, 71%.

### 1.2.1.2 Using a chiral auxiliary

In 2006 Poisson, *et al.* reported a total synthesis of (-)-swainsonine from (*S*)-stericol<sup>®</sup> ((*S*)-1-(2,4,6-triisopropylphenyl)ethanol, **37**).<sup>26</sup> The synthesis began with the treatment of **37** with potassium hydride and trichloroethylene to give the dichloroenol ether **38**. The alkylation reaction of **38** with *n*-BuLi (2 equivalents) and allyl iodide afforded ynol ether **39**. Reduction of **39** with DIBAL-H gave enol ether **40**, which was subjected to a [2+2] cycloaddition with dichloroketene to yield the cyclobutanone **41**. The Beckmann ring expansion of **41** using *O*-mesitylenesulfonylhydroxylamine followed by dechlorination with zinc-copper couple gave pyrrolidinone **42**, which was oxidized with SeO<sub>2</sub> and *t*-butyl peroxide to give a 1:1 mixture of enols **43a,b**. This diastereomeric ratio was improved to 92:8 (**43a**:**43b**) *via* an oxidation-reduction sequence with Dess-Martin periodinane followed by LiAlH<sub>4</sub>. Selective protection of the allylic alcohol as a TIPS ether and allylation with allyl bromide using a phase transfer catalyst gave diene **45**, which was cyclized in the RCM reaction with Grubbs' II catalyst forming the indolizidine

**46.** Hydrogenation with Pd/C and cleavage of the stericol<sup>®</sup> moiety with trifluoroacetic acid gave the indolizidinone **46**. Lactam reduction followed by dehydration with Martin's sulfurane gave the dehydroindolizidine **48**, which then underwent dihydroxylation, desilylation and triacetylation to give triacetylswainsonine **49**. Global deprotection using a basic ion-exchange resin gave **1** in a total of 18 steps (Scheme 1.5).

## Scheme 1.5



**Reagents and conditions:** (a) KH, THF,  $\text{Cl}_2\text{CCHCl}$ , 79%; (b) *n*-BuLi, allyliodide, THF; (c) DIBAL-H, THF; (d) dichloroketene,  $\text{Et}_2\text{O}$ ; (e) *O*-mesitylenesulfonylhydroxylamine,  $\text{CH}_2\text{Cl}_2$ ; Zn/Cu,  $\text{NH}_4\text{Cl}$ , MeOH, 34%, 5 steps; (f)  $\text{SeO}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , 56%; (g) (i) DMP,  $\text{CH}_2\text{Cl}_2$ ; (ii)  $\text{LiAlH}_4$ , THF, 82%, 2 steps; (h) (i) TIPSOtF, *i*- $\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ ; (ii) AcOH, 81%, 2 steps; (i) allylbromide, *n*- $\text{Bu}_4\text{N}\cdot\text{HSO}_4$ , aq. NaOH,  $\text{CH}_2\text{Cl}_2$ , 95%; (j) Grubbs II cat.,  $\text{CH}_2\text{Cl}_2$ , 84%; (k) (i)  $\text{H}_2$ , Pd/C, EtOAc; (ii) TFA,  $\text{CH}_2\text{Cl}_2$ , 84%, 2 steps; (l) (i)  $\text{LiAlH}_4$ , 92%; (ii) Martin sulfurane,  $\text{Et}_2\text{O}$ ; (m) (i) AD-mix- $\alpha$ ,  $\text{H}_2\text{O}/t\text{-BuOH}$ ; (ii) TBAF, THF; (iii)  $\text{Ac}_2\text{O}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ; 41%, 4 steps; (n) IRA-402, 97%.

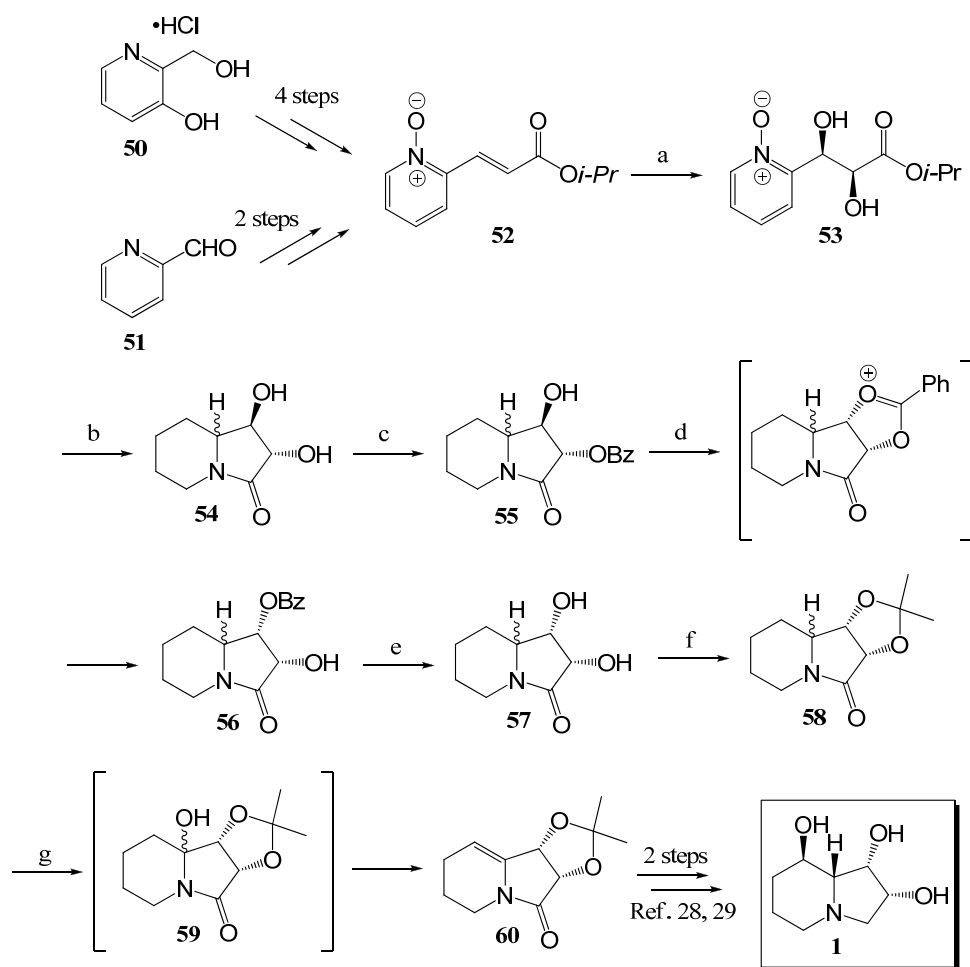


### 1.2.1.3 Synthesis from non-chiral precursors

#### *Via diastereoselective synthesis*

In 2005, Reiser *et al.* reported a formal synthesis of **1** and a total synthesis of (-)-2,8a-di-*epi*-swainsonine from substituted pyridines.<sup>27</sup> In the formal synthesis of (-)-swainsonine, the pyridines **50** and **51** were converted to the pyridine *N*-oxide **52** in four and two steps, respectively. This was followed by the Sharpless asymmetric dihydroxylation of **52** with AD-mix- $\beta$ , which produced diol **53** in 98% ee. Reduction of the pyridine-*N*-oxide moiety of **53** with PtO<sub>2</sub> resulted in concomitant cyclization to give **54** as a mixture of epimers (60:40) at the C-2 position (C-8a in swainsonine). Stereoconversion at C-1 was achieved by selective benzylation followed by treatment with triflic anhydride to give **56**. Debenzylation gave diol **57**, which was then protected as the acetonide **58**. Regioselective oxidation with RuO<sub>4</sub>, generated *in situ* from RuO<sub>2</sub> and NaOCl, afforded the tertiary alcohol **59**, which underwent elimination to give the known compound **60** in a total of seven steps from **53**. Following previously published procedures,<sup>28,29</sup> **60** was converted to (-)-swainsonine in an additional two steps (Scheme 1.6).

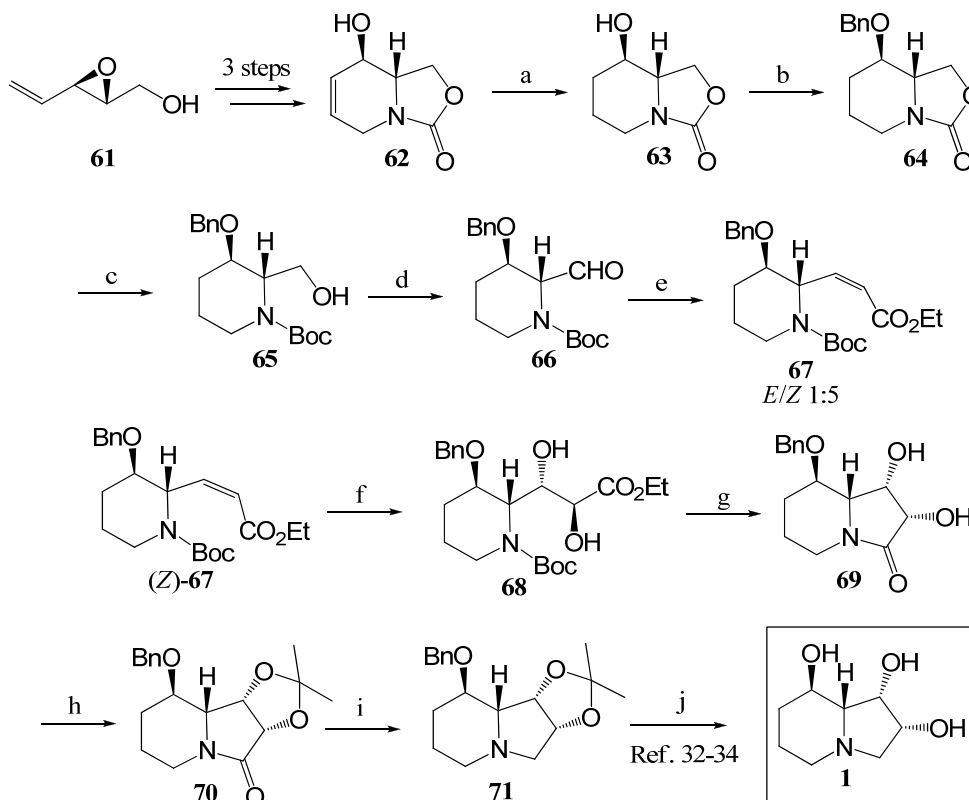
Scheme 1.6



In 2005, Riera *et al.* reported a 16-step synthesis of (-)-swainsonine from the chiral epoxide **61** (Scheme 1.7).<sup>30</sup> In a three-step sequence originally optimized for *ent*-**61**, **61** was converted to the key intermediate **62**. Hydrogenation of **62** followed by benzylation gave oxazolidinone **64**, which was then hydrolyzed and *N*-protected to give alcohol **65**. Oxidation and then a chain-lengthening olefination under Still conditions<sup>31</sup> gave preferentially *Z*-**67** (*Z*:*E* = 5:1). Dihydroxylation with catalytic  $\text{OsO}_4$  and stoichiometric NMO gave the diol **68** in excellent diastereoselectivity. *N*-Deprotection by acid hydrolysis, followed by cyclization upon treatment with DIPEA gave the cyclic amide **69**. Protection of the diol moiety in **70** as an acetal, followed by lactam reduction gave the

known compound **71**, which was converted to **1** in two steps using previously published conditions.<sup>32-34</sup>

**Scheme 1.7**



*Reagents and conditions:* (a) H<sub>2</sub>, Pd/C, 99%; (b) NaH, BnBr, DMF, reflux, 97%; (c) (i) 6 M NaOH, MeOH/H<sub>2</sub>O (9:1); (ii) Boc<sub>2</sub>O, EtOAc, NaHCO<sub>3</sub>, 87%, 2 steps; (d) DMP, NaHCO<sub>3</sub>, 98%; (e) (CF<sub>3</sub>CH<sub>2</sub>O)<sub>2</sub>POCHCH<sub>3</sub>CO<sub>2</sub>Et, KN(TMS)<sub>2</sub>, 18-Crown-6, THF, -78 °C, 82%; (f) OsO<sub>4</sub>, NMO, acetone, H<sub>2</sub>O, 72%; (g) (i) Et<sub>2</sub>O-HCl; (ii) (*i*-Pr)<sub>2</sub>EtN, THF, 65%, 2 steps; (h) 2,2-dimethoxypropane, acetone, cat. PTSA, 70%; (i) BH<sub>3</sub>•SMe<sub>2</sub>, THF, 75%; (j) (i) H<sub>2</sub>, PdCl<sub>2</sub>; (ii) 6 N HCl.

In 2006 and 2007, O'Doherty *et al.* reported the total synthesis of (+)- and (-)-swainsonine and 8-*epi*-(-)-swainsonine *via* enantioselective synthesis.<sup>35,36</sup> The synthesis of (+)-swainsonine (*ent*-**1**, Scheme 1.8) began with the addition reaction of lithiated furan **72** to dihydrofuranone **73** to give the furyl ketone **74**. Silylation of the primary alcohol followed by Noyori asymmetric reduction of the ketone moiety gave furyl alcohol **76** in 96% ee. Ring expansion of the furan was then achieved by exposing **76** to NBS in THF/H<sub>2</sub>O to give pyranone **77** with an anomeric hydroxy group at the C-2 position, which was first *O*-Boc protected and then converted to the benzyl ether **79** with palladium(0) and triphenylphosphine in benzyl alcohol. To prepare for the cyclization of the B-ring in subsequent steps, an azide group was to be diastereoselectively introduced at

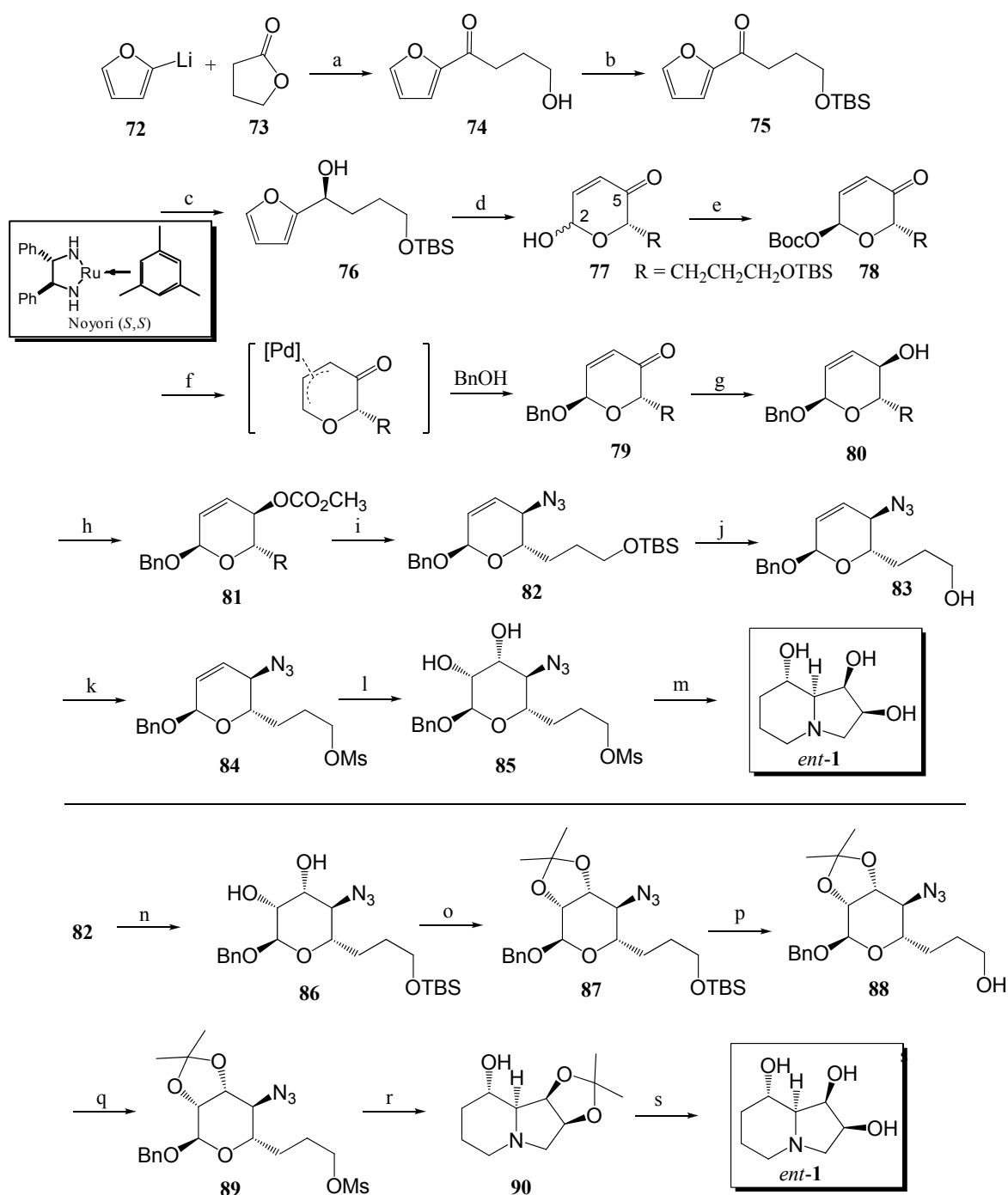
C-5. This was achieved by the reduction of the ketone moiety at C-5, conversion of the resulting allylic alcohol **80** to the mixed carbonate **81** and palladium catalysis under Sinou conditions<sup>37</sup> to give the azide **82**. Deprotection of the TBS ether in **82** followed by mesylation gave **84**. Dihydroxylation of **84** with OsO<sub>4</sub> and NMO gave the *cis*-diol **85**. This was followed by exhaustive hydrogenation to afford *ent*-**1** in a total of 13 steps.

A slightly different sequence for cyclizing the indolizidine rings was devised by first dihydroxylating **82** and protecting the diol as the acetal **87**. Desilylation, mesylation and exhaustive hydrogenation gave the acetal-protected swainonine **90**, which upon acidic treatment gave *ent*-**1** in a total of 15 steps (Scheme 1.8).

### Via *asymmetric catalysis*

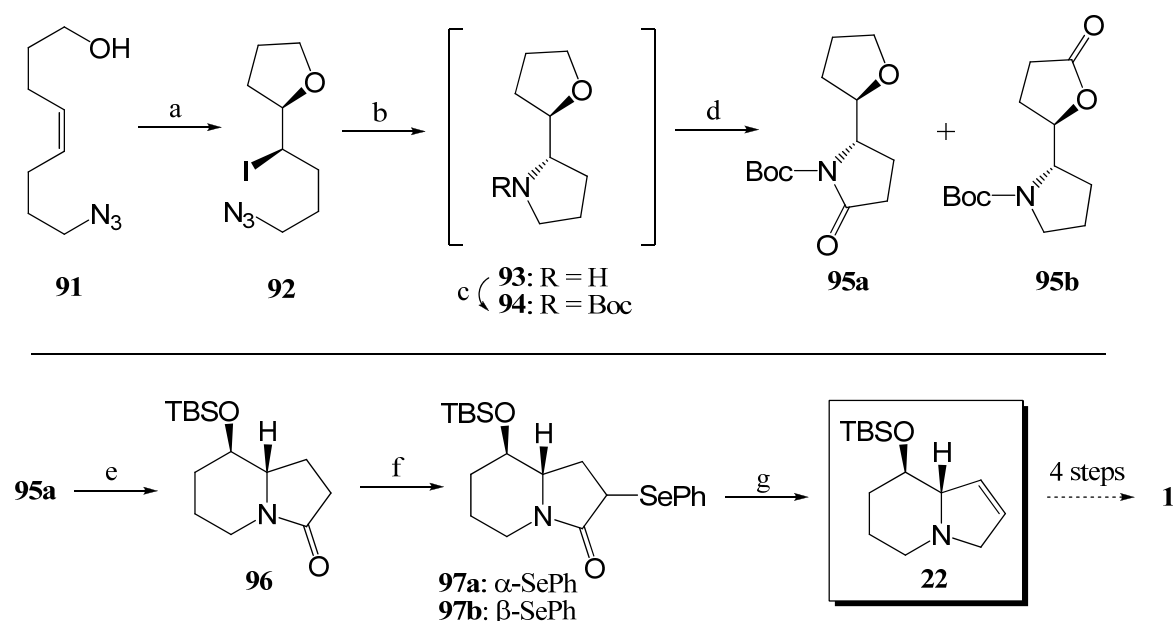
In 2008, Kang *et al.* reported a formal synthesis of **1** featuring a chiral salen-Cr<sup>III</sup>Cl catalyzed iodocyclization reaction.<sup>38</sup> Subjecting the azido alkenol **91** to optimized catalytic conditions (Scheme 1.9), the azido tetrahydrofuran **92** was prepared with a 90% ee. This was followed by the reduction of **92** with tin(II) chloride and cyclization under basic conditions to form the pyrrolidine **93**, which was then protected as the carbamate **94**. The oxidation of **94** with RuCl<sub>3</sub> and NaIO<sub>4</sub> resulted in the formation of the pyrrolidine **95a** in 65% yield and the undesired lactone **95b** in 21% yield. After treating **95a** with TMSI and BF<sub>3</sub>-etherate to open the tetrahydrofuranyl ring and protection of the resulting secondary alcohol as a TBS ether, the concomitant *N*-deprotection and cyclization with sodium hydride yielded the indolizidinone **96**. Enolization and phenylselenylation with LDA and phenylselenenyl bromide followed by treatment with 2,6-di-*tert*-butyl-4-methylphenol gave a 3:1 mixture of **97a/97b**. Finally, after the reduction of **97a** with *in situ* generated alane followed by oxidative elimination, the known indoline **22** was obtained in a total of 12 steps. This compound has been converted to **1** in four synthetic steps.<sup>21,22</sup>

Scheme 1.8



**Reagents and conditions:** (a) THF, -78 °C, 74%; (b) TBSCl, imidazole, DMF, 98%; (c) Noyori (*S,S*), HCO<sub>2</sub>H/Et<sub>3</sub>N, 89%; (d) NBS/H<sub>2</sub>O, 0 °C, 84%; (e) Boc<sub>2</sub>O, DMAP, -78 °C, 85%; (f) 2.5% Pd(0), 5% PPh<sub>3</sub>, 88%; (g) NaBH<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH, -78 °C, 94%; (h) CH<sub>3</sub>OCOCl, DMAP/pyridine, 72%; (i) (Pd(allyl)Cl)<sub>2</sub>/dppb (1:4), TMSN<sub>3</sub>, 77%; (j) TBAF, THF, 99%; (k) MsCl, Et<sub>3</sub>N, 99%; (l) OsO<sub>4</sub>, NMO, 93%; (m) H<sub>2</sub> (100 psi), Pd(OH)<sub>2</sub>/C, 3 d, 88%; (n) OsO<sub>4</sub>, NMO, 92%; (o) 2,2-dimethoxypropane, PTSA, 97%; (p) TBAF, THF, 98%; (q) MsCl, Et<sub>3</sub>N, 99%; (r) H<sub>2</sub> (100 psi), Pd(OH)<sub>2</sub>/C, 4 d, 85%; (s) HCl, 95%.

Scheme 1.9



*Reagents and conditions:* (a) (*R,R*)-salen-Cr<sup>III</sup>Cl, NCS, I<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, PhMe, -78 °C, 86%; (b) (i) SnCl<sub>2</sub>, PhSH, Et<sub>3</sub>N, MeCN, rt; (ii) NaOAc, EtOH, reflux; (c) Boc<sub>2</sub>O, NaHCO<sub>3</sub>, H<sub>2</sub>O, MeOH, rt, 80%, 2 steps; (d) RuCl<sub>3</sub>·3H<sub>2</sub>O, NaIO<sub>4</sub>, CCl<sub>4</sub>, H<sub>2</sub>O, MeCN, rt, 65% (95a), 21% (95b); (e) (i) TMSI, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (ii) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (iii) NaH, THF, 0 °C, 88%, 3 steps; (f) LDA, PhSeBr, THF, -78 °C, then 2,6-di-*tert*-butyl-4-methylphenol, -78 °C, 74% (97a/97b 3:1); (g) (i) LiAlH<sub>4</sub>, AlCl<sub>3</sub>, THF, -78 °C, 97%; (ii) NaIO<sub>4</sub>, NaHCO<sub>3</sub>, H<sub>2</sub>O, MeOH, 0 °C, 91%.

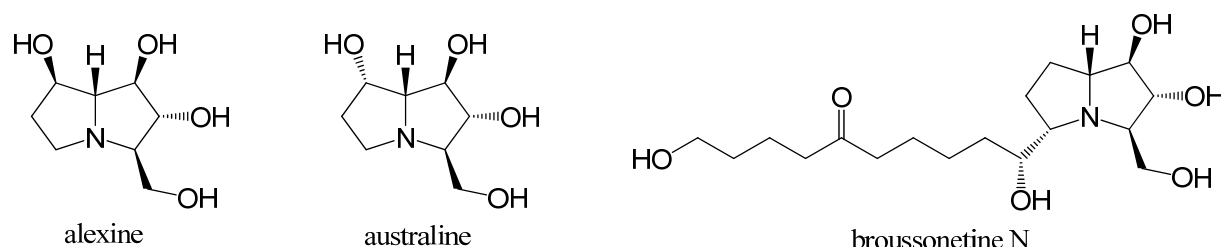
### 1.2.2 Synthesis of other swainsonine analogues since 2005

In 2006, Bhattacharjya *et al.* reported the synthesis of (-)-8-*epi*-swainsonine triacetate by a divergent synthesis<sup>39</sup> while Pinto *et al.* furnished a sulfonium analogue of 1,8,8a-tri-*epi*-swainsonine<sup>40</sup> via asymmetric synthesis. In 2007, Parsons *et al.* completed the synthesis of (-)-8-*epi*-swainsonine utilizing stereoelectronic control.<sup>41,42</sup> Tsai reported the synthesis of (+)-1,2-di-*epi*-swainsonine via α-acylamino radical cyclizations.<sup>43</sup> In 2008, 8a-*epi*-swainsonine was synthesized by Aggarwal, *et al.* via furyl-stabilized sulfur ylides<sup>44</sup> and O'Doherty *et al.* from an achiral furfural,<sup>45</sup> whereas Dhavale *et al.* reported on the synthesis of (+)-1,8,8a-tri-*epi*-swainsonine from a D-glucose derivative.<sup>46</sup>

### 1.3 Polyhydroxylated pyrrolizidine alkaloids

The structure of pyrrolizidine alkaloids comprises of a 1-aza-[3.3.0] bicyclic ring system. Polyhydroxylated pyrrolizidines, containing various numbers of hydroxy substituents at different carbons in the bicyclic structure, have been isolated from plant sources. Alexine,

isolated from the legume *Alexa leiopetala*, was the first pyrrolizidine found to bear a methyl substituent at C-3.<sup>47</sup> Australine (7a-*epi*-alexine) and four other epimers were isolated from the seeds of *Castanospermum australe*. Broussonetine N, a pyrrolizidine with a ten-carbon C-5 side chain was isolated from *Broussonetia kajinoki*.<sup>2</sup>



**Figure 1.4** Alexine, australine and broussonetine N.

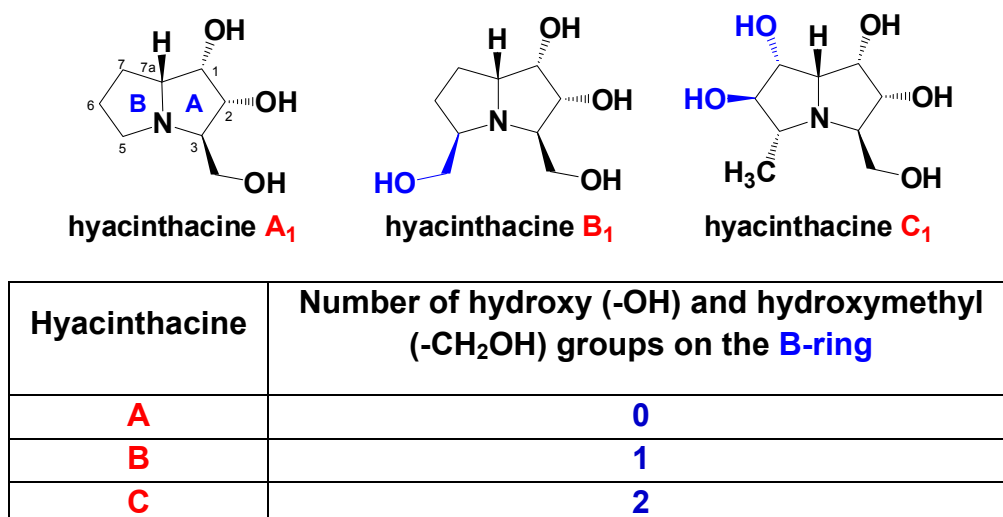
### 1.3.1 Hyacinthacines

In the past ten years, a large number of new polyhydroxylated pyrrolizidine alkaloids with a C-3 hydroxymethyl substituent have been isolated from plants belonging to the *Hyacinthaceae* family. These natural products have thus been named as the hyacinthacine alkaloids.

#### 1.3.1.1 Isolation and biological activities

In 1999, the hyacinthacines B<sub>1</sub> (**98**) and B<sub>2</sub> (**101**) were isolated from the immature fruits and stalks of *Hyacinthoides non-scripta* (commonly known as bluebell), and hyacinthacine C<sub>1</sub> (**100**) was isolated from the bulbs of *Scilla campanulata*.<sup>48</sup> The structures and relative stereochemistry of these new alkaloids were determined by NMR spectroscopic methods. The hyacinthacines B<sub>1</sub> and B<sub>2</sub> were found to be weak inhibitors of  $\beta$ -glucosidase, and while both diastereomers were inhibitors of  $\beta$ -galactosidase, hyacinthacine B<sub>2</sub> was much more potent ( $IC_{50} = 3.6 \mu M$ ) than hyacinthacine B<sub>1</sub> ( $IC_{50} = 270 \mu M$ ). Hyacinthacine C<sub>1</sub> was found to be a weak amyloglucosidase inhibitor ( $IC_{50} = 84 \mu M$ ).

The categorization of different hyacinthacines into the groups A, B, and C depends on the number of hydroxy and hydroxymethyl substituents on the B ring of the pyrrolizidine system (Figure 1.3).



**Figure 1.3.** Categorization of hyacinthacines according to the number hydroxyl or hydroxymethyl groups.

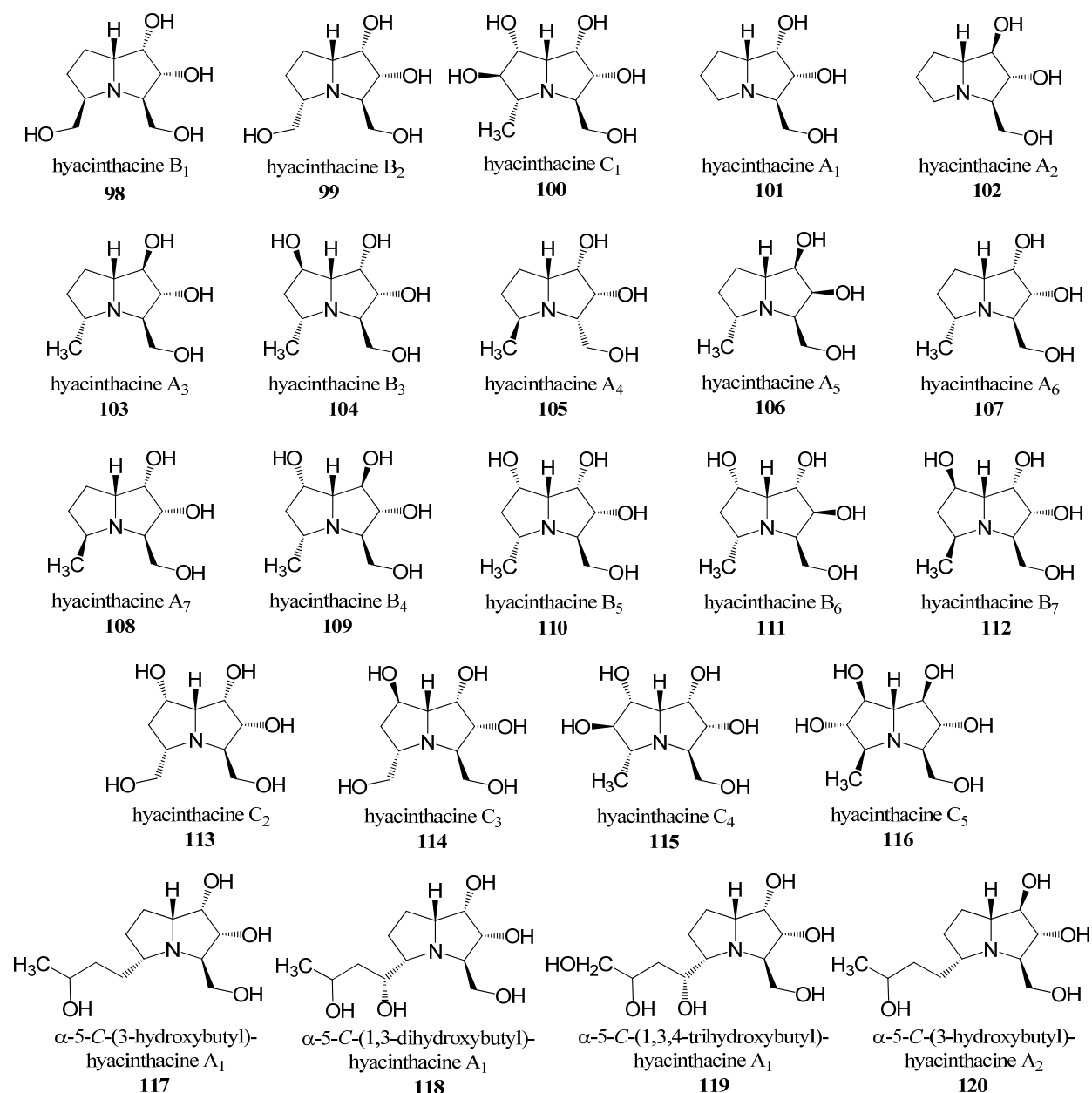
In 2000, four new hyacinthacines, A<sub>1</sub> (**101**), A<sub>2</sub> (**102**), A<sub>3</sub> (**103**) and B<sub>3</sub> (**104**) (Figure 1.4), were isolated from the fresh bulbs of the Hyacinthaceae plant *Muscari armeniacum*.<sup>49</sup> Hyacinthacine A<sub>1</sub> (**101**), which lacks the hydroxymethyl substituent in the C-5 position, exhibited similar inhibitory activities ( $IC_{50} = 4.4 \mu M$ ) towards  $\beta$ -galactosidase as hyacinthacine B<sub>2</sub> (**99**). Hyacinthacine A<sub>2</sub> (**102**) was found to be a weak inhibitor of the  $\beta$ -glucosidase and trehalase enzymes, and along with hyacinthacine A<sub>3</sub>, showed moderate inhibition ( $IC_{50} = 8.6$  and  $17 \mu M$ , respectively) towards an amyloglucosidase and weak inhibition towards a  $\beta$ -galactosidase. Hyacinthacine B<sub>3</sub> was found to be a moderate inhibitor of  $\beta$ -galactosidase ( $IC_{50} = 18 \mu M$ ) and was a weak amyloglucosidase inhibitor ( $IC_{50} = 51 \mu M$ ).

In 2002, the hyacinthacines A<sub>4</sub> (**105**), A<sub>5</sub> (**106**), A<sub>6</sub> (**107**), A<sub>7</sub> (**108**), B<sub>4</sub> (**109**), B<sub>5</sub> (**110**) and B<sub>6</sub> (**111**) (Figure 1.4) were isolated from the bulbs of *Scilla sibirica*.<sup>50</sup> Of these alkaloids, only hyacinthacine A<sub>5</sub> ( $IC_{50} = 110 \mu M$ ), B<sub>4</sub> ( $IC_{50} = 89 \mu M$ ) and A<sub>5</sub> ( $IC_{50} = 110 \mu M$ ) showed inhibitory activities towards an amyloglucosidase and hyacinthacine B<sub>4</sub> was also found to be a moderate  $\alpha$ -L-fucosidase inhibitor ( $IC_{50} = 23 \mu M$ ).

In 2004, three hyacinthacines with a C-5 butyl substituent, namely  $\alpha$ -5-C-(3-hydroxybutyl)-hyacinthacine A<sub>1</sub> (**117**),  $\alpha$ -5-C-(1,3-dihydroxybutyl)-hyacinthacine A<sub>1</sub> (**118**) and  $\alpha$ -5-C-(1,3,4-trihydroxybutyl)-hyacinthacine A<sub>1</sub> (**119**) were isolated from the bulbs of *Scilla peruviana* (Figure 1.3).<sup>51</sup>  $\alpha$ -5-C-(1,3-Dihydroxybutyl)-hyacinthacine A<sub>1</sub> was found to be a good inhibitor of bacterial  $\beta$ -glucosidase ( $IC_{50} = 5.1 \mu M$ ) and yeast  $\alpha$ -



glucosidase ( $IC_{50} = 3.6 \mu M$ ), whereas  $\alpha$ -5-C-(1,3,4-Trihydroxybutyl)-hyacinthacine A<sub>1</sub> was a less potent bacterial  $\beta$ -glucosidase ( $IC_{50} = 11 \mu M$ ) inhibitor.



**Fig. 1.4 Natural hyacinthacines**

More recently in 2007, the hyacinthacines B<sub>7</sub> (112), C<sub>2</sub> (113), C<sub>3</sub> (114), C<sub>4</sub> (115), C<sub>5</sub> (116) and another C-5-butyl substituted hyacinthacine,  $\alpha$ -5-C-(3-hydroxybutyl)-hyacinthacine A<sub>2</sub> (120) (Figure 1.4) have been isolated from the bulbs of *Scilla socialis*.<sup>52</sup> The hyacinthacines C<sub>2</sub>, C<sub>3</sub> and C<sub>5</sub> were found to be moderate to weak inhibitors towards bacterial  $\beta$ -glucosidase, with  $IC_{50}$  values of 13, 25 and 48  $\mu M$ , respectively.

Hyacinthacine C<sub>2</sub> also exhibited a moderate inhibition (IC<sub>50</sub> = 17 μM) of the human placenta α-L-fucosidase enzyme. Hyacinthacine C<sub>3</sub> showed weak inhibition (IC<sub>50</sub> = 52 μM) towards bovine liver β-galactosidase. The C-5 butyl substituted hyacinthacine, α-5-C-(3-hydroxybutyl)-hyacinthacine A<sub>2</sub>, along with hyacinthacine B<sub>7</sub>, proved to be weak inhibitors of amyloglucosidase.

### 1.3.2 Total syntheses of hyacinthacines

The structure elucidation of newly isolated hyacinthacines has relied on extensive NMR spectroscopic analysis. To date no single crystal X-ray structure has been reported of these natural products, and their relative configuration has been established exclusively by NOESY NMR experiments and from a consideration of <sup>1</sup>H NMR vicinal coupling constants. Several research groups have therefore been prompted to establish the absolute configuration of various hyacinthacines by way of total synthesis.

Synthetic efforts towards hyacinthacines can be classified into three different types: (1) from ‘chiral pool’ precursors (sugars and sugar derivatives, amino acids and tartaric acid); (2) using a chiral auxiliary; and (3) using enzymatic resolution then diastereoselective synthesis.

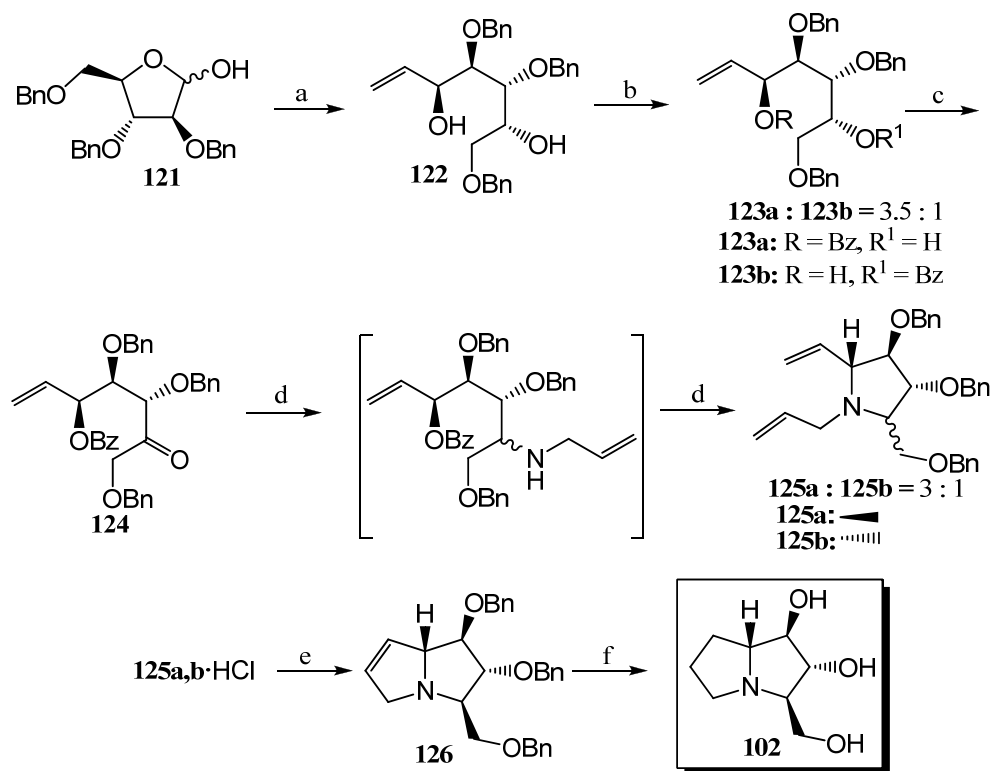
#### 1.3.2.1 Synthesis from ‘chiral pool’ precursors

##### *From sugars and sugar derivatives*

The first total synthesis of a hyacinthacine alkaloid reported was the synthesis of hyacinthacine A<sub>2</sub> **102** by Martin *et al.* in 2001 (Scheme 1.10).<sup>53</sup> This synthesis utilized commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose **121** as the starting material, which was subjected to a highly diastereoselective addition reaction of divinylzinc to give heptendiol **122** in 95% yield. Benzoylation of **122** was regioselective, favoring the less hindered allylic alcohol, giving a 3.5:1 mixture of **123a** and **123b**. Swern oxidation of the inseparable mixture of **123a** and **123b** gave the desired δ-keto benzoate **124**, which was separable from the other products. The ‘A-ring’ of the pyrrolizidine structure was built by a one-pot reaction that involved a reductive amination of **124** with allylamine, followed by an intramolecular nucleophilic displacement of the allylic benzoate ester by the secondary amine, giving epimeric dienes **125a** and **125b** as a 3:1 mixture. The ‘B-ring’ was formed by the RCM reaction of the HCl salts of the **125a,b** mixture with Grubbs’ I

catalyst. The isolated desired tetrahydropyrrolizidine **126** was then converted to the target molecule **102** (hyacinthacine A<sub>2</sub>) by hydrogenation/hydrogenolysis over 10% Pd/C under a H<sub>2</sub> atmosphere.

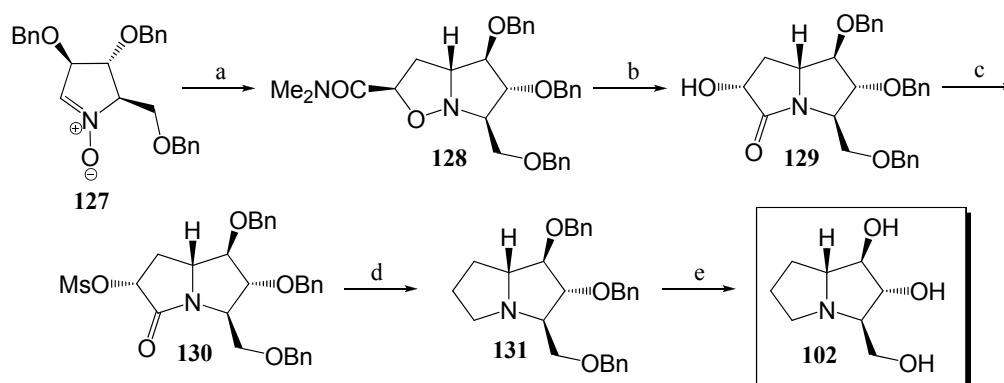
**Scheme 1.10**



*Reagents and conditions:* (a) (CH<sub>2</sub>=CH)<sub>2</sub>Zn, THF, 95%; (b) BzCl, *n*-Bu<sub>4</sub>NI, CH<sub>2</sub>Cl<sub>2</sub>/1 N NaOH (1:1), 0 °C, 3 h; (c) TFAA, DMSO, TEA, DCM, -78 °C to rt, 63%, 2 steps; (d) allylamine, AcOH, NaBH<sub>3</sub>CN, 3 Å MS, MeOH, 0 to 40 °C, 6 d, 78%; (e) Grubbs' I catalyst, toluene, 60 °C, 72 h, 30%; (f) H<sub>2</sub>, Pd/C, MeOH/THF/6 N HCl (4:1:0.25), rt, 20 h, 82%.

In 2003, Goti *et al.* furnished a total synthesis of hyacinthacine A<sub>2</sub> (**102**, Scheme 1.11) from the chiral cyclic nitron precursor **127**, which was synthesized from either L-xylose or D-arabinose.<sup>54</sup> The route using D-arabinose was deemed to be the preferred method due to its lower cost. The cyclic nitron **127** was subjected to a [3+2] cycloaddition reaction with *N,N*-dimethylacrylamide to give the required *anti-exo* adduct **128**. The reductive ring-opening of pyrroloisoxazolidine **128** gave lactam **129** in good yield. Mesylation of the hydroxy group on C-6, followed by reduction with LAH gave tribenzylated pyrrolizidine **131**, which was finally converted to hyacinthacine A<sub>2</sub> (**102**) via hydrogenolysis.

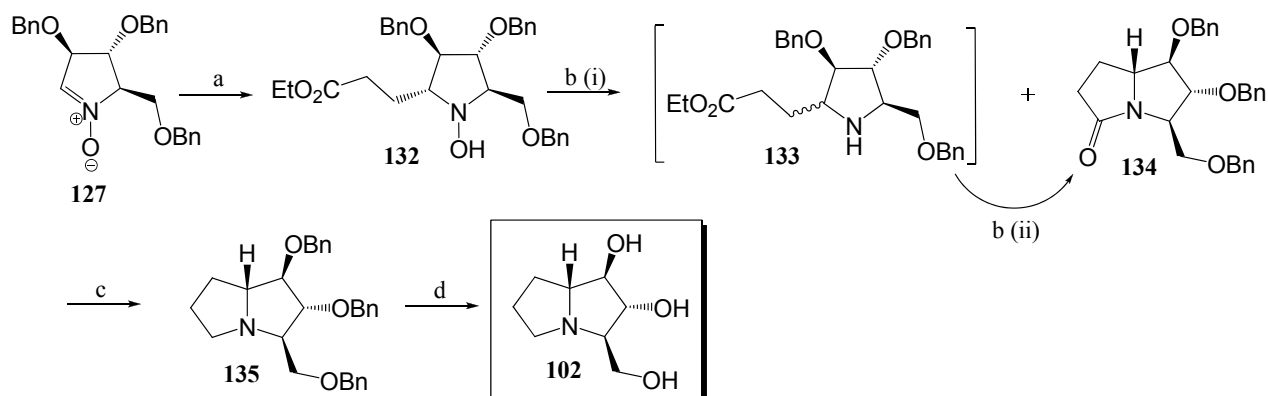
Scheme 1.11



*Reagents and conditions:* (a) *N,N*-dimethylacrylamide,  $\text{CH}_2\text{Cl}_2$ , rt, 78%; (b) Zn,  $\text{CH}_3\text{COOH}/\text{H}_2\text{O}$ , 50 °C, 4 h, 80%; (c) MsCl, TEA,  $\text{CH}_2\text{Cl}_2$ , rt, 2 h, 100%; (d)  $\text{LiAlH}_4$ , reflux, 1.5 h, 40%; (e)  $\text{H}_2$ , Pd/C, MeOH, rt, 3 d, 75%.

In 2004, Py *et al.* used the same chiral cyclic nitron **127** to accomplish another synthesis of hyacinthacine A<sub>2</sub> (**102**, Scheme 1.12).<sup>55</sup> This synthesis utilized an umpolung in the the C=N bond of the nitron induced by  $\text{SmI}_2$ , forming the  $\alpha$ -aza-nucleophilic intermediate, which coupled with ethyl acrylate to form the *N*-hydroxypyrrolidine **132**. Further reduction with  $\text{SmI}_2$  and nucleophilic cyclization formed pyrrolizidinone **134** with a diastereomeric ratio of 9:1 favoring H-7a in the configuration required for the final product. Reduction with  $\text{LiAlH}_4$  and debenzylation over Pd/C under a  $\text{H}_2$  atmosphere gave hyacinthacine A<sub>2</sub> (**102**). The relative configuration of the tribenzylate **135** was proven by X-ray diffraction studies.

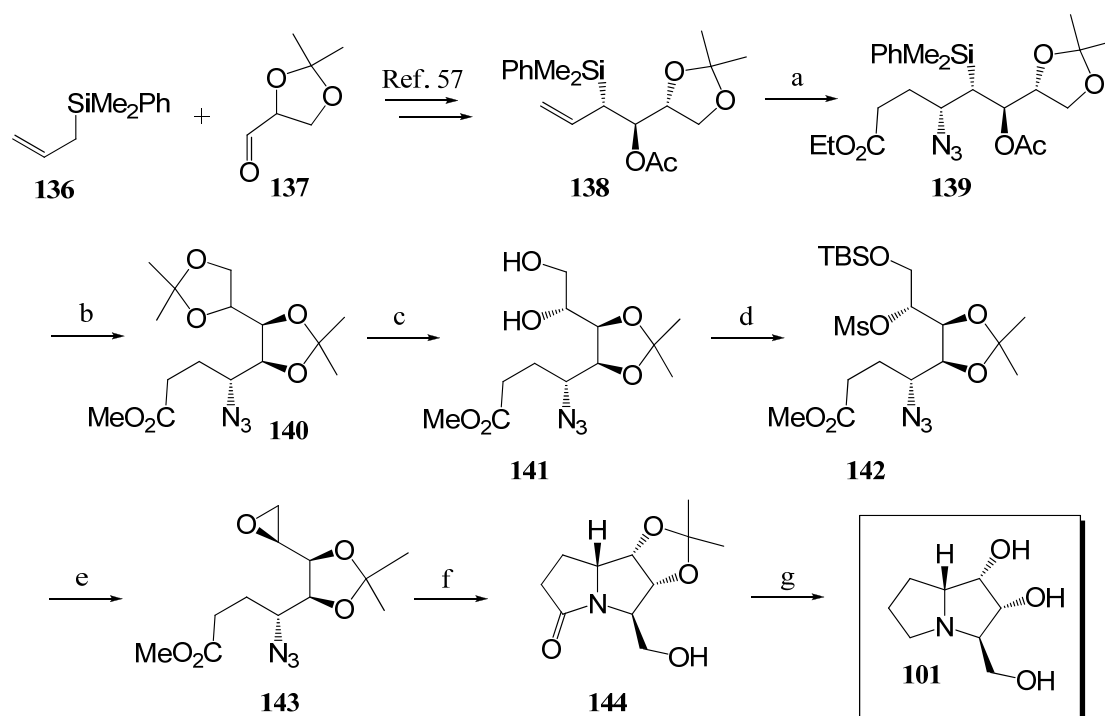
Scheme 1.12



*Reagents and conditions:* (a)  $\text{SmI}_2$ ,  $\text{H}_2\text{O}$ , ethyl acrylate,  $\text{H}_2\text{O}$ , THF, -78 °C, 3h, 64%, dr = 9:1; (b) (i)  $\text{SmI}_2$ , THF, -78 °C to rt, 24h, (ii)  $\text{K}_2\text{CO}_3$ , EtOH/ $\text{H}_2\text{O}$ , 59%, 3 steps, dr = 9:1; (c) excess  $\text{LiAlH}_4$ , THF, 66 °C, 1 h, 79%; (d) (i)  $\text{H}_2$ , Pd/C, MeOH, THF, 6 N HCl, rt, 4 d, (ii) Dowex 1x8.

In 2005, Renaud *et al.* reported the total syntheses of hyacinthacine A<sub>1</sub> (**101**) and 3-*epi*-hyacinthacine A<sub>1</sub> (**147**, Scheme 1.13).<sup>56</sup> The chiral allylsilane **138** used in these syntheses was prepared *via* the Roush allylation of the aldehyde **137**, a derivative of D-mannitol.<sup>57</sup> The free-radical carboazidation of **138** proceeded with good stereocontrol and gave **139** in 87% yield. The Tamao-Fleming oxidation of the silicon group of **139** was followed by hydrolysis, diol protection and transesterification to give bis-acetonide **140**. Selective deprotection of one of the acetonide groups with Zn(NO<sub>3</sub>)<sub>2</sub> gave diol **141**. Silylation of the primary alcohol and mesylation of the secondary alcohol afforded **142**. Desilylation and concomitant nucleophilic cyclization gave epoxide **143** and effected the first stereoinversion at the position which was to become C-3 of the final product. The azide in **143** was reduced to the amine over Pd/C under a H<sub>2</sub> atmosphere, and a cyclization-lactamization reaction upon treatment with Et<sub>3</sub>N furnished a second stereoinversion at C-3 and gave pyrrolizidinone **144**. Reduction of the lactam and acidic hydrolysis furnished hyacinthacine A<sub>1</sub> (**101**) in 13 steps from the chiral silane **138**.

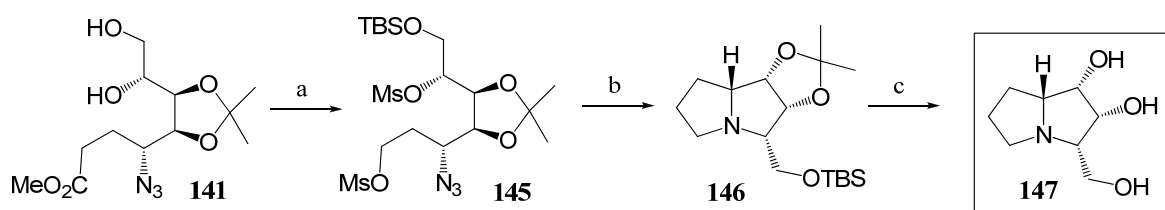
Scheme 1.13



*Reagents and conditions:* (a) EtOC(O)CH<sub>2</sub>S(C=S)OEt(Bu<sub>3</sub>Sn)<sub>2</sub>, *t*-BuON=NO*t*-Bu, PyrSO<sub>2</sub>N<sub>3</sub>, benzene, 60–80 °C, 74–87%, dr = 70:30 to 85:15; (b) (i) AcOOH, KBr, AcONa, 84%; (ii) DOWEX 1x10; (iii) Me<sub>2</sub>C(OMe)<sub>2</sub>, PTSA; (c) Zn(NO<sub>3</sub>)<sub>2</sub>, 55%, 3 steps; (d) (i) TBSCl, pyridine; (ii) MsCl, pyridine, 84%, 2 steps; (e) TBAF, CH<sub>2</sub>Cl<sub>2</sub>, then K<sub>2</sub>CO<sub>3</sub>, MeOH, 70%; (f) (i) Pd/C, H<sub>2</sub>, MeOH; (ii) Et<sub>3</sub>N, MeOH, 96%, 2 steps; (g) (i) LiAlH<sub>4</sub>, THF; (ii) HCl, MeOH, then DOWEX OH<sup>-</sup>, 65%, 2 steps.

The synthesis of 3-*epi*-hyacinthacine A<sub>1</sub> (**147**, Scheme 1.14) was largely similar to that of **101** except that only one stereoinversion at C-3 occurred throughout the synthesis. From the silyl ether of the diol **141**, the reduction of the ester function with LiBH<sub>4</sub> and mesylation reactions gave bismesylate **145**. Reduction of the azide in **145** to an amine and concomitant cyclizations gave pyrrolizidine **146**, deprotection reactions then gave 3-*epi*-hyacinthacine A<sub>1</sub> in 13 steps from the chiral silane **138**.

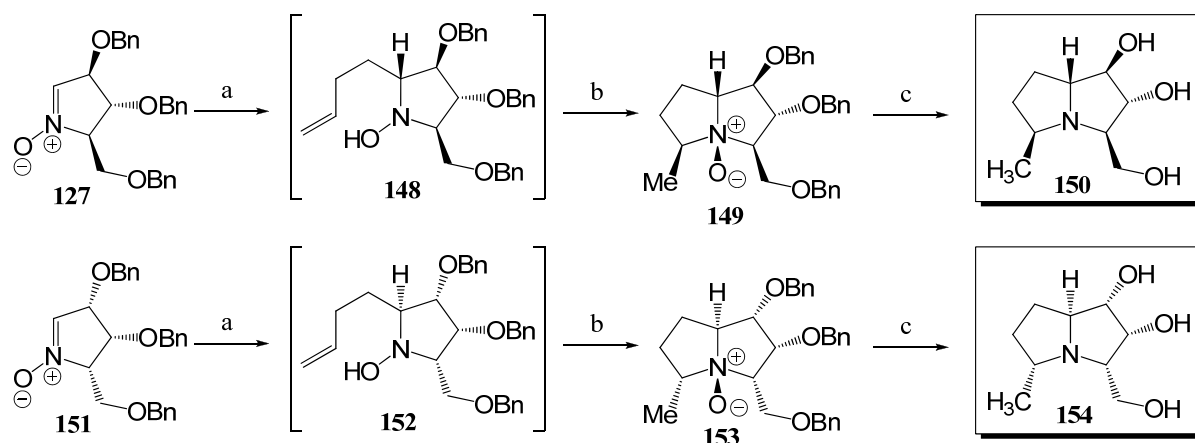
**Scheme 1.14**



*Reagents and conditions:* (a) (i) TBSCl, pyridine; (ii) LiBH<sub>4</sub>, THF; (iii) MsCl, pyridine, 73%, 3 steps; (b) Pd/C, H<sub>2</sub>, AcOEt, rt, 12 h; (c) (i) HCl, MeOH; (ii) DOWEX 1x10, 77%, 3 steps.

Another example of a hyacinthacine synthesis utilizing sugar derived chiral nitrones was Kaliappan's short syntheses of the two unnatural hyacinthacine analogues, 5-(+)-*epi*-hyacinthacine A<sub>3</sub> (**150**) and 5-(-)-*epi*-hyacinthacine A<sub>5</sub> (**154**) (Scheme 1.15).<sup>58</sup> The synthesis of **150** began with the chiral nitron **127**, derived from L-xylose. Grignard reaction of **127** with 3-butenylmagnesium bromide involved the alkenyl nucleophile attacking from a direction *anti* to the adjacent *O*-benzyl group. This gave the unstable hydroxylamine **148**, which underwent a Cope-House cyclization to form the pyrrolizidinyl *N*-oxide **149**. Global hydrogenolysis then furnished **150**. The same strategy was applied to the chiral nitron **151** in the synthesis of **154**.

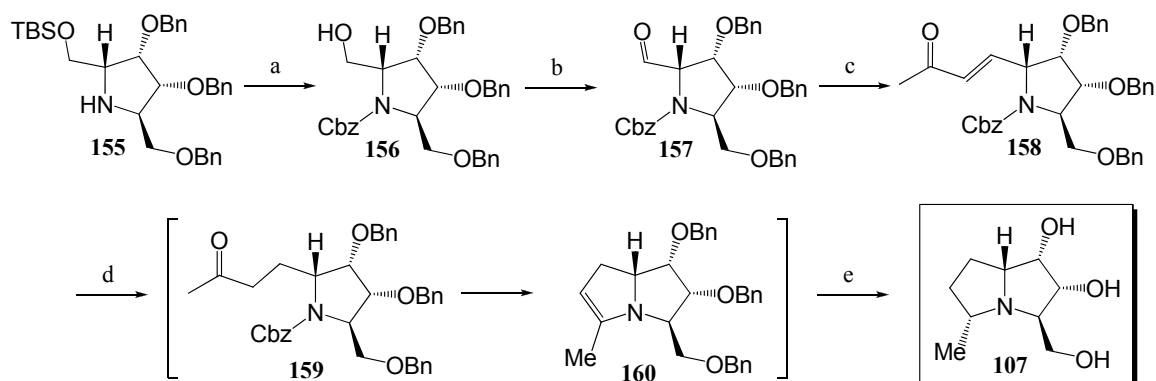
Scheme 1.15



*Reagents and conditions:* (a) 3-butenylmagnesium bromide, THF, -78 °C; (b) CHCl<sub>3</sub>, 24 h, 99% (**149**), 2 steps; 80% (**153**), 2 steps; (c) Pd/C (10%) H<sub>2</sub>, MeOH/THF (4:1), 6N HCl, 91% (**150**); 99% (**154**).

In 2008, Cao *et al.* reported a synthesis of hyacinthacine A<sub>6</sub> (**107**), which began with the D-glucose-derived chiral pyrrolidine **155** (Scheme 1.16).<sup>59</sup> This synthetic strategy was similar to that developed by Izquierdo that will be discussed in Schemes 1.17 to 1.28. Desilylation and Cbz protection of **155** gave alcohol **156**, which was oxidized under Swern reaction conditions to give aldehyde **157**. Wittig reaction of **157** with 1-triphenylphosphoranylidene-2-propanone afforded the  $\alpha,\beta$ -unsaturated ketone **158**. Hydrogenation with 10 % Pd/C and high pressure H<sub>2</sub> formed the intermediate **159** and was followed by Cbz deprotection and concomitant cyclization to give the 5,6-dihydropyrrolizidine **160**. Continued hydrogenation resulted in saturation of the enamine function from the less hindered convex face of **160** that secured the C-5 configuration of the target molecule. Finally, removal of the benzyl protecting groups gave hyacinthacine A<sub>6</sub> (**107**) in 40% overall yield from **155**.

Scheme 1.16



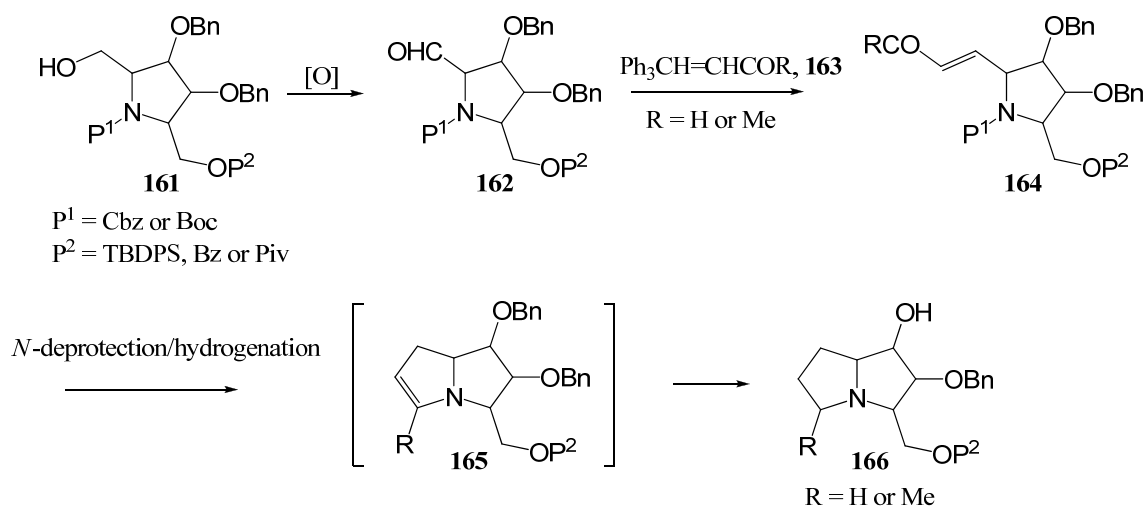
*Reagents and conditions:* (a) (i) TBAF•3H<sub>2</sub>O, THF, rt; (ii) CbzCl, Na<sub>2</sub>CO<sub>3</sub>, THF/H<sub>2</sub>O, rt, 83%, 2 steps; (b) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N, -78 °C, 91%; (c) Ph<sub>3</sub>P=CHCOCH<sub>3</sub>, toluene, reflux, 70%; (d) 10%, Pd/C, H<sub>2</sub> (4x10<sup>5</sup> Pa), MeOH; (e) 10%, Pd/C, H<sub>2</sub> (4x10<sup>5</sup> Pa), HCl, MeOH, 3 d, then Amberlite IRA-400 (OH<sup>-</sup> form), 40%, 2 steps.

Since 2001, Izquierdo *et al.* published a series of papers on the syntheses of natural polyhydroxylated pyrrolizidine alkaloids and their analogues, of which a vast majority<sup>60-67</sup> were hyacinthacines. The starting compounds used in these syntheses were various protected polyhydroxypyrrolidines (Table 1.1).<sup>68-72</sup>

Izquierdo and co-workers' general syntheses of the hyacinthacine alkaloids can be summarized in the general scheme, Scheme 1.17. Protected polyhydroxypyrrolidines **161** (specifically the compounds **167** to **171** in Table 1.1), which were prepared from carbohydrates, served as A-ring precursors from which to attach the B-ring. To construct the B-ring, the unprotected hydroxymethyl moiety of the polyhydroxypyrrolidine precursor was generally oxidized into an aldehyde, and then a Wittig reaction served as a chain lengthening step, which also installed a carbonyl tether for the subsequent nucleophilic cyclization by the deprotected amine. The Wittig reaction allowed the introduction of an  $\alpha,\beta$ -unsaturated aldehyde (R = H) or methyl ketone (R = Me) into the C-2 side chain of the pyrrolidines **164**. Under hydrogenation/hydrogenolysis conditions, the proposed bicyclic enamine intermediate **165** was formed that underwent hydrogenation to provide protected versions of the natural or unnatural hyacinthacines **166**.

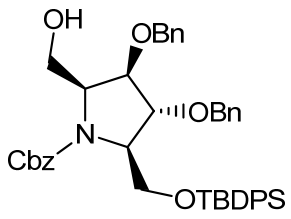
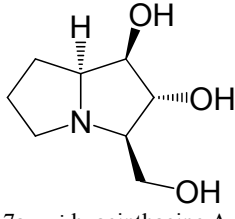
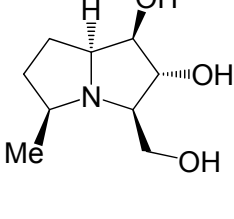
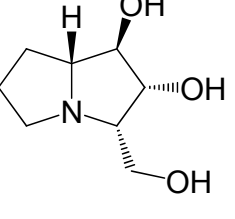
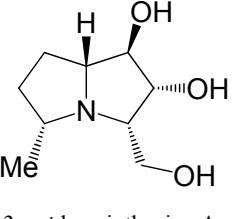
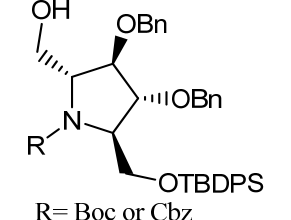
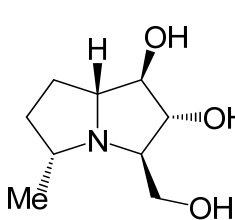
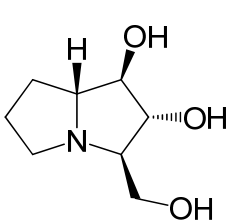
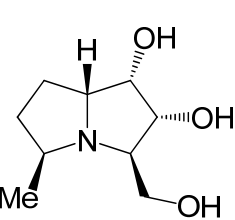
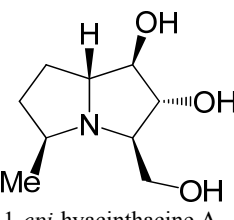
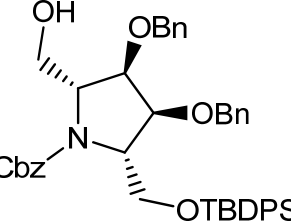
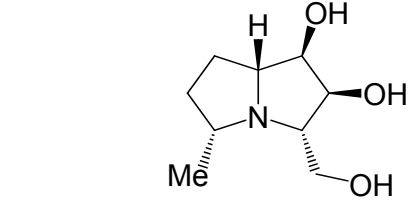
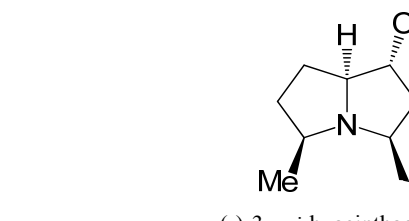
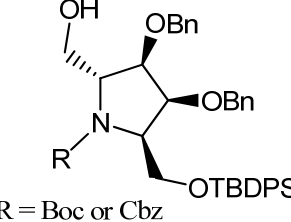
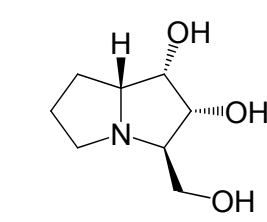
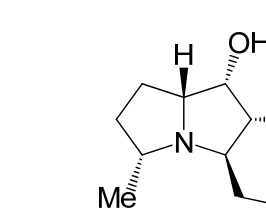
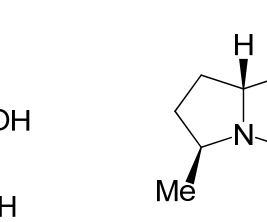
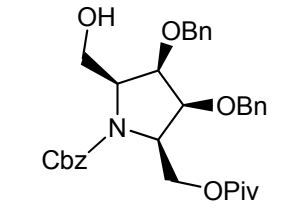
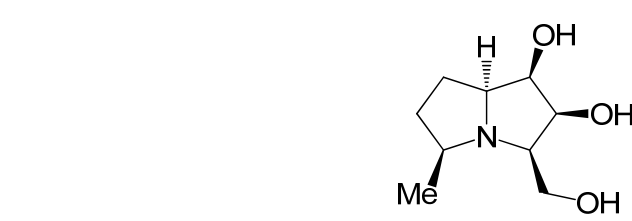


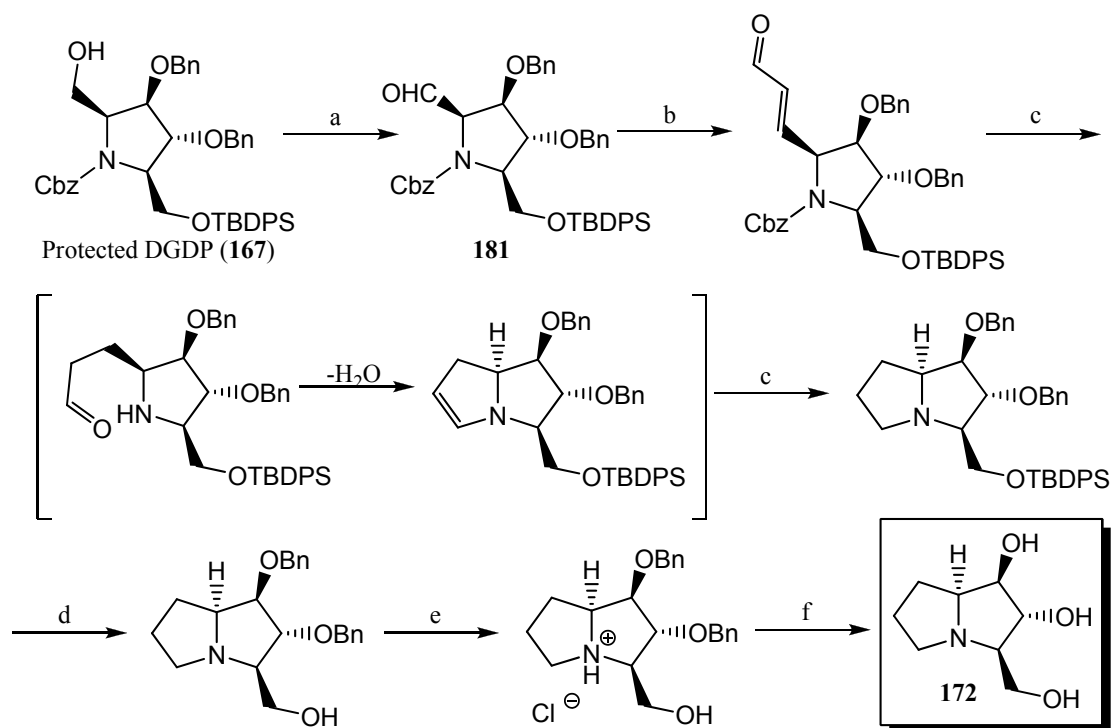
Scheme 1.17



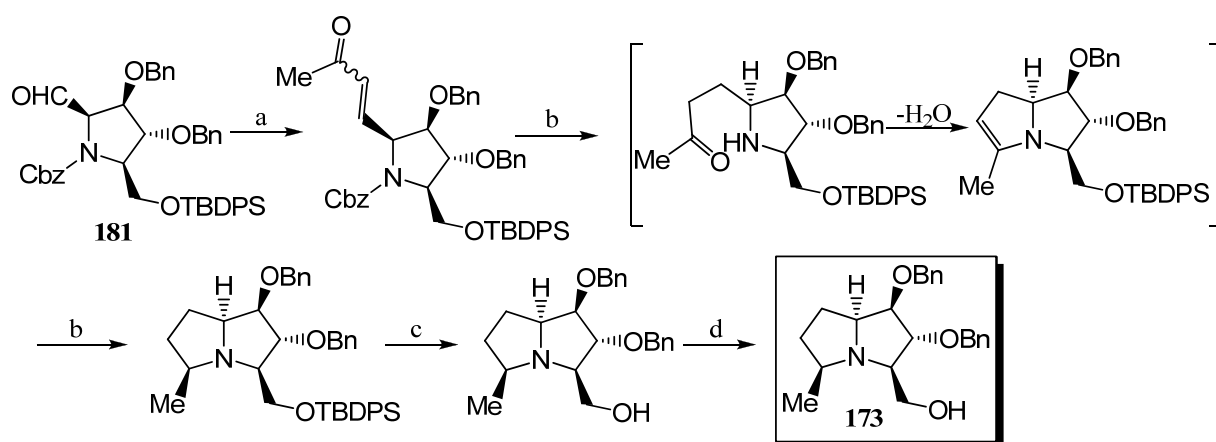
In the syntheses shown in Schemes 1.19, 1.20, 1.22 and 1.24 to 1.27, hydrogenation resulted in the delivery of hydrogen from the less hindered convex face of an intermediate similar to **165** ( $\text{R} = \text{Me}$ ). In Scheme 1.26, however, hydrogenation from the concave face of such an intermediate was reported while hydrogenation of **187** in Scheme 1.28 resulted in a 1:1 mixture of C-5 epimeric products. The exact reasons for the stereochemical outcomes of these latter two results were not made clear. In a related approach by Marco *et al.* (Scheme 1.32)<sup>73</sup>, a similar intramolecular reductive alkylation also gave a 1:1 mixture of C-5 epimer pyrrolizidine products. In 2007, Izquierdo's group reported the synthesis of (+)-hyacinthacines **A**<sub>1</sub> and **A**<sub>6</sub>,<sup>66</sup> however this paper was retracted in 2009.<sup>74</sup> These latter two syntheses, therefore, will not be discussed. The details of the synthetic contributions of this group to hyacinthacine synthesis are illustrated in Schemes 1.18 to 1.28.

**Table 1.1.** Protected polyhydroxypyrrolidine precursors and the respective products in Izquierdo's syntheses of hyacinthacines.

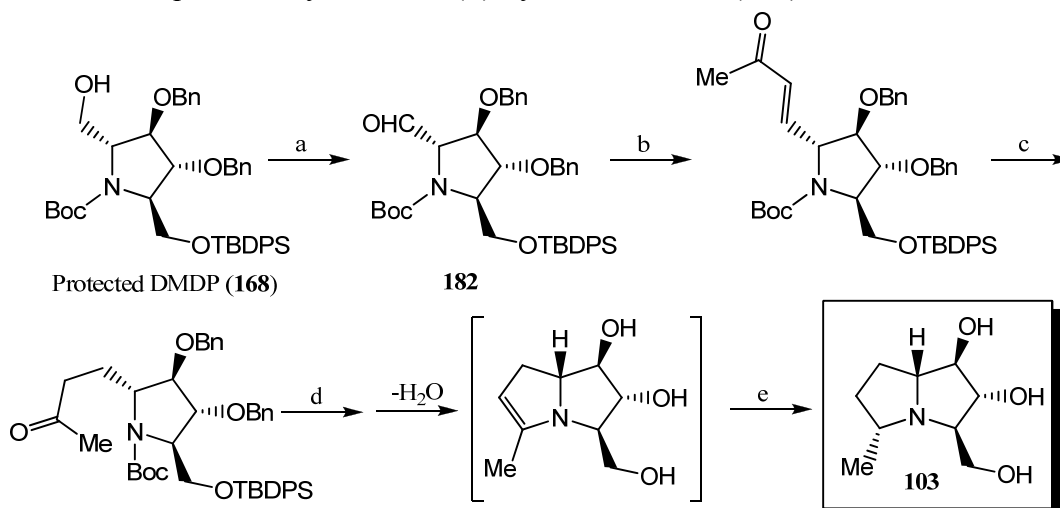
Pyrrolidine precursors	Hyacinthacine products
 <p>Partially protected DGDP (<b>167</b>)</p>	    <p><i>7a-epi</i>-hyacinthacine A<sub>2</sub> (<b>172</b>)      <i>5,7a-di-epi</i>-hyacinthacine A<sub>3</sub> (<b>173</b>)      <i>3-epi</i>-hyacinthacine A<sub>2</sub> (<b>174</b>)      <i>3-epi</i>-hyacinthacine A<sub>3</sub> (<b>175</b>)</p>
 <p>R = Boc or Cbz Partially protected DMDP (<b>168</b>)</p>	    <p>hyacinthacine A<sub>3</sub> (<b>103</b>)      hyacinthacine A<sub>2</sub> (<b>102</b>)      hyacinthacine A<sub>7</sub> (<b>108</b>)      <i>1-epi</i>-hyacinthacine A<sub>7</sub> (<b>176</b>)</p>
 <p>Partially protected DADP (<b>169</b>)</p>	  <p>(+)-<i>3-epi</i>-hyacinthacine A<sub>5</sub> (<b>177</b>)      (-)-<i>3-epi</i>-hyacinthacine A<sub>5</sub> (<b>178</b>)</p>
 <p>R = Boc or Cbz Partially protected DALDP (<b>170</b>)</p>	   <p>(+)-hyacinthacine A<sub>1</sub> (<b>101</b>)      (+)-hyacinthacine A<sub>6</sub> (<b>107</b>)      (+)-<i>5-epi</i>-hyacinthacine A<sub>5</sub> (<b>179</b>)</p>
 <p>Partially protected DGADP (<b>171</b>)</p>	 <p>(+)-<i>5-epi</i>-hyacinthacine A<sub>4</sub> (<b>180</b>)</p>

**Scheme 1.18** Izquierdo's synthesis of 7a-*epi*-hyacinthacine A<sub>2</sub> (**172**)<sup>60</sup>

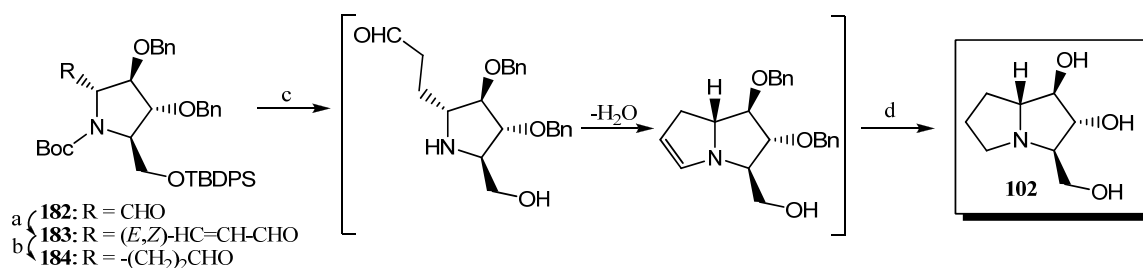
*Reagents and conditions:* (a) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS, 95%; (b) Ph<sub>3</sub>P=CHCHO, CH<sub>2</sub>Cl<sub>2</sub>, 44%; (c) H<sub>2</sub>, 10% Pd/C, 45%; (d) TBAF, THF, 59%; (e) H<sub>2</sub>, 10% Pd/C, MeOH, HCl, 93%; (f) Amberlite IRA-400 (OH<sup>-</sup> form), 76%.

**Scheme 1.19** Izquierdo's synthesis of 5,7a-di-*epi*-hyacinthacine A<sub>3</sub> (**173**)<sup>60</sup>

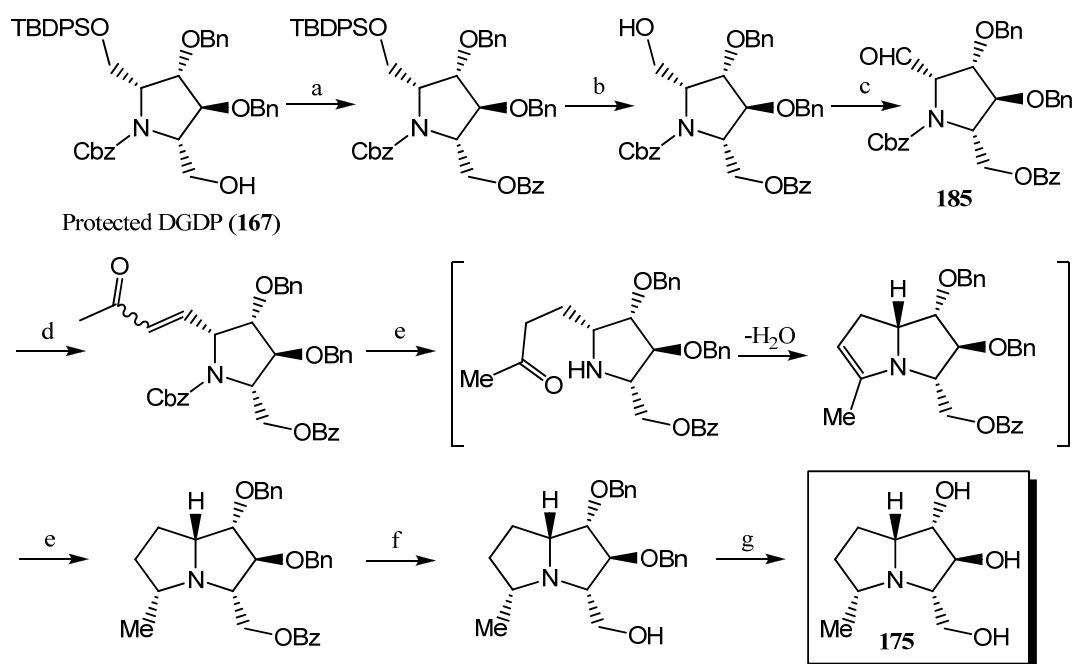
*Reagents and conditions:* (a) Ph<sub>3</sub>P=CHCOCH<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, reflux, 81%; (b) H<sub>2</sub>, 10% Pd/C, 60%; (c) TBAF, THF, 85%; (d) H<sub>2</sub>, 10% Pd/C, MeOH, HCl then Amberlite IRA-400 (OH<sup>-</sup> form), 83%.

**Scheme 1.20** Izquierdo's synthesis of (+)-hyacinthacine A<sub>3</sub> (**103**)<sup>61</sup>

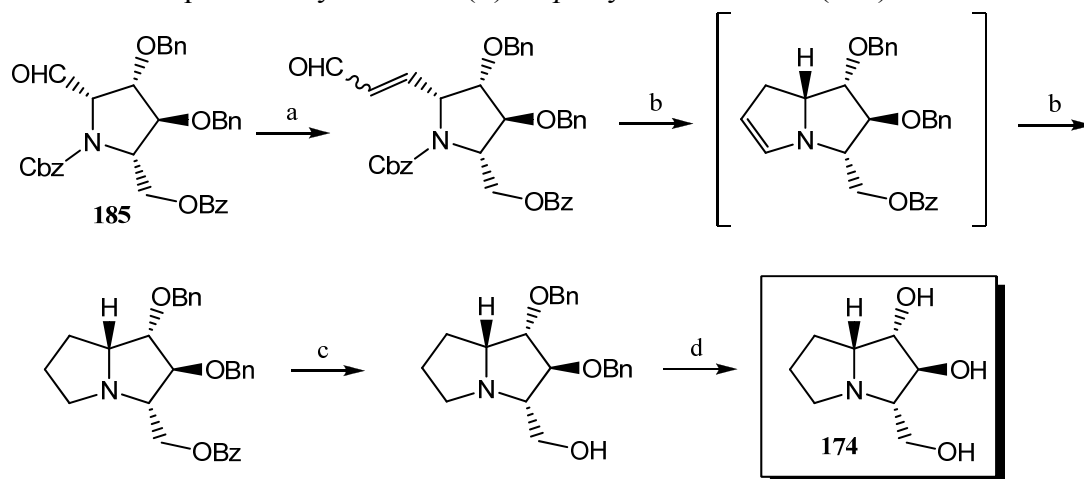
*Reagents and conditions:* (a) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS; (b) Ph<sub>3</sub>P=CHCOCH<sub>3</sub>, PhMe, reflux, quant., 2 steps; (c) H<sub>2</sub>, 10% Pd/C; (d) H<sub>2</sub>, 10% Pd/C, HCl; (e) H<sub>2</sub>, 10% Pd/C then Amberlite IRA-400 (OH<sup>-</sup> form), 70%, 3 steps.

**Scheme 1.21** Izquierdo's synthesis of (+)-hyacinthacine A<sub>2</sub> (**102**)<sup>62</sup>

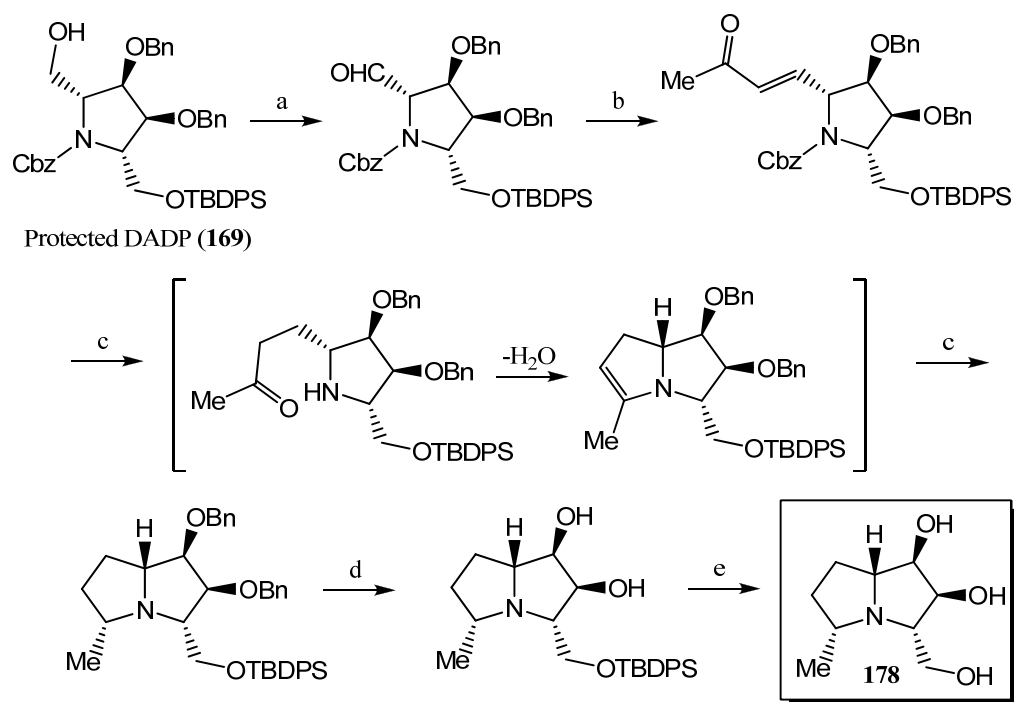
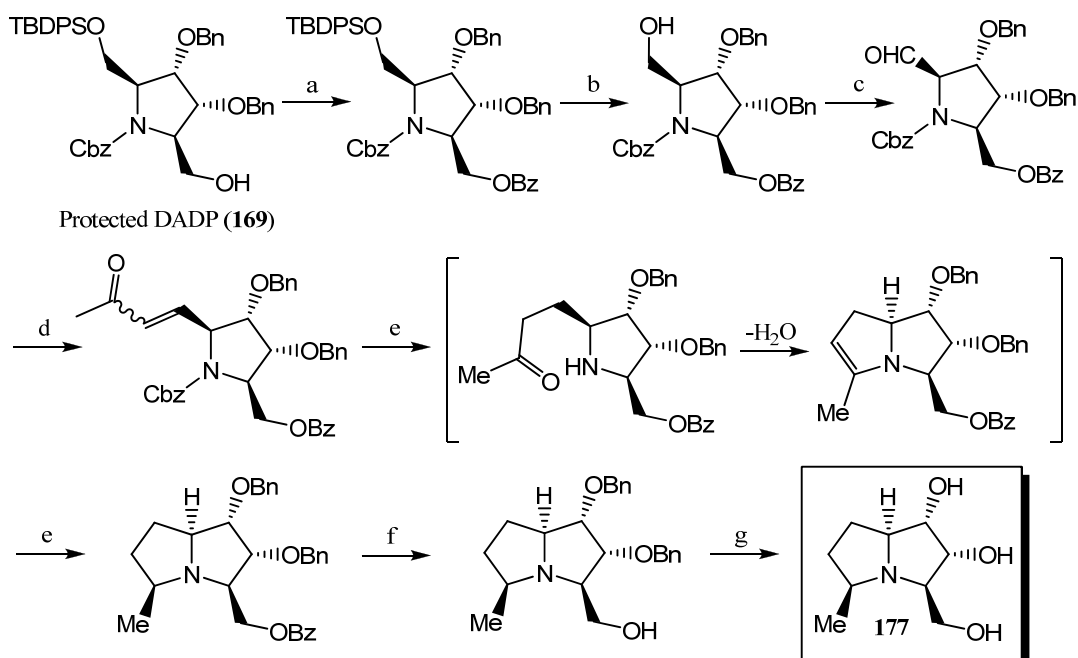
*Reagents and conditions:* (a) Ph<sub>3</sub>P=CHCHO, PhMe, reflux, 57%; (b) H<sub>2</sub>, 10% Pd/C; (c) HCl, then Amberlite IRA-400 (OH<sup>-</sup> form); (d) 10% Pd/C, HCl, then Amberlite IRA-400 (OH<sup>-</sup> form), 26%, 3 steps.

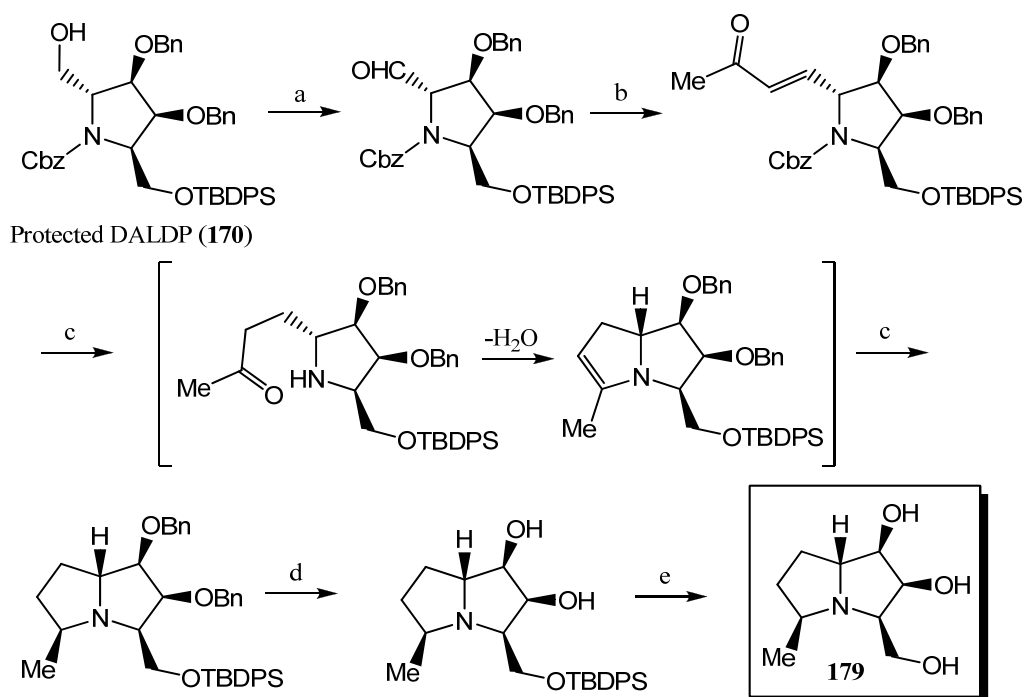
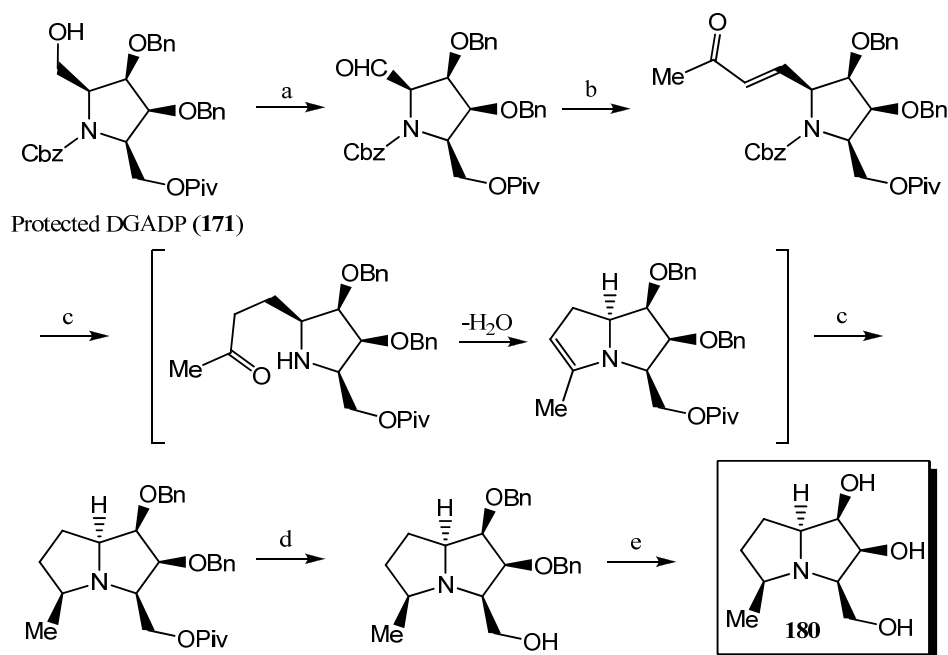
**Scheme 1.22** Izquierdo's synthesis of (+)-3-*epi*-hyacinthacine A<sub>3</sub> (**175**)<sup>63</sup>

*Reagents and conditions:* (a) BzCl, CH<sub>2</sub>Cl<sub>2</sub>, TEA, quant.; (b) TBAF, THF, quant.; (c) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 4 Å MS; (d) Ph<sub>3</sub>PCHCOCH<sub>3</sub>, PhMe, reflux, 90%, 2 steps; (e) H<sub>2</sub>, 10% Pd/C, MeOH, 90%; (f) NaOMe, MeOH; (g) H<sub>2</sub>, 10% Pd/C, HCl, then Amberlite IRA-400 (OH<sup>-</sup> form), 64%, 2 steps.

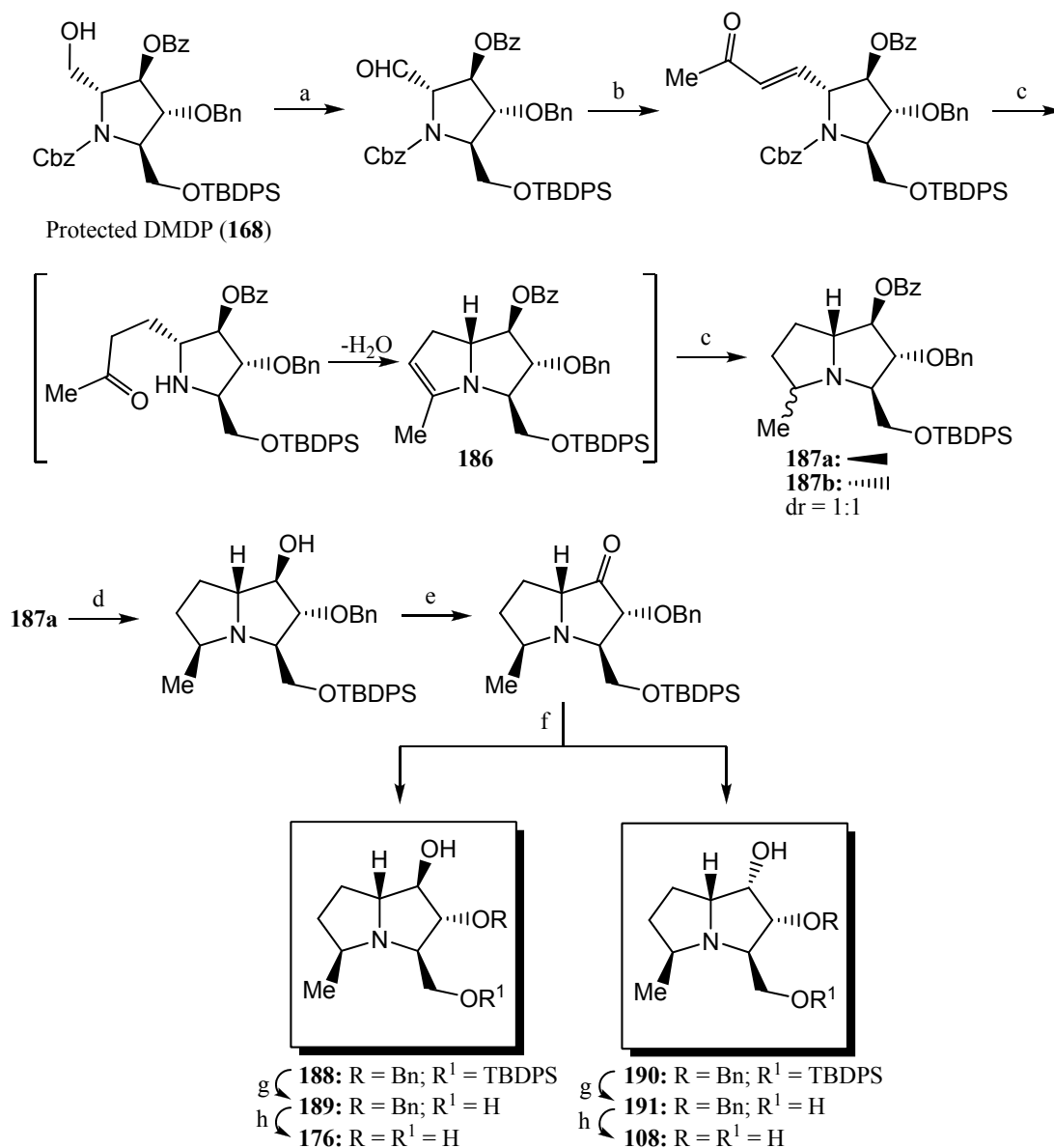
**Scheme 1.23** Izquierdo's synthesis of (+)-3-*epi*-hyacinthacine A<sub>2</sub> (**174**)<sup>63</sup>

*Reagents and conditions:* (a) Ph<sub>3</sub>PCHCHO, PhMe, 60 °C, 67%; (b) H<sub>2</sub>, 10% Pd/C, MeOH, 55%; (c) NaOMe, MeOH, 92%; (d) H<sub>2</sub>, 10% Pd/C, HCl, then Amberlite IRA-400 (OH<sup>-</sup> form), 80%.

**Scheme 1.24** Izquierdo's synthesis of (-)-3-*epi*-hyacinthacine A<sub>5</sub> (**178**)<sup>64</sup>**Scheme 1.25** Izquierdo's synthesis of (+)-3-*epi*-hyacinthacine A<sub>5</sub> (**177**)<sup>64</sup>

**Scheme 1.26** Izquierdo's synthesis of (+)-5-*epi*-hyacinthacine A<sub>5</sub> (**179**)<sup>65</sup>**Scheme 1.27** Izquierdo's synthesis of (+)-5-*epi*-hyacinthacine A<sub>4</sub> (**180**)<sup>65</sup>

**Scheme 1.28** Izquierdo's synthesis of (-)-1-*epi*-hyacinthacine A<sub>7</sub> (**176**) and (-)-hyacinthacine A<sub>7</sub> (**108**)<sup>67</sup>



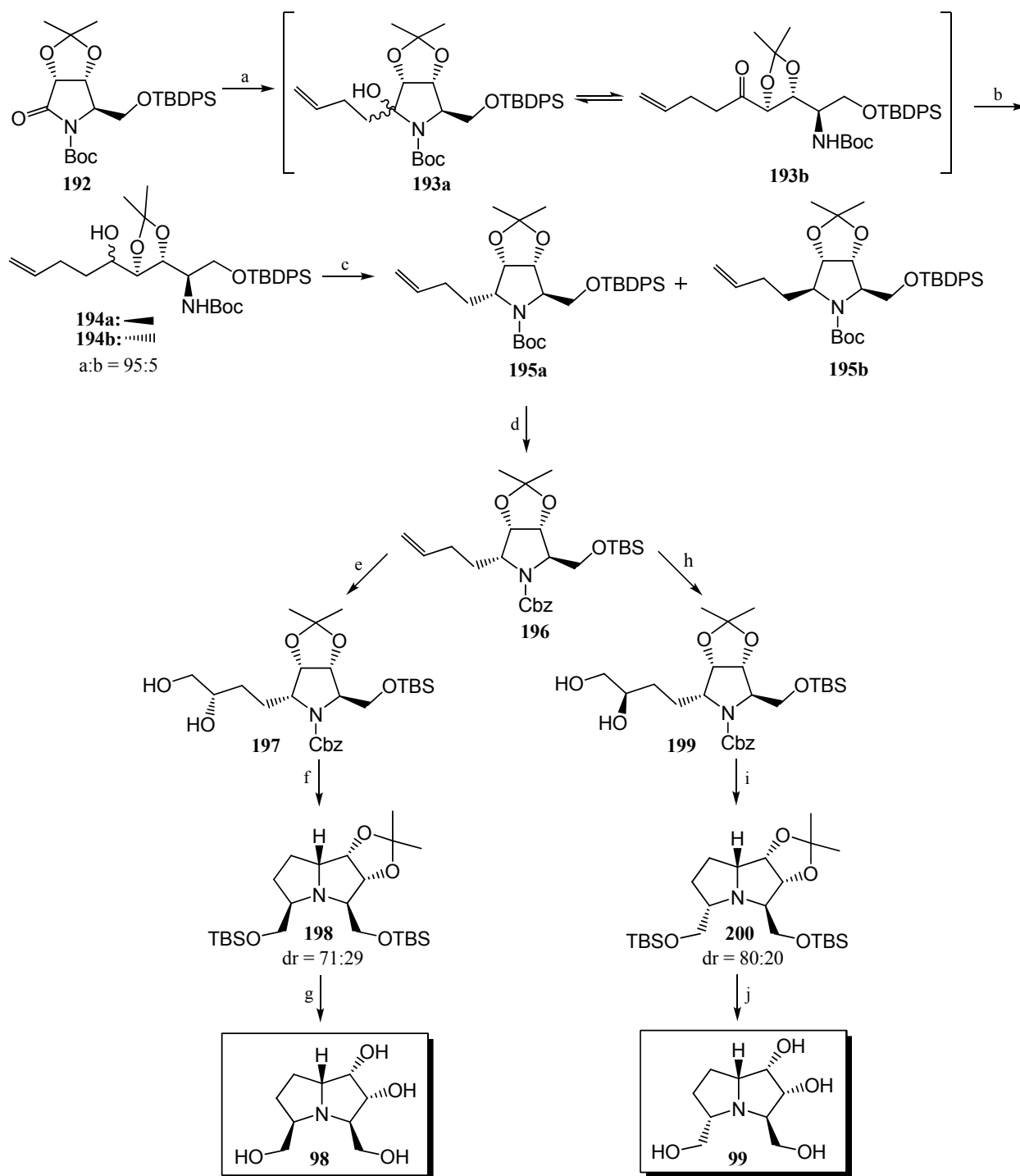


### *From Amino Acid Derivatives*

Amino acid derivatives are another source of starting materials selected from the chiral pool for hyacinthacine synthesis. In 2008, Yoda *et al.* reported the synthesis of the (+)-hyacinthacines B<sub>1</sub> (**98**) and B<sub>2</sub> (**99**) from a derivative of (*S*)-(-)-pyroglutamic acid. Starting from *N*-Boc lactam **192** in a chain-lengthening Grignard reaction, the resulting hydroxyl pyrrolidine **193a**, which upon reduction with NaBH<sub>4</sub> in EtOH, gave predominantly (95:5) the desired alcohol **194**. Mesylation and cyclization with *t*-BuOK gave a separable mixture of pyrrolidines **195a,b**. The change of the *N*- and *O*- protecting groups, through a high-yielding sequence, was required for easier purification in subsequent steps. The Sharpless ADH of **196** with AD-mix- $\alpha$  proceeded with moderate diastereoselectivity (**197a**:**197b** = 71:29). The diol mixture **197a,b** was then subjected to silylation of the primary alcohol, mesylation of the secondary alcohol, *N*-deprotection and concomitant cyclization to give a separable diastereomeric mixture of **198a** and **198b**. Deprotection reactions with TBAF and TFA gave hyacinthacine B<sub>1</sub> (**98**) in 15 steps from **192**.

Subjecting pyrrolidine **196** to Sharpless ADH with AD-mix- $\beta$  and followed by the same subsequent steps, hyacinthacine B<sub>2</sub> (**99**) was synthesized in 15 steps from **192**.

Scheme 1.29



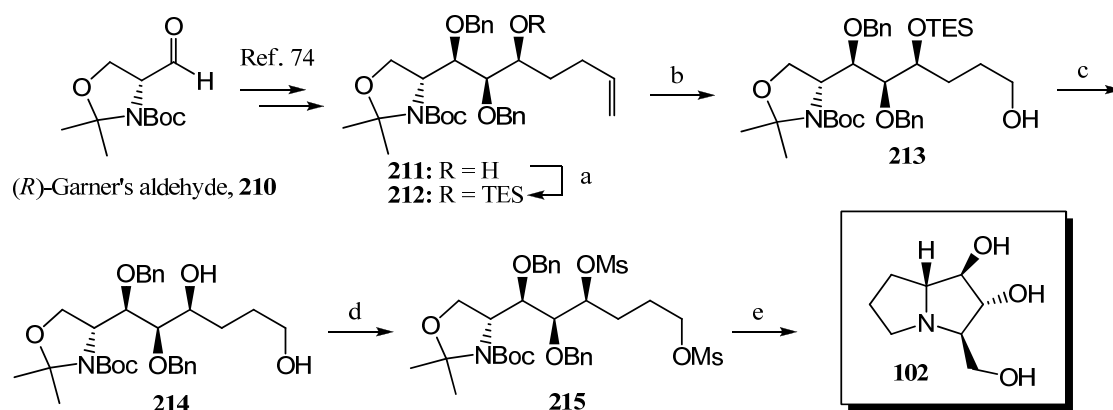
*Reagents and conditions:* (a)  $\text{CH}_2=\text{CH}(\text{CH}_2)_2\text{MgBr}$ , THF, rt, 5 min; (b)  $\text{NaBH}_4$ ,  $\text{CeCl}_3$ , EtOH, 0 °C, 4h, quant., 2steps; (c) (i)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (ii)  $t\text{-BuOK}$ , THF, 96%, 2 steps; (d) (i) TBAF, THF, quant.; (ii)  $\text{NaH}$ , THF, rt, 2h, quant.; (iii)  $\text{CbzCl}$ ,  $\text{NaHCO}_3$ , MeOH, 97%; (iv)  $\text{TBSCl}$ , imidazole, DMF, 97%; (e) AD-mix- $\alpha$ ,  $t\text{-BuOH}/\text{H}_2\text{O}$  (1:1), 0 °C, 48 h, 98%; (f) (i)  $\text{TBSCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 97%; (ii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 92%; (iii)  $\text{H}_2$ , Pd/C, EtOH, 97%; (g) (i) TBAF, THF, 97%; (ii) TFA,  $\text{H}_2\text{O}$ , 92%; (h) AD-mix- $\beta$ ,  $t\text{-BuOH}/\text{H}_2\text{O}$  (1:1), 0 °C, 24 h, 98%; (i) (i)  $\text{TBSCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 97%; (ii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 92%; (iii)  $\text{H}_2$ , Pd/C, EtOH, 99%; (j) (i) TBAF, THF, 97%; (ii) TFA,  $\text{H}_2\text{O}$ , 94%.

In 2009, Yoda *et al.* reported the synthesis of hyacinthacines C<sub>2</sub> (**113**) and C<sub>3</sub> (**114**) and their C-5 epimers **208** and **209**, respectively (Scheme 1.30). In these syntheses, the *N*-Boc lactam **192** was first subjected to a series of reactions which included the Grignard reaction, the 1,2-reduction of an unsaturated ketone and a diastereomeric cyclization to give *N*-Boc-**201**. In three steps *N*-Boc-**201a** was converted to *N*-Cbz-**201b**, which was then subjected to oxidative cleavage with OsO<sub>4</sub> and NaIO<sub>4</sub> to give the aldehyde **202**. Allylation of **202** under Reformatsky-type conditions then gave a 79:21 separable mixture of **203a,b**. After TBS protection of the hydroxyl group of **203a**, dihydroxylation of the terminal olefin and subsequent TBS protection of the primary alcohol gave a 1:1 mixture of diastereomers **204a,b**. Mesylation of the secondary alcohol in **204a,b**, followed by Cbz-deprotection and concomitant cyclization afforded **205a,b**. Finally, global *O*-deprotection gave hyacinthacine C<sub>2</sub> (**113**) and 5-*epi*-hyacinthacine C<sub>2</sub> (**208**). Using **203b**, the same strategy was followed for the synthesis of hyacinthacine C<sub>3</sub> (**114**) and 5-*epi*-hyacinthacine C<sub>2</sub> (**209**).



oxidative cleavage and reduction to give alcohol **213**. Desilylation with TBAF and mesylation gave bismesylate **215**, which was then subjected to a one-pot cleavage of the Boc and aminoacetal groups with HCl. Debenzylolation over Pd/C under a H<sub>2</sub>, followed by base treatment then gave hyacinthacine A<sub>2</sub> (**102**).

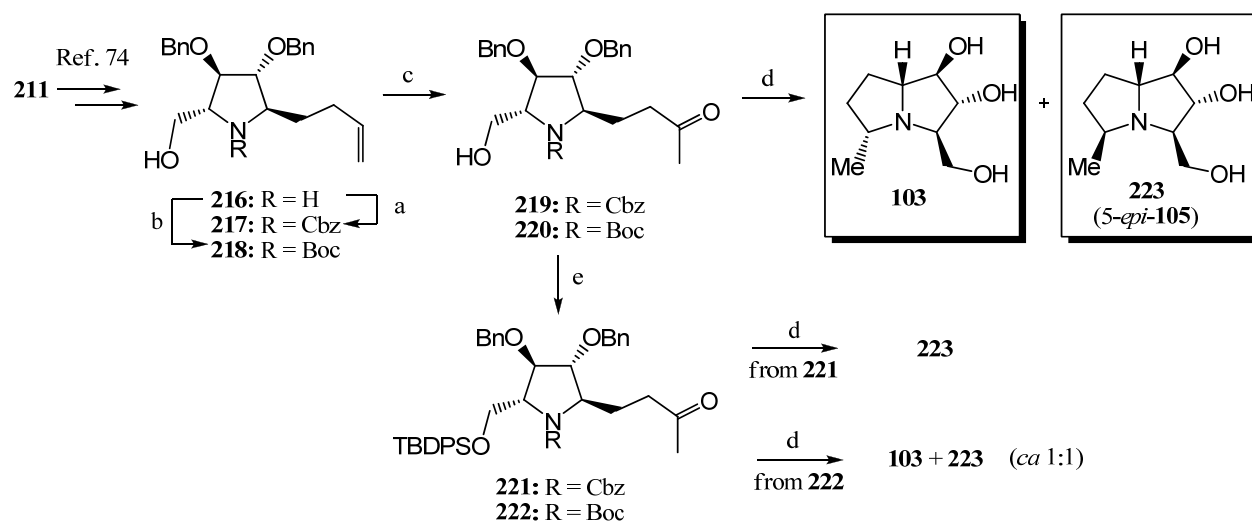
### Scheme 1.31



*Reagents and conditions:* (a) TESCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h, 87%; (b) (i) OsO<sub>4</sub>, NMO, *t*-BuOH, aq. THF, rt, 2 h; (ii) aq NaIO<sub>4</sub>, rt, 2 h; (iii) NaBH<sub>4</sub>, MeOH, 0 °C, 1.5 h, 70%, 3 steps; (c) TBAF, THF, rt, 40 min, 99%; (d) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h; (e) (i) 6 M HCl/MeOH (1:10), 10% Pd/C, H<sub>2</sub>, 40 h, RT; (ii) NH<sub>4</sub>OH, MeOH, 62 %, 3 steps.

In the synthesis of hyacinthacine A<sub>3</sub> (**103**) and 5-*epi*-hyacinthacine A<sub>3</sub> (**223**), **211** was first converted into the pyrrolidinol **216** in a two step process.<sup>75</sup> Wacker oxidation of the Cbz and Boc derivatives of **216** gave, respectively, methyl ketones **219** and **220**. The hydrogenolysis reactions of **219** and **220** both gave mixtures of **103** and **223** (5-*epi*-**103**) in variable ratios (dr **103**:**223** = 1.2:1 to 0:1), depending upon whether acid (HCl) was added before or after the hydrogenolysis reaction. An alternative route to synthesizing the final products was pursued by first protecting **219** and **220** as the TBDPS ethers **221** and **222**, respectively. Hydrogenolysis of **221** and concomitant cyclization gave almost exclusively **223**, while **222** gave *ca.* a 1:1 mixture of **103** and **223** (Scheme 1.32). This disparity in stereoselectivity was not fully understood.<sup>73</sup>

Scheme 1.32



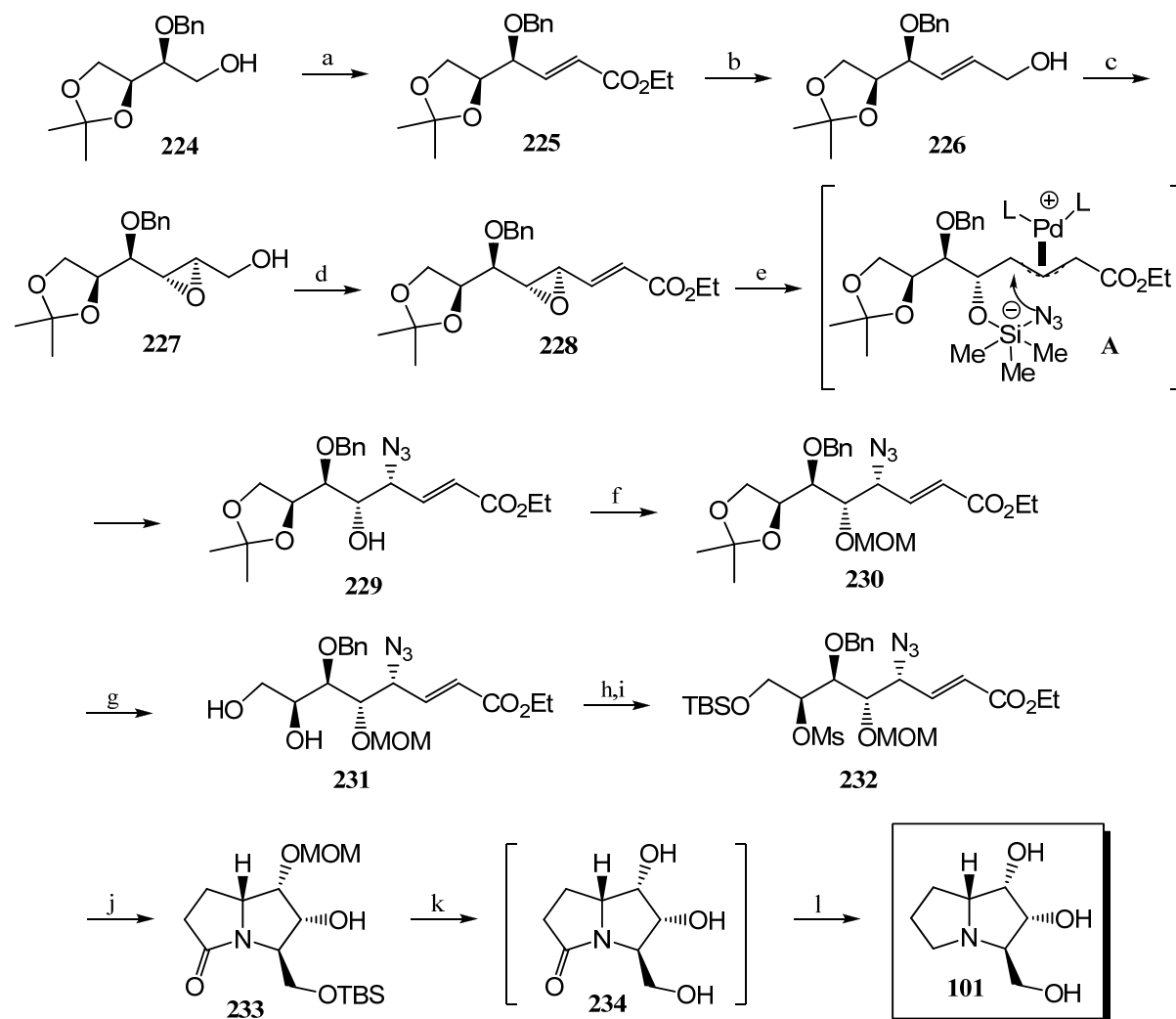
*Reagents and conditions:* (a) CbzCl, Na<sub>2</sub>CO<sub>3</sub>, aq. THF, RT, 93%; (b) Boc<sub>2</sub>O, Et<sub>3</sub>N, 68%; (c) PdCl<sub>2</sub>, CuCl, aq DMF, O<sub>2</sub>, 88% (**219**), 86% (**220**); (d) aq. HCl/MeOH (1:10), H<sub>2</sub>, Pd/C, RT, 2d; (e) TBDPSCl, imidazole, 88-90%.

### From Tartaric acid

In addition to amino acids, the diethyl ester of tartaric acid was used in the synthesis of hyacinthacine A<sub>1</sub> (**101**) as reported in 2008 by Chandrasekhar *et al.* (Scheme 1.33).<sup>76</sup> The synthesis began with the oxidation of the (+)-diethyl tartrate derivative **224** into an aldehyde. This was followed by a chain-lengthening Wittig reaction with Ph<sub>3</sub>P=CHOCO<sub>2</sub>Et to give the  $\alpha,\beta$ -unsaturated ester **225**, which was then reduced to the alcohol **226** with DIBAL-H. The Sharpless asymmetric epoxidation of the alkene in **226** with (-)-DET gave epoxide **227** in greater than 98% de and ee. The IBX oxidation and Wittig chain-lengthening reactions were repeated to give the  $\alpha,\beta$ -unsaturated  $\gamma,\delta$ -epoxy ester **228**. The ring-opening-azidation reaction of the epoxide in **228** was achieved with retention of configuration at the azidation site, having Pd(0) first complexing with the  $\alpha,\beta$ -olefin (intermediate **A** in Scheme 1.33) followed by azide attack to give the *syn*-azido alcohol **229**. A series of protecting group manipulations gave the secondary alcohol **231**, which was then converted into the mesylate **232**. Reduction of the azide in **232** to an amine under H<sub>2</sub> over Pd/C, followed by treatment with K<sub>2</sub>CO<sub>3</sub>, triggered the intramolecular S<sub>N</sub>2 displacement and amidation reactions to form the A and B rings, respectively, of the pyrrolizidone **233**. Global hydrogenolysis, PTSA deprotection of the

MOM and silyl protecting groups and reduction of the lactam with  $\text{LiAlH}_4$  gave hyacinthacine A<sub>1</sub> (**101**).

**Scheme 1.33**



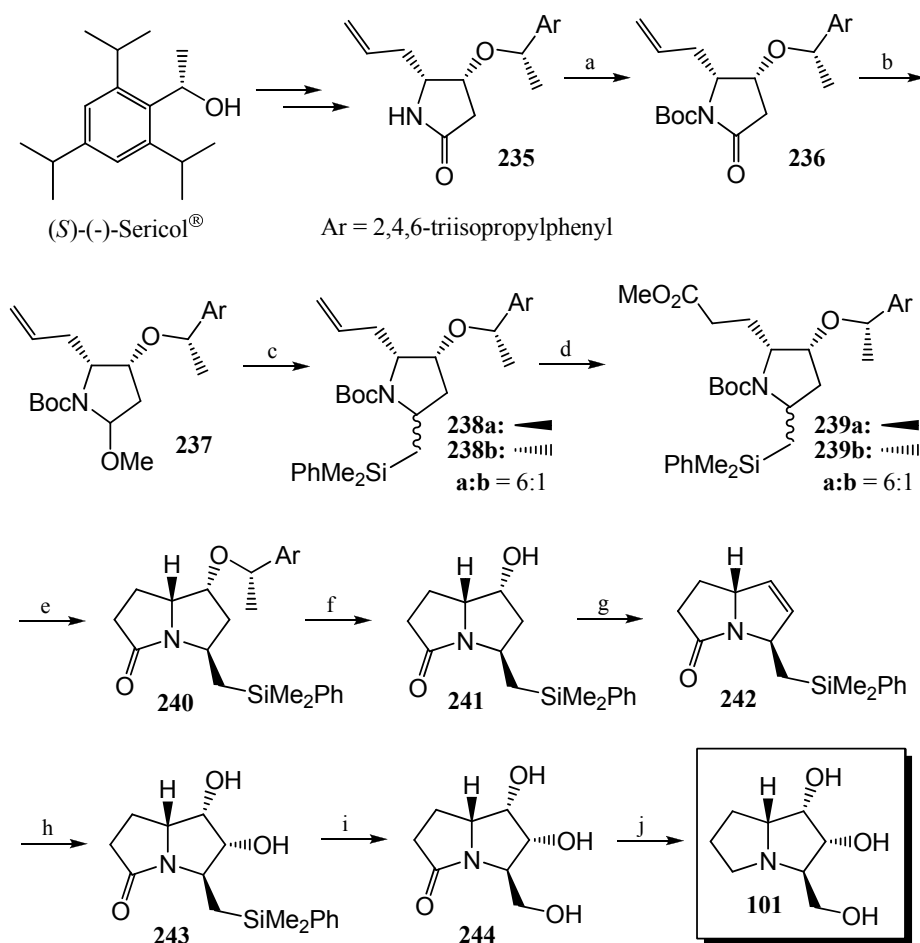
*Reagents and conditions:* (a) (i) IBX, EtOAc, reflux, 3 h; (ii)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt, 30 min, 90%, 2 steps; (b) DIBALH, THF, -10 °C to 0 °C, 1 h, 96%; (c) (-)-DET,  $\text{Ti}(\text{O}i\text{-Pr})_4$ , TBHP,  $\text{CH}_2\text{Cl}_2$ , -23 °C, 10 h, 93 %; (d) (i) IBX, EtOAc, reflux, 3h; (ii)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ , benzene, °C to rt, 10 min, 90%, 2 steps; (e)  $\text{TMSN}_3$ ,  $\text{Pd}^0$ ; (f) MOMCl, DIPEA,  $\text{CH}_2\text{Cl}_2$ , rt, 48 h, 77%; (g) PPTS, MeOH, rt, 24 h, 74%; (h) TBSCl, imidazole,  $\text{CH}_2\text{Cl}_2$ , rt, 30 min, 78%; (i) MsCl,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , -10 °C, 10 min, 88%; (j) (i)  $\text{H}_2$ , Pd/C, EtOH, rt, 12 h; (ii)  $\text{K}_2\text{CO}_3$ , EtOH,  $\text{H}_2\text{O}$ , reflux, 2 h, 65%; (k) PTSA, MeOH, rt, 12 h; (l)  $\text{LiAlH}_4$ , THF, reflux, 2 h, 58 %, 2 steps.

### 1.3.2.2 Using a chiral auxiliary

In 2008 and 2009, Delair *et al.* reported, respectively, the syntheses of (+)-hyacinthacine A<sub>1</sub> (**101**)<sup>77</sup> and (+)-hyacinthacine B<sub>1</sub> (**98**)<sup>76</sup> starting from the lactam **235** derived from the chiral auxiliary (*S*)-(-)-stericol<sup>®</sup>.<sup>78,79</sup> In the synthesis of **101**, the chiral lactam **235** was first *N*-protected to give carbamate **236**. Reduction with lithium triethylborohydride (Super Hydride<sup>®</sup>) followed by reaction with MeOH/PTSA gave the hemiaminal **237**, which reacted in a copper(I) salt-catalyzed Grignard reaction to diastereoselectively (6:1) install a surrogate hydroxymethyl group at the C-3 position of the hyacinthacine target. The epimeric pyrrolidine mixture **238a,b** underwent hydroboration, oxidation and esterification to give a mixture (6:1) of esters **239a,b**. After *N*-deprotection with TMSOTf, only the major diastereomer cyclized to form pyrolizidinone **240**. The selectivity in the cyclization reaction was attributed to the steric interactions between the ester side chain and the surrogate hydroxymethyl group of the minor diastereomer. The hydroxyl group in the C-1 position was removed by first converting the alcohol into a xanthate followed by pyrolysis to afford alkene **242**. *cis*-Dihydroxylation gave exclusively diol **243**, resulting from reaction with OsO<sub>4</sub> from the concave face of the molecule. The hydroxymethyl group on C-3 was installed by a Tamao-Fleming oxidation. Finally borane reduction of **244** gave **101** in 6.5 % overall yield (Scheme 1.34).

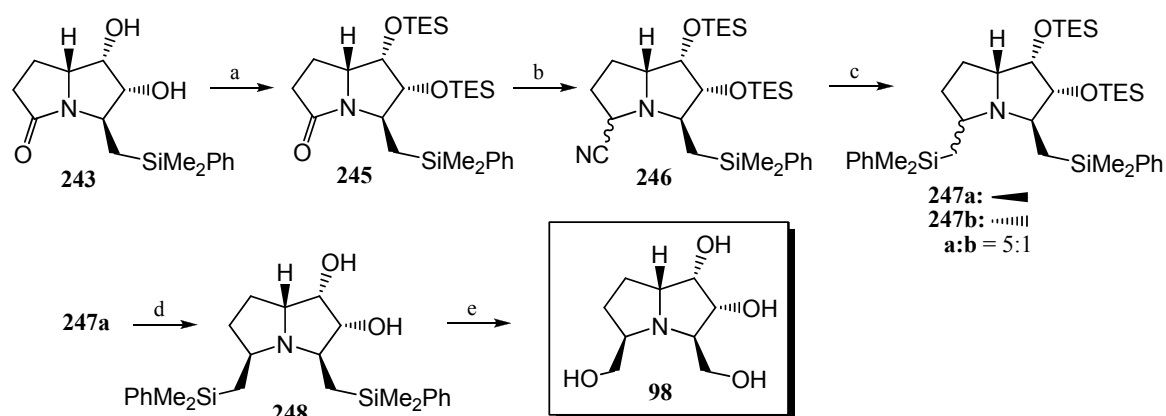


Scheme 1.34



The synthesis of **98** followed the same synthetic route from the chiral lactam **235** up to the diol **243**. Triethylsilylation followed by DIBAL-H reduction and *in situ* treatment with TMSCN gave an epimeric mixture of aminonitriles **246**. To install a second hydroxymethyl surrogate at the C-5 position, the nitriles **246** were subjected to a Grignard reaction to give a separable 5:1 mixture of the pyrrolizidines **247a,b**. After *O*-desilylation of **247a** to give the diol **248**, a double Tamao-Fleming oxidation gave **98** (Scheme 1.35).

Scheme 1.35

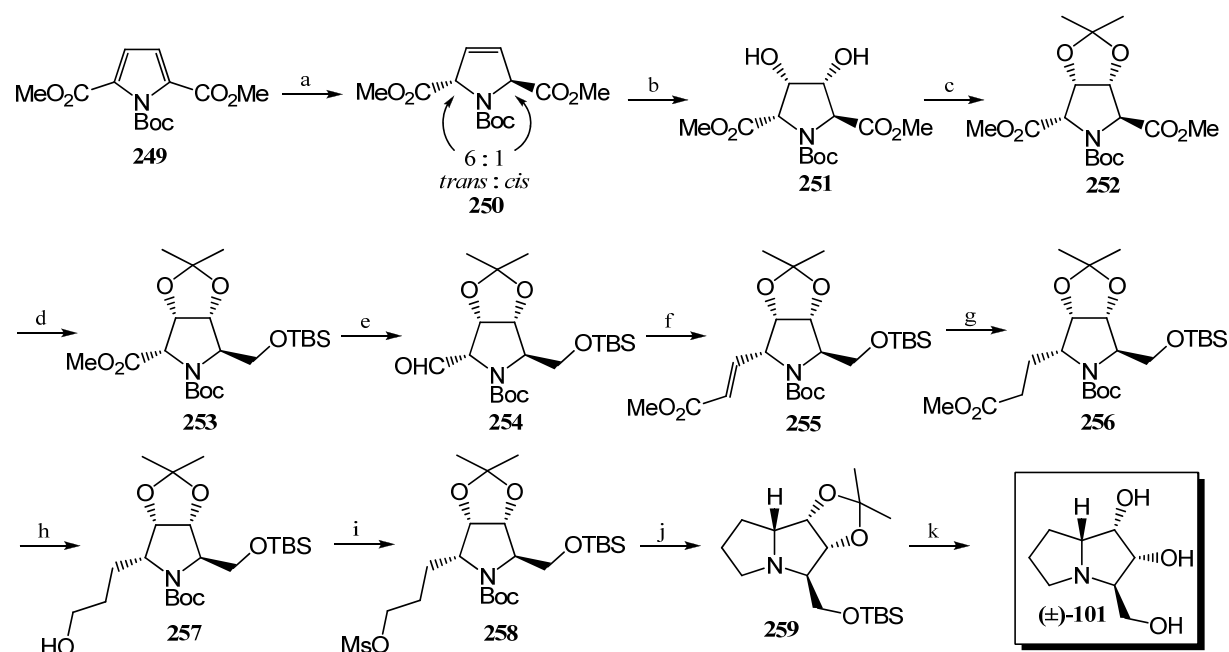


Reagents and conditions: (a) TESCl, imidazole, 94%; (b) DIBAL-H, BuLi, TMSCN, 89%; (c) PhMe<sub>2</sub>SiCH<sub>2</sub>MgCl, THF-Et<sub>2</sub>O; (d) TBAF, 68%, 2 steps; (e) (i) HBF<sub>4</sub>•OMe<sub>2</sub>, KOH (aq); (ii) H<sub>2</sub>O<sub>2</sub>, KF, DMF, 61%.

### 1.3.2.3 Synthesis from non-chiral precursors

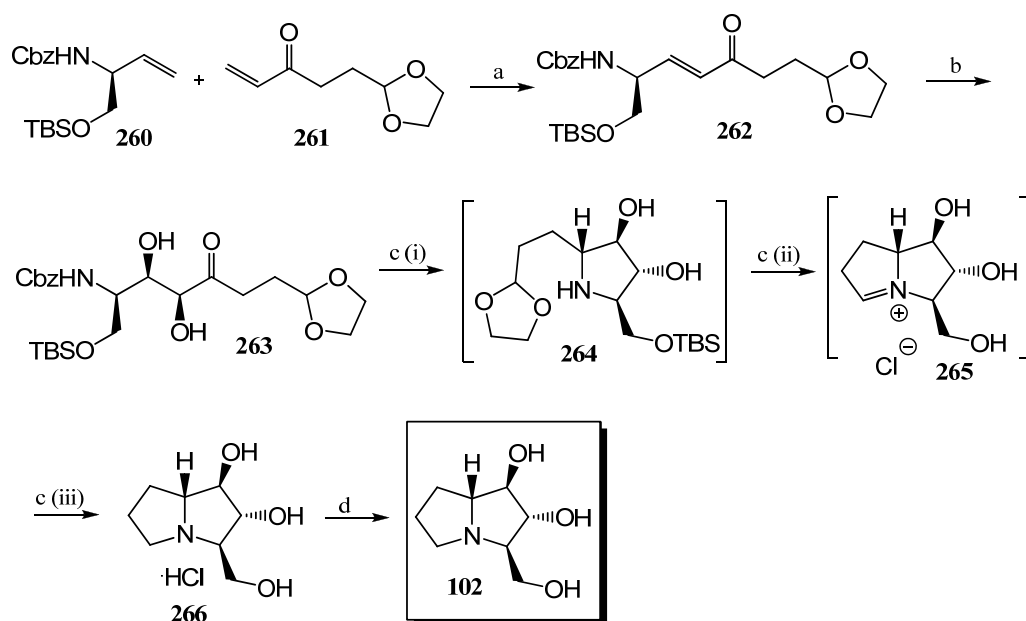
#### Using diastereoselective synthesis

An approach to synthesizing a racemic hyacinthacine alkaloid has been developed by subjecting achiral starting compounds through highly diastereoselective reactions to install the various stereocenters of the target compound. In 2007, Donohoe *et al.* reported the synthesis of (±)-hyacinthacine A<sub>1</sub> ((±)-**101**) from achiral pyrrole **249** (Scheme 1.36).<sup>80</sup> Birch reduction of **249** gave pyrroline **250** with greater than 6:1 diastereoselectivity, followed by *cis*-dihydroxylation which gave exclusively the racemic diol **251**, which was then protected as the acetal **252**. Reduction with NaBH<sub>4</sub> at the least hindered C-3 position, followed by TBS protection gave racemic **253**, which was subjected to further reduction with DIBAL-H to afford aldehyde **254**. A chain-lengthening Wittig reaction with Ph<sub>3</sub>P=CHCO<sub>2</sub>Me gave racemic ester **255**, which was subsequently hydrogenated and reduced to give primary alcohol **257**. Cyclization of the B-ring was achieved by mesylation of alcohol **257**, followed by Boc-deprotection with TESOTf and 2,6-lutidine. Global deprotection gave (±)-**101** in 13 steps and 31% overall yield.

**Scheme 1.36** (All chiral molecules are racemic)**Using enzymatic resolution and then diastereoselective synthesis**

In 2006, Blechert *et al.* reported a synthesis of hyacinthacine A<sub>2</sub> (**102**)<sup>81</sup> from a chiral allylamine **260** prepared from the enzymatic resolution<sup>82</sup> of (±)-*N*-Cbz-vinylglycine (Scheme 1.37). In this synthesis, the (*S*)-allylamine **260** was first reacted with the enone **261**<sup>83</sup> in a CM reaction with Grubbs' II catalyst to give enone **262**. Sharpless asymmetric dihydroxylation of the alkene in **262** with AD-mix-β gave diol **263** in 88% de. Cbz-deprotection with Pd/C and a diastereoselective intramolecular reductive alkylation gave the 2,5-*trans*-pyrrolidine intermediate **264**. Acid deprotection of the TBS and acetal groups of **264** led to a second cyclization to give the iminium salt **265**. Further hydrogenation and ion-exchange and preparative TLC gave **102** in six steps from the chiral allylamine **260** in 12 % overall yield.

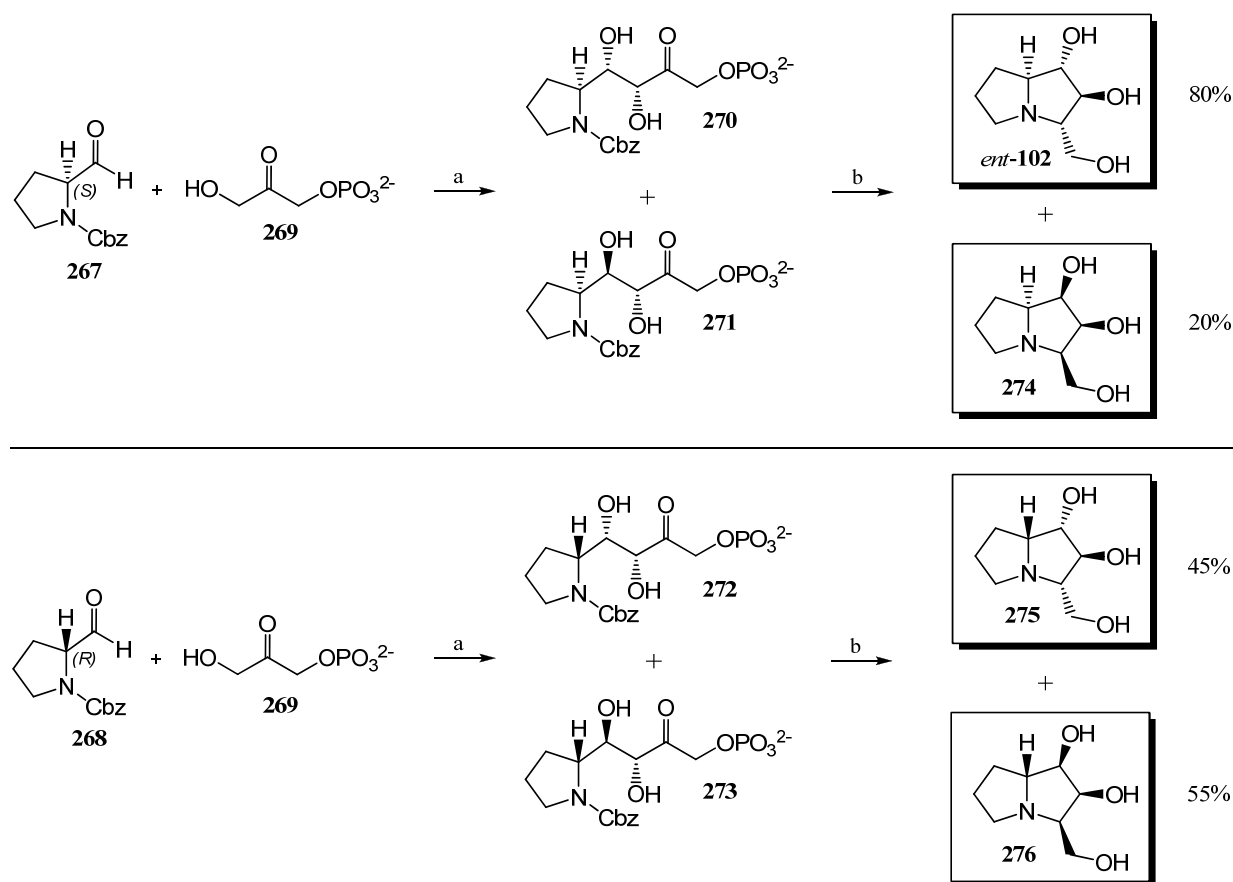
Scheme 1.37



*Reagents and conditions:* (a) Grubbs' II cat. 10 mol%, DCM, 40 °C, 73%; (b) AD-mix-β, 67%; (c) (i) H<sub>2</sub> (4 bar), 10% Pd/C; (ii) cat. HCl; (iii) H<sub>2</sub> (4 bar); (d) Amberlite IRA (OH<sup>-</sup> form), NH<sub>4</sub>OH, 39% over 4 steps.

In 2007 Clapés *et al.* achieved the synthesis of four stereoisomers of hyacinthacines A<sub>1</sub> (**101**) and (-)-hyacinthacine A<sub>2</sub> (*ent*-**102**, Scheme 1.38).<sup>84</sup> Catalyzed by L-rhamnulose 1-phosphate aldolase (RhuA), the aldol reaction of dihydroxyacetone phosphate (DHAP, **269**) with (*S*)-*N*-Cbz-prolinal (**267**) and (*R*)-*N*-Cbz-prolinal (**268**) produced the respective pairs of *syn* and *anti* adducts (**270** to **273**). These were not separated and the mixtures were treated under hydrogenation/hydrogenolysis conditions to give mixtures of two pyrrolizidine products. The four hyacinthacine diastereomers, namely (-)-hyacinthacine A<sub>2</sub> (*ent*-**102**), *ent*-3-*epi*-hyacinthacine A<sub>1</sub> (**274**), *ent*-7-deoxyalexine (**275**) and 2-*epi*-hyacinthacine A<sub>2</sub> (**276**) could be obtained pure after extensive chromatographic separations.

Scheme 1.38

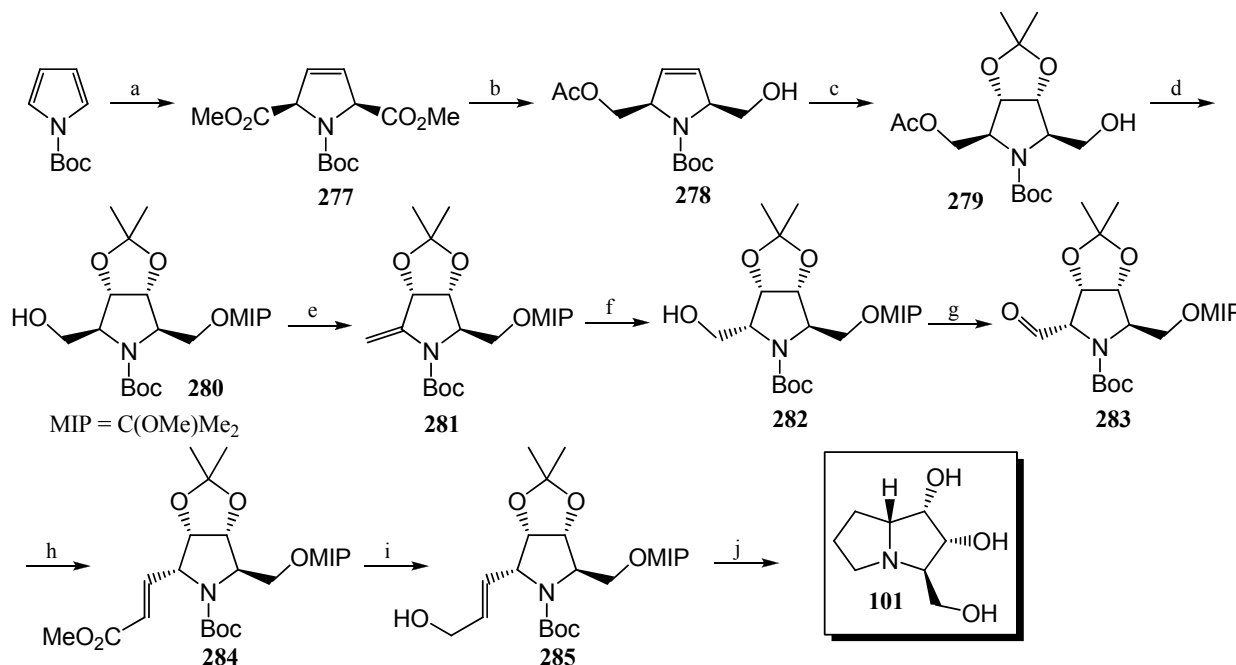


Reagents and conditions: (a) DHAP, RhA, 4 °C; (b) H<sub>2</sub>, Pd/C.

Donohoe's 2007 synthesis of (±)-**101** was optimized in 2008 by incorporating enzymatic resolution early in the synthetic route to give natural (+)-**101** as the sole product (Scheme 1.39).<sup>85</sup> The first part of this synthesis focused on establishing the *trans*-stereochemistry between the C-3 and C-7a substituents in **101** via stereoinversion at C-3. Monoacetate **278** was first synthesized from pyrroline **277** via enzymatic desymmetrization with lipase, *cis*-dihydroxylation of **278** and ketal protection of the diol gave **279**. Protecting group manipulation then gave the alcohol **280**, which underwent mesylation and elimination with DBU to give the enamine **281**. The stereoinversion at C-3 was achieved by a stereoselective and regioselective hydroboration-oxidation on the less hindered β-face of **281**, affording the alcohol **282**. Oxidation with TPAP and a chain-lengthening Wittig reaction gave ester **284**, which was then subjected to Pt-catalyzed hydrogenation and exhaustive reduction with LiBH<sub>4</sub> to afford the alcohol **285**. The formation of the B-ring was achieved by mesylation of **285**, followed by *N*-deprotection with ZnBr<sub>2</sub>. Finally

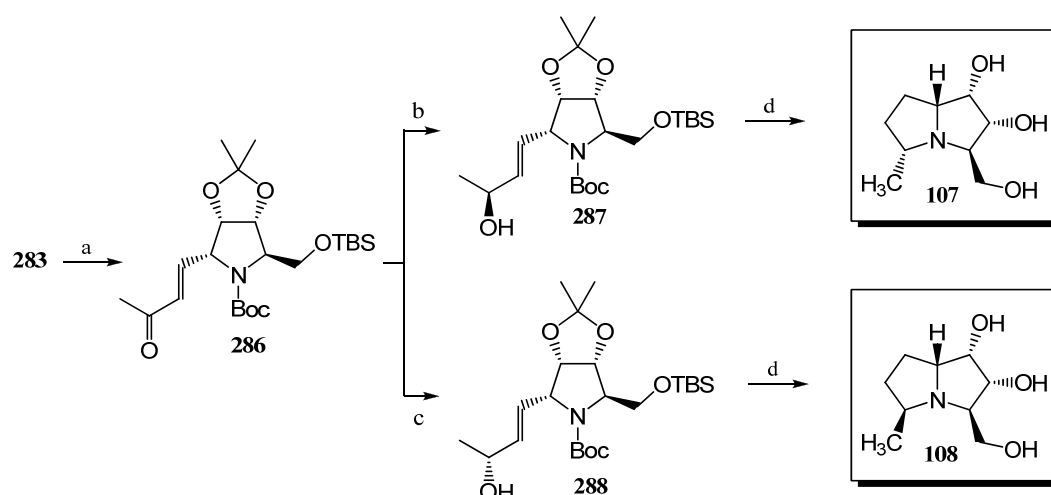
aqueous workup afforded **101** in 15% overall yield and a total of 16 steps from *N*-Boc pyrrole (Scheme 1.39).

**Scheme 1.39**



Following the success in synthesizing (+)-**101**, a similar methodology was applied to the synthesis of hyacinthacines **A<sub>6</sub>** (**107**) and **A<sub>7</sub>** (**108**).<sup>85</sup> Starting with aldehyde **283**, a modified Wittig reaction gave the  $\alpha,\beta$ -unsaturated ketone **286**. Reduction with (*R*)- and (*S*)-*n*-Bu-CBS afforded, respectively, diastereomeric alcohols **287** and **288**, which were finally subjected to hydrogenation, *N*-deprotection, mesylation-cyclization, and global deprotection to give, respectively, **107** and **108** in a total of 18 synthetic steps (Scheme 1.40).

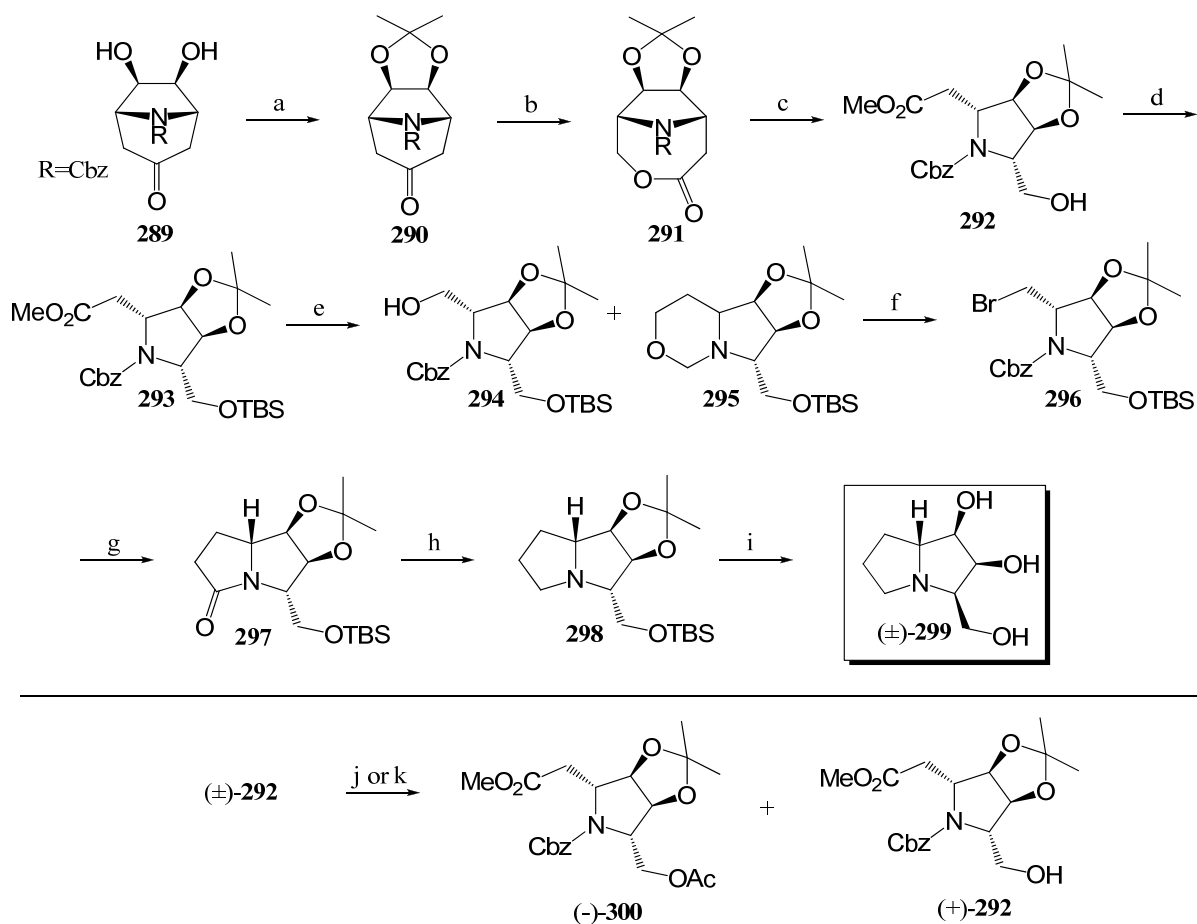
Scheme 1.40



*Reagents and conditions:* (a) (i) NaH, MeOCCH<sub>2</sub>P(O)(OEt)<sub>2</sub>, then HCl; (ii) TBSCl, imidazole, 63%, 2 steps; (b) *n*-Bu(*R*)-CBS, BH<sub>3</sub>, THF, 93%; (c) *n*-Bu(*S*)-CBS, BH<sub>3</sub>, THF, 91%; (d) (i) H<sub>2</sub>, PtO<sub>2</sub>; (ii) ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (iii) MsCl, Et<sub>3</sub>N; (iv) H<sub>3</sub>O<sup>+</sup>, 48% (**107**, 4 steps), 51% (**108**, 4 steps).

In 2009, Laschat *et al.* reported the total synthesis of (±)-7a-*epi*-hyacinthacine A<sub>1</sub> ((±)-**299**) from Cbz-protected tropane diol **289** (Scheme 1.41).<sup>86</sup> The acetal protected diol **290** was subjected to Baeyer-Villiger oxidation to give the ring-expanded tricyclic lactone **291**. The lactone ring was then opened upon treatment with K<sub>2</sub>CO<sub>3</sub> in MeOH to give pyrrolidine methyl ester **292**. The resulting primary alcohol in **292** was silylated to give the TBS ether **293**. Reduction of the ester moiety in **293** with LiAlH<sub>4</sub> gave predominantly (94%) the primary alcohol **294** with a small amount (3%) of the hemiaminal **295** as a side product. Under Appel reaction conditions,<sup>87</sup> **295** was converted to the primary bromide **296**. This was followed by a one-step *N*-deprotection and nucleophilic cyclization with *t*-BuLi in THF to give pyrrolizidinone **297** with the desired configuration at C-7a. Reduction of the lactam was achieved by treatment with BH<sub>3</sub>•SMe<sub>2</sub> in THF, followed by heating at reflux in MeOH to give pyrrolizidine **298**. Finally, global deprotection of **298** afforded (±)-**299** in a total of 10 synthetic steps from **283**. To provide routes to enantiopure (+)-**292** and (-)-**292**, pyrrolidine methyl ester **292** was enzymatically resolved with lipase, affording the acetate (-)-**300** in 56% ee when toluene was used as the solvent. Alternately, the recovered (+)-**292** was obtained in 99% ee when the resolution was carried out in Et<sub>2</sub>O.

Scheme 1.41



*Reagents and conditions:* (a)  $(\text{MeO})_2\text{CMe}_2$ , TsOH, acetone, rt, 2 h, quant.; (b) *m*-CPBA,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , 2,4,6-*t*-Bu<sub>3</sub>C<sub>6</sub>H<sub>2</sub>OH, 55 °C, 55%, 4 d; (c)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 18 h, quant.; (d) TBSCl, imidazole, DMF, rt, 18 h, 97%; (e)  $\text{LiAlH}_4$ , Et<sub>2</sub>O, 5 °C, 1 h, 94% (**294**), 3% (**295**); (f)  $\text{CBr}_4$ ,  $\text{PPh}_3$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 3 h, quant; (g) *t*-BuLi, THF, -80 °C, 1 h, 59 %; (h) (i)  $\text{BH}_3\cdot\text{SMe}_2$ , THF, rt, 6 h; (ii) MeOH, reflux, 3.5 h, 60 %; (i) (i) HCl, MeOH, reflux, 1 h; ( $\text{H}_2\text{O}$ , DOWEX 1x8 ( $\text{OH}^-$ ), 1.5 h, quant.; (j) Chirazyme L-6, toluene, 20 °C, 1.5 h, 42%, 99% ee (**(-)-300**); 48%, 75 % ee (**(+)-292**); (k) Chirazyme L-6, toluene, 20 °C, 1 h, 65% conversion, 56% ee (**(-)-300**); 99 % ee (**(+)-292**).

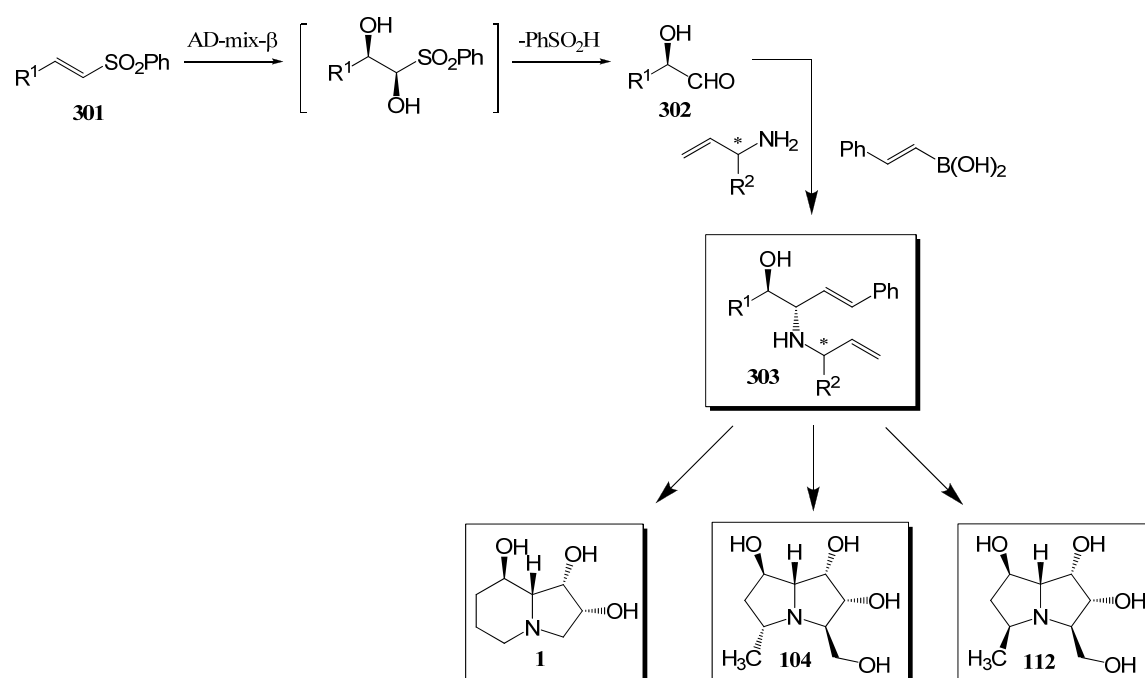


## 1.4 Aims of project

The main aims of this PhD project were:

1. To develop a synthesis of 1,2-*anti* amino alcohols **303** from the Petasis borono-Mannich reaction of  $\alpha$ -hydroxy aldehydes **302** that are generated *in situ* from the asymmetric dihydroxylation (ADH) reactions of vinyl sulfones **301** (Scheme 1.42);
2. To use 1,2-*anti* amino alcohols **303** prepared above in the synthesis of swainsonine;
3. To use the above methods to synthesize the hyacinthacine alkaloids B<sub>3</sub> (**104**) and B<sub>7</sub> (**112**); and
4. To confirm the structures and the absolute configurations of the hyacinthacines B<sub>3</sub> and B<sub>7</sub>.

**Scheme 1.42**



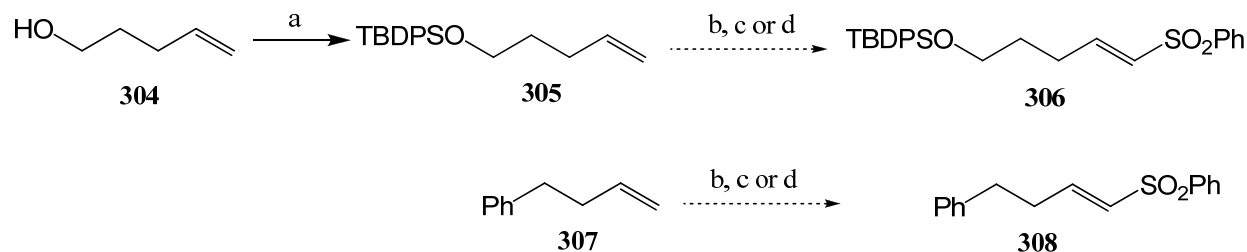
## CHAPTER 2: SYNTHESIS OF 1,2-*anti* AMINO ALCOHOLS

This Chapter concerns the development of an efficient synthetic route to 1,2-*anti* amino alcohols **303**. These alcohols have been used as important chiral building blocks in the synthesis of polyhydroxylated pyrrolizidine and indolizidine alkaloids.<sup>88-94</sup> In 1998, Petasis *et al.* reported a one-pot, three-component synthesis of 1,2-*anti* amino alcohols involving aryl or vinyl boronic acids, primary or secondary amines and chiral  $\alpha$ -hydroxy aldehydes.<sup>95</sup> In a paper published in 2003, Evans *et al.* described the *in situ* preparation of chiral  $\alpha$ -hydroxy aldehydes from the Sharpless asymmetric dihydroxylation (ADH) of vinyl sulfones.<sup>96</sup> Before examining the viability of sequentially using the above two reactions to synthesize 1,2-*anti* amino alcohols **303**, the synthesis of vinyl sulfones **301** will first be discussed.

### 2.1 Synthesis of vinyl sulfones

Three methods were investigated for the conversion of terminal alkenes **304** and **307** into vinyl sulfones: (1) Grubbs olefin cross metathesis; (2) a ceric ammonium nitrate (CAN) mediated radical reaction; and (3) an iodosulfonation-dehydroiodination reaction with benzenesulfonyl iodide (Scheme 2.1). Alkenyl silyl ether **305** was prepared by treating commercially available 4-penten-1-ol **304** with TBDPSCl and imidazole in 92% yield.

Scheme 2.1



*Reagents and conditions:* (a) TBDPSCl, imidazole, DMF, 92%; (b) phenyl vinyl sulfone, Grubbs' II cat., CH<sub>2</sub>Cl<sub>2</sub>, 45 °C reflux; (c) CAN, NaSO<sub>2</sub>Ph, NaI, CH<sub>3</sub>CN; (d) PhSO<sub>2</sub>I, toluene, then DBU.

### 2.1.1 Grubbs cross metathesis reaction

In 2003, Grubbs *et al.* categorized alkenes into four different types according to their reactivities in cross metathesis (CM) reactions and their tendencies of forming homodimers under catalyzed conditions (Figure 2.1).<sup>97</sup> According to Grubbs' classification, terminal alkenes, such as **305** and **307**, belong to Type I and undergo rapid homodimerization in the presence of Grubbs' II catalyst. Under the same conditions, phenyl vinyl sulfone, a Type III alkene, does not dimerize but participates in CM reactions with other alkenes (Figure 2.1).

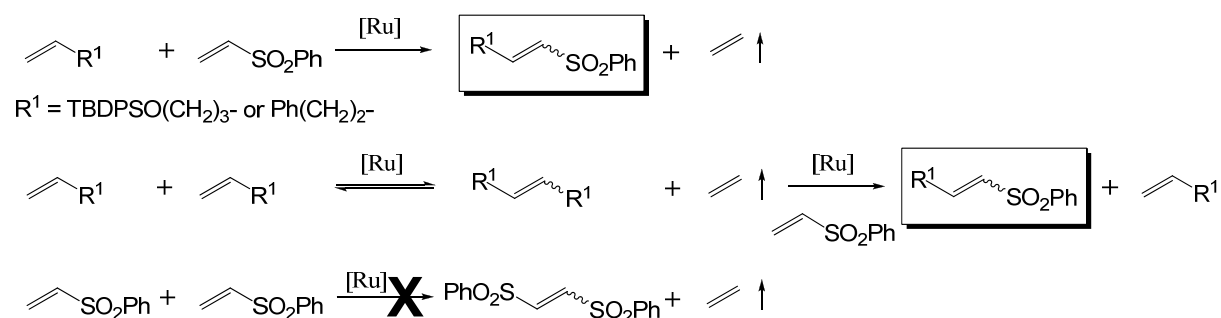
- Type I alkenes dimerize rapidly.
  - Type II alkenes dimerize slowly.
  - Type III alkenes do not dimerize.
  - Type IV alkenes do not participate in CM.
- ↑

Reactivity in cross metathesis reactions

**Figure 2.1** Olefin reactivities in cross metathesis reactions.

The CM reactions between terminal alkenes **305** and **307** with phenyl vinyl sulfone should be favored, as only the terminal alkenes form homodimers, which should then be consumed by the ruthenium catalyst to couple with phenyl vinyl sulfone to form the CM product (Scheme 2.2).

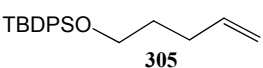
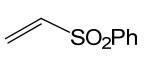
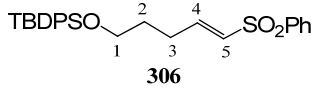
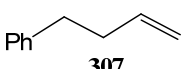
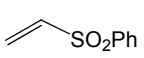
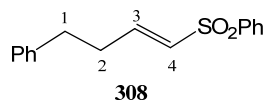
**Scheme 2.2**



With these predictions, the reactions between alkenes **305** and **307** and phenyl vinyl sulfone proceeded to give CM products **306** and **308** in 91% and 70%, respectively. In the <sup>1</sup>H NMR spectra of **306** and **308**, the doublets belonging to H-5 in **306** (δ<sub>H</sub> = 6.30 ppm) and H-4 in **308** (δ<sub>H</sub> = 6.32 ppm) both had a coupling constant of 15.1 Hz for *J*<sub>4,5</sub> in **306**

and  $J_{3,4}$  in **308**, respectively, which indicated *trans*-configurations between the alkenyl protons. (Table 2.1).

**Table 2.1** Summary of CM reactions.<sup>a</sup>

Type I Alkene	Type III Alkene	CM Product	Yield
 <b>305</b>		 <b>306</b>	91%
 <b>307</b>		 <b>308</b>	70%

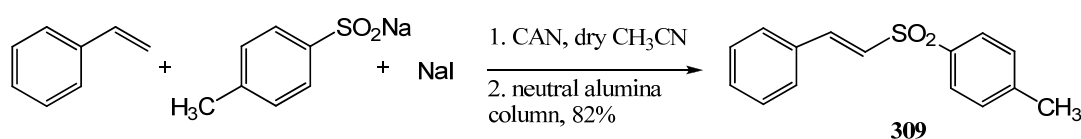
<sup>a</sup> Grubbs' II catalyst (5.3 mol%), 1.0 mol equiv. of alkene, 2.0 mol equiv. of phenyl vinyl sulfone, CH<sub>2</sub>Cl<sub>2</sub> reflux for 18 h.

### 2.1.2 CAN-mediated radical reaction

The Grubbs CM reaction proved to be a very efficient method for making vinyl sulfones **301**. The Grubbs second generation catalyst is however a rather expensive reagent to use on a large scale. More economical ways of synthesizing **301** in comparable yields and stereoselectivity to the CM reaction were therefore explored.

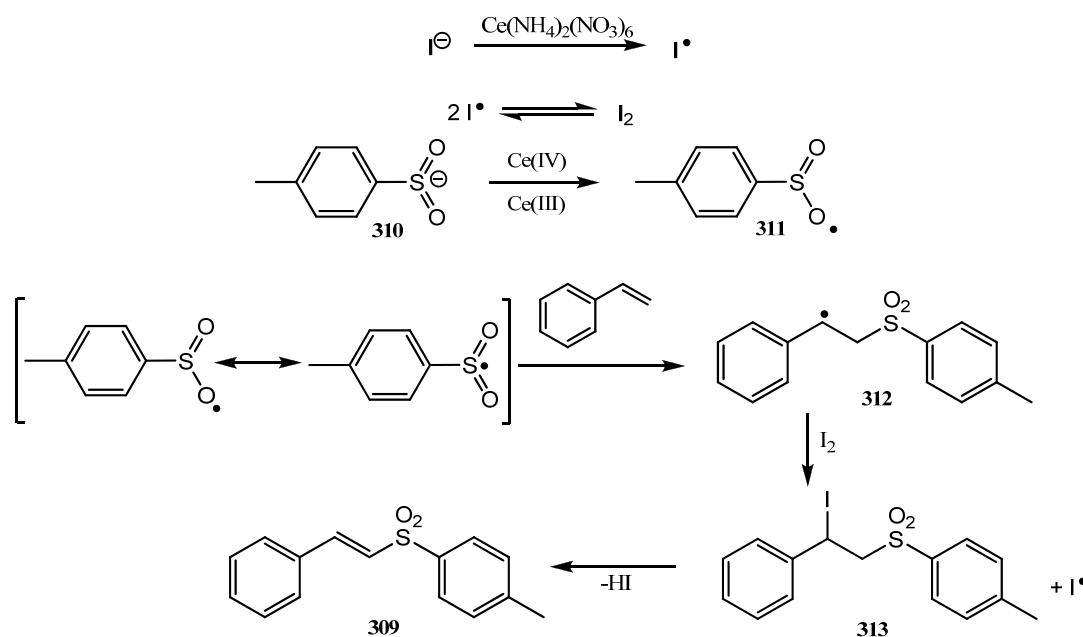
In 2001, Nair *et al.* reported a synthesis of *trans*- $\alpha,\beta$ -unsaturated sulfones in satisfactory yields (70-88%) through a CAN-mediated reaction of alkenes with sodium iodide and aryl sulfinates followed by neutral alumina column chromatography.<sup>98</sup>

**Scheme 2.3**<sup>98</sup>



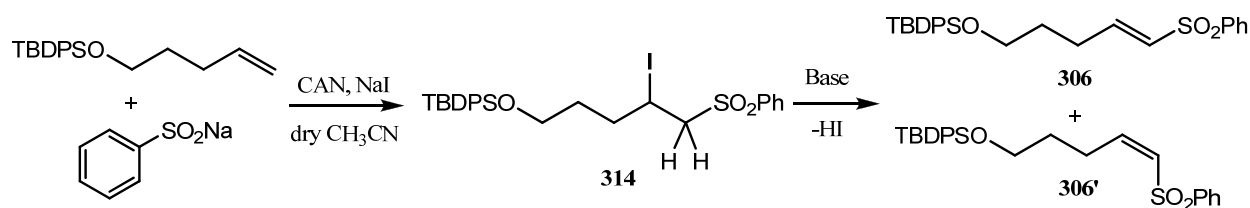
According to Nair *et al.* the mechanism of this reaction involves the addition of the phenyl sulfonyl radical **311** to styrene to give the secondary radical **312**, which then reacts with *in situ* generated molecular iodine to give the  $\beta$ -iodosulfone **313**. Finally, elimination of hydrogen iodide (HI) from **313** upon treatment with alumina gives the vinyl sulfone **309** (Scheme 2.4).

Scheme 2.4



Using the above reaction as a model for an alternative synthesis of vinyl sulfone **306**, we discovered that following the radical reaction, a base was necessary to induce the elimination of HI from the β-iodo sulfone **314** to give vinyl sulfone **306** (Scheme 2.#). Triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and basic alumina column were used to test the actions of different bases in the elimination of HI from **314** to give the desired vinyl sulfone **306**.  $^1H$  NMR decoupling and H-H COSY NMR analyses helped to determine the presence of the **306'**, the (*Z*)-isomer of **306**, as a minor product in the CAN-mediated reactions using three different bases in the dehydroiodination step. The allylic methylene protons labeled H-3 of the (*Z*)-isomer **306'** are deshielded by their closer proximity to the  $SO_2$  group and have a greater chemical shift ( $\delta_H$  2.77 ppm) in the  $^1H$  NMR spectrum than H-3 of the (*E*)-isomer **306** ( $\delta_H$  2.35 ppm) (Figure 2.2). The (*E*) to (*Z*) ratios of the vinyl sulfone products were determined by integration of the peaks representing H-3 in the  $^1H$  NMR spectra of the vinyl sulfones **306** and **306'**, respectively. These results are summarized in Entries 2 to 5 in Table 2.2, and Figures 2.3b to 2.3e show the  $^1H$  NMR spectra of the alkene region of the products formed from the CAN-mediated reaction.

## Scheme 2.5



Compared with the Grubbs CM reaction, although the CAN-mediated reaction had comparable stereoselectivity when DBU was used as the base in the elimination step, the yields of the CAN-mediated reactions were generally unsatisfactory (26-52%). Therefore, another method of making vinyl sulfone **306** in better yields and good stereocontrol was sought after.

**Table 2.2** Summary of different methods used to synthesize the vinyl sulfone **306**.

Entry	Reaction	Base	Reaction Temperature	( <i>E</i> )/( <i>Z</i> ) Ratio	Yield
1	Grubbs CM	–	45 °C	99 : 1	91%
2	CAN-mediated	basic $\text{Al}_2\text{O}_3$ column	rt	88 : 12	26%
3	CAN-mediated	DBU	0 °C	99 : 1	27%
4	CAN-mediated	$\text{Et}_3\text{N}$	rt	85 : 15	33%
5	CAN-mediated	$\text{Et}_3\text{N}$	0 °C	83 : 17	52%
6	$\text{PhSO}_2\text{I}$	DBU	0 °C	98 : 2	93%

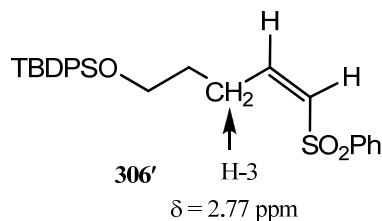
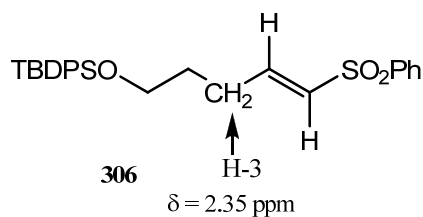
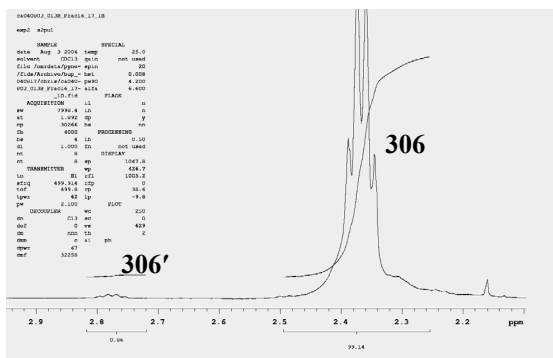
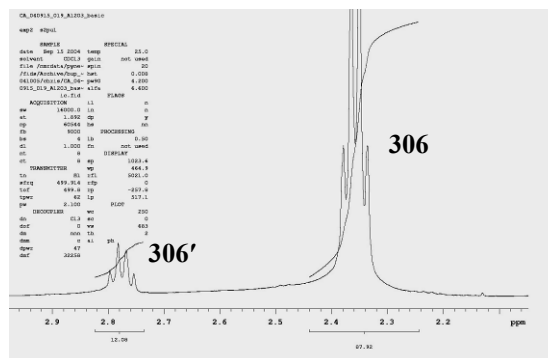
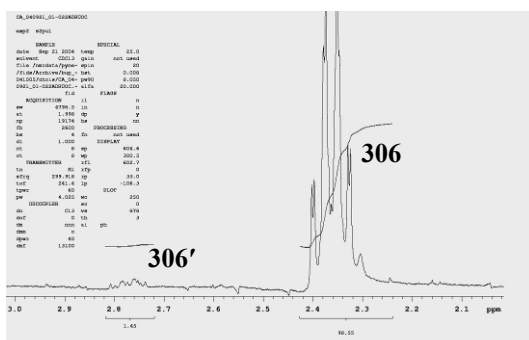
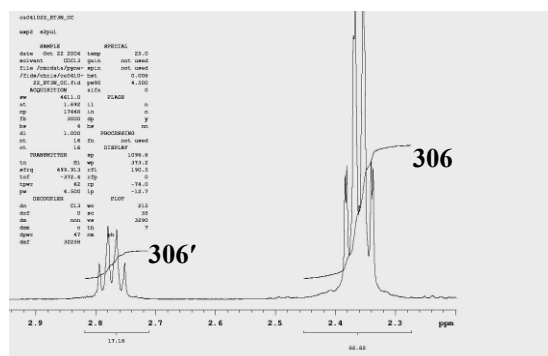
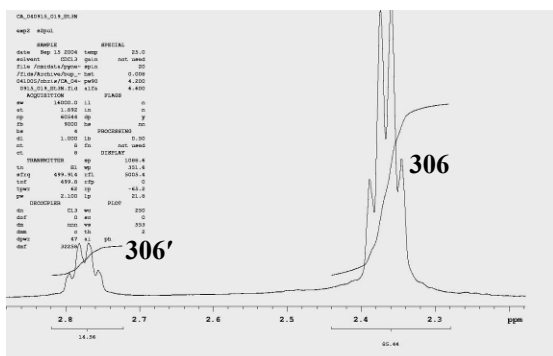
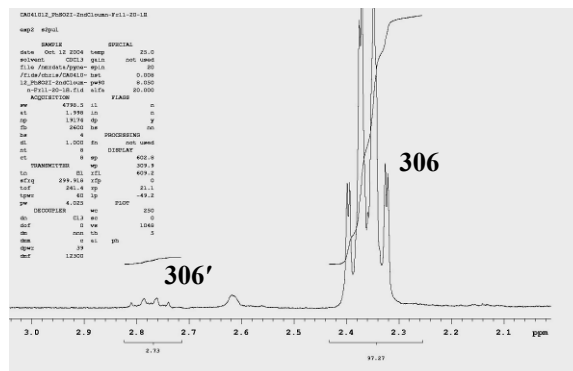
Figure 2.2  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) chemical shifts for H-3 in **306** and **306'**.

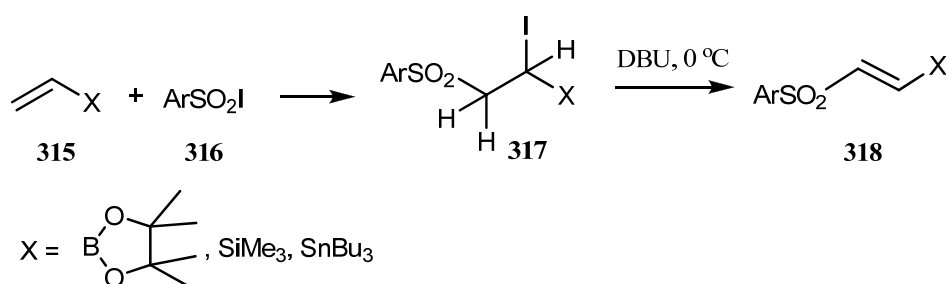
Figure 2.3a Grubbs Olefin Metathesis.

Figure 2.3b CAN Reaction,  $\text{Al}_2\text{O}_3$  Column.Figure 2.3c CAN Reaction, DBU as base,  $0^\circ\text{C}$ .Figure 2.3d CAN Reaction,  $\text{Et}_3\text{N}$  as base,  $0^\circ\text{C}$ .Figure 2.3e CAN Reaction,  $\text{Et}_3\text{N}$  as base, rt.Figure 2.3f  $\text{PhSO}_2\text{I}$  Reaction, DBU as base,  $0^\circ\text{C}$ .Figures 2.3a-f Integration ratios of  $^1\text{H}$  NMR peaks of H-3 in vinyl sulfones **306** and **306'**.

### 2.1.3 Iodosulfonation-dehydroiodination using benzenesulfonyl iodide

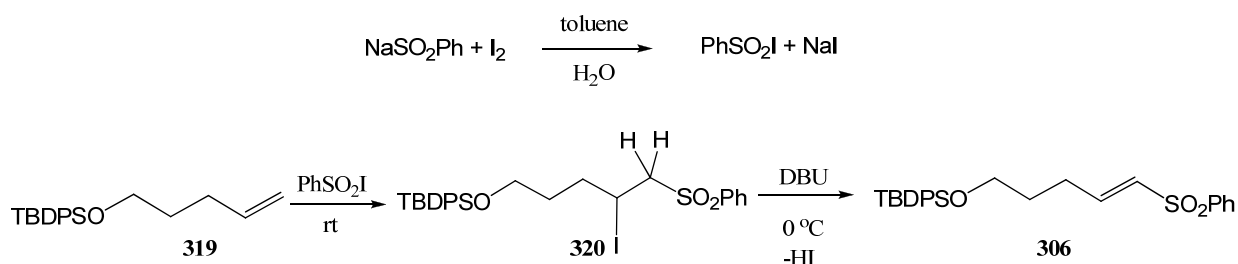
In 1992, Vaultier *et al.* reported an iodosulfonation-dehydroiodination reaction similar to the CAN-mediated reaction to give *trans*-vinyl sulfones (Scheme 2.6).<sup>99</sup> In this reaction, the arylsulfonyl iodide **316** was used as the iodosulfonating agent and was speculated to involve the radical addition of the arylsulfonyl iodine across the terminal alkene **315**, forming the  $\beta$ -iodo sulfone **317**. Treatment with DBU eliminates hydrogen iodide from **317** and gives the vinyl sulfone product **318** (Scheme 2.6).

**Scheme 2.6**



In our synthesis of the vinyl sulfone **306**, we followed a method by Liu *et al.*<sup>100</sup> to first synthesize benzenesulfonyl iodide ( $\text{PhSO}_2\text{I}$ ) in toluene, which was then added to alkene **304** to give the  $\beta$ -iodo sulfone **320**. Treatment with DBU at  $0^\circ\text{C}$  gave the vinyl sulfone **306** in 93% yield and with a 98:2 (*E*)/(*Z*) ratio (Table 2.2, Entry 6 and Scheme 2.7).

**Scheme 2.7**



In conclusion, the iodosulfonation-dehydroiodination with benzenesulfonyl iodide demonstrated to be a facile and inexpensive method of preparing vinyl sulfone **306** in excellent yield and high stereoselectivity on a multigram scale.

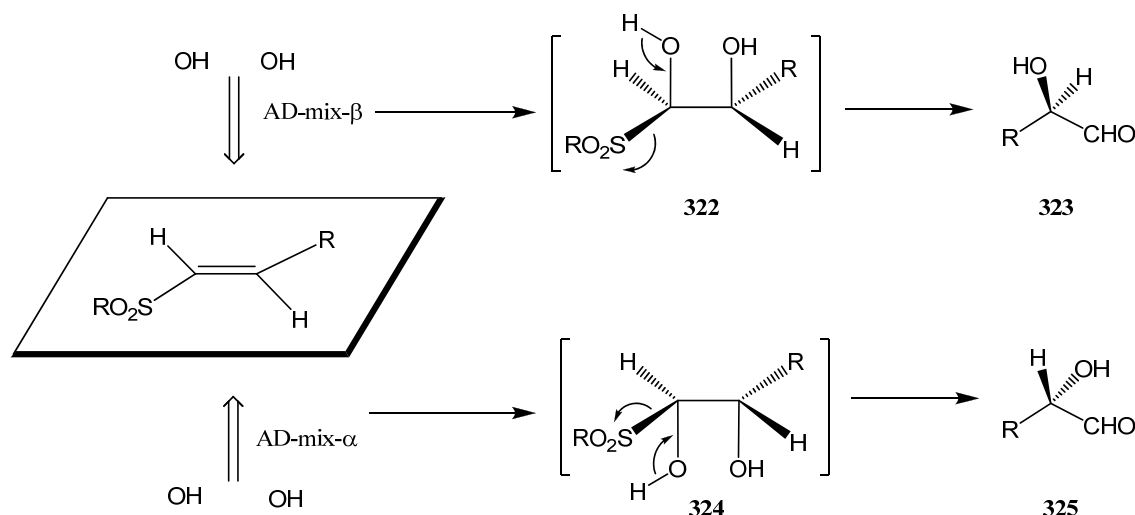


## 2.2 Sharpless asymmetric dihydroxylation (ADH) and Petasis borono-Mannich reaction

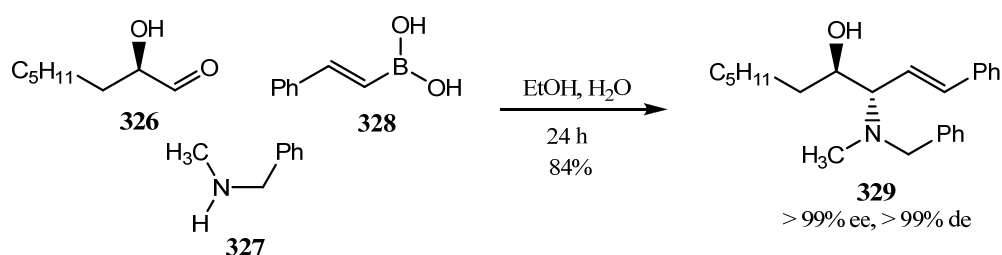
The next step in our synthesis of 1,2-*anti* amino alcohols **303** involved the *in situ* synthesis of  $\alpha$ -hydroxy aldehydes **302** for the subsequent Petasis borono-Mannich reaction.

In 2003, Evans and Leffray described the asymmetric dihydroxylation (ADH) of vinyl sulfones using Sharpless AD-mixes to generate dihydroxy sulfone intermediates, which spontaneously eliminated  $\text{RSO}_2\text{H}$  to give chiral  $\alpha$ -hydroxy aldehydes (Scheme 2.8).<sup>96</sup> The  $\alpha$ -hydroxy aldehydes were not isolated and were immediately treated with methyl diethylphosphonoacetate or bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphonate to give  $\gamma$ -hydroxy enoates in 73-97% enantiomeric excess.

**Scheme 2.8**

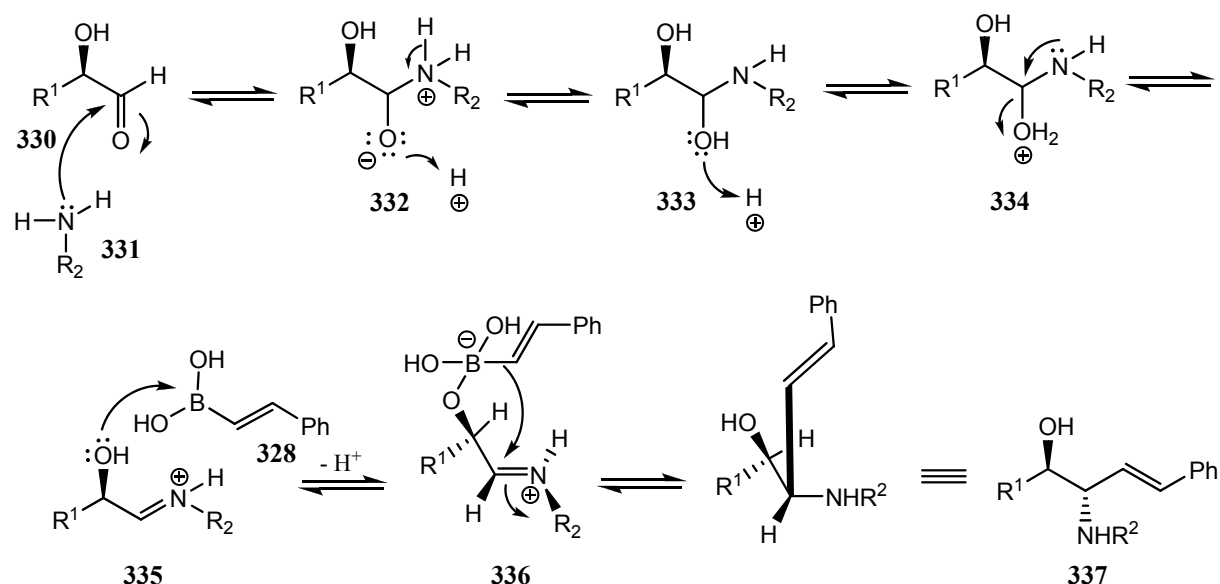


A 1998 paper by Petasis *et al.* described the synthesis of 1,2-*anti* amino alcohols in a one-step three-component reaction involving  $\alpha$ -hydroxy aldehydes, primary and secondary amines and aryl or vinyl boronic acids. An example of the Petasis reaction is shown in Scheme 2.9.<sup>95</sup>

Scheme 2.9<sup>95</sup>

The Petasis reaction gave 1,2-*anti* amino alcohols **329** in greater than 99% enantiomeric excess, which was a result of the enantiopurity of the parent  $\alpha$ -hydroxy aldehydes **326**. The high diastereoselectivity of the Petasis reaction also gave exclusively *anti* products. Although the exact mechanism of the borono-Mannich reaction is not known, we speculate that it involves the formation of the iminium ion intermediate **335**, followed by nucleophilic attack of the boronic acid and the elimination of B(OH)<sub>3</sub>, forming the 1,2-amino alcohol **337**. The diastereoselectivity of the Petasis reaction is believed to be the result of the formation of the boronate complex intermediate **336**, in which the iminium ion adopts a reactive conformation to minimize 1,3-allylic strain between the *N*-substituent of the iminium ion and the substituents of the allyl ( $\alpha$ ) carbon (Scheme 2.10).

Scheme 2.10

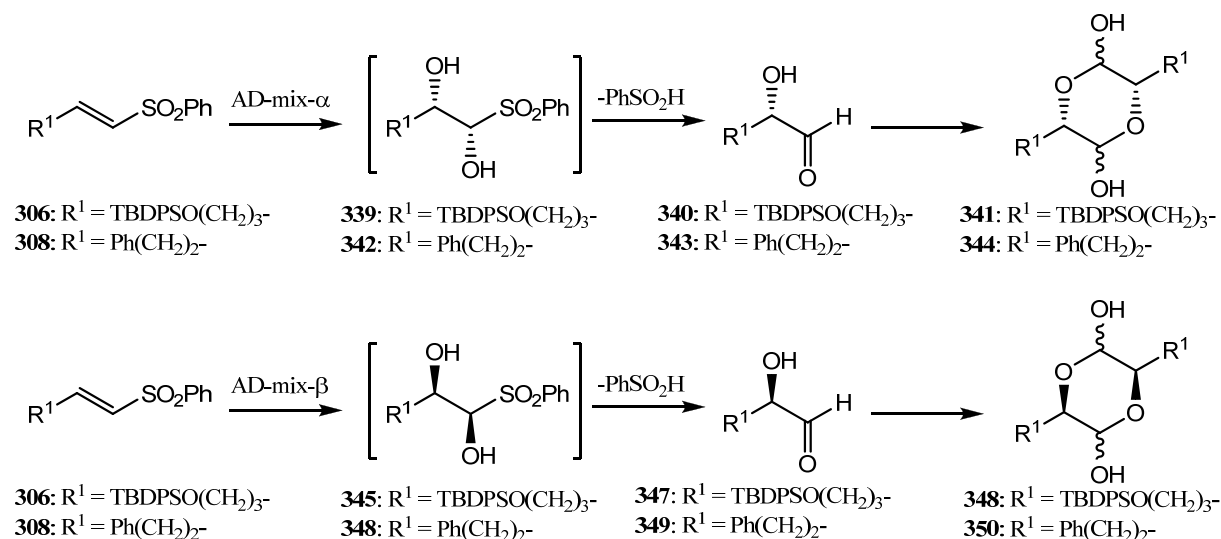


We envisioned that using the Sharpless ADH and Petasis reactions in sequence would enable us to readily obtain 1,2-*anti* amino alcohols **303** as valuable intermediates in our synthesis of (-)-swainsonine and perhaps other indolizidine and pyrrolizidine alkaloids. The efficacy and generality of the Sharpless-Petasis sequence was therefore tested on

vinyl sulfones **306** and **308** with AD-mixes  $\alpha$  and  $\beta$ , and a variety of primary and secondary amines.

The reactions of vinyl sulfones **306** and **308** with AD-mix- $\alpha$  and AD-mix- $\beta$ , carried out in 1:1 *t*-BuOH/H<sub>2</sub>O required loadings of AD-mix which were equivalent to 1.6 to 2 mol % of osmium. The reaction times were limited to 24 h to minimize the decomposition of the reactive  $\alpha$ -hydroxy aldehydes. After extraction into EtOAc and evaporation, the crude material showed no characteristic downfield aldehyde <sup>1</sup>H NMR resonances, more consistent with a mixture of acetal-like structures (Scheme 2.11). The crude products obtained from the Sharpless ADH were used in the Petasis reaction without further purification.

**Scheme 2.11**



Following the conditions described in Petasis' paper, ethanol was originally used as the solvent of choice but produced a poor yield of the desired product **353** (Entry 1, Table 2.3). Referring to previous work done by our group,<sup>101</sup> we switched to using dichloromethane as solvent due to higher yields in similar systems. A basic workup with 5% aq. NaOH was required at the end of the Petasis reaction to remove excess boronic acid from the crude product. The Petasis products were obtained as single diastereomers following purification by column chromatography. A summary of the results of the various attempted Petasis reactions is shown in Scheme 2.12 and Table 2.3.

From the ADH reactions of TBDPS-protected vinyl sulfone **306**,  $\alpha$ -hydroxy aldehydes **340** and **347** were treated with allylamine (1.06 mol equiv.) and  $\beta$ -styrenyl boronic acid (1.0 mol equiv.) to give the *anti*-1,2-amino alcohols **354** and **353** as single diastereomers in overall yields of 35% and 38%, respectively, for the two-step sequence (Entries 2 and 3, Table 2.3).

To determine the enantiomeric purity of **353** and **354**, the Mosher's esters of these amino alcohols were synthesized using (*S*)-Mosher's acid chloride, and the  $^{19}\text{F}$  NMR spectrum of each (*R*)-Mosher's ester was then compared with that of the enantiomeric 1,2-*anti* amino alcohol's Mosher's ester (Scheme 2.13 and Figure 2.4). By integrating the peaks belonging to the diastereomeric (*R*)-Mosher's ester products **360** ( $\delta_{\text{F}} = -71.65$  ppm) and **361** ( $\delta_{\text{F}} = -71.85$  ppm), the amino alcohols **353** and **354** were determined to be, respectively, in 93% and 83% enantiomeric excess. The optical rotation of the amino alcohols **353** ( $[\alpha]_D^{24} +7.5$  (c 1.08,  $\text{CHCl}_3$ )) and **354** ( $[\alpha]_D^{24} -12.7$  (c 1.10,  $\text{CHCl}_3$ )), being opposite in sign and comparable in magnitude, provided further assurance that **353** and **354** were in fact enantiomeric.

Scheme 2.12

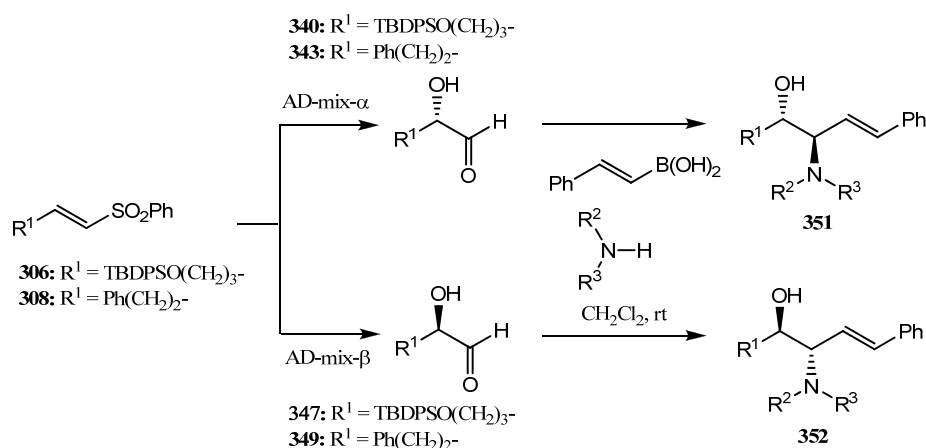
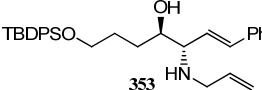
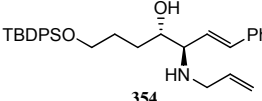
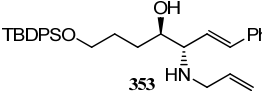
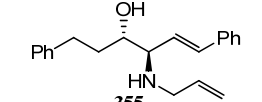
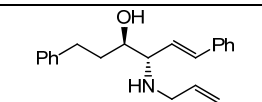
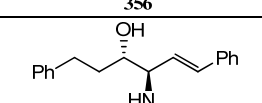
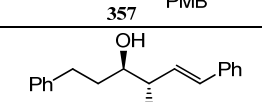
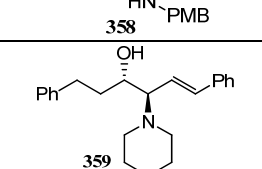
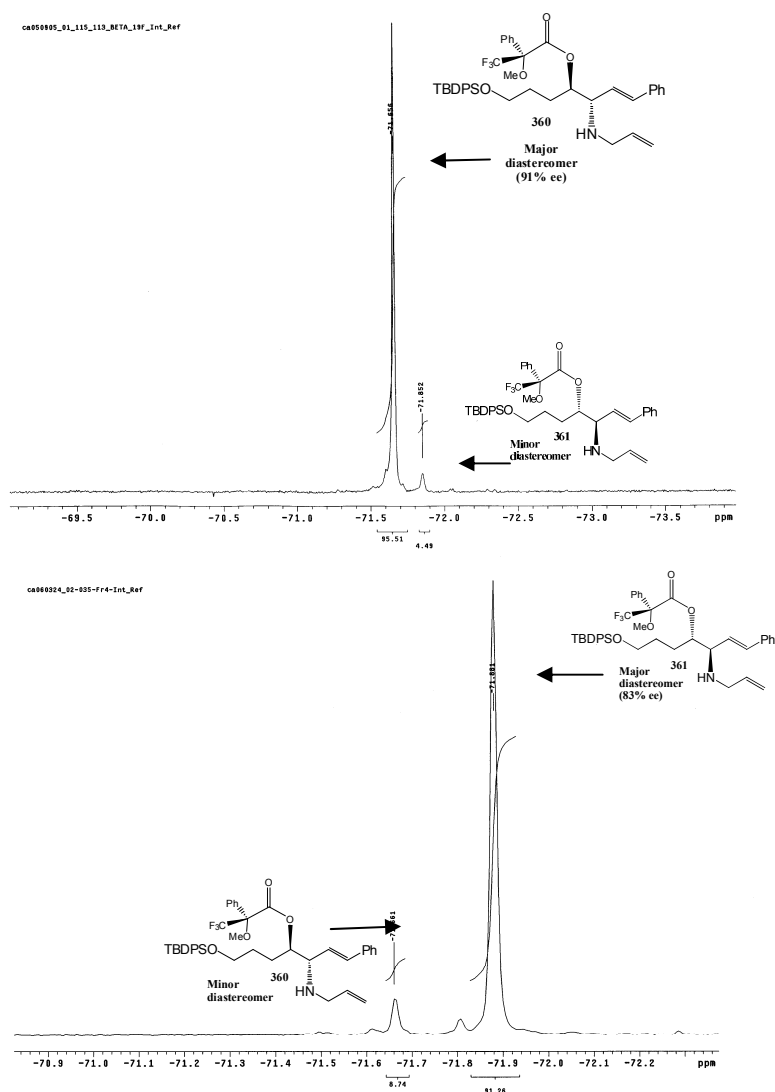
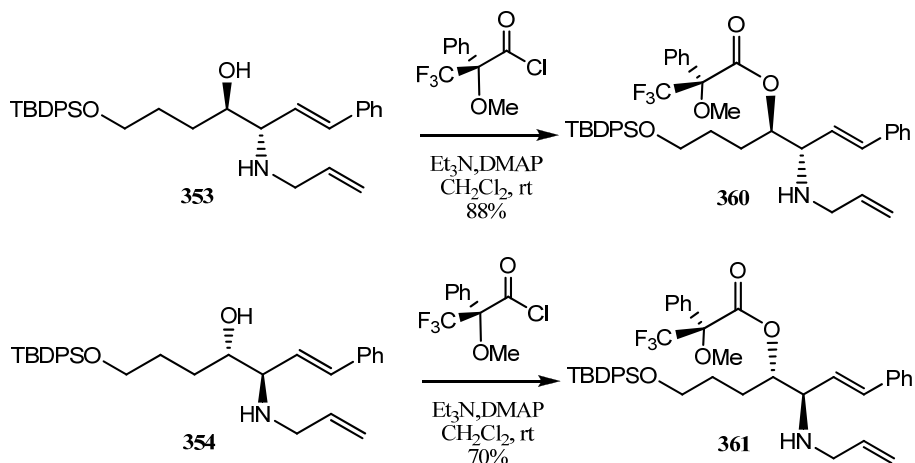


Table 2.3 Summary of the Sharpless-Petasis sequence shown in Scheme 2.12.

Entry	Vinyl sulfone	Solvent	AD-mix	R <sup>2</sup>	R <sup>3</sup>	Overall yield <sup>a</sup> (%) from vinyl sulfone	ee (%) <sup>b</sup>	Product
1	<b>306</b>	EtOH	$\beta$	allyl	H	28	-	
2	<b>306</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\alpha$	allyl	H	35	83	
3	<b>306</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\beta$	allyl	H	38	91	
4	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\alpha$	allyl	H	44	91	
5	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\beta$	allyl	H	51	94	
6	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\alpha$	PMB	H	46	91	
7	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\beta$	PMB	H	43	95	
8	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\alpha$	morpholine		12	-	
9	<b>308</b>	CH <sub>2</sub> Cl <sub>2</sub>	$\alpha$	PMP	H	0	-	-

<sup>a</sup> Overall yield based on 1.0 equiv. of vinyl sulfone, 1.0 equiv. of  $\beta$ -styrenyl boronic acid and 1.06 equiv. amine.<sup>b</sup> Determined by <sup>19</sup>F NMR spectroscopy on the corresponding Mosher's ester.

Scheme 2.13

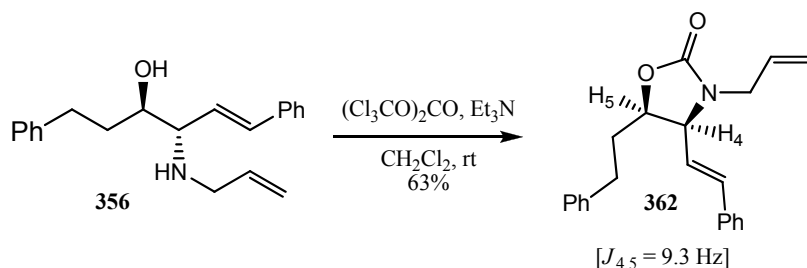


**Figure 2.4**  $^{19}\text{F}$  NMR (CDCl<sub>3</sub>, 282 MHz) spectra of the (*R*)-Mosher's esters **360** and **361**, respectively synthesized from the amino alcohols **353** and **354**, with  $\text{CF}_3\text{CH}_2\text{OH}$  referenced at -77.8 ppm.

The Sharpless-Petasis sequence was also performed on the vinyl sulfone **308** using AD-mix  $\alpha$  or  $\beta$  in the Sharpless ADH and was followed by treatment with allylamine and  $\beta$ -styrenyl boronic acid gave the 1,2-*anti* amino alcohols **355** and **356** in 44 and 51% overall yields from **308**, and in 91 and 94% enantiomeric excess, respectively (Entries 4 and 5, Table 2.3). When 4-methoxybenzylamine (PMBNH<sub>2</sub>) was used as a source of amine in the Petasis reaction, the amino alcohols **357** and **358** were obtained in 46 and 43% overall yields from **308**, and in 91 and 95% enantiomeric excess, respectively (Entries 6 and 7, Table 2.3).

The enantiomeric excess of the aforementioned products was determined from <sup>19</sup>F NMR analysis of their (*R*)-Mosher's esters. To verify the relative *anti* configuration of **356** (*R*<sup>2</sup> = allyl), it was converted to the oxazolidinone **362** by treatment with triphosgene under basic conditions. The 9.3 Hz vicinal coupling constant, *J*<sub>4,5</sub>, in the <sup>1</sup>H NMR spectrum of **362** was consistent with the 4,5-*cis* relative configuration as demonstrated by Lindström to be *ca.* 8 Hz, thereby confirming the *anti* configuration of **356** (Scheme 2.14).<sup>94,102,103</sup> Earlier work by Bergmeier illustrated that the coupling constant of oxazolidinones with a structure similar to **362** but in a 4,5-*trans* relative configuration would be likely to fall between 2 to 4 Hz.<sup>104</sup>

**Scheme 2.14**



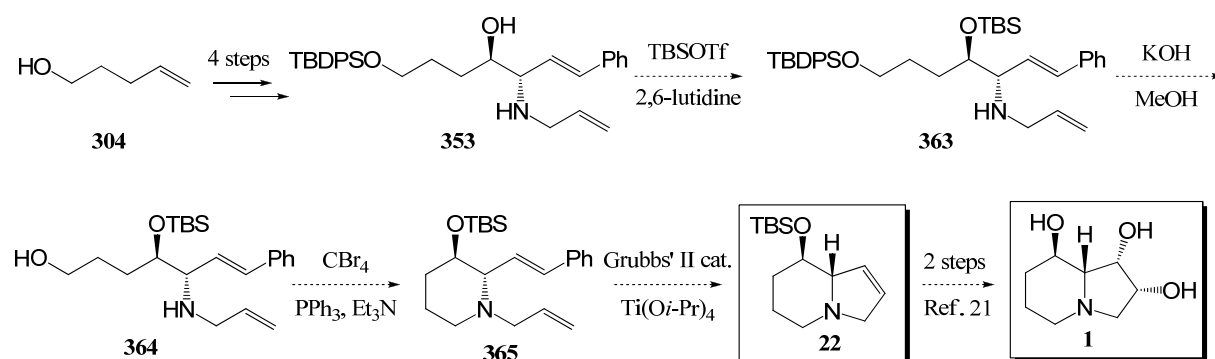
Starting with **308** in the Sharpless ADH and using the secondary amine, morpholine (Entry 8, Table 2.3), and the aromatic amine, 4-methoxyaniline (PMPNH<sub>2</sub>, Entry 9, Table 2.3) in the Petasis reaction, the morpholine-derived 1,2-*anti* amino alcohol product was obtained as a single diastereomer in only 12% yield (ee not determined), while none of the 4-methoxyaniline-derived adduct was isolated, perhaps due to the lower nucleophilicity of the latter aromatic amine.

## CHAPTER 3: A FORMAL SYNTHESIS OF

### (-)-SWAINSONINE

The success in the development of a highly enantioselective and diastereoselective synthesis of 1,2-*anti* amino alcohols **303** helped us reach an important milestone in our quest towards developing a general and efficient synthetic route to polyhydroxylated indolizidine and pyrrolizidine alkaloids. To exemplify the utility of these amino alcohols, we proposed to use the amino alcohol **353** as a key intermediate to synthesizing (-)-swainsonine **1**. Through a four-step transformation illustrated in Scheme 3.1, including: (1) protection of the secondary alcohol **353** as TBS ether **363**; (2) selective deprotection of the terminal TBDPS ether in **363**; (3) activation of the terminal hydroxyl group in **364** followed by concomitant intramolecular nucleophilic alkylation to form the six-membered ring in **365** and (4) ring closing metathesis of the dienyl moiety in **365**, we should obtain the known indolizidine **22**, which was converted to **1** in two steps by Blechert *et al.* in 2002.<sup>21</sup> This would constitute the latter portion of our ten-step formal synthesis of **1** from 4-penten-1-ol **304** (Scheme 3.1).

**Scheme 3.1**



### 3.1 Preparing for the first cyclization

The main focus of the synthetic route from **353** to **22** was to build the two fused rings of the indolizidine **22**. As proposed earlier, the six-membered 'B-ring' of **22** could be



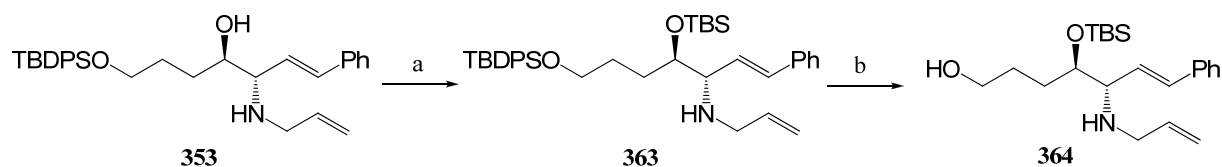
formed *via* nucleophilic *N*-alkylation,<sup>105,106,32</sup> which first required protecting group manipulations in the amino alcohol **353**, starting with the silyl protected hydroxy groups.

### 3.1.1 Protecting group manipulations

The first step in a series of protecting group manipulations was the protection of the secondary hydroxy group. Following conditions used previously by our group, we utilized *t*-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine in CH<sub>2</sub>Cl<sub>2</sub>, which were proven to result in a higher yield in similar systems than TBSCl and imidazole in DMF.<sup>107</sup> The reaction of **353** with TBSOTf and 2,6-lutidine gave the amino disilyl ether **363** in 70% yield (Scheme 3.2).

To facilitate the nucleophilic cyclization to form the six-membered ‘B-ring’ of (-)-swainsonine, the primary TBDPS ether in **363** was to be deprotected and then activated. Selective removal of the TBDPS ether in the presence of the secondary TBS ether was achieved by heating a solution of **363** in 10% KOH in methanol at reflux<sup>108,109</sup> for 7 h, affording the primary alcohol **364** in 60% yield (Scheme 3.2).

#### Scheme 3.2

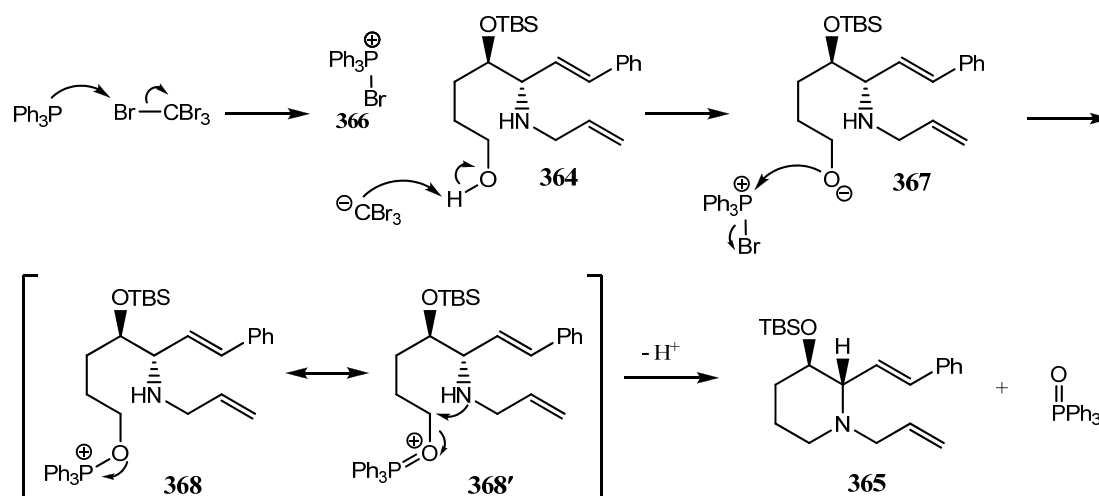


*Reagents and conditions:* (a) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C 2.5 h, 70%; (b) KOH, MeOH, reflux, 7 h, 60%.

### 3.1.2 Cyclization by intramolecular *N*-alkylation

The activation of the primary alcohol in **364** was carried out under Appel reaction conditions with carbon tetrabromide and triphenylphosphine to presumably form the oxyphosphonium intermediate **368**. Addition of triethylamine induced the S<sub>N</sub>2 displacement of triphenylphosphoxide by the free amine of **368'**, resulting in an intramolecular *N*-alkylation to give the piperidine derivative **365** in 71% yield (Scheme 3.3). With the ‘B-ring’ of our target molecule now at hand, we continued on to cyclizing the ‘A-ring’ utilizing a Grubbs ring-closing metathesis reaction of the diene in **365**.

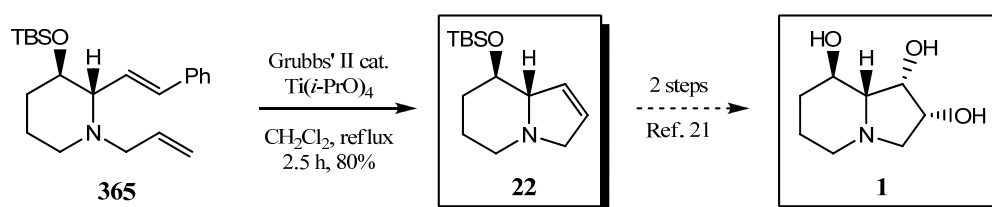
Scheme 3.3



### 3.2 Utilizing Lewis-acid assisted RCM to construct the ‘B-ring’

The metathesis of diene substrates containing free amines was previously considered a limitation in the scope of the Grubbs RCM reaction. The nucleophilic or basic nitrogen atom could complex with the ruthenium catalyst as ligands and retard the metathesizing activity of the Grubbs’ catalyst.<sup>110</sup> In 2005, Xiao *et al.* reported that the RCM of chiral diallyl amines were indeed feasible if a Lewis acid, such as titanium tetrakisopropoxide, were added in catalytic quantities (20 mol %) to deactivate the free amine by complexation.<sup>111</sup> Following Xiao’s method, the metathesis of the styrenyl and allyl moieties of **363** proceeded smoothly to give the silica gel sensitive indolizidine **22** in 80% yield after purification on basic alumina (Scheme 3.4).

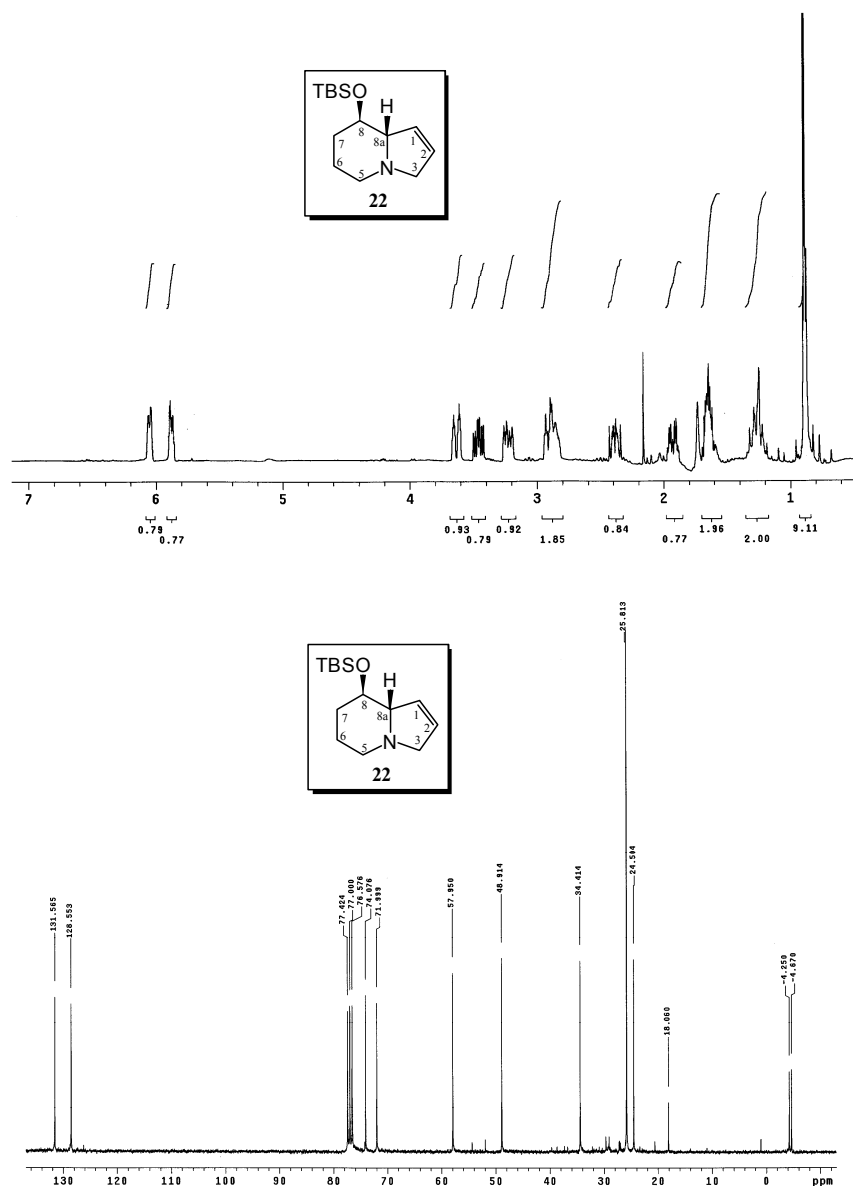
Scheme 3.4



### 3.3 A formal synthesis complete

The indolizidine **22** was previously prepared in >99% ee ( $[\alpha]_D^{26}$  -91.73,  $c$  0.955, benzene),<sup>21</sup> and in racemic form and converted to (-)-<sup>21</sup> and ( $\pm$ )-swainsonine, respectively.<sup>108</sup>

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (Figure 3.1) of our synthesized indolizidine **22** matched with those reported by Blechert *et al.*<sup>21</sup> The optical rotation of our synthesized **22** ( $[\alpha]_D^{20}$  -72,  $c$  0.65, benzene) was smaller in magnitude but of the same sign to that reported. We assume the enantiomeric purity of our **22** is 92% based on the ee of its precursor **353**. Thus our expected optical rotation for **22** would be -84.3. We attribute this difference to the sensitive nature of the product and the relatively small scale of our reactions.

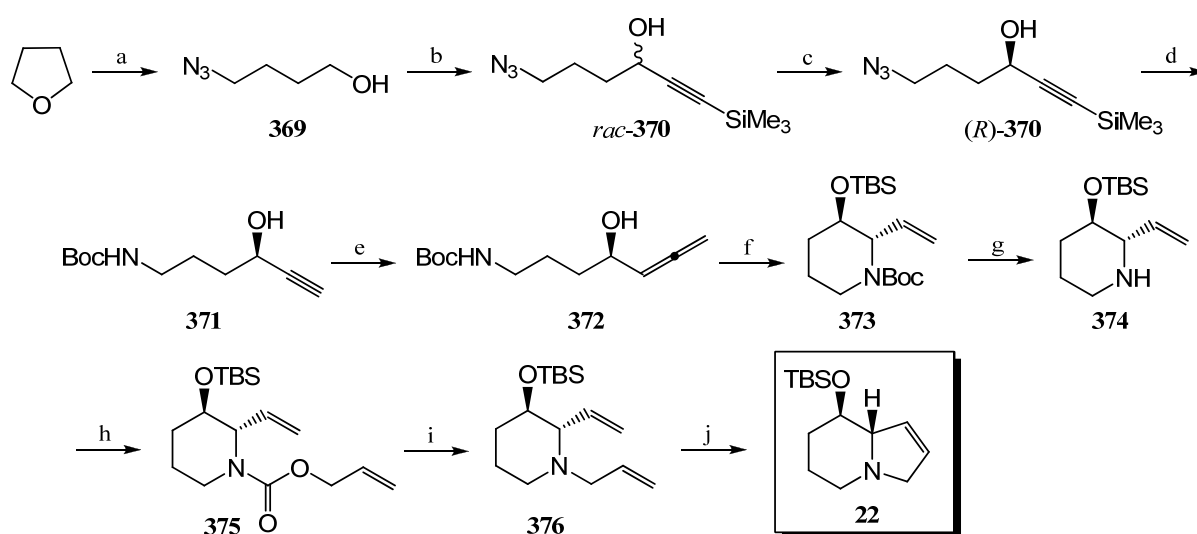


**Figure 3.1**  $^1\text{H}$  (300 MHz,  $\text{CDCl}_3$ ) and  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) spectra of the indolizidine **22**

During the writing of this Chapter, Bates *et al.* reported a formal synthesis of (-)-swainsonine, which concluded at the same indolizidine **22** (Scheme 3.5).<sup>112</sup> In five synthetic steps, tetrahydrofuran (THF) was converted into the racemic azidoalkyne

alcohol *rac*-**370**. Resolution of *rac*-**370** via an oxidation-reduction sequence afforded the (*R*)-**370** in 75-99% ee, which was then converted to the key allene intermediate **372** in four synthetic steps. The highlight of this formal synthesis was the highly diastereomeric gold-catalyzed cyclization of the allene **372** to give the *N*-Boc piperidine **373** as a single diastereomer. Having installed both of the stereogenic centers of the target molecule, the *N*-Boc piperidine **373** was subjected to *N*-deprotection, allyloxycarbonylation of the amine in **375** and a palladium(0) catalyzed alloc contraction to give the piperidinyll diene **376**, which was then converted to the indolizidine **22** in a total of 16 steps from THF.

### Scheme 3.5



*Reagents and conditions:* (a) (i) PhOCl, NaI, THF; (ii) NaN<sub>3</sub>, DMF; (iii) LiOH, THF/MeOH/H<sub>2</sub>O, 86%, 3 steps; (b) (i) IBX, DMSO; (ii) lithium trimethylsilylacetylene, THF, 66%, 2 steps; (c) (i) Dess-Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>; (ii) (*S*)-CBS, BH<sub>3</sub>·SMe<sub>2</sub> or catechol-borane, CH<sub>2</sub>Cl<sub>2</sub>, 59%, 2 steps; (d) (i) Zn, AcOH, Boc<sub>2</sub>O, Na<sub>2</sub>CO<sub>3</sub>, THF; (ii) K<sub>2</sub>CO<sub>3</sub>, MeOH, 71% 2 steps; (e) paraformaldehyde, *i*-Pr<sub>2</sub>NH, CuBr, dioxane; (ii) TBSCl, imid., DMAP, THF, 79%, 2 steps; (f) AuCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN, CaCO<sub>3</sub>, 99%; (g) CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>, 89%; (h) AllocCl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 92%; (i) Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, 85%; (j) Grubbs' II cat., TsOH, CH<sub>2</sub>Cl<sub>2</sub>, then 2M NaOH, 73%.

The <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data of Bates' indolizidine **22** were consistent with those of both Belchert's and our versions of the same compound. The optical rotation of Bates' **22** ([α]<sub>D</sub><sup>26</sup> -59.6, *c* 1, CH<sub>2</sub>Cl<sub>2</sub>) was of the same magnitude as that of Blechert's and ours although a different solvent was used by Bates.

In conclusion, our synthesis of the indolizidine **22** in a total of eight synthetic steps from 4-penten-1-ol and 7.7% overall yield represented a formal synthesis of (-)-swainsonine and proved the efficacy of using a 1,2-*anti* amino alcohol as a valuable chiral building block for the synthesis of an indolizidine alkaloid. The methodology developed herein

could, in theory, be applied to the synthesis of more complex alkaloids, which will be the focus of the remainder of this thesis.

## CHAPTER 4: TOTAL SYNTHESIS OF

### HYACINTHACINE B<sub>3</sub>

The polyhydroxylated pyrrolizidine alkaloid hyacinthacine B<sub>3</sub> (**104**) was first isolated in 2000 by Asano *et al.* from the fresh bulbs of the herbaceous plant *Muscari armeniacum*, commonly known as the grape hyacinth (Figure 4.1), yielding 72 mg of **104** among other alkaloids from 4 kg of grape hyacinth bulbs.<sup>113</sup>



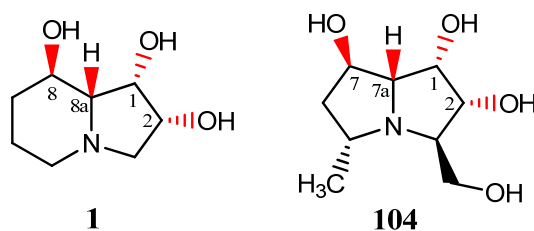
**Figure 4.1** Flowers and dissected fresh bulb of the grape hyacinth (*Muscari armeniacum*).

The HRFAB mass spectrum of the natural product showed an  $[MH]^+$  molecular ion at 204.1236 amu and when combined with the  $^{13}C$  NMR spectroscopic results revealed a molecular formula of  $C_9H_{17}NO_4$ . The connectivities of the carbon and hydrogen atoms and the relative stereochemistry were confirmed, respectively, by the  $^1H$ - $^{13}C$  COSY and 2D NOESY NMR experiments.<sup>113</sup>

At the beginning of this project, there was no known synthesis of the hyacinthacine B<sub>3</sub>; therefore, the main focus of this project was to furnish the first total synthesis of the hyacinthacine B<sub>3</sub>, consequently confirming the structural identity and absolute configuration of the pyrrolizidine alkaloid.

#### 4.1 Overview of synthetic plan

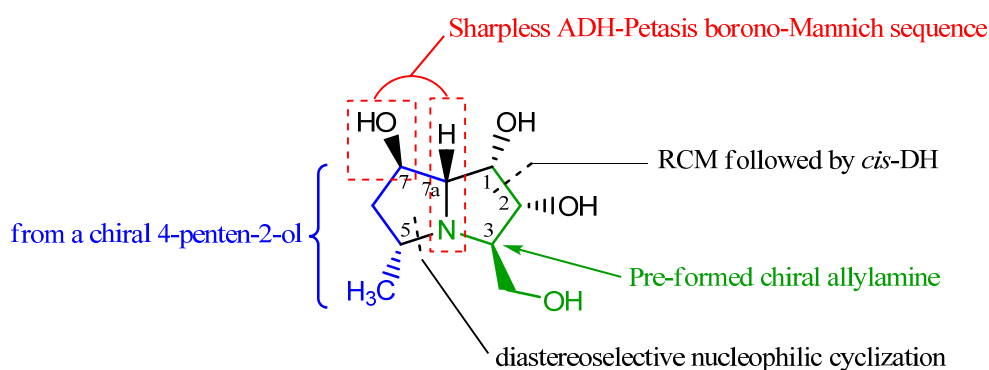
Comparing the structures of hyacinthacine B<sub>3</sub> (**104**) and (-)-swainsonine (**1**), the stereochemical configurations of the former alkaloid at the C-1, C-2, C-7 and C-7a positions are, respectively, identical to those at the C-1, C-2, C-8 and C-8a positions of the latter (shown in red in Figure 4.3).



**Figure 4.2** Stereochemical similarities between (-)-swainsonine (**1**) and hyacinthacine B<sub>3</sub> (**104**).

Noting these similarities, we envisioned using the Sharpless ADH and the Petasis borono-Mannich reactions, which respectively formed the hydroxy and amino groups of **1** in an *anti* configuration, to furnish in a similar fashion the C-7 and C-7a positions of **104**. Additionally, by using a pre-formed chiral allyl amine, the Petasis reaction could be utilized to construct the stereogenic hydroxymethyl substituent at the C-3 position of **104**. (Figure 4.3)

The (*R*)-methyl substituent at C-5 could originate from (*S*)-4-penten-2-ol, using a cyclization method that involved a S<sub>N</sub>2 displacement reaction. The *syn* diol on the C-7 and C-7a positions of **104** could be formed by the RCM reaction of a diene precursor,<sup>110</sup> followed by a *cis* dihydroxylation<sup>22,77</sup> of the resultant alkene with K<sub>2</sub>OsO<sub>4</sub> and NMO. (Figure 4.3).



**Figure 4.3** Synthetic analysis for hyacinthacine B<sub>3</sub> (**104**).

The synthetic analysis shown in Figure 4.3 is further elaborated in Scheme 4.1. We planned to use commercially available (*S*)-4-penten-2-ol **377** as the starting compound to cater for a subsequent stereoinversion in our synthetic scheme. Upon protecting **377** as the PMB ether **378**, an olefin cross-metathesis reaction would give the (*E*) vinyl sulfone **379**, which would then be used in the Sharpless-Petasis sequence to give the 1,2-*anti* amino alcohol **382**.

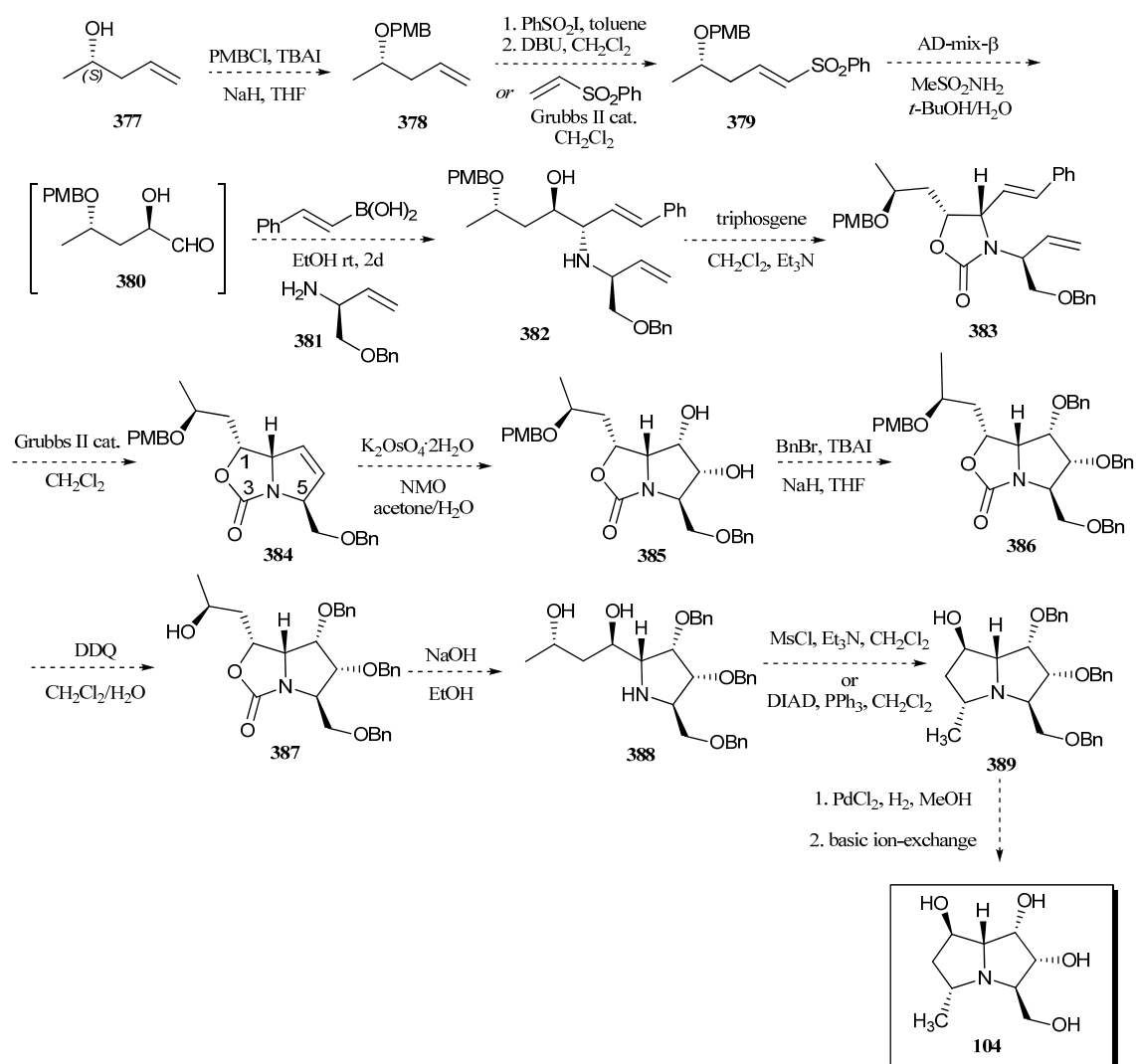
To prepare for the RCM reaction to form the A-ring, the amino and hydroxy moieties of **382** would have to be protected as the oxazolidinone **383** by treatment with triphosgene. The RCM product **384** would undergo a *cis*-dihydroxylation with K<sub>2</sub>OsO<sub>4</sub> and NMO to give the *syn*-diol **385**, which would then be protected as the bis-benzyl ether **386** (Scheme 4.1).

Anticipating the upcoming nucleophilic cyclization of the B-ring, we proposed to hydrolyze the oxazolidinone in **386** to liberate the amino and hydroxy groups at C-1 and C-7a, respectively, and to deprotect the PMB ether on C-2' with DDQ in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (Scheme 4.1).

The cyclization of the B-ring could then be achieved either by the Mitsunobu reaction or *via* mesylation of the hydroxy group on the C-3' position of **388** followed by nucleophilic cyclization. Both the Mitsunobu reaction and the mesylation-cyclization sequence would effect an inversion of stereochemistry at the C-3 position of the resultant pyrrolizidine. Following global debenzylation and basic ion-exchange chromatography, the target hyacinthaine B<sub>3</sub> (**104**) would be afforded in a total of 13 steps from (*S*)-4-penten-2-ol (Scheme 4.1).



Scheme 4.1

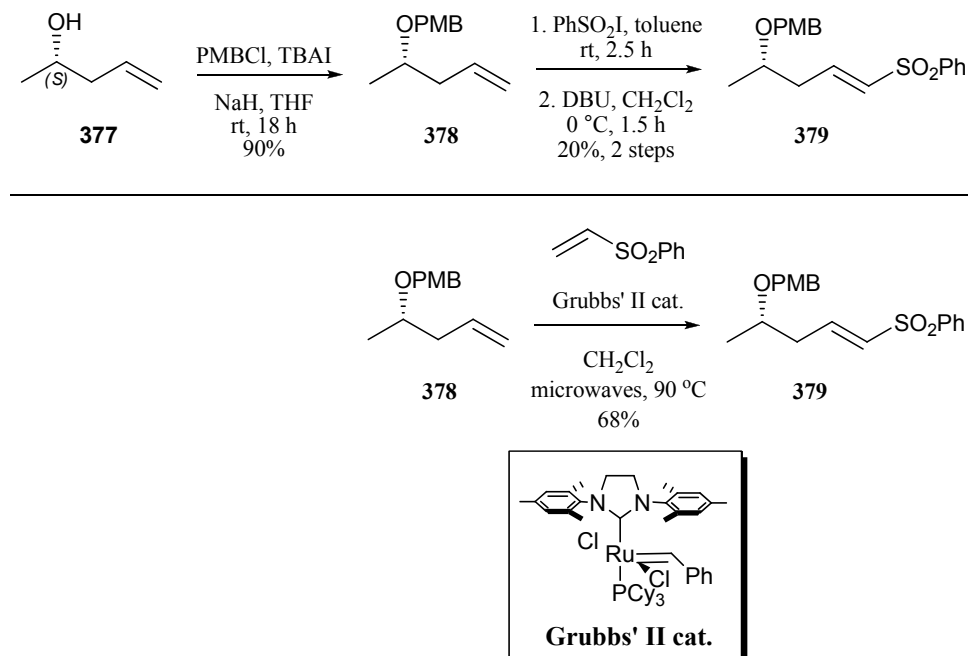


## 4.2 Vinyl sulfone synthesis *via* a cross-metathesis reaction

Our synthesis of hyacinthacine B<sub>3</sub> began with the protection of commercially available (*S*)-4-penten-2-ol **377** (ee > 98%) as a PMB ether **378** (Scheme 4.2). The relatively economical route using PhSO<sub>2</sub>I, which was developed in the formal synthesis of (-)-swainsonine was originally intended for preparing the vinyl sulfone **379**. Disappointingly, the iodosulfonylation-dehydroiodination of **378** resulted in a low yield (20%) of the vinyl sulfone **379** and several by-products inseparable by column chromatography. We then subjected the PMB ether **378** to an olefin cross metathesis reaction with phenylvinylsulfone catalyzed by Grubbs' II catalyst to give the vinyl sulfone **379** in 68% yield. Examination of the <sup>1</sup>H NMR spectrum of the cross-metathesis product **379** revealed the doublet of triplet signals for H-1 and H-2 at, respectively, 6.37 and 7.01 ppm. The

common coupling constant ( $J_{1,2}$ ) for these signals was 15.0 Hz, indicating that the (*E*) vinyl sulfone **379** was obtained as the sole product (Scheme 4.2).

**Scheme 4.2**



### 4.3 The Sharpless-Petasis sequence revisited

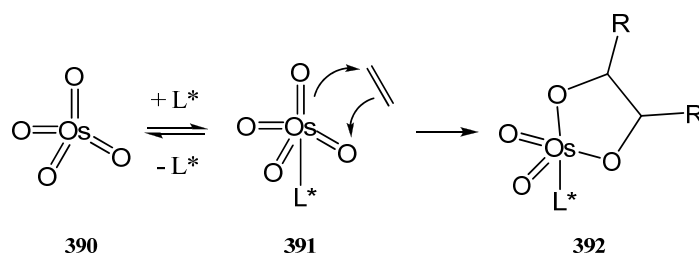
Following the success in using the Sharpless-Petasis sequence in synthesizing 1,2-*anti* amino alcohols in our formal synthesis of (-)-swainsonine, we hoped to further demonstrate the utility of this reaction sequence in constructing the *anti* configuration of the C-7 and C-7a positions of hyacinthacine B<sub>3</sub>.

#### 4.3.1 Dihydroxylation of **379** using AD-mix

The vinyl sulfone **379** was subjected to conditions described by Evans and Leffray<sup>96</sup> with commercially available AD-mix-β and MeSO<sub>2</sub>NH<sub>2</sub> in *t*-BuOH/H<sub>2</sub>O. Disappointingly, the reaction of **379** with this dihydroxylating mixture was very sluggish, and TLC analysis showed only slight consumption of **379**. We decided that it was not worthwhile to proceed with the Petasis reaction without exploring possible ways to improve the ADH component of the Sharpless-Petasis sequence by examining some mechanistic considerations.

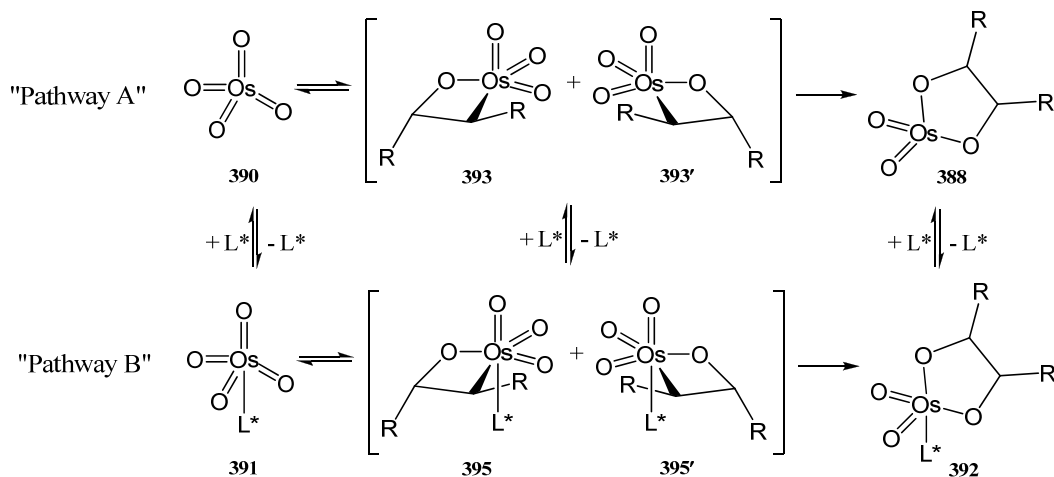
The two plausible and most discussed mechanisms for the osmium-catalyzed dihydroxylation of alkenes are the concerted [3+2] and the stepwise [2+2] pathways. Originally postulated by Criegee, who discovered the osmium-catalyzed dihydroxylation of alkenes in the 1930s and 40s,<sup>114-116</sup> the [3+2] pathway involves a concerted cycloaddition between the OsO<sub>4</sub> catalyst and the alkene to form the five-membered Os(VI) ester adduct **392** (Scheme 4.3). Criegee also observed that when ligands such as pyridine were added, the rate of the osmylation of alkenes was enhanced.<sup>116</sup>

**Scheme 4.3**



Proposed by Sharpless *et al.* in 1977,<sup>117</sup> the stepwise [2+2] mechanism for the ADH reaction involves the cycloaddition of one of the Os=O bonds across an alkene to first form the oxasmetane intermediate **393** which then undergoes bond migration to give the Os(VI) ester **394** (Scheme 4.4). In this model, an amine ligand could, in theory, complex with the osmium center at any point of the reaction. Subsequent mechanistic studies by Sharpless<sup>118</sup> and Lohray,<sup>119</sup> however, showed that ligand involvement occurs before the formation of the oxasmetane intermediate **393**, ruling out the feasibility of Pathway A in Scheme 4.4.

**Scheme 4.4**



Further experimental studies on the mechanism of ADH of alkenes could not exclude either of the [3+2] and [2+2] pathways, although available evidences seem to incline towards the [3+2] mechanism.<sup>120,121</sup>

Applying these mechanistic considerations to the ADH reaction of the vinyl sulfone **379** with commercially available AD-mix- $\beta$ , the OsO<sub>4</sub> catalyst must first form a complex with the dimeric (DHQD)<sub>2</sub>-PHAL chiral ligand contained in AD-mix- $\beta$  before coordinating to the alkene in **379**. Therefore, it was possible that the bulkiness of the OsO<sub>4</sub>-(DHQD)<sub>2</sub>-PHAL complex impeded its approach to the alkene and failed to generate the required  $\alpha$ -hydroxy aldehyde **380** in appreciable amounts.

#### 4.3.2 Dihydroxylation of **379** using the DHQD-IND chiral ligand

We then considered modifying our ADH approach by using the less bulky, monomeric ligand, DHQD-IND, synthesized from dihydroquinidine and indole. This monomeric ligand has been shown to be useful in the ADH reaction of (*Z*)-1,2-disubstituted alkenes.<sup>122</sup>

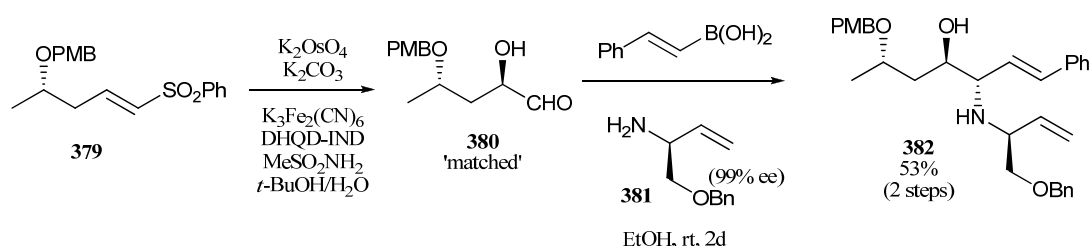
Comparing the ADH reaction of the vinyl sulfone **379** with that of the vinyl sulfone **306** in our synthesis of (-)-swainsonine, the *O*-PMB protecting group of **379** is one carbon closer to the alkene than the *O*-TBDPS protecting group of **306**. Given its smaller size, the osmium-ligand complex containing the monomeric DHQD-IND ligand might have an advantage in approaching the alkene and result in faster turnover of the  $\alpha$ -hydroxy aldehyde intermediate. A potential drawback that we considered when we decided to use the DHQD-IND ligand was the possible lower enantioselectivity of the ADH reaction, as in the case of the ADH of (*Z*)-disubstituted alkenes.<sup>123,124</sup>

The reaction of the vinyl sulfone **379** with DHQD-IND proceeded in *t*-BuOH/H<sub>2</sub>O, with K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O as the source of OsO<sub>4</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub> as the reoxidant, and the reaction was buffered with K<sub>2</sub>CO<sub>3</sub>. Methanesulfonamide was used to aid the hydrolysis of the osmate ester. The reaction mixture was initially sonicated to ensure better solubility of the salts. At 24 h, TLC analysis showed almost complete consumption of the starting vinyl sulfone. After quenching and aqueous workup, the crude reaction mixture containing presumably acetal forms of the desired  $\alpha$ -hydroxy aldehyde **380** was used in the Petasis reaction (Scheme 4.5).

### 4.3.3 The Petasis reaction using a chiral allyl amine

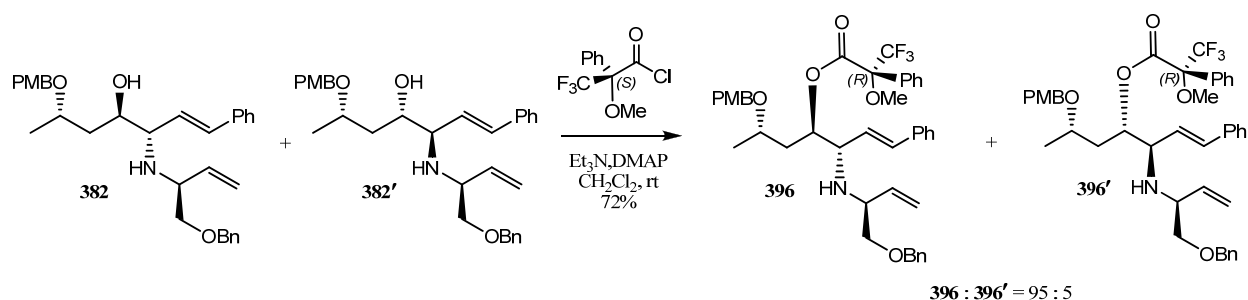
To build the hydroxymethyl group at the C-3 position of the hyacinthacine B<sub>3</sub>, we used the chiral allylamine **381**, prepared in 99% enantiomeric excess according to the methods of Trost,<sup>107</sup> along with styrenyl boronic acid and the “ $\alpha$ -hydroxy aldehyde **380**” in the three-component, one-pot Petasis reaction. The reaction proceeded for 48 h, and gave the *anti* amino alcohol **382** in an overall yield of 53% in two steps from the vinyl sulfone **379** (Scheme 4.5).

**Scheme 4.5**



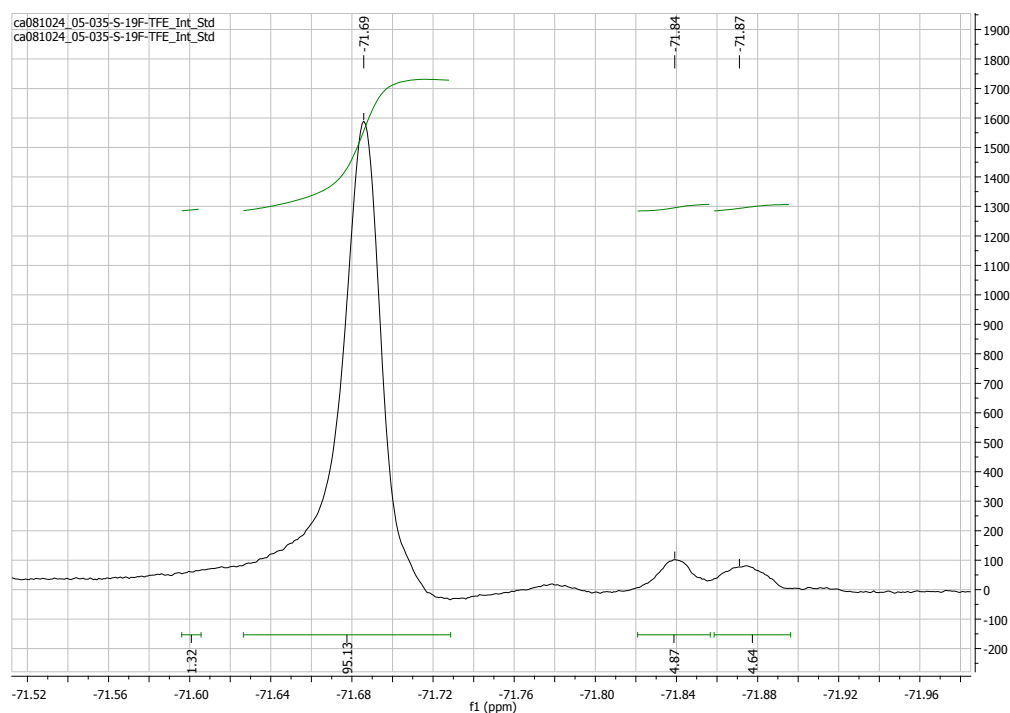
The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the amino alcohol **382** showed the presence of two apparently diastereomeric minor products. We were anxious to resolve the diastereoselectivity of the Sharpless-Petasis sequence and decided to do so by synthesizing and examining the (*R*)-Mosher's ester of the *anti* amino alcohol **382** (Scheme 4.6).

**Scheme 4.6**



The  $^{19}\text{F}$  NMR spectrum of the (*R*)-Mosher's ester **396** (Figure 4.4) showed one major peak at -71.68 ppm, belonging to the *anti* amino alcohol **382**. Two minor peaks at -71.84 ppm and 71.87 ppm account for approximately 10% of the total product, indicating that the diastereomeric ratio of the parent amino alcohol **382** was *ca.* 90:5:5. We speculate that one minor product **382'** arises from a “mismatched” case in the Sharpless ADH reaction,

producing an *anti* amino alcohol with the opposite configuration at C-3 and C-4. The other minor product most likely arises from the small amount of (*R*)-4-penten-2-ol in the starting (*S*)-penten-2-ol **377**, although this was claimed to be > 98% ee.

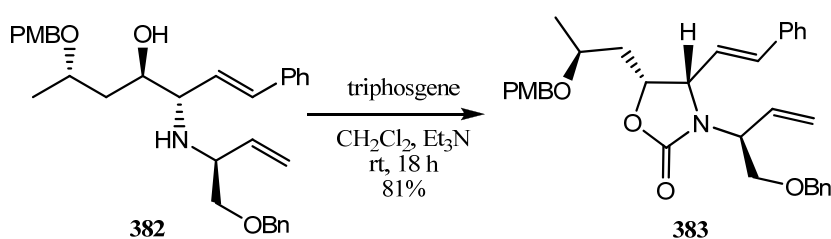


**Figure 4.4**  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 282 MHz) spectrum of the (*R*)-Mosher's ester **396** with  $\text{CF}_3\text{CH}_2\text{OH}$  referenced at -77.8 ppm.

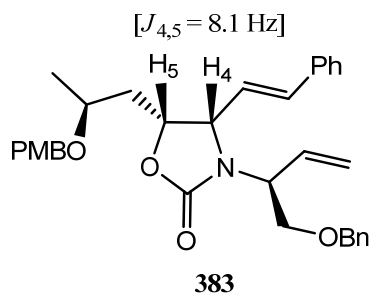
#### 4.4 Oxazolidinone synthesis with triphosgene

To protect the amino and alcohol moieties of **382** from subsequent synthetic steps, we protected it as its oxazolidinone derivative *via* a reaction with triphosgene and  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$ . The reaction proceeded smoothly to give the diastereomerically pure oxazolidinone **383** in 81% yield (Scheme 4.7).

**Scheme 4.7**



Having access to the oxazolidinone **383** allowed us to examine its <sup>1</sup>H NMR spectrum in order to determine the relative stereochemistry of the amino alcohol **382**. The vicinal coupling between H-4 and H-5 of **383** showed a magnitude of 8.1 Hz which was consistent with the *cis* relative stereochemistry between H-4 and H-5 and established the *anti* configuration of the amino and alcohol groups.

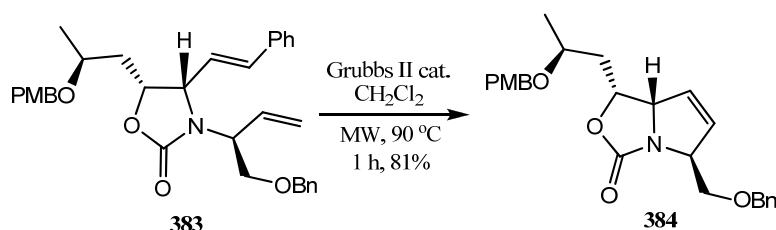


**Figure 4.5** Vicinal coupling between H-4 and H-5 of the oxazolidinone **383**

#### 4.5 Formation of the A-ring by RCM with Grubbs' II catalyst

We were now ready to form the A-ring of our target molecule. Utilizing the RCM reaction using the Grubbs' II catalyst with microwave heating for 1 h in CH<sub>2</sub>Cl<sub>2</sub>, the pyrrolidine product **384** was obtained in 81% yield (Scheme 4.8). The same yield was obtained with conventional oil-bath heating at 45 °C for 18 h.

#### Scheme 4.8

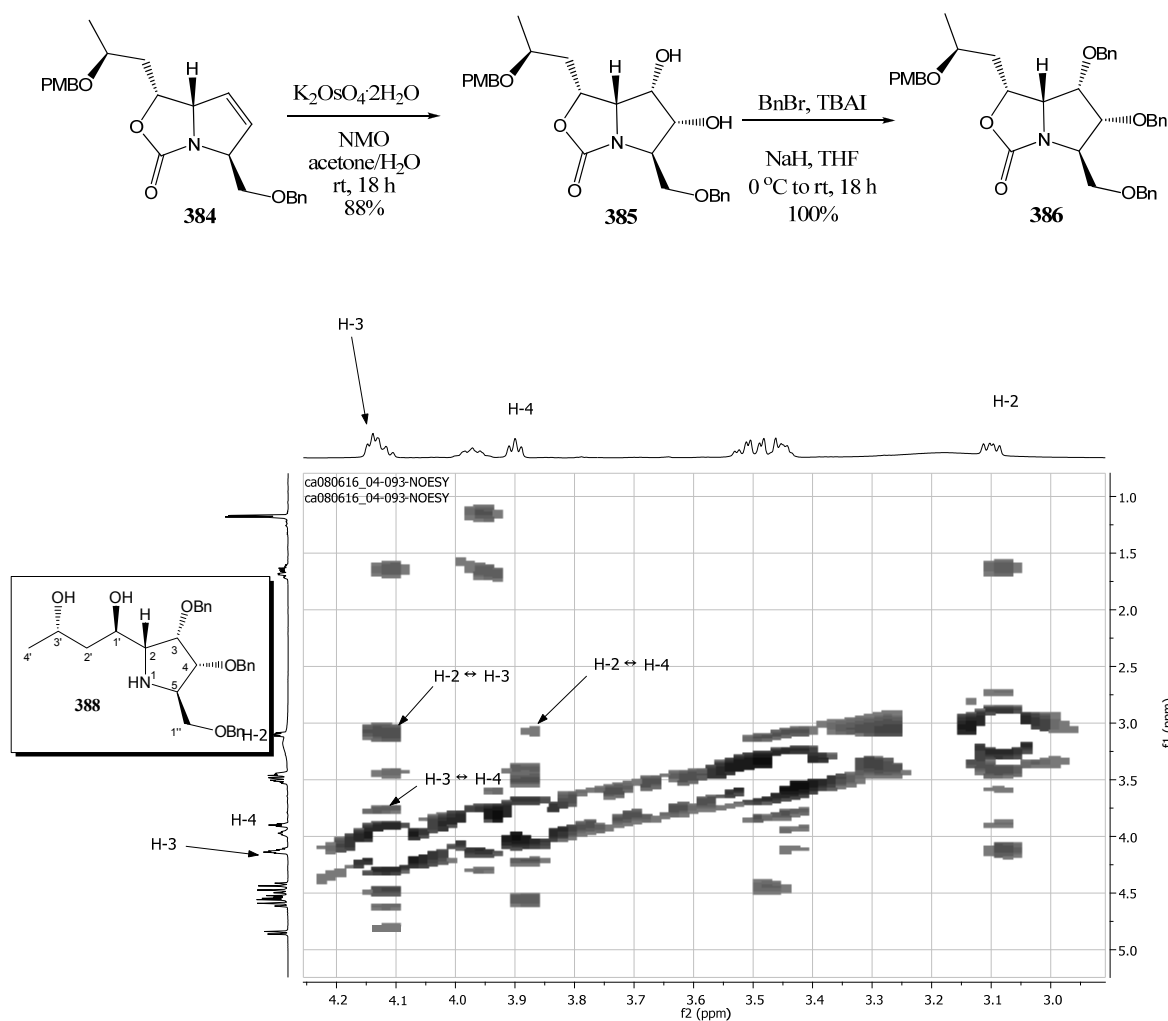


#### 4.6 *cis*-Dihydroxylation with OsO<sub>4</sub> and NMO and bis-benylation of the resultant diol

Based on previous work by Parsons<sup>41</sup> and our group,<sup>94</sup> we expected that the *syn*-dihydroxylation (DH) of **384** would furnish the corresponding 6β,7β-diol **385** with the desired configuration for the synthesis of the target alkaloid. In the event, the Os(VIII)-catalysed *syn*-DH of **384** provided the desired diol **385** as a single diastereoisomer in 88% yield (Scheme 4.9). This result is also consistent with the result of the DH reaction of a

similar system reported by Delair *et al.* in their total synthesis of (+)-hyacinthacine A<sub>1</sub> (Scheme 1.34).<sup>77</sup> The diastereoselectivity of the DH reaction was proven later in the synthetic path in the NOESY NMR spectrum of compound **388** (Figure 4.6), which showed NOE correlations between H-2 and H-4, H-3 and H-4, and H-2 and H-3, indicating the *syn* relationships among these protons.

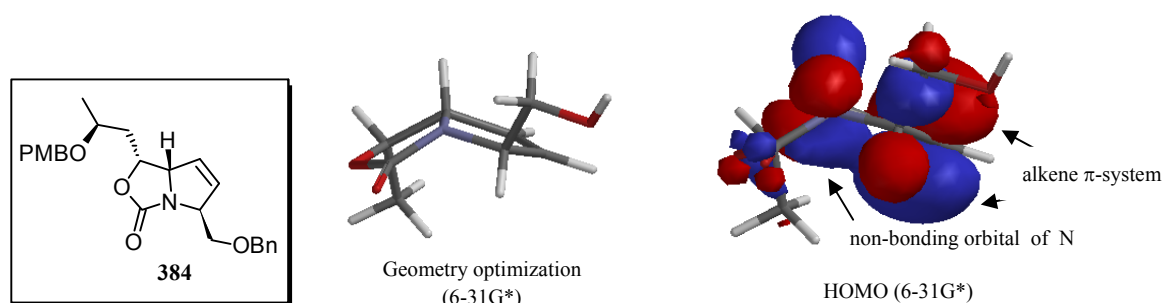
#### Scheme 4.9



**Figure 4.6** 2-D NOESY NMR (CDCl<sub>3</sub>, 500 MHz) of diol **388**.



This high level of diastereoselectivity can be explained based on stereoelectronic effects and an examination of the HOMO of **384** about the alkene moiety (Figure 4.7). The non-bonding orbital bearing the electron pair on the N-atom overlaps more effectively with the  $\pi$ -system of the alkene moiety on the  $\alpha$ -(concave) face of the molecule making this face more prone to dihydroxylation.<sup>41</sup> The  $\beta$ -benzyloxymethyl substituent at C-5 also contributed partially to the diastereofacial selectivity, since the DH of a similar substrate which lacked this C-5 substituent was less diastereoselective.<sup>125</sup>



**Figure 4.7** HF/6-31G\* (SPARTAN) geometry and HOMO energy surface optimizations for **384**.

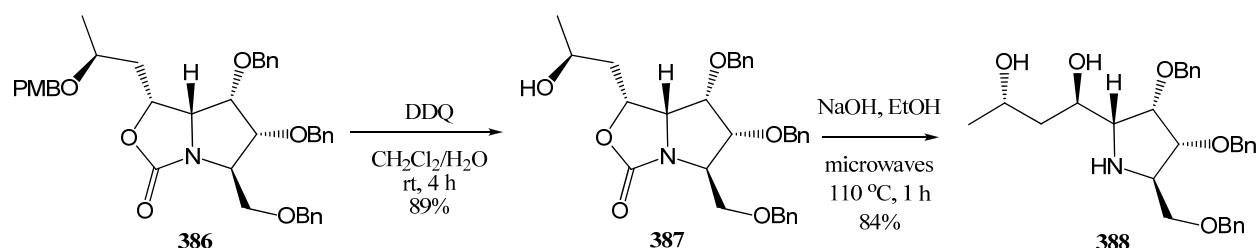
Using benzyl bromide and sodium hydride in THF, the newly formed diol **385** was protected as the bisbenzyl ether **386** in quantitative yield (Scheme 4.10).

#### 4.7 DDQ deprotection of the PMB ether and hydrolysis of the oxazolidinone

Delighted that the structure and substituents of the A-ring had been properly installed and protected, we turned our focus to setting up the cyclization of the five-membered B-ring by first deprotecting the PMB-ether in **386** to free the hydroxy group and then hydrolyze the oxazolidinone in **387** to expose the amino and hydroxy moieties.

The selective *O*-deprotection of the PMB ether **386** was achieved by the facile reaction with DDQ in wet CH<sub>2</sub>Cl<sub>2</sub>, producing the secondary alcohol **387** in 89% yield and leaving the benzyl ethers intact. Base-catalyzed hydrolysis of the oxazolidinone in **387** with NaOH in ethanol with microwave heating at 110 °C for 1 h afforded the amino diol **388** in 84% yield (Scheme 4. 10).

Scheme 4.10



## 4.8 Towards the Hyacinthacine B<sub>3</sub>

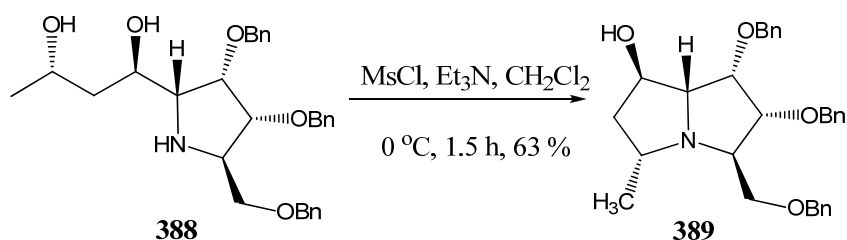
### 4.8.1 Nucleophilic cyclization of the B-ring *via* *O*-mesylation and S<sub>N</sub>2 displacement

Two choices for the formation of the B-ring *via* nucleophilic cyclization were the Mitsunobu reaction or regioselective *O*-mesylation followed by S<sub>N</sub>2 displacement by the amine. In our group's syntheses of polyhydroxylated pyrrolizidine alkaloids, the Mitsunobu reaction has been a reliable method of forming similar ring structures, albeit in yields that are often unsatisfactory.<sup>126,92</sup>

We made several attempts at cyclizing the B-ring under Mitsunobu conditions using DIAD, PPh<sub>3</sub> and Et<sub>3</sub>N in THF. However, after 24 h of stirring at rt, there was no cyclized product detectable by TLC or mass spectrometric analyses of the reaction mixture. Pyridine was then used instead of Et<sub>3</sub>N, and yet no reaction was observed.

Cyclization of the B-ring was finally achieved *via* a mesylation-S<sub>N</sub>2 displacement sequence. Upon reaction with MsCl at 0 °C, the amino diol **388** underwent a regioselective *O*-mesylation and then S<sub>N</sub>2 cyclization with inversion at the less hindered secondary carbinol carbon upon exposure to 1.05 equivalents of MsCl<sup>85</sup> under basic conditions (Et<sub>3</sub>N) at 0 °C to give the pyrrolizidine **389** in 63% yield (Scheme 4.11). A small amount of the *N*-*O*-di-mesylate of **388** was also produced but was readily separated from the desired cyclized product **389** by column chromatography.

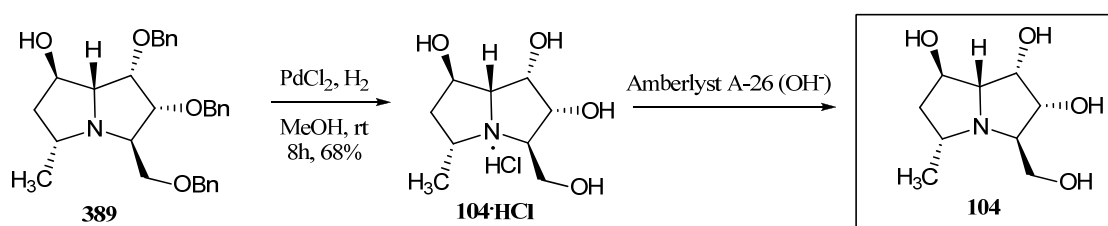
Scheme 4.11



#### 4.8.2 Global debenzylation and purification by basic ion-exchange chromatography

Using palladium(II) chloride in methanol, the three benzyl protecting groups on the pyrrolizidine **389** was removed under an atmosphere of hydrogen. The debenzylation product, presumably an HCl salt, was passed through a pad of Amberlyst A-26 ( $\text{OH}^-$ ) ion-exchange resin to afford the natural product **104** as a free base (Scheme 4.12).

Scheme 4.12



#### 4.8.3 Comparing spectral data with natural hyacinthacine B<sub>3</sub>

The  $^1\text{H}$  NMR spectrum of the synthesized pyrrolizidine **104** was compared with that of the natural hyacinthacine B<sub>3</sub> (Figure 4.8a). The multiplicities of the synthesized **104** observed at various chemical shifts were essentially identical to those reported of the natural product (Table 4.1). The doublet of doublet of doublets signal observed for H-7 of the natural product at  $\delta_{\text{H}}$  4.52 ppm ( $J = 3.9, 4.6, 6.8$  Hz) appeared in the spectrum of the synthetic product to be a doublet of triplet ( $J = 4.1, 5.6$  Hz). The 5.6 Hz triplet coupling constant observed in the synthetic product was most likely a lower resolution representation of the original 4.6 and 6.8 Hz doublet of doublets.

The NOESY NMR spectrum of the synthetic product **104** revealed all the NOE correlations observed in the natural hyacinthacine B<sub>3</sub> (Figure 4.9). Comparing the  $^{13}\text{C}$  NMR spectrum of synthetic **104** (referenced to  $\text{CH}_3\text{OH}$  at 49.05 ppm) with that of the

natural product (referenced to CH<sub>3</sub>OH at 49.05 ppm) revealed consistent differences in chemical shifts of -0.7 to -0.9 ppm (Figure 4.8b and Table 4.2).

The specific rotations of synthetic **104** ( $[\alpha]_D^{23} +10.8$  ( $c$  0.33, H<sub>2</sub>O)) and natural hyacinthacine B<sub>3</sub> ( $[\alpha]_D +3.3$  ( $c$  0.31, H<sub>2</sub>O)) were of the same sign. The difference in magnitudes between the two rotations was unexpected and somewhat puzzling, as all of the spectroscopic data of **104** was very consistent with those reported of the natural product. One possible explanation for the difference is that the natural product could be a mixture of **104** and a small amount of *ent*-**104**, thus resulting in the smaller magnitude in specific rotation.

In summary we have prepared the alkaloid hyacinthacine B<sub>3</sub> in 13 steps and 5.6% overall yield from commercially available (*S*)-4-penten-2-ol. This synthesis confirms and structure and configuration of the natural product.

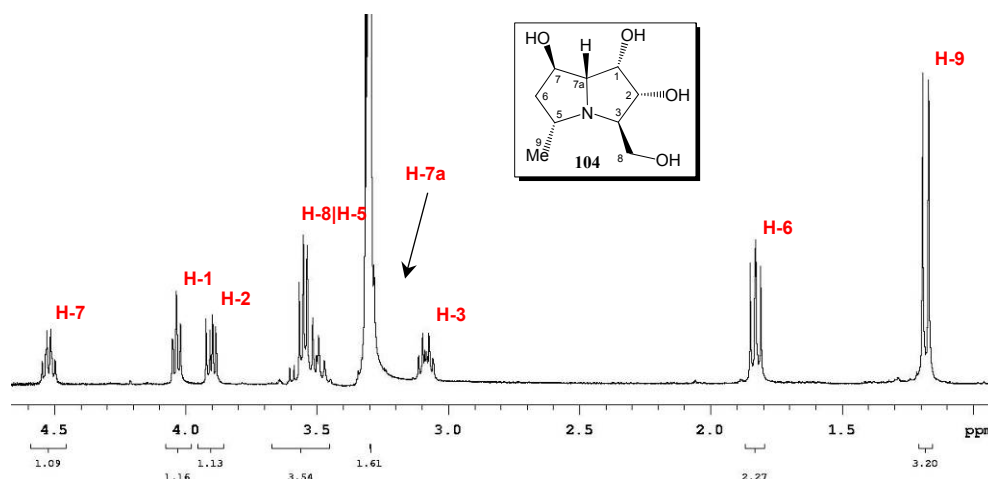


Figure 4.8a <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) spectrum of synthetic **104**.

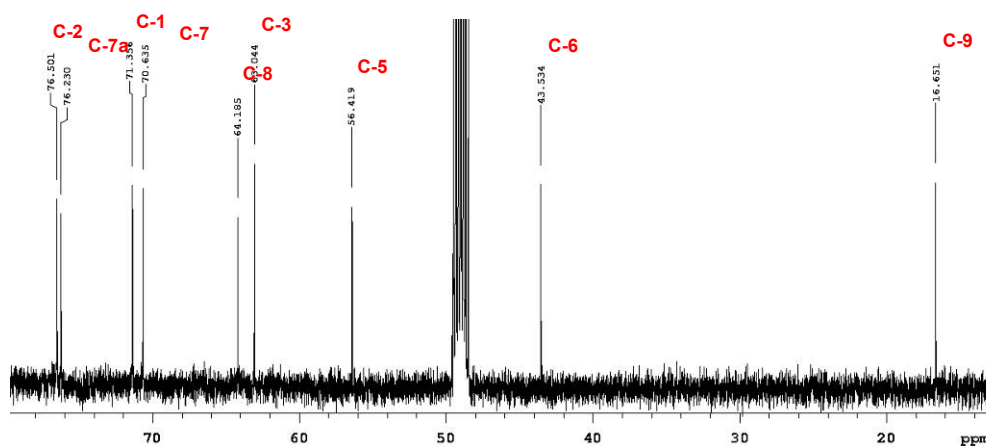
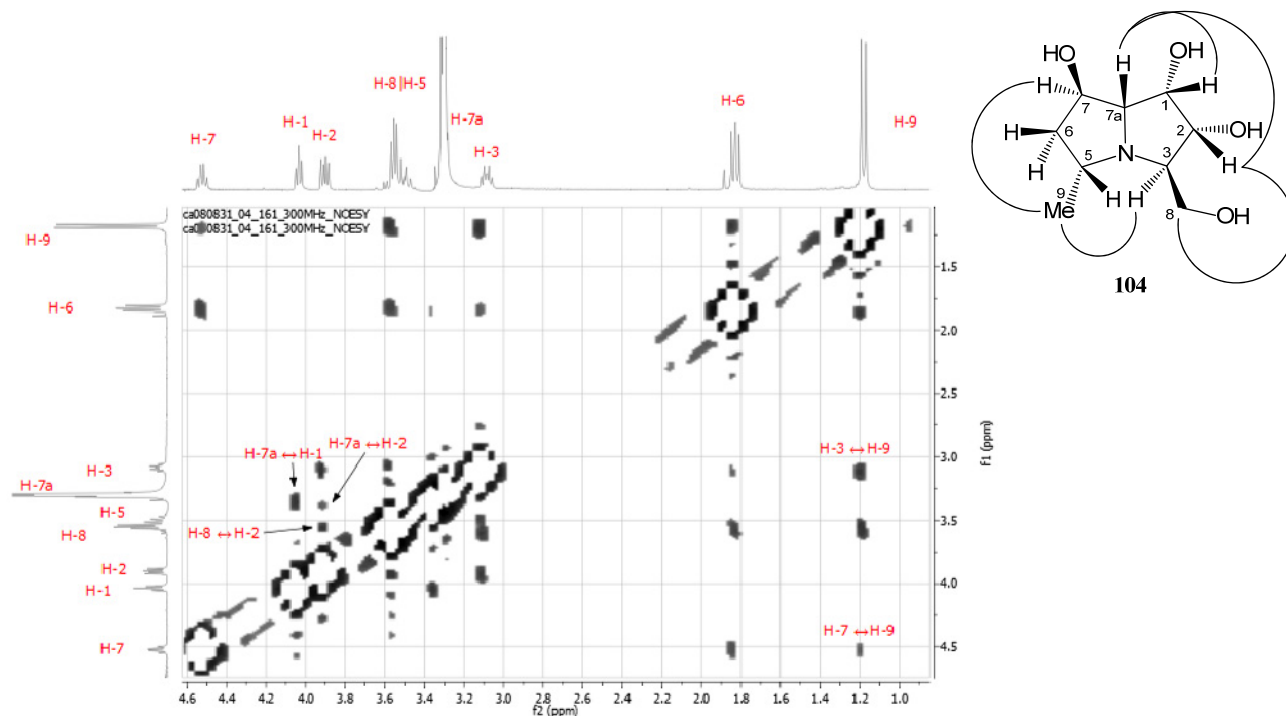


Figure 4.8b <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz) spectrum of synthetic **104**.

**Table 4.1** Comparison of <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) data between natural hyacinthacine B<sub>3</sub> and synthetic **104**.

H	Natural Hyacinthacine B <sub>3</sub>		Synthetic <b>104</b>	
	$\delta_{\text{H}}$ (ppm)	Mult., $J$ (Hz)	$\delta_{\text{H}}$ (ppm)	Mult., $J$ (Hz)
<b>1</b>	4.03	dd (4.2, 4.6)	4.04	t (4.4)
<b>2</b>	3.91	dd (4.2, 7.3)	3.91	dd (4.1, 7.4)
<b>3</b>	3.08	ddd (4.4, 4.9, 7.3)	3.08	ddd (4.7, 4.9, 7.3)
<b>5</b>	3.50	m	3.50	m
<b>6a</b>	1.82	m	1.82	m
<b>6b</b>	1.82	m	1.82	m
<b>7</b>	4.52	ddd (3.9, 4.6, 6.8)	4.52	dt (4.1, 5.6)
<b>7a</b>	3.30	t (4.6)	3.30	t (4.6)
<b>8a</b>	3.53	dd (4.4, 11.0)	3.53	dd (4.5, 11.0)
<b>8b</b>	3.57	dd (4.9, 11.0)	3.58	dd (5.0, 11.0)
<b>9</b>	1.17	d (6.8)	1.18	d (6.8)

**Figure 4.9** 2-D NOESY NMR (CD<sub>3</sub>OD, 300 MHz) spectrum of synthetic **104**.

**Table 4.2** Comparison of <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD) data between natural hyacinthacine B<sub>3</sub> and synthetic **104**.

C	Natural Hyacinthacine B <sub>3</sub>	Synthetic <b>104</b>	$\delta_{\text{C-synthetic}} - \delta_{\text{C-natural}}$ (ppm)
	$\delta_{\text{C}}$ (ppm)	$\delta_{\text{C}}$ (ppm)	
<b>1</b>	72.2	71.3	-0.9
<b>2</b>	77.4	76.5	-0.9
<b>3</b>	63.8	63.0	-0.8
<b>5</b>	57.1	56.4	-0.7
<b>6</b>	44.4	43.5	-0.9
<b>7</b>	71.5	70.6	-0.9
<b>7a</b>	77.0	76.2	-0.8
<b>8</b>	65.0	64.2	-0.8
<b>9</b>	17.5	16.7	-0.8

## CHAPTER 5: TOTAL SYNTHESIS OF PURPORTED HYACINTHACINE B<sub>7</sub>

### 5.1 Isolation and structure elucidation of the hyacinthacine B<sub>7</sub>

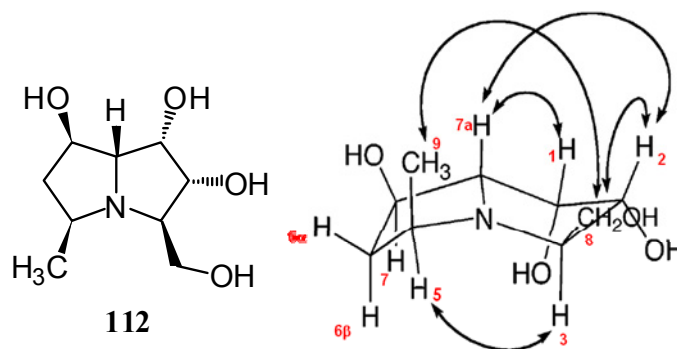
In 2007, Kato *et al.* reported the isolation of six polyhydroxylated pyrrolizidine alkaloids from the bulbs of the plant *Scilla socialis* (Figure 5.1).<sup>52</sup> Among these alkaloids, one had the molecular formula of C<sub>9</sub>H<sub>17</sub>NO<sub>4</sub> as determined by HRFABMS analysis. While the <sup>1</sup>H and <sup>13</sup>C NMR spectra of this alkaloid were similar to those of the hyacinthacine B<sub>3</sub> (**104**, Table 5.2), HMQC, COSY and HMBC spectral data further indicated that the new alkaloid had the same connectivities as **104**. The authors determined from NOESY correlations as shown in Figure 5.1 and <sup>3</sup>J<sub>H,H</sub> coupling patterns for H-1 and H-2 (Table 5.1) that the new alkaloid was the C-3 epimer of **104** and named it hyacinthacine B<sub>7</sub> (**112**). In glycosidase inhibitory activity studies, **112** was found to be a weak inhibitor (IC<sub>50</sub> = 270 μM) of the amyloglycosidase enzyme.



**Figure 5.1** Flowers and fresh bulb of *Scilla socialis*.

**Table 5.1** Comparison of  $^1\text{H}$  NMR spectral data between hyacinthacines  $\text{B}_3$  (**104**) and  $\text{B}_3$  (**112**) isolated from natural sources.

H/C	Natural hyacinthacine $\text{B}_3$ , <b>104</b>			Natural hyacinthacine $\text{B}_7$ , <b>112</b>		
	$\delta_{\text{H}}$ (ppm) <sup>*</sup>	Mult., $J(\text{Hz})$ <sup>*</sup>	$\delta_{\text{C}}$ (ppm) <sup>*</sup>	$\delta_{\text{H}}$ (ppm) <sup>#</sup>	Mult., $J(\text{Hz})$ <sup>#</sup>	$\delta_{\text{C}}$ (ppm) <sup>#</sup>
<b>1</b>	4.03	dd (4.6, 4.2)	72.2	4.35	t (4.4)	77.9
<b>2</b>	3.91	dd (4.2, 7.3)	77.4	3.97	dd (4.4, 7.6)	74.9
<b>3</b>	3.08	ddd (4.4, 4.9, 7.3)	63.8	3.29	ddd (3.5, 5.5, 7.6)	66.2
<b>5</b>	3.50	m	57.1	3.22	m	57.7
<b>6a</b>	1.82	m	44.4	1.68	m	45.2
<b>6b</b>	1.82	m		2.16	m	
<b>7</b>	4.52	ddd (3.9, 4.6, 6.8)	71.5	4.50	m	76.5
<b>7a</b>	3.30	t (4.6)	77.0	3.45	dd (4.4, 7.6)	69.9
<b>8a</b>	3.53	dd (4.4, 11.0)	65.0	3.57	dd (5.5, 11.5)	66.8
<b>8b</b>	3.57	dd (4.9, 11.0)		3.63	dd (5.5, 11.5)	
<b>9</b>	1.17	d (6.8)	17.5	1.25	d (7.0)	18.4

<sup>\*</sup> in  $\text{CD}_3\text{OD}$ <sup>#</sup> in  $\text{D}_2\text{O}$ **Figure 5.2** Proposed structure of the hyacinthacine  $\text{B}_7$  (**112**) and reported NOESY correlations.

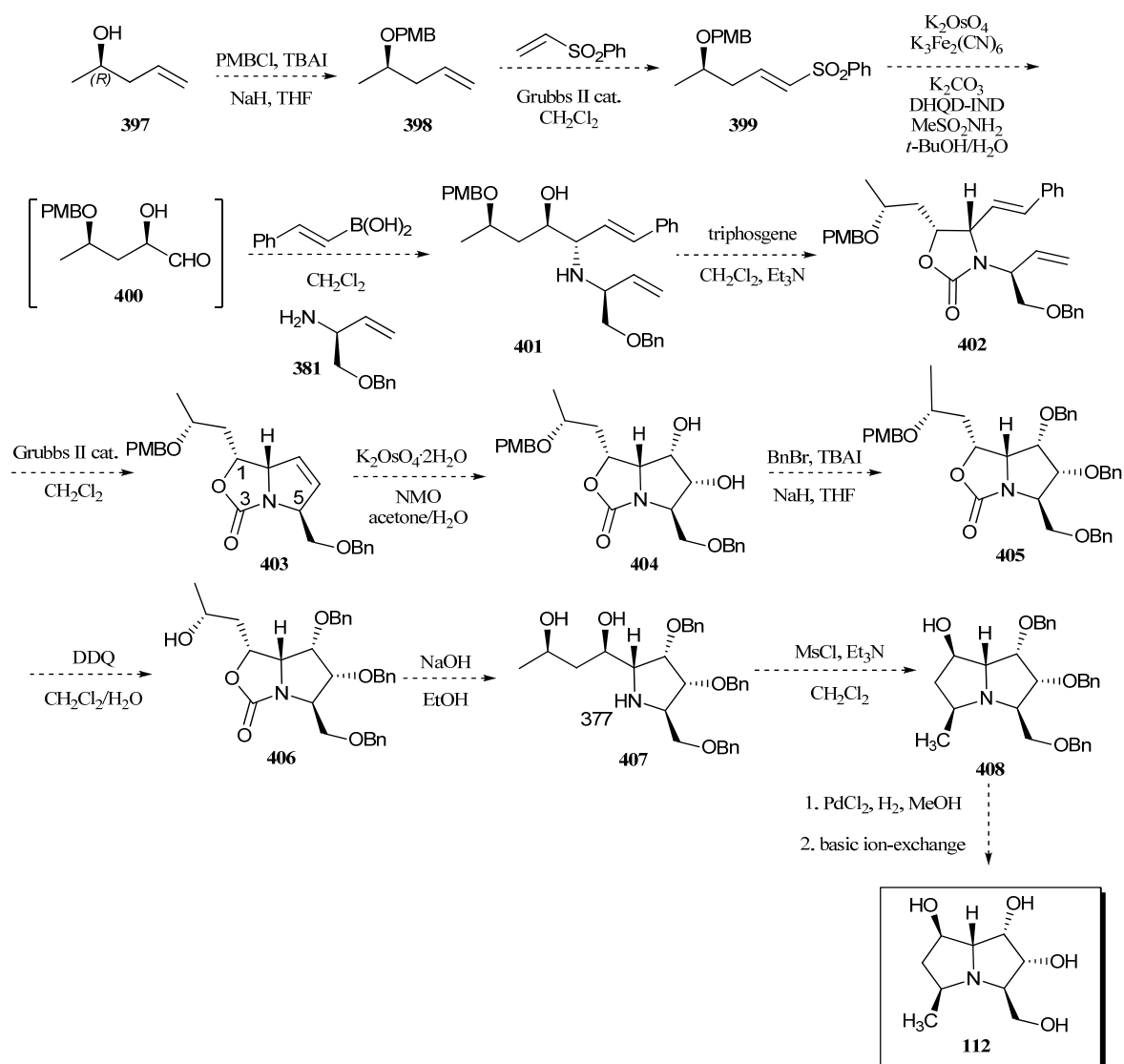


## 5.1 Synthetic plan

Owing to the structural similarities between the hyacinthacines **B**<sub>3</sub> and **B**<sub>7</sub>, we were prompted to apply the methods developed in our synthesis of **104** in furnishing the first total synthesis of **112**, which would also allow us to confirm the latter alkaloid's structure and absolute configuration.

Using (*R*)-4-penten-2-ol (**397**) as the starting material, the key reactions of this synthetic sequence would include: (1) the Sharpless-Petasis sequence to give the 1,2-*anti* amino alcohol **401**; (2) *syn*-dihydroxylation of the RCM reaction product **403** to give the amino diol **404**; and (3) cyclization and deprotection leading to **112** in a total of 13 steps (Scheme 5.1).

**Scheme 5.1**

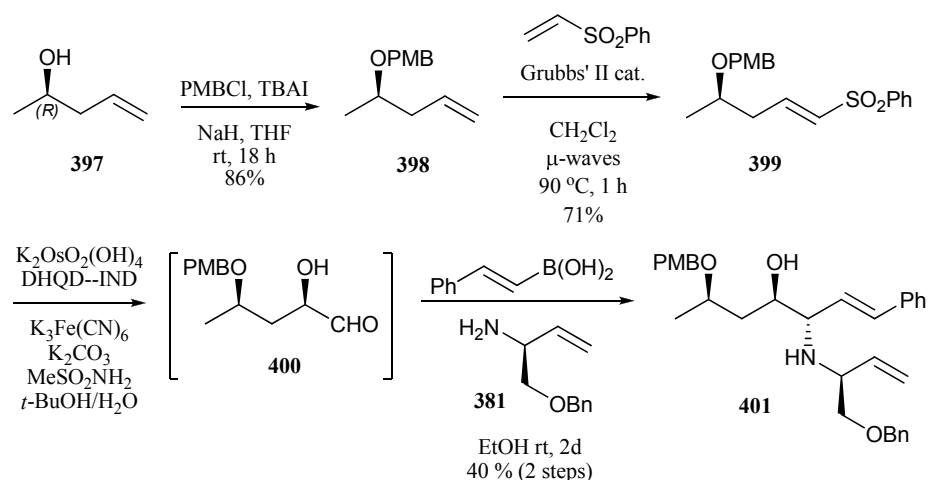


## 5.2 From (*R*)-4-penten-2-ol to the *anti* amino alcohol **401**

The CM reaction of PMB-protected (*R*)-4-penten-2-ol (**398**) with phenyl vinyl sulfone and the Grubbs' II catalyst proceeded smoothly to give the vinyl sulfone **399** in 71% yield. This was followed by the Sharpless ADH reaction of **399** using DHQD-IND and the Petasis reaction with (*E*)-styrenyl boronic acid and the chiral allyl amine **381** to afford the amino alcohol **401** in 40% yield over two steps (Scheme 5.2).

The yield obtained in this Sharpless-Petasis sequence was significantly lower than that achieved in our previous synthesis of hyacinthacine B<sub>3</sub> since a significant amount of another diastereomer of **401** (*ca.* 20% of the crude reaction mixture from <sup>1</sup>H NMR analysis) was also formed. This diastereomer could not be characterized since it could not be isolated in pure form. We suspect that this diastereomer arises in the conversion of **399** to the  $\alpha$ -hydroxy aldehyde **400** due to a mismatched situation between the chiral reagent and the chiral substrate.

**Scheme 5.2**

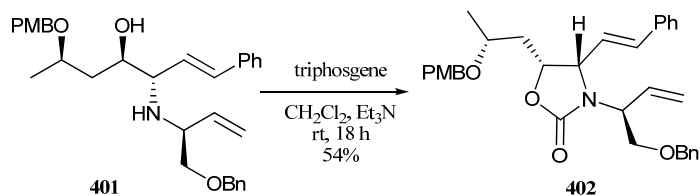


## 5.3 Towards the purported structure of hyacinthacine B<sub>7</sub>.

The protection of the *anti* amino alcohol **401** with triphosgene resulted in the formation of the oxazolidinone **402** in 54% yield (Scheme 5.3), which was significantly lower than what we achieved in the synthesis of **104**. This lower yield could be explained by the presence of a side-product formed from the presumably mismatched diastereomer from the Sharpless-Petasis sequence. We were able to isolate the oxazolidinone **402** in pure

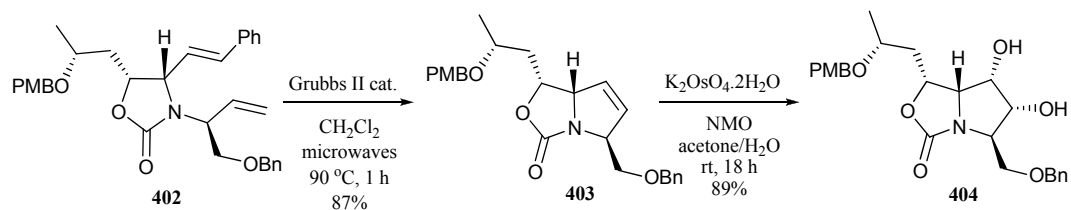
form, but the more polar side-product was not separable from other impurities from the reaction with triphosgene.

### Scheme 5.3



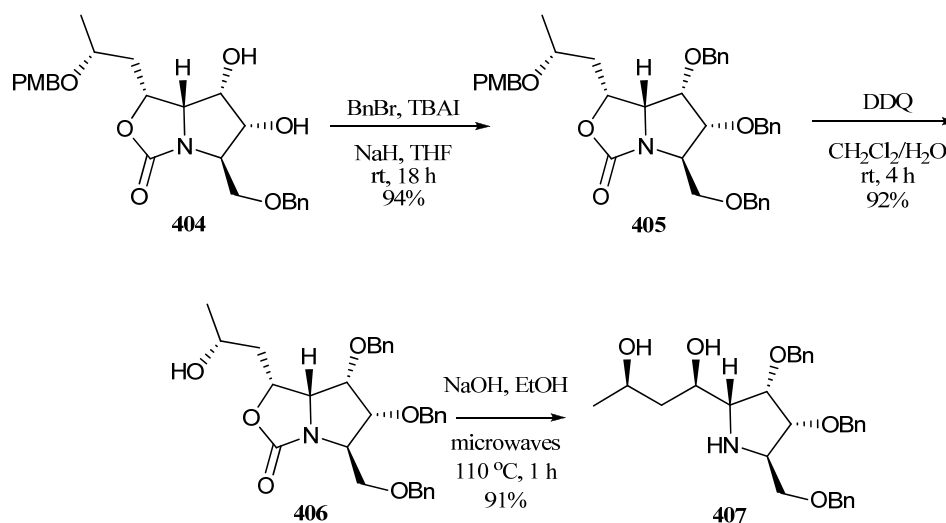
The RCM reaction of the dienyli moiety of **402** with Grubbs' II catalyst proceeded smoothly to give the pyrrolidine **403** in 87% yield. This was followed by the *syn*-dihydroxylation of **403** with  $\text{OsO}_4$  and NMO, which afforded exclusively the *syn* diol **404** in 89% yield (Scheme 5.4).

### Scheme 5.4



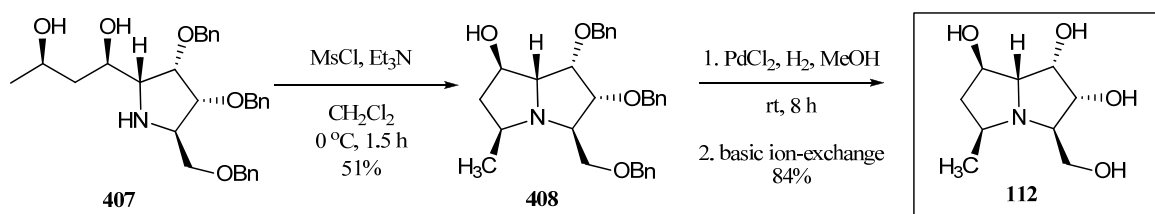
The bisbenzylation of the diol **404**, the PMB deprotection with DDQ and the oxazolidinone hydrolysis under basic conditions were accomplished in, respectively, 94%, 92% and 91% yield, similar to those achieved in the synthesis of **104** (Scheme 5.5).

Scheme 5.5



The mesylation of **407** and concomitant S<sub>N</sub>2 cyclization between the amine and mesylate groups gave the pyrrolizidine **408** in 51% yield, which upon global debenzoylation with H<sub>2</sub> and PdCl<sub>2</sub> in methanol and basic ion-exchange chromatography gave, in 84% yield, (1*S*,2*R*,3*R*,5*S*,7*R*,7*aR*)-3-hydroxymethyl-5-methyl-1,2,7-trihydroxypyrrolizidine (**112**), which is the purported structure of hyacinthacine B<sub>7</sub> (Scheme 5.6).

Scheme 5.6



#### 5.4 Comparison of spectral data with the natural product

The <sup>1</sup>H NMR and H-H COSY spectra of the synthesized **112** showed the connectivities of a 3-hydroxymethyl-5-methyl-1,2,7-trihydroxypyrrolizidine. We then compared the <sup>1</sup>H NMR spectra of the natural product and the synthesized **112**, as summarized in Table 5.2. Unlike the comparison between natural and synthesized hyacinthacine B<sub>3</sub>, the <sup>1</sup>H NMR spectrum of the synthesized **112** did not agree with that of the natural product. Although similar splitting patterns were observed at the various chemical shifts, the coupling constants of the multiple peaks were not consistent with one another.

While the  $^{13}\text{C}$  NMR chemical shifts of the natural and synthesized versions of **104** had consistent differences of 0.7 to 0.9 ppm, we were disappointed to learn that the disparities between the chemical shifts of the synthesized **112** and the natural product were largely inconsistent (Table 5.3).

**Table 5.2**  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ ) spectral data of natural and synthesized hyacinthacine B<sub>7</sub> (**112**).

H	Natural		Synthetic	
	$\delta_{\text{H}}$ (ppm)	Mult., J(Hz)	$\delta_{\text{H}}$ (ppm)	Mult., J(Hz)
<b>1</b>	4.35	t (4.4)	4.13	t (3.9)
<b>2</b>	3.97	dd (4.4, 7.6)	4.03	dd (3.9, 9.0)
<b>3</b>	3.29	ddd (3.5, 5.5, 7.6)	2.81	ddd (4.9, 4.9, 9.0)
<b>5</b>	3.22	m	3.01	m
<b>6a</b>	1.68	m	1.60	m
<b>6b</b>	2.16	m	2.38	m
<b>7</b>	4.50	m	4.61	m
<b>7a</b>	3.45	dd (4.4, 7.6)	3.32	dd (3.9, 5.9)
<b>8a</b>	3.57	dd (5.5, 11.5)	3.70	dd (4.9, 11.5)
<b>8b</b>	3.63	dd (5.5, 11.5)	3.74	dd (4.9, 11.5)
<b>9</b>	1.25	d (7.0)	1.17	d (6.4)

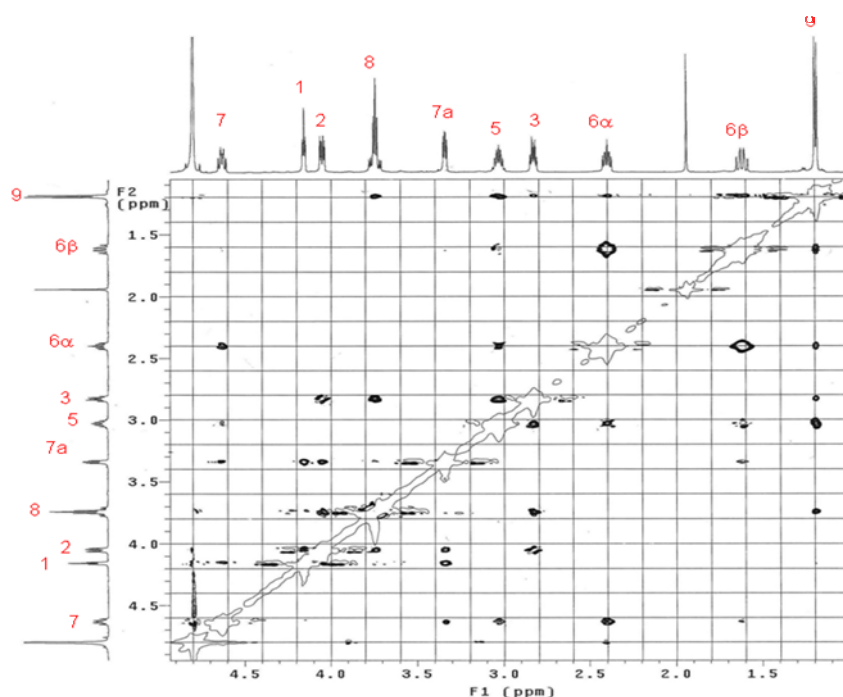
**Table 5.3**  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ ) spectral data of natural and synthesized hyacinthacine B<sub>7</sub> (**112**).

C	Natural $\delta_{\text{C}}$ (ppm)	Synthetic $\delta_{\text{C}}$ (ppm)	Difference (ppm)
<b>1</b>	77.9	73.6	-4.3
<b>2</b>	74.9	78.1	+3.2
<b>3</b>	66.2	71.8	+5.6
<b>5</b>	57.7	65.2	+7.5
<b>6a</b>	45.2	46.2	+1.0
<b>7</b>	76.5	71.3	-5.2
<b>7a</b>	69.9	75.4	+5.5
<b>8a</b>	66.8	65.6	-1.2
<b>9</b>	18.4	22.5	+4.1

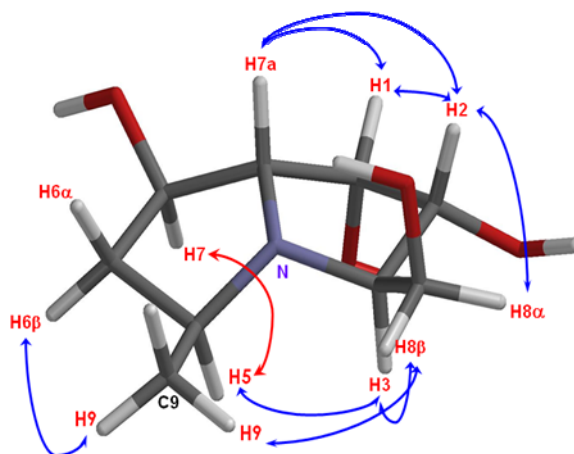
We then resorted to the 2-D NOESY NMR spectrum of the synthesized **112** (Figure 5.3), which showed the same NOE correlations as reported of the natural product (blue double-

headed arrows in Figure 5.4). Furthermore, we observed in the synthesized product a NOE correlation between H-5 and H-7 (red double-headed arrow in Figure 5.4), which was not reported for natural hyacinthacine B<sub>7</sub> in the original isolation paper. This important NOE correlation, along with the HF/6-31G\* (Spartan) optimized structure, indicates that the methyl and hydroxyl substituents on C-5 and C-7, respectively, adopt pseudo-equatorial positions. H-5 and H-6 are both pseudo-axial and in close proximity, consistent with the observed NOE correlation between these protons. With this information, we were confident that the synthesized product indeed matched the reported structure of the hyacinthacine B<sub>7</sub>.

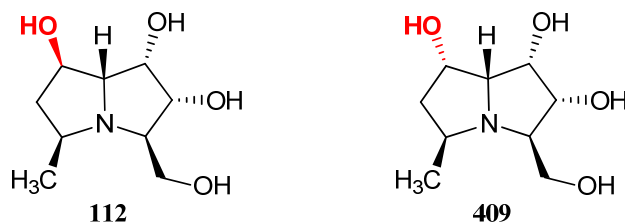
The NOESY correlation between H-5 and H-7 in our synthesized **112** but not observed in the natural hyacinthacine B<sub>7</sub> (Figures 5.3 and 5.4) indicated that it was possible that H-5 and H-7 of the natural product do not have a *syn* relationship. This also triggered us to question whether the natural product is actually compound **409**, the C-7 epimer of **112** (Figure 5.5).



**Figure 5.3** 2-D NOESY NMR spectrum (D<sub>2</sub>O, 500 MHz) of synthetic **112**.



**Figure 5.4** HF/6-31G\* optimized structure (Spartan) and NOESY correlations of compound **112**.

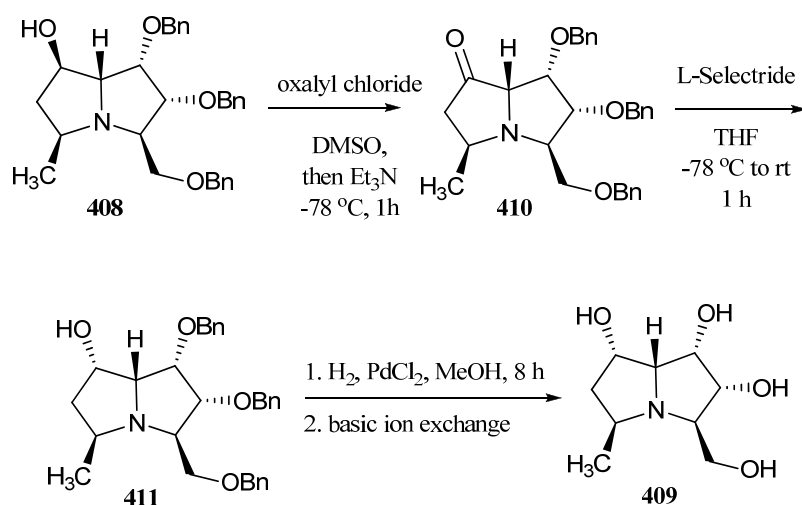


**Figure 5.5** The purported structure of the hyacinthacine B<sub>7</sub> (**112**) and its C-7 epimer (**409**)

### 5.5 Synthesis of the C-7 epimer of the pyrrolizidine **112**

To further investigate the absolute configuration of the natural product, we decided to synthesize compound **409** from the tribenzylpyrrolizidine **408**, utilizing an oxidation-reduction sequence to invert the hydroxy group on C-7, which would then be followed by global debenylation and ion-exchange chromatography to give the pyrrolizidine **409** (Scheme 5.7). Because of the limited amount of **408** that was at hand, this sequence was performed only once and on a small scale.

Scheme 5.7



The Swern oxidation step with DMSO and oxalyl chloride in CH<sub>2</sub>Cl<sub>2</sub> proceeded smoothly to give a mixture containing mainly the pyrrolizidinone **410**. The <sup>13</sup>C NMR spectrum of the crude mixture contained a peak at 214.5 ppm, indicating the presence of the carbonyl group of the oxidized product. After aqueous work up the crude mixture containing the pyrrolizidine **410** was used in the subsequent reduction reaction without further purification.

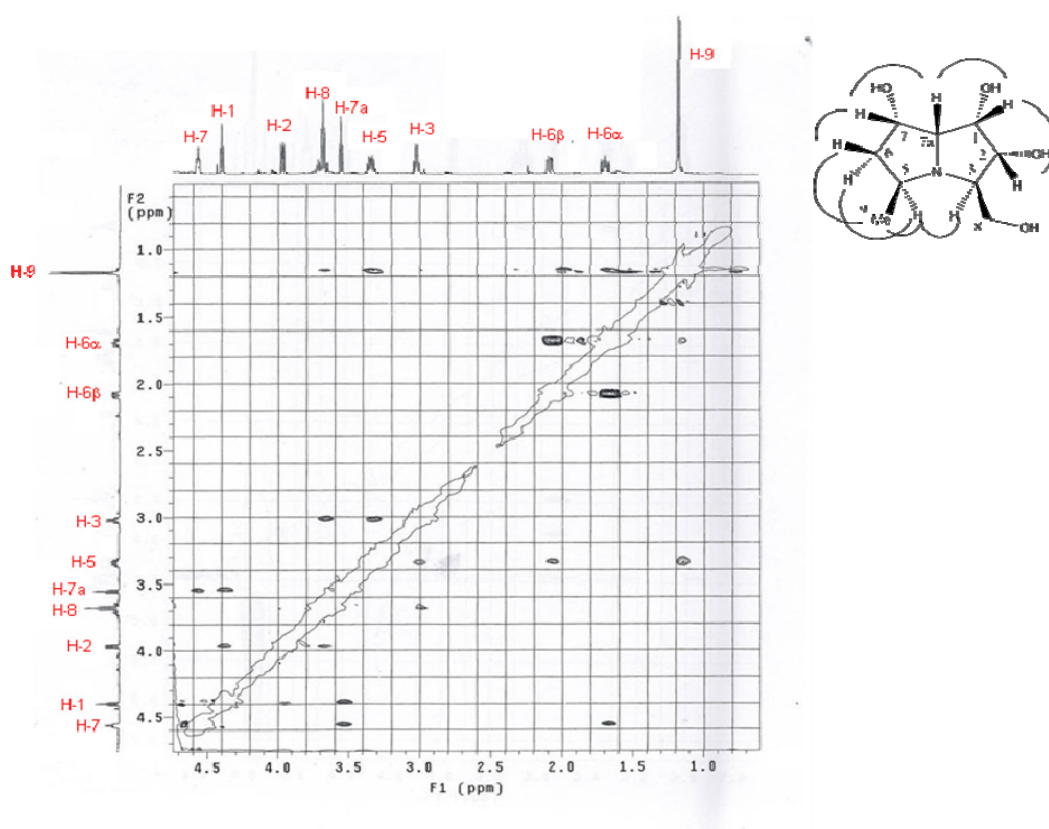
Using a method reported by Chamberlin *et al.* in 1985,<sup>127</sup> stereoselective reduction of the pyrrolizidinone **410** was achieved by taking advantage of the bulkiness of L-Selectride (lithium tri-*sec*-butylhydroborate) and delivered the hydride at the less congested β-face of the pyrrolizidinone **410**, giving exclusively the tribenzylpyrrolizidine **411** in 30% yield across the two steps. After global debenzoylation with H<sub>2</sub> and PdCl<sub>2</sub> in MeOH and basic ion-exchange chromatography, the tetrahydroxypyrrolizidine **409** (7-*epi*-**112**) was obtained (Scheme 5.7).

The <sup>1</sup>H NMR spectrum of **409** was different from that of **112** and was closer to that of the natural product but did not match with that of the natural hyacinthacine B<sub>7</sub> (Table 5.4). Indicating the occurrence of inversion at C-7, the NOESY NMR spectrum of **409** showed an NOE correlation between H-1 and H-7, whereas the NOE correlation formerly observed between H-5 and H-7 in **112** was absent in the case of **409** (Figure 5.6).



**Table 5.4**  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ ) spectral data of natural hyacinthacine  $\text{B}_7$  and the synthetic compounds **112** and **409**.

H	Natural		Synthetic <b>112</b>		<b>409</b> (7- <i>epi</i> - <b>112</b> )	
	$\delta_{\text{H}}$ (ppm)	Mult., $J(\text{Hz})$	$\delta_{\text{H}}$ (ppm)	Mult., $J(\text{Hz})$	$\delta_{\text{H}}$ (ppm)	Mult., $J(\text{Hz})$
<b>1</b>	4.35	t (4.4)	4.13	t (3.9)	4.40	t (5.1)
<b>2</b>	3.97	dd (4.4, 7.6)	4.03	dd (3.9, 9.0)	3.97	dd (5.1, 7.1)
<b>3</b>	3.29	ddd (3.5, 5.5, 7.6)	2.81	ddd (4.9, 4.9, 9.0)	3.02	ddd (5.3, 5.3, 7.1)
<b>5</b>	3.22	m	3.01	m	3.34	m
<b>6a</b>	1.68	m	1.60	m	1.60	ddd (5.3, 9.9, 14.4)
<b>6b</b>	2.16	m	2.38	m	2.08	appar. dd. (5.8, 13.6)
<b>7</b>	4.50	m	4.61	m	4.56	m
<b>7a</b>	3.45	dd (4.4, 7.6)	3.32	dd (3.9, 5.9)	3.55	dd (3.9, 5.9)
<b>8a</b>	3.57	dd (5.5, 11.5)	3.70	dd (4.9, 11.5)	3.66	dd (5.3, 11.8)
<b>8b</b>	3.63	dd (5.5, 11.5)	3.74	dd (4.9, 11.5)	3.79	dd (5.3, 11.8)
<b>9</b>	1.25	d (7.0)	1.17	d (6.4)	1.17	d (6.3)



**Figure 5.6** NOESY (500 MHz,  $\text{D}_2\text{O}$ ) NMR spectrum of **409** (7-*epi*-**112**).

### 5.6 Further comparison of **112** and **409** with natural hyacinthacine B<sub>7</sub>.

To further study the differences between natural hyacinthacine B<sub>7</sub> and the synthetic product **112**, we sent samples of the synthesized pyrrolizidines **112** and **409** to Dr. Robert Nash from the UK and Prof. Atsushi Kato from Japan, who participated in the identification of natural hyacinthacine B<sub>7</sub> in 2007,<sup>52</sup> for help in GC-MS analysis of the tetra-TMS derivative and biological assay of the synthetic products.

The GC-MS analysis of the extract of the same *S. socialis* plants used in the original isolation showed no hyacinthacine corresponding to the retention time of 10.71 min of **112**. This was a clear indication that neither natural hyacinthacine B<sub>7</sub> nor other natural hyacinthacines isolated from *S. socialis* matched the structure of **112**. Biological assays showed that the synthetic pyrrolizidines **112** and **409** had weak inhibitory activities towards  $\beta$ -glucosidase but had no activity towards amyloglucosidase, further confirming that **112** was not hyacinthacine B<sub>7</sub>. The same was true for **409** (Table 5.5).

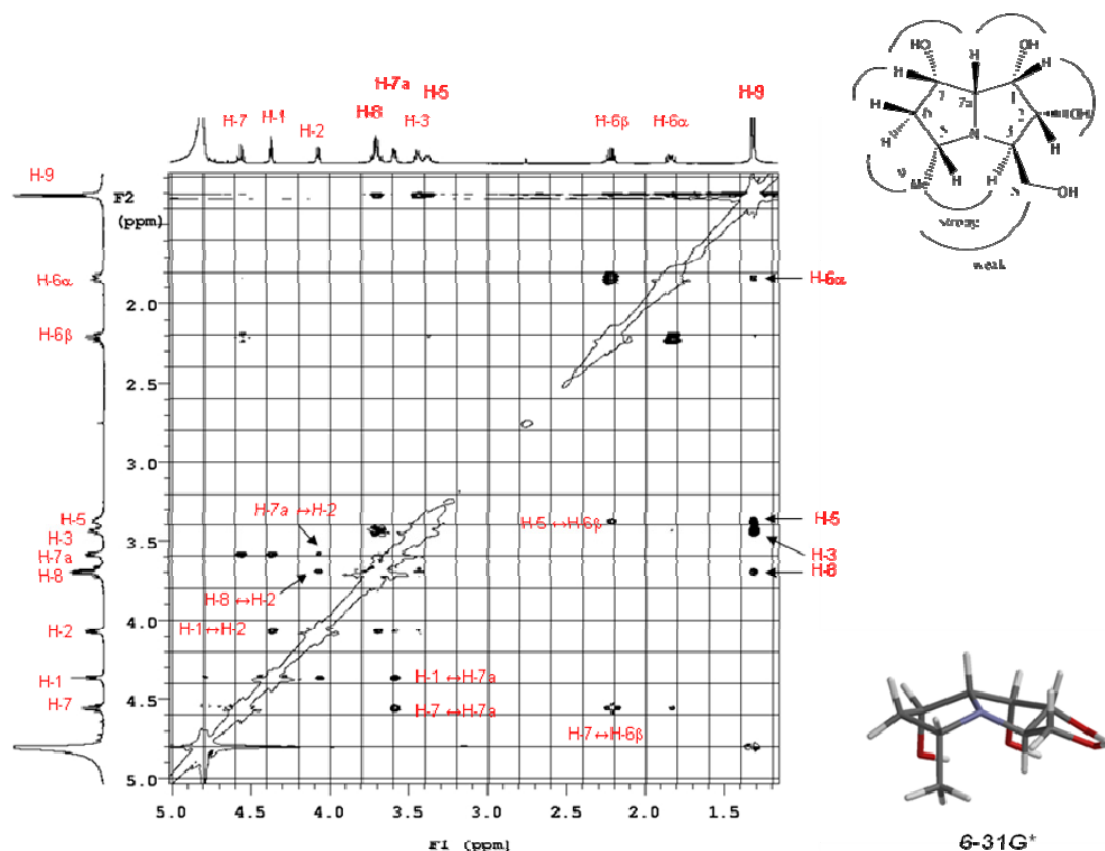
**Table 5.5** Biological assays of the synthetic pyrrolizidines **112** and **409** at 1000  $\mu$ M in comparison with natural hyacinthacine B<sub>7</sub>.

Enzyme	IC <sub>50</sub>		
	<b>112</b>	<b>409</b>	natural hyacinthacine B <sub>7</sub> <sup>52</sup>
$\alpha$ -glucosidase			
rice	NI (11.0%)	NI (16.5%)	NI
rat intestinal maltase	NI (19.2%)	NI (0%)	NI
$\beta$ -glucosidase			
<i>C. saccharolyticum</i>	175 $\mu$ M	743 $\mu$ M	NI
$\alpha$ -galactosidase			
coffee beans	NI (0.71%)	NI (34.0%)	NI
$\beta$ -galactosidase			
bovine liver	NI (11.3%)	NI (14.9%)	NI
$\alpha$ -mannosidase			
jack beans	NI (20.7%)	NI (8.2%)	NI
$\alpha$ -L-fucosidase			
bovine epididymis	NI (7.8%)	NI (0%)	NI
amyloglucosidase			
<i>Aspergillus niger</i>	NI (42.8%)	NI (0%)	270 $\mu$ M

NI : less than 50% inhibition at 1000  $\mu$ M

We also requested a sample of the authentic natural hyacinthacine B<sub>7</sub> from Prof. Kato for NMR comparison with our synthetic products. Upon receiving the natural product, we obtained a NOESY NMR spectrum (Figure 5.7) of the sample and discovered that, apart from the missing NOESY correlation between H-7 and H-5, a strong NOE correlation between H-9 and H-3 was observed. Based on all these spectral observations, we concluded that they had sent us a sample of hyacinthacine B<sub>5</sub> (Figure 5.7). It was later discovered that the original natural product samples had been mislabeled and authentic hyacinthacine was no longer available.

To summarize, we have synthesized the purported structure of hyacinthacine B<sub>7</sub> (**112**) in 13 synthetic steps from (*R*)-4-penten-2-ol (**397**) and 3.4% overall yield. Based on our extensive NMR studies on the pyrrolizidine alkaloid **112**, and supported by the GC-MS analysis and biological assay of our synthetic **112**, performed respectively by Dr. Robert Nash and Prof. Atsushi Kato, we conclude that the proposed structure of hyacinthacine B<sub>7</sub> is incorrect.



**Figure 5.7** NOESY NMR (500 MHz, D<sub>2</sub>O) spectrum of supposedly ‘natural hyacinthacine B<sub>7</sub>’ sent to us by Prof. Kato.

## CHAPTER 6: CONCLUSIONS

The initial aims of this PhD project were to synthesize 1,2-*anti* amino alcohols **303** and utilize them in the synthesis of the polyhydroxylated indolizidine (-)-swainsonine **1** and the pyrrolizidine alkaloids hyacinthacine B<sub>3</sub> **104** and hyacinthacine B<sub>7</sub> **112**. The aim of synthesizing **1**, which was previously synthesized by various research groups, was to develop a shorter and more effective synthetic pathway to the alkaloid. The syntheses of **104** and **112** would constitute the first syntheses of these alkaloids and also provided an opportunity to examine and verify their structures and stereochemical configurations.

In Chapter 1, a review of the syntheses of (±)-swainsonine and swainsonine analogues reported since 2005 and the syntheses of hyacinthacine alkaloids to date was given.

The synthesis of 1,2-*anti* amino alcohols of the general structure **303** from commercially available 4-penten-1-ol and 4-phenyl butene were reported in Chapter 2, highlighting the olefin cross-metathesis reaction using Grubbs' II catalyst to give (*E*)- vinyl sulfones **306** and **308** in, respectively, 70% and 91% yield and 99:1 (*E*)/(*Z*) ratio. The radical addition reaction of PhSO<sub>2</sub>I across an alkene, followed by elimination of HI using DBU provided a more economical alternative to (*E*)- vinyl sulfones **301** in equally high yields and comparable (*E*):(*Z*) ratios.

The Sharpless ADH of vinyl sulfones **301** generated *in situ* chiral α-hydroxy aldehydes **302** that undergo the borono-Mannich reaction with styrenyl boronic acid and primary amines to give 1,2-*anti* amino alcohols **303** in high enantiomeric purities. The reactions of vinyl sulfones **306** and **308** with AD-mix-α and followed by the Petasis reaction resulted in slightly lower enantioselectivity (83-91%), compared with analogous reactions with AD-mix-β (91-95%). Specifically, this newly developed method allowed us to gain rapid access to the 1,2-*anti* amino alcohol **382**, which was used as a chiral building block in our synthesis of (-)-swainsonine.

The conversion of the 1,2-*anti* amino alcohol **382** into the known indoline **22** was reported in Chapter 3. The 'A' and 'B' rings of the indoline structure were constructed *via* intramolecular *N*-alkylation and ring-closing metathesis reactions, respectively. The

synthesis of **22** represented a ten-step synthesis of (-)-swainsonine **1** from 4-penten-1-ol and in 7.7% overall yield.

The utility of 1,2-*anti* amino alcohols **303** were further demonstrated in the novel total synthesis the polyhydroxylated pyrrolizidine alkaloid, hyacinthacine B<sub>3</sub> **104**, which was reported in Chapter 4. Using commercially available (*S*)-4-penten-2-ol as starting material, the 1,2-*anti* amino alcohol **379** was obtained in 95:5 diastereomeric ratio *via* the Sharpless-Petasis sequence by using monomeric DHQD-IND chiral ligand in the ADH reaction and enantiopure chiral allyl amine **381** in the Petasis reaction. The key intermediate **379** was converted to hyacinthacine B<sub>3</sub> **104** in an additional nine steps, with highlights on the construction of the 'A-ring' *via* RCM reaction using Grubbs' II catalyst and formation of the 'B-ring' *via* mesylation followed by concomitant nucleophilic cyclization by the nucleophilic amino group. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the synthetic **104** matched closely with those of the natural product. Thus the first total synthesis of hyacinthacine B<sub>3</sub> was accomplished in 13 synthetic steps from (*S*)-4-penten-2-ol and 5.7% overall yield.

As reported in Chapter 5, the purported structure of hyacinthacine B<sub>7</sub> (**112**) was synthesized in 3.4% overall yield *via* an essentially identical synthetic route as the synthesis of **104** but using (*R*)-4-penten-2-ol as starting material. The yield of the Sharpless-Petasis sequence was *ca.* 20% lower than that achieved in the synthesis of **104**, presumably due to a mismatched situation between the chiral reagent and the chiral substrate. Moreover the <sup>1</sup>H and <sup>13</sup>C NMR spectral data of synthetic **112** were inconsistent with those reported of the natural product. Based on the results of further NMR analysis, the GC-MS analysis and biological assay of synthetic **112** and its C-7 epimer, we concluded that the structure reported for the natural hyacinthacine B<sub>7</sub> was incorrect.

## **CHAPTER 7: EXPERIMENTAL SECTION**

### **7.1 General Experimental**

#### **7.1.1 General reaction conditions**

In general, all reactions unless otherwise stated were performed in oven dried, single-necked round bottom flasks under an atmosphere of dry nitrogen. Progress of reactions was monitored by thin-layer chromatographic (TLC) analysis. Solvents were purchased as Analytical Reagent (AR) grade. Petroleum spirit refers to the hydrocarbon fraction of bp 40-60 °C. THF was stored over KOH pellets until needed, then distilled over sodium wire under nitrogen, using benzophenone as an indicator. Anhydrous CH<sub>2</sub>Cl<sub>2</sub> and MeOH were purchased from Aldrich.

Where 'dried' is specified, this refers to the drying of organic extract over MgSO<sub>4</sub>, unless otherwise indicated, followed by filtration. Where 'evaporation' is specified, this refers to the evaporation of solvent under reduced pressure using a rotary evaporator. Purified compounds were dried thoroughly under high vacuum. All reaction yields were obtained only after this drying process.

#### **7.1.2 Chromatography**

Thin layer chromatography (TLC) was performed using aluminium backed Merck F<sub>254</sub> sorbent silica gel. Compounds were detected under a 254 nm ultraviolet lamp, or by staining with an acidified, aqueous solution of ammonium molybdate and cerium(IV) sulfate, followed by development with a 1400 Watt heat gun. One litre of the molybdate dip contained water (950 mL), concentrated H<sub>2</sub>SO<sub>4</sub> (50 mL), (NH<sub>4</sub>)<sub>6</sub>MoO<sub>24</sub> (50 g) and Ce(SO<sub>4</sub>)<sub>2</sub> (2 g).

Purification of compounds by flash column chromatography (FCC) was achieved using Merck flash silica gel (40-63 µm) and the technique reported by Still *et al.*<sup>128</sup>

Acidic ion-exchange chromatography was performed using DOWEX 50WX4-50 acidic exchange resin. In all cases the compounds were applied as their HCl salts dissolved in distilled water. The column was first eluted with water and then eluted with 14% ammonia solution (w/w). Basic ion-exchange chromatography was performed using

Amberlyst A-26(OH) resin. The compounds were applied to the column and eluted with water.

### 7.1.3 Melting points

Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected.

### 7.1.4 Polarimetry

Optical rotations were measured using a 1 cm cell, in a Jasco DIP-370 digital polarimeter. Eight to ten measurements were taken and the average was used to calculate the specific rotation.

### 7.1.5 Mass spectrometry

Low resolution mass spectra were obtained either on a Shimadzu GC mass spectrometer (EI and CI) or a Waters LCZ single quadropole (ESI). High-resolution mass spectra were obtained either on a VG Autospec mass spectrometer (EI and CI) or a Waters QTOF (ESI). HRMS (exact masses) were used in lieu of elemental analysis and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy were used as criteria for purity.

### 7.1.6 Nuclear magnetic resonance spectroscopy

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Varian Unity-300 (300 MHz  $^1\text{H}$ , 75 MHz  $^{13}\text{C}$ ) or a Varian INOVA-500 (500 MHz  $^1\text{H}$ , 125 MHz  $^{13}\text{C}$ ) spectrometer in deuteriochloroform ( $\text{CDCl}_3$ ), unless otherwise specified. NMR assignments were based on COSY, DEPT, HSQC and HMBC experiments. NMR solvents used in the experimental and their associated referencing data are displayed in Table 9.1. Unless otherwise stated, the applied NMR frequency was 500 MHz for  $^1\text{H}$  NMR experiments and 125 MHz for  $^{13}\text{C}$  NMR experiments, with samples dissolved in deuteriochloroform. In the case of epoxide compounds NMR assignments are given based on the numbering system of the parent pyrrolidine, pyrrolizine or indolizine and not the systematic numbering.

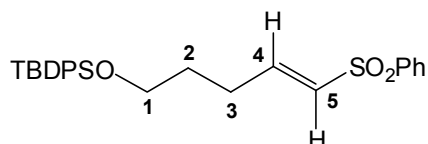
**Table 7.1** The references used for  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectroscopy.

Solvent	$^1\text{H}$ NMR		$^{13}\text{C}$ NMR	$^{19}\text{F}$ NMR
	Internal standard	Others	Others	Others
$\text{CDCl}_3$	TMS, s, 0.00 ppm	residual $\text{CHCl}_3$ , s, 7.26 ppm	$\text{CDCl}_3$ 77.0 ppm	~5% $\text{CF}_3\text{CH}_2\text{OH}$ spike, s, -77.8 ppm
$\text{CD}_3\text{OD}$	TMS, s, 0.00 ppm	residual MeOH, s, 3.31 ppm	$\text{CD}_3\text{OD}$ 49.0 ppm	-
$\text{D}_2\text{O}$	$\text{H}_2\text{O}$ , s, 4.79 ppm	~5% NaTSP* spike, s, 0.00 ppm	-	-

\*Sodium 3-(trimethylsilyl)tetradeuteriopropionate

## 7.2 Experimentals for Chapters 2 and 3

### 7.2.1 General method for Olefin Cross Methathesis using the Grubbs' II catalyst:



#### ((E)-5-(Phenylsulfonyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane (306).

To an Ar-flushed 50-mL round bottom flask containing phenyl vinyl sulfone (0.204 g, 1.213 mmol) was added *tert*-butyl(pent-4-enyloxy)diphenylsilane **305**<sup>129</sup> (0.202 g, 0.622 mmol) and distilled  $\text{CH}_2\text{Cl}_2$  (15 mL). The content of the round bottom flask was then transferred via syringe to a Ar-flushed 100-mL 2-neck round bottom flask containing a solution of Grubbs' II catalyst (0.028 g, 0.033 mmol, 5.33 mol %) in  $\text{CH}_2\text{Cl}_2$  (5 mL). The reaction mixture was stirred under Ar and heated at reflux for 18 h and then concentrated *in vacuo* to give a brown oil. Flash column chromatography (increasing polarity from 1:10:2 to 1:5:2  $\text{Et}_2\text{O}$ :petrol: $\text{CH}_2\text{Cl}_2$  as eluent) gave the title compound (0.263 g, 0.565 mmol, 90.8 %) as a yellow oil.

### 7.2.2 General method for iodosulfonation and HI elimination:

**((E)-5-(Phenylsulfonyl)pent-4-enyloxy)(*tert*-butyl)diphenylsilane (306).** To a solution of  $\text{I}_2$  (0.761 g, 3.00 mmol) in toluene (30 mL) in a 100 mL round bottom flask was added a saturated aqueous solution of sodium benzenesulfinate (0.980 g, 6.00 mmol) at rt. The

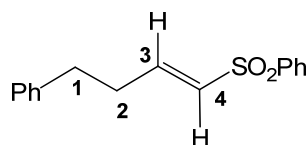


heterogenous mixture was shaken vigorously in a separation funnel until the organic layer changed from deep violet to orange then to bright yellow in color. The organic layer was collected and dried ( $\text{MgSO}_4$ ). To an aliquot (10 mL) of the freshly prepared yellow solution containing  $\text{PhSO}_2\text{I}$  (approx. 1 mmol) purged with  $\text{N}_2$  was added *tert*-butyl(pent-4-enyloxy)diphenylsilane **305** (0.162 g, 0.500 mmol) via syringe. The reaction mixture was stirred at rt until *tert*-butyl(pent-4-enyloxy)diphenylsilane was completely consumed as shown by TLC analysis (*ca.* 2 h). The reaction mixture was then cooled to 0 °C and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.08 mL, 0.08 g, 0.52 mmol) was added dropwise via syringe for 1.5 h. The reaction was quenched with  $\text{NH}_4\text{Cl}$  (sat. aq., 10 mL). The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford a brown oil. Purification by flash column chromatography (increasing polarity from 1:20:2 to 1:7:2  $\text{Et}_2\text{O}$ :petrol: $\text{CH}_2\text{Cl}_2$  as eluent) afforded the title compound (0.217 g, 93%, (*E*)/(*Z*) ratio: 97.3:2.7) as a yellow oil.

ESIMS  $m/z$  465 ( $[\text{MH}]^+$ ), HRESIMS found 465.1916, calc for  $\text{C}_{27}\text{H}_{33}\text{O}_3\text{SSi}$  465.1920 ( $[\text{MH}]^+$ ).

$\delta_{\text{H}}$  (500 MHz): 7.90-7.35 (15H, m, ArH), 7.00 (1H, dt,  $J = 6.3, 15.0$  Hz, H4), 6.30 (1H, d,  $J = 15.1$  Hz, H5), 3.65 (2H, t,  $J = 6.3$  Hz, H1), 2.36 (2H, q,  $J = 7.8$  Hz, H3), 1.69 (2H, quint.,  $J = 6.8$  Hz, H2), 1.03 (9H, s, *t*-Bu).

$\delta_{\text{C}}$  (125 MHz): 146.7 (C5), 140.6 (ArC), 135.4 (ArC), 133.5 (ArC), 133.1 (C4), 129.6 (ArC), 129.5 (ArC), 129.1 (ArC), 127.6 (ArC), 127.5 (ArC), 62.5 (C1), 30.3 (C2), 27.9 (C3), 26.8 ( $\text{C}(\text{CH}_3)_3$ ), 19.1 ( $\text{C}(\text{CH}_3)_3$ ).



**(*E*)-1-(4-(Phenylsulfonyl)but-3-enyl)benzene (308).** Following the general method described above for olefin metathesis and using 4-phenyl-1-butene (0.27 mL, 1.77 mmol) as the starting material, the title compound (0.310 g, 64.3 %) was obtained as a yellow oil after purification with column chromatography (increasing polarity from 1:20:2 to 1:7:2  $\text{Et}_2\text{O}$ : petrol:  $\text{CH}_2\text{Cl}_2$  as eluent).

$\delta_{\text{H}}$  (300 MHz): 7.87-7.13 (Ar-H), 7.03 (1H, dt,  $J = 15.1, 6.9$  Hz, H3), 6.32 (1H, dt,  $J = 15.1, 1.5$  Hz, H4), 2.80 (2H, t,  $J = 7.5$  Hz, H1), 2.57 (2H, m, H2).

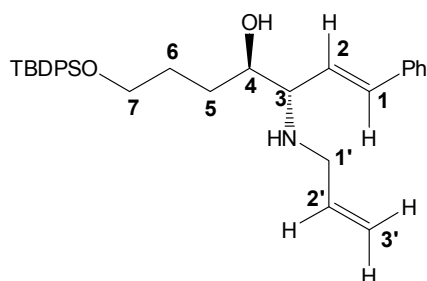
$\delta_{\text{C}}$  (125 MHz): 145.9 (C3), 113.2 (ArC), 131.0 (C4), 129.1 (ArC), 128.5 (ArC), 128.3 (ArC), 127.5 (ArC), 126.3 (ArC), 33.8 (C1), 33.0 (C2).

ESIMS  $m/z$  273  $[\text{MH}]^+$ , HRESIMS found 273.0956, calc for  $\text{C}_{16}\text{H}_{17}\text{O}_2\text{S}$  273.0949  $[\text{MH}]^+$ .

### 7.2.3 General method for the Sharpless asymmetric dihydroxylation (ADH) using the AD-mix:

To a round bottom flask containing a solution of AD-mix- $\beta$  (5.3 g) and  $\text{MeSO}_2\text{NH}_2$  (0.16 g, 1.68 mmol) in water (9 mL) was added a solution of vinyl sulfone **306** (0.406 g, 0.847 mmol) in *t*-BuOH (9 mL). Additional AD-mix- $\beta$  (1.6 g) and  $\text{MeSO}_2\text{NH}_2$  (0.040 g, 0.420 mmol) were added after 6 h, and the reaction mixture was stirred at rt for a total of 24 h and then diluted with water, followed by extraction with EtOAc (3 x 20 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to afford a brown oil.

### 7.2.4 General method for the Petasis reaction:



#### (3*S*,4*R*,*E*)-3-(Allylamino)-7-(*tert*-butyldiphenylsilyloxy)-1-phenylhept-1-en-4-ol (**353**).

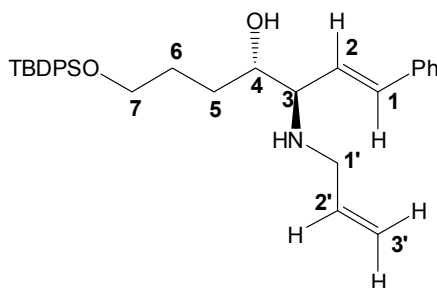
A solution of the ADH crude product in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) was purged with nitrogen and then allylamine (0.07 mL, 0.053 g, 0.927 mmol) and (*E*)-2-phenylvinylboronic acid (0.129 g, 0.874 mmol) were added. The reaction mixture was stirred at rt for 40 h. The reaction mixture was partitioned between 5% aq. NaOH (20 mL) and EtOAc (20 mL). The organic layer was washed with brine (2 x 20 mL), dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give a brown oil. Flash column chromatography (increasing polarity 2% to 4% MeOH in  $\text{CH}_2\text{Cl}_2$  as eluents) afforded the  $\beta$ -amino alcohol **353** (0.164 g, 38%, over 2 steps).

$[\alpha]_D^{24} +7.5$  ( $c$  1.08,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (300 MHz): 7.66-7.62 (4H, m, ArH), 7.42-7.26 (11H, m, ArH), 6.50 (1H, d,  $J = 15.4$  Hz, H1), 6.14 (1H, dd,  $J = 8.8, 15.4$  Hz, H2), 5.91 (1H, ddt,  $J = 5.9, 10.3, 17.0$  Hz, H2'), 5.20 (1H, d,  $J = 17.0$  Hz, H3'*trans*), 5.12 (1H, dt,  $J = 1.5, 10.3$  Hz, H3'*cis*), 3.75 (1H, dt,  $J = 3.8, 8.5$  Hz, H4), 3.67 (2H, t,  $J = 5.9$  Hz, H7), 3.39-3.15 (3H, m, H3 and H1'), 2.40 (2H, br.s, NH and OH), 1.88-1.4 (4H, m, H5 and H6), 1.01 (9H, s, *t*-Bu).

$\delta_{\text{C}}$  (75 MHz): 136.3 (C2'), 135.5 (ArC), 133.8 (C1), 129.5 (ArC), 128.5 (ArC), 127.6 (ArC), 127.2 (C2), 126.4 (ArC), 116.3 (C3'), 72.4 (C4), 64.7 (C3), 63.9 (C7), 49.5 (C1'), 29.9 (C5), 29.0 (C6), 29.8 (C(CH<sub>3</sub>)<sub>3</sub>), 19.1 (C(CH<sub>3</sub>)<sub>3</sub>).

ESIMS  $m/z$  500 ( $[\text{MH}]^+$ ), HRESIMS found 500.2987, calc for C<sub>32</sub>H<sub>42</sub>NO<sub>2</sub>Si, 500.2985 ( $[\text{MH}]^+$ ).

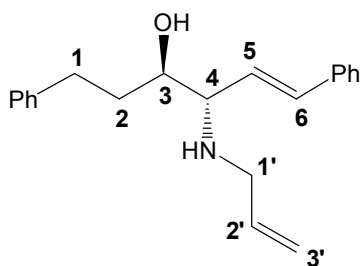


**(3*R*,4*S*,*E*)-3-(Allylamino)-7-(*tert*-butyldiphenylsilyloxy)-1-phenylhept-1-en-4-ol (354).**

Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **306** (0.258 g, 0.555 mmol), MeSO<sub>2</sub>NH<sub>2</sub> (0.085 g, 0.894 mmol) and AD-mix- $\alpha$  (2.9 g in total) in the Sharpless ADH, and using allylamine (0.04 mL, 0.6 mmol) and (*E*)-2-phenylvinylboronic acid (0.081 g, 0.555 mmol) in the Petasis reaction, the title compound (0.097 g, 35.0 %) was obtained as a brown oil after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent).

$[\alpha]_D^{24} -12.7$  ( $c$  1.10,  $\text{CHCl}_3$ ).

Other spectral data (<sup>1</sup>H, <sup>13</sup>C NMR, LRMS, HRMS) were identical to those of **353**.



**(3*R*,4*S*,*E*)-4-(Allylamino)-1,6-diphenylhex-5-en-3-ol (356).** Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **308** (0.100 g, 0.367 mmol), MeSO<sub>2</sub>NH<sub>2</sub> (0.057 g, 0.599 mmol) and AD-mix-β (2.0 g in total) in the Sharpless ADH, and using allylamine (0.03 mL, 0.4 mmol) and (*E*)-2-phenylvinylboronic acid (0.054 g, 0.367 mmol) in the Petasis reaction, the title compound (0.058 g, 51.4 %) was obtained as an off-white crystalline solid after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent).

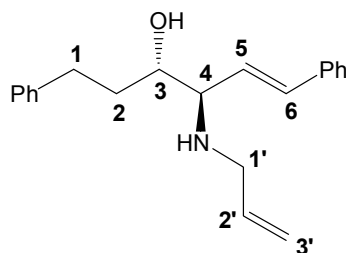
m.p. 83 - 86 °C

$[\alpha]_D^{24} +15.96$  (*c* 1.18, CHCl<sub>3</sub>).

$\delta_H$ (500 MHz): 7.50-7.17 (10H, m, ArH), 6.51 (1H, d, *J* = 16.1 Hz, H6), 6.16 (1H, dd, *J* = 8.7, 15.6 Hz, H5), 5.90 (1H, ddt, *J* = 5.9, 10.5, 17.3 Hz, H2'), 5.19 (1H, dt, *J* = 1.5, 17.0 Hz, H3'<sub>trans</sub>), 5.13 (1H, dt, *J* = 1.5, 10.5 Hz, H3'<sub>cis</sub>), 3.76 (1H, dt, *J* = 3.5, 9.0 Hz, H3), 3.34 (2H, dd, *J* = 5.5, 14.0 Hz, H1'<sub>A</sub>), 3.27 (1H, dd, *J* = 3.0, 8.5 Hz, H4), 3.22 (2H, dd, *J* = 5.5, 14.0 Hz, H1'<sub>B</sub>), 2.91-2.66 (2H, m, H1), 1.81-1.69 (2H, m, H2).

$\delta_C$ (125 MHz): 142.0 (ArC), 136.5 (ArC), 136.3 (C1'), 133.8 (C2'), 128.6 (ArC), 128.6 (ArC), 128.5 (ArC), 128.3 (ArC), 127.7 (ArC), 126.9 (ArC), 126.4 (ArC), 125.7 (C5), 116.4 (C3'), 71.7 (C3), 64.7 (C4), 45.5 (1'), 35.1 (C2), 32.4 (C1).

ESIMS *m/z* 308 ([MH]<sup>+</sup>), HRESIMS found 308.2029, calc for C<sub>21</sub>H<sub>26</sub>NO, 308.2014 ([MH]<sup>+</sup>).

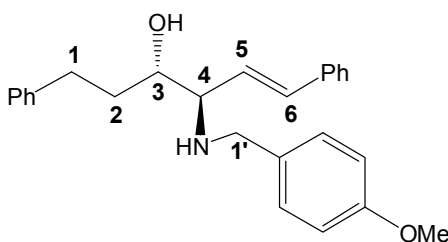


**(3*S*,4*R*,*E*)-4-(Allylamino)-1,6-diphenylhex-5-en-3-ol (355).** Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **308** (0.103 g, 0.378 mmol), MeSO<sub>2</sub>NH<sub>2</sub> (0.057 g, 0.599 mmol) and AD-mix- $\alpha$  (2.0 g in total) in the Sharpless ADH, and using allylamine (0.04 mL, 0.5 mmol) and (*E*)-2-phenylvinylboronic acid (0.067 g, 0.45 mmol) in the Petasis reaction, the title compound (0.051 g, 43.5 %) was obtained as an off-white crystalline solid after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent).

m.p. 84 - 86 °C

$[\alpha]_D^{24}$  -9.96 (*c* 1.18, CHCl<sub>3</sub>).

Other spectral data (<sup>1</sup>H, <sup>13</sup>C NMR, LRMS, HRMS) were identical to those of **356**.

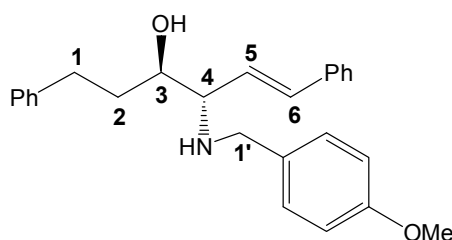


**(3*S*,4*R*,*E*)-4-(4-Methoxybenzylamino)-1,6-diphenylhex-5-en-3-ol (357).** Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **308** (0.103 g, 0.378 mmol), MeSO<sub>2</sub>NH<sub>2</sub> (0.057 g, 0.599 mmol) and AD-mix- $\alpha$  (2.0 g in total) in the Sharpless ADH, and using 4-methoxybenzylamine (0.06 mL, 0.5 mmol) and (*E*)-2-phenylvinylboronic acid (0.067 g, 0.45 mmol) in the Petasis reaction, the amino alcohol title compound (0.068 g, 46.3 %) was obtained as an off-white crystalline solid after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent).

m.p. 73 - 76 °C

$[\alpha]_D^{25} -39.1$  ( $c$  0.89,  $\text{CHCl}_3$ ).

Other spectral data ( $^1\text{H}$ ,  $^{13}\text{C}$  NMR, LRMS, HRMS) were identical to those of **358**.



**(3*R*,4*S*,*E*)-4-(4-Methoxybenzylamino)-1,6-diphenylhex-5-en-3-ol (358)**. Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **308** (0.100 g, 0.367 mmol,  $\text{MeSO}_2\text{NH}_2$  (0.057 g, 0.599 mmol) and AD-mix- $\beta$  (2.0 g in total) in the Sharpless ADH, and using 4-methoxybenzylamine (0.05 mL, 0.4 mmol) and (*E*)-2-phenylvinylboronic acid (0.0540 g, 0.367 mmol) in the Petasis reaction, the title compound (0.060 g, 42.9 %) was obtained as an off-white crystalline solid after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in  $\text{CH}_2\text{Cl}_2$  as eluent).

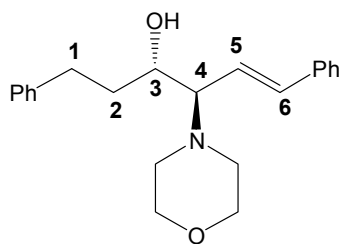
m.p. 73-76 °C

$[\alpha]_D^{25} +53.1$  ( $c$  0.78,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (500 MHz): 7.39-7.14 (12H, m, ArH), 6.86-6.84 (2H, d,  $J = 8.5$  Hz, ArH), 6.48 (1H, d,  $J = 16.0$  Hz, H6), 6.17 (1H, dd,  $J = 16.0, 9.0$  Hz, H5), 3.78 (3H, s,  $\text{OCH}_3$ ), 3.76 (2H, m, H3), 3.66 (1H, d,  $J = 12.5$  Hz, H4), 2.84, (1H, m, H1<sub>A</sub>), 2.65 (1H, m, H1<sub>B</sub>), 1.76 (2H, m, H2).

$\delta_{\text{C}}$  (125 MHz): 136.5 (C6), 133.8 (ArC), 131.8 (ArC), 129.4 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 127.7 (ArC), 127.1 (ArC), 126.4 (ArC), 125.7 (C5), 113.8 (ArC), 71.7 ( $\text{OCH}_3$ ), 64.6 (C4), 55.2 (C3), 50.4 (C1'), 35.0 (C2), 32.3 (C1).

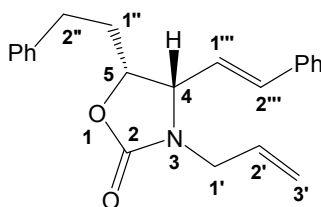
ESIMS  $m/z$  388 ( $[\text{MH}]^+$ ), HRESIMS found 388.2281, calc for  $\text{C}_{26}\text{H}_{30}\text{NO}_2$ , 388.2277 ( $[\text{MH}]^+$ ).



**(3*S*,4*R*,*E*)-4-Morpholino-1,6-diphenylhex-5-en-3-ol (359).** Following the general method described above for the Sharpless asymmetric dihydroxylation and the Petasis reaction and using the vinyl sulfone **308** (0.112 g, 0.411 mmol), MeSO<sub>2</sub>NH<sub>2</sub> (0.085 g, 0.888 mmol) and AD-mix- $\alpha$  (3.0 g in total) in the Sharpless ADH, and using morpholine (40  $\mu$ L, 0.50 mmol), and (*E*)-2-phenylvinylboronic acid (0.061 g, 0.411 mmol) in the Petasis reaction, the amino alcohol title compound (0.011 g, 12 %, over 2 steps) was obtained as a pale yellow film after purification by column chromatography (increasing polarity from 2.0 to 4.0 % MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent).

$\delta_{\text{H}}$  (300 MHz): 7.40-7.16 (10H, m, ArH), 6.51 (1H, d,  $J$  = 15.9 Hz, H6), 6.18 (1H, dd,  $J$  = 15.9, 9.6 Hz, H5), 3.98 (1H, dt,  $J$  = 7.2, 4.8 Hz, H3), 3.75-3.72 (5H, m, 2 x CH<sub>2</sub>O and H4), 2.89-2.54 (5H, m), 2.82 (1H, dd,  $J$  = 9.5, 5.1 Hz, H4), 1.85-1.72 (1H, m), 1.70-1.58 (1H, m).

ESIMS  $m/z$  338 ([MH]<sup>+</sup>), HRESIMS found 338.2136, calc for C<sub>22</sub>H<sub>28</sub>NO<sub>2</sub>, 338.2120 ([MH]<sup>+</sup>).



**(4*S*,5*R*,*E*)-3-Allyl-5-phenethyl-4-styryloxazolidin-2-one (362).** To a 0 °C solution of amino alcohol **356** (0.022g, 0.070 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under argon was added a solution of Et<sub>3</sub>N (0.01 mL, 0.07 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL) and triphosgene (0.010 g, 0.035 mmol). The reaction mixture was stirred under argon and allowed to warm to rt

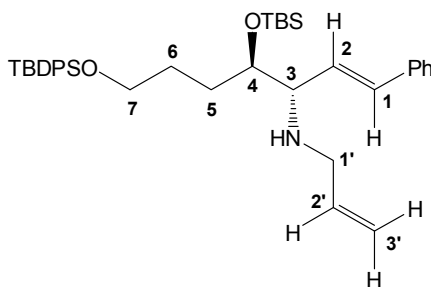
overnight and concentrated *in vacuo* to afford a light yellow residue. Flash column chromatography (0.06:3:1 MeOH: DCM: pet. sp. as eluent) afforded the title compound (15.0 mg, 63 %) as a colorless film.

$[\alpha]_D^{26} -25.1$  (*c* 0.98, CHCl<sub>3</sub>).

$\delta_H$  (300 MHz): 7.48-7.24 (10H, m, ArH), 6.63 (1H, d,  $J = 15.6$  Hz, H2'''), 6.10 (1H, dd,  $J = 15.6, 1.9$  Hz, H1'''), 5.84 (1H, m, H2'), 5.29 (1H, d,  $J = 9.3$  Hz, H3'*trans*), 5.26 (1H, d,  $J = 16.8, 1.5$  Hz, H3'*cis*), 4.56 (1H, ddd,  $J = 10.2, 8.1, 3.9$  Hz, H5), 4.30 (1H, t,  $J = 9.3$  Hz, H4), 4.18 (1H, ddd,  $J = 15.6, 3.0, 1.8$  Hz, H1'<sub>A</sub>), 3.57 (1H, dd,  $J = 15.3, 7.2$  Hz, H1'<sub>B</sub>), 2.94-2.66 (2H, m, H2''), 2.17-1.85 (2H, m, H1'').

$\delta_C$  (75 MHz): 157.4 (C2), 136.5 (C2'''), 132.1 (C2'), 128.8 (ArC), 128.7 (ArC), 128.6 (ArC), 128.5 (ArC), 126.7 (ArC), 126.2 (ArC), 122.3 (C1'''), 118.4 (C3'), 76.6 (C5), 61.2 (C4), 44.6 (C1'), 32.5 (C1''), 31.8 (C2'').

ESIMS  $m/z$  334 ( $[MH]^+$ ), HRESIMS found 334.1820, calc for C<sub>22</sub>H<sub>24</sub>NO<sub>2</sub>, 334.1820 ( $[MH]^+$ ).



**(3*S*,4*R*,*E*)-*N*-Allyl-4-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-1-**

**phenylhept-1-en-3-amine (363).** To a 0°C, argon-flushed solution of  $\beta$ -amino alcohol **353** (0.164 g 0.327 mmol), in dry CH<sub>2</sub>Cl<sub>2</sub> was added *via* syringe 2,6-lutidine (0.085 mL, 0.720 mmol) and TBSOTf (0.150 mL, 0.655 mmol). The reaction mixture was stirred at 0°C for 2.5 h and was then diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. Flash column



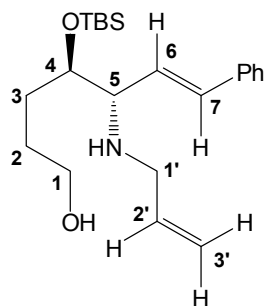
chromatography (2.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> as eluent) afforded the title compound (0.141 g, 70%) as a yellow film.

$[\alpha]_D^{26}$  -11.58 (*c* 1.11, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.62-7.17 (15H, m, ArH), 6.43 (1H, d, *J* = 16.5 Hz, H1), 6.06 (1H, dd, *J* = 15.5, 8.5 Hz, H2), 5.91 (1H, ddt, *J* = 17.0, 10.5, 4.5 Hz, H2'), 5.14 (1H, d, *J* = 17.0 Hz, H3'<sub>trans</sub>), 5.05 (1H, d, *J* = 10.5 Hz, H3'<sub>cis</sub>), 3.80 (1H, m, H4), 3.67 (2H, t, *J* = 6.0 Hz, H7), 3.30 (1H, dd, *J* = 14.5, 5.5 Hz, H1'<sub>A</sub>), 3.23 (1H, dd, *J* = 8.5, 3.0 Hz, H3), 3.07 (1H, dd, *J* = 14.0, 6.5 Hz, H1'<sub>B</sub>), 1.62-1.48 (4H, m, H5 and H6), 1.02-0.84 (18H, m, *t*-Bu), 0.09 (3H, s, CH<sub>3</sub>-Si), 0.05 (3H, s, CH<sub>3</sub>-Si).

$\delta_C$  (75 MHz): 137.0 (C2'), 135.5 (ArC), 134.0 (ArC), 129.5 (ArC), 128.5 (ArC), 127.6 (ArC), 127.3 (ArC), 126.3 (ArC), 132.7 (C1), 129.0 (C2), 115.6 (C3'), 75.6 (C4), 64.8 (C3), 63.9 (C7), 50.0 (C1'), 29.5 (C5/C6), 29.0 (C5/C6), 26.8 (*t*-Bu), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 25.7 (C(CH<sub>3</sub>)<sub>3</sub>), 19.2 (C(CH<sub>3</sub>)<sub>3</sub>), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>), -2.94 (CH<sub>3</sub>-Si), -4.30 (CH<sub>3</sub>-Si), -4.35 (CH<sub>3</sub>-Si).

ESIMS *m/z* 614 ([MH]<sup>+</sup>), HRESIMS found 614.3833, calc for C<sub>38</sub>H<sub>56</sub>NO<sub>2</sub>Si, 614.3850 ([MH]<sup>+</sup>).



**(4*R*,5*S*,*E*)-5-(Allylamino)-4-(*tert*-butyldimethylsilyloxy)-7-phenylhept-6-en-1-ol (364).**

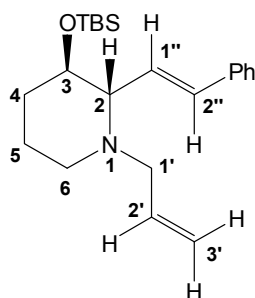
To a solution of **363** (0.413 g, 0.672 mmol) in dry MeOH (40 mL) purged with argon was added methanolic KOH (10%, 20 mL). The reaction mixture was stirred under argon and heated at reflux for 7 h. After dilution with EtOAc (25 mL), the reaction mixture was washed with brine (25 mL). The aqueous layers were further extracted with EtOAc (2 x 25 mL). The organic layers were collected, dried (MgSO<sub>4</sub>), and concentrated to give the crude product as a yellow oil. Flash column chromatography (4% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded the title compound (0.152 g, 60%) as a light yellow film.

$[\alpha]_D^{26} +3.5$  ( $c$  1.59,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (300 MHz): 7.42-7.22 (5H, m, ArH), 6.50 (1H, d,  $J = 16.1$  Hz, H7), 6.09 (1H, dd,  $J = 16.0, 8.6$  Hz, H6), 5.91 (1H, m, H2'), 5.19 (1H, ddd,  $J = 17.3, 3.2, 1.5$  Hz, H3' *trans*), 5.12 (1H, dd,  $J = 10.3, 1.5$  Hz, H3' *cis*), 3.84 (1H, m, H4), 3.62 (2H, t,  $J = 6.2$  Hz, H1), 3.36-3.27 (2H, m, H1' <sub>A</sub> and H5) 3.07 (1H, ddt,  $J = 14.2, 6.7, 1.2$  Hz, H1' <sub>B</sub>), 1.69-1.46 (4H, m, H2 and H3), 0.92-0.90 (9H, m, *t*-Bu), 0.11 (3H, s,  $\text{CH}_3\text{-Si}$ ), 0.09 (3H, s,  $\text{CH}_3\text{-Si}$ ).

$\delta_{\text{C}}$  (75 MHz): 136.4 (C2'), 136.4 (C7), 136.8 (C6), 128.5 (ArC), 127.4 (ArC), 126.3 (ArC), 116.1 (C3'), 75.4 (C1), 65.0 (C5), 62.7 (C4), 49.9 (C1'), 29.2 and 28.9 (C2 and C3), 25.8 ( $\text{C}(\text{CH}_3)_3$ ), 18.0 ( $\text{C}(\text{CH}_3)_3$ ), -4.38 ( $\text{CH}_3\text{-Si}$ ), -4.43 ( $\text{CH}_3\text{-Si}$ ).

ESIMS  $m/z$  376 ( $[\text{MH}]^+$ ), HRESIMS found 376.2672, calc for  $\text{C}_{22}\text{H}_{38}\text{NO}_2\text{OSi}$ , 376.2672 ( $[\text{MH}]^+$ ).



**(2*S*,3*R*,*E*)-1-Allyl-3-(*tert*-butyldimethylsilyloxy)-2-styrylpiperidine (365).** To a stirred solution of the amino alcohol **364** (0.197 g, 0.523 mmol, 1.0 eq) at 0 °C under argon was added triethylamine (1.0 mL, 7.2 mmol), triphenylphosphine (0.343 g, 1.309 mmol) and carbon tetrabromide (0.434 g, 1.309 mmol). The reaction mixture was stirred at 0 °C for 2 h, then poured into water and partitioned with  $\text{CH}_2\text{Cl}_2$  (25 mL). The aqueous layer was further extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20 mL). The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo* to give an orange oil. Flash column chromatography (1<sup>st</sup> column: 4% MeOH in  $\text{CH}_2\text{Cl}_2$ , 2<sup>nd</sup> column: 3:1 petrol:EtOAc) afforded the title compound (0.132 g 70.5 %) as a yellow oil.

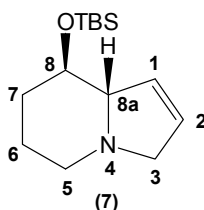
$[\alpha]_D^{26} +70.6$  ( $c$  1.26,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (300 MHz): 7.41-7.21 (5H, m, ArH), 6.55 (1H, d,  $J = 16.0$  Hz, H2''), 6.04 (1H, dd,  $J = 16.0, 9.1$  Hz, H1''), 5.89 (1H, m, H2'), 5.18-5.12 (2H, m, H3'), 3.54 (2H, m, H3 and

H1'<sub>A</sub>), 2.98 (1H, dt,  $J = 11.4, 2.6$  Hz, H6<sub>A</sub>), 2.84 (1H, dd,  $J = 13.8, 8.2$  Hz, H1'<sub>B</sub>), 2.64 (1H, t,  $J = 8.8$  Hz, H2), 2.02 (2H, m, H6<sub>B</sub> and H5<sub>A</sub>), 1.66 (2H, m, H4), 1.38 (1H, m, H5<sub>B</sub>), 0.82-0.80 (9H, br. s, *t*-Bu), 0.01 (3H, s, CH<sub>3</sub>-Si), -0.12 (3H, s, CH<sub>3</sub>-Si).

$\delta_C$  (75 MHz): 136.9 (C2'), 134.8 (C2''), 134.1 (ArC), 130.4 (C1''), 128.5 (ArC), 127.3 (ArC), 126.2 (ArC), 117.8 (C3'), 73.1 (C2), 71.9 (C3), 58.5 (C1'), 51.7 (C6), 34.1 (C5), 25.7 (C(CH<sub>3</sub>)<sub>3</sub>), 23.3 (C4), 17.9 (C(CH<sub>3</sub>)<sub>3</sub>), -4.51 (CH<sub>3</sub>-Si), -4.58 (CH<sub>3</sub>-Si).

ESIMS  $m/z$  358 ([MH]<sup>+</sup>), HRESIMS found 358.2569, calc for C<sub>22</sub>H<sub>38</sub>NO<sub>2</sub>OSi, 358.2566 ([MH]<sup>+</sup>).



**(8*R*,8*aS*)-8-(*tert*-Butyldimethylsilyloxy)-3,5,6,7,8,8*a*-hexahydroindolizine (22).** To a solution of piperidine **365** (42 mg, 0.118 mmol), in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added via syringe a solution of Ti(*Oi*-Pr)<sub>4</sub> (7.0  $\mu$ L, 0.024 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.4 mL). The above solution was stirred at rt for 0.5 h, then a solution of the Grubbs II catalyst (12 mg, 0.014 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added via cannula. The reaction mixture was heated at reflux for 2.5 h, when TLC analysis showed complete consumption of **365**. The reaction mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL) and washed with sat. aq. NaHCO<sub>3</sub> (10 mL). The aqueous layer was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The organic layers were dried (MgSO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>) and concentrated *in vacuo* to afford a dark brown oil as the crude product. Column chromatography on basic alumina (5 % EtOAc in petrol as eluent) afforded the title compound (24 mg, 80%) as a colorless film.

$[\alpha]_D^{26} -71.6$  ( $c$  0.65, C<sub>6</sub>H<sub>6</sub>). (lit.  $[\alpha]_D^{20} -91.73$  ( $c$  0.955, C<sub>6</sub>H<sub>6</sub>))

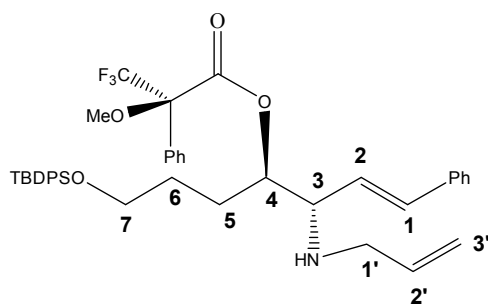
$\delta_H$  (300 MHz): 6.05 (1H, dd,  $J = 6.0, 1.5$  Hz), 5.88 (1H, m), 3.63 (1H, dddd,  $J = 12.9, 5.1, 2.1, 1.5$  Hz), 3.46 (1H, ddd,  $J = 13.8, 9.3, 4.5$  Hz), 3.23 (1H, dddd,  $J = 12.6, 6.0, 2.3, 1.2$  Hz), 2.91 (1H, dt,  $J = 11.1, 3.6$  Hz), 2.86 (1H, m), 2.39 (1H, ddd,  $J = 11.1, 9.0, 6.3$  Hz),

1.92 (1H, m), 1.68-1.62 (2H, m), 1.32-1.19 (2H, m), 0.89 (9H, s), 0.06 (3H, s), 0.05 (3H, s).

$\delta_C$  (75 MHz): 131.6 (C1), 128.5 (C2), 74.1 (C4), 72.0 (C8a), 58.0 (C3), 48.9 (C5), 34.41 (C7), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 24.5 (C6), 18.1 (C(CH<sub>3</sub>)<sub>3</sub>), -4.25 (CH<sub>3</sub>-Si), -4.67 (CH<sub>3</sub>-Si).

ESIMS  $m/z$  254 ([MH]<sup>+</sup>), HRESIMS found 254.1946, calc for C<sub>14</sub>H<sub>28</sub>NOSi, 254.1940 [MH]<sup>+</sup>).

### 7.2.5 General method for the synthesis of Mosher's esters:

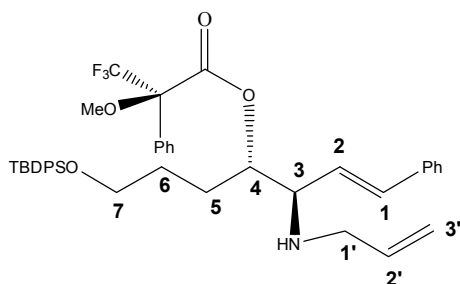


**(*R*)-((3*S*,4*R*,*E*)-3-(Allylamino)-7-(*tert*-butyldiphenylsilyloxy)-1-phenylhept-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**360**).** To a solution of **353** (7.0 mg, 0.014 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) under argon were added Et<sub>3</sub>N (40 μL), DMAP (6.7 mg, 0.055 mmol), and (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol). The reaction mixture was stirred overnight at rt and concentrated *in vacuo* to give a light brown oil. Purification by column chromatography (2.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) gave the title compound as a yellow oil (8.8 mg, 88%).

$\delta_{\text{H}}$  (500 MHz): 7.64-7.24 (15H, m, ArH), 6.50 (1H, d,  $J$  = 16.5 Hz, H1, major diastereomer), 6.44 (1H, d,  $J$  = 16.5, H1 minor diastereomer), 5.97 (1H, dd,  $J$  = 16.5, 9.0 Hz, H2), 5.85 (1H, m, H2'), 5.29 (1H, dt,  $J$  = 8.0, 3.0 Hz, H4), 5.15 (1H, dd,  $J$  = 17.0, 1.0 Hz, H3'<sub>trans</sub>), 5.10 (1H, d,  $J$  = 10.5 Hz, H3'<sub>cis</sub>), 3.60 (2H, q,  $J$  = 6 Hz, H7), 3.55 (3H, s, OCH<sub>3</sub>), 3.42 (1H, dd,  $J$  = 8.5, 3.0 Hz, H3), 3.29 (1H, dd,  $J$  = 14.0, 5.5 Hz, H1'<sub>A</sub>), 3.16 (1H, dd,  $J$  = 14.0, 6.5 Hz, H1'<sub>B</sub>), 1.75 (2H, dt,  $J$  = 8.0, 4.0 Hz, H5), 1.51 (2H, m, H6), 1.00 (9 H, s, *t*-Bu).

$\delta_{\text{F}}$  (282 MHz): -71.65 (major diastereomer, integral = 96.7%), -71.85 (minor diastereomer, integral = 3.4%). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

ESIMS  $m/z$  716 ([MH]<sup>+</sup>), HRESIMS found 716.3412, calc for C<sub>42</sub>H<sub>49</sub>NO<sub>4</sub>F<sub>3</sub>Si, 716.3383 ([MH]<sup>+</sup>).

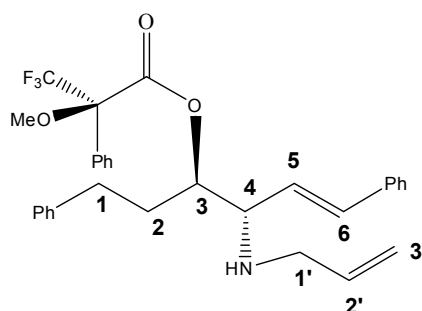


***R*)-((3*R*,4*S*,*E*)-3-(Allylamino)-7-(*tert*-butyldiphenylsilyloxy)-1-phenylhept-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**361**). Following the general method of the synthesis of Mosher's esters using **354** (12.0 mg, 0.024 mmol), Et<sub>3</sub>N (40  $\mu$ L), DMAP (6.7 mg, 0.055 mmol), (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the title compound (10.0 mg, 70 %) was obtained as a yellow oil.**

$\delta_{\text{H}}$  (500MHz): 6.50 (1H, d,  $J = 16.5$  Hz, H1, minor diastereomer), 6.44 (1H, d,  $J = 16.5$  Hz, H1, major diastereomer). Other <sup>1</sup>H NMR signals were identical to those of **360**.

$\delta_{\text{F}}$  (282 MHz): -71.66 (minor diastereomer, integral = 8.7%), -71.87 (major diastereomer, integral = 91.3%). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

ESIMS  $m/z$  716 ([MH]<sup>+</sup>), HRESIMS found 716.3367, calc for C<sub>42</sub>H<sub>49</sub>NO<sub>4</sub>F<sub>3</sub>Si, 716.3383 ([MH]<sup>+</sup>).



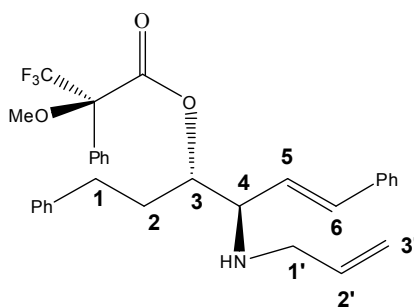
**(*R*)-((3*R*,4*S*,*E*)-4-(Allylamino)-1,6-diphenylhex-5-en-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (412).**

Following the general method of the synthesis of Mosher's esters using **356** (7.6 mg, 0.025 mmol), Et<sub>3</sub>N (40  $\mu$ L), DMAP (6.7 mg, 0.055 mmol), and (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the title compound was obtained as a yellow film (7.0 mg, 45%).

$\delta_{\text{H}}$  (300 MHz): 7.70-7.05 (15H, m, ArH), 6.49 (1H, d,  $J$  = 16.0 Hz, H6, major diastereomer), 6.46 (1H, d,  $J$  = 16.2, H6, minor diastereomer), 5.97 (1H, dd,  $J$  = 16.0, 8.7 Hz, H5), 5.84 (1H, ddt,  $J$  = 6.0, 11.5, 17.0 Hz, H2'), 5.41 (1H, dt,  $J$  = 8.1, 4.2 Hz, H3), 5.15 (1H, d,  $J$  = 17.0 Hz, H3' *trans*), 5.09 (1H, d,  $J$  = 11.5 Hz, H3' *cis*), 3.58 (3H, s, OCH<sub>3</sub>), 3.44 (1H, dd,  $J$  = 8.7, 3.6 Hz, H4), 3.29 (1H, dd,  $J$  = 14.1, 5.4 Hz, H1' <sub>A</sub>), 3.15 (1H, dd,  $J$  = 14.1, 6.0 Hz, H1' <sub>B</sub>), 2.55 (2H, dt,  $J$  = 9.9, 6.0 Hz, H1), 1.97 (2H, m, H2).

$\delta_{\text{F}}$  (282 MHz): -71.41 (major diastereomer, integral = 97.1%), -71.60 (minor diastereomer, integral = 2.9%). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

ESIMS  $m/z$  524 ([MH]<sup>+</sup>), HRESIMS found 524.2431, calc for C<sub>31</sub>H<sub>22</sub>NO<sub>3</sub>F<sub>3</sub>, 524.2413 ([MH]<sup>+</sup>).

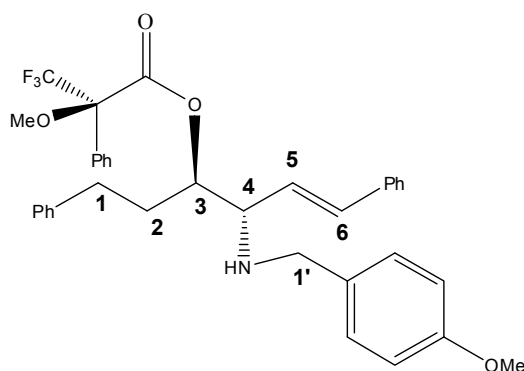


**(*R*)-((3*S*,4*R*,*E*)-4-(Allylamino)-1,6-diphenylhex-5-en-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (413).** Following the general method of the synthesis of Mosher's esters using **355** (7.3 mg, 0.024 mmol), Et<sub>3</sub>N (40  $\mu$ L), DMAP (6.7 mg, 0.055 mmol), (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the title compound (6.0 mg, 48 %) was obtained as a yellow oil.

$\delta_{\text{H}}$  (300 MHz): 6.49 (1H, d,  $J$  = 16.0 Hz, H6, minor diastereomer), 6.45 (1H, d,  $J$  = 16.0 Hz, H6, major diastereomer). Other <sup>1</sup>H NMR signals were identical to those of **412**.

$\delta_{\text{F}}$  (282 MHz): -71.41 (minor diastereomer, integral = 4.3%), -71.61 (major diastereomer, integral = 95.7 %). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

Other spectral data (LRMS, HRMS) were identical to those of **412**.



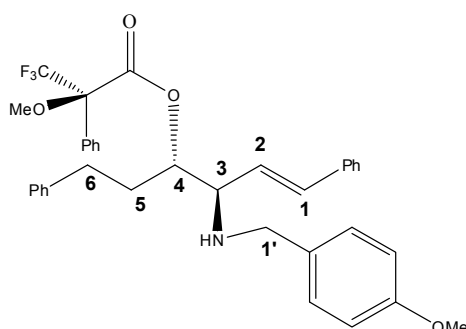
**(*R*)-((3*R*,4*S*,*E*)-4-(4-Methoxybenzylamino)-1,6-diphenylhex-5-en-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (414).** Following the general method of the synthesis of Mosher's esters using **358** (8.3 mg, 0.021 mmol), Et<sub>3</sub>N (40  $\mu$ L), DMAP (6.7 mg, 0.055 mmol), (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the title compound (8.0 mg, 62 %) was obtained as a yellow oil.



$\delta_{\text{H}}$  (300 MHz): 7.66-7.05 (19H, m, ArH), 6.48 (1H, d,  $J = 16.1$  Hz, H6, major diastereomer), 6.45 (1H, d,  $J = 16.1$  Hz, H6, minor diastereomer), 6.01 (1H, dd,  $J = 16.1$ , 8.7 Hz, H5), 5.34 (1H, dt,  $J = 8.1$ , 4.2 Hz, H3), 3.79 (3H, s, OCH<sub>3</sub>), 3.74 (1H, d,  $J = 13.2$  Hz, H1'<sub>A</sub>), 3.64 (1H, d,  $J = 13.2$  Hz, H1'<sub>B</sub>), 3.56 (3H, s, OCH<sub>3</sub>), 3.41 (1H, dd,  $J = 8.7$ , 3.9 Hz, H4), 2.52 (2H, m, H1), 1.95 (2H, m, H2).

$\delta_{\text{F}}$  (282 MHz): -71.50 (major diastereomer, integral=97.3%), -71.77 (minor diastereomer, integral=2.7%). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

ESIMS  $m/z$  603.5 ( $\text{M}^+$ ), HRESIMS found 604.2669, calc for C<sub>36</sub>H<sub>37</sub>NO<sub>4</sub>F<sub>3</sub>, 604.2675 ( $[\text{MH}]^+$ ).



**(*R*)-((3*S*,4*R*,*E*)-4-(4-Methoxybenzylamino)-1,6-diphenylhex-5-en-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**415**).** Following the general method of the synthesis of Mosher's esters using **357** (6.7mg, 0.017 mmol), Et<sub>3</sub>N (40  $\mu$ L), DMAP (6.7 mg, 0.055 mmol), (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetyl chloride (20 mg, 0.080 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (2 mL), the title compound (9.0 mg, 86 %) was obtained as a yellow oil.

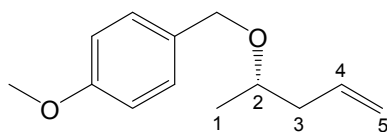
$\delta_{\text{H}}$  (300 MHz): 6.48 (1H, d,  $J = 16.1$  Hz, H6, minor diastereomer), 6.45 (1H, d,  $J = 16.1$  Hz, H6, major diastereomer). Other <sup>1</sup>H NMR signals were identical to those of **414**.

$\delta_{\text{F}}$  (282 MHz): -71.50 (minor diastereomer, integral = 4.5%), -71.77 (major diastereomer, integral = 95.5%). CF<sub>3</sub>CH<sub>2</sub>OH referenced at -77.8 ppm.

Other spectral data (LRMS, HRMS) were identical to those of **414**.

## 7.3 Experimentals for Chapter 4

### 7.3.1 General method for *O*-PMB protection:



**(*S*)-1-Methoxy-4-((pent-4-en-2-yloxy)methyl)benzene (378).** A solution of (*S*)-4-penten-2-ol (1.070 g, 12.423 mmol), 4-methoxybenzyl chloride (3.15 mL, 23.220 mmol) and tetrabutylammonium iodide (0.369 g, 1.161 mmol) in anhydrous THF (40 mL) under a N<sub>2</sub> atmosphere was cooled to 0 °C, sodium hydride (50% dispersion in mineral oil, 0.836 g, 0.418 g NaH, 17.415 mmol) was then added, and the reaction mixture was allowed to warm to rt and stirred under nitrogen for 18 h. Quenching with H<sub>2</sub>O (30 mL) gave a cloudy mixture, which was extracted with diethyl ether (30 mL). The aqueous layer was further extracted with diethyl ether (3 x 30 mL), and the combined ethereal extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a brown oil. Purification by flash column chromatography (increasing polarity from 0:100 to 5:95 Et<sub>2</sub>O/petrol) gave the title compound as a colorless oil (2.309 g, 90%).

*R<sub>f</sub>* 0.43 (5:95 EtOAc/petrol).

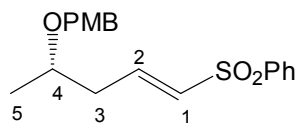
$[\alpha]_D^{24} +8.0$  (*c* 1.00, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz):  $\delta_H$  (500 MHz): 7.26 (2H, d, *J* = 8.8 Hz, ArH), 6.86 (2H, d, *J* = 8.8 Hz, ArH), 5.87-5.78 (2H, m, H<sub>4</sub>), 5.07 (1H, d, *J* = 17.3 Hz, H<sub>5<sub>trans</sub></sub>), 5.04 (1H, d, *J* = 10.7 Hz, H<sub>5<sub>cis</sub></sub>), (1H, d, *J* = 17.3 Hz, H<sub>5<sub>trans</sub></sub>), 4.48 (1H, d, *J* = 11.5 Hz, OCHHPMP), 4.27 (1H, d, *J* = 11.5 Hz, OCHHPMP), 3.77 (3H, s, OCH<sub>3</sub>), 3.58-3.52 (1H, m, H<sub>2</sub>), 2.36 (1H, ddd, *J* = 5.9, 6.6, 13.7 Hz, H<sub>3A</sub>), 2.21 (1H, ddd, *J* = 6.7, 7.1, 13.9 Hz, H<sub>3B</sub>), 1.17 (3H, d, *J* = 6.1 Hz, H<sub>1</sub>)

$\delta_C$  (125 MHz): 159.0 (ArC), 135.0 (C<sub>4</sub>), 130.9 (ArC), 129.0 (ArC), 116.6 (C<sub>5</sub>), 113.6 (ArC), 74.0 (C<sub>2</sub>), 69.9 (OCH<sub>2</sub>PMP), 55.1 (OCH<sub>3</sub>), 40.8 (C<sub>3</sub>), 19.3 (C<sub>1</sub>).

### 7.3.2 Preparation of vinyl sulfone **379**

#### 7.3.2.1 *Via* iodosulfonation and HI elimination using benzenesulfonyl iodide



**(1E,4S)-4-[(4-Methoxybenzyl)oxy]pent-1-en-1-yl phenyl sulfone (379).** Following the general method for iodosulfonation and HI elimination using the alkene **378** (0.391 g, 1.889 mmol), PhSO<sub>2</sub>I (*ca.* 7.6 mmol in 25 mL toluene), DBU (282  $\mu$ L) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL), the title compound (0.133 g, 20%) was obtained as a yellow oil.

$R_f$  0.52 (1:5:2 Et<sub>2</sub>O/petrol/CH<sub>2</sub>Cl<sub>2</sub>).

$[\alpha]_D^{22}$  -6.7 (*c* 2.90, CHCl<sub>3</sub>).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2965, 2909, 2832, 1613, 1511, 1444, 1305, 1246, 1144, 1085, 1031, 750.

$\delta_H$  (300 MHz): 7.87-7.84 (2H, m, ArH), 7.60-7.48 (3H, m, ArH), 7.20-7.17 (2H, m, ArH), 7.01 (1H, dt,  $J$  = 7.4, 15.0 Hz, H2), 6.86-6.83 (2H, m, ArH), 6.37 (1H, dt,  $J$  = 1.4, 15.0 Hz, H1), 4.48 (1H, d,  $J$  = 11.2 Hz, OCHHAr), 4.34 (1H, d,  $J$  = 11.2 Hz, OCHHAr), 3.80 (3H, s, OCH<sub>3</sub>), 3.65 (1H, dq,  $J$  = 6.2, 12.4 Hz, H4), 2.46-2.39 (2H, m, H3), 1.20 (3H, d,  $J$  = 6.2 Hz, H5).

$\delta_C$  (75 MHz): 159.1 (ArC), 143.6 (C2), 140.5 (ArC), 133.2 (ArC), 132.0 (C1), 130.2 (ArC), 129.2 (ArC), 127.5 (ArC), 113.8 (ArC), 72.5 (C4), 70.1 (O-CH<sub>2</sub>-Ar), 55.2 (OCH<sub>3</sub>), 38.5 (C3), 19.6 (C5).

ESIMS  $m/z$  364 (100%) [MNH<sub>4</sub>]<sup>+</sup>, 369 (12%) [MNa]<sup>+</sup>, HRESIMS found 369.1151, calc for C<sub>19</sub>H<sub>22</sub>O<sub>4</sub>NaS, 369.1137 [MNa]<sup>+</sup>.

#### 7.3.2.2 General method for olefin cross metathesis using the Grubb's II catalyst under microwaves irradiation:

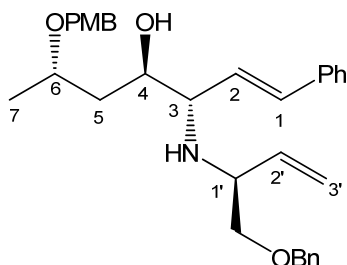
**(1E,4S)-4-[(4-Methoxybenzyl)oxy]pent-1-en-1-yl phenyl sulfone (379).** To a nitrogen-flushed solution of **378** (100 mg, 0.483 mmol) and phenylvinylsulfone (0.163 g, 0.966 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added the Grubbs II catalyst (21 mg, 0.0242

mmol). The reaction mixture was stirred and irradiated with microwaves in a CEM microwave reactor for 1 h at 90 °C using a maximum applied power of 200 W. After cooling the reaction mixture was concentrated *in vacuo* to give a black semi-solid. Purification by flash column chromatography (increasing polarity from 1:10:2 to 1:5:2 Et<sub>2</sub>O/petrol/CH<sub>2</sub>Cl<sub>2</sub> as eluent) gave the title compound (0.114g, 68%) as a pale yellow oil.

### 7.3.3 General method for the Sharpless asymmetric dihydroxylation using DHQD-IND:

To a solution of potassium ferric cyanide (0.322 g, 0.977 mmol), potassium carbonate (0.135 g, 0.977 mmol), methanesulfonamide (0.031 g, 0.326 mmol), potassium osmate.dihydrate (1.4 mg, 0.0039 mmol) and DHQD-IND (2.3 mg, 0.0049 mmol) in H<sub>2</sub>O (1.5 mL) was added a solution of **379** (0.113 g, 0.326 mmol) in *tert*-butanol (1.5 mL). The reaction mixture was agitated with ultrasound waves in a sonicator fitted with a water bath for 6 h, stirred at rt for 12 h and then sonicated again for an additional 6 h. The mixture was diluted with H<sub>2</sub>O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried and concentrated *in vacuo* to afford a yellow oil, which was used unpurified in the subsequent Petasis reaction.

### 7.3.4 General method for the Petasis reaction



**(3*S*,4*R*,6*S*,*E*)-3-((*S*)-1-(Benzyloxy)but-3-en-2-ylamino)-6-(4-methoxybenzyloxy)-1-phenylhept-1-en-4-ol (382).** To a stirred solution of the crude Sharpless ADH product in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL) stirring under nitrogen was added (*E*)-2-phenylvinylboronic acid (0.058 g, 0.326 mmol) and (2*S*)-1-(benzyloxy)but-3-en-2-amine (**381**, 0.048 g, 0.326 mmol). The reaction mixture was stirred at rt for 48 h, diluted with EtOAc (10 mL) and washed with 0.5 M aq NaOH (3 x 10 mL). The organic layer was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a black oil. Purification by flash column chromatography

(2.5:97.5 to 5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent) gave the title compound (0.087 g, 53%, over 2 steps) as a brown oil.

$R_f$  0.25 (5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub>).

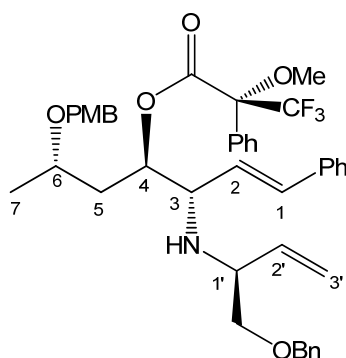
$[\alpha]_D^{24} +18.2$  ( $c$  1.00, CHCl<sub>3</sub>).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3421, 3078, 3027, 2965, 2909, 2852, 1613, 1512, 1444, 1247, 1085, 1034.

$\delta_H$  (500 MHz): 7.36-7.19 (12H, m, ArH), 6.85-6.79 (2H, m, ArH), 6.43 (1H, d,  $J$  = 16.0 Hz, H1), 6.09 (1H, dd,  $J$  = 8.5, 16.0 Hz, H2), 5.59 (1H, ddd,  $J$  = 7.7, 9.9, 17.4 Hz, H2'), 5.22-5.15 (2H, m, H3'), 4.55-4.36 (4H, m, OCH<sub>2</sub>Ph and OCH<sub>2</sub>PMP), 4.02 (dt,  $J$  = 3.8, 6.3 Hz, H4), 3.88-3.78 (1H, m, H6), 3.77 (3H, s, OCH<sub>3</sub>), 3.24 (1H, dd,  $J$  = 3.8, 8.5 Hz, H3), 3.50-3.40 (3H, m, H1' and H1''), 1.57 (2H, dd,  $J$  = 5.7, 6.3 Hz, H5), 1.21 (3H, d,  $J$  = 6.2 Hz, H7).

$\delta_C$  (125 MHz): 159.1 (ArC), 138.1 (ArC), 137.8 (C2'), 136.9 (ArC), 135.3 (ArC), 132.9 (C1), 130.9 (ArC), 129.3 (ArC), 128.5 (ArC), 128.4 (ArC), 127.9 (C2), 127.6 (ArC), 127.4 (ArC), 126.4 (ArC), 118.0 (C3'), 113.8 (ArC), 73.3 (C1''), 73.0 (OCH<sub>2</sub>PMP), 72.1 (C6), 70.4 (OCH<sub>2</sub>Bn), 70.2 (C4), 62.3 (C3), 58.0 (C1'), 55.3 (OCH<sub>3</sub>), 40.1 (C5), 19.7 (C7).

ESIMS  $m/z$  502 (100%) [MH]<sup>+</sup>, HREIMS found 502.2954, calc for C<sub>32</sub>H<sub>40</sub>NO<sub>4</sub>, 502.2957 [MH]<sup>+</sup>.



**(*R*)-((3*S*,4*R*,6*S*,*E*)-3-((*S*)-1-(Benzyloxy)but-3-en-2-ylamino)-6-(4-methoxybenzyloxy)-1-phenylhept-1-en-4-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (396).**

Following the general method of the synthesis of Mosher's esters using **382** (14 mg, 0.028 mmol), Et<sub>3</sub>N (50  $\mu$ L), DMAP (10 mg, 0.083 mmol), (*S*)-(+)- $\alpha$ -methoxy- $\alpha$ -

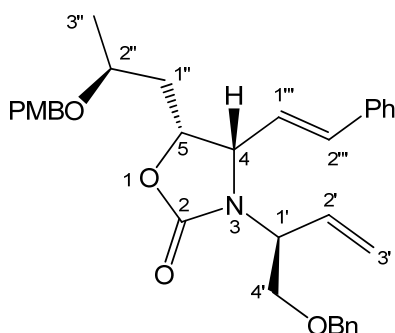
trifluoromethylphenylacetyl chloride (33 mg, 0.132 mmol) and  $\text{CH}_2\text{Cl}_2$  (2 mL), the title compound (17 mg, 88%) was obtained as a yellow oil.

$\delta_{\text{H}}$  (500 MHz): 7.62 (2H, d,  $J = 7.9$  Hz, ArH), 7.37-7.20 (15H, m, ArH), 6.86 (2H, d,  $J = 8.4$  Hz, ArH), 6.40 (1H, d,  $J = 16.0$  Hz, H1), 5.89 (1H, dd,  $J = 8.9, 16.0$  Hz, H2), 5.61-5.52 (2H, m, H2' and H4), 5.18-5.12 (2H, m, H3'), 4.52-4.44 (2H, m,  $\text{OCH}_2\text{PMP}$ ), 4.44 (1H, d,  $J = 10.5$  Hz,  $\text{OHCHPh}$ ), 4.26 (1H, d,  $J = 10.5$  Hz,  $\text{OHCHPh}$ ), 3.78 (3H, s,  $\text{OCH}_3\text{Ar}$ ), 3.52 (3H, s,  $(\text{OCH}_3)(\text{CF}_3)\text{PhC}$ ), 3.48-3.35 (5H, m, H3, H1', H1'' and H6), 1.88-1.81 (1H, m, H5<sub>A</sub>), 1.69-1.60 (1H, m, H5<sub>B</sub>), 1.12 (3H, d,  $J = 6.0$  Hz, H7).

$\delta_{\text{F}}$  (282 MHz): -71.68 (major diastereomer, integral = 95.1%), -71.84 (minor diastereomer, integral = 4.9%).  $\text{CF}_3\text{CH}_2\text{OH}$  referenced at -77.8 ppm.

ESIMS  $m/z$  718 (100%)  $[\text{MH}]^+$ , HREIMS found, calc for  $\text{C}_{42}\text{H}_{47}\text{F}_3\text{NO}_6$  718.3763,  $[\text{MH}]^+$ .

### 7.3.5 General method for the synthesis of oxazolidinones



**(4*S*,5*R*)-3-((*S*)-1-(Benzyloxy)but-3-en-2-yl)-5-((*S*)-2-(4-methoxybenzyloxy)propyl)-4-styryloxazolidin-2-one (383).** To solution of the 1,2-amino alcohol **382** (0.020 g, 0.040 mmol) and triethylamine (11  $\mu\text{L}$ , 0.080 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3 mL) at 0  $^\circ\text{C}$  was added triphosgene (6 mg, 0.020 mmol). The reaction mixture was allowed to warm to rt and was stirred for 18 h and then concentrated *in vacuo* to give a yellow solid. Purification by flash column chromatography using  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$  (1:30) as eluent gave the title compound (0.017 g, 81%) as a colorless oil.

$R_f$  0.39 (1:3 EtOAc/petrol).

$[\alpha]_D^{21} +3.6$  ( $c$  8.30,  $\text{CHCl}_3$ ).

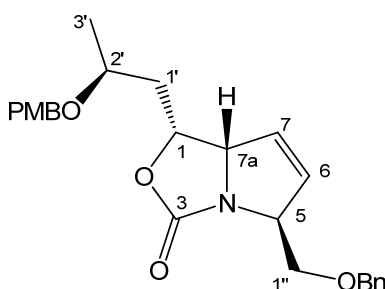
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2970, 2924, 2847, 1746, 1513, 1247, 1073.

$\delta_{\text{H}}$  (300 MHz): 7.33-7.24 (12H, m, ArH), 6.88-6.85 (2H, m, ArH), 6.30 (1H, d,  $J = 16.2$  Hz, H2'') 5.82 (1H, ddd,  $J = 7.2, 10.1, 17.6$  Hz, H2'), 6.00 (1H, dd,  $J = 9.3, 15.9$  Hz, H1''), 5.25 (1H, d,  $J = 17.2$  Hz, H3'*trans*), 5.18 (1H, dd,  $J = 10.4$  Hz, H3'*cis*), 4.86 (1H, ddd,  $J = 2.6, 8.1, 10.7$  Hz, H5), 4.61 (1H, d,  $J = 11.7$  Hz, OCHHPH), 4.52 (1H, d,  $J = 10.7$  Hz, OCHHPMP), 4.48 (1H, d,  $J = 11.7$  Hz, OCHHPH), 4.41-4.32 (1H, m, H4), 4.39-4.32 (1H, m, H1'), 4.34 (1H, d,  $J = 10.7$  Hz, OCHHPMP), 3.90-3.76 (1H, m, H2''), 3.90-3.76 (1H, m, H4'<sub>A</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 3.61 (1H, dd,  $J = 5.4, 10.2$  Hz, H4'<sub>B</sub>), 1.74-1.55 (2H, m, H1''), 1.19 (3H, d,  $J = 6.3$  Hz, H3'').

$\delta_{\text{C}}$  (75 MHz): 159.2 (ArC), 157.4 (CO), 137.8 (ArC), 135.6 (ArC), 135.0 (C2''), 133.6 (C2'), 130.6 (ArC), 128.4 (ArC), 128.6 (ArC), 128.4 (ArC), 128.3 (ArC), 127.9 (ArC), 127.8 (ArC), 126. (ArC), 124.9 (C1''), 118.4 (C3'), 113.8 (ArC), 74.6 (C5), 73.0 (OCH<sub>2</sub>Ph), 71.3 (C2''), 70.9 (OCH<sub>2</sub>PMP), 68.9 (C4'), 61.3 (C4), 56.2 (C1'), 55.3 (OCH<sub>3</sub>), 38.7 (C1''), 20.1 (C3'').

ESIMS  $m/z$  550 (80%) [MNa]<sup>+</sup>, 528 (18%) [MH]<sup>+</sup>, HREIMS found 528.2737, calc for C<sub>33</sub>H<sub>38</sub>NO<sub>5</sub>, 528.2750 [MH]<sup>+</sup>.

### 7.3.6 General method for ring-closing metathesis (RCM) of oxazolidinones



**(1R,5S,7aS)-5-(Benzyloxymethyl)-1-((S)-2-(4-methoxybenzyloxy)propyl)-1,7a-dihydropyrrolo[1,2-c]oxazol-3(5H)-one (384).** To a nitrogen-flushed solution of the oxazolidinone **383** (0.165 g, 0.313 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added the Grubbs II catalyst (13 mg, 0.0157 mmol). The reaction mixture was stirred and irradiated with microwaves in a CEM microwave reactor for 1 h at 90 °C using a maximum applied power of 200 W. After cooling the reaction mixture was concentrated *in vacuo* to give a black semi-solid. Purification by flash column chromatography using EtOAc/petrol (3:7) as eluent gave the title compound (0.100 g, 76%) as a yellow oil.

$R_f$  0.25 (1:3 EtOAc/petrol).

$[\alpha]_D^{24}$  -32.4 (c 1.00,  $\text{CHCl}_3$ ).

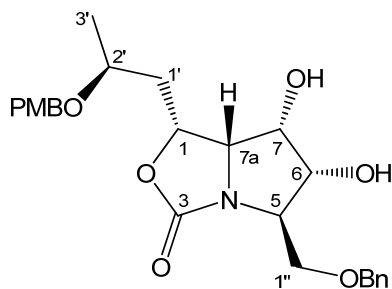
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 2970, 2929, 2858, 1752, 1513, 1375, 1248, 1030.

$\delta_{\text{H}}$  (500 MHz): 7.35-7.24 (7H, m, ArH), 6.92-6.86 (2H, m, ArH), 6.01 (1H, dd,  $J = 2.3$ , 6.0 Hz, H7), 5.91 (1H, dd,  $J = 1.1$ , 6.1 Hz, H6), 5.00 (1H, dt,  $J = 3.4$ , 8.9 Hz, H1), 4.82-4.77 (2H, m, H7a and H5), 4.58 (1H, d,  $J = 12.0$  Hz, OCHHPMP), 4.56 (1H, d,  $J = 10.8$  Hz, OCHHPh), 4.54 (1H, d,  $J = 12.0$  Hz, OCHHPMP), 4.34 (1H, d,  $J = 10.8$  Hz, OCHHPh), 3.81-3.76 (1H, m, H2'), 3.80 (3H, s,  $\text{OCH}_3$ ), 3.54 (2H, dd,  $J = 2.1$ , 5.0 Hz, H1''), 1.73 (1H, ddd,  $J = 3.6$ , 10.3, 14.3 Hz, H1'A), 1.62 (1H, ddd,  $J = 2.8$ , 9.7, 14.3 Hz, H1'B), 1.22 (3H, d,  $J = 6.0$  Hz, H3').

$\delta_{\text{C}}$  (125 MHz): 162.4 (ArC), 159.2 (C3), 137.9 (ArC), 132.8 (C7), 130.5 (ArC), 129.4 (ArC), 128.4 (ArC), 128.4 (C6), 127.6 (ArC), 127.5 (ArC), 113.9 (ArC), 76.3 (C1), 73.2 ( $\text{OCH}_2\text{PMP}$ ), 71.3 (C1''), 71.1 (C2'), 70.8 ( $\text{OCH}_2\text{Ph}$ ), 68.2 (C5), 66.8 (C7a), 55.1 ( $\text{OCH}_3$ ), 40.0 (C1'), 19.9 (C3').

ESIMS  $m/z$  446 (100%)  $[\text{MNa}]^+$ , HREIMS found 446.1956 calc for  $\text{C}_{25}\text{H}_{29}\text{NO}_5\text{Na}$ , 424.2124  $[\text{MNa}]^+$ .

### 7.3.7 General method for *syn*-dihydroxylation



**(1*R*,5*R*,6*R*,7*S*,7*aS*)-5-(Benzyloxymethyl)-6,7-dihydroxy-1-((*S*)-2-(4-methoxybenzyloxy)propyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (385).** To a solution of the RCM product **384** (0.600 g, 1.420 mmol) in 3:2 acetone/water (20 mL) was added *N*-morpholine-*N*-oxide (0.333 g, 2.840 mmol) and potassium osmate dihydrate (26 mg, 0.071 mmol). The reaction mixture was stirred at rt for 18 h, diluted with  $\text{H}_2\text{O}$  and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and



concentrated *in vacuo* to afford a black oil. Purification by flash column chromatography (increasing polarity from 0:100 to 5:95 MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluent) gave the title compound (0.572 g, 88%) as a brown oil.

$R_f$  0.26 (1:1 EtOAc/petrol).

$[\alpha]_D^{24} +2.0$  ( $c$  1.00, CHCl<sub>3</sub>).

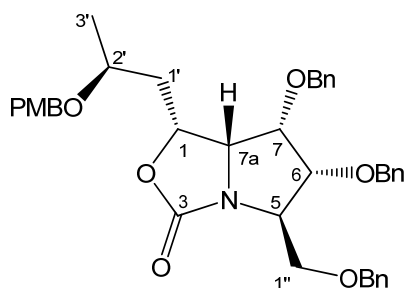
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3421, 2934, 2909, 2863, 1727, 1513, 1247, 1123, 1061.

$\delta_H$  (500 MHz): 7.36-7.21 (7H, m, ArH), 6.86 (2H, d,  $J = 8.5$  Hz, ArH), 4.86 (1H, td,  $J = 3.9, 8.2$  Hz, H1), 4.57 (2H, q,  $J = 11.1$  Hz, OCH<sub>2</sub>PMP), 4.54 (1H, d,  $J = 10.8$  Hz, OHCHPh), 4.31 (1H, d,  $J = 10.8$  Hz, OHCHPh), 4.30-4.27 (1H, m, H7), 3.97-3.95 (1H, m, H6), 3.80-3.77 (1H, m, H5), 3.78 (3H, s, OCH<sub>3</sub>), 3.78-3.76 (1H, m, H2'), 3.74 (1H, dd,  $J = 3.8, 9.6$  Hz, H1''<sub>A</sub>), 3.67-3.65 (1H, m, H7a), 3.63 (1H, dd,  $J = 5.3, 9.6$  Hz, H1''<sub>B</sub>), 2.36 (1H, ddd,  $J = 2.4, 8.8, 14.6$  Hz, H1'<sub>A</sub>), 1.94 (1H, ddd,  $J = 4.0, 10.4, 14.6$  Hz, H1'<sub>B</sub>), 1.24 (3H, d,  $J = 6.0$  Hz, H3').

$\delta_C$  (125 MHz): 162.7 (C3), 159.2 (ArC), 137.8 (ArC), 130.5 (ArC), 129.5 (ArC), 128.4 (ArC), 127.8 (ArC), 127.6 (ArC), 113.8 (ArC), 76.3 (C7), 73.9 (C1), 73.5 (C3''), 72.3 (C6), 72.1 (C2'), 70.7 (C5'), 70.4 (1''), 65.1 (C7a), 62.3 (C5), 55.3 (OCH<sub>3</sub>), 37.5 (C1'), 19.9 (C3').

ESIMS  $m/z$  480 (100%) [MNa]<sup>+</sup>, 458 (10%) [MH]<sup>+</sup>, HREIMS found 458.2187, calc for C<sub>25</sub>H<sub>32</sub>NO<sub>7</sub>, 458.2179 [MH]<sup>+</sup>.

### 7.3.8 General method for bisbenzylation of secondary diols



**(1R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((S)-2-(4-methoxybenzyloxy)propyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (386).** A solution of the diol **385** (0.018 g, 0.0391 mmol), benzyl bromide (0.020 mL, 0.157 mmol) and

tetrabutylammonium iodide (1 mg, 0.004 mmol) in anhydrous THF (5 mL) was cooled to 0 °C. To the above solution was added sodium hydride (50% dispersion in mineral oil, 6 mg, 3 mg NaH, 0.117 mmol), and the reaction mixture was allowed to warm to rt and was stirred for 18 h. Quenching with H<sub>2</sub>O gave a cloudy mixture, which was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined ethereal extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (increasing polarity from 1:9 to 1:4 EtOAc/petrol) gave the title compound (0.025 g, 100%) as a colorless oil.

*R<sub>f</sub>* 0.19 (1:10 EtOAc/petrol).

$[\alpha]_D^{22} +9.3$  (*c* 1.23, CHCl<sub>3</sub>).

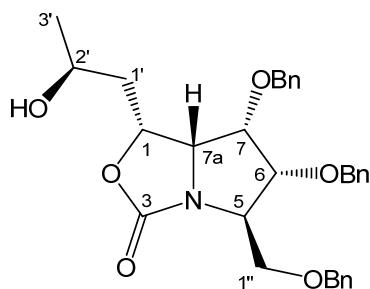
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2929, 2858, 1750, 1516, 1239, 1096, 1067, 1028, 906.

$\delta_H$  (500 MHz): 7.35-7.19 (17H, m, ArH), 6.88-6.84 (2H, m, ArH), 5.01 (1H, d, *J* = 11.5 Hz, OCHHAr), 4.80 (1H, ddd, *J* = 4.8, 7.8, 8.0 Hz, H1), 4.63-4.50 (3H, m, 3 x OCHHAr), 4.55-4.50 (1H, m, OCHHAr), 4.43 (1H, d, *J* = 16.3 Hz, OCHHAr), 4.41 (1H, d, *J* = 16.3 Hz, OCHHAr), 4.26 (1H, d, *J* = 10.6 Hz, OCHHAr), 4.18 (1H, dd, *J* = 2.7, 8.1 Hz, H6), 3.98 (1H, dt, *J* = 3.0, 8.1 Hz, H5), 3.94 (1H, t, *J* = 2.7 Hz, H7), 3.78 (3H, s, OCH<sub>3</sub>), 3.78-3.75 (1H, m, H1''<sub>A</sub>), 3.70-3.67 (1H, m, H2'), 3.65 (1H, dd, *J* = 2.7, 7.8 Hz, H7a), 3.59 (dd, *J* = 2.9, 10.3 Hz, H1''<sub>B</sub>), 2.12 (1H, ddd, *J* = 2.7, 8.3, 14.7 Hz, H1'<sub>A</sub>), 1.75 (1H, ddd, *J* = 4.7, 10.4, 14.7 Hz, H1'<sub>B</sub>), 1.09 (3H, d, *J* = 6.1 Hz, H3').

$\delta_C$  (125 MHz): 162.0 (C3), 159.2 (ArC), 138.1 (ArC), 138.0 (ArC), 137.5 (ArC), 130.5 (ArC), 129.5 (ArC), 128.5 (ArC), 128.3 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.6 (ArC), 127.4 (ArC), 127.2 (ArC), 113.8 (ArC), 83.1 (C6), 77.1 (C7), 73.8 (C1), 73.3 (OBn), 73.2 (OBn), 72.8 (OBn), 72.2 (C2), 70.7 (OPMB), 69.2 (C1''), 64.2 (C7a), 60.9 (C5), 55.2 (OCH<sub>3</sub>), 37.3 (C1'), 19.8 (C3').

ESIMS *m/z* 660 (70%) [MNa]<sup>+</sup>, 638 (3%) [MH]<sup>+</sup>, HREIMS found 638.3093, calc for C<sub>39</sub>H<sub>44</sub>NO<sub>7</sub>, 638.3118 [MH]<sup>+</sup>.

### 7.3.9 General method for PMB deprotection using DDQ



**(1*R*,5*R*,6*R*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((*S*)-2-hydroxypropyl)-tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (387).** To a solution of **386** (0.131 g, 0.206 mmol) in 8:1 CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (9 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (0.103 g, 0.453 mmol). The reaction mixture was stirred at rt for 4 h, when TLC analysis (EtOAc/petrol (1:1)) showed complete consumption of **386**. Purification by flash column chromatography (increasing polarity from 1:1 to 4:1 EtOAc/petrol as eluent) gave the title compound (0.094 g, 89%) as a yellow oil.

*R<sub>f</sub>* 0.16 (1:1 EtOAc/petrol).

$[\alpha]_D^{24} +19.8$  (*c* 1.31, CHCl<sub>3</sub>).

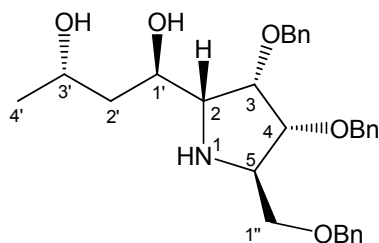
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3436, 3057, 3021, 2924, 2863, 1747, 1454, 1357, 1203.

$\delta_H$  (500 MHz): 7.37-7.19 (15H, m, ArH), 5.04 (1H, d, *J* = 11.6 Hz, OCHHPh), 4.79 (1H, td, *J* = 4.8, 8.0 Hz, H1), 4.65 (1H, d, *J* = 11.9 Hz, OCHHPh), 4.56 (1H, d, *J* = 11.5 Hz, OCHHPh), 4.54 (1H, d, *J* = 14.0 Hz, OCHHPh), 4.51 (1H, d, *J* = 14.0 Hz, OCHHPh), 4.41 (1H, d, *J* = 11.9 Hz, OCHHPh), 4.29 (1H, dd, *J* = 2.1, 7.9 Hz, H6), 4.05-4.02 (1H, m, H7), 4.00 (1H, dt, *J* = 3.1, 8.0 Hz, H5), 3.92 (1H, ddd, *J* = 3.1, 6.3, 9.5 Hz, H2'), 3.76 (1H, dd, *J* = 3.2, 10.3 Hz, H1''<sub>A</sub>), 3.73 (1H, dd, *J* = 2.6, 7.6 Hz, H7a), 3.60 (1H, dd, *J* = 3.0, 10.3 Hz, H1''<sub>B</sub>), 2.10 (1H, ddd, *J* = 2.9, 8.5, 14.5 Hz, H1'<sub>A</sub>), 1.64 (1H, ddd, *J* = 4.7, 9.9, 14.5 Hz, H1'<sub>B</sub>), 1.08 (3H, d, *J* = 6.2 Hz, H3').

$\delta_C$  (125 MHz): 162.0 (C3), 138.1 (ArC), 137.9 (ArC), 137.5 (ArC), 128.5 (ArC), 128.3 (ArC), 128.3 (ArC), 127.8 (ArC), 127.6 (ArC), 127.4 (ArC), 127.3 (ArC), 83.2 (C6), 77.0 (C7), 73.8 (C1), 73.3 (OCH<sub>2</sub>Ph), 73.2 (OCH<sub>2</sub>Ph), 72.9 (OCH<sub>2</sub>Ph), 69.3 (C1''), 65.1 (CH), 64.2 (C7a), 61.0 (C5), 38.1 (C1'), 24.4 (C3').

ESIMS  $m/z$  540 (100%)  $[\text{MNa}]^+$ , 518 (48%)  $[\text{MH}]^+$ , HREIMS found 518.2523, calc for  $\text{C}_{31}\text{H}_{36}\text{NO}_6$ , 518.2543  $[\text{MH}]^+$ .

### 7.3.10 General method for hydrolysis of oxazolidinones



**(1R,3S)-1-((2R,3S,4R,5R)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)butane-1,3-diol (388).** To a solution of 387 (0.270 g, 0.521 mmol) in ethanol (3 mL) was added sodium hydroxide (0.042 g, 1.042 mmol). The reaction mixture was stirred and irradiated with microwaves in a CEM microwave reactor for 1 h at 110 °C using a maximum applied power of 200 W. After cooling the reaction mixture was concentrated *in vacuo* to give a yellow semi-solid. Purification by flash column chromatography (increasing polarity from 2.5:97.5 to 7.5:92.5 MeOH/ $\text{CH}_2\text{Cl}_2$  as eluent) gave the title compound (0.216 g, 84%) as a light yellow oil.

$R_f$  0.32 (7.5:92.5 MeOH/ $\text{CH}_2\text{Cl}_2$ ).

$[\alpha]_D^{24} +13.6$  ( $c$  1.00,  $\text{CHCl}_3$ ).

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ): 3359, 3088, 3062, 3032, 2955, 2893, 2858, 1147, 1085, 1049.

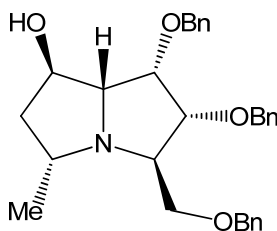
$\delta_{\text{H}}$  (500 MHz): 7.36-7.23 (15H, ArH), 4.86 (1H, d,  $J = 11.4$  Hz, OCHHPh), 4.60 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.55 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.54 (1H, d,  $J = 11.4$  Hz, OCHHPh), 4.48 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.43 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.14 (1H, t,  $J = 5.0$  Hz, H3), 4.13-4.10 (1H, m, H1'), 4.01-3.93 (1H, m, H3'), 3.90 (1H, t,  $J = 5.0$  Hz, H4), 3.54-3.46 (2H, m, H1''), 3.47-3.44 (1H, m, H5), 3.10 (1H, dd,  $J = 5.0$ , 8.5 Hz, H2), 1.73-1.60 (2H, m, H2'), 1.17 (3H, d,  $J = 6.3$  Hz, H4').

$\delta_{\text{C}}$  (125 MHz): 137.9 (ArC), 137.8 (ArC), 137.7 (ArC), 128.6 (ArC), 128.4 (ArC), 128.4 (ArC), 128.0 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (ArC), 127.7 (ArC), 127.7 (ArC).

80.5 (C4), 79.9 (C3), 73.3 (OCH<sub>2</sub>Ph), 73.2 (OCH<sub>2</sub>Ph), 72.6 (OCH<sub>2</sub>Ph), 70.5 (C1'), 69.7 (C1''), 65.3 (C3'), 63.0 (C2), 60.7 (C5), 44.5 (C2'), 23.8 (C4').

ESIMS  $m/z$  492 (100%) [MH]<sup>+</sup>, HREIMS found 492.2758, calc for C<sub>30</sub>H<sub>38</sub>NO<sub>5</sub>, 492.2750 [MH]<sup>+</sup>.

### 7.3.11 General method for mesylation-cyclization



**(1R,3R,5R,6R,7S,7aR)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1H-pyrrolizin-1-ol (389).** To solution of **388** (0.130 g, 0.264 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C was added *via* syringe triethylamine (20.4 μL, 0.264 mmol) and a 0.11 M solution of MeSO<sub>2</sub>Cl in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL, 0.264 mmol MeSO<sub>2</sub>Cl). The reaction mixture was stirred at 0 °C for 1.5 h and quenched with sat. NaHCO<sub>3</sub> solution (3 mL), followed by extractions with EtOAc (3 x 15 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (increasing polarity from 4:1 to 100:0 EtOAc/petrol as eluent) gave the title compound (0.079 g, 63%) as a colorless oil.

$R_f$  0.20 (4:1 EtOAc/petrol).

$[\alpha]_D^{25} +25.0$  ( $c$  1.00, CHCl<sub>3</sub>).

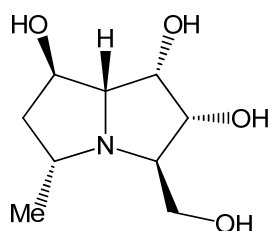
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3380, 2955, 2919, 2858, 1362, 1127, 1096, 1055, 1024.

$\delta_H$  (500 MHz): 7.36-7.25 (15H, m, ArH), 4.73 (1H, d,  $J$  = 11.7 Hz, OCHHPh), 4.67-4.63 (1H, dd,  $J$  = 4.4, 10.5 Hz H7), 4.59-4.50 (5H, m, 5 x OCHHPh), 4.15 (1H, t,  $J$  = 4.8 Hz, H1), 3.91 (1H, t,  $J$  = 4.5 Hz, H2), 3.77 (1H, dq,  $J$  = 6.6, 15.6 Hz, H5), 3.66 (1H, dd,  $J$  = 4.7, 7.0 Hz, H7a), 3.48 (1H, dd,  $J$  = 4.2, 8.5 Hz, H8<sub>A</sub>), 3.43-3.40 (1H, m, H3), 3.41-3.37 (1H, m, H8<sub>B</sub>), 1.90-1.86 (2H, m, H6<sub>A</sub> and H6<sub>B</sub>), 1.19 (3H, d,  $J$  = 6.8 Hz, H9).

$\delta_C$  (125 MHz): 138.1 (ArC), 138.1 (ArC), 137.9 (ArC), 128.4 (ArC), 128.4 (ArC), 128.3 (ArC), 127.8 (ArC), 127.8 (ArC), 127.7 (ArC), 127.7 (ArC), 127.6 (ArC), 127.6 (ArC), 81.0 (C2), 76.2 (C1), 75.7 (C7a), 73.4 (OCH<sub>2</sub>Ph), 73.1 (OCH<sub>2</sub>Ph), 72.2 (OCH<sub>2</sub>Ph), 71.1 (C7), 71.1 (C8), 60.1 (C3), 57.1 (C5), 42.3 (C6), 16.0 (C9).

ESIMS  $m/z$  474 (100%) [MH]<sup>+</sup>, HREIMS found 474.2624, calc for C<sub>30</sub>H<sub>36</sub>NO<sub>4</sub>, 474.2644 [MH]<sup>+</sup>.

### 7.3.12 General method for hydrogenolysis of benzyl ethers



**(1S,2R,3R,5R,7R,7aR)-3-(Hydroxymethyl)-5-methylhexahydro-1H-pyrrolizine-1,2,7-triol (Hyacinthacine B<sub>3</sub>, 104).** To a H<sub>2</sub> flushed solution of the cyclized product **389** (17 mg, 0.036 mmol) in MeOH (2 mL) was added PdCl<sub>2</sub> (7 mg, 0.039 mmol). The reaction mixture was stirred at rt under a H<sub>2</sub> atmosphere (balloon) for 8 h and then filtered through a pad of celite and the solids were washed with MeOH. The combined filtrates were concentrated *in vacuo* to give a colorless film, which was dissolved in water (2 mL) and held for 15 min in a column containing Amberlyst A-26 (OH<sup>-</sup>) ion-exchange resin (1 g). Elution with water (5 x 5 mL) followed by evaporation *in vacuo* gave the title compound (5 mg, 68%) as a colorless film.

$[\alpha]_D^{23} +10.8$  ( $c$  0.33, H<sub>2</sub>O). [Lit.  $[\alpha]_D +3.3$  ( $c$  0.31, H<sub>2</sub>O), temperature unknown].

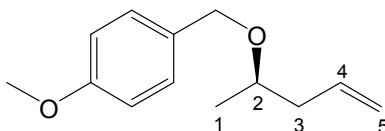
IR  $\nu_{\max}$  (cm<sup>-1</sup>): 3317, 2960, 2929, 2878, 1652, 1338, 1133.

$\delta_H$  (500 MHz, CD<sub>3</sub>OD): 4.52 (1H, m, H7), 4.04 (1H, t,  $J$  = 4.4 Hz, H1), 3.91 (1H, dd,  $J$  = 4.2, 7.3 Hz, H2), 3.57 (1H, dd,  $J$  = 4.9, 11.0 Hz, H8<sub>β</sub>), 3.53 (1H, dd,  $J$  = 4.5, 11.1 Hz, H8<sub>α</sub>), 3.50 (1H, m, H5), 3.30 (1H, t,  $J$  = 4.6 Hz, H7a), 3.10 (1H, ddd,  $J$  = 4.7, 4.9, 7.3 Hz, H3), 1.86-1.82 (2H, m, H6<sub>α</sub> and H6<sub>β</sub>), 1.19 (3H, d,  $J$  = 6.9 Hz, H9).

$\delta_{\text{H}}$  (75 MHz,  $\text{CD}_3\text{OD}$ ): 76.5 (C2), 76.2 (C7a), 71.4 (C1), 70.6 (C7), 64.2 (C8), 63.0 (C3), 56.4 (C5), 43.5 (C6), 16.7 (C9).

ESIMS  $m/z$  204 (100%)  $[\text{MH}]^+$ , HREIMS found 204.1297, calc for  $\text{C}_9\text{H}_{18}\text{NO}_4$ , 204.1236  $[\text{MH}]^+$ .

#### 7.4 Experimentals for Chapter 5

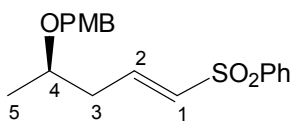


**(*R*)-1-Methoxy-4-((pent-4-en-2-yloxy)methyl)benzene (398).** Following the general method described for *O*-PMB protection using (*R*)-4-penten-2-ol (1.008 g, 11.703 mmol), 4-methoxybenzyl chloride (3.15 mL, 23.242 mmol), tetrabutylammonium iodide (0.369 g, 1.161 mmol) and sodium hydride (0.418 g, 17.415 mmol) in THF (50 mL), the title compound was obtained as a colorless oil (2.062 g, 86 %).

$[\alpha]_D^{23}$  -11.0 ( $c$  1.00,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (500 MHz): 7.26 (2H, d,  $J$  = 8.8 Hz, ArH), 6.86 (2H, d,  $J$  = 8.8 Hz, ArH), 5.87-5.78 (2H, m, H4), 5.07 (1H, d,  $J$  = 17.3 Hz,  $\text{H5}_{\text{trans}}$ ), 5.04 (1H, d,  $J$  = 10.7 Hz,  $\text{H5}_{\text{cis}}$ ), (1H, d,  $J$  = 17.3 Hz,  $\text{H5}_{\text{trans}}$ ), 4.48 (1H, d,  $J$  = 11.5 Hz, OCHHPMP), 4.27 (1H, d,  $J$  = 11.5 Hz, OCHHPMP), 3.77 (3H, s,  $\text{OCH}_3$ ), 3.58-3.52 (1H, m, H2), 2.36 (1H, ddd,  $J$  = 5.9, 6.6, 13.7 Hz,  $\text{H3}_\text{A}$ ), 2.21 (1H, ddd,  $J$  = 6.7, 7.1, 13.9 Hz,  $\text{H3}_\text{B}$ ), 1.17 (3H, d,  $J$  = 6.1 Hz, H1)

$\delta_{\text{C}}$  (125 MHz): 159.0 (ArC), 135.0 (C4), 130.9 (ArC), 129.0 (ArC), 116.6 (C5), 113.6 (ArC), 74.0 (C2), 69.9 ( $\text{OCH}_2\text{PMP}$ ), 55.1 ( $\text{OCH}_3$ ), 40.8 (C3), 19.3 (C1).



**(1*E*,4*R*)-4-[(4-Methoxybenzyl)oxy]pent-1-en-1-yl phenyl sulfone (399).** Following the general method described for olefin cross metathesis using **398** (0.066 g, 0.319 mmol), phenyl vinyl sulfone (0.107 g, 0.638 mmol), Grubbs II catalyst (14 mg, 0.160 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL), the title compound (0.079 g, 71 %) was obtained as a pale yellow oil.

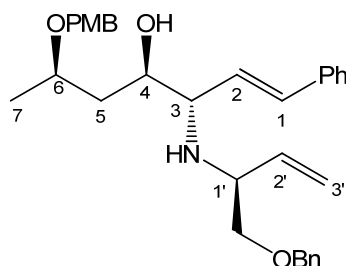
$[\alpha]_D^{23} +17.5$  (*c* 1.0, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.87-7.84 (2H, m, ArH), 7.60-7.48 (3H, m, ArH), 7.20-7.17 (2H, m, ArH), 7.01 (1H, dt, *J* = 7.2, 14.8 Hz, H<sub>2</sub>), 6.86-6.83 (2H, m, ArH), 6.37 (1H, dd, *J* = 1.2, 15.1 Hz, H<sub>1</sub>), 4.50-4.48 (1H, d, *J* = 11.2 Hz, OCHHPMP), 4.34 (1H, d, *J* = 11.2 Hz, OCHHPMP), 3.80 (3H, s, OCH<sub>3</sub>), 3.65 (1H, dq, *J* = 6.2, 12.4 Hz, H<sub>4</sub>), 2.46-2.39 (2H, m, H<sub>3</sub>), 1.20 (3H, d, *J* = 6.2 Hz, H<sub>5</sub>).

$\delta_C$  (125 MHz): 159.1 (ArC), 143.6 (C<sub>2</sub>), 140.6 (ArC), 133.2 (ArC), 132.1 (C<sub>1</sub>), 130.2 (ArC), 129.2 (ArC), 127.5 (ArC), 113.8 (ArC), 72.6 (C<sub>4</sub>), 70.2 (O-CH<sub>2</sub>-Ar), 55.2 (OCH<sub>3</sub>), 38.5 (C<sub>3</sub>), 19.6 (C<sub>5</sub>).

ESIMS *m/z* 369 (100%) [MNa]<sup>+</sup>, HRESIMS found 369.1151, calc for C<sub>19</sub>H<sub>22</sub>O<sub>4</sub>NaS, 369.1137 [MNa]<sup>+</sup>.





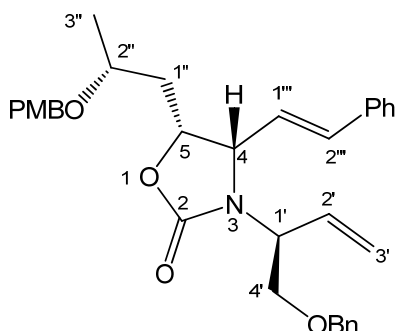
**(3*S*,4*R*,6*R*,*E*)-3-((*S*)-1-(Benzyloxy)but-3-en-2-ylamino)-6-(4-methoxybenzyloxy)-1-phenylhept-1-en-4-ol (401).** Following the general method described for Sharpless asymmetric dihydroxylation and the Petasis reaction using the vinyl sulfone **399** (0.849 g, 2.451 mmol), potassium ferric cyanide (2.420g, 7.352 mmol), potassium carbonate (1.016 g, 7.352 mmol), methanesulfonamide (0.233 g, 2.451 mmol), potassium osmate.dihydrate (5 mg, 0.015 mmol), DHQD-IND (17 mg, 0.0368 mmol), H<sub>2</sub>O (23 mL) and *t*-BuOH (23 mL) in the Sharpless ADH and using (*E*)-2-phenylvinylboronic acid (0.363 g, 2.451 mmol), (2*S*)-1-(benzyloxy)but-3-en-2-amine (0.434 g, 2.451 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) in the Petasis reaction gave the title compound (0.491 g, 40 %, 2 steps) as a brown oil.

$[\alpha]_D^{23} +10.6$  (*c* 2.00, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.36-7.19 (12H, m, ArH), 6.85-6.79 (2H, m, ArH), 6.43 (1H, d, *J* = 16.0 Hz, H1), 6.09 (1H, dd, *J* = 8.5, 16.0 Hz, H2), 5.59 (1H, ddd, *J* = 7.7, 9.9, 17.4 Hz, H2'), 5.22-5.15 (2H, m, H3'), 4.55-4.36 (4H, m, OCH<sub>2</sub>Ph and OCH<sub>2</sub>PMP), 4.02 (dt, *J* = 3.8, 6.3 Hz, H4), 3.88-3.78 (1H, m, H6), 3.77 (3H, s, OCH<sub>3</sub>), 3.24 (1H, dd, *J* = 3.8, 8.5 Hz, H3), 3.50-3.40 (3H, m, H1' and H1''), 1.57 (2H, dd, *J* = 5.7, 6.3 Hz, H5), 1.21 (3H, d, *J* = 6.2 Hz, H7).

$\delta_C$  (125 MHz): 159.2 (ArC), 138.1 (ArC), 137.9 (C2'), 136.9 (ArC), 132.8 (C1), 129.4 (ArC), 130.2 (ArC), 128.4 (ArC), 128.3 (ArC), 128.2 (C2), 127.6 (ArC), 127.5 (ArC), 127.4 (ArC), 126.3 (ArC), 117.9 (C3'), 113.9 (ArC), 75.3 (C6), 73.8 (C4), 73.4 (C1'), 72.9 (OCH<sub>2</sub>Ph), 70.0 (OCH<sub>2</sub>PMP), 62.1 (C3), 57.7 (C1'), 55.2 (OCH<sub>3</sub>), 40.3 (C5), 19.5 (C7).

ESIMS *m/z* 502 (100%) [MH]<sup>+</sup>, HRESIMS found 502.2954, calc for C<sub>32</sub>H<sub>40</sub>NO<sub>4</sub>, 502.2957 [MH]<sup>+</sup>.



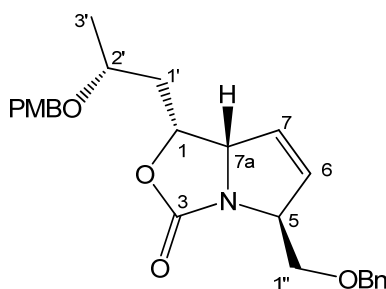
**(4*S*,5*R*)-3-((*S*)-1-(Benzyloxy)but-3-en-2-yl)-5-((*R*)-2-(4-methoxybenzyloxy)propyl)-4-styryloxazolidin-2-one (402).** Following the general method for the synthesis of oxazolidinones using the 1,2-amino alcohol **401** (0.288 g, 0.574 mmol), triethylamine (160  $\mu$ L, 1.148 mmol), triphosgene (0.085 g, 0.287 mmol) and dry  $\text{CH}_2\text{Cl}_2$  (20 mL), the title compound (0.163 g, 54%) was obtained as a colorless oil.

$[\alpha]_D^{22} +7.1$  ( $c$  5.20,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (300 MHz): 7.37-7.19 (12H, m, ArH), 6.89-6.82 (2H, m, ArH), 6.23 (1H, d,  $J = 15.9$  Hz, H2'''), 5.99 (1H, dd,  $J = 9.6, 15.9$  Hz, H1'''), 5.79 (1H, ddd,  $J = 7.4, 10.3, 17.5$  Hz, H2'), 5.25 (1H, d,  $J = 17.3$  Hz, H3'<sub>trans</sub>), 5.17 (1H, d,  $J = 10.3$  Hz, H3'<sub>cis</sub>), 4.67 (1H, dt,  $J = 5.1, 8.7$  Hz, H5), 4.60 (1H, d,  $J = 11.7$  Hz, OCHHPH), 4.49 (1H, d,  $J = 11.4$  Hz, OCHHPMP), 4.48 (1H, d,  $J = 11.7$  Hz, OCHHPH), 4.35-4.27 (1H, m, H4), 4.31 (1H, d,  $J = 11.4$  Hz, OCHHPMP), 4.29-4.21 (1H, m, H1'), 3.89-3.78 (1H, m, H4'<sub>A</sub>), 3.79 (3H, s, OCH<sub>3</sub>), 3.70-3.63 (1H, m, H2''), 3.61 (1H, dd,  $J = 5.2, 10.2$  Hz, H4'<sub>B</sub>), 2.02 (1H, ddd,  $J = 5.7, 9.0, 14.5$  Hz, H1''<sub>A</sub>), 1.66-1.57 (1H, m, H1''<sub>B</sub>), 1.20 (3H, d,  $J = 6.1$  Hz, H3'').

$\delta_{\text{C}}$  (75 MHz): 159.2 (ArC), 157.2 (ArC), 137.9 (ArC), 135.5 (ArC), 135.1 (C2'''), 133.7 (C2'), 130.6 (ArC), 129.4 (ArC), 128.7 (ArC), 128.5 (ArC), 128.4 (ArC), 128.0 (ArC), 127.8 (ArC), 126.6 (ArC), 124.7 (C1'''), 118.5 (C3'), 113.8 (ArC), 74.9 (C5), 73.0 (OCH<sub>2</sub>Ph), 70.8 (C2'), 69.9 (OCH<sub>2</sub>PMP), 68.9 (C4'), 61.4 (C1'), 56.1 (C4), 55.2 (OCH<sub>3</sub>), 37.3 (C1''), 19.0 (C3'').

ESIMS  $m/z$  550 (100%)  $[\text{MNa}]^+$ , 528 (10%)  $[\text{MH}]^+$ , HRESIMS found 528.2845, calc for  $\text{C}_{33}\text{H}_{38}\text{NO}_5$ , 528.2750  $[\text{MH}]^+$ .



**(1*R*,5*S*,7*aS*)-5-(Benzyloxymethyl)-1-((*R*)-2-(4-methoxybenzyloxy)propyl)-1,7*a*-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one (403).** Following the general method for the ring-closing metathesis of oxazolidinones using the oxazolidinone **402** (0.0400 g, 0.759 mmol), the Grubbs II catalyst (32 mg, 0.038 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL), the title compound (0.280 g, 87 %) was obtained as a yellow oil.

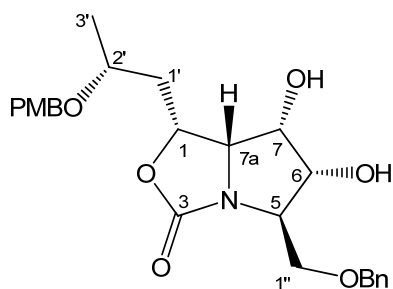
$[\alpha]_D^{24}$  -87.6 (*c* 1.00, CHCl<sub>3</sub>).

IR  $\nu_{\max}$  (cm<sup>-1</sup>): 2960, 2929, 2858, 1752, 1512, 1247, 1030.

$\delta_H$  (500 MHz): 7.38-7.22 (7H, m, ArH), 6.89-6.86 (2H, m, ArH), 6.04-6.02 (1H, m, H7), 5.86 (1H, dd, *J* = 1.7, 6.1 Hz, H6), 4.87 (1H, dt, *J* = 5.5, 8.4 Hz, H1), 4.82-4.79 (1H, m, H5), 4.70 (1H, dd, *J* = 3.5, 11.8 Hz, H7a), 4.57-4.56 (2H, m, OCH<sub>2</sub>PMP), 4.53 (1H, d, *J* = 11.3 Hz, OCHHPh), 4.35 (1H, d, *J* = 11.3 Hz, OCHHPh), 3.79 (3H, s, OCH<sub>3</sub>), 3.75-3.69 (1H, m, H2'), 3.54 (1H, d, *J* = 5.1 Hz, H1''), 1.96 (1H, ddd, *J* = 5.5, 8.6, 14.1 Hz, H1'A), 1.73-1.67 (1H, m, H1'B), 1.28 (3H, d, *J* = 6.1 Hz, H3').

$\delta_C$  (125 MHz): 162.3 (ArC), 159.2 (ArC), 137.9 (ArC), 133.2 (C7), 130.4 (ArC), 129.2 (ArC), 128.3 (ArC), 127.8 (C6), 127.6 (ArC), 127.4 (ArC), 113.8 (ArC), 75.8 (C1), 73.2 (OCH<sub>2</sub>PMP), 71.0 (C1''), 70.9 (C2'), 70.1 (OCH<sub>2</sub>Ph), 68.2 (C7a), 66.9 (C5), 55.2 (OCH<sub>3</sub>), 38.7 (C1'), 19.0 (C3').

ESIMS *m/z* 446 (60%) [MNa]<sup>+</sup>, HRESIMS found 446.1938, calc for C<sub>25</sub>H<sub>29</sub>NO<sub>5</sub>Na 446.1943 [MNa]<sup>+</sup>.



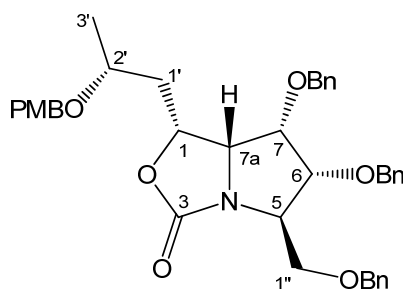
**(1*R*,5*R*,6*R*,7*S*,7*aS*)-5-(Benzyloxymethyl)-6,7-dihydroxy-1-((*R*)-2-(4-methoxybenzyloxy)propyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (404).** Following the general method for *syn*-dihydroxylation using the RCM product **403** (0.203 g, 0.480 mmol), *N*-morpholine-*N*-oxide (0.113 g, 0.961 mmol) and potassium osmate dihydrate (9 mg, 0.024 mmol), acetone (4 mL) and H<sub>2</sub>O (2.5 mL), the title compound (0.196 g, 89 %) was obtained as a brown oil.

$[\alpha]_D^{24}$  -35.2 (*c* 1.00, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.39-7.17 (7H, m, ArH), 6.84 (1H, d,  $J$  = 8.3 Hz, ArH), 4.78 (1H, q,  $J$  = 7.1 Hz, H1), 4.56 (2H, q,  $J$  = 11.9 Hz, OCH<sub>2</sub>PMP), 4.51 (1H, d,  $J$  = 11.4 Hz, OCHHPh), 4.31 (1H, d,  $J$  = 11.4 Hz, OCHHPh), 4.23-4.18 (1H, m, H7), 3.87-3.85 (1H, m, H6), 3.76 (3H, s, OCH<sub>3</sub>), 3.76-3.70 (1H, m, H5), 3.72-3.65 (1H, m, H1''<sub>A</sub>), 3.70-3.66 (1H, m, H2'), 3.63-3.58 (1H, m, H1''<sub>B</sub>), 3.43 (1H, dd,  $J$  = 4.1, 6.6 Hz, H7a), 2.35 (1H, dt,  $J$  = 6.9, 14.0 Hz, H1'<sub>A</sub>), 2.14 (1H, m, H1'<sub>B</sub>), 1.25 (1H, d,  $J$  = 6.1 Hz, H3').

$\delta_C$  (125 MHz): 162.7 (C3), 159.2 (ArC), 137.9 (ArC), 130.4 (ArC), 129.5 (ArC), 128.4 (ArC), 127.8 (ArC), 127.7 (ArC), 113.8 (ArC), 76.3 (C7), 73.5 (OCH<sub>2</sub>PMP), 73.4 (C1), 72.1 (C6), 71.0 (C2') 70.3 (C1''), 69.8 (OCH<sub>2</sub>Ph), 64.8 (C7a), 62.2 (C5), 55.3 (OCH<sub>3</sub>), 36.2 (C1'), 19.2 (C3').

ESIMS  $m/z$  480 (82%) [MH]<sup>+</sup>, HRESIMS found 480.2035, calc for C<sub>25</sub>H<sub>31</sub>NO<sub>7</sub>Na 480.1998 [MNa]<sup>+</sup>.



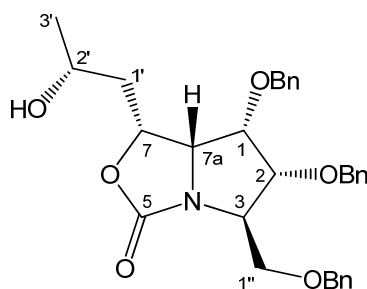
**(1*R*,5*R*,6*R*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((*R*)-2-(4-methoxy-benzyloxy)propyl)tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (405).** Following the general method for bisbenzylation using diol **404** (0.160 g, 0.350 mmol), benzyl bromide (0.170 mL, 0.239 mmol) and tetrabutylammonium iodide (13 mg, 0.035 mmol), sodium hydride (50% dispersion in mineral oil, 50 mg, 25 mg NaH, 1.050 mmol) and THF (25 mL), the title compound (0.210 g, 94 %) was obtained as a colorless oil.

$[\alpha]_D^{24} +2.4$  ( $c$  1.00,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (500 MHz): 7.36-7.20 (15H, m, ArH), 7.14 (2H, d,  $J = 8.6$  Hz, ArH), 6.82 (2H, d,  $J = 8.6$  Hz, ArH), 5.02 (1H, d,  $J = 11.5$  Hz, OCHHAr), 4.74 (1H, dd,  $J = 7.3, 14.2$  Hz, H1), 4.61-4.37 (6H, m, 6 x OCHHAr), 4.19 (1H, d,  $J = 11.6$  Hz, OCHHAr), 4.16 (1H, dd,  $J = 2.8, 8.3$  Hz, H6), 3.96 (1H, dt,  $J = 3.0, 8.1$  Hz, H5), 3.82 (1H, t,  $J = 2.4$  Hz, H7), 3.75 (3H, s,  $\text{OCH}_3$ ), 3.74 (1H, dd,  $J = 2.9, 10.2$  Hz, H1''<sub>A</sub>), 3.60 (1H, dd,  $J = 2.9, 10.2$  Hz, H1''<sub>B</sub>), 3.59-3.56 (1H, m, H2'), 3.52 (1H, dd,  $J = 2.3, 7.5$  Hz, H7a), 2.24 (1H, ddd,  $J = 6.0, 7.4, 13.9$  Hz, H1'<sub>A</sub>), 1.90 (1H, dt,  $J = 6.2, 13.9$  Hz, H1'<sub>B</sub>), 1.16 (3H, d,  $J = 6.2$  Hz, H3')

$\delta_{\text{C}}$  (125 MHz): 162.0 (C3), 159.2 (ArC), 138.2 (ArC), 137.9 (ArC), 137.5 (ArC), 130.5 (ArC), 129.4 (ArC), 128.5 (ArC), 128.3 (ArC), 128.3 (ArC), 128.0 (ArC), 127.7 (ArC), 127.6 (ArC), 127.6 (ArC), 127.3 (ArC), 127.0 (ArC), 113.7 (ArC), 83.3 (C6), 76.9 (C7), 73.3 ( $\text{OCH}_2\text{Ar}$ ), 73.2 ( $\text{OCH}_2\text{Ar}$ ), 72.9 (C1), 72.7 ( $\text{OCH}_2\text{Ar}$ ), 70.8 (C2), 69.7 ( $\text{OCH}_2\text{Ar}$ ), 69.2 (C1''), 64.0 (C7a), 60.8 (C5), 55.2 ( $\text{OCH}_3$ ), 35.2 (C1'), 18.9 (C3').

ESIMS  $m/z$  660 (100%)  $[\text{MNa}]^+$ , HRESIMS found 660.2987, calc for  $\text{C}_{39}\text{H}_{43}\text{NO}_7\text{Na}$ , 660.2937  $[\text{MNa}]^+$ .



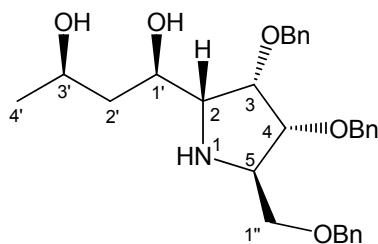
**(1*R*,5*R*,6*R*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-1-((*R*)-2-hydroxypropyl)-tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one (406).** Following the general method for PMB deprotection using **405** (0.173 g, 0.272 mmol), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (0.136 g, 0.598 mmol), CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and H<sub>2</sub>O (1.25 mL) the title compound (0.130 g, 92 %) was obtained as a yellow oil.

$[\alpha]_D^{24} +14.3$  (*c* 1.00, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.35-7.17 (15H, m, ArH), 5.01 (1H, d, *J* = 11.4 Hz, OCHHPh), 4.74 (1H, dd, *J* = 7.5, 13.5 Hz, H1), 4.64 (1H, d, *J* = 11.8 Hz, OCHHPh), 4.56 (1H, d, *J* = 11.8 Hz, OCHHPh), 4.51 (1H, d, *J* = 11.4 Hz, OCHHPh), 4.48 (1H, d, *J* = 11.7 Hz, OCHHPh), 4.38 (1H, d, *J* = 11.7 Hz, OCHHPh), 4.27 (1H, dd, *J* = 1.7, 7.8 Hz, H6), 4.02-4.01 (1H, m, H7), 4.00-3.96 (1H, m, H5), 3.89-3.82 (1H, dd, *J* = 6.1, 11.2 Hz, H2'), 3.74 (1H, dd, *J* = 3.4, 10.4 Hz, H1''<sub>A</sub>), 3.74-3.71 (1H, m, H7a), 3.58 (1H, dd, *J* = 2.4, 10.4 Hz, H1''<sub>B</sub>), 2.09 (1H, dt, *J* = 7.6, 14.6 Hz, H1'<sub>A</sub>), 1.81 (1H, *J* = 4.9, 14.6 Hz, H1'<sub>B</sub>), 1.10 (3H, d, *J* = 6.2 Hz, H3').

$\delta_C$  (125 MHz): 161.9 (C3), 137.9 (ArC), 137.7 (ArC), 137.3 (ArC), 128.4 (ArC), 128.2 (ArC), 128.2 (ArC), 127.9 (ArC), 127.6 (ArC), 127.6 (ArC), 127.5 (ArC), 127.3 (ArC), 127.1 (ArC), 83.1 (C6), 76.5 (C7), 73.9 (C1), 73.1 (OCH<sub>2</sub>Ph), 73.1 (OCH<sub>2</sub>Ph), 72.6 (OCH<sub>2</sub>Ph), 69.1 (C1''), 65.5 (C2'), 64.0 (C7a), 60.8 (C5), 37.7 (C1'), 23.0 (C3').

ESIMS *m/z* 540 (100%) [MH]<sup>+</sup>, 518 (40%) [MNa]<sup>+</sup>, HRESIMS found 518.2532, calc for C<sub>31</sub>H<sub>36</sub>NO<sub>6</sub>, 518.2543 [MH]<sup>+</sup>.



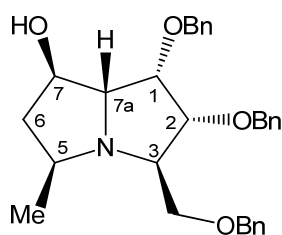
**(1*R*,3*R*)-1-((2*R*,3*S*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)butane-1,3-diol (407).** Following the general method for the hydrolysis of oxazolidinones using 406 (0.105 g, 0.203 mmol), sodium hydroxide (0.016 g, 0.406 mmol) and EtOH (4 mL), the title compound (0.090 g, 91 %) was obtained as a light yellow oil.

$[\alpha]_D^{24} +14.2$  ( $c$  1.00,  $\text{CHCl}_3$ ).

$\delta_{\text{H}}$  (500 MHz): 7.39-7.22 (15H, ArH), 4.88 (1H, d,  $J = 11.4$  Hz, OCHHPh), 4.61 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.56 (1H, d,  $J = 11.4$  Hz, OCHHPh), 4.53 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.50 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.44 (1H, d,  $J = 11.9$  Hz, OCHHPh), 4.17 (1H, t,  $J = 4.2$  Hz, H3), 4.06 (1H, ddd,  $J = 2.9, 7.7, 10.2$  Hz, H1'), 4.02 (1H, ddd,  $J = 2.7, 6.2, 8.9$  Hz, H3'), 3.89 (1H, dd,  $J = 4.2, 6.5$  Hz, H4), 3.54 (1H, dd,  $J = 5.6, 11.5$  Hz, H1''<sub>A</sub>), 3.49-3.46 (1H, m, H5), 3.48-3.46 (1H, m, H1''<sub>B</sub>), 3.02 (1H, dd,  $J = 4.2, 7.7$  Hz, H2), 1.73 (1H, dt,  $J = 2.6, 14.3$  Hz, H2'<sub>A</sub>), 1.44 (1H, ddd,  $J = 8.9, 10.2, 14.3$  Hz, H2'<sub>B</sub>), 1.16 (3H, d,  $J = 6.2$  Hz, H4').

$\delta_{\text{C}}$  (125 MHz): 138.0 (ArC), 137.9 (ArC), 137.8 (ArC), 128.5 (ArC), 128.4 (ArC), 128.3 (ArC), 128.0 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (ArC), 127.7 (ArC), 127.6 (ArC), 81.1 (C4), 79.0 (C3), 73.4 (OCH<sub>2</sub>Ph), 73.2 (OCH<sub>2</sub>Ph), 72.7 (OCH<sub>2</sub>Ph), 72.6 (C1'), 70.1 (C1''), 68.1 (C3'), 62.9 (C2), 60.2 (C5), 42.4 (C2'), 23.6 (C4').

ESIMS  $m/z$  492 (100%)  $[\text{MH}]^+$ , HRESIMS found 492.2765, calc for  $\text{C}_{30}\text{H}_{38}\text{NO}_5$ , 492.2750  $[\text{MH}]^+$ .



**(1*R*,3*S*,5*R*,6*R*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-1-ol (408).** Following the general method for mesylation-cyclization using **407** (0.056 g, 0.115 mmol), triethylamine (79  $\mu$ L, 0.573 mmol), MeSO<sub>2</sub>Cl (8.9  $\mu$ L, 0.115 mmol) and dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL), the title compound (0.028 g, 51 %) was obtained as a colorless oil.

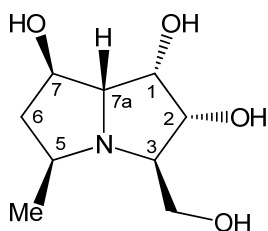
$[\alpha]_D^{25} +7.2$  (*c* 1.00, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz): 7.39-7.18 (15H, m, ArH), 4.74 (1H, *J* = 11.8 Hz, OCHHPh), 4.68 (1H, dt, 6.6, 9.1, H7), 4.56-4.48 (5H, m, 5 x OCHHPh), 4.06 (1H, dd, *J* = 4.0, 5.4 Hz, H1), 3.93 (1H, dd, *J* = 4.0, 6.0 Hz, H2), 3.45 (1H, dd, *J* = 4.7, 9.8 Hz, H8<sub>A</sub>), 3.42 (1H, dd, *J* = 5.4, 6.3 Hz, H7<sub>a</sub>), 3.42 (1H, dd, *J* = 5.3, 9.8 Hz, H8<sub>B</sub>), 3.09 (1H, dd, *J* = 5.3, 10.9 Hz, H3), 3.07-3.01 (1H, m, H5), 2.27 (1H, ddd, *J* = 5.4, 6.9, 12.1 Hz, H6<sub>A</sub>), 1.62-1.5 (1H, m, H6<sub>B</sub>), 1.14 (3H, d, *J* = 6.3 Hz, CH<sub>3</sub>).

$\delta_C$  (125 MHz): 138.6 (ArC), 138.4 (ArC), 138.2 (ArC), 128.4 (ArC), 128.3 (ArC), 128.3 (ArC), 127.8 (ArC), 127.7 (ArC), 127.6 (ArC), 127.6 (ArC), 127.6 (ArC), 127.5 (ArC), 81.7 (C2), 77.6 (C1), 73.3 (OCH<sub>2</sub>Ph), 73.0 (C7<sub>a</sub>), 73.0 (OCH<sub>2</sub>Ph), 72.3 (OCH<sub>2</sub>Ph), 71.7 (C8), 71.1 (C7), 68.1 (C3), 62.1 (C5), 43.8 (C6), 22.1 (C9).

ESIMS *m/z* 474 (100%) [MH]<sup>+</sup>, HRESIMS found 474.2665, calc for C<sub>30</sub>H<sub>36</sub>NO<sub>4</sub>, 474.2644 [MH]<sup>+</sup>.





**(1*S*,2*R*,3*S*,5*R*,7*R*,7*aR*)-3-(Hydroxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2,7-triol (112).** Following the general method for the hydrolysis of benzyl ethers using the cyclized product **408** (27 mg, 0.059 mmol), PdCl<sub>2</sub> (16 mg, 0.088 mmol), MeOH (2 mL) and H<sub>2</sub> (in balloon), the title compound (10 mg, 84 %) was obtained as a colorless film.

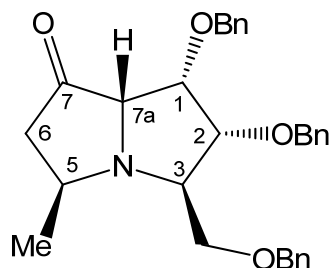
$[\alpha]_D^{24} + 31.2$  (*c* 0.20, CHCl<sub>3</sub>).

$\delta_H$  (500 MHz, D<sub>2</sub>O): 4.60 (1H, ddd, *J* = 5.8, 7.0, 9.2 Hz, H7), 4.13 (1H, app. t, *J* = 4.0 Hz, H1), 4.03 (1H, dd, *J* = 4.0, 9.1 Hz, H2), 3.74 (1H, dd, *J* = 4.9, 11.7 Hz, H8<sub>β</sub>), 3.70 (1H, dd, *J* = 4.9, 11.7 Hz, H8<sub>α</sub>), 3.32 (1H, dd, *J* = 4.0, 5.8 Hz, H7a), 3.06-2.97 (1H, m, H5), 2.81 (1H, app. dd, *J* = 4.9, 9.1 Hz, H3), 2.38 (1H, ddd, *J* = 5.0, 7.0, 12.2 Hz, H6<sub>β</sub>), 1.60 (1H, ddd, *J* = 9.3, 11.0, 12.2 Hz, H6<sub>α</sub>), 1.17 (1H, d, *J* = 6.3 Hz, H9).

$\delta_C$  (125 MHz, D<sub>2</sub>O): 78.1 (C2), 73.6 (C1), 71.8 (C3), 71.3 (C7), 75.4 (C7a), 65.6 (C8), 65.2 (C5), 46.2 (C6), 22.5 (C9).

ESIMS *m/z* 204 ([MH]<sup>+</sup>), HRESIMS found 204.1319, calc for C<sub>9</sub>H<sub>18</sub>NO<sub>4</sub>, 204.1236 ([MH]<sup>+</sup>).

### 7.4.1 General method for Swern oxidation

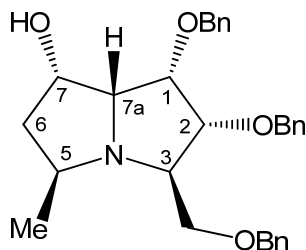


**(3*S*,5*R*,6*R*,7*S*,7*aS*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-1-one.** To a stirred solution of DMSO (39  $\mu$ L, 0.548 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) cooled to  $-78^\circ\text{C}$  was added oxalyl chloride (24  $\mu$ L, 0.274 mmol) dropwise *via* syringe. The resulting mixture was stirred at  $-78^\circ\text{C}$  for 5 min and a solution of **408** (0.013 g, 0.027 mmol) in  $\text{CH}_2\text{Cl}_2$  cooled to  $-78^\circ\text{C}$  was transferred *via* cannula, followed by  $\text{Et}_3\text{N}$  (0.15 mL, 1.084 mmol). The reaction mixture was stirred at  $-78^\circ\text{C}$  for 1 h and then poured into  $\text{H}_2\text{O}$  (10 mL), the organic layer was collected and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 20 mL). The combined organic extracts were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give a yellow oil containing the oxidized product, which was used without further purification in the reduction reaction with L-Selectride<sup>®</sup>.

$\delta_{\text{C}}$  (125 MHz,  $\text{CDCl}_3$ ): 214.5 (C=O).

ESIMS  $m/z$  472 ( $[\text{MH}]^+$ ).

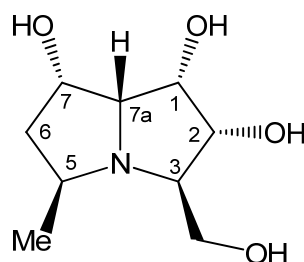
### 7.4.2 General method for the reduction of ketones to secondary alcohols with L-selectride<sup>®</sup>



**(1*S*,3*S*,5*R*,6*R*,7*S*,7*aR*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-3-methylhexahydro-1*H*-pyrrolizin-1-ol.** To a solution of the above Swern oxidation crude product **410** in THF (1 mL) cooled to  $-78^\circ\text{C}$  was added L-selectride<sup>®</sup> (1.0 M solution in THF, 110  $\mu$ L,

0.110 mmol). The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 h, warmed to rt, stirred for an additional 2 h and then quenched with ammonia solution (1.0 M, 5 mL). The resulting mixture was extracted with EtOAc, and the combined organic extracts was washed with brine, dried ( $\text{K}_2\text{CO}_3$ ) and concentrated *in vacuo* to give a light brown film, which was used without further purification in the global debenzylolation reaction with  $\text{PdCl}_2$ .

ESIMS  $m/z$  474 ( $[\text{MH}]^+$ ).



**(1*S*,2*R*,3*S*,5*R*,7*S*,7*aR*)-3-(Hydroxymethyl)-5-methylhexahydro-1*H*-pyrrolizine-1,2,7-triol (409).** Following the general method for the hydrolysis of benzyl ethers using the crude mixture from the reduction reaction with L-selectride<sup>®</sup>,  $\text{PdCl}_2$  (7 mg, 0.041 mmol), MeOH (2 mL) and  $\text{H}_2$  (in balloon), the title compound (1.6 mg, 29 %, 3 steps) was obtained as a colorless film.

$\delta_{\text{H}}$  (500 MHz,  $\text{D}_2\text{O}$ ): 4.56 (1H, m, H7), 4.40 (1H, t,  $J = 5.1$  Hz, H1), 3.97 (1H, dd,  $J = 5.1$ , 7.1 Hz, H2), 3.79 (1H, dd,  $J = 5.3$ , 11.8 Hz,  $\text{H8}_{\beta}$ ), 3.66 (1H, dd,  $J = 5.3$ , 11.8 Hz,  $\text{H8}_{\alpha}$ ), 3.55 (1H, dd,  $J = 3.9$ , 5.9 Hz, H7a), 3.34 (1H, m, H5), 3.02 (1H, ddd,  $J = 5.3$ , 5.3, 7.1 Hz, H3), 2.08 (1H, appar. dd,  $J = 5.8$ , 13.6 Hz,  $\text{H6}_{\beta}$ ), 1.69 (1H, ddd,  $J = 5.3$ , 9.9, 14.4 Hz,  $\text{H6}_{\alpha}$ ), 1.17 (3H, d,  $J = 6.3$  Hz, H9).

ESIMS  $m/z$  204 ( $[\text{MH}]^+$ ), HRESIMS found 204.1236, calc for  $\text{C}_9\text{H}_{18}\text{NO}_4$ , 204.1236 ( $[\text{MH}]^+$ ).

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