STUDIES TOWARDS THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-CASTANOSPERMINE

BY

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Abstract

A study has been carried out on the enantioselective total synthesis of the indolizidine alkaloid (+)-castanospermine. The aim was to develop a convergent synthesis based on a C-8/C-8a disconnection. A distinguishing feature of this method is that it is non-carbohydrate-based.

The synthetic component of the project was divided into three parts. The first part involved the design and synthesis of a 5-membered nitracycle, one half of the C-8/C-8a disconnection of the target. The second half of the disconnection was provided by an L-tartrate-based aldehyde.

The second part involved the exploration of the coupling of the two halves, thus forming the C-8/C-8a bond. Of the reactions explored, a vinylogous Mukaiyama aldol reaction was found to be optimal in that it led to the correct stereochemistry at the centres which correspond to C-8 and C-8a of (+)-castanospermine as determined by NMR data and a single crystal X-ray determination. Various aspects of this aldol reaction were explored including the effect of the substituents on the nitracycle.

The third part involved studies towards the conversion of the aldol adduct to an indolizidine skeleton and ultimately (+)-castanospermine. The synthesis of an indolizidine precursor to (+)-castanospermine was successful, but the total synthesis of (+)-castanospermine remained elusive. However, the route developed in this work provides a basis of a potential enantioselective synthesis of (+)-castanospermine.

Abbreviations

$[\alpha]_D$	Optical rotation
Ac	Acetyl
Ar	Aromatic
Ax	axial
AIBN	2,2'-Azobisisobutyronitrile
Bz	Benzoyl
Bn	Benzyl
CBz	Benzyloxycarbamate
Bp	boiling point
9-BBN	9-Borabicyclo[3.3.1]nonane
BH_3.DMS	Borane dimethyl sulphide
Bu	Butyl
t-Bu	*t*-Butyl
TBDMS	*tert*-butyldimethylsilyl
TBSOF	2-(tert-butyldimethyloxy)furan
TBSOP	N-(*tert*-butyldimethylsilyloxy)pyrrole
TBS	*tert*-butyldimethylsilyl
TBSOT	2-(*tert*-butyldimethylsilyloxy)thiophene
TBDPS	*tert*-butyldiphenylsilyl
Boc	*tert*-butyloxycarbamate
CSA	Camphorsulfonic acid
cat	catalytic
CAN	Ceric ammonium nitrate
m-CPBA	meta-Chloroperbenzoic acid
NCS	*N*-Chlorosuccinimide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-Dicyano-*p*-benzoquinone
DCC	Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
DIBAL	Diisobutyl aluminium hydride
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxude
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
d	doublet
dd	doublet of doublets
dt	doublet of triplets
eq	equivalents or equatorial
Et	Ethyl
EDTA	Ethylenediaminetetraacetic acid
g	grams
Hz	Hertz

HMDS	Hexamethyldisilane
HMPA	Hexamethylphosphoric triamide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resonance mass spectrometry
h	hour
HOBt	1-Hydroxybenzotriazole
IR	Infra red spectroscopy
IDCP	Iodonium diicollidine perchlorate
J	Coupling constant
LAH	Lithium Aluminium hydride
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
MS	Mass spectrometry or Molecular sieves
MHz	Megahertz
M.p	Melting point
m	*meta*
m	multiplet
Ms	Methanesulfonyl
PMB	*p*-Methoxybenzyl
MOM	Methoxymethyl
Me	Methyl
mg	milligrams
ml	millilitres
mmHg	millimetre mercury, torr
mmol	millimole
min	minute
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
o	orthro
p	para
Ph	Phenyl
Pf	9-Phenylfluorenyl-9-yl
PPTS	Pyridinium *p*-toluenesulfonate
q	quartet
R	Rectus
rt	Room temperature
s	singlet
S	Sinster

TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium Iodide
THF	Tetrahydrofuran
TPAP	Tetrapropylammonium perruthenate
tlc	Thin layer chromatography
Ts	p-Toluenesulfonyl
Tf	Triflate
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
t	triplet
td	triplet of doublets

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I would like to show my gratitude to the following people for their help and support during this thesis:

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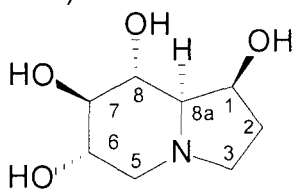
My family and friends, thank you all for all of your support, I really appreciate it.

I would like to dedicate this thesis to my grandparents. Professor Stephen and Margaret Rees Jones (Taid and Nain) and Jean and Mauricette Pognon (Pepe et meme) who I loved very much and miss a lot.

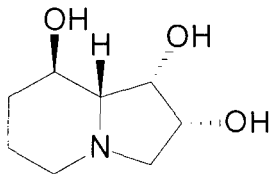
Contents

Chapter 1: Introduction

(+)-Castanospermine **1.1** is a naturally occurring indolizidine alkaloid, isolated from the seeds of the Australian legume *Castanosperminium australe* and the dried pods of *Alexia leiopetala*, (Figure 1.1).[1,2]



(+)-Castanopermine **1.1**



(-)-Swainsonine **1.2**

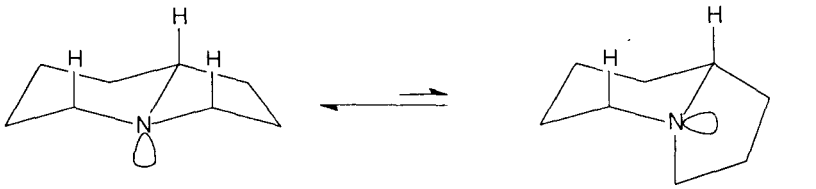
Figure 1.1 Structures of (+)-castanospermine **1.1** and (-)-swainsonine **1.2**

Like other indolizidine alkaloids such as (-)-swainsonine **1.2**, it has emerged as having potent biological activity as an α- and β-glycosidase inhibitor with promising anti-diabetic,[3] anti-cancer,[4] anti-viral[5] and anti-AIDS[6,7] activity. (-)-Swainsonine **1.2** is an α-D-mannosidase I and mannosidase II inhibitor with promising anti-cancer and other biological activities.[8,9]

1.1 Structural Aspects

1.1.1 Conformation

The indolizidine and quinolizidine nucleus can be found in a large number of natural products. The study of conformational aspects of indolizidines dates back to 1968, when Theobald identified that the *trans*-fused conformer is more stable than the *cis*-fused based on IR spectroscopic data.[10] A *trans*-fused junction is assigned to the conformer in which the bridgehead hydrogen is *trans*-diaxial to the lone-pair of electrons of nitrogen. Unlike hydrindanes, indolizidines can interconvert from *trans* to *cis* via inversion of orientation of the nitrogen lone pair from axial to equatorial. The *trans*-fused conformer is more stable than the *cis* due to the stereoelectronic interaction of three trans-diaxial hydrogen atoms α to nitrogen with the nitrogen lone pair via a hyperconjugative σ*/n interaction. This interaction leads to a stabilizing effect known as the Bohlmann effect. The *cis*-conformer has no such interactions (Figure 1.2). Theobald estimated the enthalpy difference between **1.3** and **1.4** to be around 0.9 kcal/mol.[10]



trans-3 diaxial interactions **1.3** *cis* - 0 diaxial interactions **1.4**

Figure 1.2

1.1.2 Infra-red spectroscopy

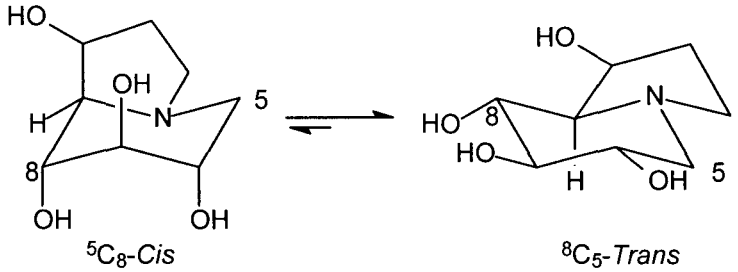
In 1957,[11] Bohlmann carried out an investigation on the infra-red spectra of several quinolizidines and found a characteristic band in the region of 2700-2860 cm^{-1} for *trans*-fused systems. These bands were absent in *cis*-fused systems. Skolik *et al.*[12] confirmed these results and found that at least two *trans*-diaxial interactions between the hydrogens α- to nitrogen and the lone pair of electrons of nitrogen were required in order for these 'bands' to be observed. The same observations were also recorded by Theobald *et al.*[10] for indolizidines. Such bands are ofter referred to now as "Bohlman bands".

1.1.3 ^{1}H NMR Spectroscopy

In more recent times, NMR spectroscopy has been used to determine conformation. Craig *et al.*[13] investigated the ^{1}H NMR spectrum of a *trans*-indolizidine and observed that the equatorial protons on the carbon α- to nitrogen in the six-membered ring (piperidine) resonate at around δ 3.00 ppm while the axial α- protons resonate at around δ 2.00 ppm. This was attributed to the nitrogen lone-pair shielding the axial protons and this type of shielding would not be observed in the *cis* conformer. Thus, comparing the chemical shifts of the protons α to the nitrogen aids conformational assignments.

1.1.4 Conformation in (+)-castanospermine **1.1**

(+)-Castanospermine **1.1**, with its five contiguous chiral centres adopts a *trans*-fused $^8C_5$ conformation to ensure that the hydroxyl groups adopt equatorial configurations. Such a conformation is significantly preferred energetically to the much higher energy $^5C_8$ alternative, which would necessitate a *cis*-fused ring junction. Figure 1.3 (see next page) illustrates this. Note that $^8C_5$ refers to carbon 8 being at a higher vertical level than carbon 5 in the chair and vice-versa for $^5C_8$.

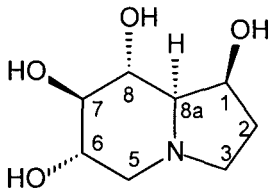


$^{5}C_{8}$-*Cis* $^{8}C_{5}$-*Trans*

Figure 1.3

(+)-Castanospermine's structure was first established by Hohenschutz *et al.*[1] in 1981 and was fully characterized using UV, IR, elemental analysis, mass spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and X-ray crystallography. The Table below summarizes assignments for the ^{1}H and ^{13}C NMR spectra for (+)-castanospermine (Figure 1.4).

Figure 1.4



1.1

Assignment	^{1}H Chemical Shift	Multipicity	*J* Value	^{13}C Chemical Shift
1	4.40	ddd	7.0, 4.4, 2.0 Hz	69.4
2α	2.33	ddd	14.0, 7.0, 2.0 Hz	33.1
2β	1.70	dddd	14.0, 10.0 10.0, 2.0 Hz	
3α	3.06	td	10.0, 2.0Hz	51.6
3β	2.20	q	10.0 Hz	
5ax	2.04	t	10.7, 10.0 Hz	55.4
5eq	3.16	dd	10.7, 5.0 Hz	
6	3.60	m		68.8
7	3.30	t	8.5 Hz	78.7
8	3.58	t	8.5 Hz	69.9
8a	2.01	dd	10.0, 4.4 Hz	71.2

The chemical shift of the 5 ax and 5 eq protons are consistent with the values reported by Craig *et al.*[13] for a *trans*-fused conformer, thus indicating *trans* as the favoured conformation of (+)-castanospermine **1.1**.

1.1.5 Biological activity of (+)-castanopermine **1.1**

(+)-Castanospermine **1.1**, as mentioned previously, is a potent glycosidase inhibitor. Glycosidase is an enzyme involved in many glycosidation processes of sugars or amino acids via an oxocarbenium ion (S_N1) to form a glycosidic bond, leading to polysaccharides or glycoproteins respectively, which are all major components found in Nature (Figure 1.5).

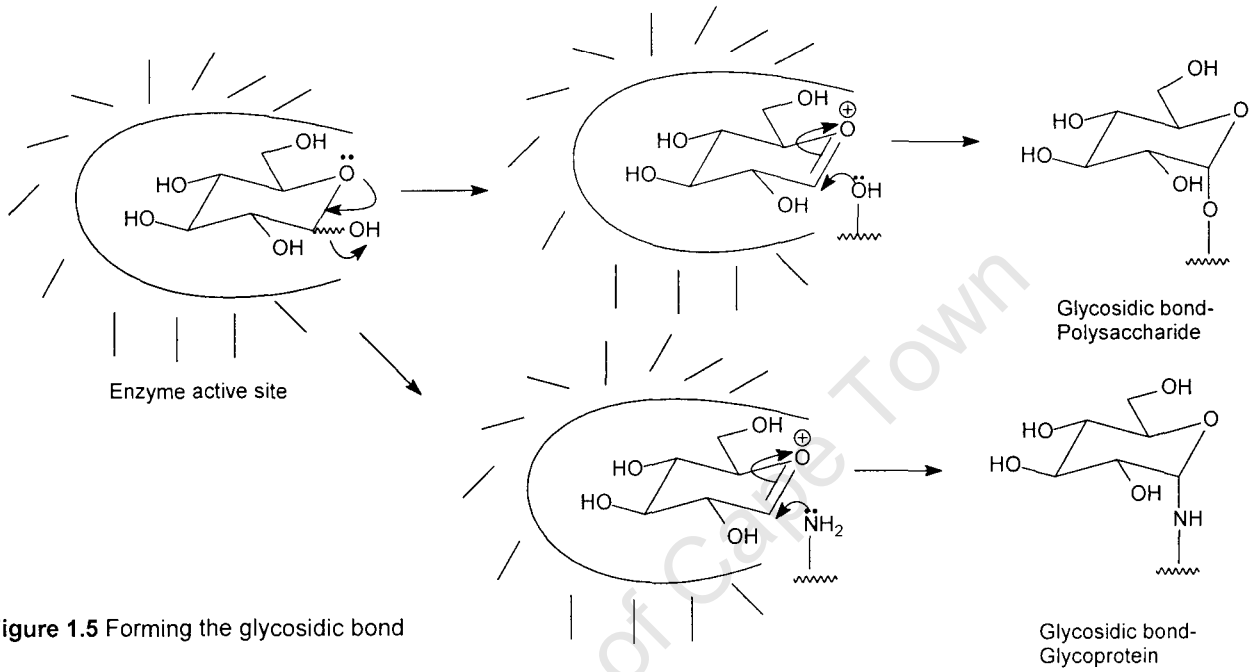


Figure 1.5 Forming the glycosidic bond

(+)-Castanospermine's 6-membered ring is similar in structure to that of glucose and when it binds to the enzyme active site, it is thought that the nitrogen becomes protonated.[14] The resultant ammonium ion mimics the oxocarbenium ion intermediate that is formed during glycosidation resulting in competitive inhibition of glycosylation, since castanospermine cannot glycosylate (Figure 1.6).

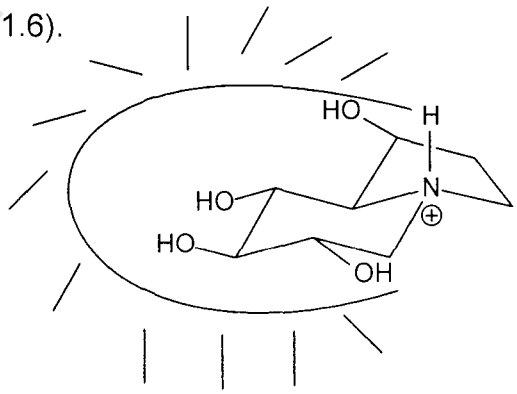
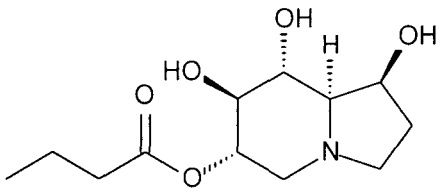


Figure 1.6 (+)-Castanospermine mimicking glucose

One of the many medical uses of (+)-castanospermine **1.1** is in the chemotherapy of human immunodeficiency viral (HIV) infection. HIV infects a human cell by binding its viral

surface glycoprotein (gp120) to the host's cellular viral receptor CD4. (+)-Castanospermine slows down intramolecular glycosylation that forms the gp120 glycoproteins, an essential process for new viruses to become active (infectivity).[15] A (+)-castansopermine derivative (+)-6-butanoyl-castanospermine **1.5** (MDL 28574) has been patented for use as a drug in the treatment of HIV, by the Merrell Dow company (Figure 1.7).[16] This drug underwent phase I clinical trials in 1996 for the treatment of HIV but due to side effects development was halted.[17]



1.5

Figure 1.7

Owing to its biological activity as well as its challenging structure, (+)-castanospermine **1.1** has generated significant interest in the synthetic community and many syntheses of it and its analogues have been reported.

The following chapter will now review the various syntheses published to date.

1.2 Review of Syntheses

The first reported syntheses of (+)-castanospermine **1.1** and its analogues date back to 1984. These focused on using carbohydrates such as D-glucose **1.6** or D-mannose **1.7** as the starting material and making use of stereogenic centres already present in the molecule. Conversely, the later syntheses focused on asymmetric induction from simpler chiral pool materials such as tartrate. This provides a useful categorization as:

- Carbohydrate-based syntheses
- Non-Carbohydrate-based syntheses

Most of the carbohydrate-based syntheses in the literature have employed D-glucose **1.6** as their starting material, with a few starting from other sugars such as D-mannose **1.7** and D-xylose **1.8**, which are shown in Schemes 1.19-1.21. Thus, a further sub-classification of the syntheses can be:

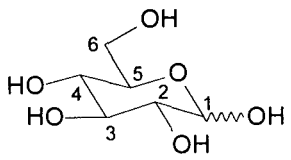
i) Glucose-Based

ii) Non-Glucose-Based

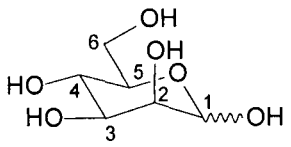
1.2.1 Glucose-Based Syntheses

Comparing the structures of D-glucose **1.6** and (+)-castanospermine **1.1** as shown in Figure **1.8** below, it becomes apparent why many syntheses have chosen D-glucose **1.6**

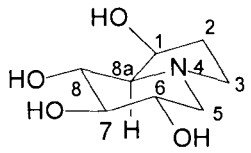
as a starting point. This is a consequence of (+)-castanospermine retaining the same sense of stereogenicity as glucose in its azaglucose six-membered ring.



D-Glucose **1.6**



D-Mannose **1.7**



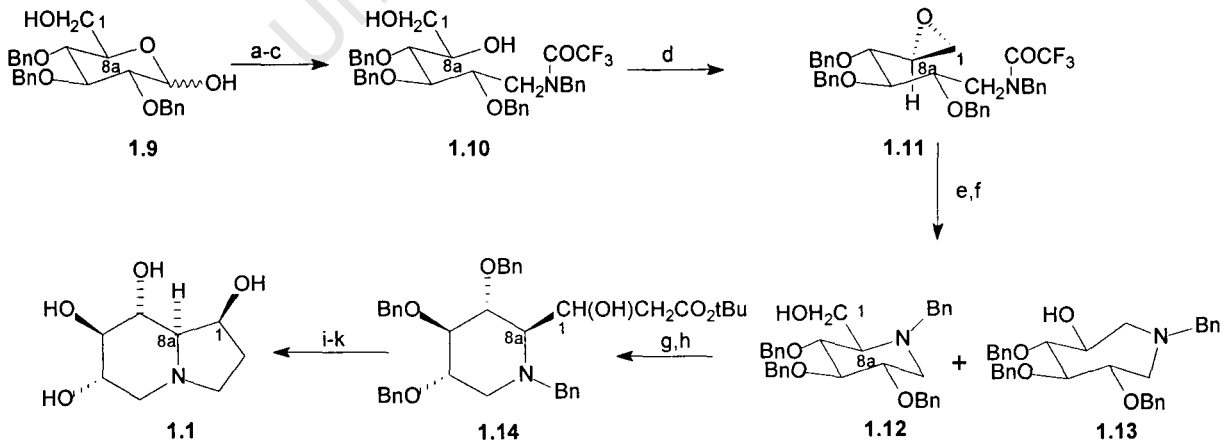
(+)-Castanospermine **1.1**

Figure 1.8. Comparison of D-glucose **1.6**, D-mannose **1.7** and (+)-castanospermine **1.1**.

Thus, four of the five stereogenic centres at C-2, C-3, C-4 and C-5 of D-glucose **1.6** are the same becoming C-6, C-7, C-8 and C-8a respectively in (+)-castanospermine.

Such a topology leaves deoxygenation of C-1 (glucose), the substitution of anomeric oxygen (glucose) with nitrogen and annulation of a pyrrolidine ring between C-6 and N with creation of a new stereogenic centre at C-1 of the target (castanospermine numbering) as the objectives. The numbering used in the syntheses in this review will refer to that used in the target (+)-castanospermine so as to avoid confusion in the numbering cross-over.

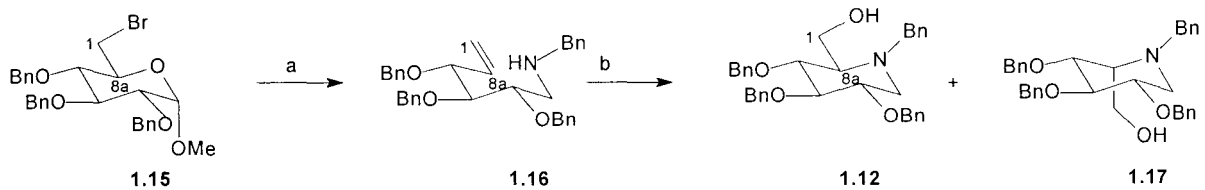
Ganem *et. al.*[18] reported the first enantiospecific total synthesis of (+)-castanospermine **1.1** from D-glucose **1.6** in 1984 involving a total of fourteen steps from the triprotected glucose **1.9** (Scheme 1.1).



Scheme 1.1. *Reagents and Conditions*: a) $BnNH_2$, $CHCl_3$; b) $LiAlH_4$, THF, Δ; c) $(CF_3CO)_2O$, DCM; d) i) TBDMSCl, imidazole; ii) MsCl, NEt_3, DCM; iii) TBAF, THF; iv) NaOMe, MeOH; e) $NaBH_4$, EtOH, 40°C; f) Spontaneous cyclization; piperidine **1.12**, azepane **1.13**; g) Swern oxidation; h) *t*-butyl lithioacetate 1:1; i) Hydrogenolysis; j) TFA, H_2O, 60°C; k) DIBAL, THF.

Reductive amination of the tribenzyl-protected glucose **1.9** via reaction with benzylamine followed by reduction with LAH, and subsequent *N*-trifluoroacetylation gave amide **1.10**. Chemoselective monoprotection of the primary hydroxyl group of **1.10**, followed by mesylation, deprotection and cyclization with inversion of configuration at C-8a (castanospermine numbering) furnished epoxy amide **1.11**. Deprotection of the amide led to spontaneous non-regioselective cyclization to give piperidine **1.12** and azepane **1.13** in a ratio of approximately 1:1, which were readily separated by chromatography. This non-regioselectivity is a major drawback of the synthesis, rendering it a non-viable route for scale-up. The piperidine product was formed via nitrogen attack at C-8a with inversion of configuration and opening of the epoxide via a 6-*exo-tet* process, while the azepane was formed by nitrogen attack at C-1 and opening of the epoxide in a 7-*endo-tet* process. According to the Baldwin rules, both processes are favoured although one would have expected the 6-*exo* process to have been kinetically preferred. The double inversion at C-8a in the sequence ensured the correct absolute configuration for the target overall. To complete the synthesis, piperidine **1.12** was oxidized to the corresponding aldehyde under Swern conditions and then reacted in a non-stereoselective aldol condensation with *t*-butyl lithioacetate. The resulting diastereomeric mixture was separated and the less polar epimer transformed to (+)-castanospermine **1.1** in three steps via hydrogenolysis of the benzyl protecting groups, ester aminolysis, which resulted in the formation of a cyclized lactam, followed by reduction to give the target. Although effective as proof of principle, the synthesis was overall low-yielding and suffered from two key, non-selective steps.

Ganem *et. al.*[19] later reported on an alternative approach to address these shortcomings. Firstly, the lack of regioselectivity in the synthesis of key intermediate **1.12** was addressed by means of the route shown in Scheme 1.2.



1.15 **1.16** **1.12** **1.17**

Scheme 1.2. *Reagents and Conditions*: a) Zn, $BnNH_2$, $NaBH_3CN$, PrOH : H_2O (19 :1), Δ, 2h, 91%; b) $Hg(TFA)_2$, THF; **1.12**, 61% , **1.17**, 39%.

The starting point for this synthesis was tribenzyl-6-bromopyranoside **1.15** derived in 4 straightforward steps from methyl-α-D-glucopyranoside. **1.15** was subjected to a well-

established zinc-mediated reductive ring opening to give the enal, which was transformed *in situ* by concomitant reductive amination of the aldehyde with benzylamine and cyanoborohydride to form amine **1.16**. The latter underwent a 6-*exo-tet* regioselective, but poorly stereoselective intramolecular aminomercuration to give a 6 : 4 mixture of the C-8a epimeric alcohols **1.12** and **1.17** following oxidative treatment of the mercurials. The poor stereoselectivities could be accommodated by oxidizing **1.17** to the aldehyde, which underwent epimerization. Facile reduction then gave the desired aminoalditol **1.12**.

The second improvement in the Ganem synthesis was the implementation of a chelation-controlled allylation for stereoselective C-1 hydroxyl group introduction (Scheme 1.3).[20] This was achieved by oxidation of aminoalditol **1.12**, to the corresponding aldehyde, which was then subjected to a chelation-controlled allylation. The stereoselectivity could be rationalized using a Felkin-Ahn chelation model via a cyclic chelate formed between $TiCl_4$ and the α-aminocarbonyl moiety, inducing the nucleophile to approach from the less-hindered *Si* face as shown in Figure 1.9.

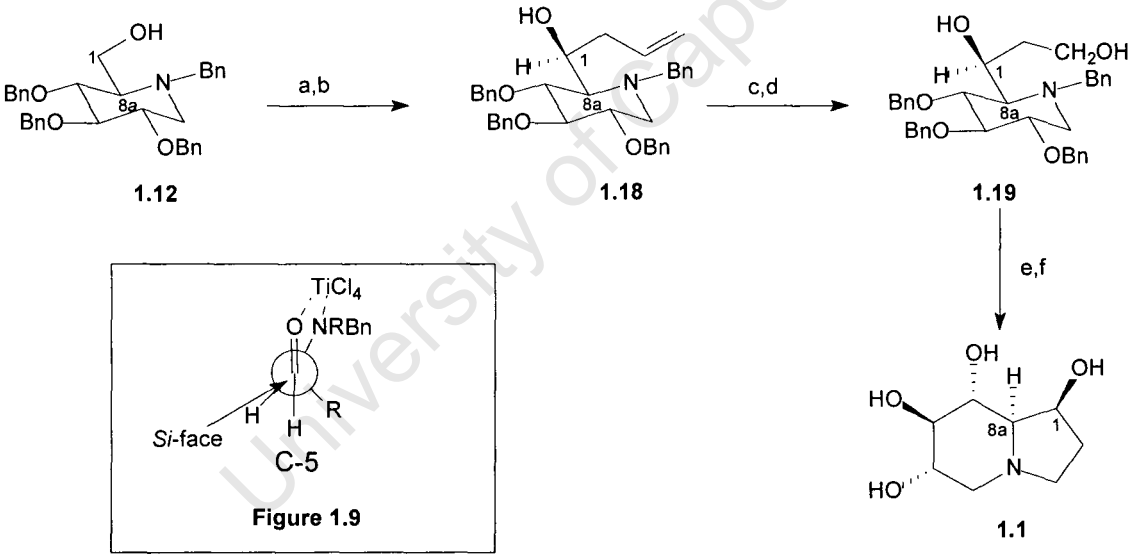


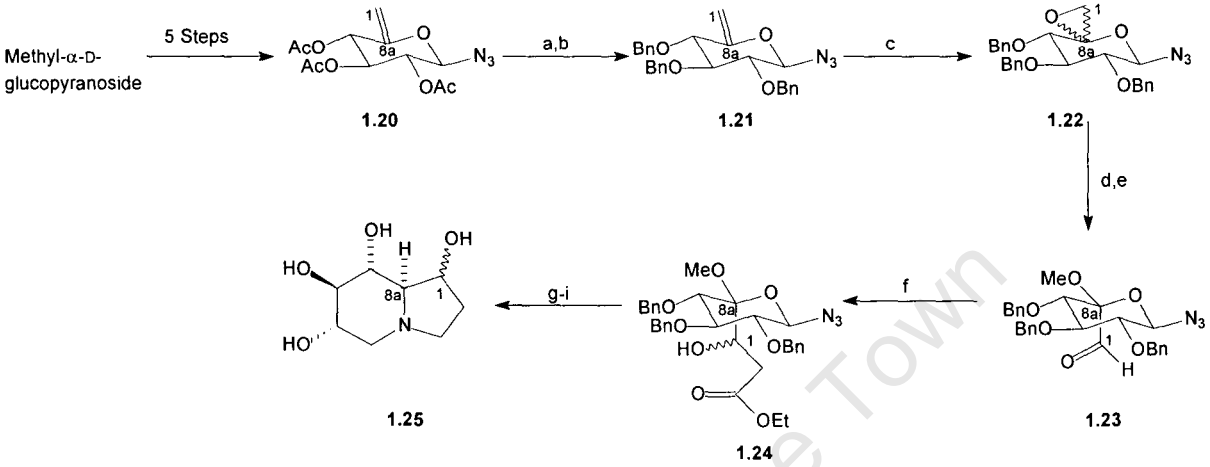
Figure 1.9

Scheme 1.3. *Reagents and Conditions*: a) Swern Oxidation; b) Allyltrimethylsilane (3.6 eq), $TiCl_4$ (2.4 eq), DCM, -85°C, 16h; c) O_3, DCM, -78°C; d) $NaBH_4$, ethanol; e) MsCl (1 eq), Et_3N, DCM; f) H_2, Pd/C.

The resultant allylic alcohol **1.18** was subjected to ozonolysis and reduced to give diol **1.19**, which was carefully monomesylated at the primary hydroxyl with one equivalent of mesyl chloride. Exhaustive hydrogenolysis gave (+)-castanospermine **1.1**, following cyclization onto the mesylate. This elegant total synthesis involved a total of 14 steps with an overall yield of 19% from methyl-α-D-glucopyranoside.

Following on from Ganem's syntheses, the groups of Anzeveno[21] and more recently Murphy[22] independently achieved successful syntheses, also using non-stereoselective aldol extensions for annulation of the pyrrolidine ring.

In spite of using a non-stereoselective aldol reaction as a method for chain extension, Murphy[22] reported a novel method of transforming a glucose intermediate to an indolizidine in a single step using reductive amination (Scheme 1.4).

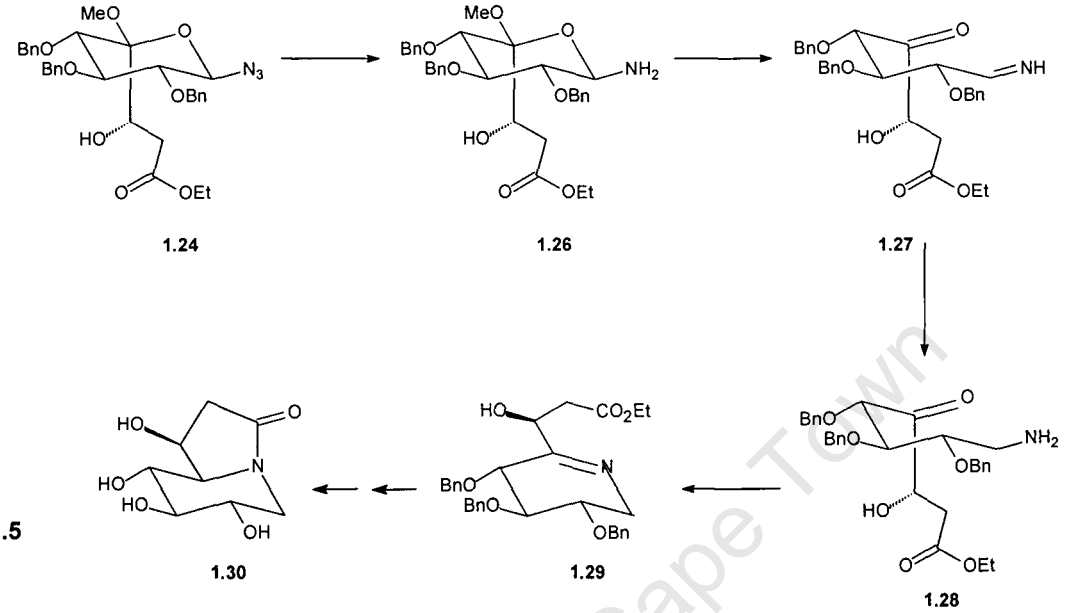


Scheme 1.4. *Reagents and Conditions*: a) NaOMe, MeOH, rt, 1h; b) BnBr (3 eq), DMF, 0°C, 3h, 62%; c) 1,1,1-trifluoroacetone, Oxone, $NaHCO_3$, Na_2EDTA, CH_3CN, 0°C, 1-5h; d) CSA, MeOH, 10 min, 95%; e) TPAP, NMO, DCM, 4 Å MS, rt, 5h, 67% (5:2 mixture); f) LDA, EtOAc, THF, -78°C to rt, 51% (2:1 mixture); g) $Pd(OH)_2$, H_2, MeOH, HCO_2H, 500 psi, rt, 48h, 70%; h) TMSOTf, pyridine, 2,6-lutidine, 0°C to rt, 12h; i) $LiAlH_4$, THF, 16h, 54% over two steps.

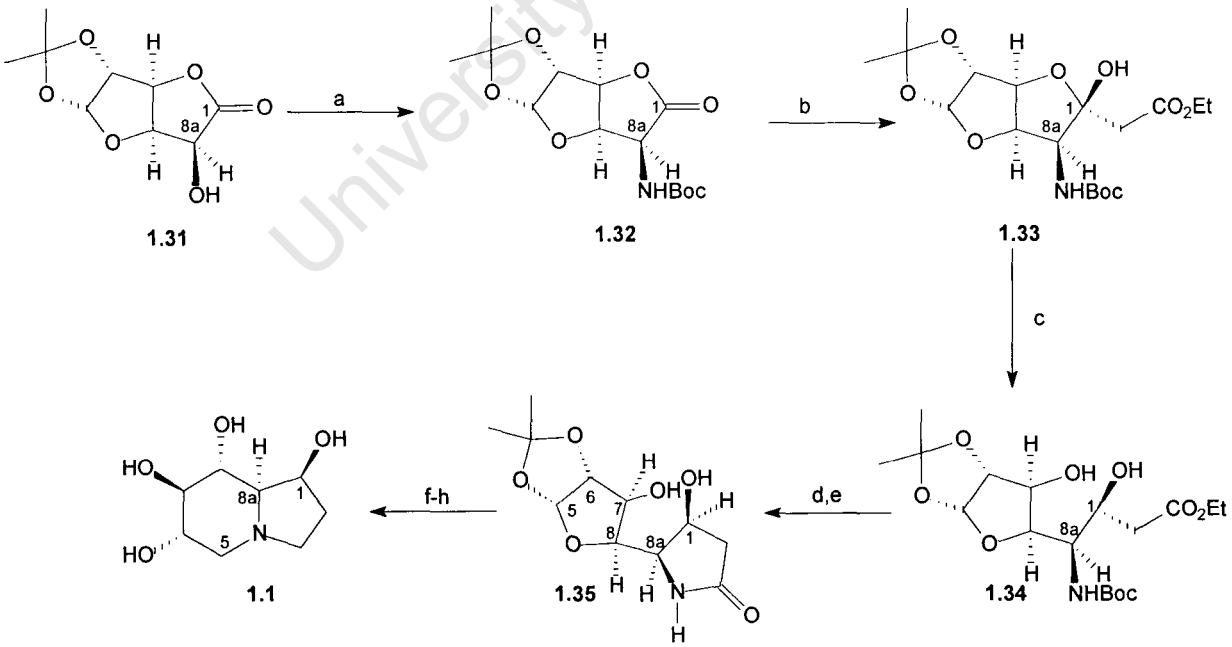
The starting material for the synthesis was 1-azido-6-deoxyhex-5-enopyranoside **1.20**, which was synthesized in 5 steps from methyl-α-D-glucopyranoside.[23] Following a protecting group switch (acetate to benzyl) by standard methods, epoxidation afforded a mixture of epimeric epoxides **1.22**, which were opened with methanol under acid catalysis. The resulting C-1 alcohols were oxidized under Ley conditions[24] to give a mixture of C-8a epimeric aldehydes, which were separated via chromatography to assign configuration. Aldehyde **1.23** underwent addition with ethyl lithioacetate to give an epimeric mixture (7 : 3) of (C-1) alcohols, which were separated by chromatography. The stage was now set for the key reaction involving a catalytic reductive amination [indolizidine-ring generation] cascade reaction involving the chemistry of the azido and ketal functionalities, resulting in lactam **1.30** (Scheme 1.5). This was achieved via reduction of the azide **1.24** to give a pyranosylamine **1.26**, which underwent ring-opening to form an acyclic keto-imine **1.27**. Further reduction of **1.27** and cyclization of **1.28** generated a cyclic imine **1.29** which underwent stereoselective reduction and cyclization with benzyl group deprotection to give lactam **1.30**. From lactam **1.30**, the hydroxyl groups were protected as their silyl ethers

using TMSOTf (step h, Scheme 1.4) to assist isolation, and the silylated lactam reduced to give (+)-castanospermine **1.25** as a mixture of epimers. The reductive amination cascade cleverly manipulated C-8a epimeric ketals **1.24** into the indolizidine framework with correct stereochemistry at C-8a. However, the synthesis failed to control generation of C-1 in an appropriate stereoselective manner in what was a relatively low-yielding addition reaction.

Scheme 1.5



By starting with the readily available 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone **1.31**,[21,25] Anzeveno achieved a series of stereoselective reactions by using the roof-shaped topology of the bicyclic furanolactone **1.31** (Scheme 1.6).

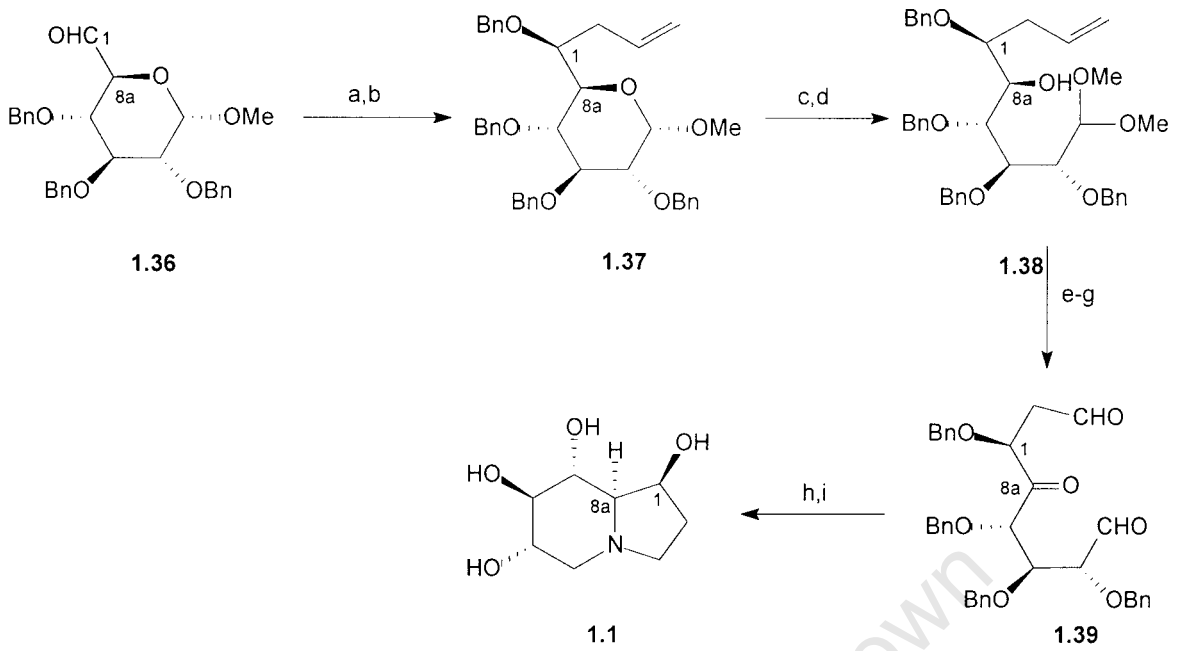


Scheme 1.6. *Reagents and Conditions*: a) i) Swern oxidation, 90%; ii) $H_2NOBn.HCl$, C_6H_6, Δ, 95%; iii) H_2, Pd/C, $(Boc)_2O$, EtOAc, 57%; b) EtOAc (3 eq), LDA (3 eq), THF, -78°C, 97%; c) H_2, PtO_2, EtOAc, 100%; d) HCO_2H (98%), DCM, 0-5°C, 2h, then 25°C, 6h; e) Dowex 1 x 2 (OH^-) resin, H_2O, 75% over 2 steps; f) $LiAlH_4$ (5 eq), THF, reflux 20h, 75%; g) CF_3CO_2H, 25°C, 20h; h) H_2 (50 psi), Pd/C, H_2O, 20h, 61% over 2 steps.

Thus the first of the two stereoselective reactions for C-8a installation was achieved by oxidizing the hydroxyl group of **1.31** under Swern conditions to the ketone followed by oxime formation and subsequent *exo*-stereoselective reduction in the presence of di-*tert*-butyl dicarbonate (Boc_2O) to give protected amine **1.32**. Stereoselective *exo*-addition of lithioacetate to the lactone carbonyl as the desired chain extension gave rise to a single hemiketal epimer **1.33**, which in turn was subjected to stereoselective catalytic hydrogenation of the hemiketal carbonyl in its open form (7 : 2 mixture in favour of the desired product). In establishing the stereogenic centre C-1, the stereoselectivity was explained by hydrogen delivery to the carbonyl group *anti* to the carbamate in the *zig-zag* conformation. In contrast, when **1.33** was reduced with standard reducing agents like sodium borohydride, the resulting diol **1.34** was obtained as a diastereomeric mixture in favour of the undesired product. This was rationalized by coordination of the reducing agent and oxygens of the functionalities of the keto-ester. The next stage of the synthesis was to form the pyrrolidine ring. Thus, acid hydrolysis of the Boc protecting group of **1.34** to give the amino ester was followed by purification on a basic Dowex ion-exchange column resulting in pyrrolidinone formation. The lactam **1.35** was then reduced to the pyrrolidine with LAH, which was followed by acid hydrolysis of the ketal with final catalytic hydrogenation (reductive amination) to give (+)-castanospermine **1.1**. This templated synthesis by and large solved the challenge of stereoselective introduction of the C-1 and C-8a stereogenic centres.

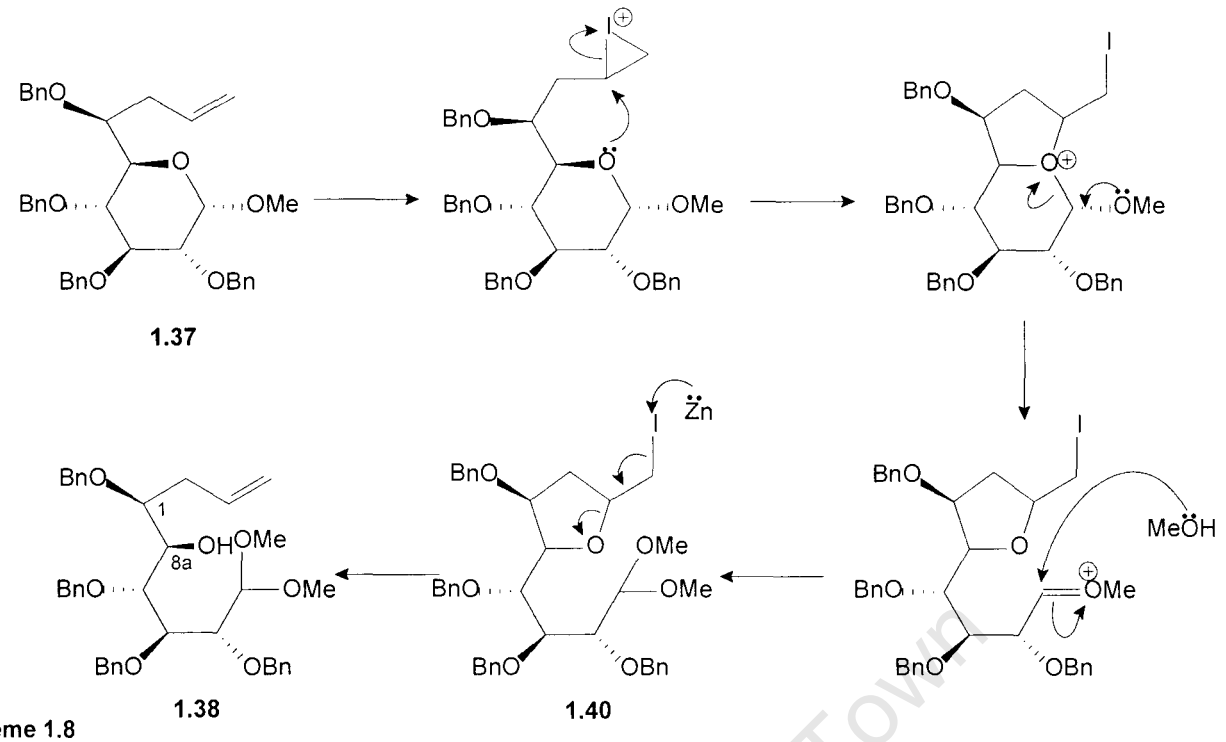
In the literature, Mootoo *et. al.*[26] and Park *et. al.*[27] have reported alternative syntheses to that of Ganem's,[20] both of which utilize a stereoselective allylation as a means to chain-extend.

Mootoo *et. al.*[26] synthesis of (+)-castanospermine is a concise synthesis, transforming aldehyde **1.36** to the target in 9 steps. The key steps include a Whitesides allylation and a triple reductive amination (Scheme 1.7).



Scheme 1.7. *Reagents and Conditions*: a) Allyl Bromide, Sn, CH_3CN-H_2O, ultrasound, 83%; b) BnBr, NaH, TBAI, DMF; c) IDCP, DCM-MeOH; d) Zn, 95% EtOH, heat, 74% over 2 steps; e) Swern oxidation; f) O_3, DCM, -78°C, then Ph_3P; g) THF, 9M HCl, 90% over three steps; h) NH_4HCO_3 (1.3 eq), $NaCNBH_3$ (30 eq), MeOH, 53%; i) 10% Pd/C, MeOH, HCOOH.

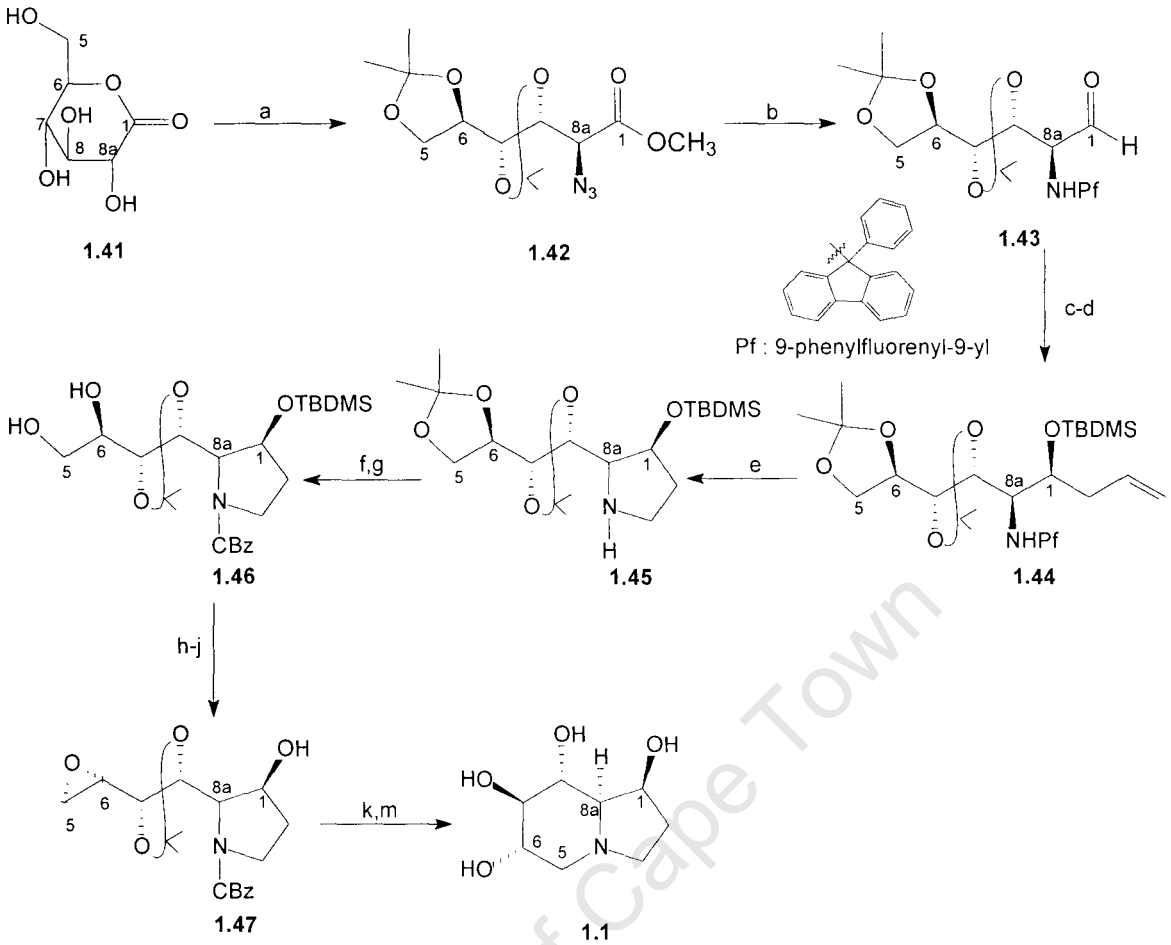
The benzyl-triprotected aldehyde **1.36**, synthesized in four straightforward steps from methyl α-D-glucopyranoside, underwent stereoselective allylation under Whitesides conditions[28] using tin, allyl bromide and ultrasound to give a 9 : 1 epimeric mixture of alcohols. The major diastereomer had the correct *S*-configuration, which may be rationalized in terms of a Felkin-Ahn chelate model similar to that described in Scheme 1.3 for the Ganem synthesis (nitrogen instead of oxygen). The diastereomers could be separated by chromatography and the major one was then benzylated to give tetraprotected pyranoside alkene **1.37**. In order to open the pyranose ring in preparation for the reductive amination step, a clever strategy originally developed by Arnold[29] was utilized. Reaction of **1.37** with iodonium dicollidine perchlorate (IDCP) resulted in formation of the opened iodotetrahydrofuran. The mechanism is shown in Scheme 1.8



Scheme 1.8

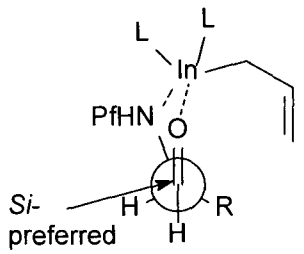
Treament of pyranose-opened **1.40** with zinc in refluxing ethanol opened the THF ring and restored the double bond forming **1.38**. The scene was now set for construction of the bicyclic ring system via intramolecular reductive amination (Scheme 1.7). Thus Swern oxidation of alcohol **1.38** followed by ozonolysis of the terminal alkene gave an intermediate aldehyde. Acetal hydrolysis to key tricarbonyl intermediate **1.39** could now proceed to the unprecedented triple reductive amination which resulted in the formation of the indolizidine skeleton stereoselectively. Final deprotection gave the target in an overall yield of 22% over 9 steps.

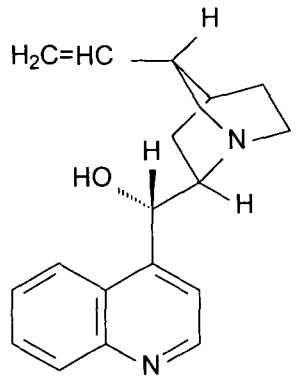
Similarly, Park *et. al.*[27] have described a route to (+)-castanospermine, which also involves a stereoselective allylation as a key step, but on an acyclic precursor rather than on a bicyclic template. It is a much longer synthesis than the one described by Mootoo,[26] involving a total of 17 steps from D-glucono-δ-lactone **1.41** (Scheme 1.9). It is interesting to note that in this synthesis, rather than utilizing the glucose in the conversional manner via chain extension at C-6 (glucose numbering) and cyclization to nitrogen, the chain extension occurs at C-1 and the cyclization to nitrogen at C-6 (glucose numbering) which becomes C-5 of the target. A drawback of this type of approach is that C-6 (castanospermine numbering) has the incorrect stereochemistry. Scheme 1.9 depicts this using castanospermine numbering of gluconolactone **1.41**.



Scheme 1.9. *Reagents and Conditions*: a) i) $(CH_3O)_2CH_2$, acetone, MeOH, TsOH, rt, 84%; ii) $(CF_3SO)_2O$, DCM, pyridine, -10°C; 90%; iii) CH_3CN, Bu_4NN_3, rt, 95%; b) i) H_2, Pd/C; ii) PtBr, Et_3N, $Pb(NO_3)_2$, 82% over two steps; iii) DIBAL; iv) NCS, Me_2S, 90% over 2 steps; c) Allyl Bromide, In, (+)-cinchonine, THF, -78°C, 87%; d) TBDMSCl, imidazole, DMF, rt, 98%; e) i) O_3, DCM, -78°C; ii) 10% $Pd(OH)_2$, H_2, EtOH, rt, 63% over 2 steps; f) CBzCl, K_2CO_3, DCM, 100%; g) DOWEX 50W-X8, MeOH, 90%; h) TBDMSCl, imidazole, DCM, rt, 99%; i) MsCl, Et_3N, DCM, 0°C, 92%; j) TBAF, K_2CO_3, THF, rt, 90%; k) 10% Pd/C, NaOAc, MeOH, 60°C, 65%; m) DOWEX 50W X8, THF-H_2O (3:1), 92%.

α-Azidoester **1.42** with inversion by azide at C-8a (originally C-2 of D-glucose) was synthesized from readily available D-glucono-δ-lactone **1.41** via a known sequence.[30] Compound **1.42** was then transferred into key intermediate **1.43**, which underwent a stereoselective allylation in the presence of a chiral promoter, the alkaloid (+)-cinchonine, resulting in the formation of the *syn*-aminoalcohol, (50 : 1) with the correct *S*-configuration at C-1, which was subsequently protected as its TBDMS silyl ether to give **1.44**. The high *syn*-diastereoselectivity was interpreted as being a result of a matched double-asymmetric induction process involving both substrate and reagent control, the latter in the form of a homochiral allylindium reagent, and the outcome was in agreement with a Felkin-Ahn chelated transition state (Figure 1.10).



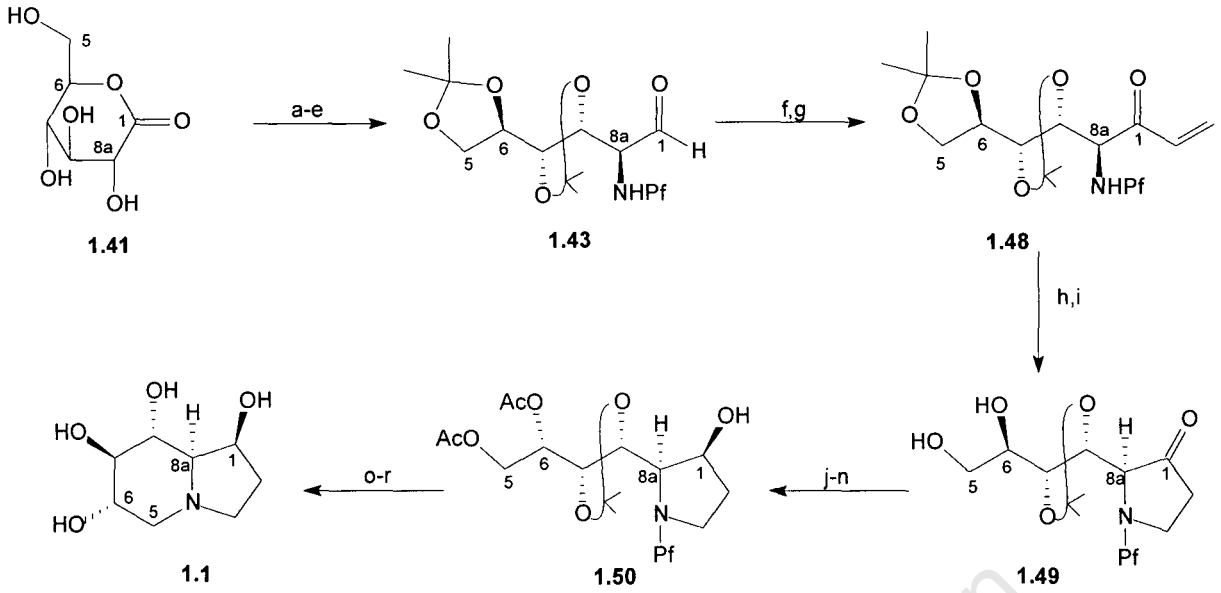


L= (+)-Cinchonine

Figure 1.10

With all stereogenic centres now in place, the rest of the synthesis focused upon the installation of the pyrrolidine ring for cyclization to the indolizidine target. Thus the terminal alkene was subjected to ozonolysis, with spontaneous cyclization to the hemiaminal. This was followed by catalytic hydrogenolysis of the nitrogen protecting group with concomitant reduction of the α-hydroxyl to the pyrrolidine ring. Reprotection of the amine as its CBz derivative and chemoselective hydrolysis of the terminal *O*-isopropylidene under acidic conditions gave diol **1.46.** TBDMS protection of the primary hydroxyl group followed by mesylation of the secondary hydroxyl, then deprotection of the primary hydroxyl followed by treatment with base resulted in the formation of epoxide **1.47** with inversion of configuration at C-6. Hydrogenolysis of the carbamate gave the secondary amine, which spontaneously cyclized regioselectively at C-5 in a 6-*endo* fashion, to the indolizidine. This is an interesting case of regiocontrol by a neighbouring protecting group. *Exo*-opening at C-5 would have generated a strained pyrrolizidine bicycle containing a *trans*-fused dioxolane ketal. Final hydrolysis of the remaining isopropylidene group gave (+)-castanospermine **1.1**.

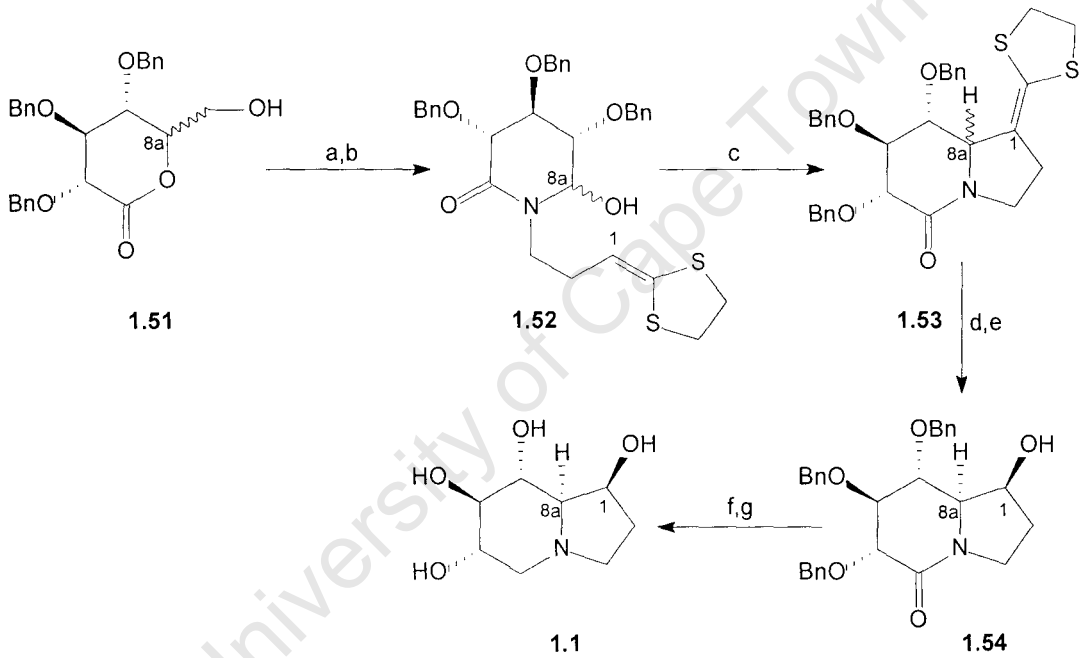
Another synthesis, which was based upon a similar approach to that of Park's[27] was reported by Rapoport.[31] The main purpose of the synthesis was to demonstrate that key intermediate **1.43** could be a useful building block for the synthesis of indolizidines (Scheme 1.10).



Scheme 1.10. *Reagents and Conditions*: a) 3 steps as in step a) in Scheme 1.9; b) H_2, Pd/C; c) PfBr, Et_3N, $Pb(NO_3)_2$, 82% over two steps; d) DIBAL, THF; e) NCS, Me_2S, 90%; f) Vinylmagnesium Bromide, THF, -40°C - rt, 91%; g) NCS, Me_2S, 92%; h) HBr, Et_2O, H_2O; i) $NaHCO_3$, Na_2CO_3 70-90% over two steps; j) Ac_2O, py; k) $(CF_3SO_2)O$, pyridine; l) Bu_4NOAc; m) Ac_2O, pyridine, DMAP, 85% over 4 steps; n) $NaBH_4$, 93%; o) K_2CO_3, 93%; p) Tosylation, 65%; q) H_2, Pd/C, NaOAc, 89%; r) i) CF_3COOH; ii) DOWEX 50W, 95%.

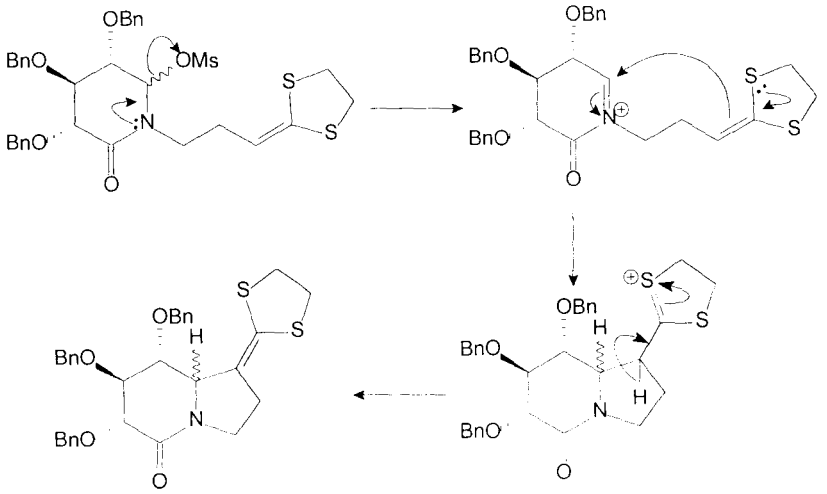
Aldehyde **1.43** was synthesized as previously described in Park's synthesis.[27] The synthesis then focused upon building the key intermediate **1.49**. Aldehyde **1.43** was subjected to a Grignard addition of vinyl, rather than a stereoselective allylation as in Park's synthesis, and the resulting mixture of alcohols was then oxidized to an α,β-unsaturated ketone **1.48**. Addition of hydrogen bromide to the terminal double bond gave the primary bromide, which was not isolated, but subjected to a base-promoted cyclization to give key intermediate pyrrolidine **1.49**. The rest of the synthesis was a series of functional group interconversions to give intermediate **1.50**, which was then cyclized to form the indolizidine ring. Thus, selective monoacetylation of the primary hydroxyl of **1.49** followed by conversion of the secondary hydroxyl to its triflate, was followed by immediate treatment with tetrabutylammonium acetate resulting in the inversion of configuration at C-6 by acetate ion. The ketone carbonyl group was then reduced stereoselectively to give acetate **1.50**. With all the stereogenic centres now in place, all that remained was the formation of the indolizidine skeleton, which was achieved by acetate hydrolysis, conversion of the C-5 primary hydroxyl to its tosylate, followed by hydrogenolysis of the nitrogen protecting group with cyclization to the indolizidine. Finally, the acetonide was then hydrolysed to give (+)-castanospermine **1.1**.

Another interesting approach has been to chain extend via the nitrogen and cyclize to the indolizidine via the C-8a/C-1 bond using electrophilic character at C-8a. Given the well-known and exploitable ability of nitrogen to stabilize an α-carbocation as an iminium species, it is not surprising that at least one synthesis has used this C-8a/C-1 disconnection. Chamberlin *et. al.*[32] has reported on a synthesis utilizing this type of disconnection in which triprotected D-glucono-1,5-lactone **1.51** was first condensed with 2-[3-aminopropylidene]-1,3-dithiane via lactone substitution and the product oxidatively cleaved with lead tetraacetate to give a mixture of hydroxylactams **1.52** and open chain aldehyde. The mixture was treated with acetic acid which cyclized the remaining aldehyde to the hydroxylactam **1.52** (Scheme 1.11).



Scheme 1.11. *Reagents and Conditions*: a) 2-(3-aminopropylidene)-1,3-dithiane, MeOH; b) $Pd(OAc)_4$, CH_3CN, then AcOH, 66% over two steps; c) Et_3N, MsCl, DCM, 84%; d) $^1O_2$, CCl_4, MeOH; e) L-Selectride®, THF, over two steps 39%; f) BH_3-DMS, THF, 67%; g) H_2, 10% Pd/C, MeOH, HCl, 82%.

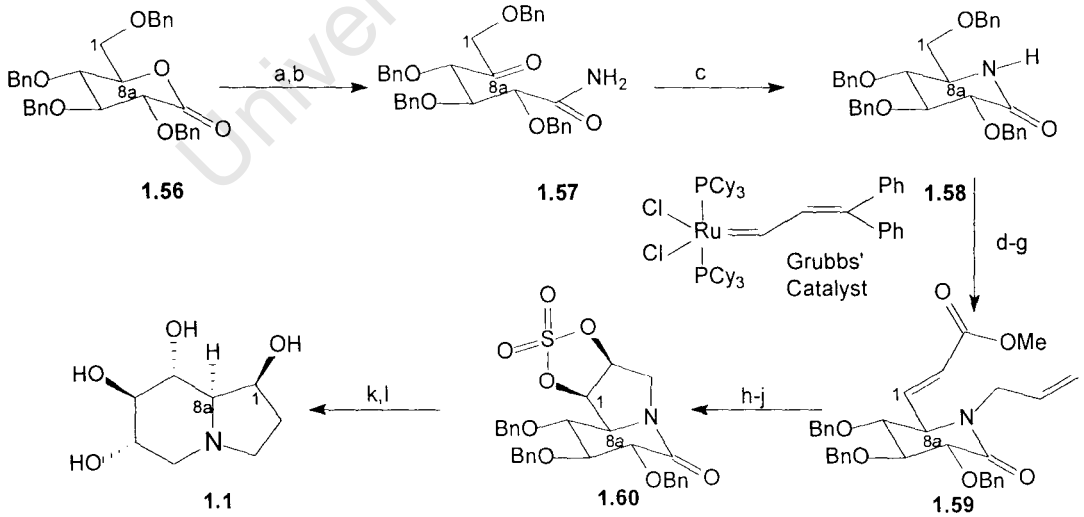
The secondary hydroxyl group of **1.52** was converted to its mesylate, which brought about spontaneous cyclization to yield indolizidine **1.53** as a mixture (1 : 1) of diastereomers (C-8a). Scheme 1.12 depicts the mechanism of the cyclization via acyliminium-ion chemistry. Varying the solvent and temperature did not affect the stereochemical outcome of the reaction.



Scheme 1.12

The diastereomers of **1.53** were separated and subjected to the same sequence of reactions, involving conversion of the ketene dithioacetal to the C-1 ketone via oxidative cleavage, followed by stereoselective reduction to give lactam **1.54** with the correct *S*-stereochemistry at C-1. Lactam reduction with borane-dimethyl sulfide followed by global hydrogenolytic debenzylation gave (+)-castanospermine **1.1** and (+)-1,8a-di*epi*-castanospermine respectively.

Pandit *et al.*[33-35] has also developed a concise synthesis for pyrrolidine ring installation using new methodology proceeding via a chain-extension on a glucose intermediate, the key step being a ring-closing metathesis. The synthesis began with aminolysis of the tetrabenzylgluconolactone **1.56** to afford the hydroxyamide, which was oxidized and cyclized to glucolactam **1.58** via stereoselective reductive amination (Scheme 1.13).

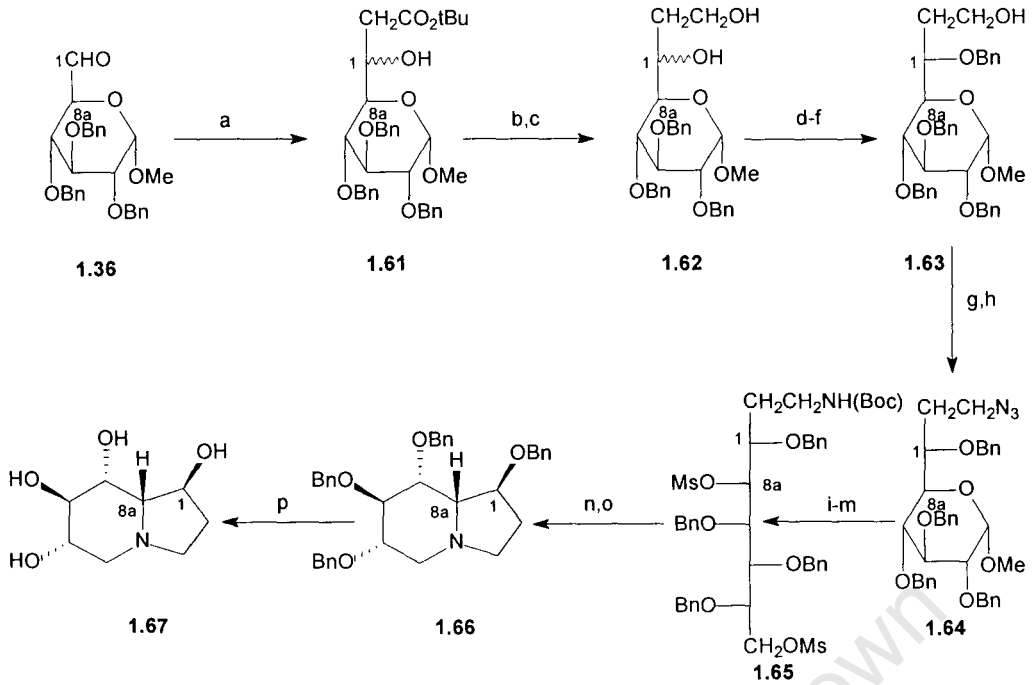


Scheme 1.13. *Reagents and Conditions*: a) NH_3, MeOH, 86% b) DMSO, Ac_2O; c) $NaCNBH_3$, HCO_2H, over two steps 58%; d) Allyl Bromide, KOH (50% aq): DCM (1:1), TBAI, 93%; e) Ac_2O, $FeCl_3$, then NH_3, MeOH; f) Dess-Martin periodinane, 80% over two steps; g) $Ph_3P{=}CHCO_2Me$, 85%; h) Grubbs' catalyst, toluene, 110°C, 48h, 70%; i) OsO_4, NMO, $SOCl_2$, Et_3N, 55%; j) $NaIO_4$, $RuCl_3$ (cat), DCM: H_2O: CH_3CN (2: 3: 2), 98%; k) $NaBH_4$, DMAC, then H_2SO_4, 98%; l) BH_3.DMS, H_2, Pd/C.

Glucolactam **1.58** was then converted to the key immediate diene **1.59** over four steps, via *N*-allylation in excellent yield using a phase-transfer method followed by regioselective cleavage at C-1 of the primary benzyl ether with iron chloride and acetic anhydride. The resulting primary alcohol was oxidized to the aldehyde using Dess-Martin periodinane which was then subjected to a Wittig chain extension at C-1 to give key intermediate **1.59**. The stage was now set for the key ring-closing metathesis using Grubbs' first-generation catalyst to generate the pyrrolidine ring. The notable feature was the use of an α,β-unsaturated ester in the reaction which was unprecedented at the time. The metathesis, although sluggish, resulted in the formation of the indolizidine ring in good yield. Hydroxylation of the double bond with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide as the cooxidant, gave a mixture of *syn*-diols, which were converted to their cyclic sulfate **1.60** via oxidation of the sulfite, and the diastereomers separated via chromatography. A cyclic sulfate behaves in a similar fashion towards nucleophilic opening to an epoxide and can be regarded as a chemical equivalent, and chosen in this case as epoxidation of the double bond had been problematic. The cyclic sulfate **1.60** was reduced regioselectively with hydride attacking at the less-hindered carbon, and then hydrolyzed to the hydroxylactam. Finally, the lactam was reduced and subjected to global hydrogenolytic debenzylation to afford (+)-castanospermine **1.1**.

The following series of synthetic routes describe syntheses of (+)-castanospermine stereoisomers. These were carried out to explore the relationship between the structure and biological activity of castanospermine stereoisomers.

Zamojski *et. al.*[36] focused their work on the synthesis of epimers of (+)-castanospermine with special attention to 8a-*epi* and 1,8a-di*epi*-castanospermine and therefore were not worried about the stereoselectivity of the aldol reaction (Scheme 1.14). The synthesis began with the same starting material as Ganem's first synthesis, namely 2,3,4-tri-*O*-benzyl-D-glucopyranose **1.9**.

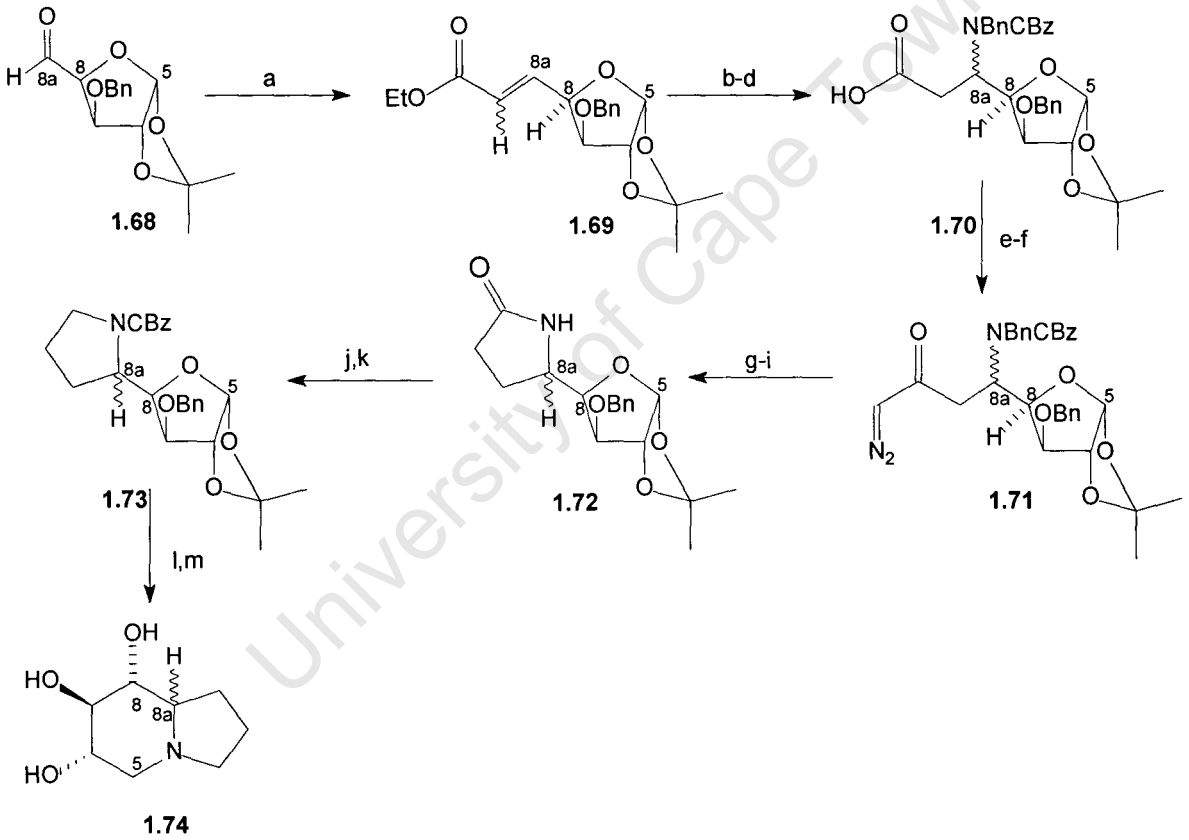


Scheme 1.14. *Reagents and Conditions*: a) $MeCO_2tBu$, LDA, THF, -78°C, 37% (3:2 mixture); b) HBF_4, H_2O, DCM, 98%; c) BH_3.THF, THF, 95%; (3:2 mixture); d) TBDPSCl, imidazole, DMF, 97%; e) BnBr, NaH, DMF, 91%; f) TBAF, THF, 87%; g) MsCl, DMAP, Pyridine, 96%; h) NaN_3, DMF, 60°C, 92%; i) Ac_2O, AcOEt, H_2SO_4, 95%; j) $NaBH_4$, EtOH, Δ; k) $NaBH_4$, $NiCl_2.6H_2O$, EtOH; l) $(Boc)_2O$, AcOEt, $NaHCO_3$, 95%; m) MsCl, DMAP, pyridine, -10°C, 81%; n) PhOH, TMSCl, DCM, 85%; o) AcONa, EtOH, reflux, 53%; p) H_2, 10% Pd/C, MeOH, HCl, 87%.

The tribenzyl-protected glucose **1.9** was converted to its methyl glycoside and then oxidized under Swern conditions to the C-1 aldehyde **1.36**. This was then condensed with *t*-butyl lithioacetate to give an aldol product as a 3 : 2 mixture, and in low yield (37%). The mixture of esters **1.61** was then chemoselectively hydrolyzed to a mixture of carboxylic acids with fluoroboric acid without hydrolyzing the anomeric position and then reduced to give diols **1.62**, which were separated by chromatography. Chemoselective conversion of the primary alcohol to the azide in anticipation of pyrrolidine ring construction was achieved by a standard sequence involving monosilylation, secondary hydroxyl-group benzylation, silyl deprotection to give **1.63**, mesylation and displacement with azide to afford **1.64**. The functionalized pyranose was converted to its C-1 anomeric *O*-acetate which was then reduced by borohydride to the open chain diol. This was followed by a sequence of functional group interconversions in order to install the pyrrolidine ring. Thus Ni(II)-promoted borohydride reduction of the azide, subsequent amino group protection as its Boc-carbamate and double mesylation of both hydroxyl groups gave carbamate **1.65**. Boc deprotection with HCl generated from phenol and TMSCl in DCM was followed by double intramolecular substitution, both steps proceeding with inversion of configuration to

give benzylated 8a-*epi*-castanospermine **1.66**, which was subjected to hydrogenolytic removal of the protecting groups to afford the target alkaloid 8a-epimer **1.67**. The same sequence was carried out on the epimeric aldol **1.61** product to give 1,8a-di-*epi*-castanospermine. This is an extremely long synthesis, involving a total of 19 steps from methyl-D-glycopyranoside, but did establish that a linear precursor could cyclize efficiently to the bicyclic indolizidine using the nucleophilic properties of nitrogen.

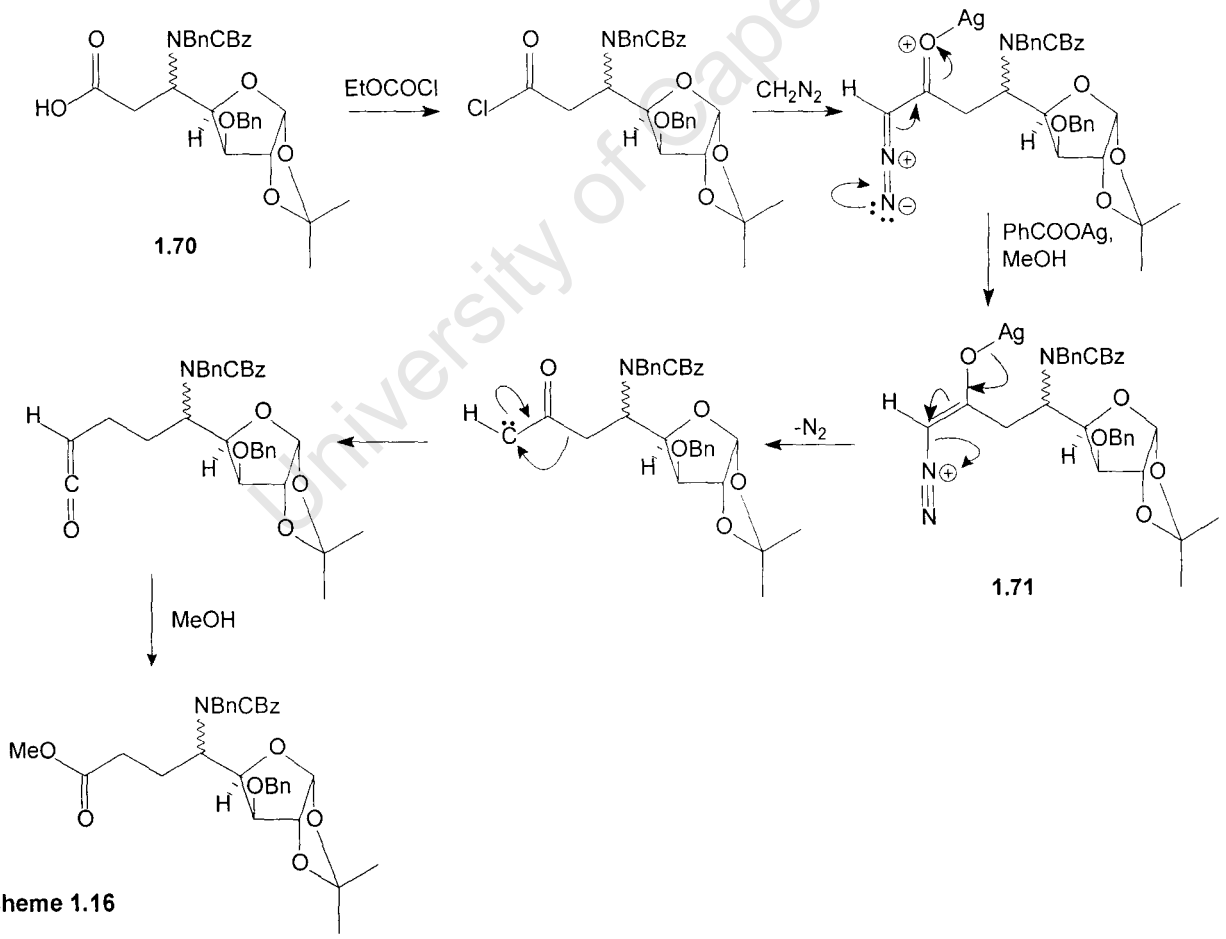
A rather interesting approach was demonstrated by Dhavale *et al.*[37-41] who described two syntheses of both (+)-1-deoxy-castanospermine and (+)-1-deoxy-8a-*epi*-castanospermine as well as one of 2-hydroxy-1-deoxy-castanospermine utilizing three different chain extension methodologies on the same starting material aldehyde **1.68**.[37] The first synthesis involved a phosphorane Wittig reaction (Scheme 1.15).[38]



Scheme 1.15. *Reagents and Conditions*: a) Ph_3PCHCO_2Et, CH_3CN, reflux, 2h, *E* 64%, *Z* 24%; b) $BnNH_2$, rt, 12h, 90%; c) CBzCl, $NaHCO_3$, EtOH-H_2O (9:1), rt, 4h, 95%; d) LiOH, MeOH-H_2O (4:1), rt, 4h, 96%; e) EtOCOCl, NEt_3, MeOH, rt, 1.5h; f) CH_2N_2, Et_2O, 0 to 25°C, 1.5h, 69%; g) PhCOOAg, NEt_3, MeOH, rt, 1.5h, 85%; h) 10% Pd/C, H_2, MeOH; i) CH_3COONa, MeOH, reflux, 4h, 80%; j) $LiAlH_4$, THF, reflux, 20h; k) CBzCl, $NaHCO_3$, EtOH, rt, 1.5h; l) TFA-H_2O, (3:2), rt, 2h; m) 10% Pd/C, H_2, MeOH.

Rather than utilizing an aldol or allylation as a chain extension, in his first synthesis Dhavale[38] employed a phosphorane Wittig reaction to form the chain-extended α,β-

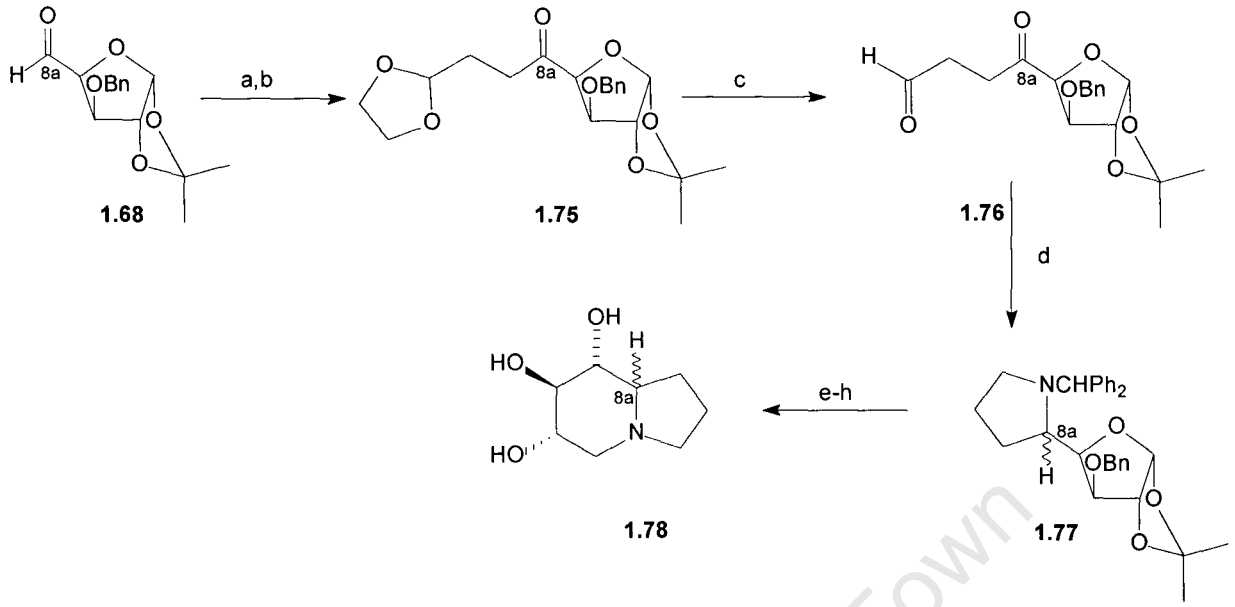
unsaturated ester **1.69** as a 73 : 27 *E : Z* mixture. A Michael addition of benzylamine to set up C-8a followed to give a mixture (7 : 3) of amine diastereomers which were separated. Each diastereoisomer was carried through the same sequence of protection as its CBz carbamate, followed by ester hydrolysis to acid **1.70**, before being converted to a mixed anhydride and reacted with diazomethane to give α-diazo ketone **1.71**. The latter underwent a silver (I)-promoted Wolff rearrangement to the γ-amino ester. The mechanism of this interesting reaction is shown in Scheme 1.16 to proceed via a carbene rearrangement to a ketene.[42,43] Cleavage of both amine protecting groups was achieved under hydrogenolysis conditions resulting in subsequent cyclization to the lactam **1.72**. The lactam was reduced to the pyrrolidine and subsequently protected as its CBz-carbamate **1.73**. Unravelling to the indolizidine involved hydrolysis of the 1,2 acetonide, followed by hydrogenolysis of the carbamate and benzyl protecting groups which led to (+)-1-deoxy-castanospermine and (+)-1-deoxy-8a-*epi*-castanospermine after cyclization and reduction of the imine.



Scheme 1.16

The "second" synthesis of (+)-1-deoxy-castanospermine reported by Dhavale[39] involved very similar construction of the indolizidine as the one previously reported, but in this case

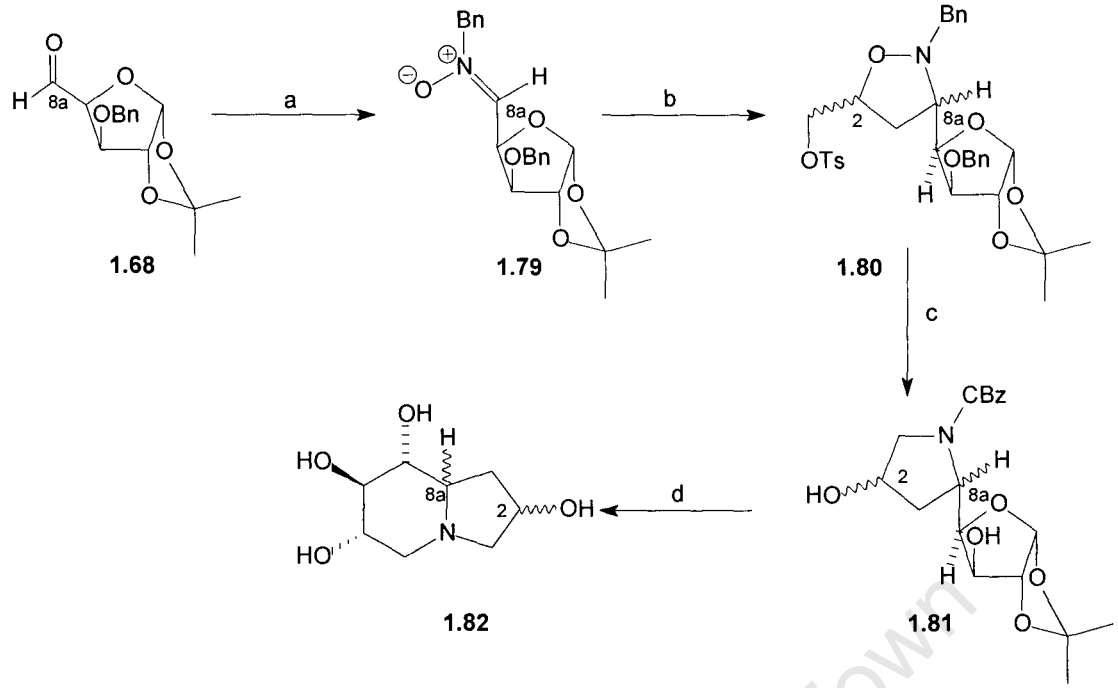
a Grignard reaction was used rather than the Wittig as a method for achieving the chain extension (Scheme 1.17).



Scheme 1.17. *Reagents and Conditions*: a) Mg, 2-(2-bromoethyl)-1,3-dioxolane (1.2 eq), Et_2O, -78°C to rt, 90%; b) Swern Oxidation, 92%; c) 80% aq acetic acid, 80%; d) Ph_2CHNH_2, (1.1 eq), AcOH (1.1 eq), $NaCNBH_3$ (2.5 eq), MeOH, 95%; e) 10% Pd/C, MeOH, 80 Psi; f) CBzCl (1.1 eq), $NaHCO_3$, EtOH-H_2O (8:2), 85%; g) TFA-H_2O (3:2); h) 10% Pd/C, H_2, MeOH, 80 Psi, 90%.

Thus subjecting the same starting aldehyde **1.68** as before to a Grignard addition with the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxolane followed by oxidation under Swern conditions gave ketone **1.75**. Chemoselective hydrolysis of the terminal acetal gave aldehyde **1.76**, which was subjected to a double reductive amination with diphenylmethylamine to give pyrrolidine **1.77** as a mixture of diastereomers at C-8a. Hydrogenolysis followed by reprotection of the amine as its CBz derivative **1.73** (as in the previous sequence) allowed the mixture of stereoisomers to be separated. Thereafter, the same sequence of reactions was followed as before to afford (+)-1-deoxy-castanospermine and (+)-1-deoxy-8a-*epi*-castanospermine.

Finally, in the synthesis of the castanospermine structural isomer 2-hydroxy-1-deoxy-castanospermine as reported by Dhavale,[40] the key step involved a nitrone 1,3-dipolar cycloaddition as the chain extension reaction (Scheme 1.18).



Scheme 1.18. *Reagents and Conditions*: a) N-Benzylhydroxylamine HCl, AcONa, EtOH/H_2O, rt; b) i) allyl alcohol, acetone, 70°C, 48h, 95%; ii) TsCl, pyridine, 0°C to 25°C, 2h, 87%; c) i) $HCOONH_4$, Pd/C, MeOH, 80°C, 1h; ii) CBzCl, $NaHCO_3$, MeOH, 0°C to 25°C, 2h, 70%; d) i) TFA-H_2O (3:2), 25°C, 2h, ii) H_2, Pd/C, MeOH, 80psi, 25°C, 12h.

Once again, using the same starting aldehyde **1.68**, the synthesis began with condensation with *N*-benzylhydroxylamine to afford nitrone **1.79**,[41] which underwent a 1,3-dipolar cycloaddition with allyl alcohol, resulting in a mixture of 4 diastereoisomers (ratio of *syn* : *anti* = 76 : 24), which were separated as their tosylates **1.80**. The next step was a one-pot, three-step hydrogenation involving N-O bond cleavage, intramolecular aminocyclization to form the pyrrolidine ring and hydrogenolysis of both benzyl protecting groups. The resultant amino group was reprotected and isolated as a carbamate **1.81**, which underwent reductive amination with hydrogen over Pd/C under pressure to the target following hydrolysis of the acetonide protecting group.

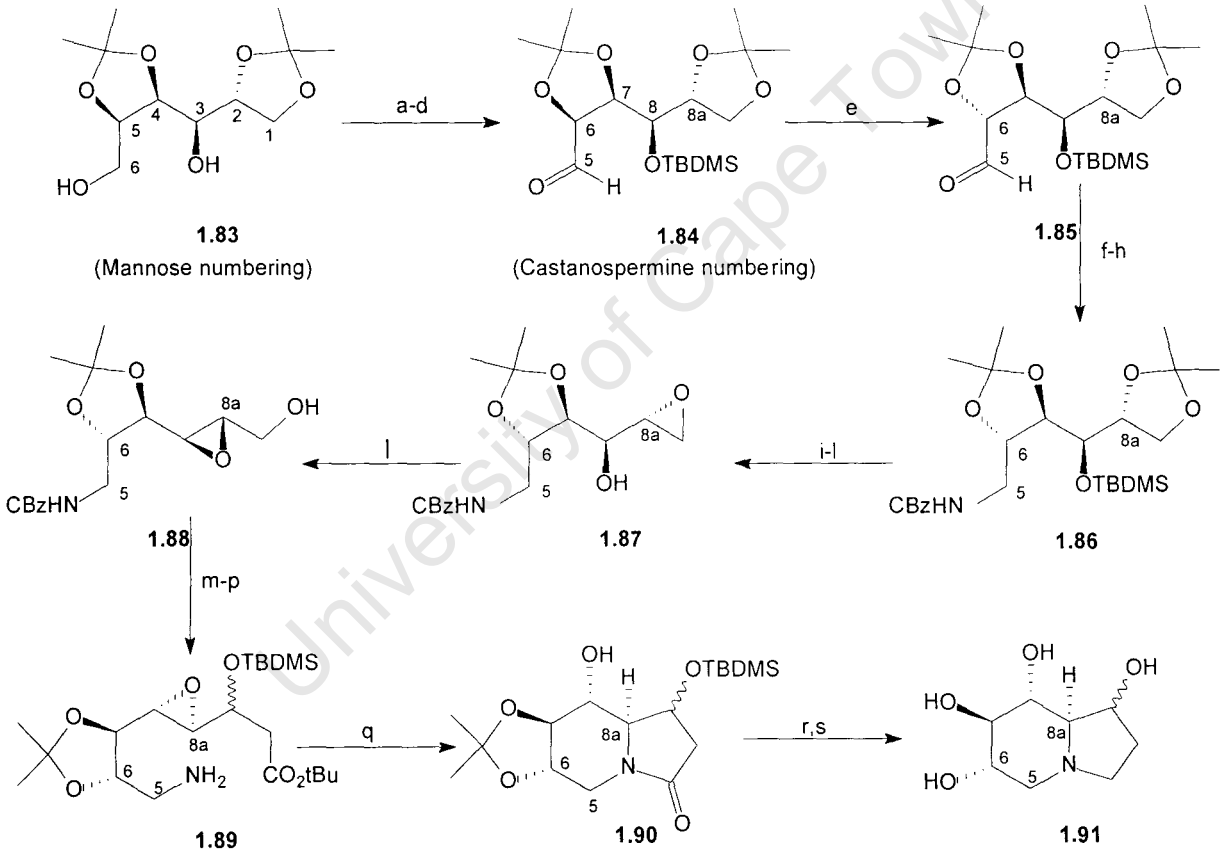
In summary, many syntheses of (+)-castanospermine and its analogues have utilized D-glucose as starting material, in which the main challenge has centred around stereoselective formation of the C-8a and C-1 stereogenic centres.

1.2.2 Other Carbohydrate-Based Syntheses

There have been a few reported syntheses, which use other sugars as starting materials such as D-mannose **1.7** and D-xylose **1.8**. These sugars could provide alternative routes to castanospermine or new analogues that could be potentially biologically active. These

routes could also help to explore and develop new methodologies or expand on existing ones.

In 1985, Hashimoto *et. al.*[44] reported on the total synthesis of (+)-castanospermine in 20 steps from a protected D-mannose **1.7** (Scheme 1.19). Hashimoto utilized mannose as the starting material to expand on previous work in which he used a double intramolecular cyclization as a key step to access the indolizidine swainsonine **1.2**. It's important to note that mannose differs from glucose at one stereogenic centre (C-2 glucose numbering), which requires epimerization in order to be correct for C-6 in castanospermine. Hashimoto utilized the same approach as previously reported by Park[27] and Rapoport[31] in which chain extension occurred at C-1 (of mannose) and annulation at C-6, to become C-1 and C-5 of castanospermine respectively.



Scheme 1.19. *Reagents and Conditions*: a) BzCl, pyridine, 25°C, 62%; b) TBDMSCl, Imidazole, DMF, 80°C; c) 1M NaOH, MeOH, 25°C, 99% over two steps; d) DMSO, DCC, TFA, pyridine, benzene, 25°C, 91%; e) K_2CO_3 (3 eq), MeOH, 25°C, 87%; f) $H_2NOH.HCl$, $NaHCO_3$, EtOH, H_2O, 60°C, 99%; g) $LiAlH_4$, THF, 25°C; h) CBzCl, THF, H_2O, 0°C, 78% over two steps; i) TsOH, (0.1 eq), MeOH: H_2O (9:1), 15°C, 41%; j) TBAF, THF, 0°C, 85%; k) MsCl, pyridine, 5°C, 68%; l) NaOMe (1.4 eq), MeOH, 20°C, 60% m) CrO_3.pyridine, DCM, 5°C; n) *t*-butyl lithioacetate, 24% over two steps o) TBDMSCl, imidazole, DMF, 80°C; p) H_2, 10% Pd/C, EtOH; q) Methoxyethanol, Δ, 51% over three steps; r) BH_3-THF, THF, Δ; s) 6M HCl, THF, Δ, 83%.

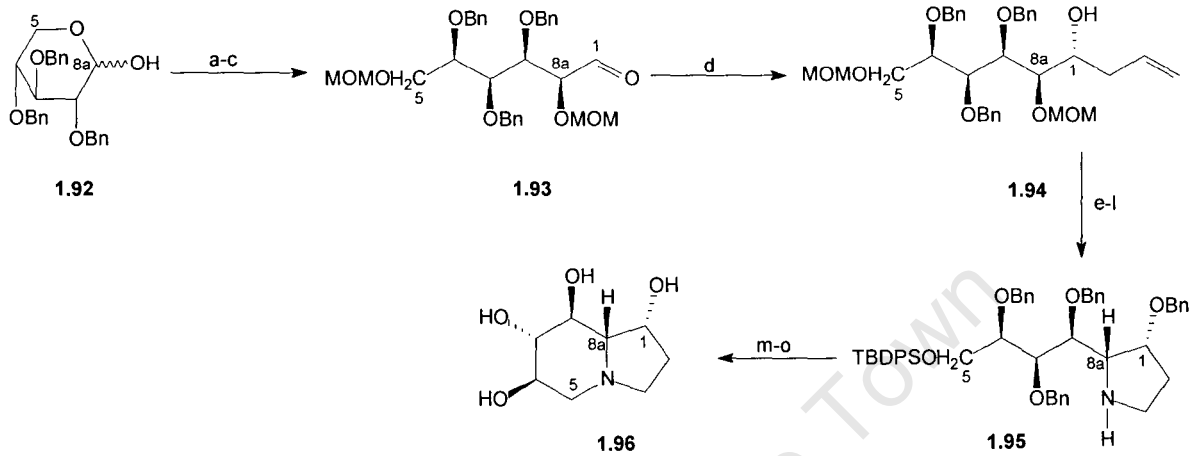
The synthesis begins with the known protected mannose **1.83**, synthesized from mannose **1.7** in 3 steps. Chemoselective benzoylation of the primary hydroxyl group of **1.83** followed by conversion of the secondary alcohol to its silyl ether, deprotection of benzoate with base and oxidation under Moffat conditions gave aldehyde **1.84**. The next step of the synthesis was epimerization of C-6 (castanospermine numbering) under basic conditions to give the more stable *trans*-dioxolane aldehyde **1.85**, which was then converted to its oxime, reduced and derivatised to carbamate **1.86**. Attempted selective hydrolysis of the terminal acetonide with *p*-TsOH gave a mixture of diol with triol, since the silyl ether was also hydrolysed under the same conditions. Thus, following hydrolytic acetonide cleavage, the remaining silyl ether was removed with fluoride ion and the primary alcohol of the resultant triol converted to its mesylate, which under basic conditions (pyridine) cyclized to form epoxide **1.87**. On prolonged treatment with base (NaOMe), **1.87** underwent a Payne rearrangement to the more stable epoxide **1.88** with inversion of configuration at C-8a.[45] The primary alcohol of **1.88** was then oxidized with Collins reagent[46] and condensed with *t*-butyl lithioacetate resulting in a mixture of aldol products (3 : 2), which were inseparable. The mixture was protected as silyl ethers and hydrogenated to remove the nitrogen protecting group, resulting in the formation of key intermediate **1.89**, which underwent the key double cyclization under reflux to form the indolizidine skeleton as a mixture of separable isomers. Noteworthy is the use of the isopropylidene group to control the regioselectivity, precluding 5-*exo*-*tet* opening to afford a strained 5,5-*trans* bicycle. This regiocontrol was seen in Park's synthesis, Scheme 1.9. The individual lactams **1.90** were then reduced and hydrolysed to yield (+)-castanospermine **1.1** and 1-*epi*-castanospermine **1.91**.

Hashimoto's synthesis shares several characteristics in common with Ganem's first synthesis. Notably, the use of an epoxide opening to create the heterocycle as well as the use of a non-stereoselective aldol chain extension resulting in C-1 epimers of the target.

There have been two syntheses reported which utilize pentose sugars as starting materials. The purpose of these syntheses was to generate stereoisomers to carry out structure-activity studies. The focal point of these syntheses is the necessary three-carbon chain extension, as well as the introduction of the C-1 hydroxyl and C-8a stereogenic centres. C-1 of the sugar becomes C-8a of the target.

The first of the syntheses was described by Mulzer *et. al.*[47] whose target was the enantiomer of (+)-castanospermine, utilizing D-xylose **1.8** as starting material and involving two stereoselective chain extensions (Scheme 1.20). The first one was a vinylation of the

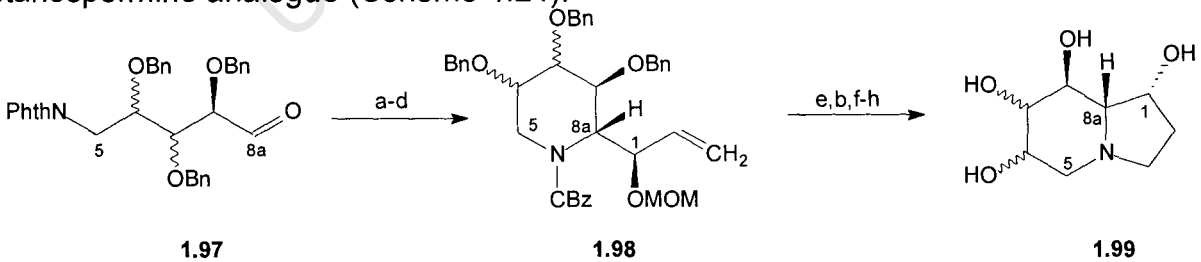
tribenzyl-protected xylose **1.92** which introduced C-8a stereoselectively, and could be rationalized in terms of a Felkin-Ahn chelate model. The hydroxyl groups were then protected as MOM ethers and the terminal alkene ozonised to afford aldehyde **1.93**. This was then subjected to a second chain-extension in the form of a stereoselective allylation, introducing the C-1 centre stereoselectively in a similar fashion as described previously, but via a Felkin-Ahn non-chelate model.



Scheme 1.20. *Reagents and Conditions*: a) CH_2=CHMgBr, ether; 94%; b) MOMCl, DCM, EtN(*i*-Pr)$_2$, HPLC-Sep; c) O_3, DCM, PPh_3, 82% over two steps. d) Allyl bromide, $CrCl_3$, $LiAlH_4$, 55% (85:15) or $AllylSnBu_3$, $MgBr_2$, 76% (5:95); e) NaH, DMF, BnBr, 77%; f) O_3, DCM, PPh_3; g) LAH, ether, 0°C-rt; 60%; h) Phthalimide, PPh_3, DEAD, THF, 85%; i) HCl, MeOH, 50-60°C, 97%; j) TBDPSCl, DMF, imidazole, 91%; k) MsCl, pyridine, 81%; l) $N_2H_4.H_2O$, EtOH, 79%; m) TBAF, THF, rt, 88%; n) PPh_3, CCl_4, NEt_3, CH_3CN, 78%; o) 10% Pd/C, H_2, MeOH, 91%

Conversion of **1.94** to the target involved a lengthy sequence of steps for constructing firstly the pyrrolidine ring and then the indolizidine ring. The key C-N bond connections were provided by phthalimide Mitsunobu chemistry and S_N2 inversion of a C-8a mesylate.

Burgess *et al.*[48] developed a general route of converting a pentose sugar **1.97** into a castanospermine analogue (Scheme 1.21).



Scheme 1.21. *Reagents and Conditions*: a) (Z)-(MOMO)CH=CHCH$_2^{\delta}$Bipc$_2$, $BF_3.OEt_3$, then H_2O_2, $NaHCO_3$; b) MsCl, NEt_3; c) $MeNH_2$; d) CBzCl, $NaHCO_3$; e) BH_3.THF then H_2O_2, $NaHCO_3$; f) H_2, cat. Pd/C, MeOH; g) HCl (aq); h) ion-exchange.

In this case, the route involved a three-carbon chain extension, as a stereoselective allylation to introduce the stereogenic C-1 and C-8a centres in a single step. This powerful

reaction involved a *syn*-stereoselective reagent-controlled allylboration using a *Z*-γ-alkoxyallylborane. The stereoselectivity could be rationalized using a Felkin-Ahn non-chelate model in conjunction with a chelated Zimmermann-Traxler transition state.[49] The rest of the synthesis involved conventional functionalisation and ring closure via the terminal mesylate to afford the required analogue.

It can be concluded that the D-glucose-based syntheses in general are more efficient than the non-glucose-based ones. The syntheses which stand out are: Ganem's (second) stereoselective synthesis which is short, concise and high yielding, and is arguably one of the best syntheses; Pandit's for the introduction of new methodology involving metathesis and Murphy's, although not very stereoselective, for developing a new "one-pot" method for the formation of the indolizidine ring. Burgess has developed a general synthesis for (+)-castanospermine analogues for broader access to new active analogues. Anzeveno's synthesis was an interesting approach and it is surprising that no further work has been reported. A notable short synthesis is that of Mootoo's, but perharps the triple reductive amination would be difficult to reproduce on a larger scale. However, none of the above syntheses stand out as possible candidates for industrial scale-up. Either the syntheses are too long, non-stereoselective or use expensive reagents which cannot be utilized on an industrial scale.

1.3 Non Carbohydrate-Based Syntheses

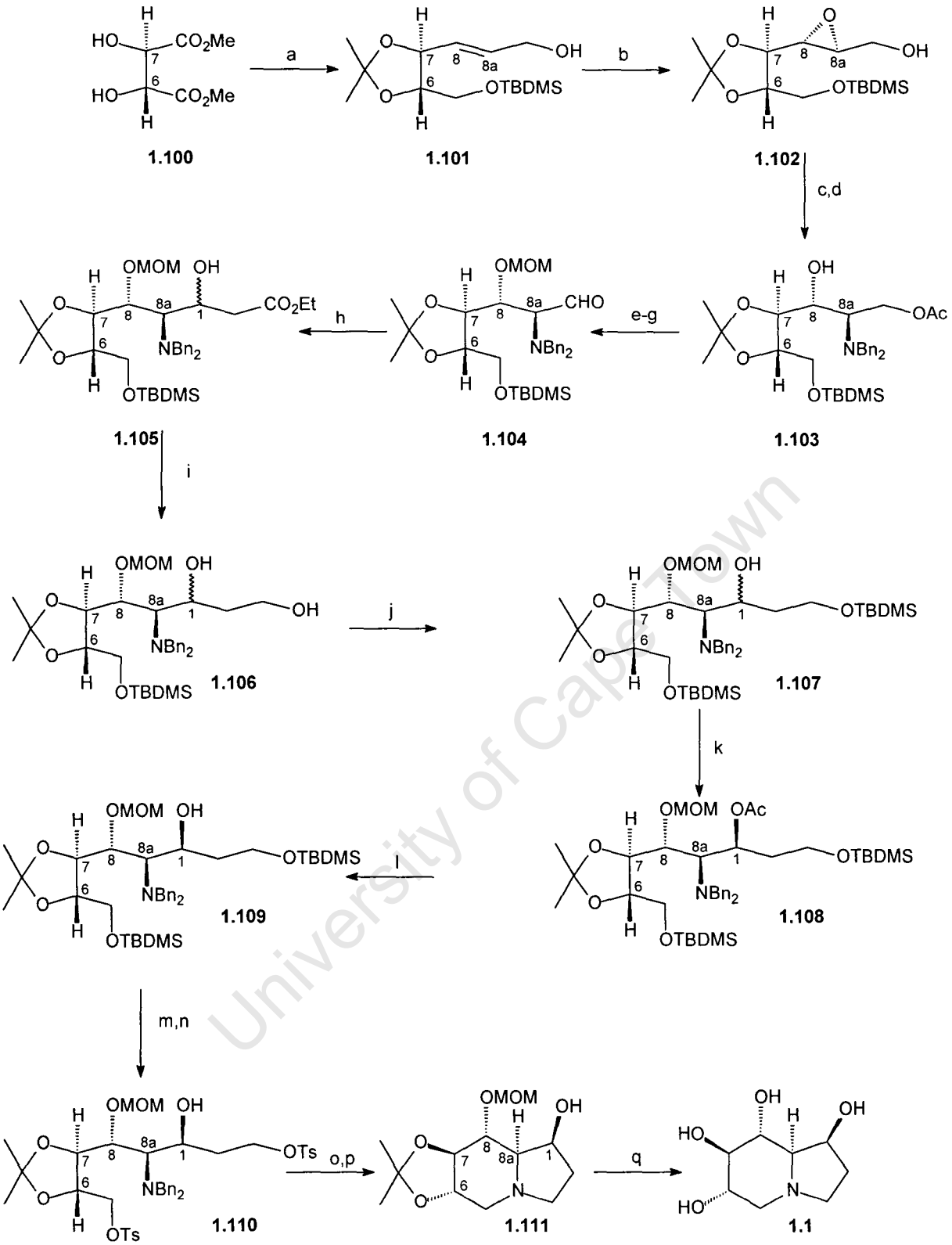
Although a large proportion of syntheses reported in the literature utilize carbohydrates as their starting material, there has recently been a trend in using other building blocks from the chiral pool. These syntheses can be placed into two categories:

- Linear-based
- Convergent-based.

1.3.1 Linear-Based Syntheses

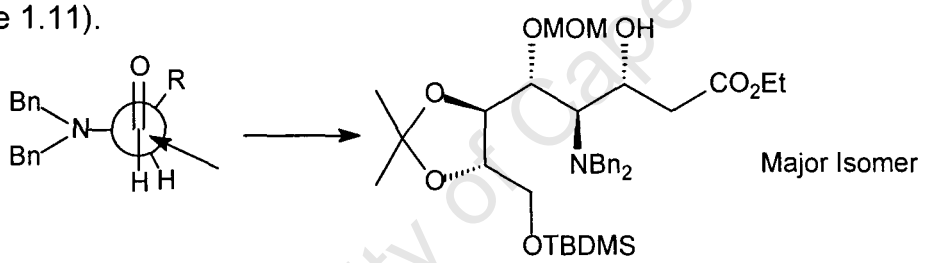
The main strategy in these syntheses is to use a chiral starting material with only one or two stereogenic centres and to build the target stepwise using asymmetric induction principles for introducing the required stereogenic centres.

The first total synthesis of (+)-castanospermine **1.1** using a chiral building block in this manner was described by Kibayashi *et. al.*[50] utilizing commercially available L-dimethyl tartrate to provide stereogenic centres C-6 and C-7 of castanospermine. Overall this is an extremely long synthesis involving a total of 20 steps (Scheme 1.22).



Scheme 1.22. *Reagents and Conditions*: a) ref 51; b) L-tartrate, Ti(O*i*-Pr)$_4$, *t*-BuOOH; c) $Et_2AlN(CH_2Ph)_2$, DCM, 72% over two steps; d) AcCl, Et_3N; e) MOMCl, *i*-Pr_2NEt, 75% over two steps; f) $LiAlH_4$; g) Swern Oxidation, 73% over two steps; h) LiHMDS, EtOAc, THF, -80°C, 92%; i) $LiAlH_4$, Et_2O; j) TBDMSCl, imidazole, DMF, 90%; k) AcOH, Ph_3P, DEAD; l) $LiAlH_4$, Et_2O, 46% over two steps; m) TBAF, THF; n) TsCl, pyridine, 60% over two steps; o) H_2, $Pd(OH)_2$, MeOH; p) Et_3N, MeOH, reflux, 78% over two steps; q) Conc HCl, MeOH, 71%.

Allylic alcohol **1.101** was synthesized in 6 straightforward steps from L-dimethyl tartrate, and subjected to a Katsuki-Sharpless asymmetric epoxidation to give **1.102** establishing the C-8 and C-8a (inverted) stereogenic centres. This was followed by the regio- and stereoselective opening of the epoxide with $Et_2AlN(CH_2Ph)_2$, resulting in the formation of stereogenic centres C-8 and C-8a with the correct functional groups attached. The regio- and stereoselectivity can be explained by the bulky nucleophile opening the epoxide in S_N2 fashion at the more accessible carbon following coordination of Al to the epoxide. The primary hydroxyl group probably biases the positioning of the aluminium so as to favour attack at C-8a. The sequence continued with selective protection of the primary alcohol as its acetate and conversion of the secondary hydroxyl to its methoxymethyl (MOM) ether. The acetate was reductively removed and the resulting alcohol oxidized under Swern conditions to aldehyde **1.104**, which underwent a stereoselective aldol with ethyl lithioacetate to give diastereomeric alcohols **1.105** (89:11) as inseparable isomers. The stereoselectivity could be rationalized by the Felkin-Ahn α-heterocarbon non-chelate model (Figure 1.11).

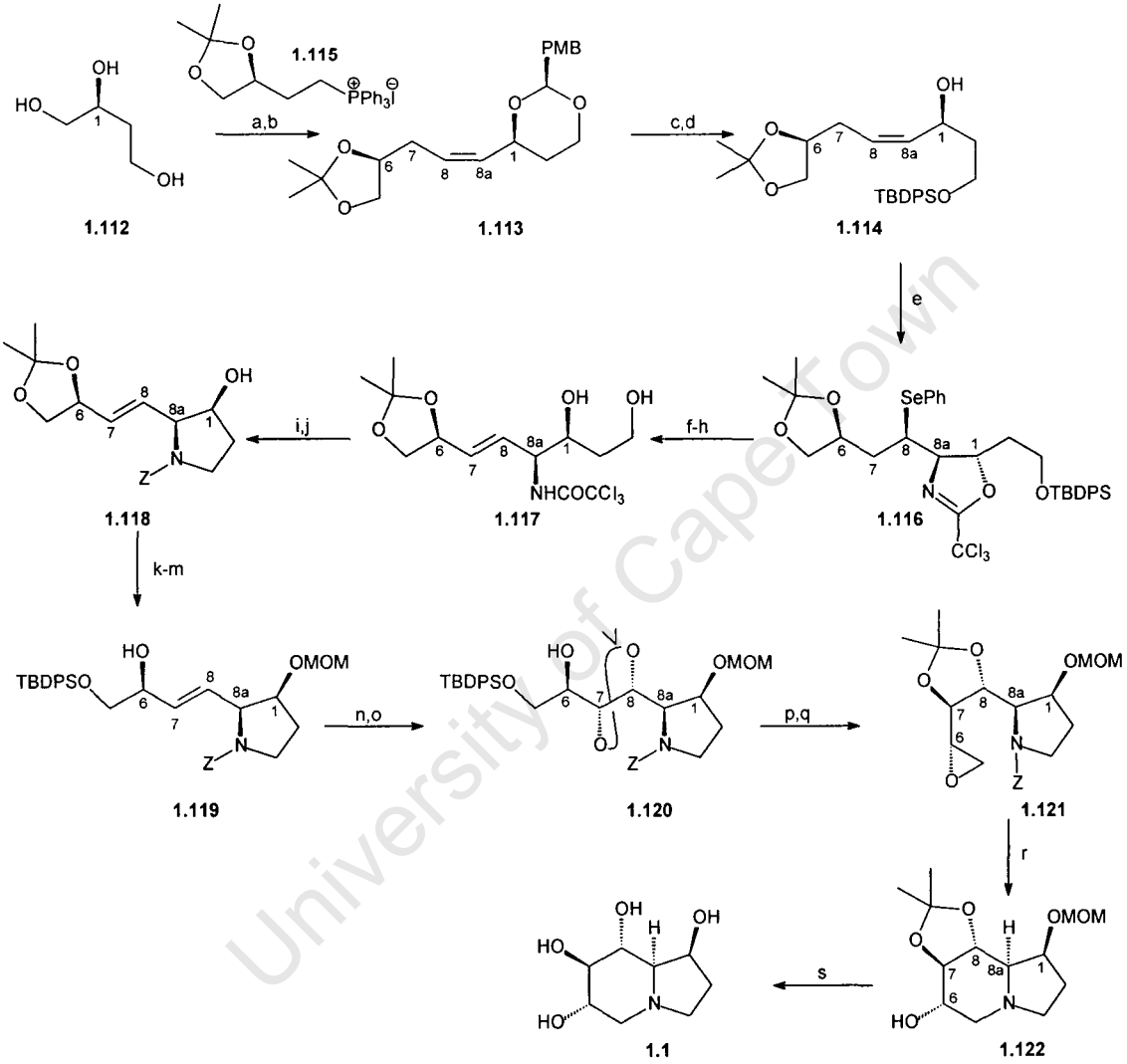


1.105

Figure 1.11

The ester of **1.105** was then reduced to diol **1.106** and the primary hydroxyl group protected as its TBDMS ether **1.107**. The diastereomers were now separable by chromatography, but the major product had the wrong configuration. This was solved by subjecting the major product to a Mitsunobu inversion reaction with acetic acid, which inverted the stereogenic centre to the correct *S*-configuration for C-1. The acetate was then reductively removed to afford alcohol **1.109**. With all of the stereogenic centres in place, the rest of the synthesis turned towards generating the indolizidine ring. The silyl groups were both removed and the resultant primary hydroxyl groups converted to tosylates. Catalytic hydrogenolytic removal of the benzyl protecting groups followed by heating in the presence of triethylamine resulted in a two-fold tandem ring-closure to the indolizidine. The final stage involved hydrolysis of the acetal and ketal protecting groups and to give (+)-castanospermine **1.1**. The major drawback of this synthesis is its length as well as the stereoselective aldol reaction, which resulted in the incorrect configuration at C-1 that had to be corrected via a Mitsunobu inversion reaction.

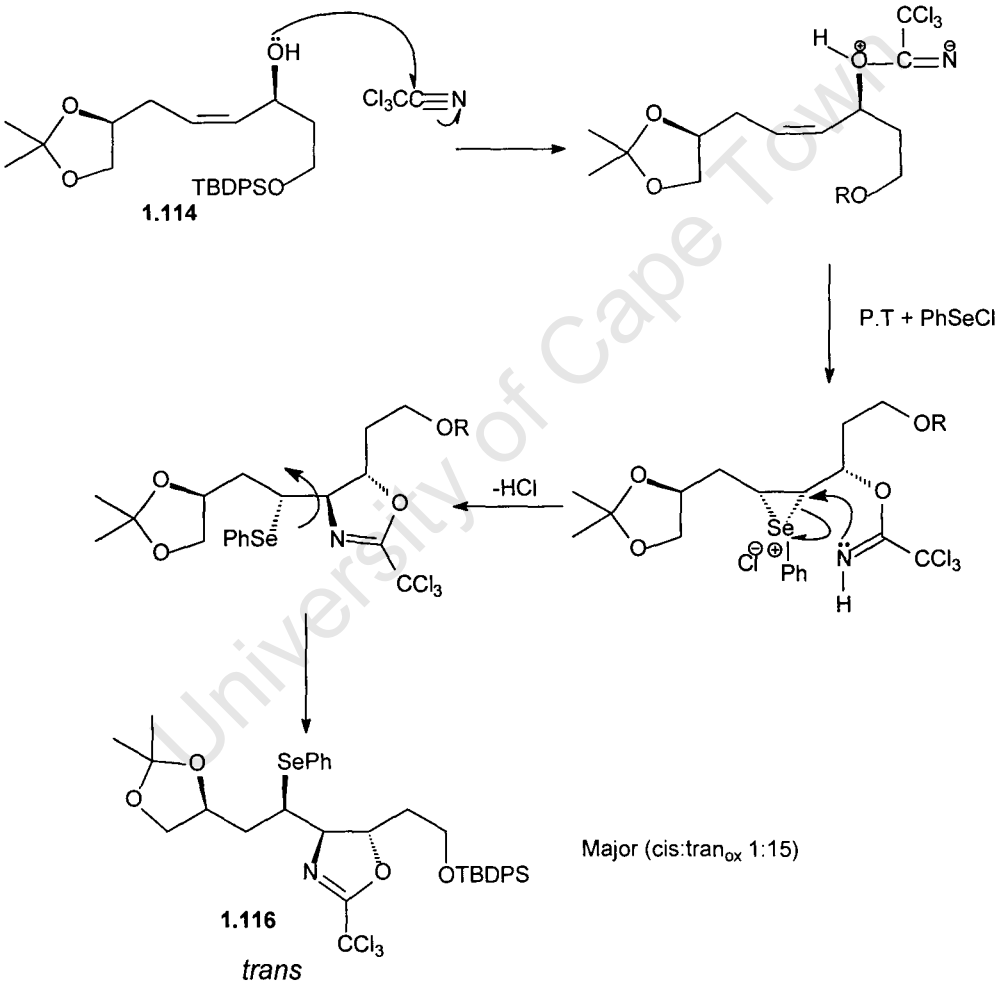
Kang *et al.*[52] described an interesting synthetic route to (+)-castanospermine **1.1** over 19 steps from readily available (*S*)-butane-1,2,4-triol, with the key step involving an unprecedented phenylselenoamidation for introducing the nitrogen and C-8a chiral centres stereoselectively. (*S*)-Butane-1,2,4-triol **1.112** provided the C-1 target stereogenic centre (Scheme 1.23), and was reacted with *p*-anisaldehyde to give a mixture of 6- and 5-membered benzylidene ketals (8:1 respectively).



Scheme 1.23. *Reagents and Conditions*: a) *p*-anisaldehyde, PPTS, PhH; b) i) Swern Oxidation; ii) **1.115**, *n*-BuLi, HMPA, THF, -78 to 0°C; c) PPTS, MeOH, 0°C; d) TBDPSCl, imidazole, DMF, DCM, -60°C; e) i) Cl_3CCN, DBU, CH_3CN; ii) PhSeCl, $Cl_3CC(OMe)NH$, Et_3N, CH_3CN, -20 to -15°C; f) PPTS, H_2O, MeOH, 20°C; g) 30% H_2O_2, THF, 0 to 20°C; h) TBAF, THF, -5 to 0°C; aq NaH_2PO_4; i) DIAD, Ph_3P, THF, 0°C; j) NaOBn, THF, 20°C; k) MOMCl, Et_3N, DCM, reflux; l) TsOH, MeOH, 20°C; m) TBDPSCl, imidazole, DMF, DCM, -60°C; n) OsO_4, NMO, H_2O, acetone 0°C; o) *p*-TsOH, acetone, 20°C; p) MsCl, DMAP, Et_3N, DCM, 20°C; q) i) TBAF, THF, 20°C; ii) 5M NaOH; r) 5% Pd/C, cyclohexene. EtOH, reflux; s) i) conc HCl, MeOH, reflux; ii) Dowex 50WX8-100 ion-exchange resin.

The primary hydroxyl group of the major component was oxidized under Swern conditions and the resulting aldehyde subjected to a Wittig-olefination reaction with the ylide of

phosphonium salt **1.115**, itself also prepared from (*S*)-butane-1,2,4-triol, to give *cis*-olefin **1.113** in a ratio of 19:1 (*Z*:*E*). Thus the chiral centres of the triol provided both the C-1 and C-6 stereogenic centres in the target. The benzylidene ketal was then selectively hydrolysed and the resultant primary hydroxyl group regioselectivily silylated to furnish silyl ether **1.114**. The stage was now set for a phenylselenoamidation reaction with Cl_3CCN in the presence of DBU followed by treatment with phenylselenyl chloride and triethylamine. Reaction proceeded via conversion of the hydroxyl group to its trichloroacetimidate, selenation of the double bond to the *epi*-selenonium followed by a regioselective, kinetically controlled 5-*exo*-*tet* cyclization to the selenated oxazoline **1.116** according to the mechanism shown in Scheme 1.24.

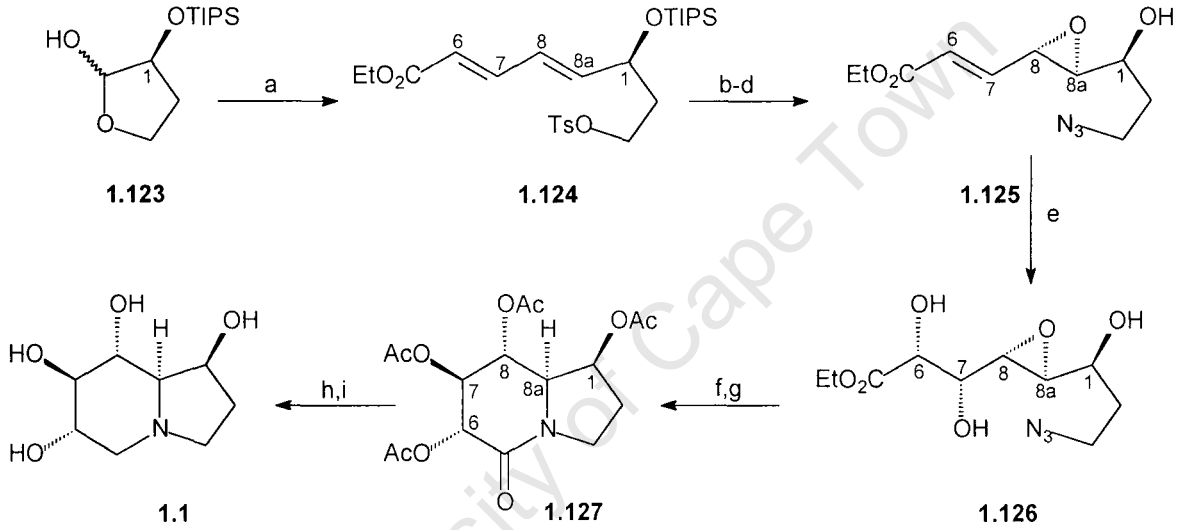


Scheme 1.24

Imperfect facial selectivity in the selenation step generated a mixture of *cis*- and *trans*-oxazolines (1:15), which were subjected to hydrolysis to give the hydroxytrichloroacetamides from which the desired (N,O) *syn*-stereoisomer (*zig-zag* conformation) was separated. Oxidative selenoxide elimination and desilylation to afford olefin **1.117**, followed by Mitsunobu cyclization gave pyrrolidine **1.118**, following exchange

of the nitrogen protecting group to its CBz carbamate via substitution with benzyloxy anion. Stereoselective installation of the C-7/C-8 hydroxyl groups was achieved via an osmium tetroxide *cis*-hydroxylation from the face *anti* to the C-6 and C-8a heteroatoms. Thereafter, conventional functional group modification and 6-*endo-tet* cyclization under the control of the C-7/C-8 acetonide as before (Park: Scheme 1.9) gave (+)-castanospermine **1.1** after protecting-group removal. This synthesis reveals a high degree of elegance in generating three new stereogenic centres with correct absolute configuration.

A concise synthesis of 9 steps involving a linear asymmetric reduction approach predominantly based on Sharpless asymmetric oxidation chemistry was described by Cha *et. al.*[53] (Scheme 1.25) in 1993.

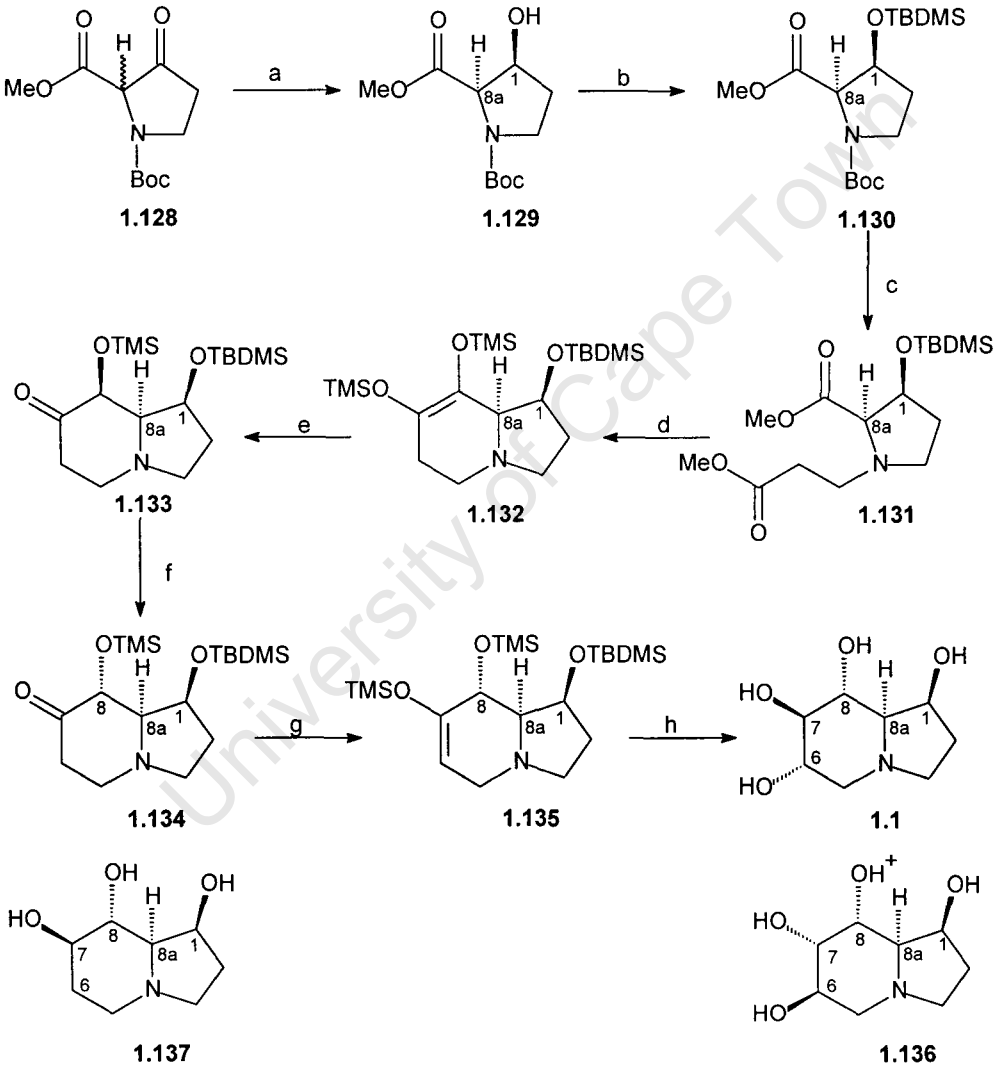


Scheme 1.25. *Reagents and Conditions*: a) i) Wittig, 41%; ii) TsCl, pyridine; b) TBAF, THF, 91%; c) (+)-Diisopropyl tartrate, *t*-BuOOH, $Ti(OiPr)_4$, 90%; d) NaN_3, DMF, 73%; e) OsO_4, $(DHQ)_2$-PHAL; f) H_2, Pd/C, EtOH, Δ; g) Ac_2O, pyridine, 13% over three steps; h) BH_3.DMS; i) NH_3, 55% over two steps.

Subjecting **1.123**, obtained in 4 steps from L-malic acid,[54] to an extended stereoselective Horner-Wadsworth-Emmons-Wittig[55] reaction gave (*E*),(*E*)-diene **1.124,** following tosylation of the primary hydroxyl group. Fluoride removal of the silyl ether followed by an asymmetric Sharpless epoxidation of the double bond allylic to the hydroxyl group, gave the anticipated epoxide with installation of stereogenic centres C-8 and C-8a. The tosylate was then converted to its azide **1.125**, which then underwent a Sharpless asymmetric dihydroxylation on the remaining double bond to give *syn*-diol **1.126**, with introduction of stereogenic centres C-6 and C-7. Finally, the azide was reduced to the amine, which cyclized to indolizidinone **1.127** (isolated as its tetraacetate) in the anticipated 5-*exo* manner on the epoxide. Reduction of the lactam and global deprotection gave (+)-castanospermine **1.1**. This is an extremely elegant, concise and highly effective synthesis,

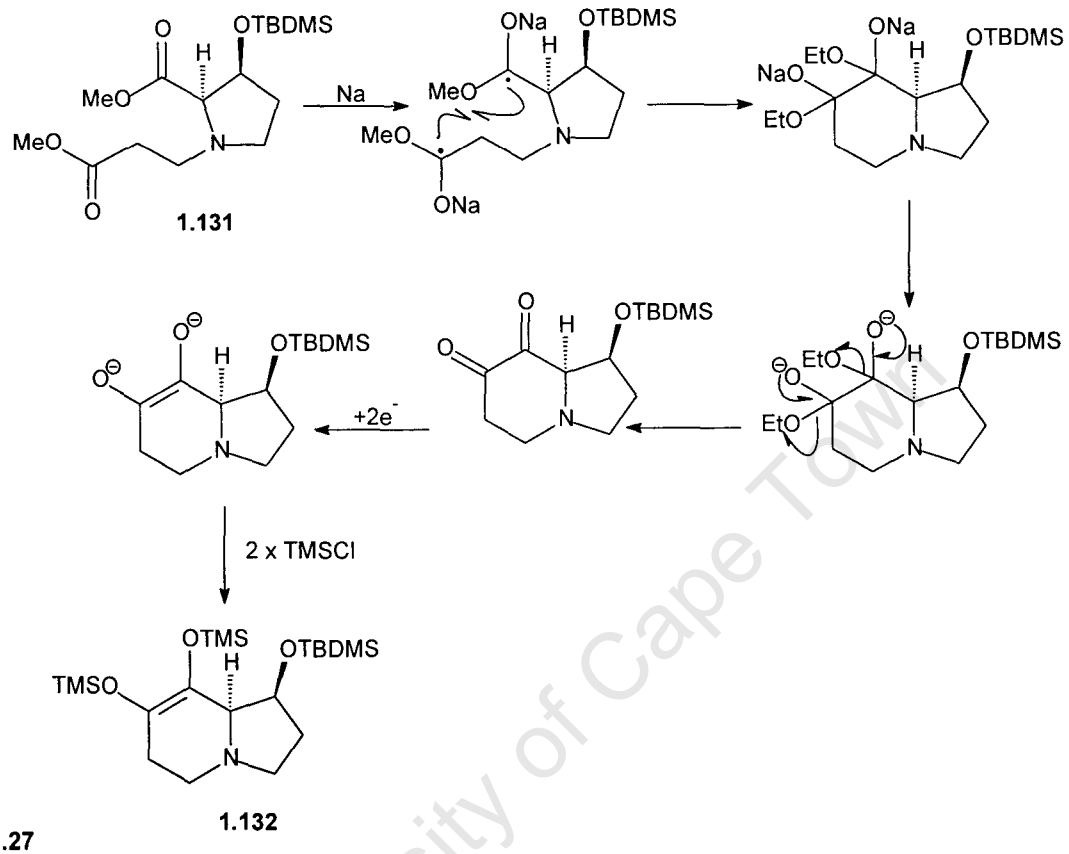
using a clever interplay of Sharpless technology to set-up four contiguous chiral centres. This is arguably one of the best syntheses of (+)-castanospermine.

In 1990, Sih *et. al.*[56] reported on the synthesis of (+)-castanospermine in 7 steps from building block **1.128** (Scheme 1.26). The first step of the synthesis was the chemoenzymatic reduction of racemic ketone **1.128** to give enantiomerically pure **1.129** in 80% chemical and 99% optical yield, to create two stereogenic centres as C-1 and C-8a of the target with correct configuration for (+)-castanospermine. Reduction proceeds stereoselectively and with kinetic resolution at C-8a. Racemisation of the unreacted (*S*)-enantiomer followed by reduction channelled all the material through to **1.129**.



Scheme 1.26. *Reagents and Conditions*: a) *Dipodascus sp*, 72 h, 80%; b) TBDMSCl, imidazole, DCM, 96%; c) i) TFA, DCM (20% v/v); ii) Et_3N, methyl acrylate, EtOH, 95% over two steps; d) Na, TMSCl, toluene, reflux, 75%; e) glacial HOAc, NaOAc (10%), 31%; f) DBU, DCM, 56%; g) TMSCl, LiHMDS, -78°C, THF; h) i) BH_3.DMS, THF, -78°C to rt; ii) Me_3NO, toluene, Δ.

Protection of the secondary hydroxyl group of **1.129** as its silyl ether, followed by hydrolysis of the carbamate and Michael addition of the resulting amine to methyl acrylate gave ether **1.131**. This was followed by an acyloin condensation[57] to afford indolizidine **1.132**, the mechanism of which is shown in Scheme 1.27.

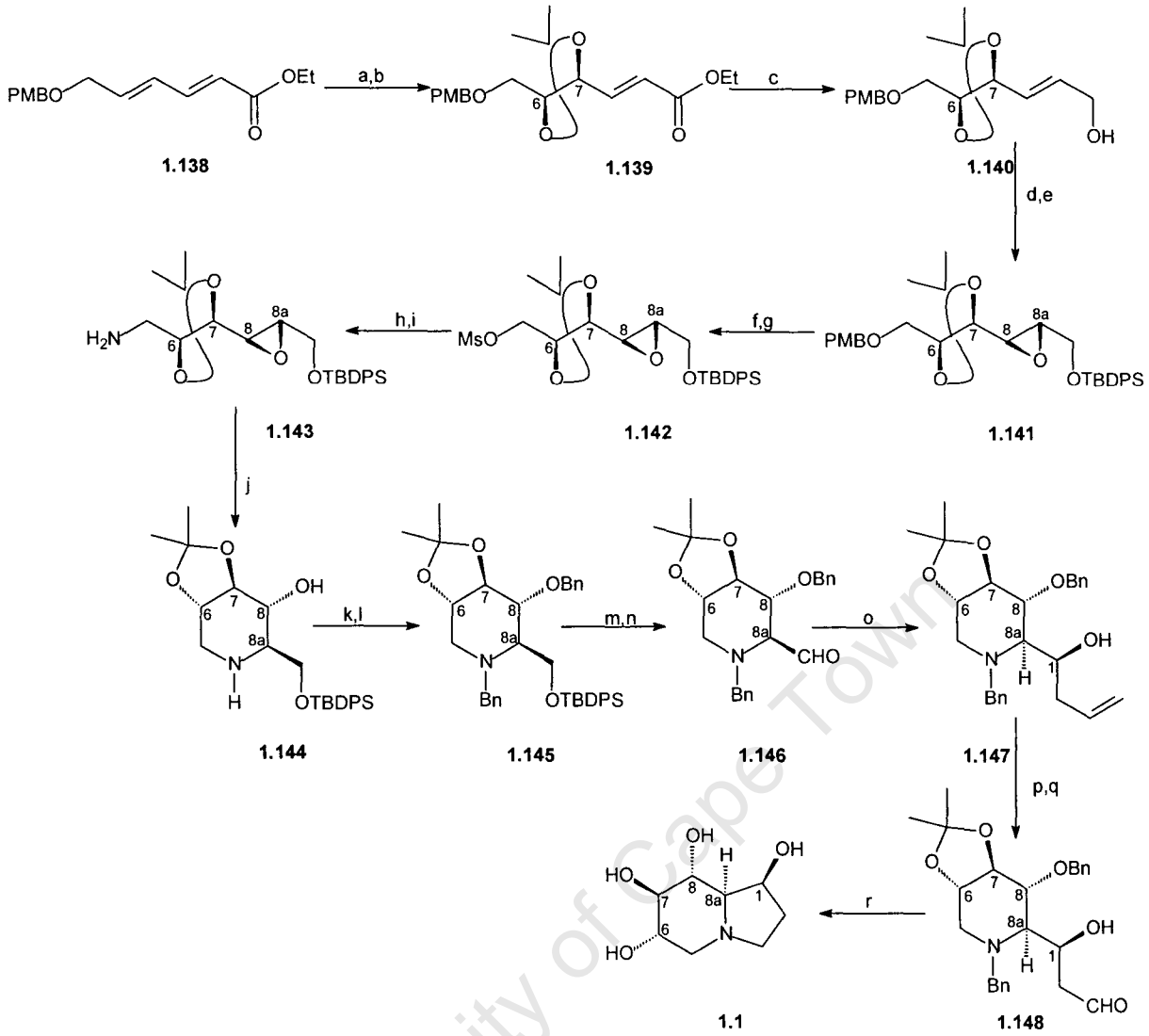


1.131 **1.132**

Scheme 1.27

Thereafter, regioselective hydrolysis of the C-7 silyl enol ether **1.132** gave ketone **1.133** (Scheme 1.26). Stereogenic centre C-8 was then epimerized under basic conditions to give ketone **1.134**. The final couple of steps of the synthesis involved formation of the silyl enol ether of the ketone carbonyl group in a regioselective manner (C-6) followed by stereoselective hydroboration and a subsequent oxidative work-up to give (+)-castanospermine **1.1**, and its isomer 6,7-di*epi*-castanospermine **1.136**. 6-Deoxy-castanospermine **1.137** could be obtained by stereoselective reduction of **1.134**.

Finally, Somfai *et al.*[58] has reported an efficient stereoselective (+)-castanospermine synthesis from an acyclic dienyl ester starting material **1.138**. As with Cha's synthesis (Scheme 1.25), it makes extensive use of Sharpless oxidation technology (Scheme 1.28).

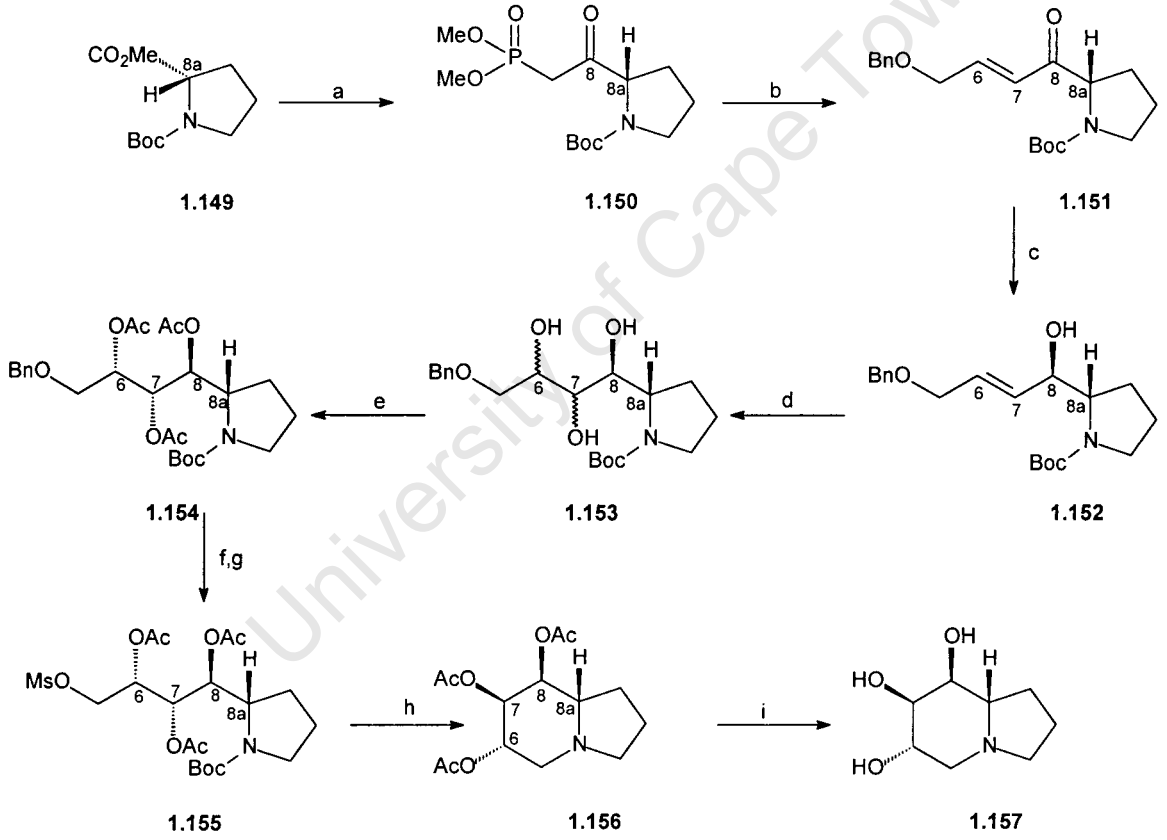


Scheme 1.28. *Reagents and Conditions*: a) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 80%; b) 2-methoxypropene, *p*-TsOH (cat), DMF, 97%; c) DIBAL, -78°C, DCM, 93%; d) (+)-Diisoproyl tartrate, Ti(O*i*-Pr)$_4$, *t*-BuOOH, DCM, -20°C; e) TBDPSCl, Et_3N, DMAP, DCM, 97%; f) DDQ, DCM, H_2O, 92%; g) MsCl, *i*-Pr_2NEt, DCM, 100%; h) NaN_3, DMF, 70°C, 91%; i) Ph_3P, THF, H_2O, 83%; j) EtOH, heat, 100%; k) KHMDS, BnBr, THF, -78°C, 82%; l) BnBr, K_2CO_3, CH_3CN, heat, 97%; m) TBAF, THF, 100%; n) Swern Oxidation, 93%; o) CH_2=$CHCH_2SiMe_3$, $TiCl_4$, DCM, -65°C, 71%; p) OsO_4, NMO, *t*-BuOH:THF:H_2O (10:3:1); q) $NaIO_4$, $NaHCO_3$, THF:H_2O (1:1), 84%; r) i) H_2, Pd/C; ii) TFA, 81%.

Thus, enantioselective Sharpless dihydroxylation of the γ,δ-olefinic bond in **1.138** gave the *syn*-diol, which was subsequently protected as its acetonide **1.139**. Chemoselective reduction of the ester with DIBAL to the allylic alcohol **1.140** was followed by a Sharpless asymmetric epoxidation and protection of the hydroxyl group as its silyl ether **1.141**. Three of the stereogenic centres were now in place for castanospermine as C-6, C-7 and C-8, while C-8a awaited an inversion. This was achieved following conversion of the primary PMB-ether **1.141** to the amine, which underwent a 6-*endo-tet* cyclization to **1.144** with the required inversion of stereochemistry at C-8a. The regiochemistry (6-*endo* favoured over

5-*exo*) was controlled by the acetonide as seen before in an earlier syntheses (Park: Scheme 1.9 and Kang: Scheme 1.23) to avoid formation of a *trans*-fused bicyclic [3.3.0] nonane system. Thereafter, conversion of **1.144** to target involved a conventional sequence of reactions encountered in previous syntheses, the key step being a stereoselective allyl-addition to aldehyde **1.146** followed by alkene cleavage to **1.147** and reductive amination to cyclize. Deprotection afforded (+)-castanospermine **1.1** in an overall 13% yield and in 19 steps.

The following series of synthetic routes describe syntheses of (+)-castanospermine stereoisomers Another approach from a common building block was described by Koskinen *et al.*[59] In this case, the target was 1-deoxy-8,8a-di*epi*-castanospermine and they utilized L-proline (*S*) to provide stereogenic centre C-8a in the target with the opposite configuration to that in (+)-castanospermine (Scheme 1.29).

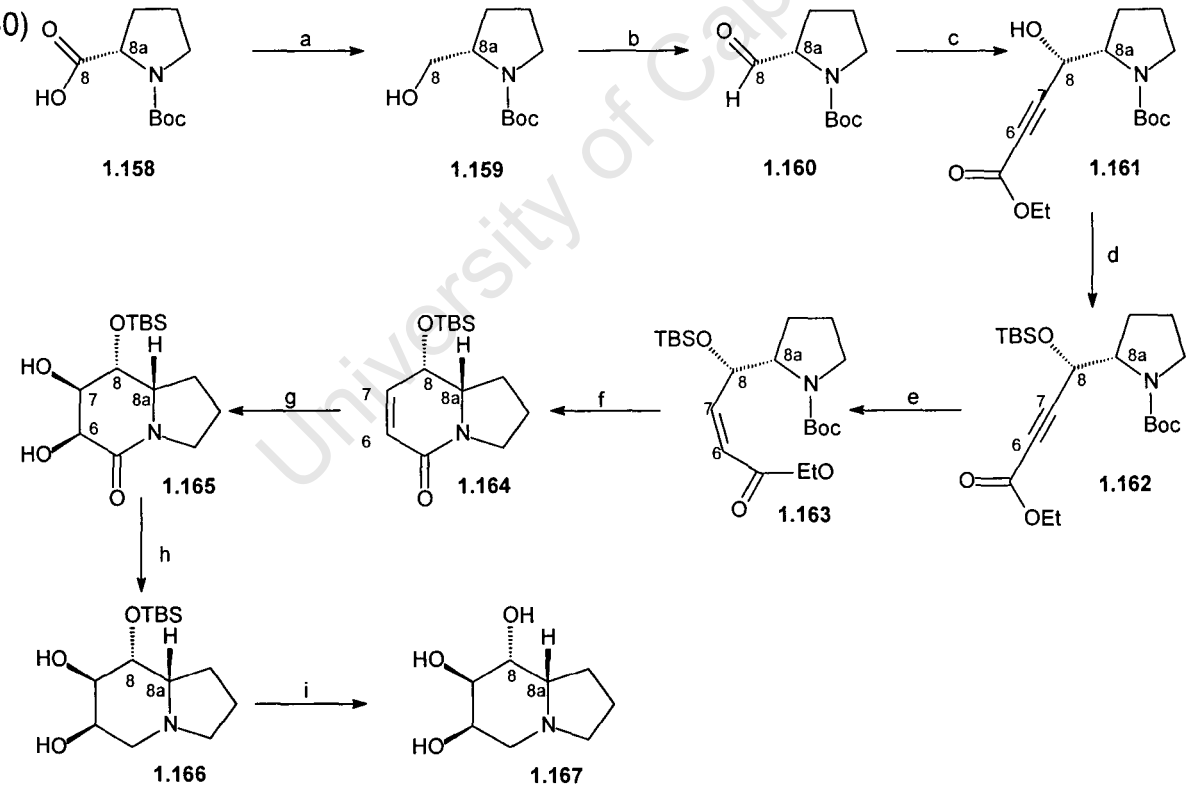


Scheme 1.29. *Reagents and Conditions*: a) *n*-BuLi, DMMP, THF, -78°C, 85%; b) $BnOCH_2CHO$, K_2CO_3, CH_3CN; c) $NaBH_4$, $CeCl_3.9H_2O$, MeOH; d) OsO_4, cat NMO, acetone, H_2O, 74%; e) Ac_2O, pyridine, DMAP, 96%; f) H_2, Pd/C, MeOH, 96%; g) MsCl, Et_3N; h) i) TFA, DCM; ii) Et_3N, CH_3CN, 50% over two steps; i) NaOMe, MeOH, 77%.

Thus, L-proline (as its *N*-Boc methyl ester) was converted to its phosphonate under Heathcock and von-Geldern conditions[60] using dimethyllithiomethylphosphonate. The resulting phosphonate was subjected to a Horner-Wadsworth-Emmons[55] olefination to

produce ketone **1.151** under conditions previously described by these researchers. Stereoselective reduction of the ketone carbonyl group to provide C-8 of the target proved to be challenging. Eventually it was established that the Lüche conditions[61,62] of $NaBH_4$, $CeCl_3.9H_2O$ in methanol furnished a product in high yield and with the correct (*R*)-configuration. The sequence continued with a *cis*-hydroxylation to the triol **1.153** in a ratio of 6:2 with the major isomer resulting from attack on the *Si*, *Si* (top) face. This was converted to its triacetate **1.154**, which was then debenzylated and the resulting hydroxyl group mesylated followed by cyclization via *N*-Boc removal to afford indolizidine **1.156**. Finally, the acetates were hydrolysed to furnish (+)-1-deoxy-8,8a-di*epi*-castanospermine **1.157**. This was a short synthesis in a fairly low overall yield of 7.4% over 9 steps.

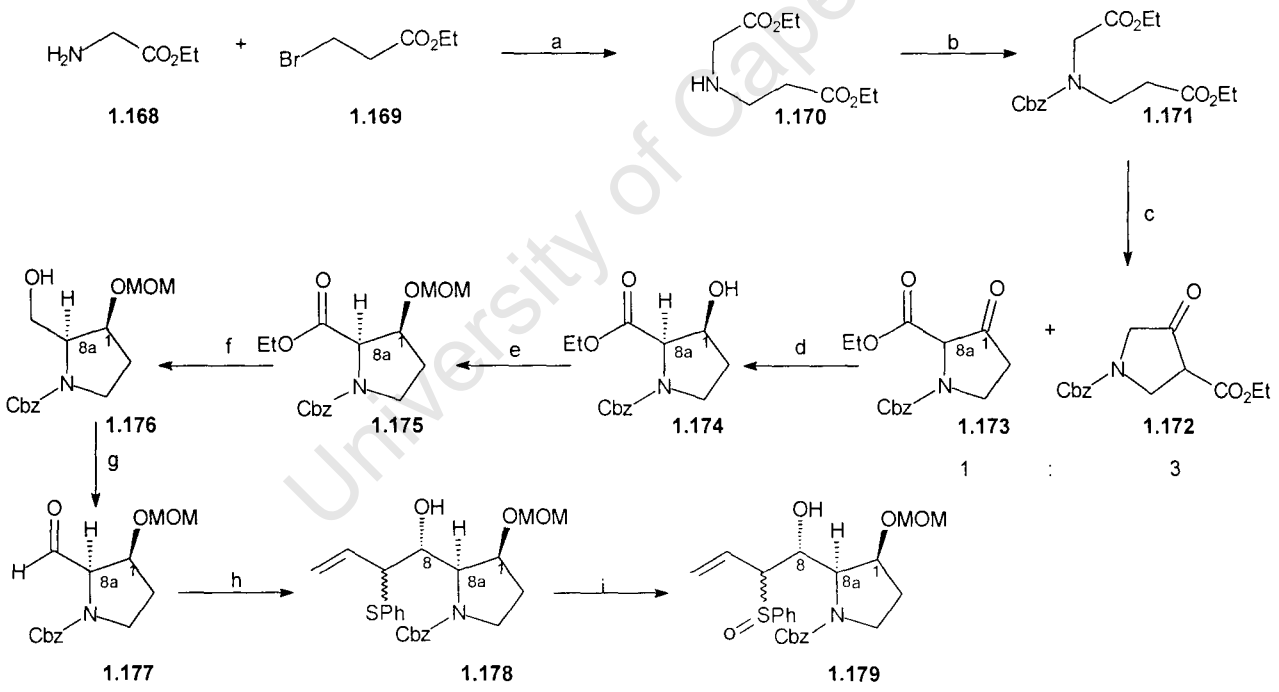
A concise synthesis of 1-deoxy-6,8a-di*epi*-castanospermine was reported recently in the literature by Zhao *et al.*[63] The synthesis began with the commercially available *N*-Boc proline **1.158**, which as before provided stereogenic centre C-8a with opposite configuration to that found in castanospermine. **1.158** was reduced to give alcohol **1.159** and subsequently oxidized under Swern conditions to afford aldehyde **1.160** (Scheme 1.30)



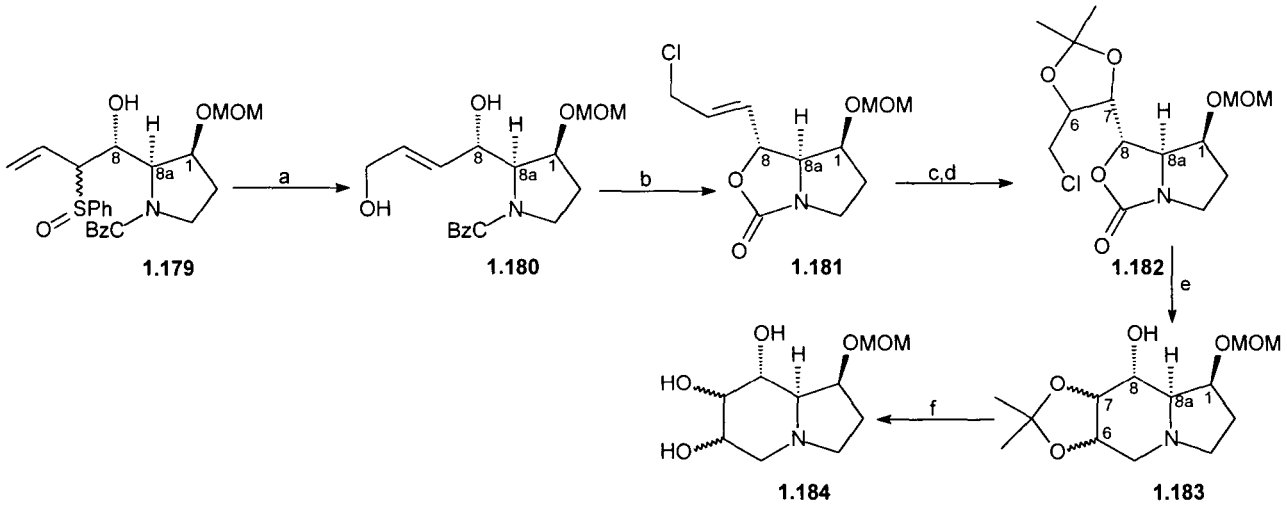
Scheme 1.30. *Reagents and Conditions*: a) BH_3.DMS, THF, 99%; b) Swern Oxidation, 95%; c) Ethyl propiolate, Ti(O-*i*Pr)$_4$) THF, -78°C, 80%; d) TBDMSCl, imidazole, DCM, 98%; e) H_2, Lindlar's Catalyst, 1 atm, quinoline, MeOH, 96%; f) i) TFA, DCM; ii) Et_3N, DCM, 61%; g) OsO_4, NMO, acetone / H_2O (10:1), 88%; h) i) BH_3.DMS, THF; ii) EtOH, reflux, 95%; i) TBAF, THF, 90%.

The aldehyde **1.160** was then subjected to an addition with ethyl propiolate to create the C-8 stereogenic centre, which resulted in a mixture of chromatographically separable alcohols (2.5:1.0). The hydroxyl group was then protected as its silyl ether, which was followed by partial *cis*-hydrogenation of the triple bond with Lindlar's catalyst to give a *Z*-double bond. This was followed by hydrolysis of the carbamate, which resulted in subsequent cyclization to the indolizidine **1.164**, which underwent a stereoselective *syn*-dihydroxylation with OsO_4, in which dihydroxylation occurred from the *exo*-face of the double bond. The final stages of the synthesis involved the reduction of the lactam followed by hydrolysis of the silyl ether to furnish the desired target. This is a concise and elegant synthesis.

Similarly, Chan *et. al.*[64] described the total synthesis of (+)-8-*epi*- and 6,7,8-tri*epi*-castanospermine from commercially available ethyl glycinate over 16 steps, via synthesis of pyrrolidine **1.173** using a Lacey-Dieckmann condensation[65] (Scheme 1.31 and Scheme 1.32).

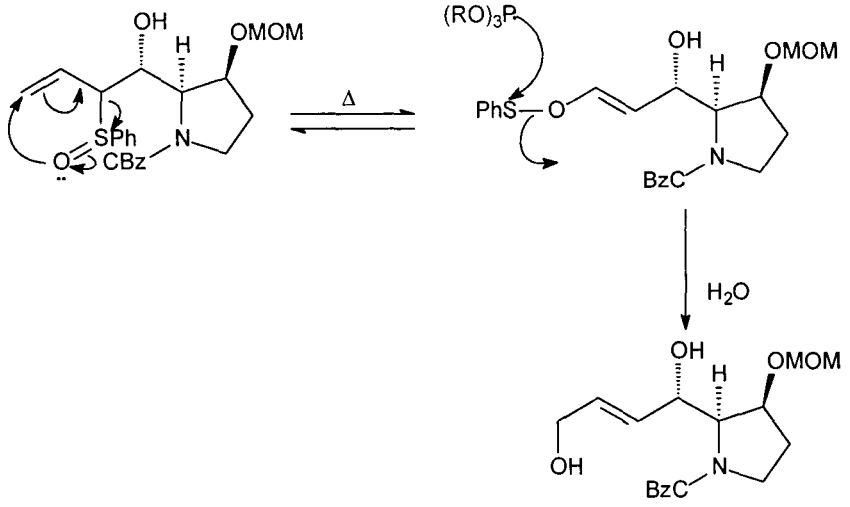


Scheme 1.31. *Reagents and Conditions*: a) Benzene, reflux, 63%; b) CBzCl, CH_3CN, 80%; c) potassium *t*-butoxide, toluene; d) Baker yeast, 45%; e) MOMCl, DCM, *i*-Pr_2NEt, 92%; f) $LiBH_4$, Et_2O, 72%; g) Swern Oxidation; h) Allyl phenyl sulfide, *n*-BuLi, $Ti(OPr)_4$, THF, 72%; i) m-CPBA, DCM.



Scheme 1.32. *Reagents and Conditions*: a) $P(OMe)_3$, MeOH, 72% over two steps; b) Ph_3P, CCl_4 : DCM (4:1), K_2CO_3, 70%; c) OsO_4, NMO, acetone : water : *t*-BuOH, 99%; d) $(MeO)_2CMe_2$, acetone, CSA, 77%; e) NaOH, MeOH : H_2O, 98%; f) i) 6M HCl : water : THF (4:4:2); ii) Amberlyst A-26 ion exchange resin (OH^- form).

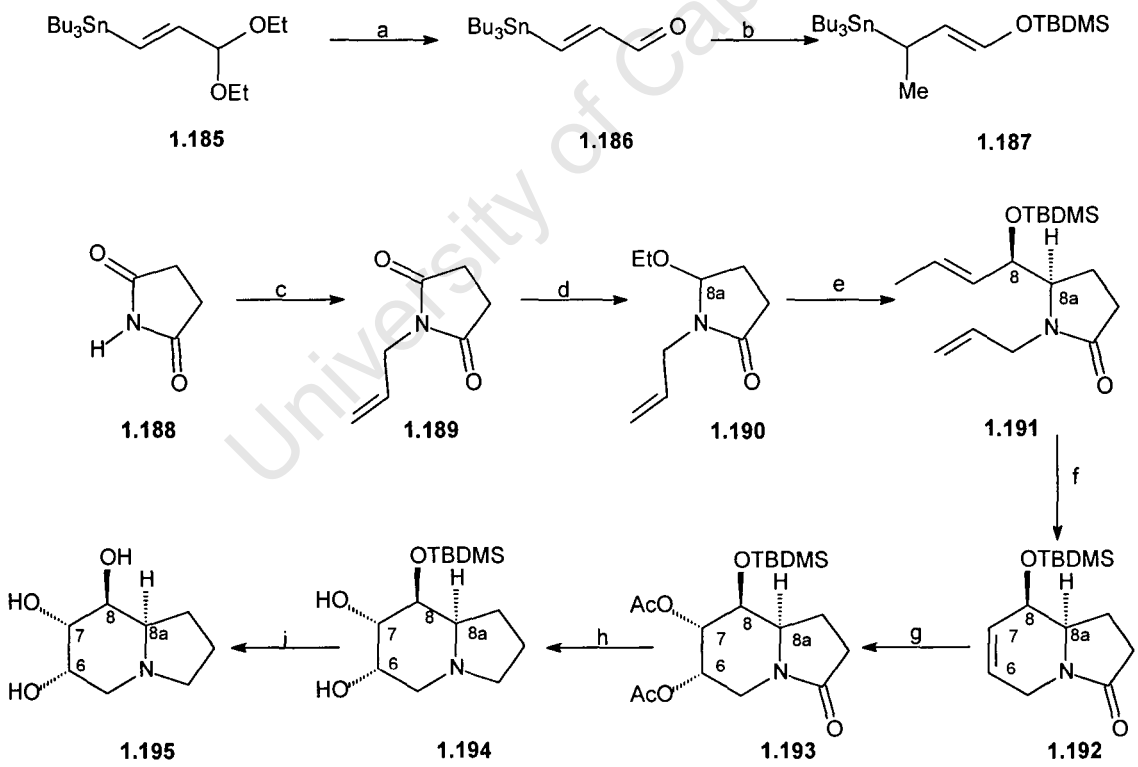
The minor isomer **1.173** of the cyclization was then reduced enzymatically to give β-hydroxyester **1.174** in a similar fashion to Sih's synthesis (Scheme 1.26) and the secondary hydroxyl group then protected as its MOM ether. Reduction of the ester to the alcohol, followed by oxidation under Swern conditions gave aldehyde **1.177** containing the stereogenic centres C-1 and C-8a with correct configurations. Pyrrolidinone **1.177** was coupled with the allyltitanate reagent from allyl phenyl sulfide in a stereoselective fashion to give one stereoisomer at C-8. The stereoselectivity could be rationalized using a Felkin-Ahn chelate model along the lines described previously. The resulting sulfide was then oxidized to its sulfoxide and subjected to an Evans-Mislow sulfoxide/sulfenate rearrangement with interception of the latter by phosphite to afford the corresponding *E*-olefin **1.180**. The mechanism of this rearrangement is shown in Scheme 1.33.[66]



Scheme 1.33

Thereafter, conversion of the two hydroxyl groups to their oxyphosphonium salts with PPh_3/CCl_4 gave an interesting product outcome as oxazolidinone **1.181**, in which the terminal oxyphosphonium ion had been substituted by chloride, while the secondary one had been intercepted by the Boc carbamate with subsequent loss of *t*-butyl. Noteworthy is the inversion of configuration at C-8 (target) to ensure the correct stereogenicity in the target (8-*epi*-castanospermine series). Thereafter, *syn*-hydroxylation of **1.181** gave a mixture of inseparable diols, which were converted to their acetonides and separated (5:3 ratio). The major isomer was hydrolysed (base) to the amine, which spontaneously cyclized to give indolizidine **1.183**. Final acidic deprotection gave the target. This interesting approach involves some elegant chemistry, but suffers from being long and having low regio- and stereoselectivity in key steps.

Another, more efficient approach, proceeding via a pyrrolidinone was reported by Quintard *et. al.*[67] to give racemic 1-deoxy-7,8a-di*epi*-castanospermine. The key step of the synthesis involved the stereoselective addition of a γ-silyloxyallyltributylstannane to an α-ethoxy lactam (Scheme 1.34).

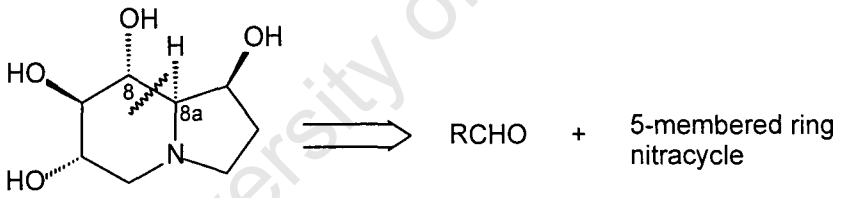


Scheme 1.34. *Reagents and Conditions*: a) SiO_2, H^+/H_2O, DCM; b) i) $Me_2Cu(CN)Li_2$, HMPA; ii) TBDMSCl, THF, -78°C; c) PPh_3, DEAD, CH_2=$CHCH_2OH$, THF, 82%; d) $NaBH_4$, EtOH, 65%; e) i) $BF_3.OEt_2$, DCM, -78°C; ii) **1.187**; f) Grubbs' catalyst, DCM, Δ, 81% over two steps; g) i) OsO_4, NMO; ii) Ac_2O, pyridine, 93%; h) BH_3.DMS, THF, 88%; i) TBAF, THF, 95%.

Thus, succinimide **1.188** was alkylated under Mitsunobu conditions to give imide **1.189**, which was then reduced to give the α-ethoxy lactam **1.190**. The stage was now set for the key step involving reaction with γ-silyloxyallyltributylstannane **1.187**, prepared in a single step from β-tributylstannylacrolein via a 1,4 conjugate addition of a cyanocuprate. The substitution proceeded via the acyliminium ion of the lactam and was diastereoselective regarding the creation of the C-8/C-8a centres as well as *E*-stereoselective on the double bond to give key intermediate **1.191**. Without any purification, **1.191** was subjected to a ring-closing metathesis with Grubbs' catalyst (2nd generation) to give indolizidine **1.192**. Thereafter, stereoselective *syn*-dihydroxylation, lactam reduction and desilylation of the silyl ether gave (±)1-deoxy-7,8-di*epi*-castanospermine **1.195**. This was a concise, efficient targeted synthesis with an overall yield of 34% over 8 steps.

1.3.2 Convergent Syntheses

There has been a series of syntheses reported which utilize a convergent strategy, *i.e.* bringing together two advanced fragments to synthesize (+)-castanospermine. Given its structure (Figure 1.11), most, but not all of the strategies have involved C-8/C-8a bond construction via a 5-membered ring hetereocycle adding to an aldehyde.



1.1

Figure 1.11

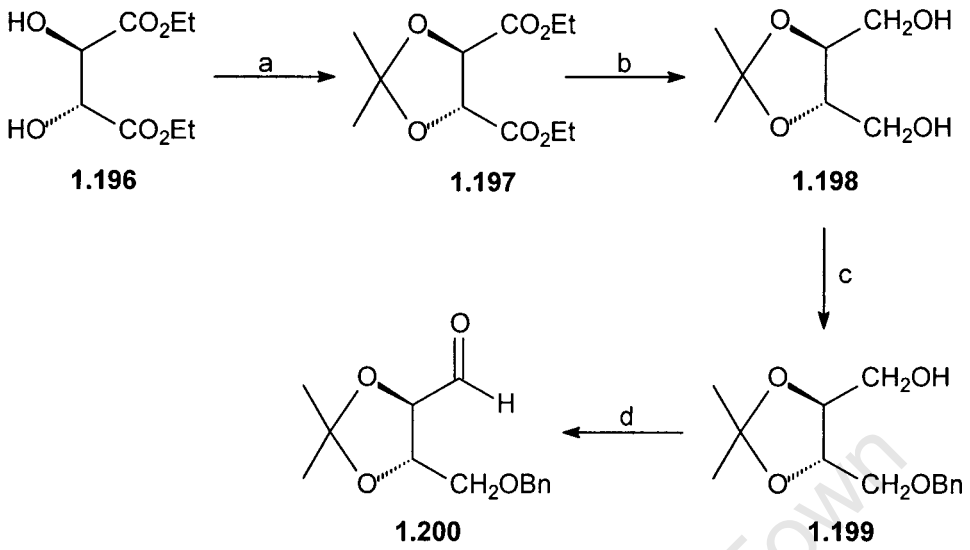
The syntheses can be subdivided into three main categories depending upon the type of character at C-8a

- Carbanionic C-8a
- Silyl dienol ether chemistry at C-8a
- Electrophilic C-8a

1.3.2.1 Carbanionic C-8a

The first research group reporting on this type of methodology was Mukaiyama *et. al.*[68] back in 1990. Although he did not report on the synthesis of (+)-castanospermine itself, he extensively explored stereoselective C-C bond-forming reactions on a chiral sugar building block for the synthesis of unnatural sugars or "rare" sugars. For this exploration, they used the known tartrate-based aldehyde **1.200**, which is readily available in four straightforward

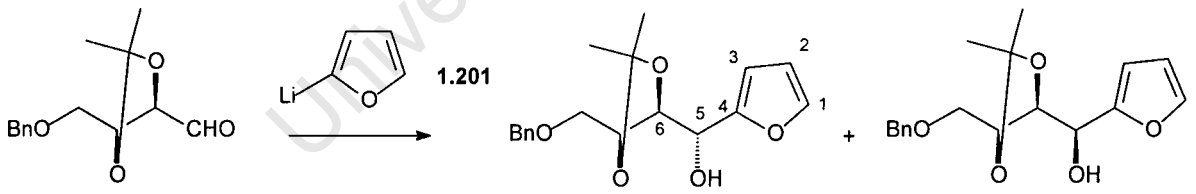
steps from L-diethyl tartrate (Scheme 1.35) and will be referred to as the Mukaiyama aldehyde.[69]



1.196 **1.197** **1.198** **1.199** **1.200**

Scheme 1.35. *Reagents and Conditions*: a) $(MeO)_2CMe_2$, *p*-TsOH, 96%; b) $LiAlH_4$, 85%; c) NaH, DMF, BnBr, 72%; d) Swern Oxidation, 88%.

Of particular interest was the diastereoselectivity of addition to the carbonyl group of **1.200**. Thus, when 2-furyllithium **1.201** was reacted with **1.200**, the addition-adduct was achieved in high chemical yield but very moderate diastereoselectivity ((5,6)-*anti / syn* : 63/37). However, when the reaction was carried out in the presence of the mild Lewis acid $ZnBr_2$, the (5,6)-*anti /syn* ratio leapt to a very respectable 98/2 (Scheme 1.36).



1.200 **1.202** 5,6-*anti* (*erythro*) **1.203** 5.6-*syn* (*threo*)

Scheme 1.36. *Reagents and Conditions*: i) THF, -78°C, 97%, *anti / syn* 63/37; ii) $ZnBr_2$, THF, 0°C, 97% *anti / syn* 98/2.

The results with $ZnBr_2$ were explained by Mukaiyama in terms of a Felkin-Ahn β-chelate model, which is depicted below (Figure 1.12), in which the Lewis acid chelates the β-oxygen of the ketal rather than the more common one α- to the carbonyl oxygen. In keeping with Felkin-Ahn transition-state models, the α-oxygen of the ketal is placed perpendicular to the C=O π-bond in order to maximize overlap of σ* with the π* of the carbonyl group to create a lower-lying π*- LUMO for donation into by the nucleophile.

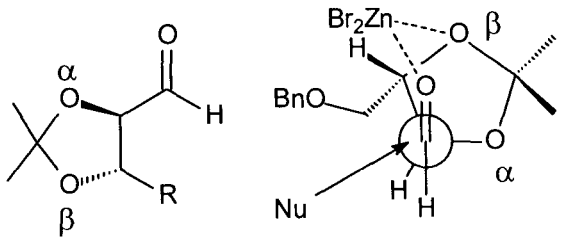
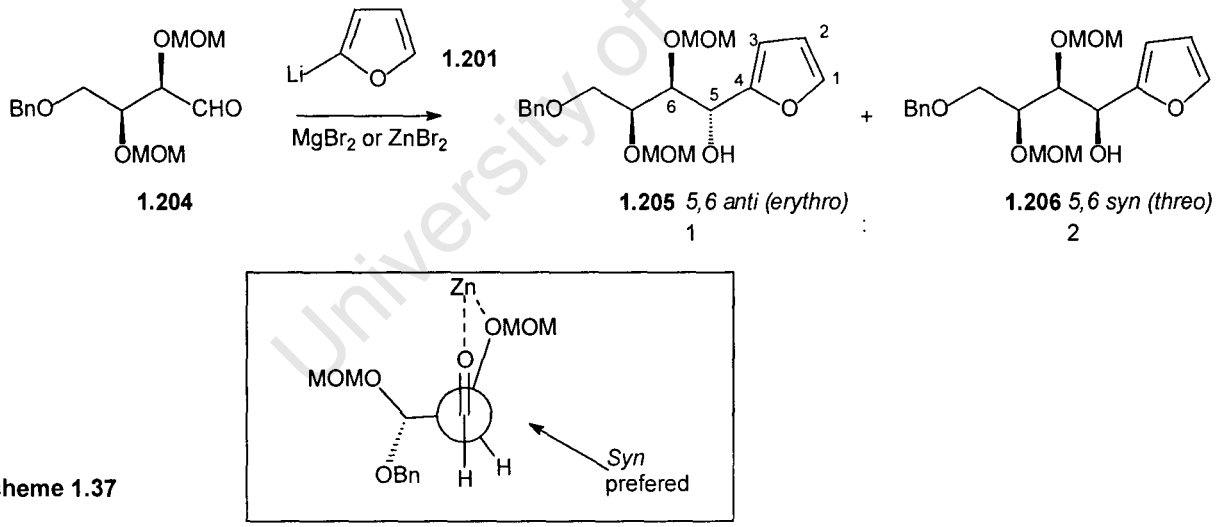


Figure 1.12

Anti-**1.202** was then transformed to L-tagatose. The group also explored the allylation of aldehyde **1.200** with other nucleophiles such as diallyltin(IV) dibromide, which also resulted in high (5,6)-*anti (erythro)* stereoselectivity. From this work it can be concluded that the aldehyde is generally promoting an *anti (erythro)* facial approach via a β-chelate.

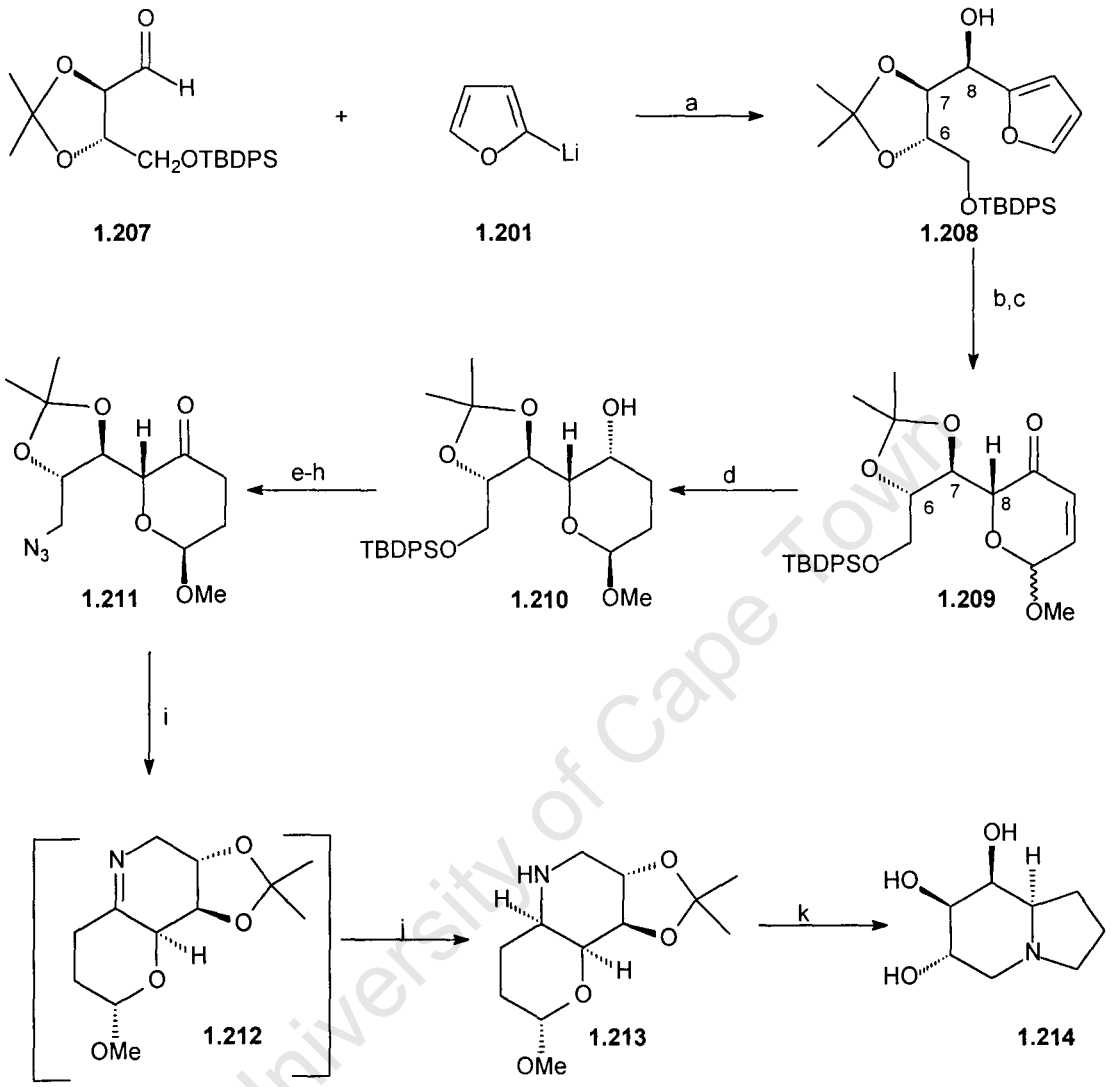
With this information in hand, Martin *et al.*[70,71] in 1993 embarked on a synthesis of (+)-castanospermine. Cognizant that the β-chelate result gives the wrong configuration for C-8 of castanospermine, Martin first attempted the addition of 2-furyllithium **1.201** to aldehyde **1.204** in the hope of forming the α-chelate for producing a (5,6)-*syn(threo)*-adduct (heterocycle numbering) with the correct configuration for (+)-castanospermine. The idea was that using a bis-MOM protection would switch the transition state to a normal α-chelate mode (Scheme 1.37).



Scheme 1.37

The reaction resulted indeed in the preferred formation of the desired 5,6-*syn*-product, but in modest stereoselectivity (*syn : anti* 2:1). Martin concluded from this result that both the Lewis acid and the hydroxyl protecting groups play an important role in the diastereoselectivity of the reaction. They reasoned that if the transition-state with the Mukaiyama aldehyde involved a β-chelate with zinc, then exchanging the benzyl group on the γ-hydroxyl with a bulkier protecting group, i.e. *tert*-butyldiphenylsilyl **1.207**, might favour the addition via an α-chelate to provide the *syn*-adduct (Sheme 1.38). Unfortunately for

Martin, though, the addition of 2-furyllithium to aldhyde **1.207** resulted in the formation of the 7,8-*anti (eythro)*-adduct (castanospermine numbering) as before with benzyl and so Martin decided to complete the synthesis of 1-deoxy-8-*epi*-castanospermine.

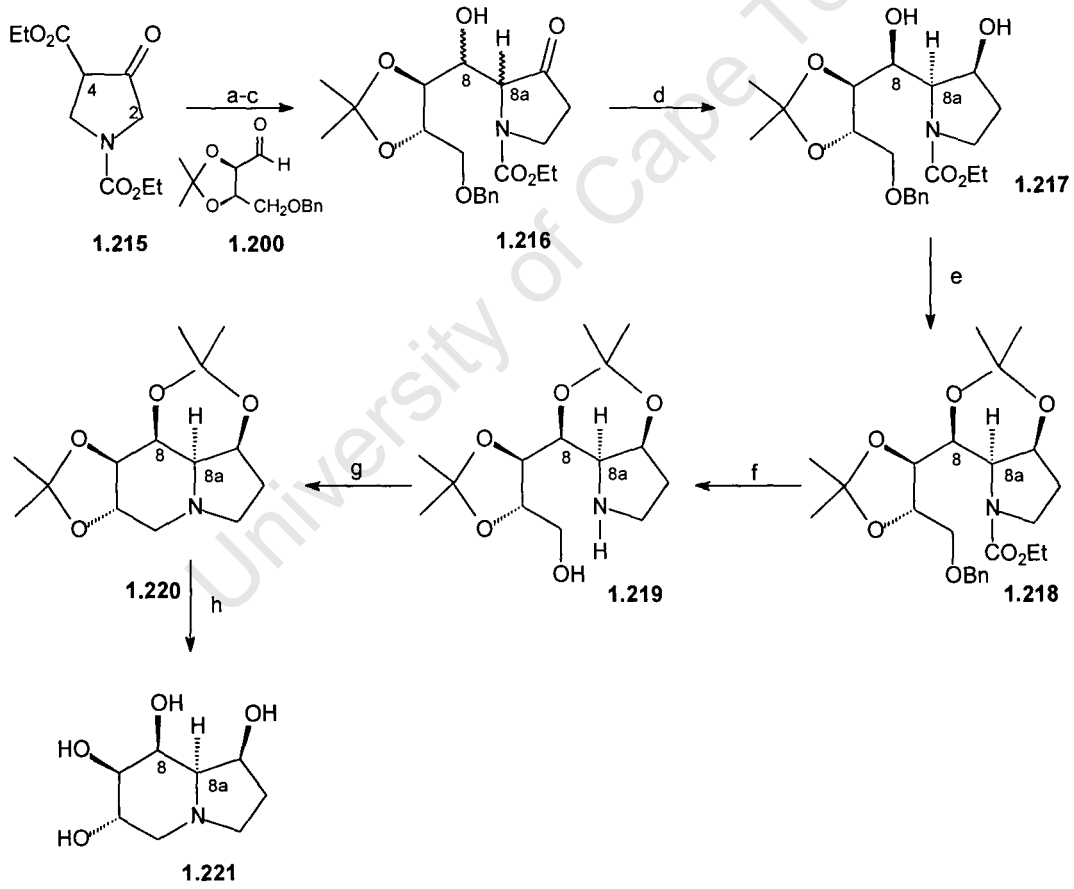


Scheme 1.38. *Reagents and Conditions:* a) 2-furyllithium, $ZnBr_2$ (xs), THF, -20°C; b) *t*-BuOOH, $VO(acac)_2$; c) MeI, Ag_2O, rt; d) K-selectride®, EtOH (2 eq); e) TBAF; f) MsCl, Et_3N, DMAP; g) NaN_3, DMF, Δ; h) Swern oxidation; i) PPh_3, PhH; j) H_2, (70 psi), 10% Pd-C, MeOH; k) i) H_3O^+; ii) H_2 (70 psi), 10% Pd-C.

Addition of 2-furyllithium to aldehyde **1.207** in the presence of $ZnBr_2$ gave aldol product **1.208** in a 7,8-*anti (erythro)*: *syn (threo)* ratio of 12:1 indicating a Felkin-Ahn β-chelate model to still be operating. The aldol product **1.208** then underwent an oxidative rearrangement involving the C-8 hydroxyl group, followed by methylation of the anomeric hydroxyl to a mixture of protected hydropyranones **1.209**, which were then reduced stereoselectively with K-selectride® to give alcohol **1.210**. This was then followed by desilylation to the primary alcohol which was subsequently selectively converted to its

mesylate, and displaced with sodium azide to give the primary azide. Oxidation under Swern conditions then gave ketone **1.211**, which was then converted to intermediate imine **1.212** with triphenylphosphine in an intramolecular Staudinger reaction, and reduced to give **1.213**. Finally, sequential hydrolysis of the two cyclic acetal protecting groups followed by an intramolecular reductive amination reaction gave 1-deoxy-8-*epi*-castanospermine. Although this synthesis is short, it suffers from the shortcomings of generating the incorrect configuration at C-8, and not providing for the C-1 hydroxyl group.

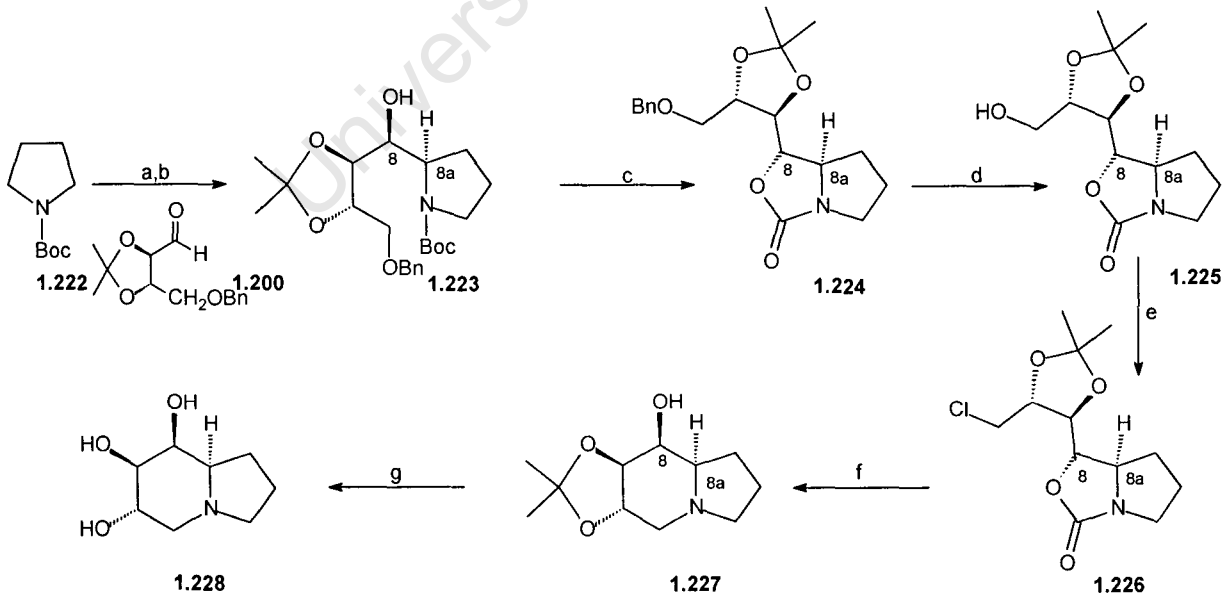
In 1992, Gallagher *et al.*[72] described a synthesis of another castanospermine stereoisomer, namely 8,8a-di*epi*-castanospermine, which involved a total of 8 steps (Scheme 1.39). The addition of the dianion of ketoester **1.215** to Mukaiyama's aldehyde **1.200** to create stereogenic centres C-8 and C-8a provided the key step, except, the reaction turned out to give predominantly the incorrect configurations at these two stereogenic centres.



Scheme 1.39. *Reagents and Conditions*: a) LDA (2 eq), dimethylpropylene urea, [*N*,*N*-dimethyl-3,4,5,6-tetrahydropyrimidine-2(1*H*)-one], THF, -78 to -50°C; b) **1.200**; c) NaCl, DMSO, H_2O, 130°C, 48%; d) $NaBH_4$, MeOH, 80%; e) $(MeO)_2CMe_2$, *p*-$MeC_6H_4SO_3H$, 77%; f) i) KOH, propane-1,2-diol, 140°C; ii) H_2, Pd/C, 61%; g) PPh_3, CBr_4, *i*-Pr_2NEt; h) i) 2M HCl; ii) ion-exchange chromatography (Dowex 50), 60% over two steps.

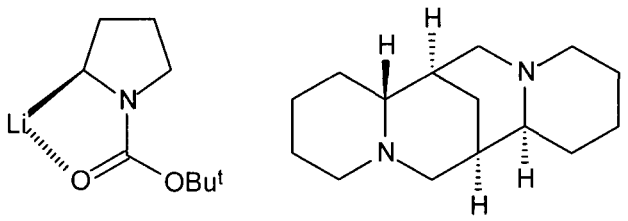
Thus, pyrrolidinone **1.215**, available via a Lacey-Dieckmann condensation[65] (Chan synthesis, Scheme 1.31), was doubly deprotonated to its 2,4-dianion, which regioselectivily added to aldehyde **1.200** involving the more reactive enolate. Subsequent ester decarboxylation using NaCl in DMSO gave aldol product **1.216**, comprising four diastereoisomers in the ratio of (3:3:1:1). The major products were separated and shown to both have the incorrect configuration at C-8; this could be rationalized by a Felkin-Ahn non-chelation model. One of them was subjected to a stereoselective ketone carbonyl reduction with borohydride to produce diol **1.217**. Protection of the 1,8-hydroxyl groups as an acetonide **1.218** in preparation for indolizidine cyclization, was followed by cleavage of the carbamate and hydrogenolysis of the benzyl ether to give alcohol **1.219**, which underwent cyclization with CBr_4/PPh_3 via the C-5 bromide to give indolizidine **1.220**. Finally, acid hydrolysis of the acetonides gave 8-*epi*-castanospermine **1.221**. 8,8a-di*epi*-castanospermine could be obtained using the same sequence from the other major aldol product. This is a concise synthesis of the indolizidine framework but failed to effectively access (+)-castanospermine owing to lack of stereochemical control in the aldol reaction.

In 1998, Majewski *et al.*[73] also reported a synthesis using a C-8a carbanion to access 1-deoxy-8*epi*-castanospermine. The synthesis began with Mukayiama's aldehyde **1.200** and the Boc-protected pyrrolidine **1.222** (Scheme 1.40), which were coupled together via the anion of **1.222** in a stereoselective fashion following similar work by Beak,[74] involving the enantioselective deprotonation of the *N*-Boc pyrrolidine.



Scheme 1.40. *Reagents and Conditions*: a) *s*-BuLi, sparteine; b) **1.200**, 45%; c) NaH, THF, 80%; d) H_2, Pd/C, 88%; e) Ph_3P, CCl_4, K_2CO_3, 74%; f) NaOH, MeOH, 83%; g) CF_3COOH, 91%.

Thus, asymmetric deprotonation of **1.222** using *s*-BuLi in the presence of the homochiral alkaloid (-)-sparteine (Figure 1.13) as described by Beak,[74] followed by addition to the Mukaiyama aldehyde gave **1.223** in 45% yield as a single isomer after chromatography. The intermediate proposed for the deprotonation to explain the observed configuration at C-8a in the product is depicted in Figure 1.13, which shows retention of configuration at the C-Li bond. Similarly, the stereochemistry at C-8 could be rationalized by a Felkin-Ahn β-Chelate model as described previously.



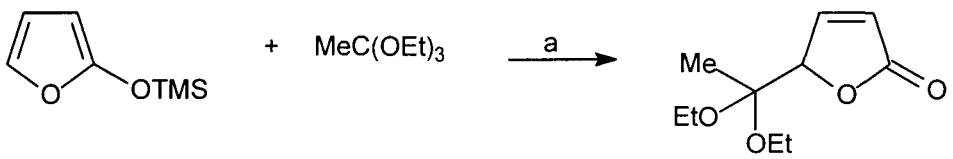
(-)-Sparteine

Figure 1.13

Adduct **1.223** was then treated with NaH resulting in formation of cyclic carbamate **1.224** as a protection of the C-8 hydroxyl group and this was followed by hydrogenolysis of the benzyl ether. Conversion of the resultant primary hydroxyl group to its chloride with PPh_3/CCl_4, base hydrolysis of the carbamate to amine followed by rapid cyclization gave indolizidine **1.227**. Final hydrolysis of the acetonide gave 1-deoxy-8*epi*-castanospermine. This also offers a short synthesis, but once again with the same shortcomings of not producing the correct configuration at C-8 as well as the lack of provision for incorporation of the C-1 hydroxyl group.

1.3.2.2 Lewis-Acid-Promoted Aldol Reaction

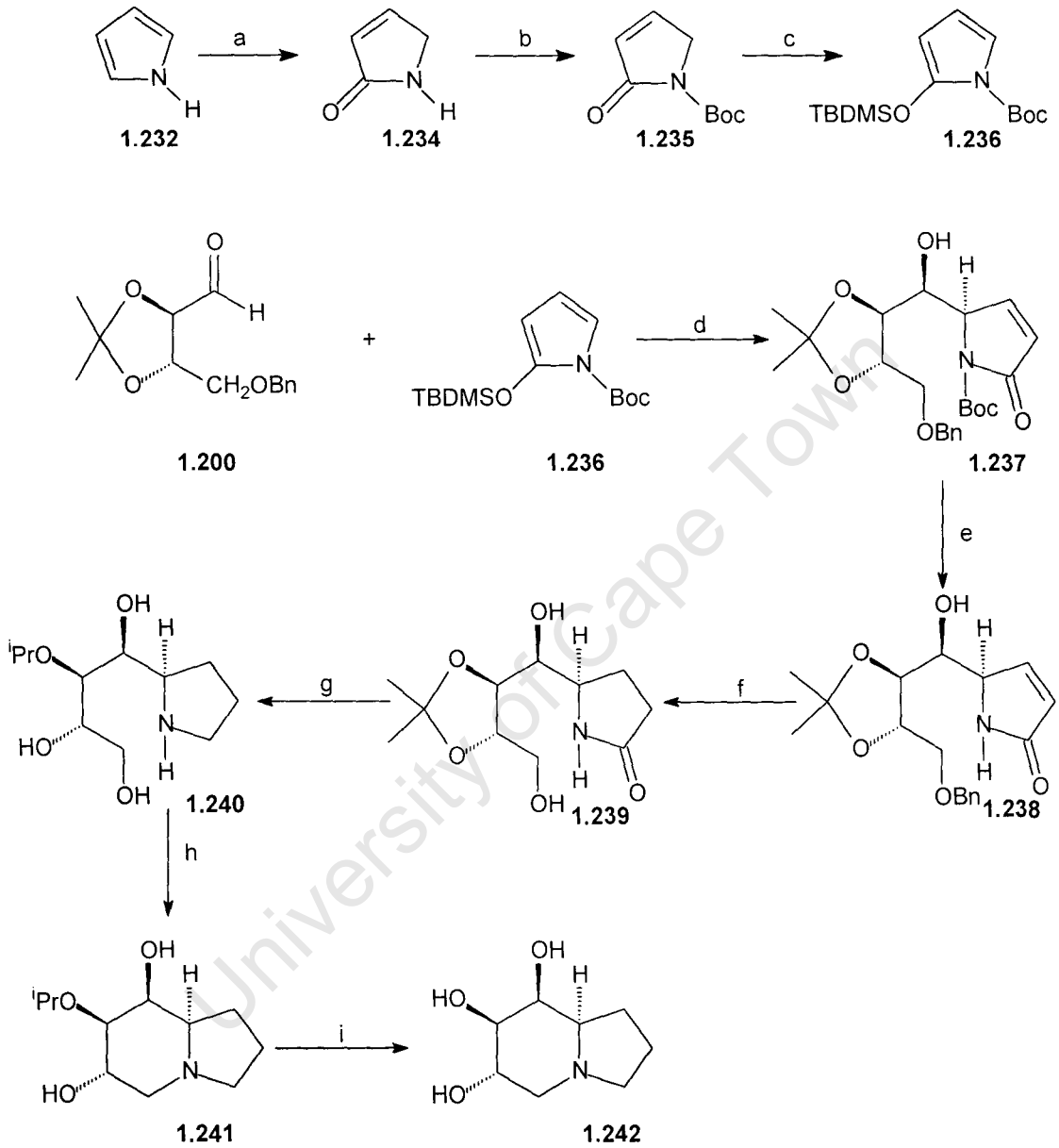
An alternative to using a hard lithium carbanion in the general synthetic repertoire is to use a silyl enol ether under Lewis-acid catalysis. The first example of silyl ether chemistry being applied to α-alkylation of an oxacycle was by Asaoka *et al.*[75] in 1979 when it was demonstrated that 2-silyloxyfuran **1.229** could undergo vinylogous aldol reactions with different orthocarboxylic esters and acetals using various Lewis acids (Scheme 1.41).



1.229 **1.230** **1.231**

Scheme 1.41. *Reagents and Conditions*: a) DCM, $SnCl_4$, -40°C to -10°C, 2h, 71%.

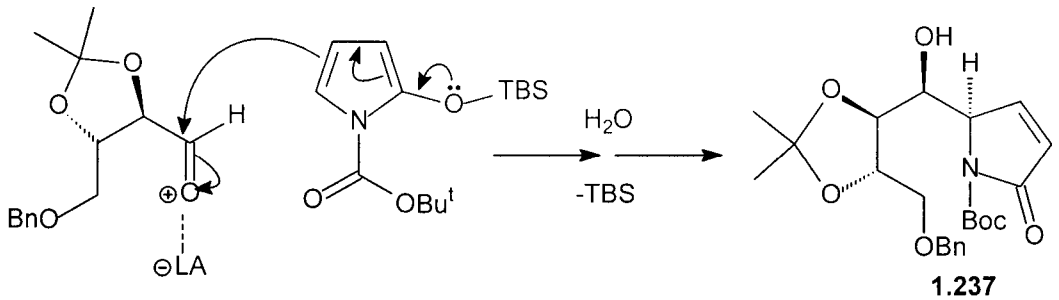
Subsequently Casiraghi picked up on this and successfully and elegantly applied it to a (+)-castanospermine synthesis.[76] He chose *N*-Boc-protected silyloxypyrrole **1.236** (TBSOP) as the nucleophile which was ready available from pyrrole **1.232** in large quantities over three steps (Scheme 1.42).[77]



Scheme 1.42. *Reagents and Conditions*: a) H_2O_2, H_2O; b) Boc_2O, CH_3CN, DMAP, 80%; c)TBSOTf, lutidine, 83%; d) $SnCl_4$, Et_2O, -80°C, 80%; e) PhSH, TMSOTf, DCM, 0°C, 75%; f) H_2, Pd-C, NaOAc, THF, 95%; g) i) BH_3DMS (50 eq), THF, rt; ii) 2M HCl, rt; iii) DOWEX (OH^-), 71%; h) i) PPh_3, CCl_4, Et_3N, pyridine, rt; ii) DOWEX (H^+), 2M NH_4OH, 79%; i) BBr_3, DCM, rt, 67%.

1.236 underwent a regio- and stereoselective vinylogous Mukaiyama aldol addition with Mukaiyama aldehyde **1.200** to give **1.237** in 80% yield and as a single diastereomer. The mechanism of this reaction is shown in Scheme 1.43.[78] The two facial selectivities are in

accordance with a β-chelated transition state for the aldehyde (*Si*-face selective) in conjunction with attack on the *Si*-face of the pyrrole. The latter facial selectivity also suggests coordination of the Lewis-acid to the Boc group. The two models are presented in Figures 1.14 and 1.15. [78]



1.237

Scheme 1.43

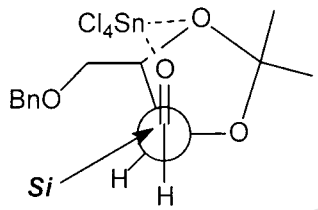


Figure 1.14 β-chelate

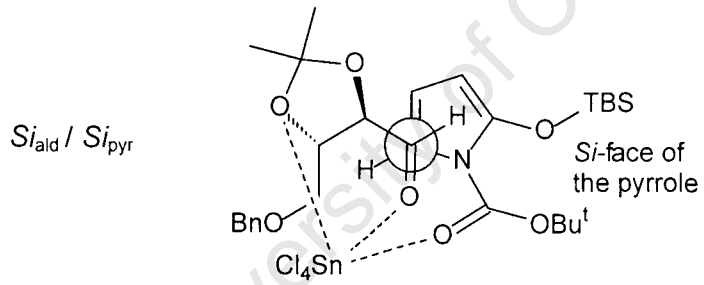
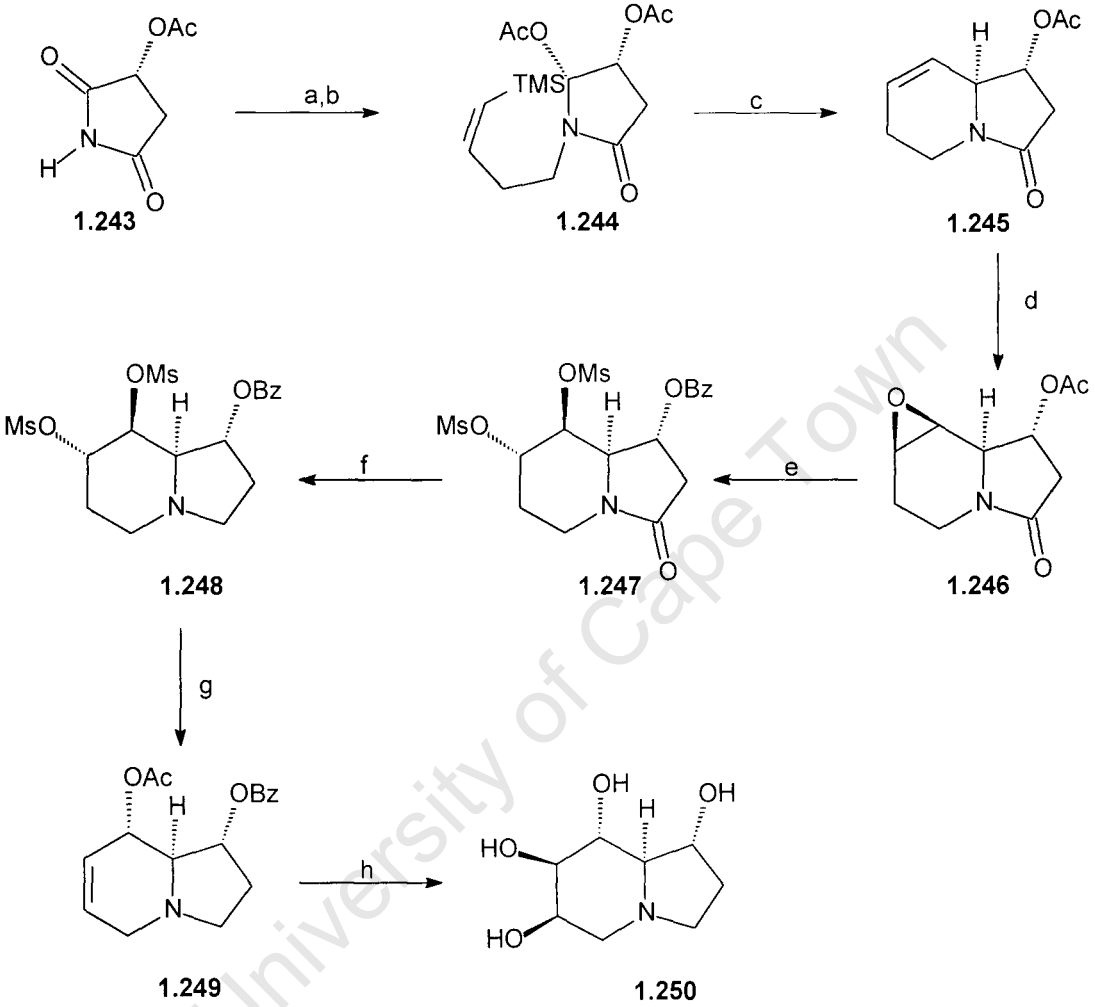


Figure 1.15 Overall transition state

For elaboration of adduct **1.237**, *N*-Boc deprotection with TMSOTf in the presence of thiophenol gave lactam **1.238**, which was hydrogenated with removal of the benzyl ether and double bond to give lactam **1.239**. Reduction of the lactam required a large excess of borane (50 eq) and resulted in regioselective opening of the acetonide to give triol **1.240**. This was then subjected to an intramolecular cyclization under conditions first described by Vogel[79] using PPh_3, and CCl_4 to give indolizidine **1.241**. The final step involved cleavage of the isopropyl ether with BBr_3 to afford (+)-1-deoxy-8*epi*-castanospermine over six steps in a 22% overall yield from **1.236**. This extremely elegant synthesis has two main drawbacks regarding (+)-castanospermine in that neither the C-1 nor the C-8 stereogenic centres are adequately accomodated.

1.3.2.3 Electrophilic C-8a

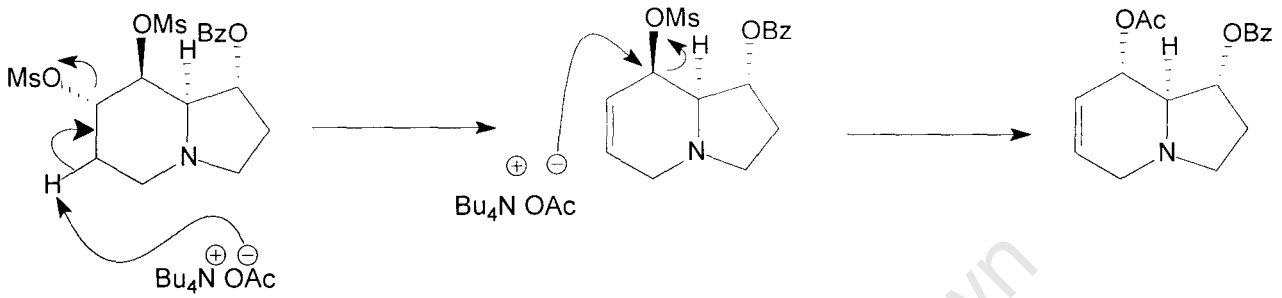
Leeper *et. al.*[80] report the only convergent synthesis using an electrophilic C-8a disconnection, starting with chiral α-acetoxyimide **1.243** prepared from L-malic acid.[81] In this synthesis, the five-membered ring synthon acts as an electrophile via acyliminum chemistry. This is the reverse (Umpölung) of the previous cases.



Scheme 1.44. *Reagents and Conditions*: a) i) TMSCH=CH(CH$_2$)$_3$OH, DEAD, Ph$_3$P, 87%; ii) NaBH$_4$, 94%; b) Ac$_2$O, pyridine, DMAP, 85%; c) i) BF$_3$.OEt$_2$, 72%; ii) Et$_3$N, MeOH, H$_2$O; iii) BzCl, Et$_3$N, DMAP, 84%; d) m-CPBA, 76%; e) i) H$^+$, THF, H$_2$O; ii) MsCl, pyridine, 41%; f) BH$_3$.DMS; g) Bu$_4$NOAc, 25%; h) i) OsO$_4$, NMO; ii) aq NH$_3$; 53% .

Thus, acetoxysuccinimide **1.243**, synthesized in three straightforward steps from L-malic acid, was subjected to a Mitsunobu reaction with 4-trimethylsilyl-3-buten-1-ol to the *N*-alkylated imide. The imide carbonyl group adjacent to the acetoxy group was regioselectively reduced to give the hydroxylactam which was acetylated to give acetoxy lactam **1.244**. Stereoselective intramolecular cyclization of **1.244** via interception by the vinylsilane of the acyliminium-ion of **1.244** generated with BF$_3$.OEt$_2$ gave indolizidine **1.245**. Thereafter, the C-6, C-7, and C-8 hydroxyl centres were introduced via a sequence

involving epoxidation, regioselective acid-catalysed opening and double mesylation to afford **1.247**. Lactam carbonyl reduction, elimination of the C-7 mesylate and inversion of the C-8 mesylate with acetate, both reactions with acetate ion gave **1.249**. Finally, stereoselective *syn*-dihydroxylation of the C-6/C-7 double bond followed by ester-group hydrolysis gave indolizidine **1.250**. The mechanism of the reactions of acetate ion with **1.248** involving both nucleophilic and basic actions is shown in Scheme 1.45.



Scheme 1.45

This was an interesting synthesis and gave rise to many analogues of (+)-castanospermine.

To conclude, there have been interesting syntheses from non-carbohydrate based starting materials and which have explored various aspects of asymmetric synthesis, such as Sharpless epoxidation and dihydroxylation reactions for introducing chiral centres. There has also been a keen interest in convergent syntheses via the C-8/C-8a disconnection. The latter syntheses have been much shorter, but all suffer from the drawback of not achieving the C-1 and C-8 centres with correct absolute configuration. None of the syntheses have stood out as capable of being easily developed on an industrial scale.

1.4 Objectives

After reviewing the literature it became apparent that there was still scope to develop a new enantioselective total synthesis of (+)-castanospermine. None of the reported syntheses could be developed to be used on an industrial scale, as they either use expensive reagents, have many steps to reach the target or they suffer from lack of regio- or stereoselectivity. Thus our main objective was to develop a synthesis which would overcome all of these drawbacks. In order to achieve this goal and owing to our group's interest in forming quaternary centres α- to nitrogen, it was felt that the best strategy would

be to carry out a convergent synthesis via a C-8/C-8a disconnection as shown in Figure 1.16.

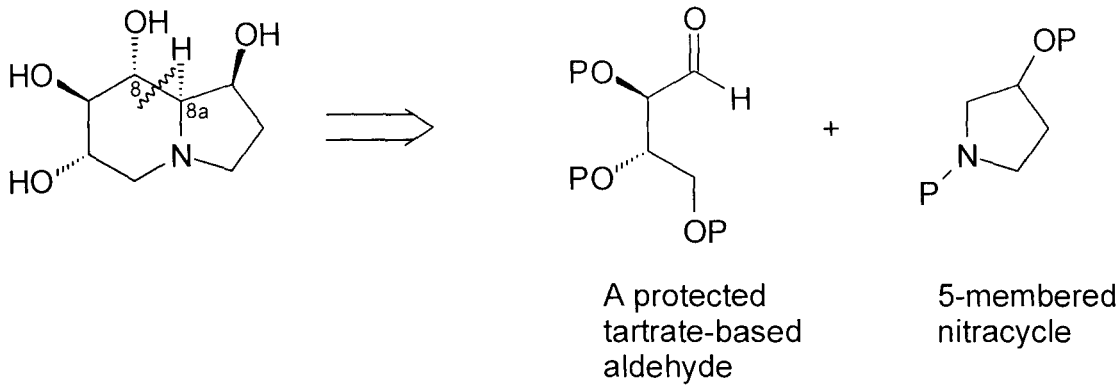


Figure 1.16 C-8/C-8a Disconnection.

Although several groups have reported on using this type of disconnection (See Section 1.3.2) none of them have successfully synthesized (+)-castanospermine. All the syntheses suffered from drawbacks such as:

- Lack of stereoselectivity
- No provision for the C-1 hydroxyl
- Incorrect configuration for the stereogenic centre C-8 of (+)-castanospermine.

Hence, our aim was to develop a synthesis that would overcome these particular drawbacks and as well as having the potential to be developed on an industrial scale.

In order to achieve these objectives the following requirements were identified:

- The development of a nitracycle that would incorporate the C-1 hydroxyl, the synthesis of which would be short, use inexpensive starting materials and reagents and could made on a large scale.
- The generation of the C-8/C-8a bond in a regio- and stereoselective fashion as well as exploration of the scope of the reaction.
- The development of a synthetic route to the indolizidine skeleton and eventully (+)-castanospermine, via the shortest and cheapest synthetic pathway possible.

Chapter 2 : Results and Discussion

After reviewing the literature, it became apparent that there was still an opportunity to explore a new synthetic route to (+)-castanospermine that was concise, enantioselective and which would introduce new or improved methodology to overcome some of the drawbacks of the other reported syntheses. It was felt that while carbohydrate-based syntheses have been pretty well exhausted, there was still room for an improved synthesis using a non-carbohydrate-based approach. Owing to an ongoing interest in creating stereogenic centres α- to nitrogen as part of a synthetic programme at the University of Cape Town,[81,82] the focus of attention turned towards a strategy involving a convergent C-8/C-8a disconnection as described in the review (section 1.3.2). This disconnection is shown in Figure 2.1.

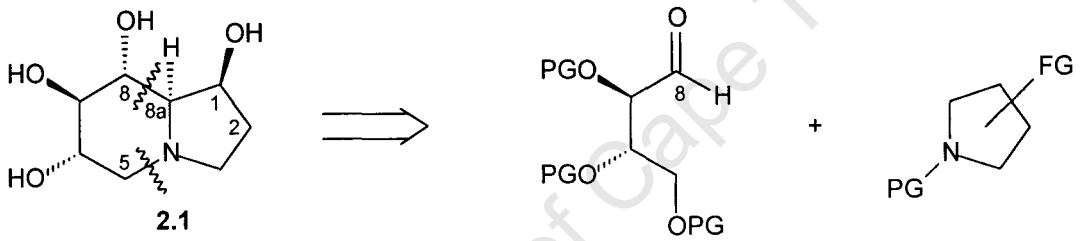


Figure 2.1

The project was thus divided into three main areas:

- The design and synthesis of appropriate 5-membered nitracycle
- The coupling of the aldehyde and 5-membered nitracycle moiety
- The generation of the indolizidine skeleton and (+)-castanospermine.

2.1 Design and synthesis of the 5-membered nitracycle

The first target that was envisaged is depicted in Figure 2.2.

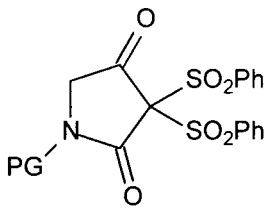


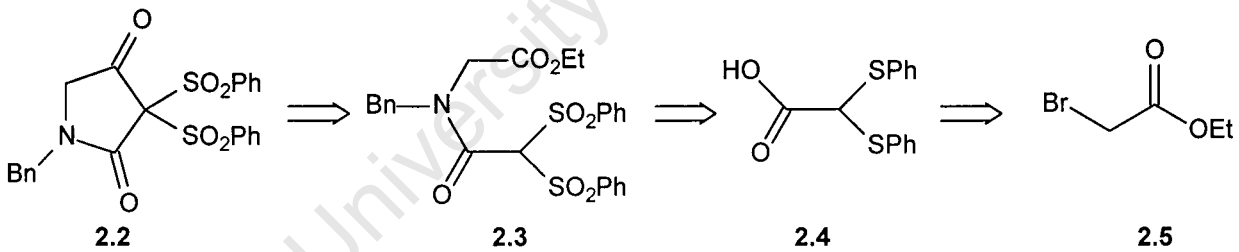
Figure 2.2

2.2

The target was chosen on the basis of the following aspects:

- The enolate formed from **2.2** would be regio-defined.
- The nitrogen protecting-group would likely play a role in the stereochemical outcome of the reaction and would need to be easily deprotected.
- The C-1 hydroxyl group would be readily accessible post-coupling. This has been a major drawback of most convergent syntheses via the C-8/C-8a disconnection.
- The possibility of introducing a C-2 substituent. This has not been addressed before.

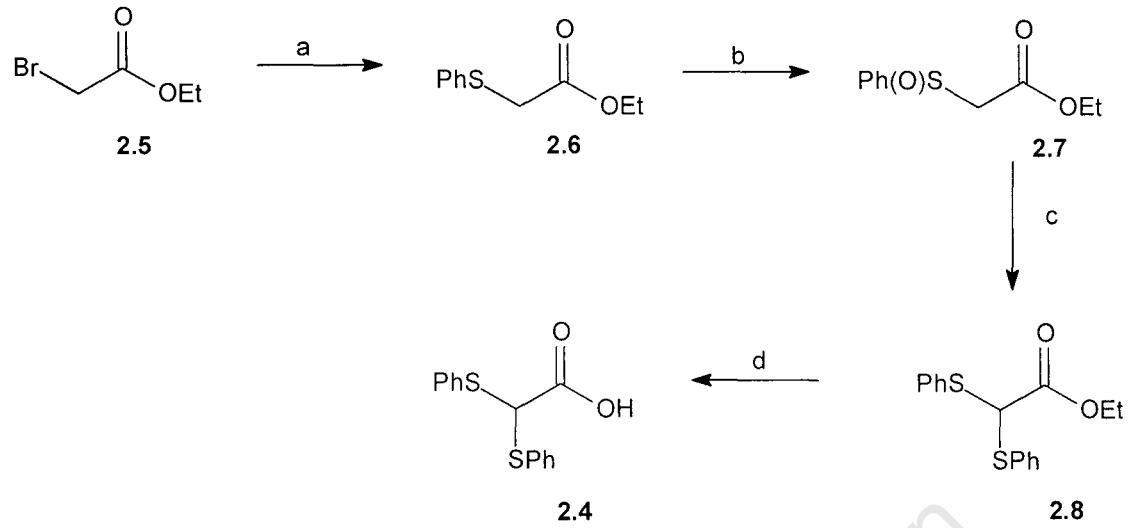
In the first instance, the nitrogen protecting-group was chosen as benzyl and retrosynthetic analysis revealed access to **2.2** to be possible via a Dieckmann-type cyclization of **2.3**, in turn available via nitrogen-alkylation chemistry (Scheme 2.1).



2.2 **2.3** **2.4** **2.5**

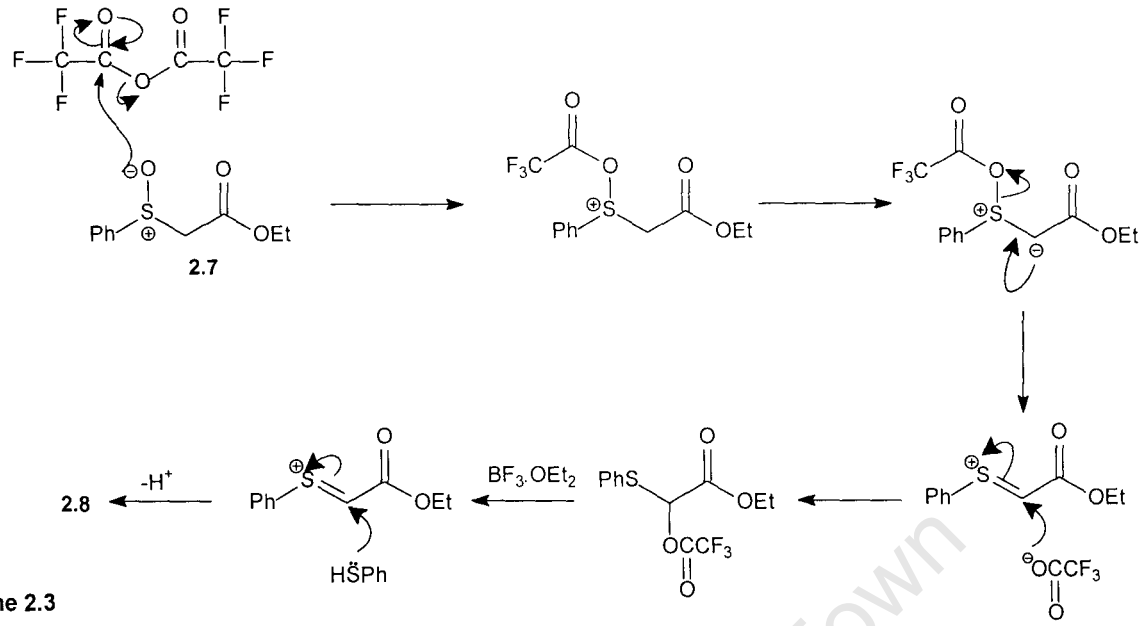
Scheme 2.1

The synthesis of acid **2.4** is outlined in Scheme 2.2 and began with commercially available bromoacetate **2.5,** which was subjected to nucleophilic displacement with thiophenol to give α-sulfanylester **2.6**. The latter was sufficiently pure by ^{1}H NMR spectroscopy to proceed to the next step without any further purification.



Scheme 2.2. *Reagents and Conditions*: a) PhS^- / MeOH; b) CH_3COOH, H_2O_2, 97% over two steps; c) $(CF_3CO)_2O$, DCM; ii) PhSH, $BF_3.OEt_2$, 82%; d) KOH, MeOH, 80%.

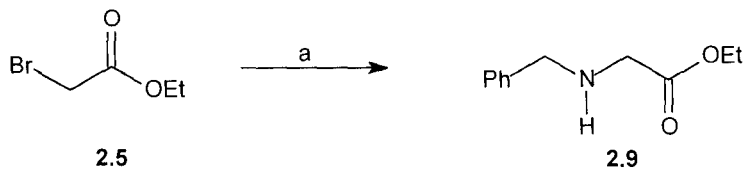
The ^1H NMR spectrum of **2.6** showed the presence of a phenyl resonance at δ 7.10-7.40 ppm integrating for 5 protons, demonstrating the presence of a phenylthio group. Ester **2.6** then underwent a mild oxidation with hydrogen peroxide and acetic acid to give sulfoxide **2.7** in 97% yield over 2 steps from **2.5** after purification via column chromatography. The ^1H NMR spectrum of **2.7** showed the appearance of an AB system integrating for 2 protons for the two diastereotopic methylene hydrogens as a result of chirality at sulfur. The presence of the sulfoxide was further corraborated by a ^{13}C resonance at δ 61.2 ppm for the α-carbon. Sulfoxide **2.7** was then subjected to a modified Pummerer reaction using trifluoroacetic anhydride to generate an α-trifluoroacetoxy sulfide. Subsequent treatment with thiophenol in DCM with BF_3.etherate via an S_N1 substitution gave thioacetal ester **2.8**. The mechanism of this transformation is shown in Scheme 2.3.[84]



Scheme 2.3

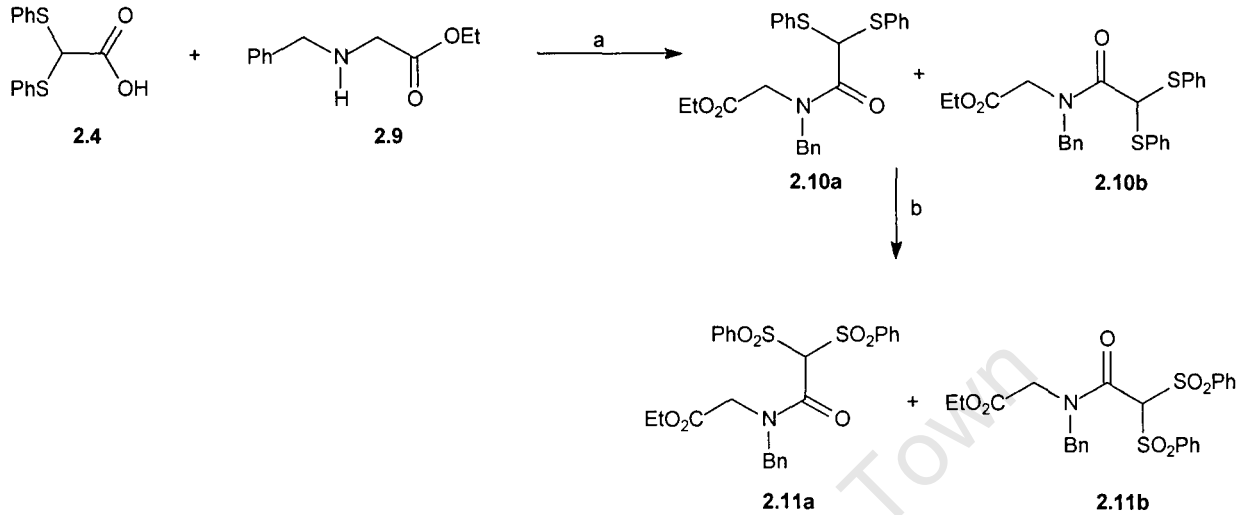
Thioacetal ester **2.8** was isolated via chromatography in 82% yield over the 2 chemical steps, and its ^{1}H NMR spectrum revealed signals at δ 7.20-7.40 ppm integrating for 10 protons for two phenyl groups, as well as a singlet at δ 4.97 ppm integrating for 1 proton for the methine proton at C-2. Finally, the ester group was hydrolysed under standard conditions to give carboxylic acid **2.4** in 80% yield, which was sufficiently pure by ^{1}H NMR spectroscopy as well as tlc to proceed to the next stage without any further purification. The ^{1}H NMR spectrum of **2.4** confirmed that the acid had been formed as there was a broad signal at δ 10.96 ppm integrating for 1 proton. Further confirmation was given by the disappearance of the ester ethyl group signals as well as the appearance of an IR broad stretch at 3444 cm^{-1}. This synthetic route was high-yielding and reproducible.

The next stage involved the coupling of aminoester **2.9**, prepared by alkylation of benzylamine as outlined in Scheme 2.4. Care was taken to minimise dialkylation by performing the alkylation reaction at low temperature (-20°). Under such conditions, the desired product could be obtained after chromatography in a respectable yield of 79%.



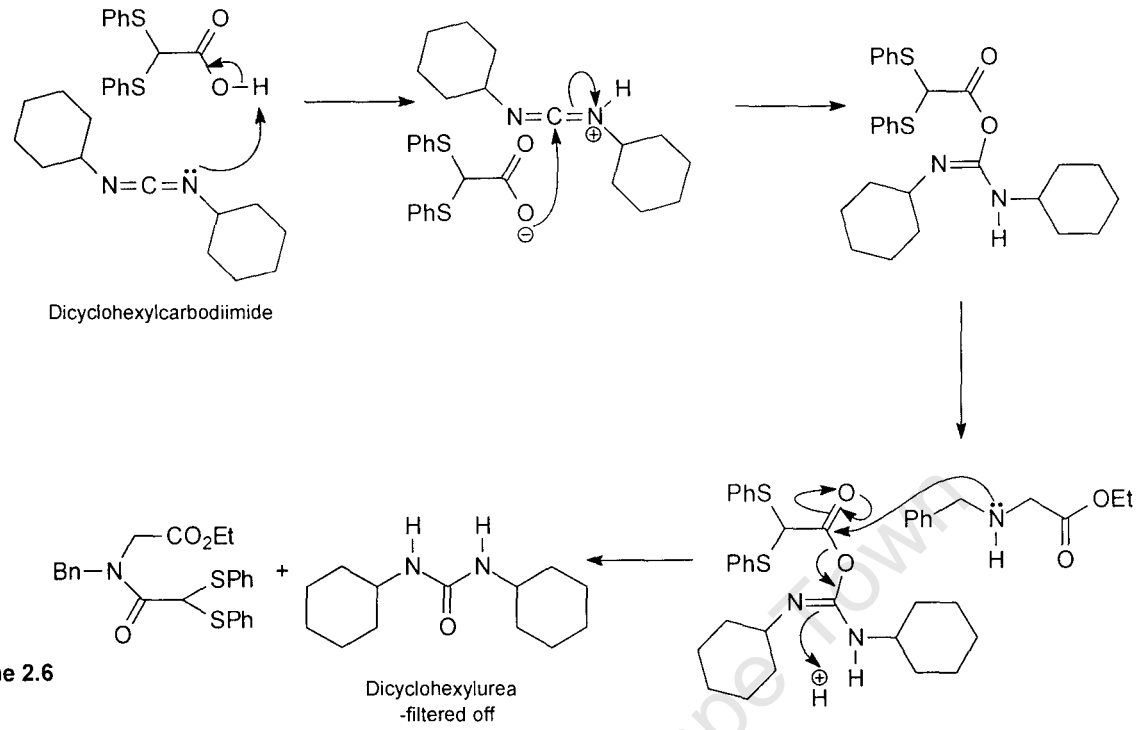
Scheme 2.4. *Reagents and Conditions*: a) $BnNH_2$, Et_3N, THF, -20°C, 79%.

Thereafter, **2.9** was coupled with acid **2.4** in a conventional DCC coupling without HOBt or DMAP, Scheme 2.5. This methodology proved to be superior to using the acid chloride of **2.4**.



Scheme 2.5. *Reagents and Conditions*: a) Dicyclohexylcarbodiimide (DCC), DCM, 0°C, 90%; b) *meta*-chloroperbenzoic acid (m-CBPA) (6 eq), DCM, 82%.

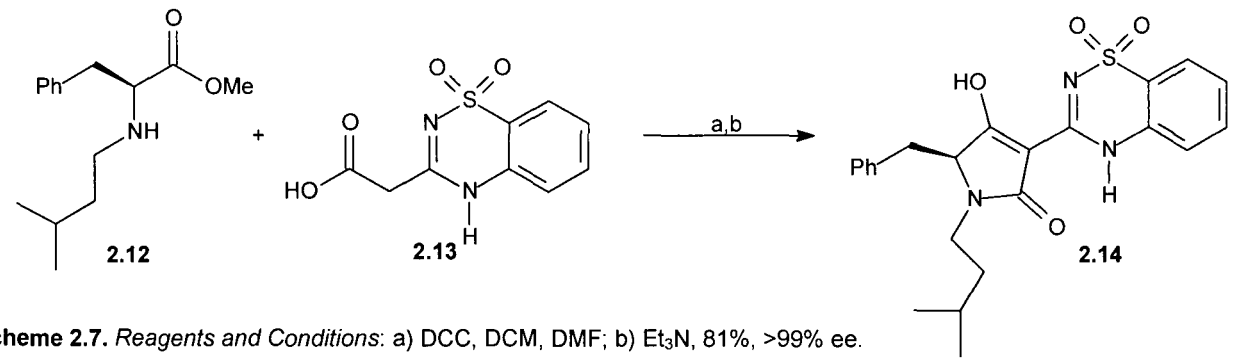
Following chromatography, tertiary amide **2.10a/b** was isolated in high yield (90%) as a mixture of s-cis and s-trans rotamers, as indicated by the duplication of resonances in both the ^{1}H and ^{13}C spectra in a ratio of 2:1. The ^{13}C spectrum revealed 15 resonance pairs, in accordance with the structure of **2.10a/b**. The ^{1}H NMR spectrum of the major product of **2.10a/b** also confirmed the structure with the following diagnostic signals: ester signals at δ 1.29 ppm, δ 4.23 ppm, as well as a singlet at δ 4.08 ppm integrating for 2 protons for the C-2 methylene protons, and a benzyl singlet at δ 4.63 ppm. Further confirmation was given by the presence of aromatic signals integrating for 15 protons. The IR confirmed the presence of both the ester and amide functionalities with absorptions at 1742 and 1654 cm^{-1}, for the ester and amide carbonyl stretches respectively. The reaction was reproducible and isolation of the product was relatively simple. The mechanism of the condensation is outlined in Scheme 2.6.[85]



Scheme 2.6

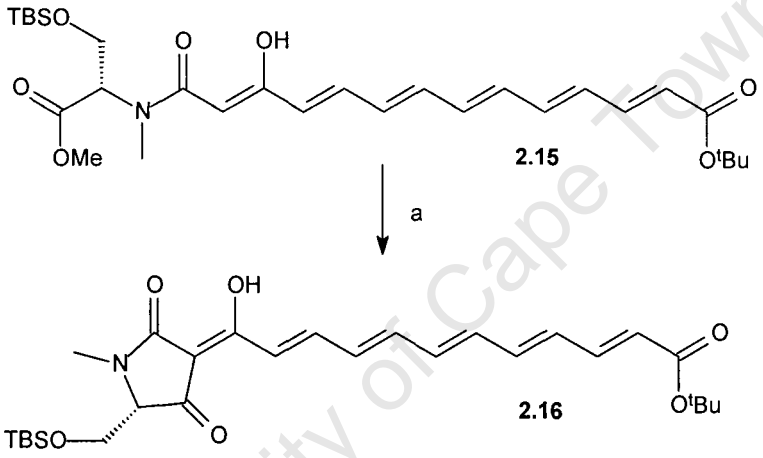
The adduct **2.10a/b** was then oxidized by excess *meta*-chloroperbenzoic acid (6 equivalents) to give bis-sulfone **2.11a/b** in 82% yield as a crystalline solid after purification via column chromatography. The formation of the sulfone as opposed to a mixed oxidation product was confirmed by both a correct elemental combustion analysis as well as the parent ion mass $[516]^+$ in the mass spectrum. The presence of rotamers was again indicated by duplication of resonances in both the ^1H and ^{13}C NMR spectra as before, in a ratio of 7:2. The ^1H NMR spectrum showed the presence of diagnostic signals resonating at δ 7.84 ppm and δ 8.00 ppm as a pair of doublet of doublets and each integrating for 4 protons, which was assigned as the protons *ortho* to the sulfonyl groups for each rotamer. The ^{13}C spectrum revealed 15 resonance pairs, in accordance with the rotameric structure of **2.11a/b**. The ^1H and ^{13}C spectra demonstrated that exhaustive oxidation had occurred as the sulfonyl groups were both equivalent according to the NMR spectra.

There have been a number of syntheses of tetramic acids reported in the literature, which have utilized a Lacey-Dieckmann cyclization involving two carboxyl functionalities as a key step. A recent example was described by Fitch *et. al.*[86] in 2005 (Scheme 2.7), involving a "one-pot" amide formation-Dieckmann cyclization, to synthesize benzothiadiazine-substituted tetramic acids.



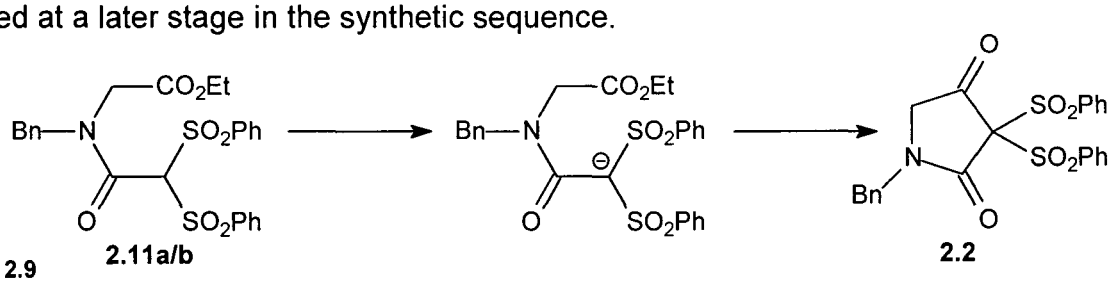
Scheme 2.7. *Reagents and Conditions*: a) DCC, DCM, DMF; b) Et_3N, 81%, >99% ee.

Another example was reported by Ley *et. al.*[87] in 1999 as part of his total synthesis of physarorubinic acid (Scheme 2.8).



Scheme 2.8. *Reagents and Conditions*: a) MeONa (5 eq), MeOH, 25°C, 120 seconds, 100%.

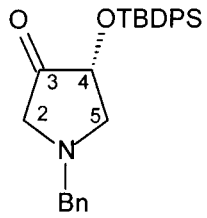
As there have been many examples of constructing tetramic acids via a Lacey-Dieckmann-type cyclization, it was felt that this would be a viable reaction to explore. In our case it was anticipated that the more acidic α-sulfonyl proton would be abstracted and cyclization would proceed onto the ester to afford **2.2** (Scheme 2.9). In this case enolization to the tetramic acid would be prevented by the presence of the sulfonyl groups, but these could be reductively removed at a later stage in the synthetic sequence.



Scheme 2.9

The cyclization was first attempted with methoxide but no product was formed. Hence stronger bases such as *n*-BuLi, LDA, NaH, and LiHMDS (lithium hexamethyldisilazide) were used in an attempt to abstract the α-sulfonyl proton and promote cyclization, but none led to the formation of the product and in each case starting material was recovered. This failure was put down to steric hindrance due to the presence of the 2 sulfonyl groups.

Owing to the difficulties in performing the closure depicted in Scheme 2.9, an alternative target was pursued shown in Figure 2.3 as (4*R*)-1-benzyl-4(*tert*-butyldiphenylsilyloxy)-pyrrolidin-3-one **2.17**.



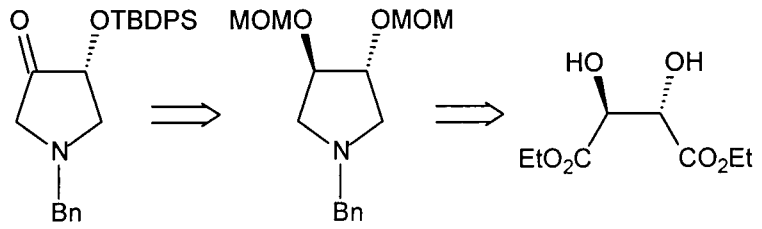
2.17

Figure 2.3

The target was designed with the following features:

- The kinetic carbanion would have a preferred regiochemistry, with kinetic deprotonation being preferred at C-2. Therefore the coupling should be regioselective.
- Introduction of chirality to the nitracycle by having a stereogenic centre at C-4 with a large protecting group offered the possibity of stereo-induction in the addition to the aldehyde (Figure 2.1), promoting addition from the desired top (*Si*) face of the nitracycle.
- Synthesis of the target should be relatively simple as it involved three steps from a known intermediate.

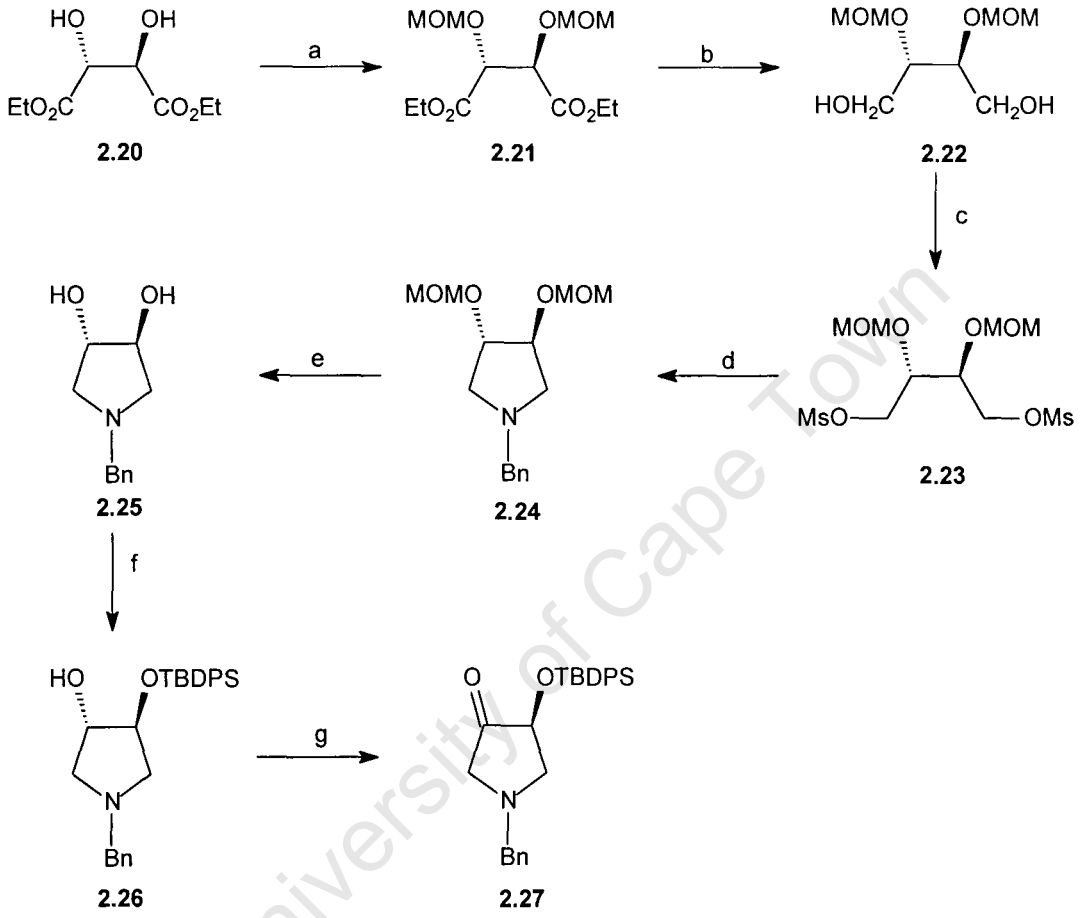
Retrosynthetic analysis revealed access to **2.17** to be possible via functional group modification of **2.18**, in turn available from a known literature procedure from D-diethyl tartrate (Scheme 2.10).



2.17 **2.18** **2.19**

Scheme 2.10

Owing to its availability in our laboratory, L-diethyl tartrate **2.20** was utilized in the development and evaluation of the viability of the route to **2.17**. The successful synthetic route realised to the enantiomer of **2.17** from commercially available L-diethyl tartrate **2.20** is outlined in Scheme 2.11.



Scheme 2.11. *Reagents and Conditions*: a) P_2O_5, $(CH_3O)_2CH_2$, DCM, rt, 91%; b) $LiAlH_4$, THF, -20°C to rt, 78%; c) MsCl (4 eq), Et_3N, DCM, 0°C, 88%; d) $BnNH_2$, 60°C, 87%; e) 2M HCl, THF, 60°C, 97%; f) TBDPSCl (1 eq), imidazole (1 eq), CH_3CN, rt, 30%; g) Swern Oxidation, 70%.

The synthesis of the known intermediate **2.24** was carried out as described in the literature and spectral data of all intermediate products were identical to those reported.[88] The MOM ethers of **2.24** were then hydrolyzed under harsh acidic conditions to give diol **2.25**, which, in view of its water solubility was isolated using a non-extractive procedure involving the addition of solid sodium carbonate to neutralize the HCl followed by filtration and removal of solvent *in vacuo*. Loss of both MOM groups was confirmed in the ^1H NMR spectrum of **2.25** by the disappearance of the diagnostic AB methylene system as well as the methoxy groups. The

next step involved chemoselective monoprotection of the diol. This step proved to be problematic and various conditions were attempted. These included the use of a strong base (*n*-BuLi, 1 eq), smaller protecting group (TBDMS) and longer reaction times, but the yields were never high. Eventually, mono-protected ether **2.26** was produced in low yield using the standard conditions of TBDPSCl (1 eq) and imidazole as both a transfer catalyst and base in acetonitrile. The ^{1}H NMR spectrum of **2.26** showed the appearance of the key silyl *t*-butyl singlet at δ 1.07 ppm integrating for 9 protons as well as the appearance of the silyl phenyl groups. **2.26** was then oxidized under Swern conditions to give ketone **2.27** in 70% yield. The ketone was isolated via chromatography and ^{1}H NMR spectroscopy confirmed that **2.27** had been formed (Figure 2.4). The diagnostic signals were the triplets at δ 2.56 ppm and δ 3.23 ppm which could be assigned to the protons at C-5, as well as the triplet at δ 4.36 ppm for the proton at C-4. Additional noteworthy signals were the 2 AB systems, one for the diastereotopic protons at C-2 resonating at δ 2.74 ppm and δ 3.34 ppm, and the other for the benzyl methylene group resonating at δ 3.54 ppm and δ 3.76 ppm.

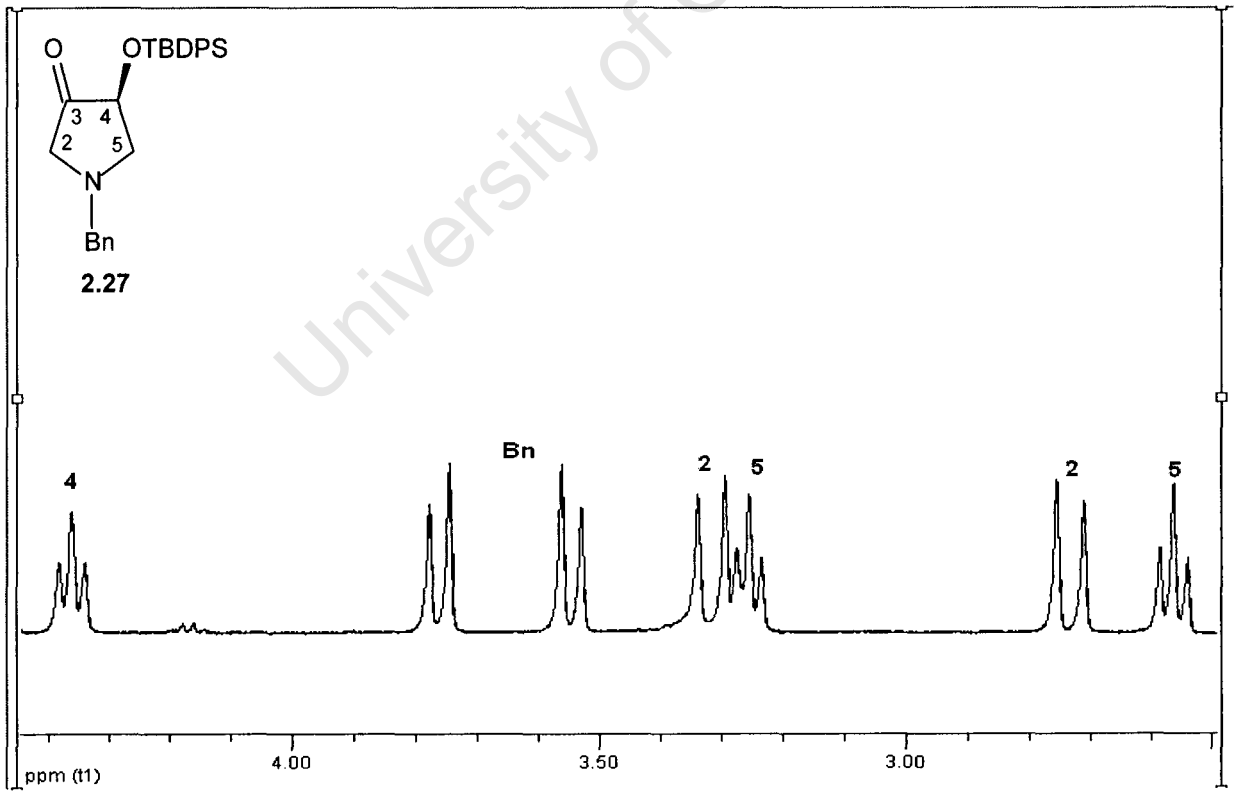
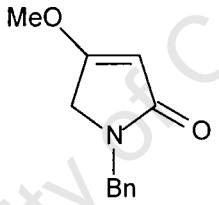


Figure 2.4

In addition, the presence of the ketone carbonyl was confirmed by the ^{13}C NMR spectrum by virtue of a diagnostic signal at δ 211.4 ppm.

With the target in hand, a study was pursued to investigate the feasibility and viability of ketone **2.27** for generating a regioselective and stereoselective carbanion. Therefore, a model study of deprotonation followed by quenching was carried out. For this study, allyl bromide was chosen as the electrophile, as the possible products from the reaction would be easily interpreted by NMR in view of the allyl group signals. The ketone was reacted with *n*-BuLi at -78°C to form the anion. Allyl bromide was added and the reaction was allowed to warm to room temperature. Tlc analysis showed the formation of several products. It was also noted that the ketone starting material was an unstable compound that decomposed readily. Therefore a full study involving other bases like LDA and LiHMDS was not undertaken. With this information, as well as the low yielding monoprotection, it was felt that this route was no longer an option. Thus another target was required, for which the synthetic route would be short and high-yielding, and this was found in 1-benzyl-4-methoxy-3-pyrrolin-2-one **2.28** as shown in Figure 2.5.



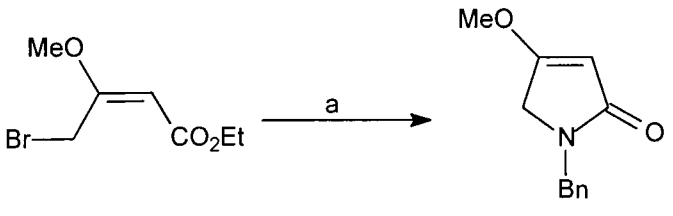
2.28

Figure 2.5

As with the previous targets, **2.28** satisfied several of the requirements:

- The vinyl ether provides functionality for C-1 elaboration post-coupling.
- It would readily provide a dienolate or dienol silyl ether for coupling.
- It can be synthesized via a short known sequence.

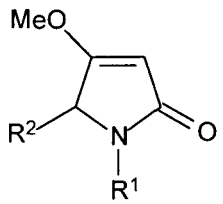
The synthesis of **2.28** was first described by Pinnick[89] from commercially available bromoester **2.29** using a double substitutive cyclization and is outlined in Scheme 2.12.



2.29 **2.28**

Scheme 2.12. *Reagents and Conditions*: a) Excess $BnNH_2$, Δ, 42%.

Pinnick,[89,90] and later Jones,[91,92] prepared a wide variety of 4-methoxy-3-pyrrolin-2-one products **2.30** using this methodology by varying the amine and "butenoate" used (Scheme 2.13).

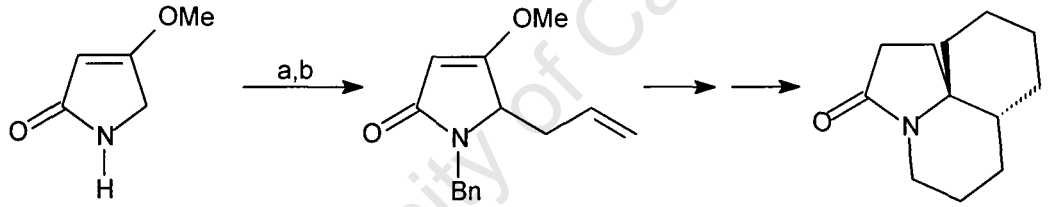


2.30

R^1	R^2
H	H
H	Me
$CHMe_2$	H
$CHMe_2$	Me
Me	Me
$CHMeCO_2Et$	Me
$(CH_2)_2CO_2Et$	Me
H	Et
Et	Et

Scheme 2.13

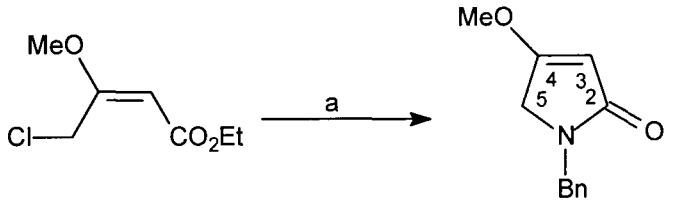
Work at UCT[82] in our group has used 3-pyrrolin-2-one **2.31** as a precursor in the synthesis of tricyclic Lepadiformine core **2.33** (Scheme 2.14).



2.31 **2.32** **2.33**

Scheme 2.14. *Reagents and Conditions*: a) i) *n*-BuLi (2 eq), THF; ii) Allyl bromide -78°C, 79%; b) BnBr, KOH, $Bu_4N^+HSO_4^-$, THF, rt, 88%.

For synthesis of pyrrolinone **2.28**, even though the yield was very low, it was decided to use Pinnick's method[87] as it is more direct than the approach used for Lepadiformine (Scheme 2.14). In order to improve the yield, the base diisopropylethylamine (Hünig's base) was added to the mixture, which was heated at reflux in acetonitrile (Scheme 2.15).



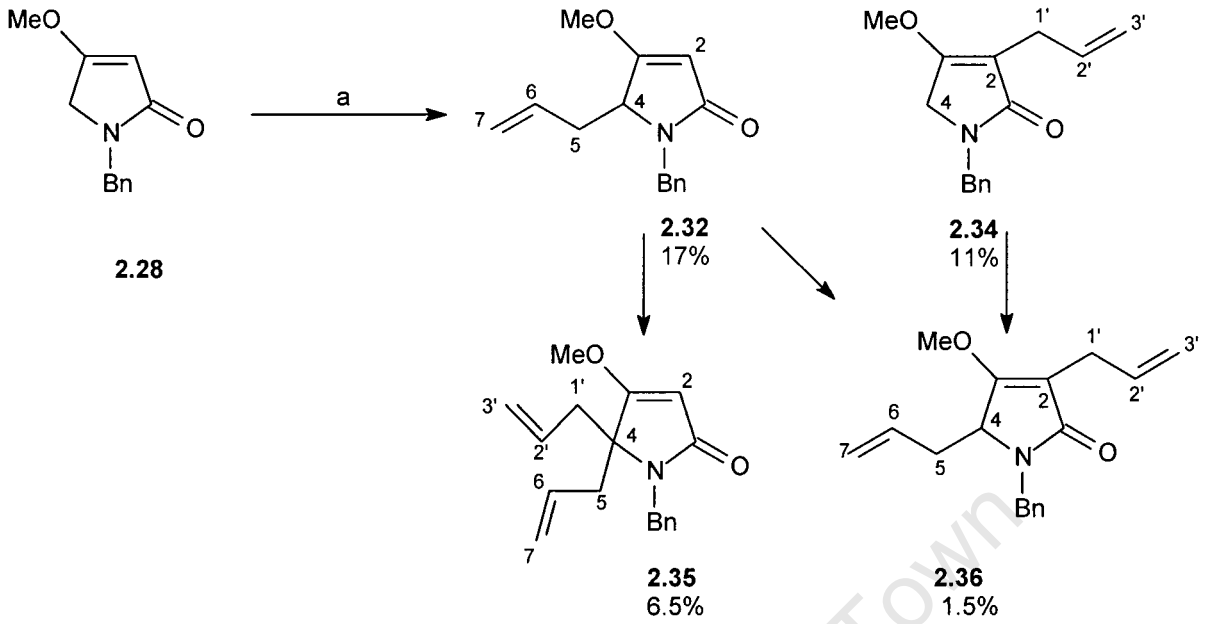
2.29 **2.28**

Scheme 2.15. *Reagent and Conditions*: a) $BnNH_2$, Hünig's base, CH_3CN, 65°C, 82%.

Thus, under these new conditions and using the chloride instead of bromide, the yield was increased to 82% compared to the 42% yield reported by Pinnick.[89] The diagnostic signals for **2.28** in its ^{1}H NMR spectrum were the singlet at δ 3.68 ppm integrating for 2 protons for the methylene at C-5, the singlet at δ 3.74 ppm integrating for 3 protons for the methoxy signal, and the singlet at δ 5.05 ppm integrating for 1 proton for the vinyl proton at C-3, all in accordance with the structure. Furthermore, although ethyl 4-chloro-3-methoxy-(*E*)-butenoate **2.29** was commercially available, it could also be accessed from ethyl chloroacetoacetate in a single step using trimethyl orthoformate with an acid catalyst.[93] The numbering system will now follow that of Casiraghi rather than the IUPAC format and follow the carbons. This is to avoid confusion when comparing results with published work.

2.2 The coupling of the aldehyde and the 5-membered nitracycle

With the nitracycle **2.28** in hand, studies on the dienolate were carried out. Once again, allyl bromide was chosen as the electrophile, as the possible products from the reaction would be easily interpreted by NMR spectroscopy. Hence, pyrrolinone **2.28** was deprotonated with *n*-BuLi (1.2 eq) at -78°C, allyl bromide added and the reaction allowed to gradually warm to -20°C before being quenched with ammonium chloride. *n*-BuLi had been used to generate the dienolate by previous workers. Tlc of the crude mixture revealed the formation of 4 products as well as the presence of unreacted starting material (51%). These were isolated via chromatography and the four ^{1}H NMR spectra analysed. The products with yields are illustrated in Scheme 2.16.



Scheme 2.16. *Reagents and Conditions*: a) *n*-BuLi (1.2 eq), Allyl bromide (3 eq), THF, -78°C to -20°C, **2.32** 17%; **2.34** 11%; **2.35** 6.5%; **2.36** 1.5%; **2.28** 51%.

The ^{1}H NMR spectra of all four products were compared to the ^{1}H spectrum of **2.28** by analyzing key signals regarding changes at H-2 and H-4 as well as the number of allyl groups observed. For all four compounds, the signals for both the methoxy and the benzyl methylene groups were present. These observation and assignments are summarized in Table 2.

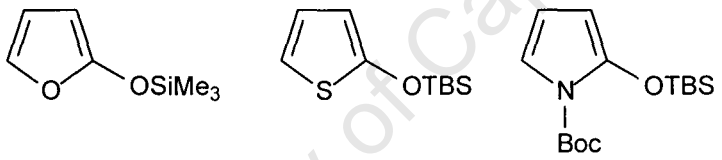
Table 2

Compound	MeO	H-2	H-4	No of Allyl groups
2.32	Singlet	Singlet	Triplet	1
2.34	Singlet	No signal	Singlet	1
2.35	Singlet	Singlet	No signal	2
2.36	Singlet	No Signal	Triplet	2

The reaction was repeated with LDA and the same four products were isolated, confirming the formation of the dienolate anion. Thus it can be concluded that the reaction is not regioselective. The formation of products **2.32** and **2.34** can be easily explained as being formed by regioselective allylation at C-4 and C-2 respectively. C-2 Allylation is followed by

isomerization to place the double bond back into conjugation. Formation of **2.35** indicates secondary deprotonation of the primary product **2.32** followed by a second C-4 allylation. Conversely, diallylated compound **2.36** could have arisen from allylation of either **2.32** or **2.34**. The allylation sequence resulted in about 50% recovery of starting material.

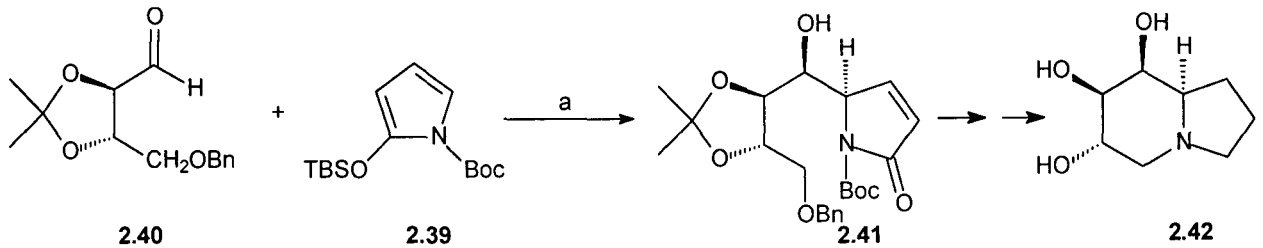
In spite of the non-regioselective result, a reaction of the dienolate of pyrrolinone **2.28** was performed with Martin's aldehyde **2.63** (for its synthesis see Scheme 2.25). However, as anticipated, several products were observed to form according to tlc analysis. As a result, it was decided to explore the coupling under softer coupling conditions via a dienol silyl ether. Silyloxypyrroles have become popular reagents in synthesis in recent times and act as silyl dienol ethers. They are part of a family of compounds known as silyloxyheterocycles consisting of silyloxyfuran, silyloxythiophene and silyloxypyrroles (Figure 2.6). Specific examples of these compounds are 2-(trimethylsilyloxy)furan **2.37**, 2-(*tert*-butyldimethylsilyloxy)thiophene **2.38** (TBSOT) and *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsilyloxy)pyrrole **2.39** (TBSOP).[94-96]



2.37 **2.38** **2.39**

Figure 2.6

Silyloxyfuran **2.37** was first used in organic chemistry in 1979 by Asaoka[75] as part of a study on extended vinylogous aldol reactions. However, it was the group of Casiraghi that elegantly pioneered the application of TBSOP **2.39** to extended vinylogous aldol reactions in many of his syntheses of natural products. The most notable is his synthesis of (+)-1-deoxy-castanospermine (the synthesis was previously described in full in Chapter 1) in which TBSOP **2.39** undergoes a vinylogous aldol reaction with Mukaiyama aldehyde **2.40** to give adduct **2.41** in a regio- and stereoselective fashion (Scheme 2.17).

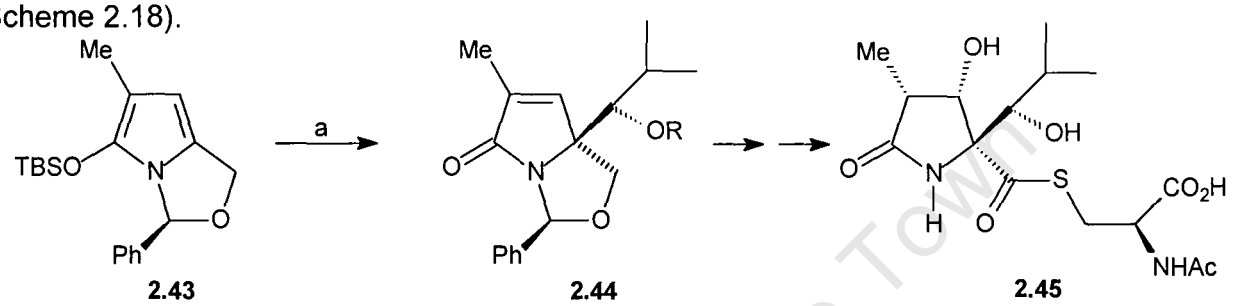


2.40 **2.39** **2.41** **2.42**

Scheme 2.17. *Reagents and Conditions*: a) $SnCl_4$, Et_2O, -80°C, 80%.

Casiraghi has also used TBSOP in syntheses of other natural products involving vinylogous aldol reactions to synthesize, for example, pyrrolizidine,[97] polyhydroxy-α-amino acids,[98] arabinofuran glycine[99] and cycloheptane amino acids,[100] thus demonstrating its versatility.

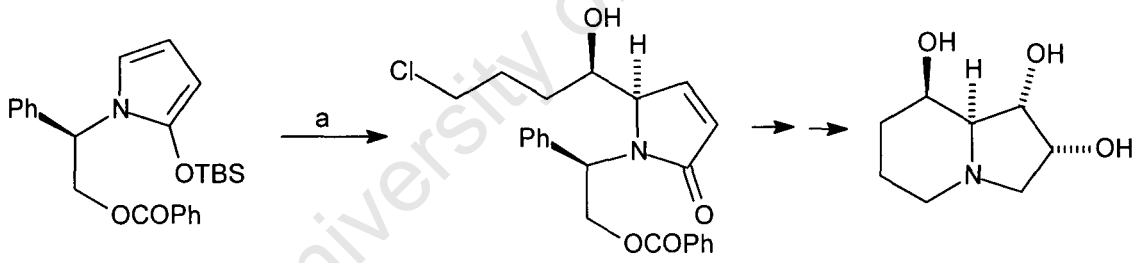
TBSOP and its derivatives have also been widely used by other groups. For example, Baldwin *et al.*[101] in 1994 used silyloxypyrrole **2.43** (a derivative of TBSOP) in a key vinylogous aldol reaction in his synthesis of (+)-lactacystin **2.45** involving 17 steps from oxazolidine **2.44** (Scheme 2.18).



2.43 **2.44** **2.45**

Scheme 2.18. *Reagents and Conditions*: a) Isobutyraldehyde, $SnCl_4$, Et_2O, -78°C, 55%.

More recently in 1998, Royer *et al.*[102] have used a chiral silyloxypyrrole **2.46** in the synthesis of (-)-8a-*epi*-swainsonine **2.48** using a vinylogous aldol reaction as the key step (Scheme 2.19).

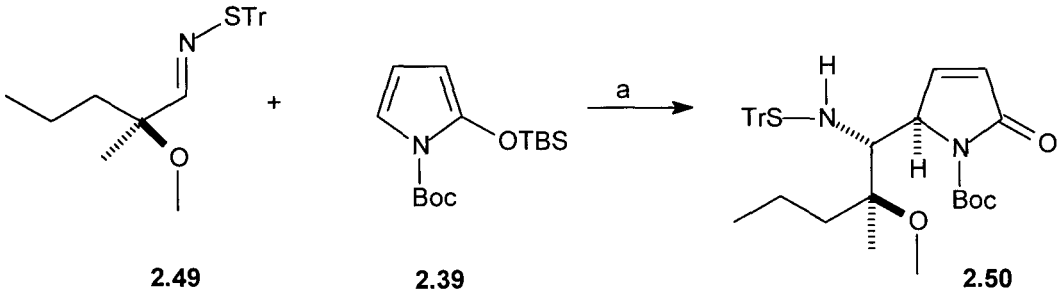


2.46 **2.47** **2.48**

Scheme 2.19. *Reagents and Conditions*: a) $Cl(CH_2)_3CHO$, $BF_3.OEt_2$, DCM, -78°C, 3h, 74%.

2.47 was obtained in 74% yield as a 9:1 diastereomic mixture (*R*,*R* and *S*,*S*). (-)-8a-*epi*-Swainsonine was subsequently synthesized in a total of 5 steps from adduct **2.47**.

TBSOP has also been used in imino-type (Mannich) vinylogous aldol reactions, and this was demonstrated by DeGoey *et al.*[103] in 2002 in his convergent total synthesis of the anti-influenza compound A-315675. In this case, TBSOP underwent the Mannich-type aldol reaction with imine **2.49** to give adduct **2.50** in 75% yield (Scheme 2.20) as a single diastereomer.

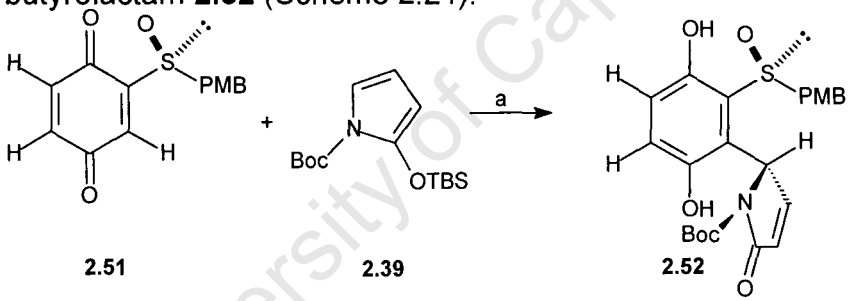


2.49 **2.39** **2.50**

Scheme 2.20. *Reagents and Conditions*: a) $BF_3.OEt_2$, DCM, -78 to -50°C, 75%.

This reaction was explored extensively by varying the functional group on the imine and using different Lewis acids. The most successful conditions were those shown in Scheme 2.20 above.

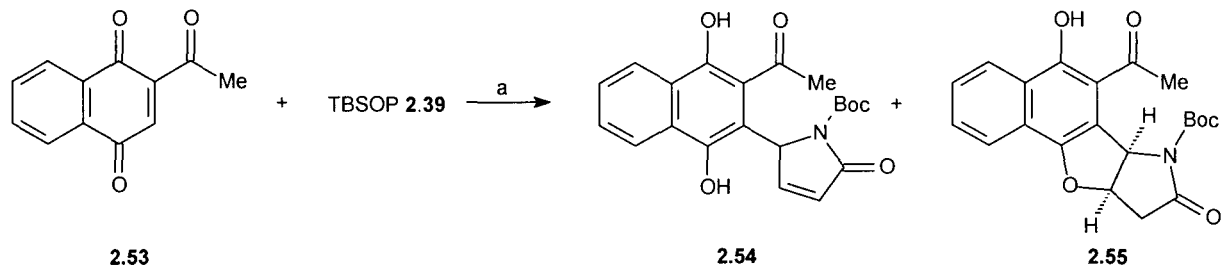
The third type of reaction which has utilized TBSOP is in Michael additions, an example of this being first reported in 2002 by Ruano *et al.*[104] who studied the BF_3.etherate-promoted addition of TBSOP to 2-(arylsulfinyl)-1,4-benzoquinone **2.51** to give hydroquinone-substituted α,β-unsaturated butyrolactam **2.52** (Scheme 2.21).



2.51 **2.39** **2.52**

Scheme 2.21. *Reagents and Conditions*: a) $BF_3.OEt_2$, DCM, -90°C, 70%.

2.52 was isolated in 70% yield as one diastereomer. In 2004, Brimble *et al.*[105] extended on Ruano's work and added TBSOP **2.39** to various quinones in an attempt to synthesize pyrrolo[3,2-*b*]naphthofuran **2.55** in one step. Thus, **2.53** underwent the addition of TBSOP in the presence of the Lewis acid $Eu(Fod_3)$ to give adducts **2.54** and **2.55** in 43% and 33% yield respectively under optimized conditions.



Scheme 2.22. *Reagents and conditions*: a) **2.53** (1 eq), **2.39** (1 eq), $Eu(Fod)_3$ (1 eq), DCM, -78°C, (1 h), then rt (16 h), **2.54** 43%; **2.55** 33%.

All the examples cited reveal the versatility of silyloxypyrroles in organic synthesis.

Comparing Casiraghi's TBSOP **2.39** and our proposed silyloxypyrrole **2.28a** derived from pyrrolinone **2.28**, revealed three differences which are highlighted in Figure 2.7 and discussed below.

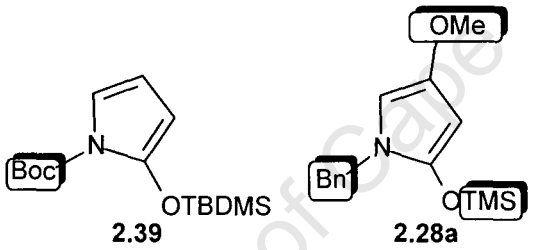


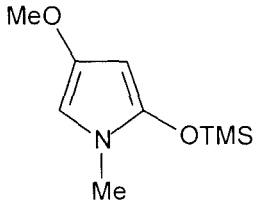
Figure 2.7

The three differences were:

- Casiraghi's silyloxy pyrrole **2.39** utilized a Boc-carbamate protecting group whereas in our case a benzyl protecting-group was chosen.
- **2.28a** contained a methoxy group at C-4 instead of a hydrogen. This would increase the nucleophilicity of the silyl dienol ether due to resonance, as well as provide an option for the C-1 hydroxyl group installation in the target.
- In keeping with our Lepadiformine work, we decided to use the trimethylsilyloxypyrrole rather that the TBS version. This change we thought would necessitate the development of a "one-pot" sequence as, unlike **2.39**, **2.28** was considered to be difficult to isolate.

There have been only two examples reported in the literature using silyloxypyrroles similar to our proposed silyloxypyrrole. Jones[91] reported in 1986 the isolation of the moisture-sensitive TMS silyl dienol ether **2.56** (Figure 2.8) of 4-methoxy-1-methyl-3-pyrrolin-2-one, as a means of characterising the corresponding dienolate, which he was using for developing a new

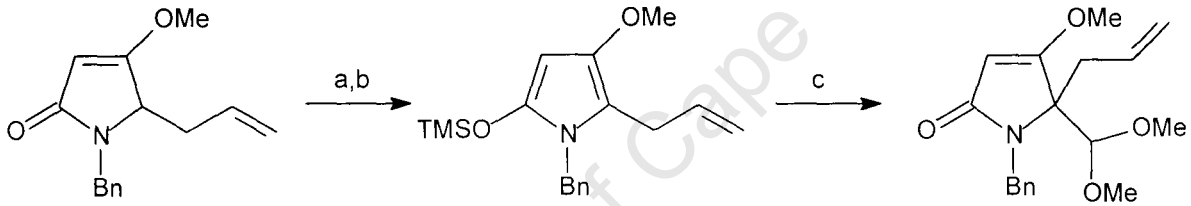
synthetic route to 5-substituted 4-*O*-methyl tetramates. He also showed that treatment of **2.56** with *n*-BuLi regenerated the dienolate.



2.56

Figure 2.8

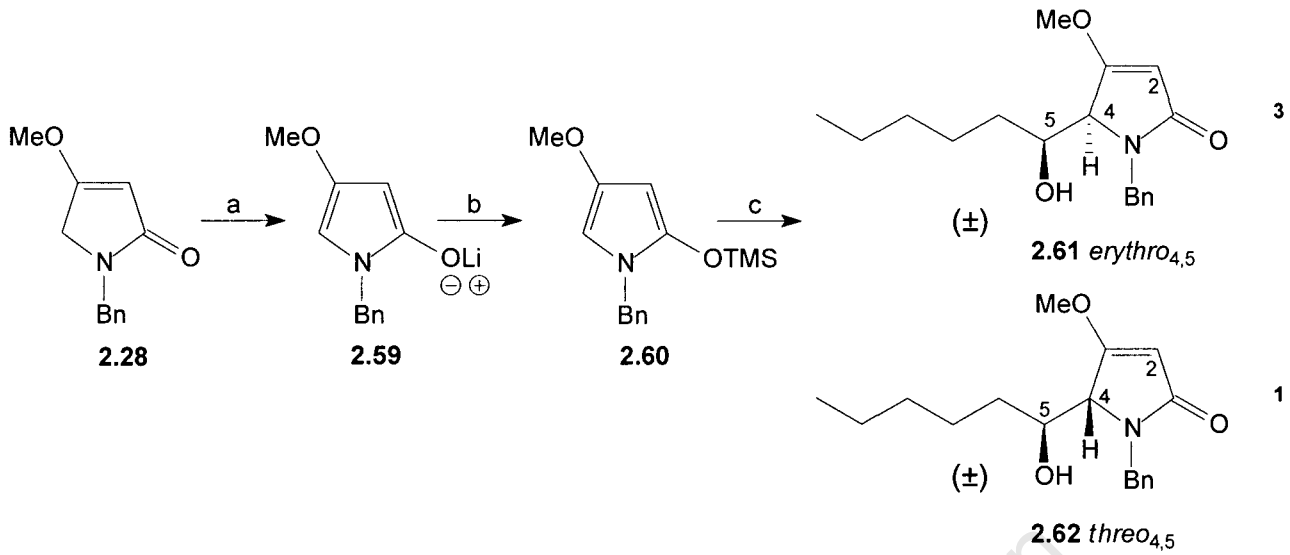
The second example comes from our group in the UCT synthesis of the tricyclic Lepadiformine core as mentioned earlier in this chapter. A novel "one-pot" procedure was reported involving the TMS silyl dienol ether of 5-allyl-1-benzyl-4-methoxypyrrolin-2-one **2.57** reacting under dissociative conditions with boron trifluoride etherate and trimethylorthoformate to give regioselectively functionalized **2.58** in 88% yield (Scheme 2.23).[82]



2.30 **2.57** **2.58**

Scheme 2.23. *Reagents and Conditions*: a) *n*-BuLi, (1.2 eq), THF, -78°C; b) TMSCl (1.5 eq); c) $HC(OCH_3)_3$, $BF_3.OEt_2$, 88%.

Both Casiraghi's and Jones' silyl dienol ethers were isolated, while ours (**2.57**) was generated *in situ*. It was decided that we would expand on previous work and adapt our conditions to pyrrolinone **2.28**. Thus, these reaction conditions were applied to our system and a model study was carried out with hexanal to establish any diastereoselective bias as well as to check regioselectivities. Before the reaction was carried out, all solvents and reagents were freshly distilled, the apparatus was dried overnight in the oven and the reaction was carried out under argon. Hence, pyrrolinone **2.28** was deprotonated with *n*-BuLi at -78°C, the enolate trapped with chlorotrimethylsilane, and then hexanal added followed by tin(IV) chloride (Scheme 2.24).



Scheme 2.24. *Reagents and Conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) hexanal; ii) $SnCl_4$ (2 eq to aldehyde), -78°C to -20°C, 70%.

The reaction was allowed to warm to -20°C gradually over 3 hours before being queuched with cold aqueous sodium bicarbonate. Tlc analysis of the crude mixture revealed that a major product had formed which was isolated by chromatography in 70% yield. Its ^{1}H NMR spectrum showed that the reaction had been regioselective as the C-2 proton was still visible. It also confirmed that the isolated product was a mixture of diastereomers as all the signals were duplicated. The ratio of diastereomers was calculated by comparing the integration of two key signals which were the doublets at δ 3.85 ppm (J = 2.0 Hz) and δ 3.95 ppm (J = 6.0 Hz) for H-4 for the two diastereomers and they were found to be in a respective ratio of 3:1. Thus it can be concluded from the NMR that the relative stereochemistry between H-4,5 was *erythro* for the major product and *threo* for the minor product as $J_{threo} > J_{erythro}$. Thus, the simple diastereselectivities favoured the desired 4,5-*erythro* stereochemistry for castanospermine. $J_{threo}>J_{erythro}$ will be discussed in greater detail at a later stage, (see page 80). With this encouraging result regarding regio- and stereoselectivity, this reaction was applied to Martin's Mukaiyama aldehyde (PG = OTBDPS) **2.63** (Figure 2.9).[69,70]

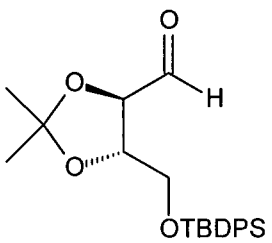
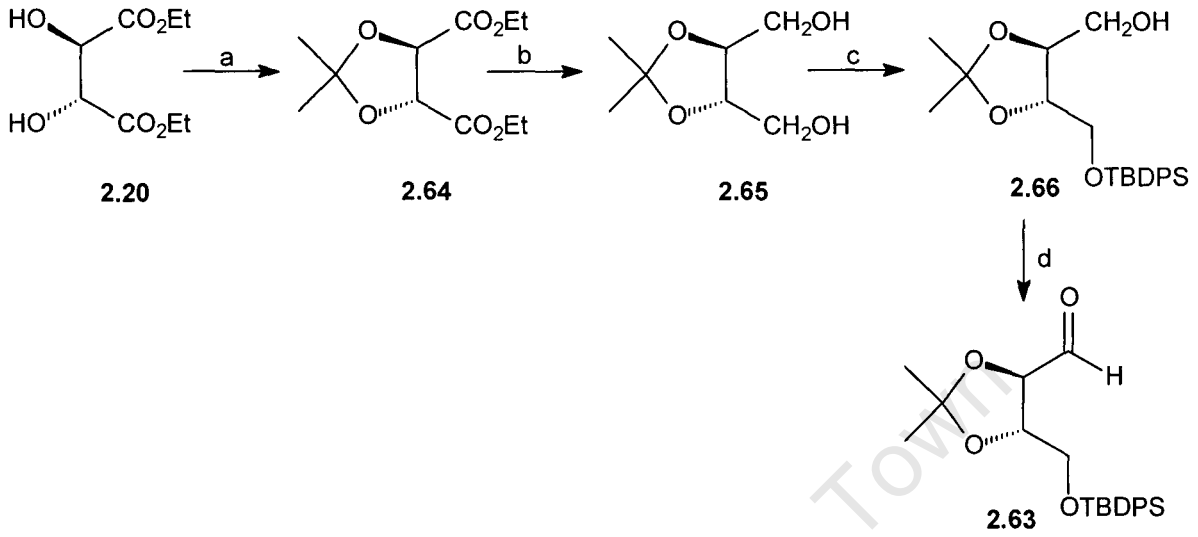


Figure 2.9

2.63

2.63 was synthesized in four straightforward steps from L-diethyl tartrate **2.20** as depicted in Scheme 2.25.

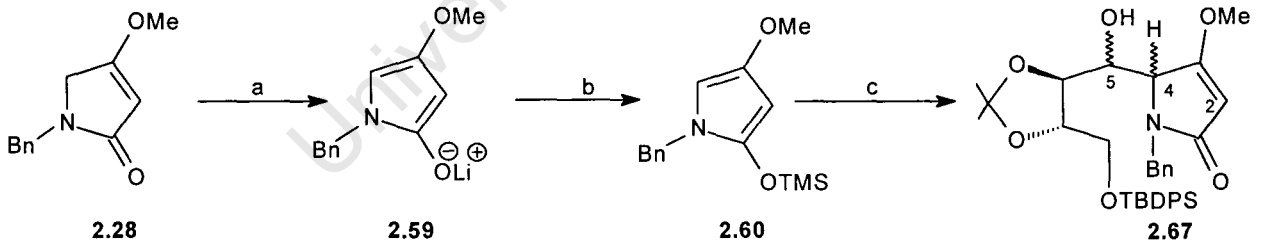


2.20 **2.64** **2.65** **2.66** **2.63**

Scheme 2.25. *Reagents and Conditions*: a) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, THF, 73%; b) $LiAlH_4$, THF, 71%; c) TBDPSCl, *n*-BuLi (1 eq), THF, 82%; d) Swern oxidation, 95%.

This synthetic route was reported by Martin and all the ^1H and ^{13}C NMR spectra of all the intermediates were identical with the ones reported by him.[70]

Pyrrolinone **2.28** was subjected to an extended Mukaiyama aldol reaction with aldehyde **2.63** under the same conditions as those for hexanal described previously.



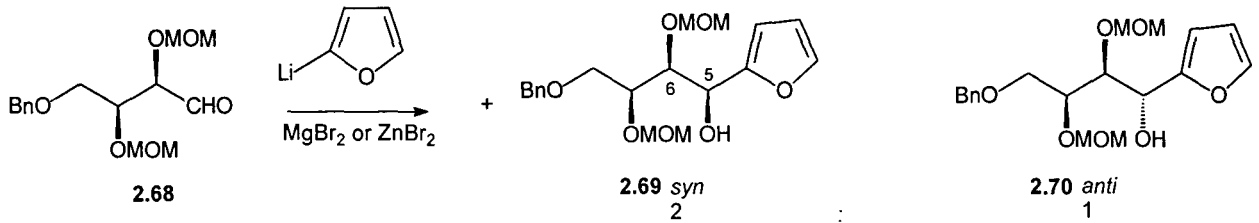
2.28 **2.59** **2.60** **2.67**

Scheme 2.26. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 min; c) i) Aldehyde **2.63**; ii) $SnCl_4$ (2 eq to aldehyde) -78°C to -20°C, 40%.

The reaction was allowed to warm to -20°C gradually over 3 hours with vigorous stirring and the reaction was quenched with cold aqueous sodium bicarbonate. Tlc analysis of the crude

mixture revealed that a major product had formed and this was isolated via chromatography in a 40% yield. Its ^{1}H and ^{13}C NMR spectra demonstrated that the reaction had been regioselective as H-2 in the ^{1}H spectrum was still intact. The ^{1}H and ^{13}C spectra also revealed that a mixture of diastereomers had formed as all the key signals were duplicated. The ratio of diastereomers was calculated by comparing the integration of the methoxy signals and found to be in a ratio of 2:1. Tlc analysis also revealed that there were very polar products forming during the course of the reaction. The reaction was repeated several times only to be found to be consistently low-yielding. The key signals in the ^{1}H NMR spectrum of the major isomer were the singlets at δ 1.07 ppm, δ 1.26 ppm, δ 1.32 ppm, δ 3.71 ppm, and δ 5.10 ppm which could be interpreted as *t*-butyl, the two ketal methyls, methoxy and H-3 respectively thus confirming that the adduct had formed. This was also confirmed by the ^{13}C spectrum which had key signals at δ 26.7, δ 44.0 ppm, δ 58.1 ppm, δ 109.6 ppm, δ 173.0 ppm and δ 174.4 ppm for the t-butyl, benzyl, methoxy, quaternary ketal, C-3 and C-1 respectively. It was difficult from the ^{1}H NMR spectrum to calculate the relative stereochemistry between C-4/C-5 as these signals overlapped with other signals to appear as a multiplet. The low yields and very polar products forming during the course of the reaction led us to speculate that perhaps the ketal protecting group was unstable in our reaction system.

Based on this result, it was decided to change the hydroxyl protecting groups to MOM (methoxymethyl) ethers, as these are more difficult to hydrolyse than an acetonide. Martin had already shown that bis-MOM ether aldehyde **2.68** reacted with 2-furyllithium to obtain the 5,6-*syn (threo)* adduct with the correct *R*-configuration for C-8 of castanospermine as the major product (Scheme 2.27).[70] Thus, by analogy, we hoped that an extended Mukaiyama aldol reaction might furnish the 5,6-*syn* (*threo*)-adduct with the correct C-8 configuration for castanospermine. It was also decided to change the primary hydroxyl protecting group from benzyl to TBDPS.

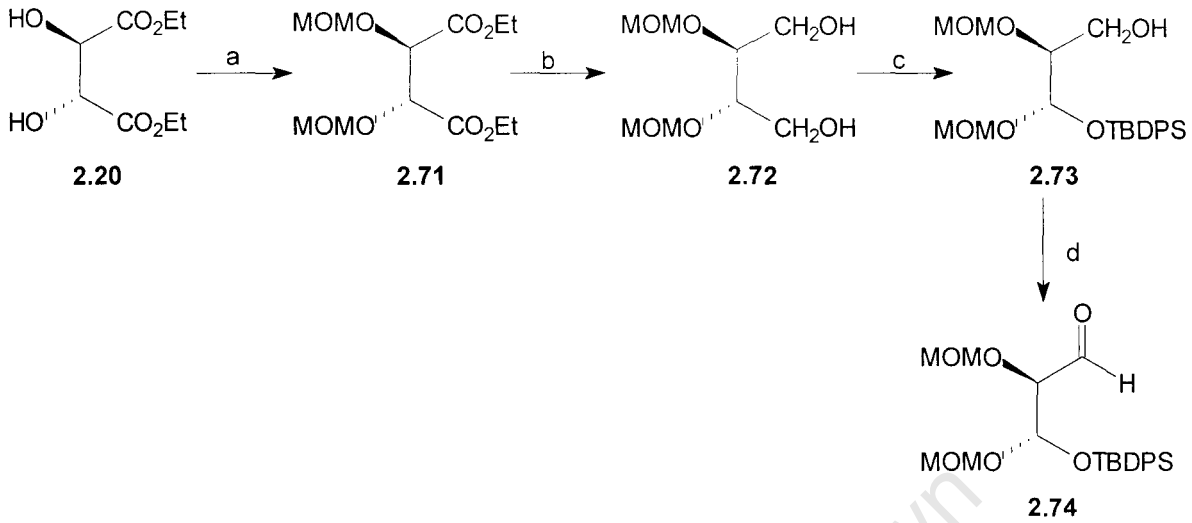


2.68 **2.69** *syn* **2.70** *anti*

2 : 1

Scheme 2.27

The synthetic route to the novel aldehyde **2.74** is shown in Scheme 2.28.



Scheme 2.28. *Reagents and Conditions*: a) $(CH_3O)CH_2$, P_2O_5, DCM, rt, 2h, 96 %; b) $LiAlH_4$, THF, -20 to rt, 4h, 78%; c) *n*-BuLi, THF, TBDPSCl, rt, 18h, 94%; d) Swern oxidation, 92%.

Its synthesis was carried out in a similar fashion to that for Martin's Mukaiyama aldehyde in four straightforward steps as shown in Scheme 2.28. In this case, the first two steps were reported in the literature and the spectral data of the intermediates were identical to those reported.[88] The diol was then treated with *n*-BuLi (1 eq) followed by TBDPSCl to give the monoprotected alcohol **2.73** in a 94% yield. The ^{1}H NMR spectrum of **2.73** showed the appearance of a *t*-butyl resonating at δ 1.06 ppm integrating correctly against the two MOM groups. The ^{13}C spectrum also confirmed the presence of the silyl ether groups with peaks at δ 19.1 ppm and δ 26.8 ppm for the two *t*-butyl carbons as well as 8 peaks in the aromatic region in view of the phenyl groups being diastereotopic. **2.73** was then oxidized under Swern conditions to give the target aldehyde **2.74**, whose ^{1}H NMR spectrum is shown below (Figure 2.10).

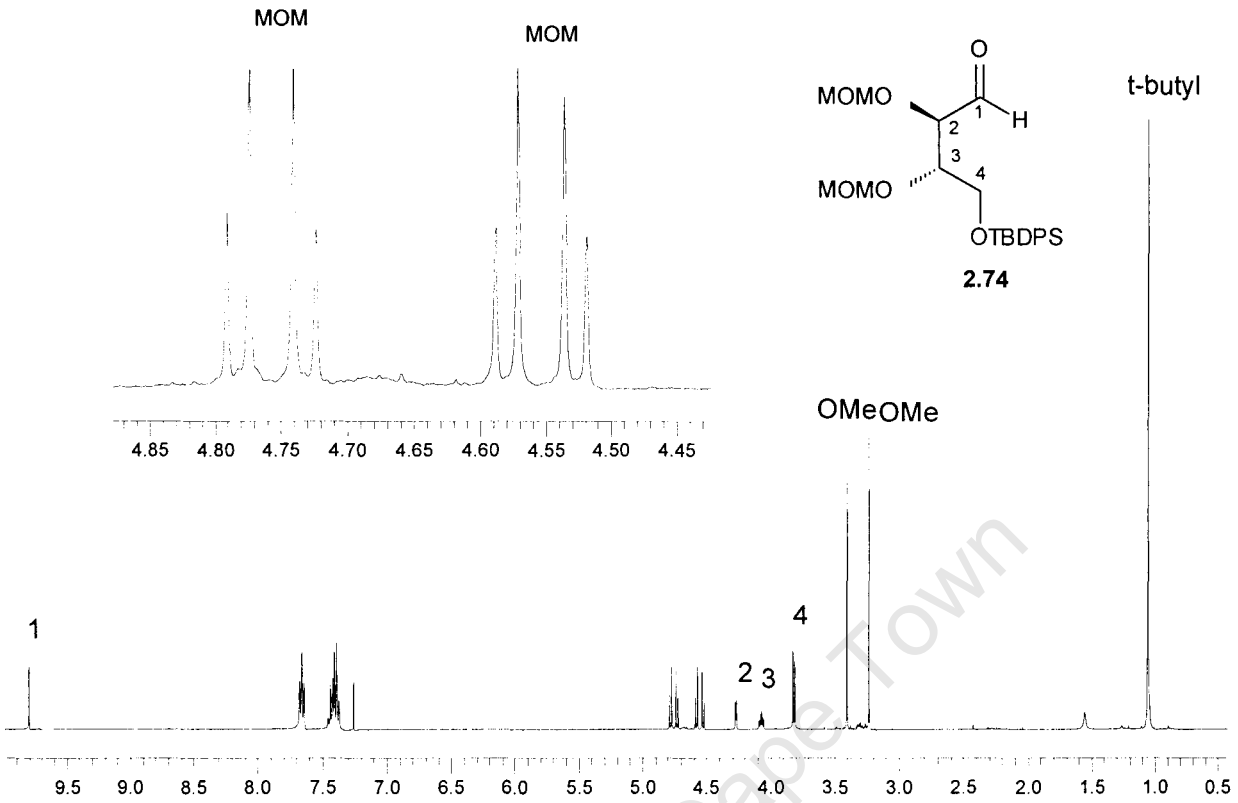
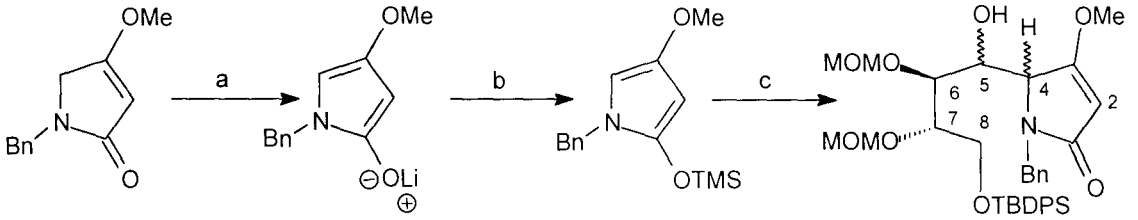


Figure 2.10

Key signals in the spectum were the doublet at δ 3.81 ppm for H-4, the triplet of doublets at δ 4.07 ppm for H-3, the doublet of doublets at δ 4.27 ppm for H-2 and the 2 AB systems for the diastereotopic methylenes of the MOM ethers. Key signals in the ^{13}C spectrum of **2.74** were observed at δ 61.4 ppm, δ 77.4 ppm, δ 81.4 ppm and δ 202.1 ppm for C-4, C-3, C-2 and C-1 respectively.

With the aldehyde now readily available we proceeded to the next step, involving an extended Mukaiyama aldol reaction using the same conditions as described before with hexanal. As before, extra care was taken to ensure that all solvents and reagents were distilled, the apparatus dried overnight in the oven and that the reaction was carried out under argon. Thus, pyrrolinone **2.28** was deprotonated with *n*-BuLi in THF at -78°C, to give a deeply red-coloured solution of anion. The enolate was trapped with chlorotrimethylsilane with disappearance of the colour to a pale yellow. Aldehyde **2.74** was then added followed by tin(IV) chloride (Scheme 2.29) in quick succession.



2.28 **2.59** **2.60** **2.75/2.76**

Scheme 2.29. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.74**; ii) $SnCl_4$ (2 eq to aldehyde), -78°C to -20°C, **2.75** 57%; **2.76** 33%; **2.74** 5%.

The reaction was allowed to warm up to -20°C gradually over 3 hours with vigorous stirring and during this time it was noted that a precipitate formed which dissolved at around -30°C. The reaction was then quenched with cold aqueous sodium bicarbonate and the tlc of the crude mixture revealed the formation of two products. The products were isolated via chromatography and the ^1H and ^{13}C NMR spectra revealed, gratifyingly, that the major product **2.75** formed in 60% yield was one pure diastereomer as evidenced by a single set of peaks in both the ^1H and ^{13}C spectra. The diagnostic signals in the ^1H NMR of the major product **2.75** were the *t*-butyl signal resonating at δ 1.06 ppm, the three methoxy signals at δ 3.04 ppm, δ 3.35 ppm, δ 3.69 ppm and the vinyl proton for H-2 at δ 5.20 ppm revealing that the two reactants had fused-together. The formation of the product was also confirmed by the ^{13}C spectrum which showed the following key signals: *t*-butyl resonating at δ 19.2 ppm and δ 26.8 ppm, the three methoxy groups resonating at δ 55.5 ppm, δ 56.3 ppm, δ 58.1 ppm, the vinyl carbon at C-2 resonating at δ 95.7 ppm, as well as 12 resonances in the aromatic region for the three aromatic rings. A portion of the ^1H NMR spectrum of **2.75** is shown in Figure 2.11 below. Resonances were assigned using 2D-techniques (COSY, HSQC). Given that tlc indicated that reaction only begins at around -50°C, that the reaction is quenched at -20°C, and that there is no strong base in the medium, we believe the major adduct to be the kinetic product. However, a more comprehensive study is needed to support this view beyond reasonable doubt.

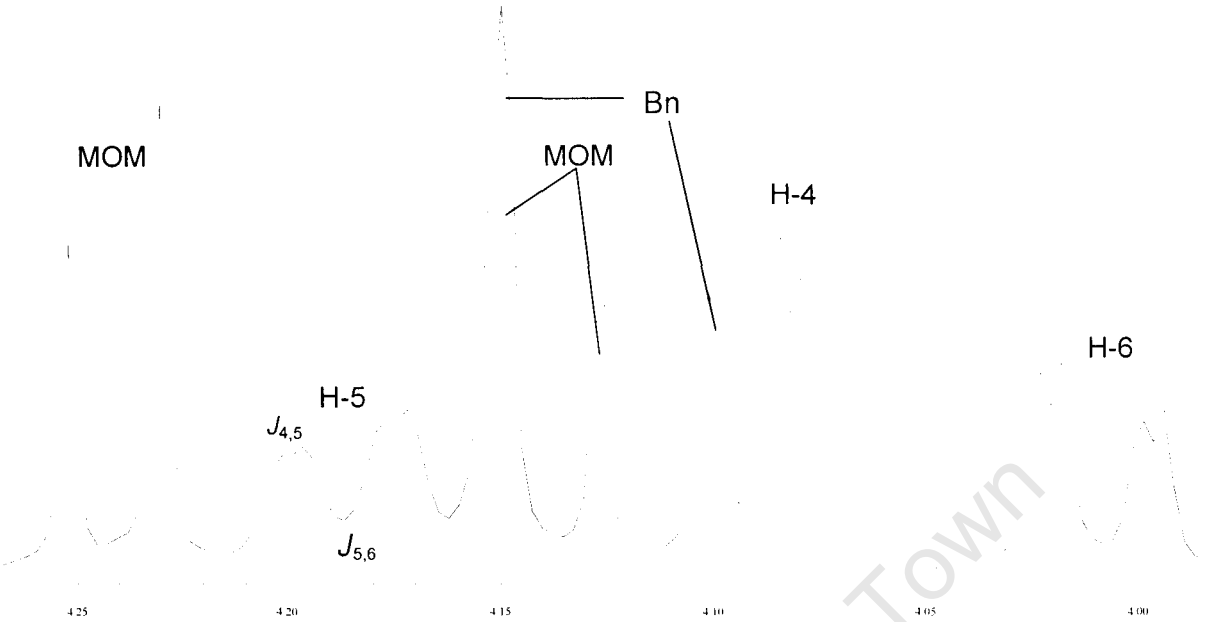
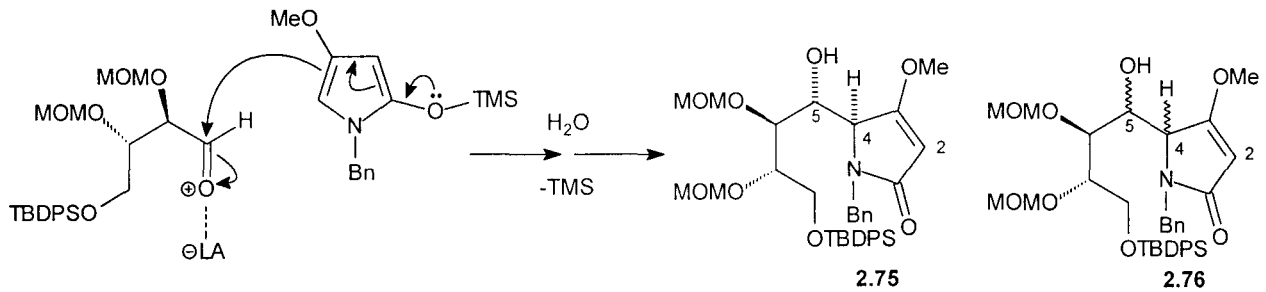


Figure 2.11

Further confirmation of the desired product was obtained from an IR spectrum which showed key signals at 1683 cm^{-1} and 1635 cm^{-1} for the lactam carbonyl and double-bond stretches respectively. Finally, formation of adduct **2.75** was confirmed by a correct elemental combustion analysis as well as a parent-ion mass $[650]^+$ in the mass spectrum. The minor product **2.76** was isolated in a yield of 34% and its ^1H NMR spectrum revealed a mixture of two diastereomers in a ratio of 2:1 as calculated by comparing the intergration of the sets of methoxy groups.

The mechanism of this reaction is outlined in Scheme 2.30.



Scheme 2.30

The relative stereochemistry between C-4 and C-5 (using the same numbering as Casiraghi) could be assigned by looking at the coupling constant of the two hydrogens. Uno, in 1999,[106] reported that an *erythro* (equivalent to *anti* in the *zig-zag* conformation) vicinal coupling constant is smaller than that for a *threo*-relationship (equivalent to *syn* in the *zig-zag* conformation); $J_{Threo} \approx 6 > J_{Erythro} \approx 2$. Figure 2.12 below illustrates the origin of the stereodescriptors from carbohydrate nomenclature.[107]

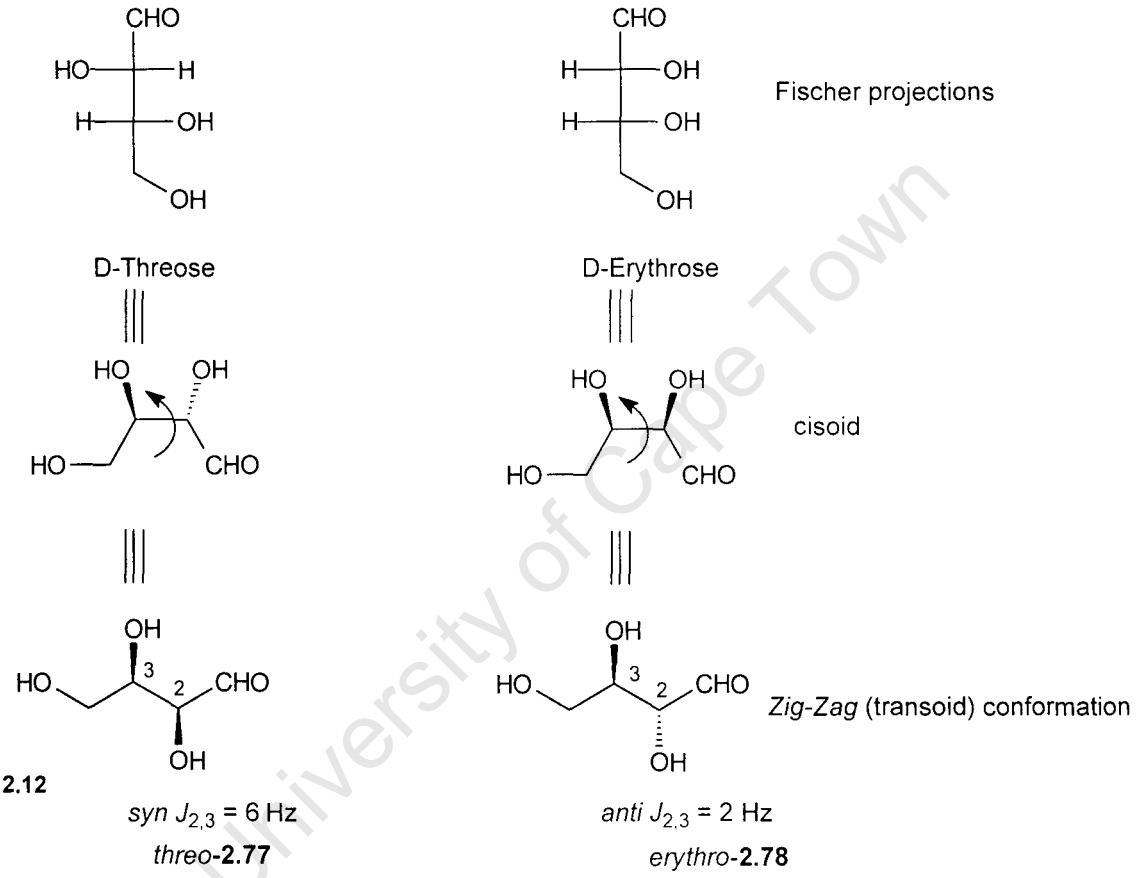
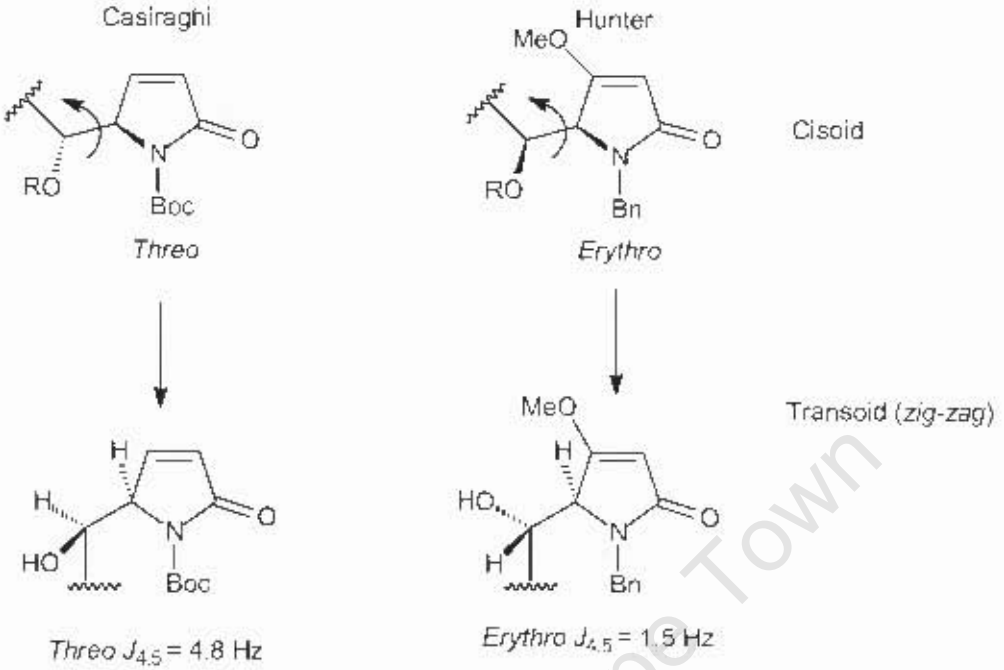


Figure 2.12

syn $J_{2,3}$ = 6 Hz
threo-**2.77**

anti $J_{2,3}$ = 2 Hz
erythro-**2.78**

In our case, it was found that the H-4/H-5 vicinal coupling constant was 1.5 Hz, revealing an *erythro*-relative stereochemical relationship. This constrasts with Casiraghi's *threo* adduct which had an H-4/H-5 coupling constant of 4.8 Hz (Scheme 2.31).[76] It was impossible to calculate the vicinal coupling constants ($J_{4,5}$) for the other diastereomers as the signals were part of a complex multiplet.



Scheme 2.31

However, the absolute stereochemistries at H-4/H-5 could not be ascertained from the NMR. Thus, **2.75** was crystallized from ethyl acetate / hexane to obtain a crystal suitable for a single crystal X-ray structure determination, to determine the absolute stereochemistry at C-4 and C-5, which is shown in Figure 2.13.

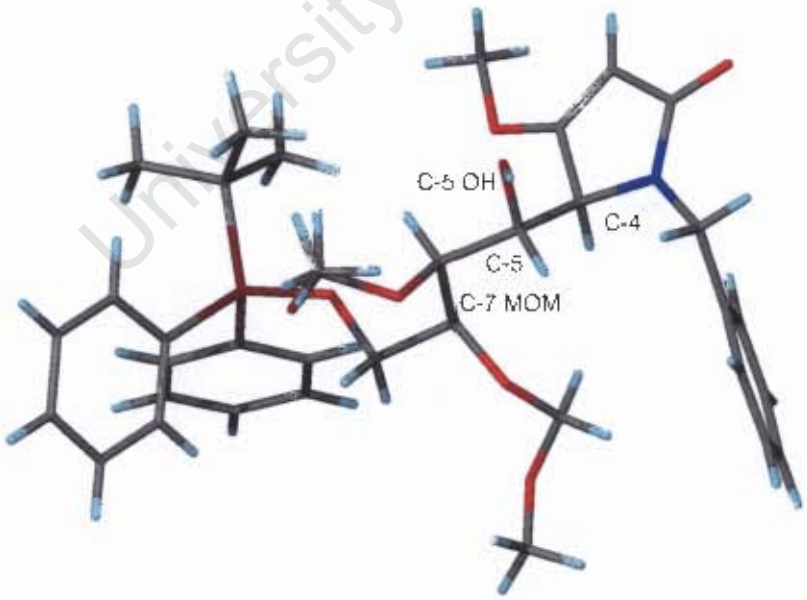
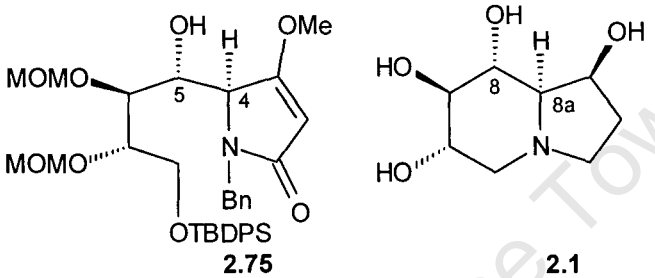


Figure 2.13. X-Ray crystal structure of **2.75**.

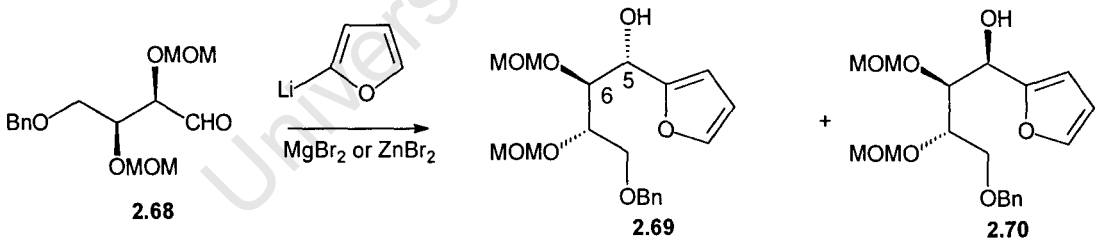
From the X-ray crystal structure it could be clearly seen that the hydrogen at C-4 was pointing downwards and that the C-5 hydroxyl was also pointing downwards. The absolute configurations at C-6 (*S*) and C-7 (*S*) were known from the L-tartrate starting material, and corresponded (Figure 2.13) correctly to those absolute configuration. The X-ray structure revealed that chiral centres C-5 and C-4 had *R*- and *S*- configurations respectively which correspond to the correct stereogencities for stereogenic centres C-8a (*R*) and C-8 (*R*) respectively for (+)-castanospermine **2.1**. Thus the absolute stereochemisty at C-4 and C-5 of **2.75** could be established as shown in Figure 2.14.



2.75 **2.1**

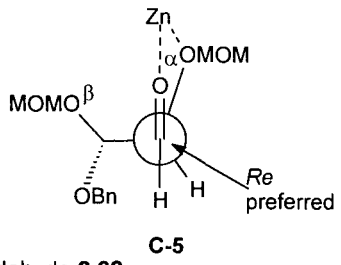
Figure 2.14

The 5,6-diastereoselectivities of the reaction can be explained by comparing it to both Martin's synthesis (Chapter 1, Scheme 1.38)[70,71] and Casiraghi's synthesis (Chapter 1, Scheme 1.42).[76] As mentioned earlier in this chapter, Martin reacted aldehyde **2.68** with 2-furyllithium to obtain the 5,6-*syn* (*threo*) and 5,6-*anti* (*erythro*) adducts (Scheme 2.32). To avoid confusion, *erythro* and *threo* terminology will be used from now.



Scheme 2.32

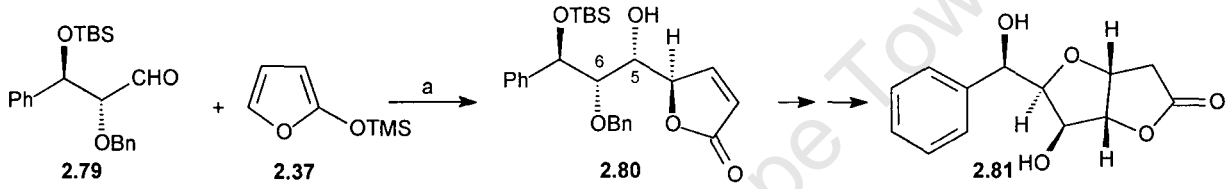
The diastereoselectivity of formation of 5,6 *threo*-adduct **2.69** was explained in this case by the aldehyde forming an α-chelate with the adjacent MOM group to form preferentially the *threo*-adduct via *Re*-face attack on the aldehyde. This is shown in Figure 2.15 below in terms of a Felkin-Ahn chelate-model transition-state.



C-5

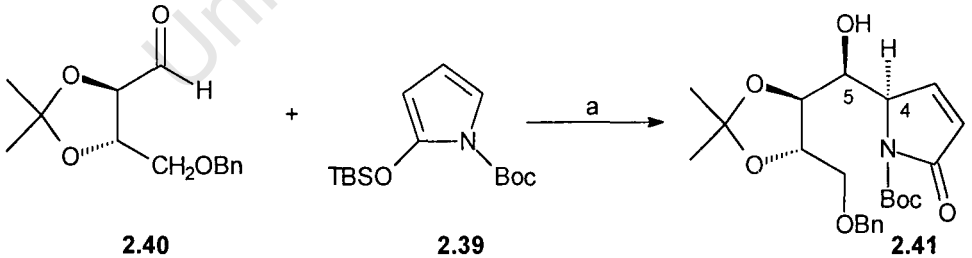
Figure 2.15. Facial selectivity of addition to aldehyde **2.68**.

Another example where the α-chelate is formed preferentially was reported by Hanaoka *et. al.*[108] in his total synthesis of (+)-goniofufurone **2.81**. In this case TMSOF **2.37** was reacted with aldehyde **2.79** via a vinylogous Mukaiyama aldol reaction and the dominant adduct **2.80** had a 5,6-*threo* stereochemistry (Scheme 2.33).

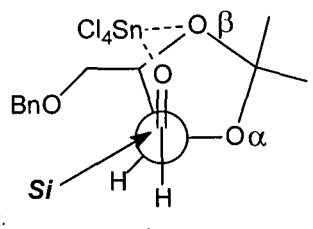


Scheme 2.33. *Reagents and Conditions*: a) $Ti(OPr^i)_2Cl_2$, CH_2Cl_2, -78°C, 54%.

By comparison, Casiraghi's synthesis, which is shown in Scheme 2.34 below, produced the incorrect *S*-configuration at C-8 for (+)-castanospermine (C-5 in Scheme 2.34). An explanation for the stereochemical outcome of the reaction has been put forward by Mukaiyama to involve a Felkin-Ahn β-chelate and this is highlighted in Figure 2.16 involving *Si*-face (undesirable for (+)-castanospermine) attack on the aldehdye.



Scheme 2.34. *Reagents and Conditions*: a) $SnCl_4$, Et_2O, -80°C, 80%.



C-5

Figure 2.16. Facial Selectivity of aldehyde **2.40**.

As Martin's adduct had the correct stereogencity at C-5 (C-8 for castanospermine), it was reasonable to conclude that our stereo-outcome at C-5 (C-8) was due to the α-chelate and that the pyrrolinone was adding to the *Re*-face of the aldehyde. This is outlined in Figure 2.17. Presumably a β-chelate only works with a cyclic ketal (acetonide) protecting group between the hydroxyl groups.

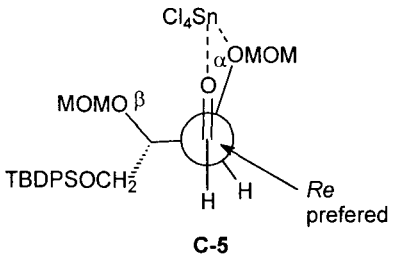


Figure 2.18. Facial Selectivity of aldehyde of **2.75**.

Both our adduct **2.75** and that of Casiraghi's **2.41** had the same and correct (for castanospermine) absolute configuration at C-4 derived from *Si* attack on the silyloxypyrrole. However, the silyloxypyrroles need to be orientated relatively differently in each case. In Casiraghi's case, the aldehyde carbonyl oxygen points towards the *N*-Boc end where possible cooperative interaction between tin and the carbamate carbonyl oxygen may play a role in the transition state. Such an arrangement also ensures that the aldehyde chain points away from the pyrrole ring. Conversely, in our case, *Si*-face selectivity on **2.28** is consistent with the carbonyl group of the aldehyde **2.74** pointing inwards over the pyrrole in an *endo*-Diels-Alder-like fashion to ensure that the C-1/C-2 bond of the aldehyde **2.74** points away from the pyrrole ring to accommodate the C-2 hydrogen. Furthermore, the C-3 methoxy group of **2.28** may develop cooperative interactions with tin as shown in Figure 2.18, which shows possible transitions-state models for the two reactions.[78,94]

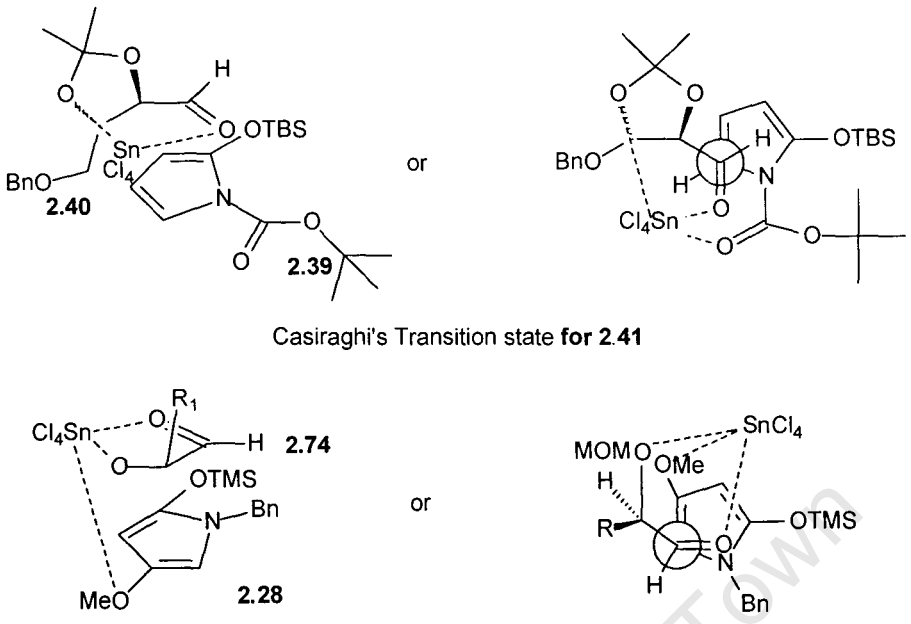


Figure 2.18. Transition-state models for formation of adducts **2.41** and **2.75**.

It can be deduced that the transition-state for Hanaoka's aldol proceeds via the same transition state as ours involving an *endo*-Diel-Alder-like model.[108] Thus, it may be deduced that if *R*-configuration is required at the chiral centre with the hydroxyl, then an open-chained aldehyde (α-chelate) should be used, while if *S*-configuration is required, then the Mukaiyama aldehyde (β-chelate) should be used.

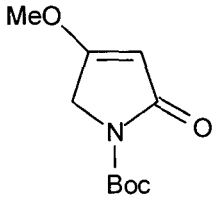
Regarding experimental considerations, as expected for a reaction involving moisture-sensitive reagents, it was found that the best results were achieved with the following:

- All solvents, apparatus and starting materials were scrupulously dried before use.
- The chlorotrimethylsilane was always freshly distilled prior to addition.
- The reaction was consistently conducted at around 0.3 M in concentration.
- Vigorous stirring was maintained in each run, especially during the period when the reaction was warming to -20°C.

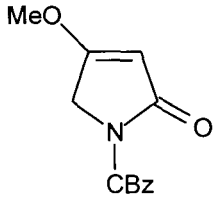
The reaction was carried out numerous times and even on a relatively large scale (2 g of pyrrolinone) the results were reproducible provided the above conditions were followed. The adduct **2.75** was found to be extremely stable towards silica-gel and showed no sign of decomposition according to ^{1}H NMR spectroscopy even after 1 year standing on the bench.

Once the conditions had been established, we then explored the coupling further by changing the nitrogen protecting-group on the pyrrolinone to establish if this would influence the reaction in some way. The first change made was to replace the *N*-benzyl group to a Boc and Cbz carbamate, in order to make pyrrolinones **2.82** and **2.83** similar to Casiraghi's silyloxy pyrrole TBSOP **2.39** (Figure 2.19).[76]

Figure 2.19

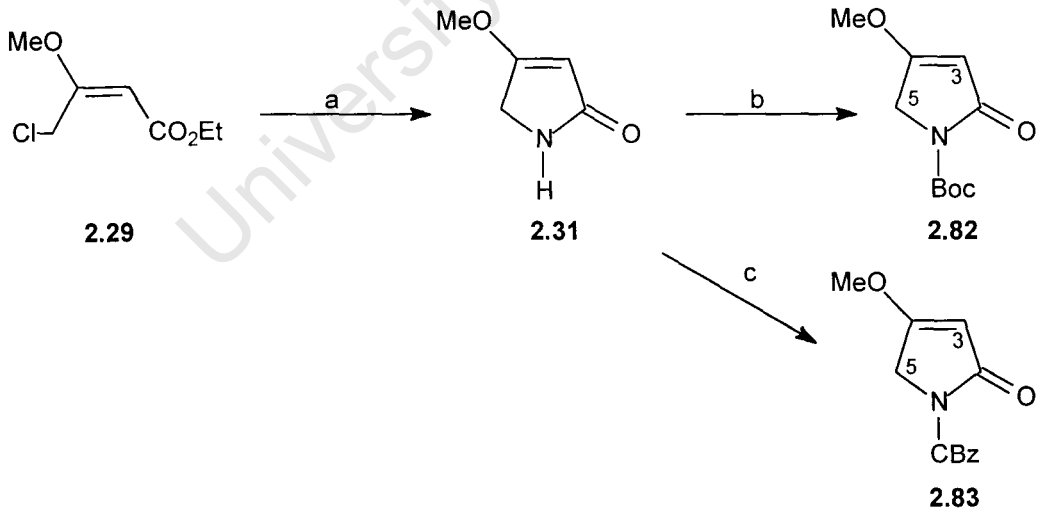


2.82



2.83

Pyrrolinones **2.82** and **2.83** were readily obtained from ethyl 4-chloro-3-methoxybut-2-enoate **2.29** in 2 steps as described in Scheme 2.35 via pyrrolinone **2.31**. Synthesis of **2.31** involved using conditions (10% ammonia) as described in our previous work. Its ^{1}H NMR spectrum was identical with the one reported.[93] Lactam **2.31** was then treated with di-*tert*-butyl dicarbonate $(Boc)_2O$ in the presence of 4-dimethylaminopyridine (DMAP) in acetonitrile to give **2.82**. To synthesize pyrrolidinone **2.83**, pyrrolinone **2.31** was treated with sodium hydride and benzyl chloroformate in tetrahydrofuran to give **2.83** in a 50% chromatographed yield (Scheme 2.35).



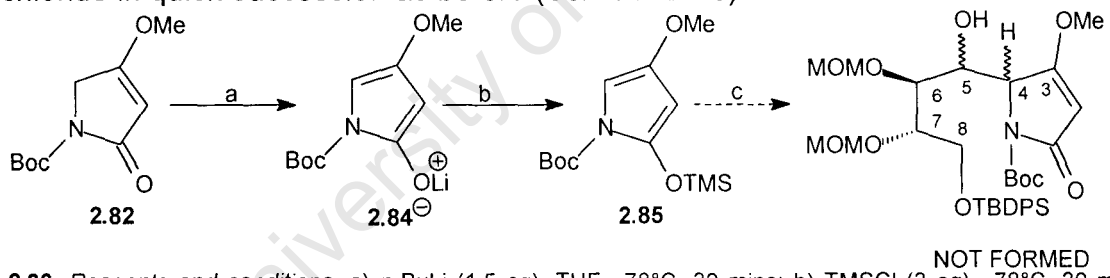
2.29 **2.31** **2.82** **2.83**

Scheme 2.35. *Reagents and Conditions*: a) 10% ammonia, 65°C, 80%; b) $(Boc)_2O$, DMAP, CH_3CN, rt, 84%; c) NaH (3 eq), Benzyl Chloroformate (1.1 eq), THF, rt, 50%.

The ^{1}H NMR spectrum of **2.82** revealed a singlet at δ 1.50 ppm integrating for 9 protons for the *t*-butyl group, a singlet at δ 4.14 ppm integrating for 2 protons for the methylene at C-5, a singlet at δ 3.80 ppm, integrating for 3 protons for the methoxy signal and finally a singlet at δ 5.05 ppm for the vinyl proton at C-2 integrating for 1 proton and all in accordance with the structure. The ^{13}C NMR spectrum confirmed the structure of **2.82** with the correct number of carbon resonances, i.e. 8, two of them as carbonyl carbons at δ 150 ppm and δ 174.5 ppm. The key signals in the IR spectrum were the signals at 1779 cm^{-1}, 1682 cm^{-1}, and 1626 cm^{-1} for the carbamate and lactam carbonyl groups and double bond respectively. Finally, formation of **2.82** was confirmed by both a correct elemental combustion analysis as well as a parent-ion mass $[214]^{+}$ in the mass spectrum.

The ^{1}H NMR spectrum of **2.83** was virtually indentical to that of **2.82** except for the appearance of the aromatic signals and the singlet at δ 5.29 ppm for the benzyl methylene group.

For the vinylogous Mukaiyama aldol reaction, pyrrolinone **2.82** was deprotonated with *n*-BuLi at -78°C, the enolate trapped with chlorotrimethylsilane, and aldehyde **2.74** added followed by tin(IV) chloride in quick succession as before (Scheme 2.36).

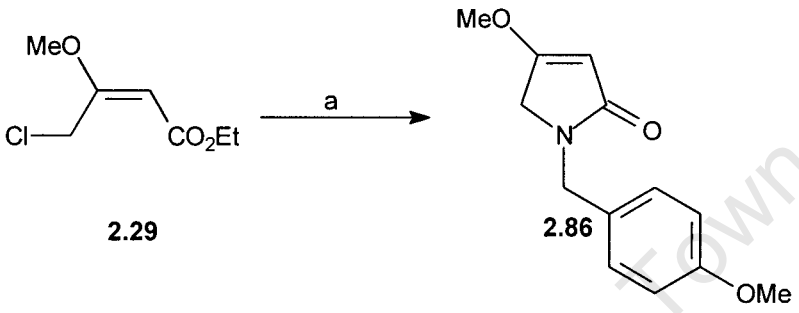


Scheme 2.36. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.74**; ii) $SnCl_4$ (2 eq to aldehyde) -78°C to -20°C.

The reaction was allowed to warm to -20°C over a 3 hr period, after which it was quenched in the normal fashion. Tlc of the crude mixture revealed the disappearance of starting material and the appearance of a streak of spots. The reaction was repeated and the same tlc profile (a streak) was obtained. The same profile was obtained reacting CBz-carbamate **2.83**. It was concluded from this that perhaps the Boc and Cbz protecting groups were unstable under these conditions towards the *n*-BuLi, since in Casiraghi's work the silyl dienol ether was generated using a milder base and was isolated (2,6 lutidine and TBSOTF). It was decided not to attempt formation of the TBS dienol ether using TBSOTF and lutidine as used by

Casiraghi, as we wanted to develop a "one-pot" methodology using the less expensive TMSCl.

The next group selected was the *p*-methoxybenzyl group, which was easily achieved by using the same conditions as described before for the synthesis of pyrrolinone **2.28** except using *p*-methoxybenzylamine (Scheme 2.39). It was anticipated that this group wouldn't affect the stereo-outcome to any great extent, but would offer an alternative deprotection methodology.

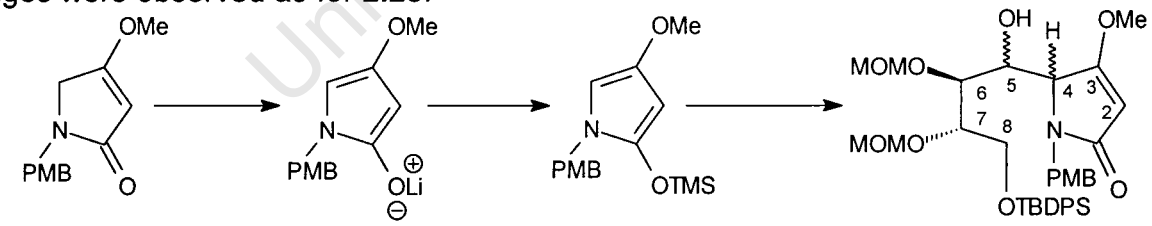


2.29 **2.86**

Scheme 2.39. *Reagent and Condition*: a) *p*-MeOBnNH$_2$, Hünig's base, CH$_3$CN, 65°C, 67%.

The ^{1}H NMR spectrum of **2.86** was virtually indentical to that of **2.28** except for the AB aromatic doublets at δ 6.83 and 7.14 ppm respectively as well as the extra methoxy singlet at δ 3.77 ppm.

2.86 was then subjected to the same sequence of events as before involving deprotonation with *n*-BuLi at -78°C, trapping of the enolate with chlorotrimethylsilane, followed by sequential addition of aldehyde **2.74** (1 eq) followed by tin(IV) chloride (Scheme 2.40). The same colour changes were observed as for **2.28**.



2.86 **2.87** **2.88** **2.89/2.90**

Scheme 2.40. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.74**; ii) SnCl$_4$ (2 eq to aldehyde), -78°C to -20°C, **2.89** 63%; **2.90** 24%; **2.74** 11%.

The reaction mixture was allowed to gradually warm to -20°C with vigorous stirring over 3 hrs and the reaction was quenched with cold aqueous sodium bicarbonate. Tlc of the mixture revealed that two products had formed which were isolated via chromatography and the ^{1}H

NMR spectrum of the major product **2.89** revealed that it was one pure diastereomer (in a 70% yield). The key diagnostic signals of the major product **2.89** were compared to adduct **2.75** and are shown in Table 3 below:

Table 3

Assignment (see Scheme **2.40** for numbering)	δ_H for **2.75** Bn, OMe	Multiplicity and Coupling Constants	δ_C for **2.75** Bn, OMe	δ_H for **2.89** PMB, OMe	Multiplicity and Coupling Constants	δ_C for **2.89** PMB, OMe
C-4	4.09	d, 1.5 Hz	60.8	4.08	d, 2.0 Hz	60.9
C-5	4.19	dd, 7.3, 1.5 Hz	68.2	4.19	dd, 7.2, 2.0 Hz	68.3
C-6	4.01	dd, 7.3, 1.5 Hz	80.5	3.99	dd, 6.9 Hz, 1.8 Hz	80.9
C-7	3.80	m	77.9	3.82	m	77.9
C-8	3.80	m	62.3	3.82	m	62.4
C-2	5.20	s	95.7	5.20	s	95.7

A comparison of the ^{1}H and ^{13}C NMR spectra of adducts **2.75** and **2.89** (Table 3) revealed a striking similarity in key signals suggesting an identical set of stereochemical relationships. Further support for this was given by the *J* value between H-4 and H-5 for the major product **2.89**, which was found to be 2.0 Hz thus confirming an *erythro* relationship. To confirm the absolute stereochemistry, the adduct was recrystallized from ethyl acetate / hexane and a single X-ray crystal determination was obtained which is shown in Figure 2.20. As with adduct **2.75** from the X-ray crystal structure it could be clearly seen that the hydrogen at C-4 was pointing downwards and that the C-5 hydroxyl was also pointing downwards. This was relative to the C-6/C-7 centres from L-tartrate appearing with their correct absolute configurations.

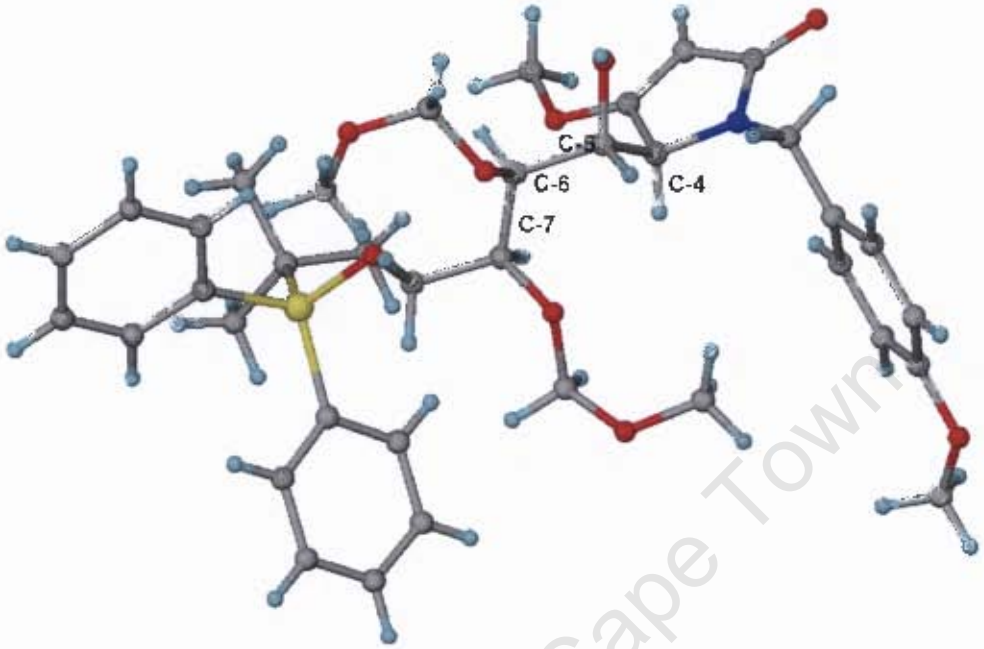
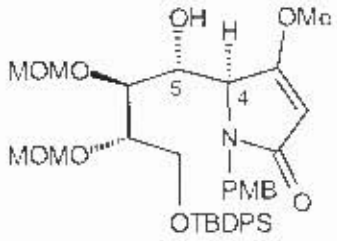


Figure 2.20. A Single Crystal X-Ray determination of **2.89**.

As with the benzyl-protected adduct **2.75**, stereogenic centres C-5 and C-4 had *R*- and *S*-configurations respectively which is the correct stereogencity for stereogenic centres C-8 (*R*) and C-8a (*R*) respectively of (+)-castanospermine. Thus, the absolute stereochemistry at C-4 and C-5 is shown in Figure 2.21.



2.89

Figure 2.21. Absolute stereochemistry at C-4 and C-5 for **2.89**.

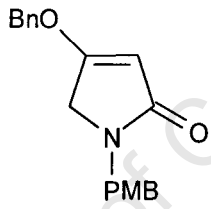
The minor product **2.90** was isolated in 30% and its ^{1}H NMR spectrum again revealed a mixture of two diastereomers in a ratio of 2:1.

The results of this "one-pot" extended Mukaiyama aldol study are summarized in the table below:

Table 4

NITROGEN PROTECTING GROUP	REACTION
Benzyl	A major adduct formed with 4,5-*erythro*-5,6-*threo* stereochemistry.
p-Methoxybenzyl	A major adduct formed with 4,5-*erythro*-5,6-*threo* stereochemistry
Boc	No adduct formed
CBz	No adduct formed

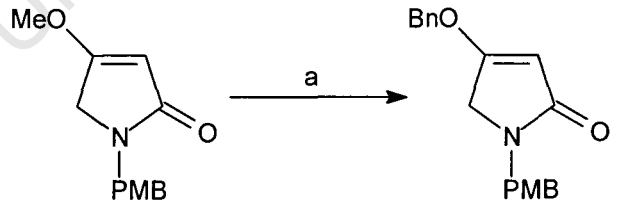
With these results in mind, it was decided next to explore the influence of the vinyl ether on the outcome of the reaction. Hence, the methyl ether was exchanged for a benzyl ether (Figure 2.22).



2.91

Figure 2.22

This was easily achieved by treating **2.86** with excess benzyl alcohol in the presence of *p*-toluenesulfonic acid at 80°C with vacuum (water-pressure) removal of methanol to give pyrrolinone **2.91** in 67% isolated yield Scheme 2.41.

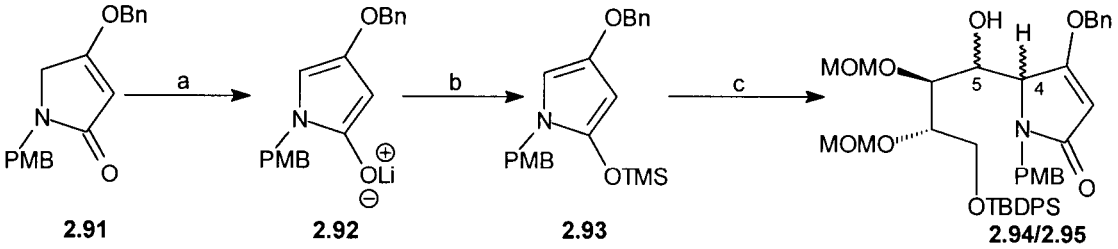


2.86 **2.91**

Scheme 2.41. *Reagents and Conditions*: a) BnOH, *p*-TsOH, 80°C, 5h, 67%.

The ^{1}H NMR spectrum of **2.91** was similar to that of **2.86** except that the methoxy signal had disappeared and replaced by a multiplet in the aromatic region as well as a singlet at δ 4.94 ppm for the benzylic methylene group.

Thereafter, pyrrolinone **2.91** was carried through the same sequence of reaction with **2.74** as before (Scheme 2.42).



Scheme 2.42. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.74**; ii) $SnCl_4$ (2 eq to aldehyde) -78°C to -20°C, **2.94** 63%; **2.95** 25%; **2.74** 12%.

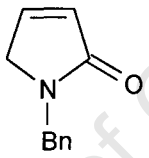
The reaction mixture was allowed to warm gradually to -20°C with vigorous stirring and was quenched with cold sodium bicarbonate. The tlc of the crude mixture showed the formation of two products and these were isolated via chromatography. The ^{1}H and ^{13}C NMR spectra of the major product **2.94** (formed in 65% yield) revealed it to be a single diastereomer. The key diagnostic signals of the ^{1}H and ^{13}C NMR of **2.94** are shown in Table 5 below and are compared to those of **2.75**.

Assignment (for numbering see Scheme 2.40)	δ_H for **2.75** Bn, OMe	Multiplicity and Coupling Constants	δ_C for **2.75** Bn, OMe	δ_H for **2.94** PMB, OBn	Multiplicity and Coupling Constants	δ_C for **2.94** PMB, OBn
C-4	4.09	d, 1.5 Hz	60.8	4.22	complex*	61.9
C-5	4.19	dd, 7.3, 1.5 Hz	68.2	4.22	complex*	68.7
C-6	4.01	dd, 7.3 1.5 Hz	80.5	3.92	dd, 6.0 , 2.1 Hz	78.4
C-7	3.80	m	77.9	3.80	m	77.9
C-8	3.80	m	62.3	3.80	m	62.3
C-2	5.20	s	95.7	5.20	s	96.7

Table 5 * Part of a complex region

It was not absolutely certain from the ^{1}H and ^{13}C NMR spectra as to whether the major product **2.94** had the same absolute stereochemistry as **2.75** and **2.89**. Presumably the introduct of a benzyl group at C-3 resulted in some inevitable shifts. Some indication came from the tlc Rf values. Thus, the major product, as in the previous couplings, appeared on the tlc plate below the excess pyrrolinone starting material, while the minor product appeared above the starting pyrrolinone and in the same ratios to the other successful coupling. It was also noted that the $[\alpha]_D$ of the adducts **2.75** and **2.89** were positive as was the case for **2.94**. In Casiraghi's synthesis of (+)-1-deoxy-castanospermine, compounds with C-5 having the hydrogen pointing down had positive $[\alpha]_D$ values.[76] With this information, it was concluded that the adduct formed likely had the same absolute stereochemistry as before.

The next structural change made was to replace the alkoxy group of the vinyl ether by a hydrogen to make the pyrrolinone once again similar to Casiraghi's silyloxy pyrrole (Figure 2.23). In so doing, the influence of the vinyl ether group on the reaction could be established.

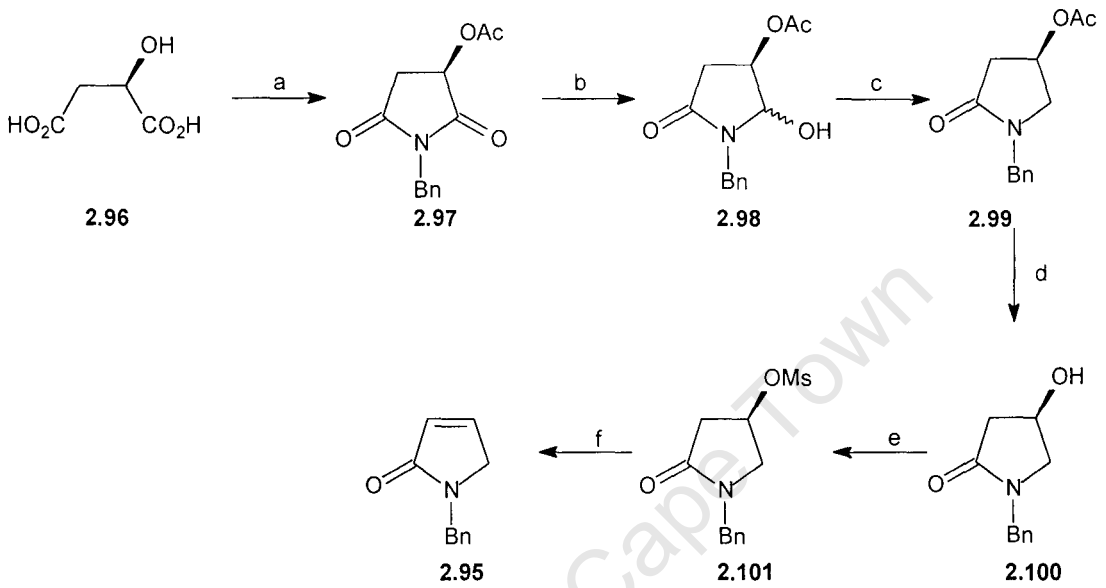


2.95

Figure 2.23

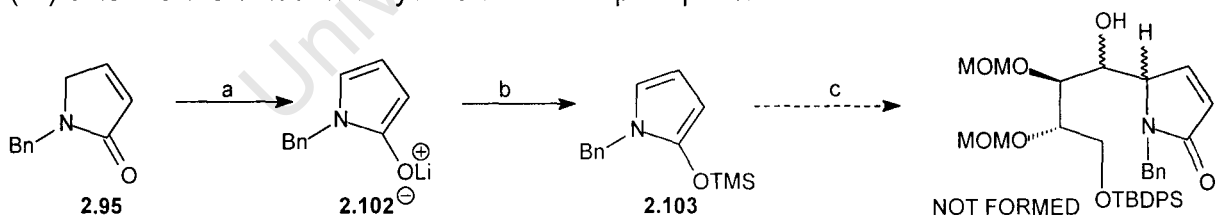
From previous work in our group, the synthesis of pyrrolinone **2.95** could be achieved in 6 steps from L-malic acid and its synthetic route is outlined in Scheme 2.43 below. Thus L-malic acid **2.96** was heated under reflux with acetyl chloride to form an acetylated anhydride, which reacted with benzylamine to give an acid amide that was cyclized with acetyl chloride to afford imide **2.97** in 84% overall yield after chromatography. The chemical shift values of the ^{1}H and ^{13}C spectra of **2.97** were identical to those reported in the literature,[109] and so it was regioselectively reduced at the more electrophilic carbonyl group adjacent to the acetoxy group to give lactol **2.98** in 96% yield.[109] **2.98** was sufficiently pure by ^{1}H NMR to proceed to the next step without any further purification. Reductive removal of the α-hydroxy group of the α-hydroxy lactam was achieved by the literature procedure of derivatising to the corresponding trifluoroacetate followed by reduction of the *N*-acyliminium ion (promoted by TFA) with Et_3SiH. This gave lactam **2.99** in 74% after column chromatography. Both its ^{1}H and ^{13}C spectra were identical with the ones reported in the literature.[110] The acetate ester of **2.99** was then base-hydrolysed, the resultant hydroxyl group converted to its mesylate to give

2.101 in an overall yield of 90% after column chromatography. Elimination of the mesylate promoted by the acidic proton α- to the carbonyl under basic conditions (NEt_3) gave the target in a 70% yield. The ^1H and ^{13}C NMR spectra of **2.95** were identical with the ones reported in the literature.[111]



Scheme 2.43. *Reagents and Conditions*: a) i) AcCl, Δ; ii) $BnNH_2$, THF, rt; iii) AcCl, Δ, 84%; b) $NaBH_4$, EtOH, 96%; c) i) $(CF_3CO)_2O$, DCM; ii) CF_3CO_2H, Et_3SiH, 74%; d) KOH, MeOH; e) MsCl, Et_3N, DMAP, 90%; f) Et_3N, THF, Δ, 70%.

Pyrrolinone **2.95** was subjected to our "one-pot" aldol conditions with aldehyde **2.74** using the standard conditions (Scheme 2.44). The only visible difference was that after the addition of tin (IV) chloride the solution stayed clear i.e no precipitate formed.



Scheme 2.44. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.74**; ii) $SnCl_4$ (2 eq to aldehyde).

The tlc of the crude mixture revealed that the two starting materials had not reacted and these were recovered via chromatography. The reaction was repeated and the same tlc profile was obtained. On the assumption that *n*-BuLi deprotonated H-4 and that the dienol silyl ether formed, this result indicates that the vinyl ether plays an important role in our reaction.

Presumably in the N-benzyl series, the presence of a C-3 methoxy group is essential to achieve appropriate nucleophilic character at C-4 of the diene by raising the energy of the HOMO, as well as ensuring a high HOMO coefficient at C-4. This contrasts with Casiraghi's *N*-Boc carbamate, in which the absence of an activating methoxy group is presumably counter-balanced by the Boc carbamate protecting group's attenuating effects on nitrogen.

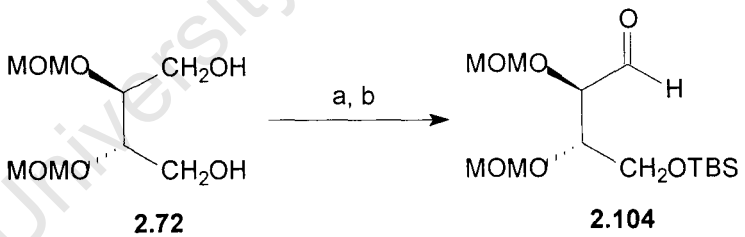
The results of this study are summarized in Table 6 below:

Table 6.

C-3 SUBSTITUENT	REACTION
OBn	Adduct formed
H	No product formed

With these results in mind, it was decided next to explore the properties of the aldehyde and its influence in the outcome of the reaction. The bulky silyl ether protecting group was exchanged for the smaller *t*-butyldimethylsilyl ether in order to see if this would have an affect on the outcome of the reaction.

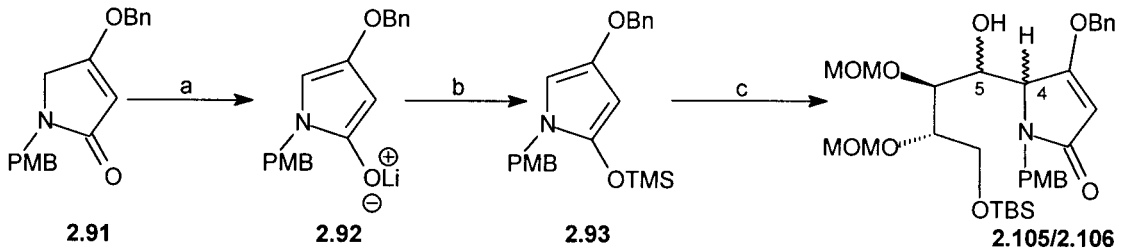
The synthesis of this new aldehyde was carried out in two straightforward steps from diol **2.72** as outlined in Scheme 2.45 below.



2.72 **2.104**

Scheme 2.45. *Reagents and Conditions*: a) *n*-BuLi (1 eq), THF, TBSCl, rt, 18h, 93%; b) Swern oxidation, 90%.

The ^{1}H and ^{13}C NMR spectra of **2.104** were identical with the ones reported in the literature.[112] Pyrrolinone **2.91** was then committed to an aldol sequence in the normal fashion (Scheme 2.46).



Scheme 2.46. *Reagents and conditions*: a) *n*-BuLi (1.5 eq), THF, -78°C, 30 mins; b) TMSCl (3 eq), -78°C, 30 mins; c) i) Aldehyde **2.104** ii) $SnCl_4$ (2 eq to aldehyde), **2.105** 57%; **2.106** 22%; **2.104** 18%.

The reaction was allowed to warm up gradually to -20°C with vigorous stirring over 3 hrs and the reaction mixture quenched with cold sodium bicarbonate. The tlc of the crude mixture revealed that two products had formed. The products were isolated via chromatography and the ^{1}H NMR spectrum of the major product **2.105** revealed that one pure diastereomer had formed (in a 57% yield). The NMR diagnostic signals of **2.105** are shown in Table 7 below, with comparison to adduct **2.75.**

Assignment (For numbering see scheme 40)	δ_H for **2.75** Bn, OMe, TBDPS	Multiplicity and Coupling Constants	δ_C for **2.75** Bn, OMe, TBDPS	δ_H for **2.105** PMB, OBn, TBS	Multiplicity and Coupling Constants	δ_C for **2.105** PMB, OBn, TBS	δ_C for **2.94** PMB, OBn, TBDPS
C-4	4.09	d, 1.5 Hz	60.8	4.22	d, 2.0 Hz	61.9	61.9
C-5	4.19	d, 7.3,1.5 Hz	68.2	4.27	m	68.5	68.7
C-6	4.01	d, 7.3, 1.5 Hz	80.5	3.78	m	78.6	78.4
C-7	3.80	m	77.9	3.70	m	78.0	77.9
C-8	3.80	m	62.3	3.70	m	62.3	62.3
C-2	5.20	s	95.7	5.22	s	96.6	96.7

Table 7

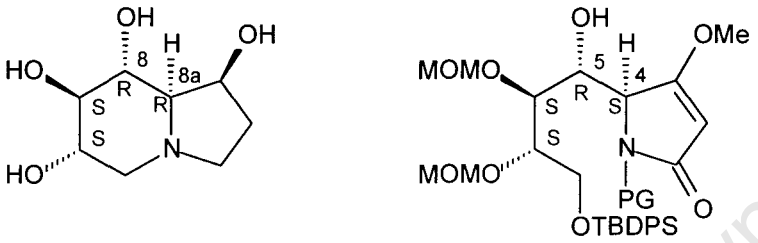
From the ^{1}H NMR spectrum of **2.105**, $J_{4,5}$ was found to 2.0 Hz, thus, confirming that the relative stereochemistry was *erythro*. Once again the major product appeared on the tlc below the excess starting material while the minor product appeared above the starting in same ratio as before. The $[\alpha]_D$ in this case was also positive hence it can be concluded that more than likely the absolute stereochemistry was *S* and *R* for C-4 and C-5 respectively as with the other adducts. The ^{13}C spectrum of **2.94** was compared to **2.105** and it was found that they were nearly identical which lent further support for this view.

Thus, it seems likely that changing the silyl protecting group does not influence the outcome of the reaction, which seems reasonable in view of its lack of proximity to the reacting centres.

From all these studies it can be concluded that for our system, the reaction only proceeds in the presence of a C-3 vinyl ether and that an *N*-carbamate protecting group as a nitrogen protecting group is incompatible with the reaction conditions.

2.3 Generation of the indolizidine skeleton towards (+)-castanospermine

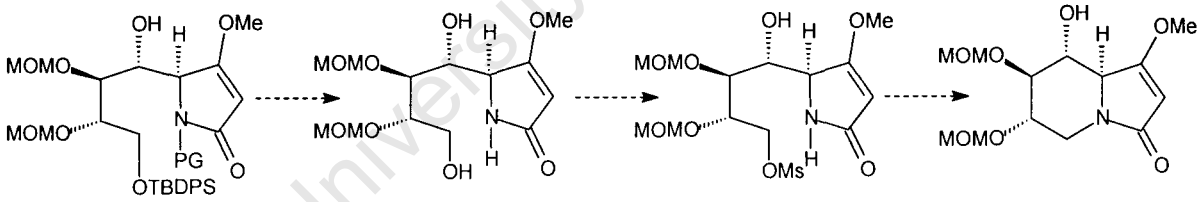
The adducts that were formed from the successful couplings had generated two stereogenic centres at C-4 and C-5 with the correct *R*- and *S*- configurations translating to 8*R* and 8a*R* for (+)-castanospermine (Figure 2.24).



(+)-Castanospermine **2.1** Adduct **2.107**

Figure 2.24

From the adducts formed, it appeared that the indolizidine skeleton could be generated in a fairly straightforward manner with careful manipulation of the various protecting groups. The first proposed route envisaged is outlined in Scheme 2.47, involving nitrogen and oxygen group deprotection followed by cyclization. The concave nature of **2.110** suggested that *exo*-reduction at C-3 would afford the correct C-3 configuration.

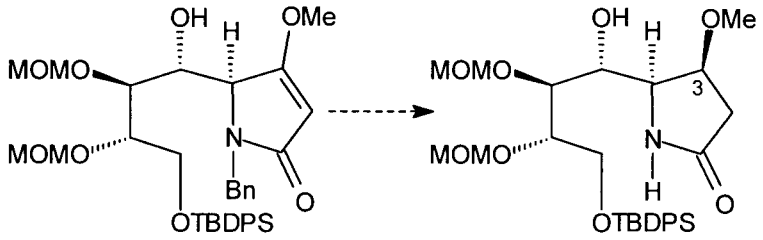


2.107
2.75 (PG =Bn)
2.89 (PG=PMB)

2.108 **2.109** **2.110**

Scheme 2.47

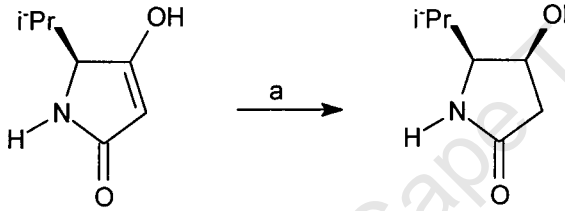
Thus, in our first route we decided to first deprotect the *N*-protecting group on the lactam via hydrogenolysis using hydrogen and a metal catalyst with the possibility of hydrogenating the double bond in the same step, and this was carried out with adduct **2.75**. In this case, hydrogenation *anti*- to the C-4 alkyl substituent was considered likely to furnish **2.111** with the correct C-3 configuration (Scheme 2.48).



Scheme 2.48

2.75 **2.111**

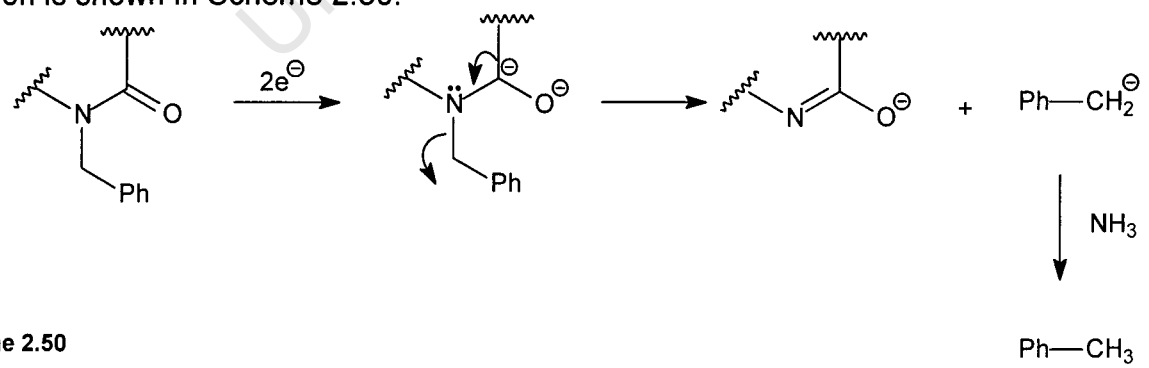
Thus, the lactam of **2.75** was subjected to hydrogenation / hydrogenolysis conditions using conventional methods, such as palladium-on-carbon with hydrogen, and palladium hydroxide-on-carbon with hydrogen. Hydrogenation of the double bond of a tetramic acid, also with addition of hydrogen *anti* to the alkyl chain at C-4, has been demonstrated by Schmidt[113] using PtO_2 (Adam's Catalyst), (Scheme 2.49).



2.112 **2.113**

Scheme 2.49. *Reagents and Conditions*: a) PtO_2, H_2, EtOAc, 98%.

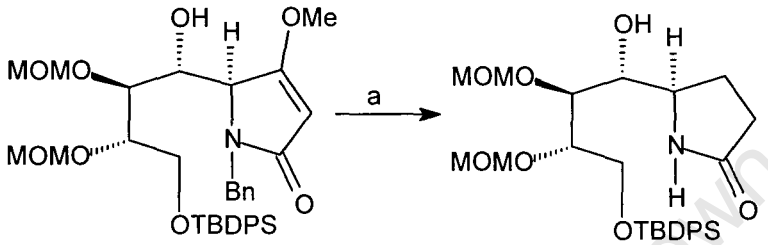
In our system, using such mild conditions (H_2, Pd/C) only resulted in the quantitative recovery of starting material. The removal of the benzyl group was then carried out under a much hasher set of conditions using a Birch reduction with sodium metal in liquid ammonia. It was thought that the tetramate double bond would also be reduced. A likely mechanism for this reaction is shown in Scheme 2.50.[114]



Scheme 2.50

The liquid ammonia was pre-dried over a small amount of sodium to remove any traces of water and then distilled into the dry reaction flask. Addition of sodium at -78°C caused the

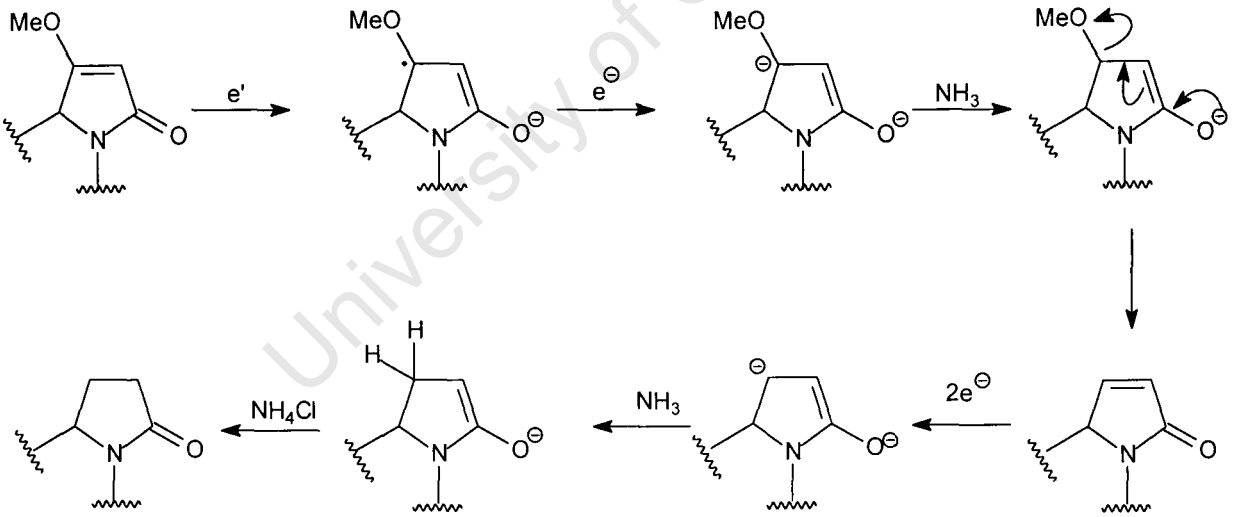
reaction solution to turn a dark blue indicating solvated-electron formation. Adduct **2.75** in THF was added shortly afterwards. The reaction was then quenched at -78°C after 30 minutes with solid ammonium chloride and a tlc of the crude reaction mixture revealed the formation of a more polar product, which was isolated via chromatography. Its ^{1}H NMR spectrum confirmed the loss of the benzyl group, but complete reduction of the vinyl ether was noted as well since these signals were also no longer present (Scheme 2.51).



2.75 **2.114**

Scheme 2.51. *Reagents and Conditions*: a) Na, NH_3, THF, -78°C, 30 mins; NH_4Cl(s), 85%.

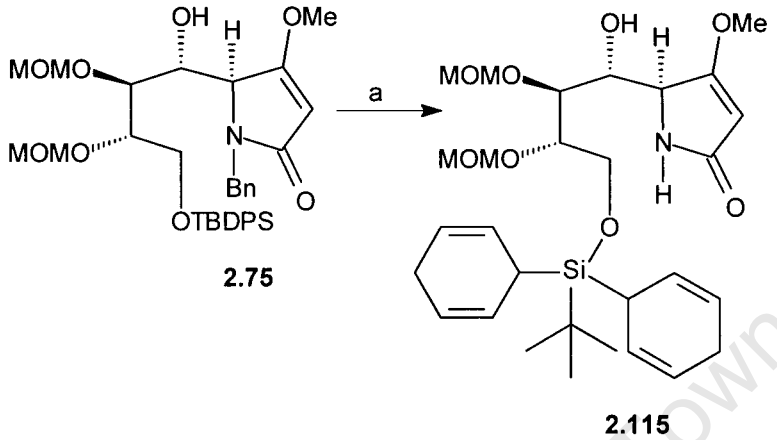
A suggested mechanism for exhaustive reduction of the vinyl ether is shown in Scheme 2.52.



Scheme 2.52

It was next decided to attenuate the level of reduction by carrying out the reaction in the presence of a proton source, *t*-butanol. Thus the reaction was repeated except with *t*-butanol present, and then quenched with solid ammonium chloride. Tlc of the crude mixture revealed the presence of a new product, which was isolated via chromatography. Its ^{1}H NMR spectrum

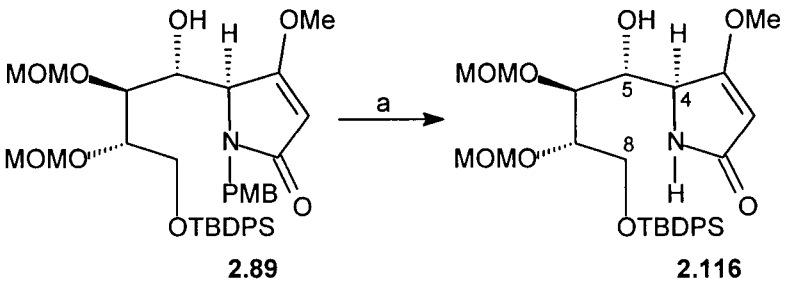
revealed that the benzyl group once again had been cleaved but that the complete vinyl ether signals were still intact. The ^{1}H NMR spectrum also revealed that both phenyl groups on the silyl ether had also been partially reduced (Scheme 2.53).



2.75 **2.115**

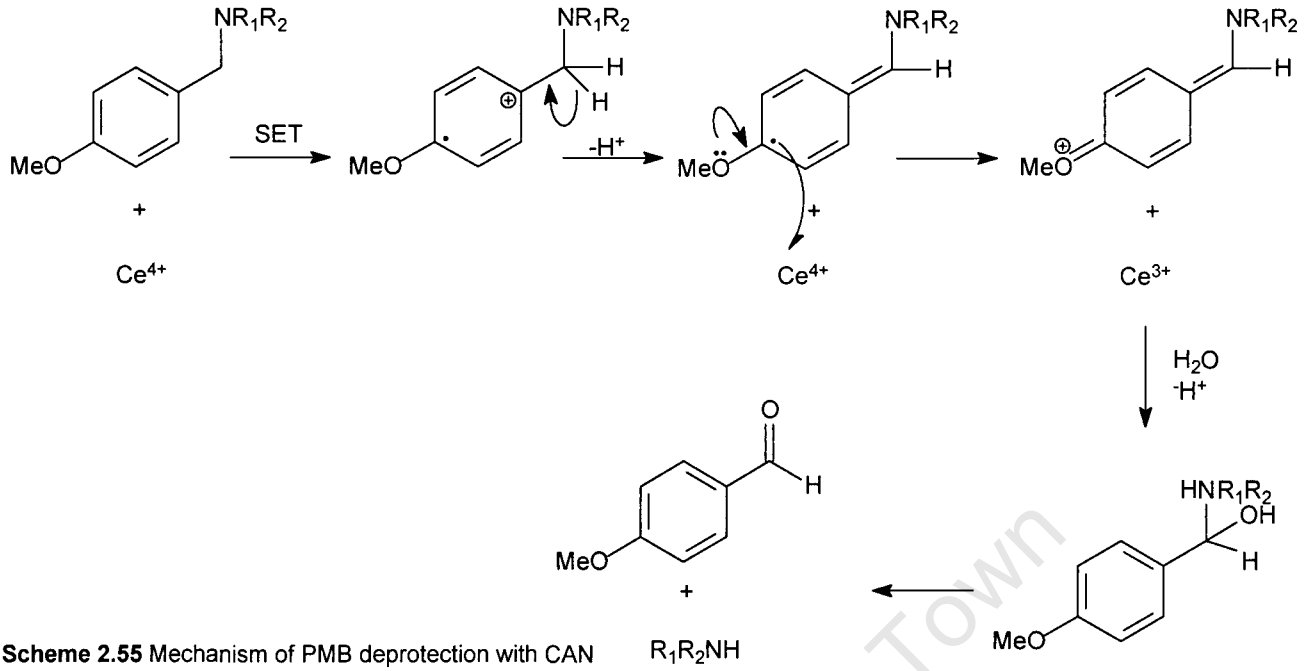
Scheme 2.53. *Reagents and Conditions:* a) Na, NH_3, *t*-butanol, THF, -78°C, 30 mins, 87%

Owing to these difficulties, it was decided to work on the deprotection of lactam **2.89** bearing an easier protecting group to remove. Hence, lactam **2.89** was subjected to an oxidative cleavage of the *p*-methoxybenzyl group using the standard conditions described in the literature of ceric ammonium nitrate (CAN) in a mixture of acetonitrile and water at -20°C over 5 hours (Scheme 2.54). Mechanistically, electron-transfer from the aryl ether oxygen to Ce(IV) is believed to initiate a cascade of reactions resulting in the loss of *p*-methoxybenzaldehyde together with the free lactam (Scheme 2.55).[115] Care was taken in the work-up to ensure that the aqueous layer was neutralized to pH 7 to minimize the possibility of epimerisation at C-4. The tlc of the reaction showed the presence of a much more polar product **2.116** and this was isolated as the free lactam via chromatography in 82% yield.



2.89 **2.116**

Scheme 2.54. *Reagents and Conditions*: a) CAN, CH_3CN: water (9:1), -20°C, 82%.

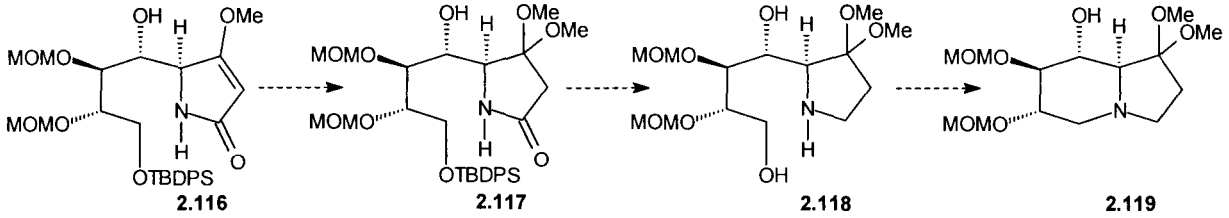


Scheme 2.55 Mechanism of PMB deprotection with CAN

The ^{1}H NMR spectrum of **2.116** revealed the loss of the PMB group and the appearance of a lactam N-H at δ 6.10 ppm indicating a successful deprotection. There was no sign of epimerization, as the $J_{4/5}$ was 1.5 Hz indicating the preservation of the *erythro*$_{4/5}$ relationship. The IR also showed the presence of an N-H by virtue of a broad absoption at 3300 cm^{-1}. The vinyl ether and MOM groups remained intact as evidenced by the retention of three methoxy singlets in the ^{1}H spectrum as well as a vinyl singlet for H-2.

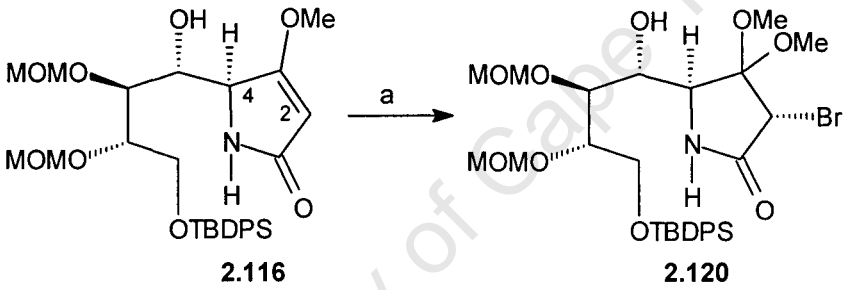
With the success of finally removing the lactam protecting group, our focus turned to converting the silyl ether to an *O*-mesylate in preparation for cyclization. As there was a free hydroxyl group at C-5 (C-8), it was decided that this should be protected before mesylation to prevent any chemoselectivity issue as well as to prevent any *O*-cyclization occurring between the oxygen at C-5 and C-8 during the formation of the indolizidine ring. Several protecting groups were tried with not much success, either resulting in the group being easily cleaved or eliminated. Owing to these difficulties, it was decided to change our approach towards obtaining the indolizidine. This time we decided to manipulate the vinyl ether, which in turn would minimize the possibility of elimination occurring at C-5 as well as epimerization at C-4. Conversion of C-3 to its ketal would allow lactam reduction to the pyrrolidine to take place,

which in turn, would be a better candidate as nucleophile for cyclization to the indolizidine. This new route proposed to the indolizidine is outlined in Scheme 2.56.



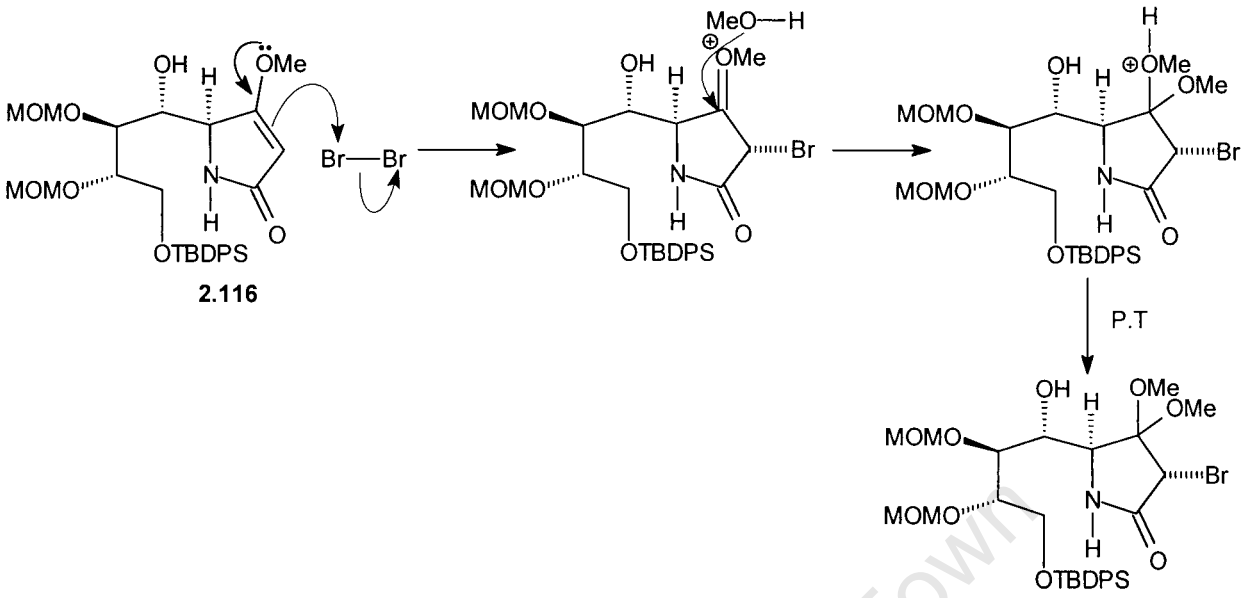
Scheme 2.56

To introduce the ketal with double-bond removal involved taking advantage of the nucleophilic nature of C-2. Thus, exposure of **2.116** to bromine in methanol at -20°C generated bromoketal **2.120** in high yield (≈ 90%) via electrophilic addition at C-2 (Scheme 2.57).



Scheme 2.57. *Reagents and Conditions*: a) Br_2, MeOH, -20°C, 30 mins, 86%.

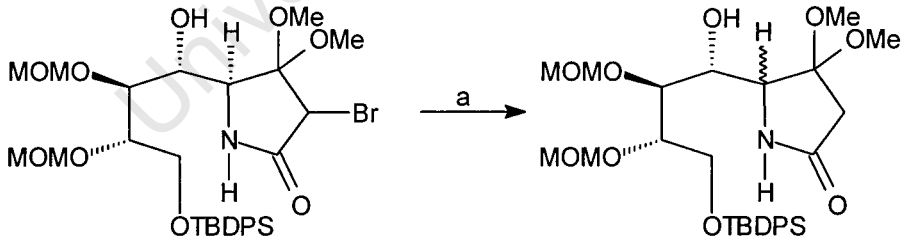
The reaction was quenched with cold sodium carbonate and the product was isolated via chromatography in 86% yield. Its ^1H NMR spectrum confirmed the addition by virtue of an extra methoxy signal as well as a singlet at δ 4.02 ppm for H-2. The product appeared to have formed as a single diastereomer, probably via addition of bromine *trans* to the C-4 alkyl chain on steric grounds. The mechanism for this reaction is likely to proceed via an open intermediate and is outlined in Scheme 2.58.



2.116 2.120

Scheme 2.58

The next step in the route was to reductively remove the bromine, and several procedures are known for this type of reaction. The first method tried was to carry out a radical substitution at H-3 using tributyltin hydride and the radical initiater AIBN in refluxing toluene (Scheme 2.59). Freshly distilled deoxygenated toluene was utilized to ensure that any radical formed would not be quenched by any impurities (e.g oxygen) present. The reaction was stirred for a couple of hours at reflux and followed on tlc to a slightly more polar product, which was isolated by chromatography in 90% yield following evaporation of solvent.



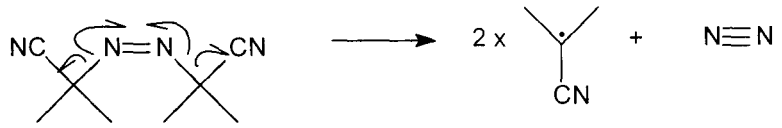
2.120 2.121

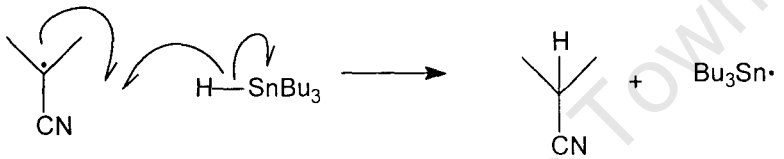
Scheme 2.59. *Reagents and Conditions*: a) Bu_3SnH, AIBN (1%), toluene, Δ, 90%.

The ^1H NMR spectrum of **2.121** revealed that reduction at C-2 had taken place as there was now a new AB system at δ 2.45 and 2.55 ppm (J = 16.1 Hz) for the two diastereotopic geminal protons at H-2. It was impossible to calculate $J_{4,5}$ as both H-4 and H-5 were buried in a complex multiplet with H-6, H-7 and H-8. However, the spectrum also showed the formation

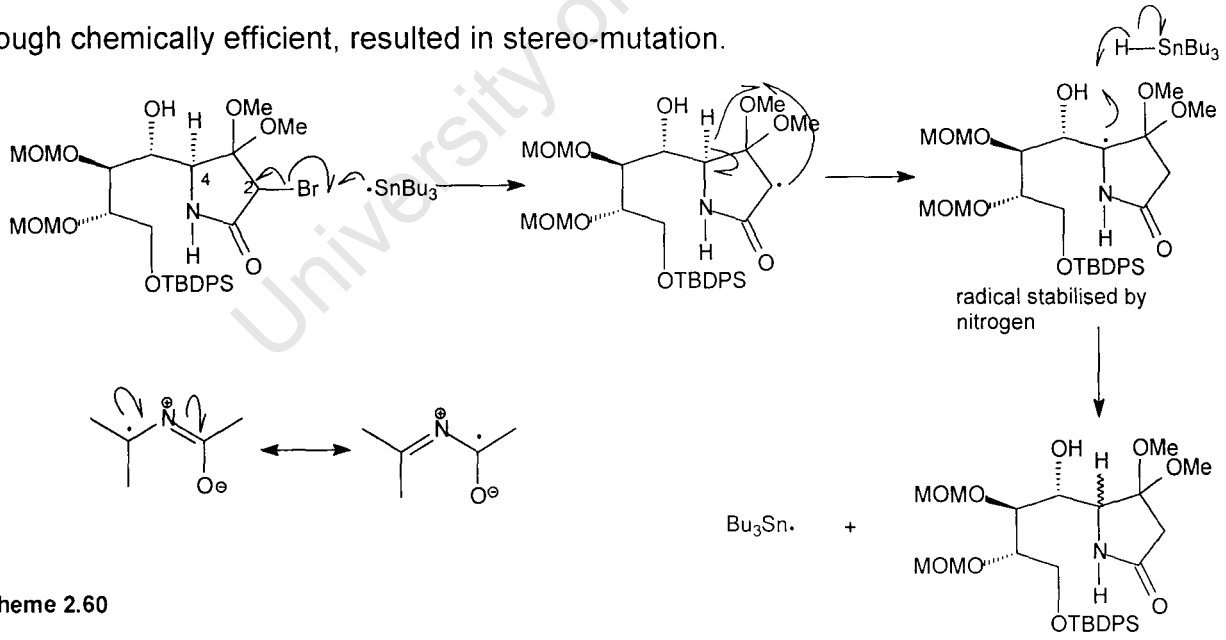
of diastereomers present as some of the signals were duplicated, particularly 2 broad singlets at δ 6.78 and 6.88 ppm for the N-H signal and 8 resonances for the methoxy groups. A tentative explanation involves radical translocation via the mechanism outlined below (Scheme 2.60) involving a 1,3 hydrogen shift.[116] The first step of the reaction is homolysis of Bu_3SnH which is promoted by the initiator AIBN.

Initiation





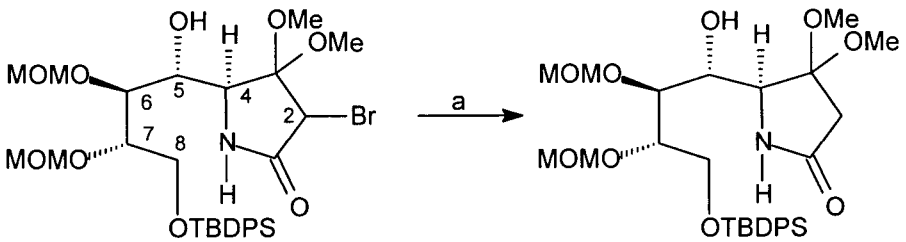
This is followed by propagation. Formation of the C-2 radical is followed by a C_2 to C_4 translocation that is thermodynamically driven by the stabilizing effect of an α-acylamino group. α-Acylamino radicals are well known in organic synthesis. This reductive method, though chemically efficient, resulted in stereo-mutation.



Scheme 2.60

The next set of conditions that were tried was the reducing agent lithium aluminium hydride in THF at room temperature for 18 hours in an attempt to reduce both the bromide and lactam in one step. The tlc of the reaction mixture revealed that the reaction progressed to an identical

spot as the previous reaction but with another, more polar spot appearing. The products were isolated via chromatography and from the ^{1}H NMR spectra it was established that the less polar spot of the two products was the desired product as it had identical signals to those of the previous reaction product with Bu_3SnH but in this case as only one diastereomer. Once again, it was difficult to calculate $J_{4,5}$ as H-4 and H-5 were part of a complex multiplet. The ^{1}H NMR spectrum of the more polar spot revealed that the lactam carbonyl group had not been reduced since the AB system was still present for C-2, but instead all the resonances associated with the silyl ether had disappeared. Thus under these conditions the silyl ether was labile. Thus, the milder reducing agent sodium borohydride in methanol was tried at room temperature. Once again, the desired product spot appeared to form by tlc, but the reaction did not progress beyond 40% conversion even when the reaction was heated. The product was isolated by chromatography and found to be identical to the lithium aluminium hydride product. The third method tried out gave the desired result. It involved using zinc in an aqueous organic medium with ammonium chloride and was described by Cheung in 2001.[117] The reaction is reported to involve a single electron-transfer reduction. Thus, **2.120** was reacted with zinc (5 eq) in a THF, methanol, aqueous ammonium chloride mixture and left to stir at room temperature for 30 minutes. Methanol was added to the conditions described by the authors to ensure that the ketal was not hydrolysed under the acidic conditions (Scheme 2.61). The tlc of the reaction mixture showed a single identical product forming as with all the previous reactions, but with complete conversion of starting material. The excess zinc was filtered off through Celite® and the reaction mixture was then quenched with sodium bicarbonate and the product was extracted followed by isolated via chromatography to give lactam **2.122** in 80% yield.

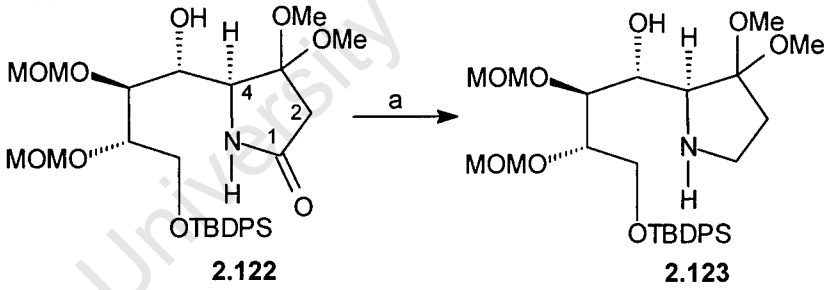


2.120 **2.122**

Scheme 2.61. *Reagents and Conditions*: a) Zn (5 eq), THF: NH_4Cl : MeOH (2 : 2 : 1), rt, 30 mins, 80%.

The ^{1}H NMR spectrum of **2.122** revealed it to be identical to all the previous products but as a single diastereomer. Once again, $J_{4,5}$ could not be calculated as H-4 and H-5 were part of a complex multiplet. It is interesting to note that in the ^{13}C spectrum C-6 was the most downfield carbon of the indolizidine skeleton resonating at δ 79.0 ppm, while C-5, C-7 and C-8 resonated at δ 70.1, 78.7 and 63.6 ppm respectively. During the synthetic route, these signals were followed as important markers.

The next step that was envisaged was the reduction of the lactam carbonyl group. There are several reducing agents appropriate for this task in the literature including 9-BBN, BH_3.DMS and $LiAlH_4$. BH_3.DMS and 9-BBN were tried first under varying conditions including reflux but each time starting material was recovered and thus we turned to the more potent $LiAlH_4$. The lactam was added to a suspension of LAH in diethyl ether and left to stir for prolonged periods of 18 hours at room temperature (Scheme 2.62). The reaction was monitored by tlc to reveal reaction progression but never to completion. At higher temperatures, side-products were formed, which were non-UV-active. Hence the reaction was carried out at room temperature to minimise side-product formation. The reaction was quenched with a mixture of THF, triethylamine and water (9:1:1) to precipitate the lithium and aluminum salts and these were filtered off through Celite®.



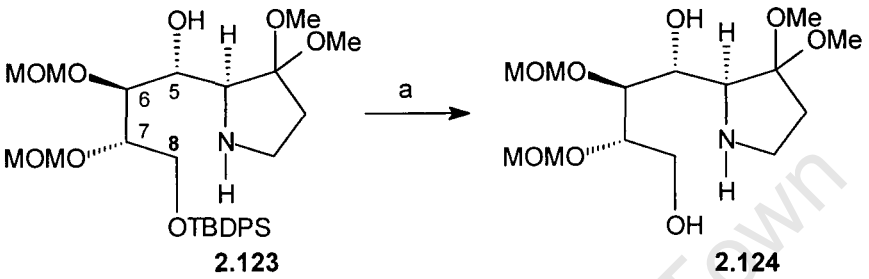
2.122 **2.123**

Scheme 2.62. *Reagents and Conditions*: a) LAH, Et_2O, rt, 50%.

The product **2.123** was isolated via chromatography in 50% yield using a mixture of methanol and ethyl acetate (1:9) containing 3 drops of aqueous ammonia as the eluent, since the pyrrolidine was extremely polar towards chromatography. The ^{1}H NMR spectrum of the product revealed that the AB system for H-2 had disappeared upfield to around δ 2.00 ppm. The N-H resonance had also moved upfield as a broad singlet at peak. Also present in the spectrum was a multiplet in the region of δ 3.00 ppm integrating for 2 protons which could be

assigned to H-1. Although repeated several times, the yield of the reaction could never be consistently raised to an acceptable yield (>70%).

The penultimate step for indolizidine cyclization involved hydrolysis of the silyl ether. This was performed using the standard conditions of tetrabutylammonium fluoride in THF and the product was isolated directly via chromatography using a slightly more polar solvent system than before (methanol : ethyl acetate 1:4), in a 70% yield (Scheme 2.63).

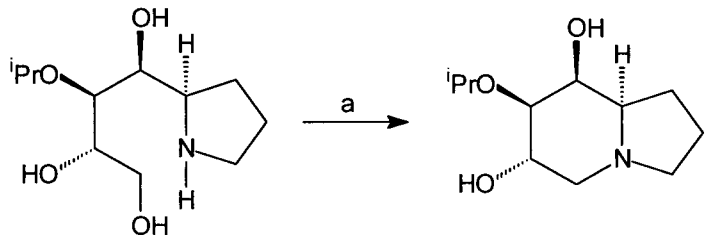


2.123 **2.124**

Scheme 2.63. *Reagents and Conditions*: a) 1M TBAF in THF (1.5 eq), THF, 0°C.

Desilylation was immediately obvious from the ^{1}H spectrum of **2.124** by the loss of the *t*-butyl and aromatic resonances, but still present were the four methoxy signals δ 3.24 ppm, δ 3.31 ppm, δ 3.38 ppm, δ 3.40 ppm as well as two broad signals at δ 3.10 ppm for the N-H and δ 3.60 ppm for the O-H resonances. The formation of the product was also confirmed by a ^{13}C spectrum which showed the disappearance of all the signals associated with the silyl ether. Furthermore, the spectrum revealed that the signal for the carbonyl carbon at δ 172.1 ppm had disappeared and replaced by a signal at δ 43.2 ppm for C-1, thus confirming from the previous step that the reduction had occurred. Once again, C-6 was the most downfield resonance of the carbons in the chain at δ 80.6 ppm.

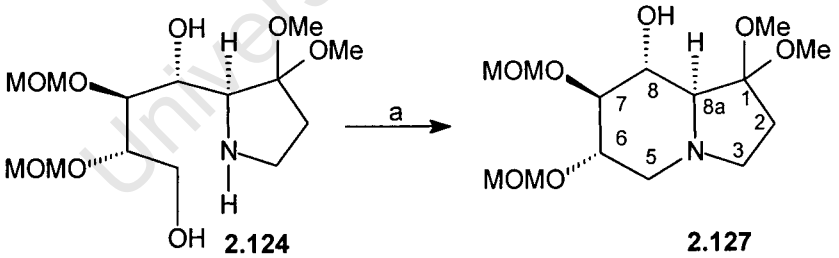
The stage was now set for cyclization. There were several methods available for carrying out the cyclization to the indolizidine in the literature. Cyclization via tosylation of the C-8 hydroxyl was attempted first, but this resulted in the tosylation of the nitrogen to give sulfonamide. As our system was analogous to Casiraghi's, we decided to use next the same cyclization conditions as his of PPh_3 and CCl_4 that were first reported by Vogel.[79] Scheme 2.64 shows Casiraghi's cyclization en route to 1-deoxy-8-*epi*-castanospermine.



2.125 **2.126**

Scheme 2.64. *Reagents and Conditions*: a) i) PPh_3, CCl_4, Et_3N, pyridine, rt; ii) DOWEX (H^+), 2M NH_4OH, 79%.

These conditions were applied to our system using carbon tetrabromide instead of carbon tetrachloride, which was unavailable. Since the reaction proceeds by halogenating the C-8 hydroxyl group this was thought to be acceptable. All the reagents and reactants that were used in this reaction were thoroughly dried and the reaction was carried out shielded from the light (Scheme 2.65). After 24 hours, the tlc of the reaction mixture revealed that a reaction had occurred. Toluene was then added to the mixture to azeotrope off the pyridine while the reaction mixture was concentrated on the rotory evaporator. In view of the product's water solubility, the residue was chromatographed directly using the same solvent system as before, as the Rf of the product was nearly identical to that of the starting material except for the slight colour change with an anisaldehyde spray from orange to brown. In this manner, **2.127** was isolated in 67% yield. Scheme 2.65 depicts the structure as an indolizidine.



2.124 **2.127**

Scheme 2.65. *Reagents and Conditions*: a) PPh_3, CBr_4, Hünig's base, pyridine, rt, 67%.

The ^1H NMR spectrum of **2.127** at first glance suggested that cyclization had occurred, in view of a spreading out of signals and the loss of the OH signal. Assignments were made on the basis of HSQC and coupling considerations. A portion of the ^1H NMR spectrum of **2.127** is shown in Figure 2.25.

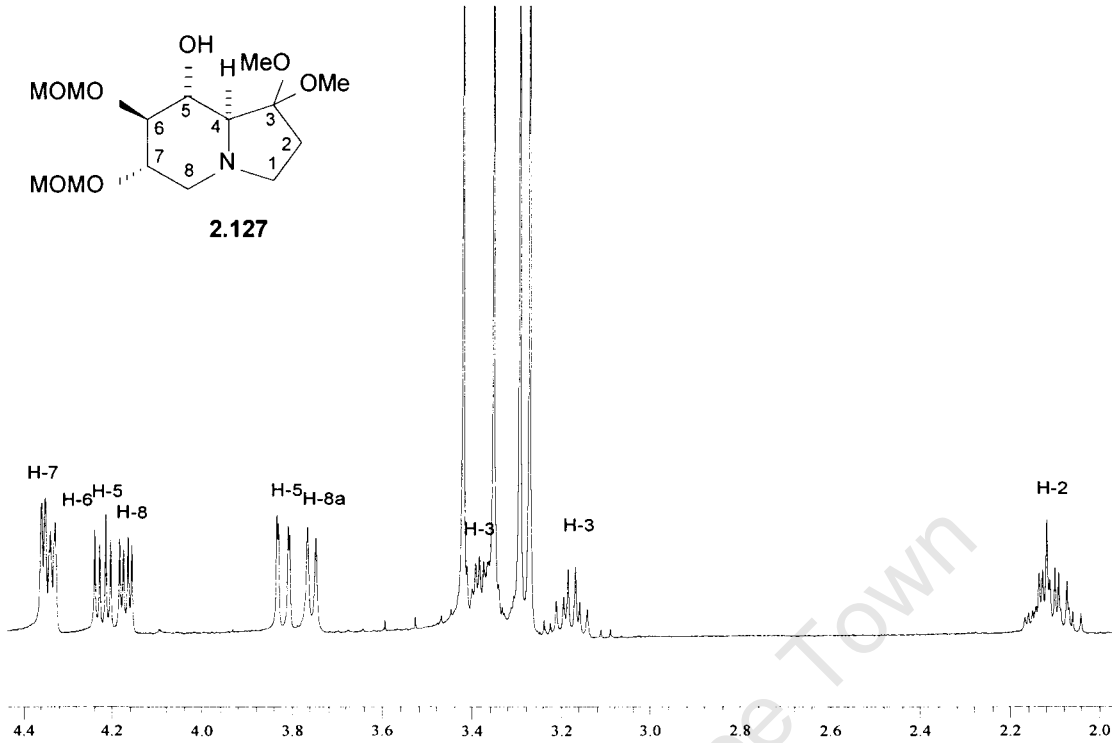


Figure 2.25

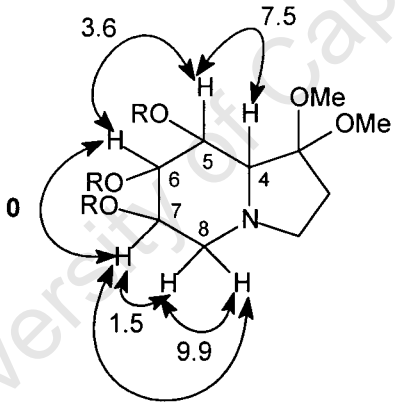


Figure 2.26. **2.127** as an indolizidine.

Table 8

ASSIGNMENT	δ_H	MULTIPICITY	*J* VALUES	δ_C*
C-4	3.75	d	7.5 Hz	61.8
C-5	4.17	dd	7.5, 3.6 Hz	77.8
C-6	4.35	d	3.6 Hz	83.4
C-7	4.33	d	4.2,1.5 Hz	79.8
C-8	3.82	dd	9.9, 1.5 Hz	72.0
C-8	4.22	dd	9.9, 4.2 Hz	

* Assigned by HSQC.

However, when the ^{1}H and ^{13}C NMR data of **2.127** was compared to that of (+)-castanospermine (Chapter 1, Table 1), several aspects of the data raised doubt regarding the indolizidine assignment. The following issues were identified:

- The coupling constant between H-6 and H-7 was 0 Hz indicating a dihedral angle of 90° between H-6 and H-7 from the Karplus equation.
- The ^{1}H chemical shifts of H-5 to H-8a were much more downfield to those of (+)-castanospermine.
- The ^{13}C chemical shift for C-5 was δ 72 ppm, when in indolizidines, the carbon α to nitrogen in the piperidine ring usually appears at around 55 ppm.

This information suggested that the following compound might have formed, in which cyclization had occurred between O-5 and C-8 (Figure 2.28).

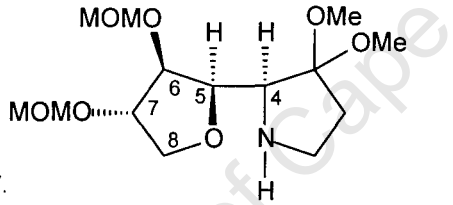


Figure 2.27. Alternative structure for **2.127**.

In this structure, the dihedral angle between H-6 and H-7 would be expected to be 90° in accordance with a 5-membered ring as observed with trans vicinal substituents, while the ^{13}C chemical shift of C-8 would be expected to appear at around 70 ppm. An analogous compound **2.128** (Figure 2.28) was synthesized by Izquierdo *et al.*[118] and the ^{1}H and ^{13}C data showed similar values to those of **2.127** as follows:

- The *J* value between H-6 and H-7 was 0 Hz.
- The ^{13}C chemical shift for C-5 was 72.0 ppm
- The ^{1}H chemical shifts of H-4 to H-8 were all downfield when compared to (+)-castanospermine.

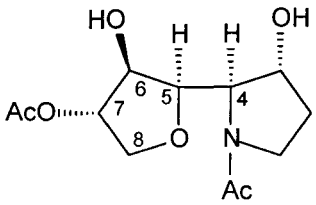


Figure 2.28

2.128

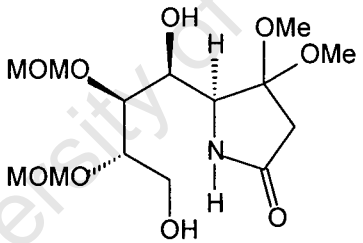
The ^{1}H and ^{13}C chemical shifts of both **2.127** and **2.128** are summarized in the table 9 below.

Table 9

ASSIGNMENT	δ_H FOR 2.127	δ_C FOR 2.127	δ_H FOR 2.128	δ_C FOR 2.128
C-4	3.75	61.8	3.62	61.3
C-5	4.17	77.8	3.61	79.1
C-6	4.35	83.4	3.97	75.3
C-7	4.33	79.8	5.17	73.6
C-8	4.22	72.0	4.28	72.0
C-8	3.82		3.69	

The final cyclization step was repeated several times but could never be reproduced much to our despair, and thus **2.127** was never isolated again and the cyclisation precursor **2.124** was always recovered quantitatively.

It was thus decided to rexamine lactam **2.129** as a cyclization precursor (Figure 2.29).



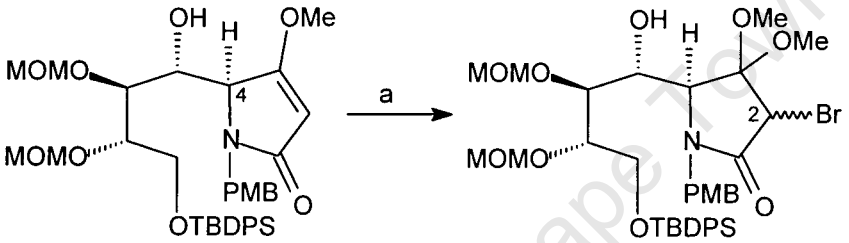
2.129

Figure 2.29

Unfortunately, neither activation of the hydroxyl (C-8) via mesylation (chemoselectivity problems with OH at C-4) followed by base treatment nor Mitsunobu conditions (PPh_3, DIAD) resulted in successful cyclization to an indolizidine.

In view of the low-yielding $LiAlH_4$ reduction and inability to reproduce the cyclization, a modified route was designed in which the cyclization step would be via conversion of the primary hydroxyl at C-8 to a mesylate, but before embarking on it, it was decided to double-check that epimerization had not occurred at C-5 even though the $J_{4,5}$ values consistently suggested it hadn't. To investigate this, other, more neutral methods for PMB deprotection were tried out such as DDQ and Palladium-on-carbon with hydrogen[119] which are both known

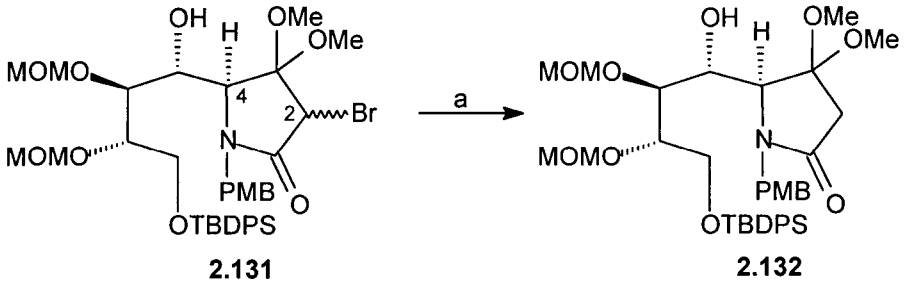
literature procedures for cleavage. However, both reagents gave total recovery of starting material. Hence, it was decided to remove the double-bond prior to the deprotection in order to eliminate the possibility of epimerization via the dienol. Thus adduct **2.89** was subjected to the bromination reaction in the presence of methanol to form bromoketal **2.130** (Scheme 2.66) in 90% yield as two diasteromers (in a ratio of approx 1:1) which were separated by chromatography. The lack of stereoselection was considered to be due to the presence of two bulky groups on either face, the alkyl chain at C-4 on the top face and the *p*-methoxybenzyl protecting group on the underneath one, leading to no obvious preference for the addition of the bromine and thus resulting in a 1:1 mixture.



Scheme 2.66. *Reagents and Conditions*: a) Br_2, MeOH, -20°C, 30 mins, 90%.

The ^1H NMR spectrum for the two diastereomers showed the appearance of two singlets at δ 4.12 ppm and δ 5.24 ppm for H-2 of each diastereomer replacing the vinyl H-2 at δ 5.20 ppm.

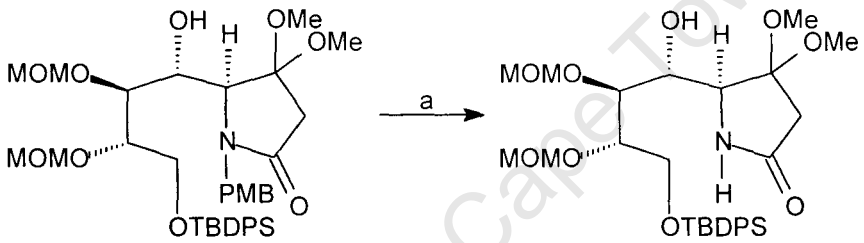
Independent zinc-mediated reduction of each diastereomer using Zn, NH_4Cl, THF, MeOH resulted in the same product **2.131** by ^1H and ^{13}C NMR spectroscopy indicating the diastereomers to have been derived from C-2 and not C-4 (Scheme 2.67).



Scheme 2.67. *Reagents and Conditions*: a) Zn (5 eq), THF: NH_4Cl : MeOH (2 : 2 : 1), rt, 30 mins, 90%.

The ^{1}H NMR spectrum of **2.131** showed the disappearance of the H-2 α-bromo methine singlets at δ 4.12 and 5.24 ppm and the appearance of an AB system at δ 2.45 ppm and δ 2.55 ppm for the two diastereotopic geminal protons at H-2. The ^{13}C NMR spectrum showed that C-2 had shifted upfield from δ 55.3 / 45.3 to 40.3 ppm consistent with C-2 reduction.

With **2.132** now in hand, oxidative cleavage with CAN in a (9:1) mixture of acetonitrile and water was carried out. The reaction was monitored by tlc but this turned out to be difficult as the Rf of the product and starting material were identical and the only evidence of a reaction taking place was the appearance of a less polar spot due to the formation of *p*-methoxybenzyaldehyde during the reaction. Hence, the reaction was monitored by ^{1}H NMR and it was found that the reaction never proceeded to more than 50% conversion (Scheme 2.68).



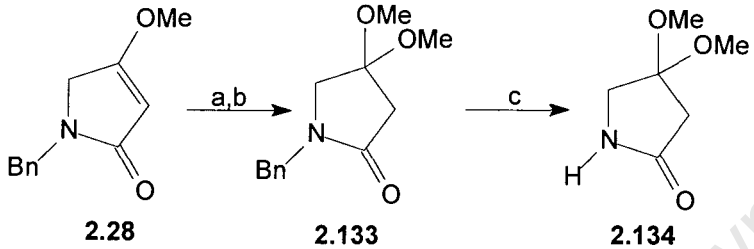
2.132 **2.122**

Scheme 2.68. *Reagents and Conditions*: a) CAN, CH_3CN : water (9:1), -20°C.

However, the deprotected product isolated from the reaction importantly had identical signals to that obtained from the other sequence in which the *N*-protecting group was removed first, inferring that epimerization was highly unlikely. The only option regarding epimerization was if complete epimerisation in the first sequence with CAN deprotection and in the second sequence with Br_2/MeOH had taken place. Using *N*-bromosuccinimide in methanol on **2.116** was tried and following reductive bromine removal resulted in the formation of **2.122** with identical ^{1}H and ^{13}C NMR spectra as the other sequence involving bromine in methanol. Given that the NBS reaction is effectively neutral it was considered highly unlikely that the Br_2/MeOH resulted in epimerization, and it was then felt that **2.132** represented an unepimerized product. Further evidence in favour of this view came from the low H_4/H_5 2.1 Hz *J* value in the ^{1}H NMR spectrum of **2.132** indicating *erythro* relative stereochemistry and not the *threo* for an epimerized product. Although it is difficult to correlate an $[\alpha]_D$ to absolute

configuration this can be used as a guide, and in this case the $[\alpha]_D$ was positive as with our coupled products, **2.75**, **2.89**, **2.94** and **2.105**.

To improve yields in the reduction for the modified yield, we resorted back to the *N*-benzyl series with Birch reductive benzyl removal. A model study was carried out to double-check that the ketal would be stable under these conditions (Scheme 2.69).

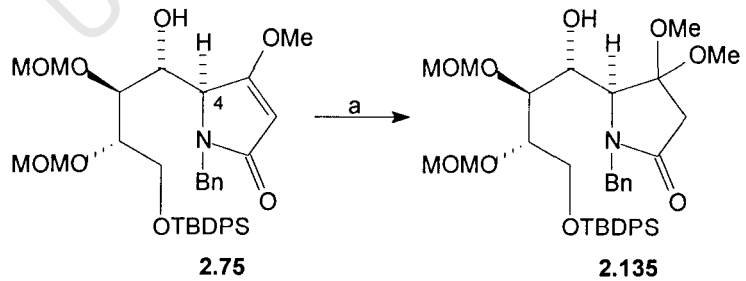


2.28 **2.133** **2.134**

Scheme 2.69. *Reagents and Conditions*: a) Br_2, MeOH, -20°C, 30 mins, 87%; b)) Zn (5 eq), THF: NH_4Cl : MeOH (2 : 2 : 1), rt, 30 mins, 82%; c) Na, NH_3, *t*-BuOH, 90%.

Pyrrolinone **2.28** was thus subjected to the methoxybromination addition reaction followed by zinc-mediated reduction to give pyrrolidinone **2.133** in high yield (82%). The key changes in the spectra were identical to the ones reported before. **2.133** was then subjected to a Birch reduction in the presence of *t*-butanol to give **2.134** in quantitative yield. The ^1H NMR spectrum of **2.134** indicated that the benzyl group had been cleaved as there were no longer any aromatic signals present. The appearance of a lactam N-H resonating at δ 5.84 ppm together with the methoxy signals for six protons indicated that the ketal was still intact.

With this encouraging result, adduct **2.75** was then subjected to the same sequence, which proceeded in a relatively high overall yield to give ketal **2.135** (Scheme 2.70).

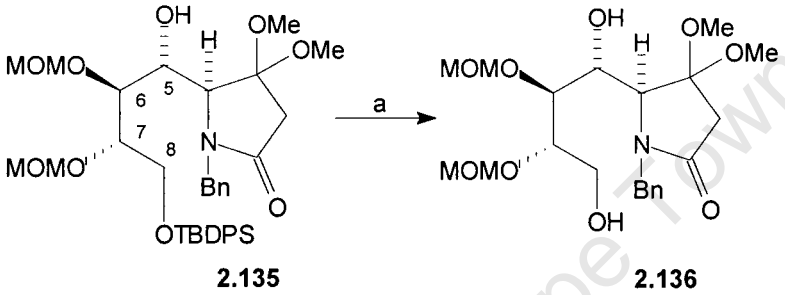


2.75 **2.135**

Scheme 2.70. *Reagents and Conditions*: a) Br_2, MeOH, -20°C, 30 mins, 88%; b) Zn (5 eq), THF: NH_4Cl : MeOH (2 : 2 : 1), rt, 30 mins, 86%.

The ^{1}H and ^{13}C spectra of the compounds formed during the transformation of **2.75** to **2.135** showed the same key changes as the transformation of **2.89** to **2.132**, except in this case with benzyl signals in the aromatic region instead of *p*-methoxybenzyl signals. Furthermore the formation of ketal **2.135** was confirmed by a correct elemental analysis and parent mass $[683.3488]^{+}$ from an HRMS mass spectrum.

In view of previous results under Birch conditions (Scheme 2.53) with the silyl ether in place, the latter was removed using tetrabutylammonium fluoride (TBAF) which gave **2.136** in high yield following evaporation of solvent followed by direct column chromatography (Scheme 2.71).

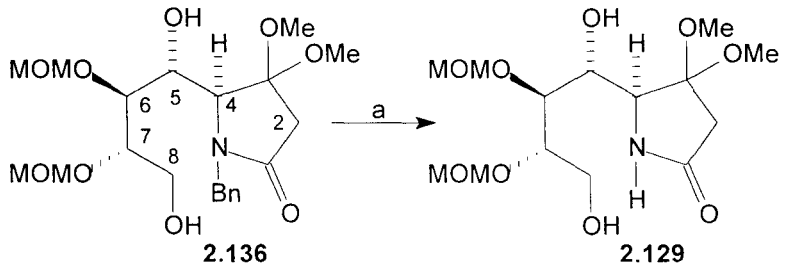


2.135 **2.136**

Scheme 2.71. *Reagents and Conditions*: a) 1M TBAF, THF, -20°C, 83%.

The ^{1}H and ^{13}C spectra of **2.136** showed the disappearance of all signals associated with the silyl moiety and the only multiplet now present in the aromatic region was due to the benzyl group aromatic ring. Furthermore, a broad singlet for the hydroxyl proton could be observed at δ 3.45 ppm. There were no significant changes in the resonances of C-5, C-6, C-7 and C-8. The mass spectrum had the following fragmentation pattern, 444.2234 $[M+H]^{+}$, 412 $[M-OCH_3]^{+}$, 380 $[M-(2 \times OCH_3)]^{+}$, 368 $[M-Ph]^{+}$, 349 $[M-Bn]^{+}$ and 305 $[M-(2 \times MOM)+ (OH))]^{+}$ which confirmed the presence of the methoxy, benzyl and MOM groups.

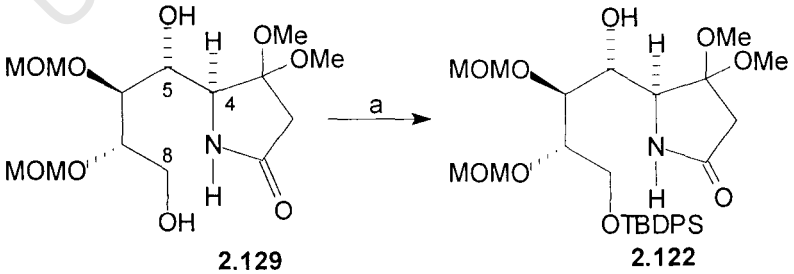
Initial attempts at reducing **2.136** in ammonia at -20°C using sodium gave mixtures of products, but after some fine-tuning, conditions were identified to chemoselectively reduce only the benzyl functionality. The ideal conditions that were identified involved using an excess of sodium (18 eq) in a mixture of ammonia and THF at -78°C in the presence of *t*-butanol for two hours. The reaction was then quenched with a mixture of methanol and acetic acid (5:1) to prevent any formation of by-products. As before, the ammonia was pre-distilled to remove water and any trace impurities (Scheme 2.72).



Scheme 2.72. *Reagents and Conditions*: a) i) Na, NH_3, THF, *t*-BuOH; ii) MeOH: AcOH, 5:1, 95%.

The product **2.136** was isolated via chromatography in 95% yield as a clear oil. Both its ^1H and ^{13}C spectra demonstrated the loss of the aromatic signals and the appearance of a lactam N-H at δ 6.77 ppm in the ^1H NMR spectrum. The ^{13}C spectra showed the signals for C-5, C-6 C-7 and C-8 at δ 69.8, 80.9, 78.0 and 61.6 ppm respectively, revealing no significant changes from the previous compound.

Owing to the previous low-yielding reduction with $LiAlH_4$, it was decided to try and reduce the lactam with diisobutylaluminium hydride (DIBAL-H) with the nitrogen protected as a carbamate. Such methodology to form an α-hydroxy lactam that is subjected to subsequent reduction with triethylsilane following conversion of the hydroxyl to a leaving group, has been frequently used in the alkaloid literature.[120] Hence, to form the carbamate, the primary hydroxyl at C-8 needed to be protected regioselectively. The best strategy identified was to reprotect the primary hydroxyl group as a silyl ether. This was carried out using the standard condtions of imidazole and TBDPSCl in acetonitrile with the use of triethylamine as base to prevent any hydrolysis of the ketal (Scheme 2.73).

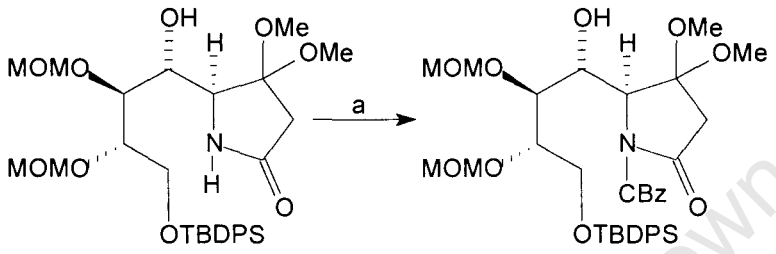


Scheme 2.73. *Reagents and Conditions*: a) TBDPSCl (2 eq), imidazole (2 eq), Et_3N, CH_3CN, 90%.

The reaction progress was monitored by tlc and it was noted that the reaction was slow, requiring an extra 2 equivalents of both imidazole and TBDPSCl to go to completion.

However, there was no sign of any diprotected silyl ether, presumably because of steric hindrance at C-5. The product was isolated via chromatography and all the spectral and analytical data were identical to the ones reported for **2.122** from **2.89**.

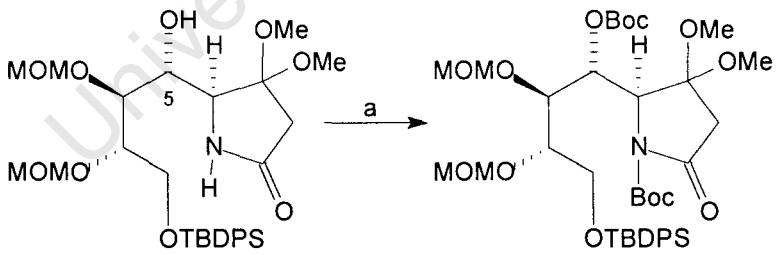
Protection of nitrogen as a CBz carbamate using benzyl chloroformate and NaH at 0°C was then attempted. CBz was selected in view of its selective and non-acidic hydrogenolytic cleavage (Scheme 2.74).



2.122 **2.137**

Scheme 2.74. *Reagents and Conditions*: a) NaH, CBzCl, THF, 0-60°C.

The tlc of the reaction mixture revealed that the reaction progressed to a single spot but not beyond a 50% conversion. Heating the reaction at reflux resulted in by-product formation. Thus, this protecting group was abandoned and our attention turned to using a Boc protecting group. Thus, **2.122** was subjected to Boc protection under the standard conditions of di-*tert*-butyl dicarbonate and DMAP (cat) in THF. Several experiments were carried out to find the optimal conditions in the hope of obtaining the *N*-Boc lactam (Scheme 2.75).



2.122 **2.138**

Scheme 2.75. *Reagents and Conditions*: a) $(Boc)_2O$ (4 eq), DMAP (10%), THF, 25°C, 85%.

However, It was found that *O*-Boc formation at O-5 competed with *N*-Boc formation to inevitably give a mixture. Thus It was decided to prepare the di-Boc protected product and leave the relatively facile deprotection of the *O*-Boc to later in the synthesis. Using an optimal set of conditions of $(Boc)_2O$ (4 eq), DMAP (10%) in a 0.01 M THF solution, the di-protected

product **2.138** was isolated via chromatography as a crystalline solid in 85% yield. Its ^{1}H NMR spectrum confirmed the presence of the two Boc protecting groups by the appearance of two *t*-butyl group signals at δ 1.42 ppm and δ 1.50 ppm as well as the disappearance of both the N-H and O-H signals. Analysis of the spectrum showed that the H-4/H-5 vicinal coupling constant was 2.0 Hz, once again confirming *erythro* stereochemistry without epimerization (Figure 2.30).

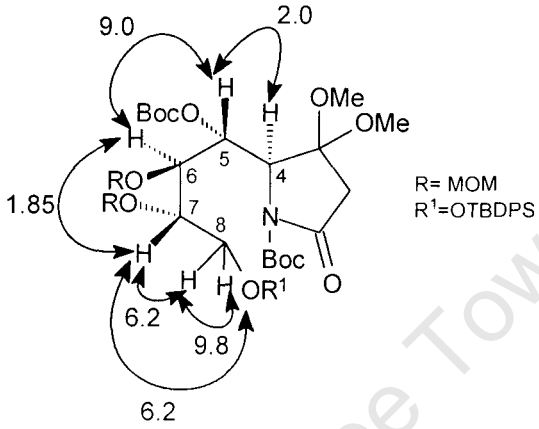


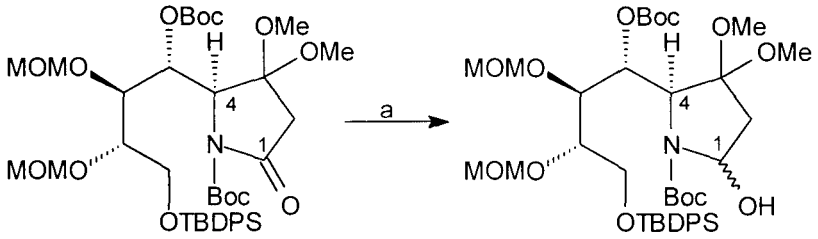
Figure 2.30

Table 10

Assignment	δ_H	**Multiplicity**	***J* Hz**	δ_C
C-4	4.64	d	2 .0 Hz	59.9
C-5	5.41	dd	9.0 and 2.0 Hz	76.0
C-6	4.45	dd	9.0 and 1.85 Hz	77.2
C-7	4.00	td	6.2 and 1.85 Hz	77.5
C-8	3.94	dd	9.8 and 6.2 Hz	63.1
	4.10	dd	9.8 and 6.2 Hz	

The presence of the Boc groups was also confirmed in the ^{13}C spectrum by the appearance of 2 new peaks at δ 149.7 ppm and δ 153.2 ppm for the carbonyl carbons. It should be noted that the signal for C-5 had shifted downfield by 6 ppm due to the presence of the electron-withdrawing carbamate on C-5 while the other signals remained essentially unchanged. All assignments were made using COSY and HSQC spectroscopy.

In the next step, **2.138** was reduced to its lactol with DIBAL-H (4 eq) at -78°C in THF (Scheme 2.76). The reaction was monitored by tlc and found to go to completion to a more polar product after 2 hours at -50°C.

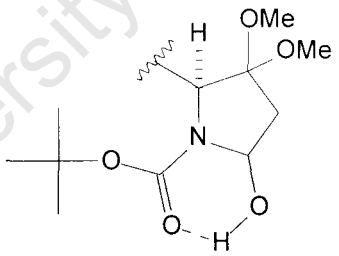


2.138 **2.139**

Scheme 2.76. *Reagents and Conditions*: a) DIBAL-H (4 eq), THF, -78°C, 86%.

The reaction was quenched with aqueous sodium acetate at -78° followed by the addition of a mixture of ammonium chloride and ethyl acetate (1:3) and then allowed to warm to room temperature. The α-hydroxy carbamate product **2.139** was isolated as a crystalline solid via chromatography in 86% yield. Its ^{1}H and ^{13}C NMR spectra were difficult to interpret owing to line broadening in the signals possibly due to intramolecular hydrogen bonding and rotameric (Boc) forms (Figure 2.31). The possibility of epimers at C-1 could have also contributed to the complexity of the spectrum

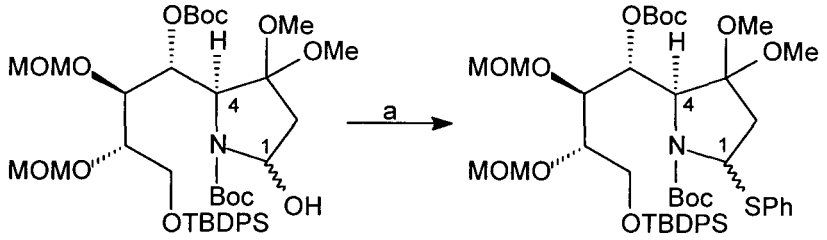
Figure 2.31



2.139

However, the IR spectrum of **2.139** revealed the disappearance of the lactam carbonyl group absorption at 1635 cm^{-1} and an appearance of a broad peak at 3445 cm^{-1} indicating the presence of a hydrogen-bonded hydroxyl, confirming that reduction had occurred.

For the reductive removal step, an α-thiocarbamate was considered to be an attractive candidate for radical reduction to the pyrrolidine. Hence, **2.139** was treated with thiophenol in the presence of BF_3.etherate at -78°C (Scheme 2.77).[121]

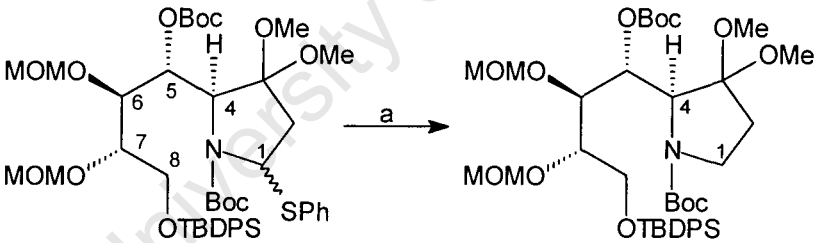


2.139 **2.140**

Scheme 2.77. *Reagents and Conditions*: a) PhSH (1.5 eq), $BF_3.OEt_2$ (1.5 eq), DCM, -78°C, 91%.

The reaction was quenched with aqueous sodium carbonate and the product **2.139** was isolated by chromatography in 91% yield. The ^1H NMR spectrum of **2.139** showed the appearance of a new set of signals in the aromatic region confirming the introduction of the phenyl group. All the MOM group signals remained intact in both the ^1H and ^{13}C spectra hence confirming that the substitution had occurred at C-1. Doubling of resonances (3:1) suggested epimers at C-1.

Sulfide **2.140** was then subjected to radical reduction under the standard conditions of tributyltin hydride with the radical initiator AIBN in refluxing toluene (Scheme 78) as previously mentioned. The reaction was monitored by tlc and went to completion after 2 hours.



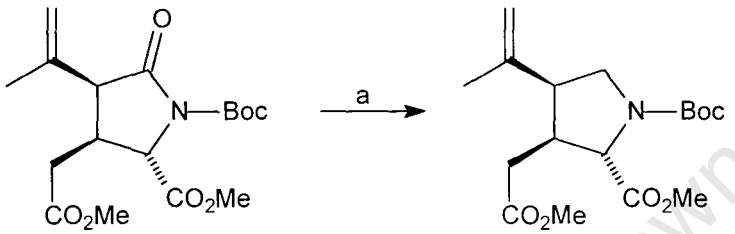
2.140 **2.141**

Scheme 2.78. *Reagents and Conditions*: a) Bu_3SnH, AIBN (Cat), Toluene, 120°C, 72%.

The product **2.141** was isolated by chromatography in 72% yield. Its ^1H and ^{13}C NMR spectra confirmed reduction had occurred with loss of the phenyl signals in the aromatic region and the appearance of a one-proton multiplet at δ 2.32 ppm and a one-proton multipet at δ 2.20 ppm for the two H-1 diastereotopic protons respectively. C-1 had moved from 66.3 / 68.2 to 32.8 / 32.0 for each rotamer respectively, thus confirming that reduction had occurred.

The above short sequence of reactions confirmed the reduction of lactam **2.138** to pyrrolidine **2.141** but it was decided to develop a shorter sequence to **2.141**. In the literature,

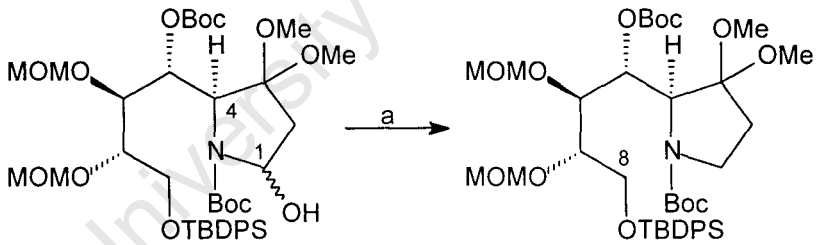
The above short sequence of reactions confirmed the reduction of lactam **2.138** to pyrrolidine **2.141** but it was decided to develop a shorter sequence to **2.141**. In the literature, it has been reported that α-hydroxycarbamate can be reduced by triethylsilane in the presence of a Lewis acid such as $BF_3.OEt_2$ at -78°C. The mechanism is ionic with H^- from Et_3SiH adding to an *N*-acyliminium ion. An example from the recent literature by Clayden relating to Kainic acid synthesis is shown in Scheme 2.79.[122]



2.142 **2.143**

Scheme 2.79. *Reagents and Conditions*: a) i), DIBAL-H, THF, -78°C; ii) Et_3SiH, $BF_3.OEt_2$, DCM, -78°C, 44% for the two steps.

Hence, **2.139** was reacted under these conditions (Scheme 2.80), followed by quenching with triethylamine at -78°C and then aqueous sodium carbonate. The product was isolated via chromatography in 91% yield.

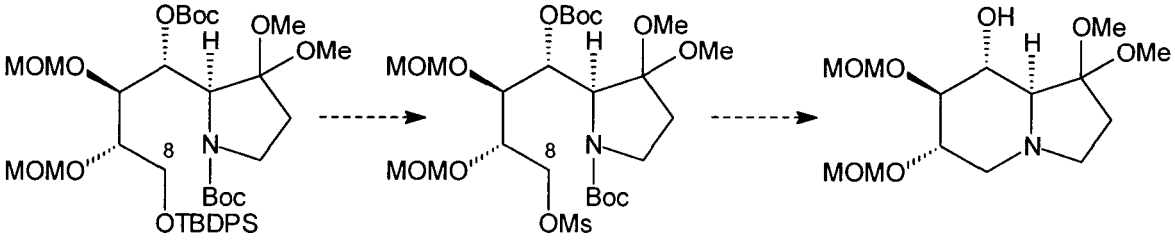


2.139 **2.141**

Scheme 2.80. *Reagents and Conditions*: a) Et_3SiH (2 eq), $BF_3.OEt_2$ (2 eq), DCM, -78°C, 1h, 91%.

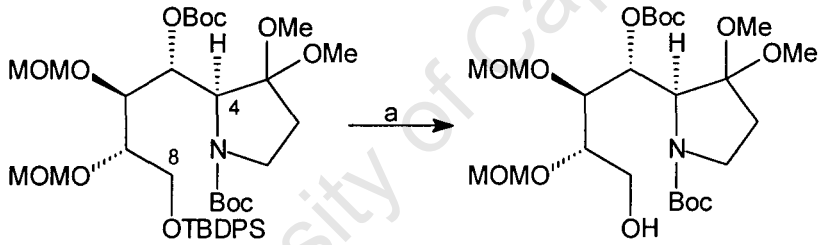
Regarding experimental considerations, it was found that the reduction was quite sensitive. In particular, higher temperatures than -78°C and/or long reaction times (> 1hr) promoted side-products. Hence, for the best results, it was found that the reaction needed to be carried out at -78°C for 1 hour with 2 equivalents of triethylsilane and BF_3.etherate, the reaction was then quenched and the unreacted starting material recovered and recycled. In this manner, **2.141** was obtained in an overall 91% yield over 4 runs. The ^1H and ^{13}C NMR spectra of the product were identical to the ones reported using the longer sequence involving sulfide reduction. It

With the protected amine **2.141** in hand, our attention now focused on generating the indolizidine bicycle. This was envisaged to straightforwardly involve converting the C-8 hydroxyl group into a leaving group (mesylate or tosylate) followed by Boc removal and cyclization (Scheme 2.81).



Scheme 2.81 **2.141** **2.144** **2.145**

Deprotection of the primary hydroxyl group was thus carried out under standard conditions using tetrabutylammonium fluoride in THF at 10°C for 5 days. The reaction mixture was quenched with aqueous ammonium chloride and the product **2.146** was isolated via chromatography to give a crystalline solid in 84% yield (Scheme 2.82).



2.141 **2.146**

Scheme 2.82. *Reagents and Conditions*: a) 1M TBAF (1.5 eq), THF, 10°C, 5 days, 84%.

At higher temperatures, by-products formed. Hence, it was decided to carry the reaction out at the lower temperature of 10°C for a longer reaction time, which gave a higher yield of product. The ^{1}H and ^{13}C spectra of **2.146** showed that all signals associated with the silyl ether protecting group had disappeared. The signals for C-5, C-6, C-7 and C-8 still showed the same patten with C-6 being the most downfield at δ 81.0/80.7 ppm for the two rotamers. **2.146** was crystallised with ethyl acetate and hexane to obtain a single-crystal X-ray structure, which is shown in Figure 2.32 below. From the X-ray crystal structure it can be seen that the hydrogen at C-4 is pointing down which relates to an *S*-configuration, while the C-5 hydrogen is in front with an *R* configuration. The hydrogen at C-6 is behind which translates to an *S*-configuration and finally for C-7 the hydrogen is also behind and also can be concluded to be

an *S*- configuration, in accordance with L-tartrate starting material. Interestingly, the *N*-Boc group appears in its s-*trans* form, with the carbonyl oxygen pointing away from C-4.

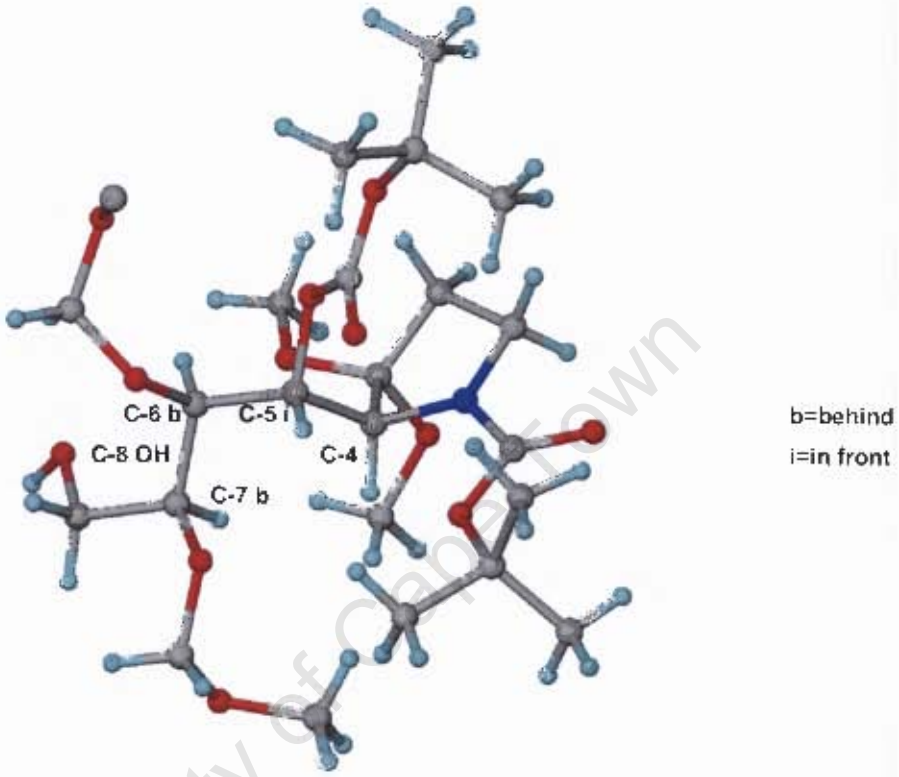
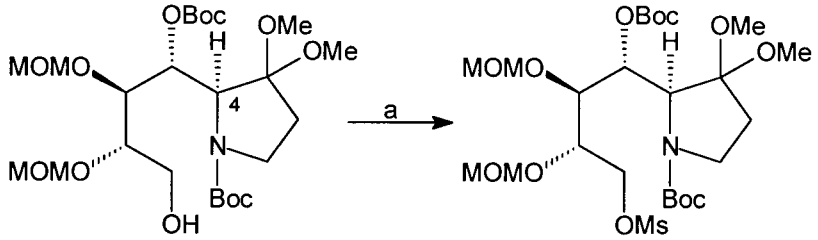


Figure 2.32. A single crystal X-ray determination of **2.146**.

Using the information obtained from the X-ray crystal structure of **2.146** it can deduced that the absolute stereochemistry at C-4 and C-5 were still *S*- and *R*-configurations respectively relative to the centres at C-6 and C-7, which are the correct configurations for C-8 and C-8a for (+)-castanospermine. Hence, no epimerization had occurred during the synthesis of **2.146**.

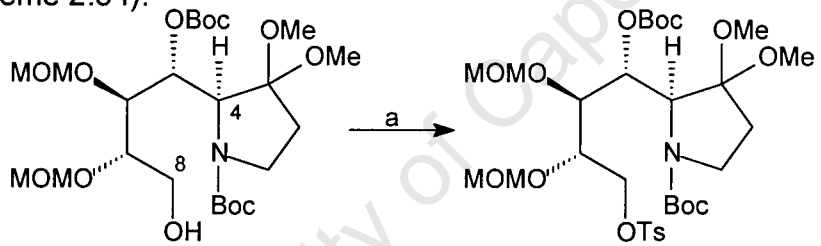
2.146 was then subjected to mesylation under standard conditions using mesyl chloride (CH_3SO_2Cl), triethylamine and dichloromethane at 0°C (Scheme 2.83). The reaction went to completion within 30 minutes and the product was isolated via chromatography to give mesylate **2.147** in 83% yield. Having the C-5 hydroxy protected as a Boc helped to remove any chemoselectivity issue with the primary hydroxyl group at C-8.



2.146 **2.147**

Scheme 2.83. *Reagents and Conditions*: a) MsCl, Et_3N, DCM, 0°C, 30 mins, 83%.

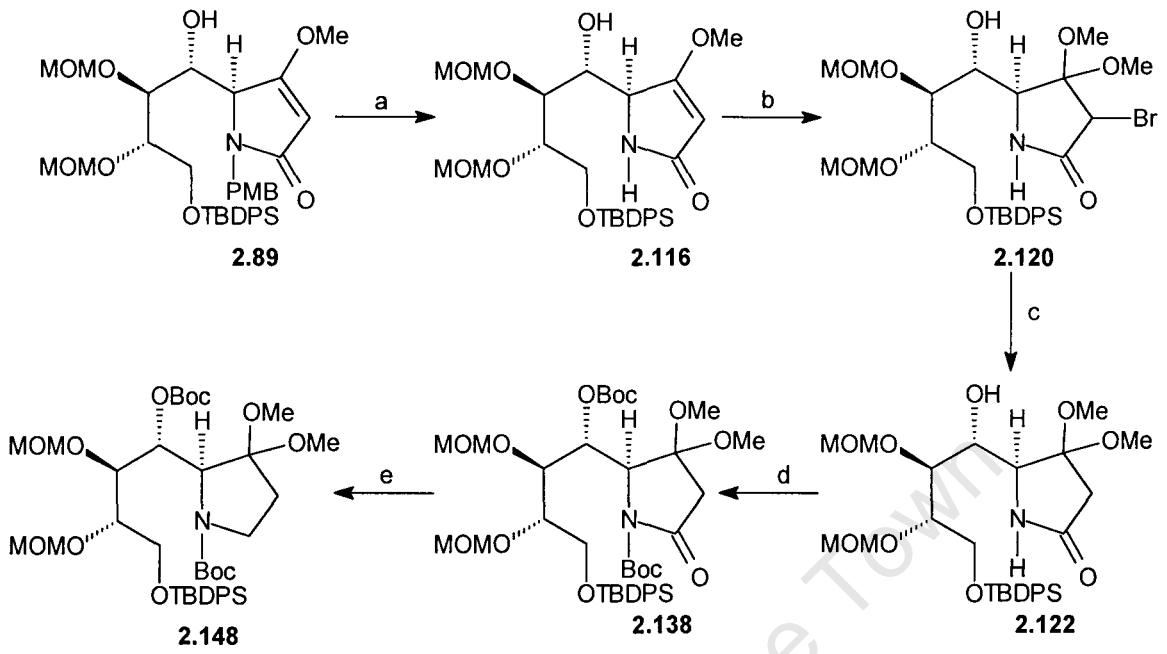
The ^1H NMR spectrum of **2.147** confirmed that the hydroxyl group had been converted to its mesylate by the presence of a singlet at δ 3.03 ppm for the methyl group of the mesylate. As there was now no UV-active group, it was decided to change the mesylate for a tosylate in order to follow the reaction more easily. Hence, **2.146** was subjected to tosylation under the standard conditions of tosyl chloride, triethylamine, DMAP (cat) in dichloromethane at 27°C for 24 hours (Scheme 2.84).



2.146 **2.148**

Scheme 2.84. *Reagents and Conditions*: a) TsCl (1.5 eq), Et_3N (2 eq), DMAP (cat), DCM, 27°C, 24 h, 100%.

The product was isolated by chromatography in 100% yield as a crystalline solid. It was noted that the reaction needed to be carried out at a higher temperature with a longer reaction time than for the mesylation for the reaction to go to completion in view of the less reactive tosyl chloride. The ^1H NMR spectrum of **2.148** showed the presence of a tosyl group by virtue of an appearance of the AB system at δ 7.82 ppm and δ 7.30 ppm (*J* 7.8 Hz). The ^{13}C spectrum of **2.148** showed that C-5 resonated downfield at δ 70.0 ppm, while its IR spectrum confirmed the presence of the tosyl group with the appearance of a sulfonyl S=O stretch at 1367cm^{-1}. The parent ion was found to be 694.3110 $[M+H]^+$ correlating to the correct molecular formula of $C_{31}H_{52}NO_{14}S$, thus confirming the presence of the tosylate.Before attempting to cyclize, it was decided to see if **2.148** could be formed from adduct **2.89**, as this route would be shorter and less expensive (Scheme 2.87).



Scheme 2.85. *Reagent and Conditions*: a) CAN, aq CH_3CN, -20°C to rt, 5h; b) Br_2, MeOH, -20°C, 30 mins, 80% over 2 steps c) Zn, aq NH_4Cl, THF, MeOH, RT, 30 mins, 86%; d) $(Boc)_2O$, THF, DMAP (cat), rt, 18h, 90%; e) i) DIBAL-H, THF, -78°C to -20°C, 2h, 86%; ii) Et_3SiH, $BF_3.OEt_2$, DCM, -70°C, 1h, 91%.

Adduct **2.89** underwent oxidative cleavage with CAN to give lactam **2.116**, which was then subjected to methoxy bromination followed by zinc reduction to give lactam **2.120**. The sequence of reactions that followed was same as described before eventually to give pyrrolidine **2.148**. Products **2.122** to **2.148** had identical ^1H and ^{13}C spectra, $[\alpha]_D$, and melting points as the one reported before during the course of this work.

The stage was now to set to proceed with the cyclization to form the indolizidine. In order to achieve this, the Boc protecting groups needed to be hydrolysed first. It was felt that this could be carried out using trifluoroacetic acid in dichloromethane and that the product formed could be subjected to base treatment to induce cyclization without further purification.

To our delight, under these conditions two polar products were formed by tlc, which were separated by direct silica-gel chromatography of the reaction mixture using 1:4 methanol : ethyl acetate with a couple of drops of ammonia as the eluent. Yields were good based on the tentative assignments as 64% and 25% for the more polar and less polar products respectively. NMR spectra were recorded for both products and resonances assigned using

HSQC 2D NMR. The ^{1}H and ^{13}C of the major product revealed some striking changes compared to starting material **2.148** and the values are given in Table 11. A portion of the ^{1}H, ^{13}C spectra and HSQC of the major product **2.149** are shown in Figures 2.33, 2.34 and 2.35 respectively. The numbering now refers to castanospermine numbering.

Table 11

ASSIGNMENT	δ_H	MULTIPICITY	*J* VALUES	δ_C*
C-8a	3.57	d	6.4 Hz	70.0
C-8	4.68	dd	6.4, 3.6 Hz	83.5
C-7	4.55	d	3.6 Hz	91.8
C-6	4.32	d	3.2 Hz	75.8
C-5	3.88	dd	9.6 Hz	77.0
C-5	4.04	dd	9.6, 3.2 Hz	

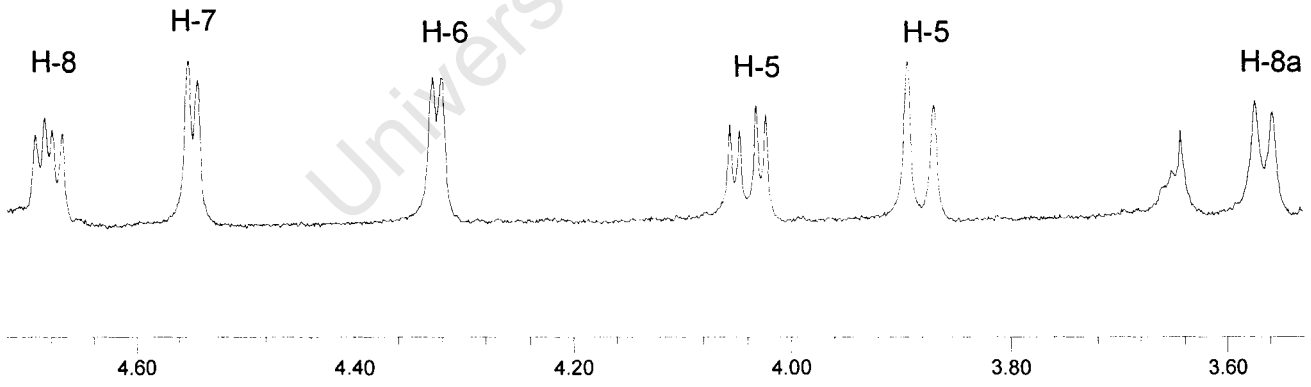


Figure 2.33. ^{1}H spectrum of **2.149**

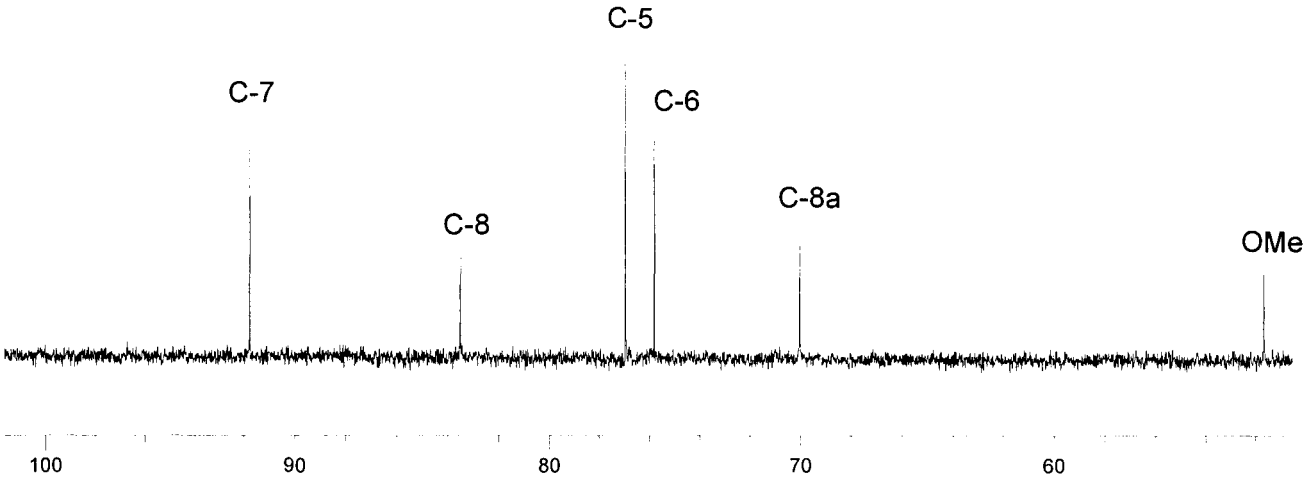


Figure 2.34 ^{13}C spectrum of **2.149**.

Using all available NMR data, structures at this stage were tentatively assigned as indolizidines **2.149** and **2.150** shown in Scheme 2.86. It was felt that cyclization to the tetrahydrofuran as before was unlikely to compete with *N*-cyclization. Figure 2.36 below summarizes the coupling patterns seen in the NMR data.

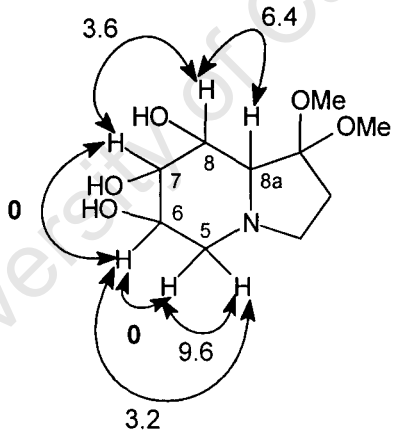
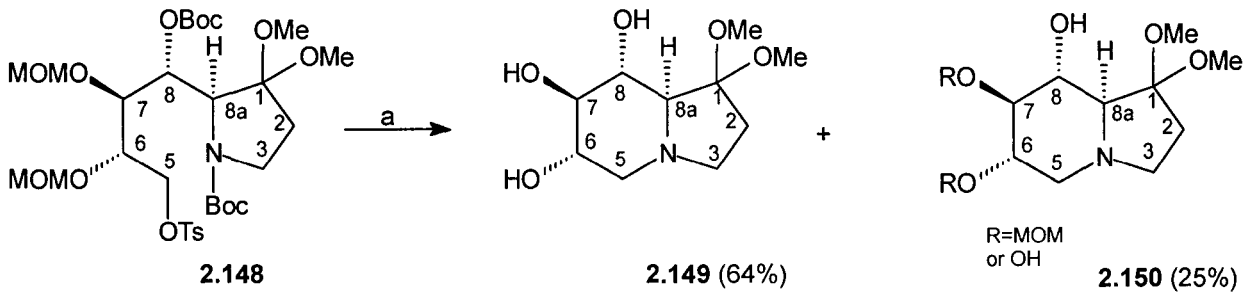


Figure 2.36 Coupling pattern for **2.149**



2.148 **2.149** (64%) **2.150** (25%)

Scheme 2.86. *Reagents and Conditions*: a) i) TFA: DCM (1:4), 0°C 2h; ii) Hünig's base (4 eq), DCM, 0°C, 18 h, **2.149** 64%, **2.150** 25%.

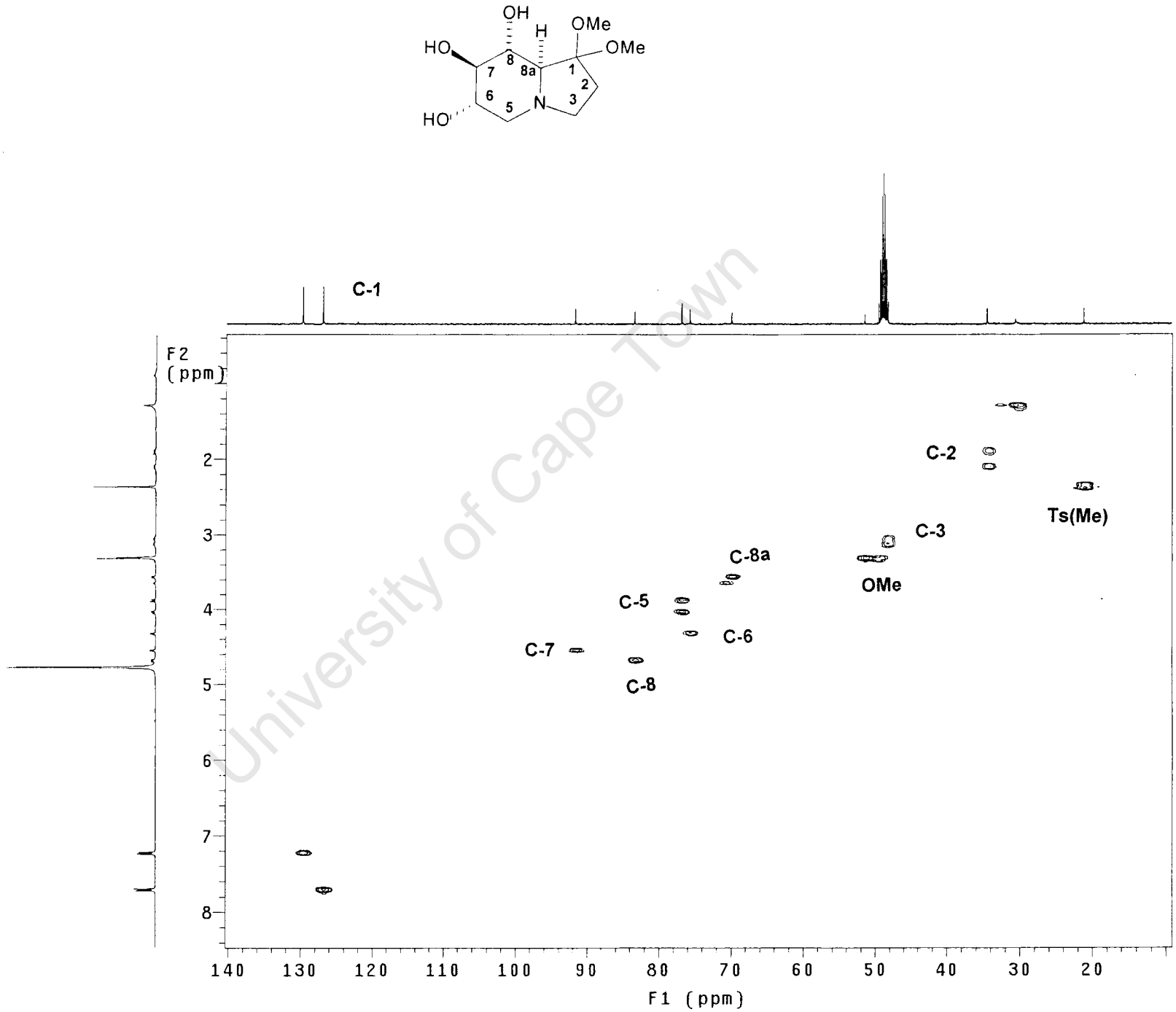
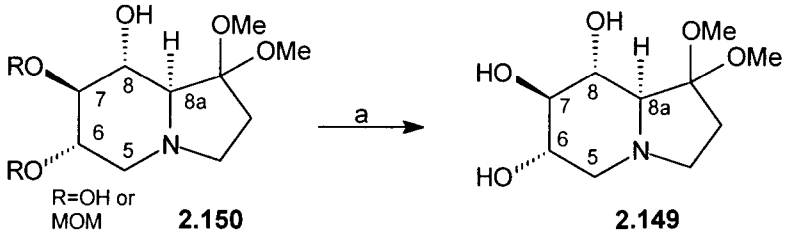


Figure 2.35 HSQC of **2.149**

The minor product **2.150** was then treated with 1M HCl at room temperature for 3 days and resulted in its conversion to the major product **2.149**, which was confirming it as an incompletely hydrolysed product (Scheme 2.86).

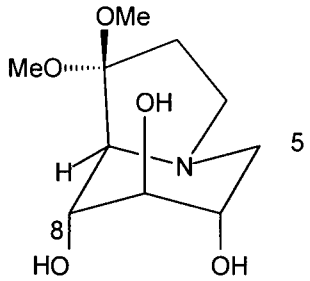


Scheme 2.87. *Reagents and Conditions*: a) HCl (1 M), 15°C, 3 days, 88%.

Noticeably, when these chemical shifts and coupling constants were compared to those of (+)-castanospermine, there were some major differences which were:

- The coupling constant between H-6 and H-7 was 0 Hz indicating a dihedral angle of 90° between H-6 and H-7 from the Karplus equation.
- The ^{1}H chemical shifts of H-5 to H-8a were much more downfield to those of (+)-castanospermine. Furthermore, coupling constants were much smaller than those for the corresponding protons of (+)-castanospermine.
- The ^{13}C chemical shift for C-5 was δ 77.0 ppm, when in indolizidines, the carbon α to nitrogen in the piperidine ring usually appears at around 55 ppm.

These observations immediately pointed towards the piperidine chair being in a $^{5}C_{8}$ conformation to ensure that the H-6, H-7 and H-8 protons are equatorial with small vicinal coupling constants. In particular, the lack of a large *trans*-diaxial coupling between one of the H-5 protons and H-6 confirmed this perception. Given that we had unambiguously proved by an X-ray determination that H-8a had not epimerized prior to cyclization, the full structure consisitent with the ^{1}H NMR data that presented itself was the *cis*-fused $^{5}C_{8}$ indolizidine **2.149** (Figure 2.37).

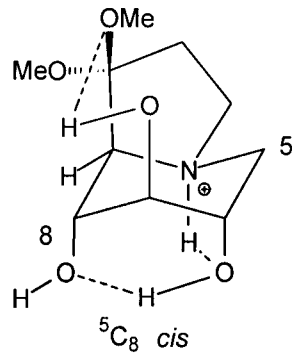


$^5C_8$ *cis*

2.149

Figure 2.37

Dhavale has recently reported on synthesis of castanospermine C-8a epimers with the piperidine in the $^5C_8$ conformation, but as a *trans*-fused system as in castanospermine (Figure 2.37). In our case, C-8a exisiting in the natural castanospermine configuration automatically excluded a *trans*-fused system for the $^5C_8$ conformation. The interpretation of the ^{13}C data proved to be baffling in that the C-5, C-6, C-7 and C-8a shifts were all downfield by at least 10 ppm. Eventually, it was realized that the major product isolated, in spite of using ammonia in the silica-gel chromatography as well as ion-exchange chromatography, was the tosylate salt. Signals for the tosyl group could be clearly discerned in the both ^1H and ^{13}C spectra (Figures 2.38 and 2.39). The presence of an ammonium cation in the molecule is postulated to account for some of the deshielding, notably of C-5 and C-8a. A further effect, however, and one which we believe contributes to the stability of this unusual conformation is the presence of multiple hydrogen-bonding. Examination of 3D-models suggests the contribution of three hydrogen-bonds as shown in Figure 2.40 to offset the unfavourable C_5-H_{ax}/C_{8a}-C_1 and C_7-O/C_{8a}-C_1 1,3 diaxial interactions.

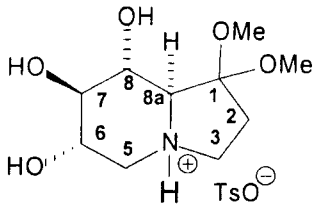


$^5C_8$ *cis*

2.149

Figure 2.40

2.149 presents a novel structure in the castanospermine repertoire, and one that present itself as an interesting candidate for biological evaluation in view of its topology. The cation, as mentioned in Chapter 1, mimics the active biological form of castanospermine.



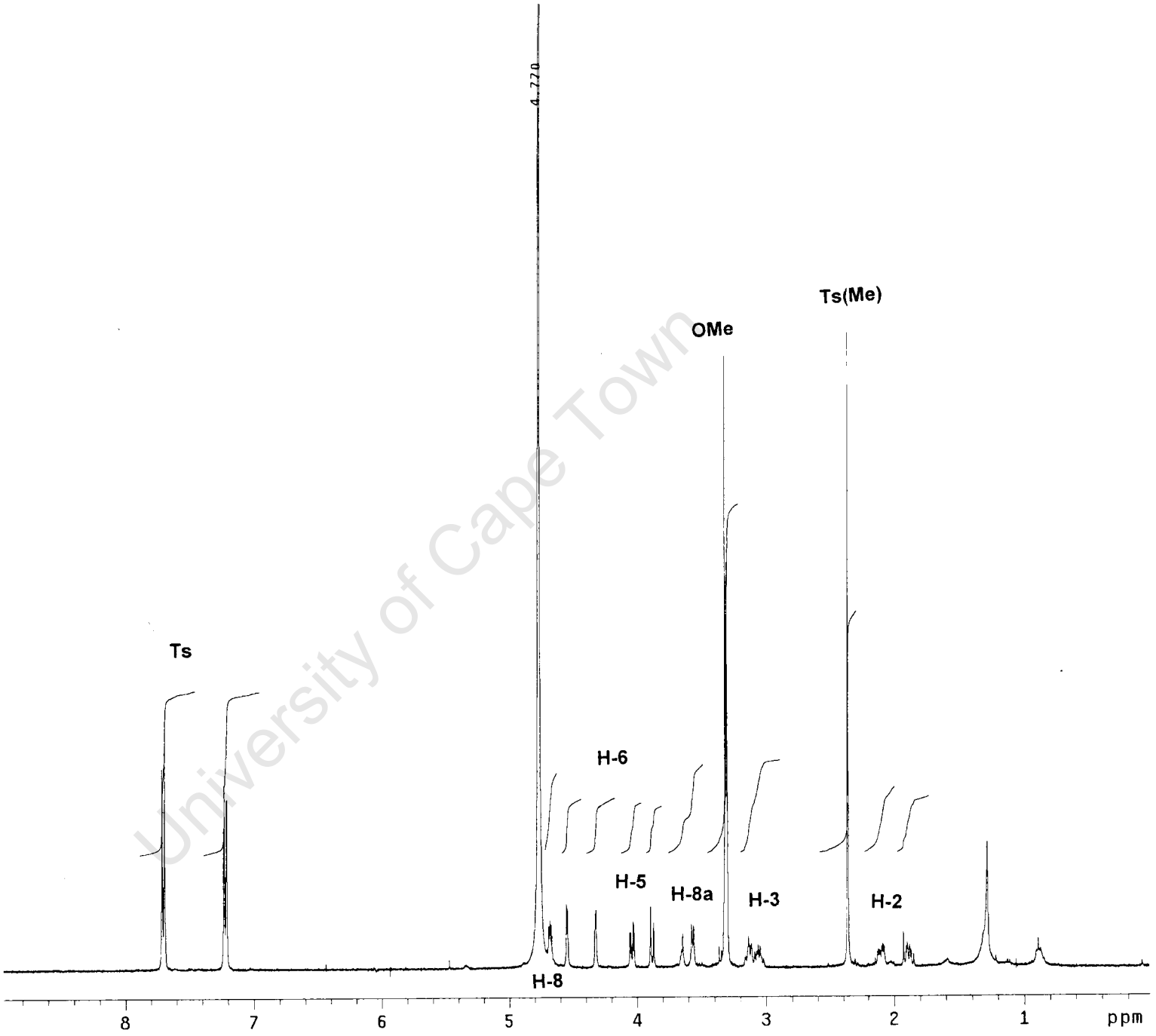
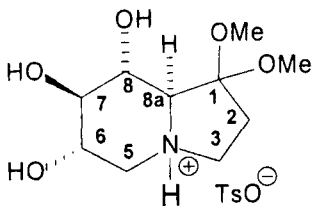


Figure 2.38 Full ^{1}H NMR spectrum of **2.149**



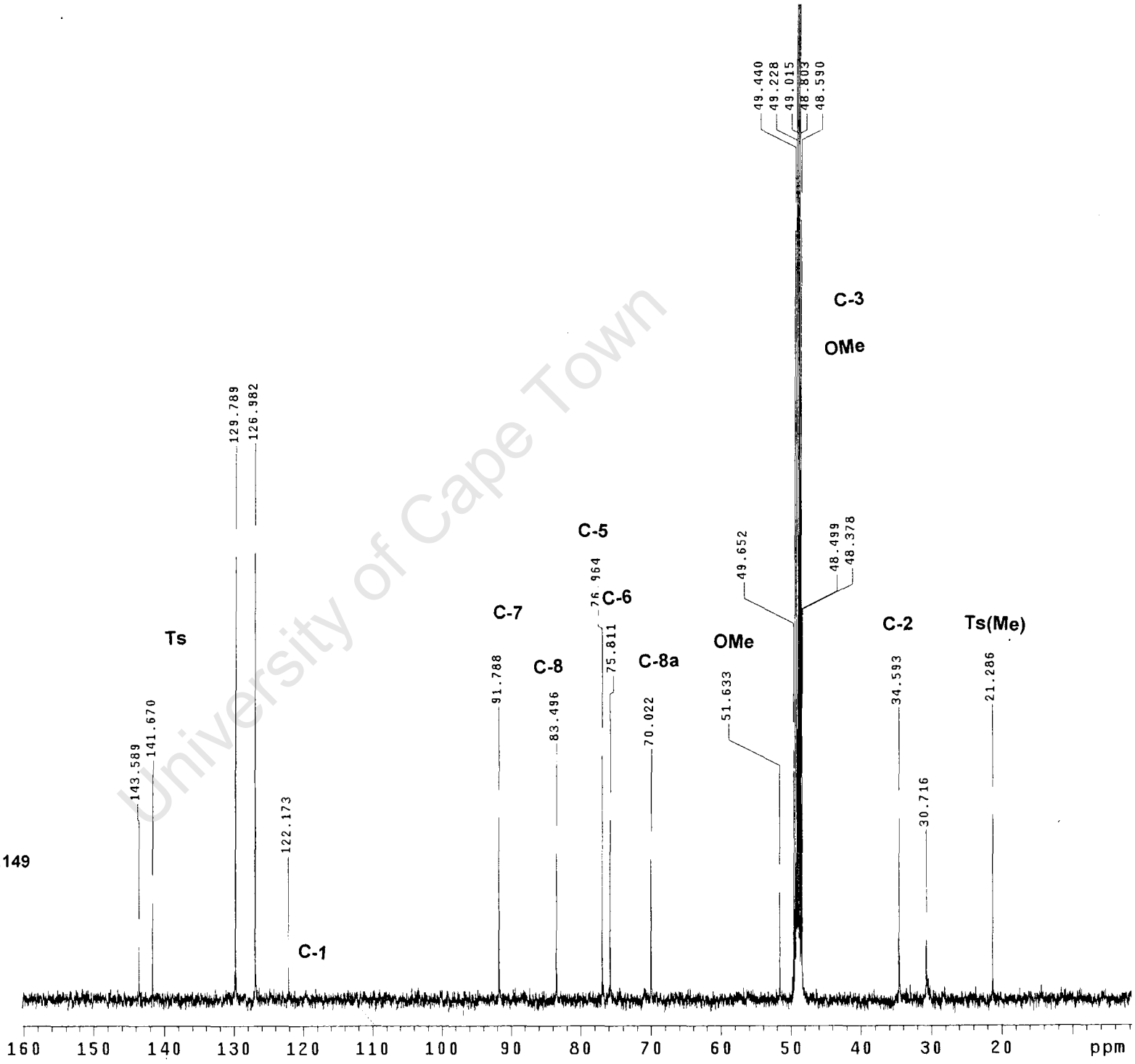


Figure 2.39 Full ^{13}C NMR spectrum of **2.149**

Preliminary studies on the hydrolysis of the ketal **2.149** were then carried out. It was difficult to follow the reaction by tlc, so ^1H NMR (in D_2O) was used, which identified optimal conditions to be 0.1 ml HCl in 0.5 ml H_2O at 30°C. Some evidence of hydrolysis in terms of changes in the methoxy region as well as the H-8a resonance was noted, but the reaction was extremely sluggish at 30°C, taking several weeks. Higher temperatures resulted in decomposition. A promising looking sample was eventually chromatographed (with methanol in the eluent) only to find that the ketal had reformed. The slow rate of hydrolysis was an unforeseen stumbling block in the end-game of the synthesis and can be rationalized by destabilization of the oxocarbenium ion intermediate by the electron-withdrawing ammonium cation (protonated in acid). Trigonalisation at C-1 also would presumably invoke angle strain (108° to 120°), as a further energy-raising parameter (Figure 2.41).

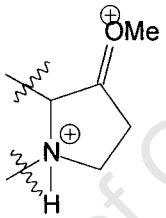


Figure 2.41. Oxocarbenium ion intermediate

This disappointing result strongly identified the need to redesign the synthesis regarding the timing of ketal hydrolysis. However such a task was beyond the scope of this thesis.
The suggested route emerging from the current work is shown in Scheme 2.88.

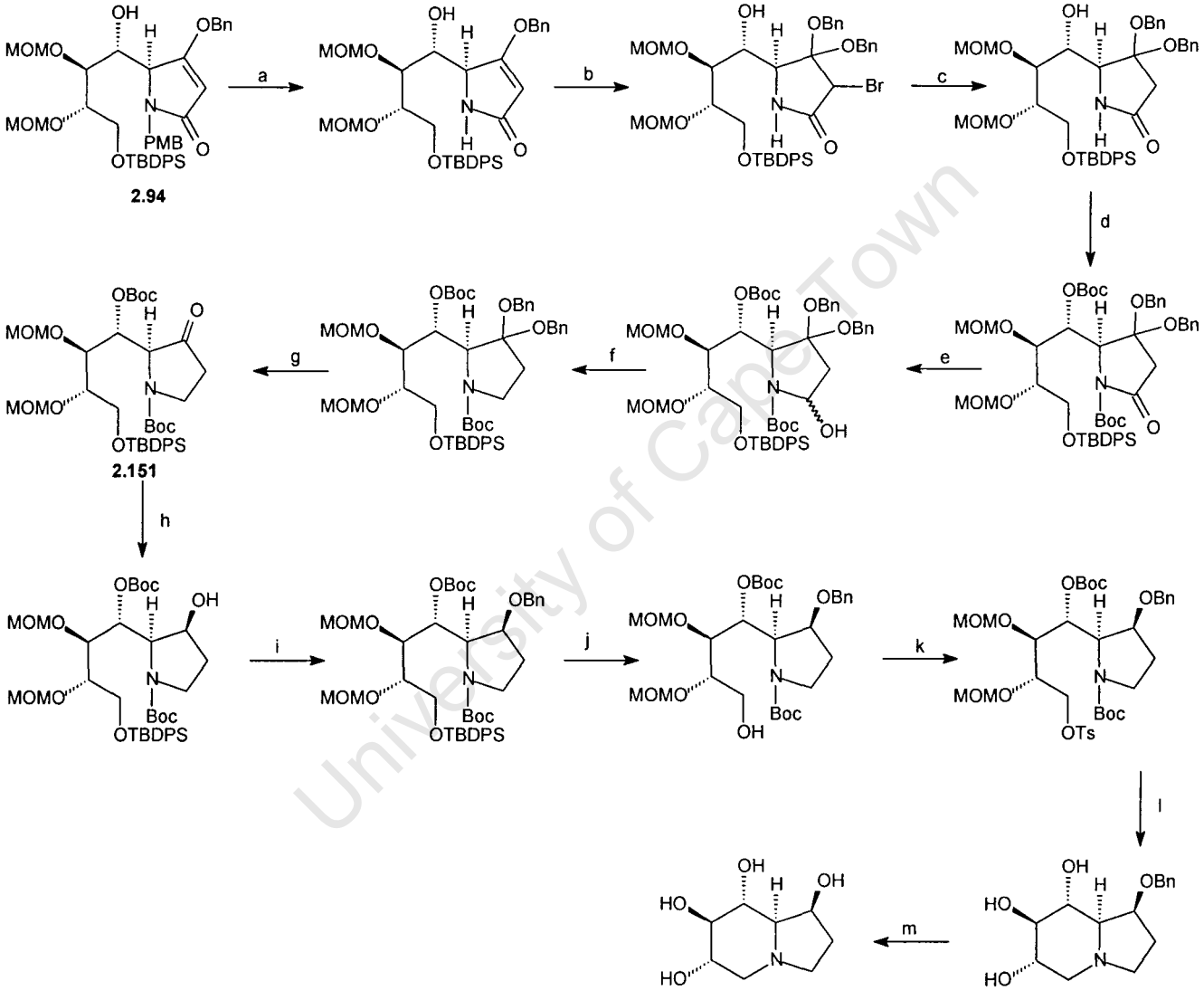
2.4 Conclusion

From this project several conclusions can be drawn:

- The project has developed a new "one pot" Mukaiyama extended aldol reaction involving a novel silyloxypyrrole.
- The above reaction when applied to a chiral threose derivative presents an adduct containing the correct relative and absolute configurations for castanospermine at C-8 and C-8a, thus providing a solution to this long-standing problem.
- A sequence for indolizidine formation pertaining to castanospermine synthesis has been developed. A novel structure in a rarely seen conformation has been uncovered.

- From the latter part of the project, it can be deduced that the ketal would have to be hydrolysed earlier on in the synthesis.

Based on results in this thesis, the suggested new route to (+)-castanospermine is shown in the Scheme 2.88 below from adduct **2.94**.



Scheme.2.88 *Reagent and Conditions*: a) CAN, aq CH_3CN, -20°C to rt, 5h; b) Br_2, BnOH, -20°C, 30 mins; c) Zn, aq NH_4Cl, THF, BnOH, RT, 30 mins; d) $(Boc)_2O$, THF, DMAP (cat), rt, 18h; e) DIBAL-H, THF, -78°C to -20°C, 2h; f) Et_3SiH, $BF_3.OEt_2$, DCM, -70°C, 1h; g) H_2/Pd-C; h) $NaBH_4$, MeOH; i) NaH, BnBr, TBAI, THF; j) TBAF, THF; k) TsCl, DMAP, DCM; l) i) TFA, DCM; ii) Hünig's Base, DCM; m) H_2, Pd/C, EtOH.

The key difference in the synthesis would be to unravel the ketal earlier in the synthesis via a hydrogenolytic (non-acidic) conversion to the ketone **2.151**. Thereafter, the sequence would be similar to that from before.

Chapter 3: Experimental Section

3.1 General methods

All solvents were freshly distilled. Tetrahydrofuran was distilled under argon from sodium wire with benzophenone. Diethyl ether was distilled from lithium aluminium hydride under argon. Acetonitrile was distilled from calcium hydride under argon. Dichloromethane was distilled from phosphorus pentoxide under nitrogen. Other reagents were purified according to standard procedures.[123]

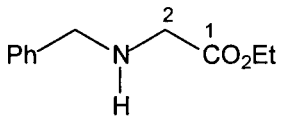
Column chromatography was performed using silica-gel 60 (Merck 7734). Thin layer chromatography (tlc) was carried out on aluminium-backed Merck silica-gel 60 F_{254}. Compounds were visualized on tlc by using one or more of the following revealing techniques: UV lamp, iodine vapour, spraying with a 2.5% solution of anisaldehyde in a mixture of sulfuric acid and ethanol (1:10 v/v) or ceric ammonium sulfate solution and then heating at 250°C.

Infra-Red (IR) absorptions were measured on a Perkin Elmer Spectrum one FT-IR Spectrometer. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 MHz (75.5 MHz for ^{13}C) or Varian Unity 400 (100.6 MHz for ^{13}C) instrument and were carried out in chloroform-d unless otherwise stated. Chemical shifts (δ) were recorded relative to residual chloroform (δ 7.26 in ^{1}H NMR) and (δ 77.00 in ^{13}C NMR). All chemical shifts are reported in ppm and resonances are assigned according to IUPAC numbering, viz H-1 = H on C-1. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20°C and a Perkin Elmer 343 at 20°C. The concentration *c* refers to g/100ml. High resolution mass spectra were recorded on a Waters API Q-TOF Ultima machine, at the Mass Spectrometry Service, School of Chemistry, University of Stellenbosch.

Melting points were obtained using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Elemental analyses were performed using a Fisons EA 1108 CHNS elemental analyzer. All reagents were purchased from Aldrich or Merck. Low temperature reactions were carried out in a bath cooled by liquid nitrogen in acetone unless otherwise stated.

3.2 Compounds

Ethyl N-benzylglycinate **2.9**[124]

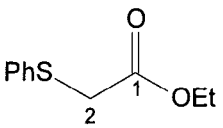


2.9

To a solution of benzylamine (5.0 g, 46.7 mmol) and triethylamine (9.1 ml, 65.3 mmol, 1.4 eq) in dry tetrahydrofuran (150 ml) at -20°C was added ethyl bromoacetate (5.7 ml, 51.3 mmol, 1.1 eq) drop-wise via a syringe over an hour. The reaction mixture was stirred at 10°C for 18h after which the suspension was filtered through Celite® and rinsed thoroughly with ethyl acetate (200 ml). The filtrate was concentrated under reduced pressure and aqueous sodium bicarbonate (150 ml) was added. The product was extracted with ethyl acetate (3 x 200ml) and the combined organic layers dried over magnesium sulfate. The organic layer was then concentrated under reduced pressure to give a residue (8.3 g), which was chromatographed on silica-gel (150 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 1 :1) as eluent to give amino ester **2.9** (7.0 g, 36 mmol, 79%).

δ_H ($CDCl_3$, 300 MHz) 1.27 (3H, t, *J* 7.2 Hz, CH_3), 2.00 (1H, s, NH), 3.40 (2H, s, H-2), 3.80 (2H, s, Bn), 4.18 (2H, q, *J* 7.2 Hz, OCH_2), 7.20-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 14.1 (CH_3), 50.0 (C-2), 53.2 (C-Bn), 60.6 (OCH_2), 127.1, 128.2, 128.4, 139.5 (Ar), 172.3 (C=O).

Ethyl 2-phenylsulfanylethanoate **2.6**[125]



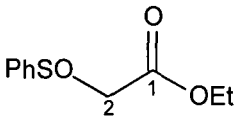
2.6

To a degassed suspension of potassium hydroxide (2.8 g, 50.0 mmol, 1 eq) in methanol (80 ml) was added benzenethiol (5.1 ml, 50.0 mmol, 1 eq). The reaction mixture was cooled to 0°C and ethyl bromoacetate (5.5 ml, 50.0 mmol) was added, after which it was allowed to warm to room temperature and left to stir for 18h. The mixture was concentrated under

reduced pressure and water (100 ml) was added. The solution was extracted with dichloromethane (3 x 100 ml), the combined organic layers dried over magnesium sulfate and concentrated to give **2.6** as an oil (10.6 g), which was pure enough by ^{1}H NMR to proceed to the next step.

δ_H ($CDCl_3$, 400 MHz) 1.18 (3H, t, *J* 7.2 Hz, CH_3), 3.59 (2H, s, H-2), 4.12 (2H, q, *J* 7.2 Hz, OCH_2), 7.10-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 13.8 (CH_3), 36.3 (C-2), 61.1 (OCH_2), 126.6, 128.7, 129.7, 134.9 (Ar), 169.2 (CO).

Ethyl 2-phenylsulfinylethanoate **2.7**[126]

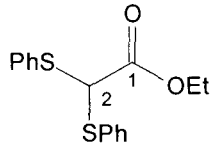


2.7

To a solution of sulfide **2.6** (7.5 g, 38.0 mmol) in acetic acid (25 ml) at 0°C, was added hydrogen peroxide (12 ml, 8.8 M, 106 mmol) slowly via a pressure-compensating dropping funnel. The reaction mixture was left at -5°C until the reaction had gone to completion (tlc). The reaction mixture was quenched with cold potassium hydroxide (1 M, 200 ml, 200 mmol) and the product extracted with ethyl acetate (3 x 150 ml), the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure to yield sulfoxide **2.7**, which was pure enough by ^{1}H NMR to proceed to the next step (7.8 g, 37.0 mmol, 97%).

δ_H ($CDCl_3$, 300 MHz) 1.08 (3H, t, *J* 7.2 Hz, CH_3), 3.58 (1H, d, J_{AB} 13.8 Hz, H-2), 3.72 (1H, d, J_{AB} 13.8 Hz, H-2), 4.02 (2H, q, *J* 7.2 Hz, OCH_2), 7.40-7.60 (5H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 13.6 (CH_3), 61.2 (C-2), 61.5 (OCH_2), 123.8, 129.0, 131.3, 142.8 (Ar), 164.31 (CO).

Ethyl 2,2-bis(phenylsulfanyl)ethanoate **2.8**[127]

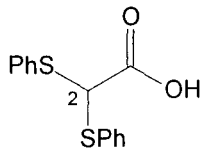


2.8

To a solution of sulfoxide **2.7** (5.7 g, 27.0 mmol) in dry dichloromethane (100 ml) at 0°C, was added trifluoroacetic anhydride (4.8 ml, 34.0 mmol, 1.25 eq). The reaction mixture was stirred for 10 minutes at 0°C, after which were added benzenethiol (3.1 ml, 30.0 mmol, 1.1 eq) followed by boron trifluoride etherate (3.7 ml, 30.0 mmol, 1.1 eq). The reaction mixture was stirred for a further 18h at room temperature. The reaction mixture was quenched with cold potassium hydroxide (1 M, 150 ml, 150 mmol) and the product was extracted with dichloromethane (3 x 150 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a residue (8.0 g), which was chromatographed on silica-gel (120 g) with ethyl acetate : petroleum ether mixtures (1 : 99 to 1 : 9) as eluent to yield thioacetal ester **2.8** (7.1 g, 22.0 mmol, 82%).

δ_H ($CDCl_3$, 400 MHz) 1.18 (3H, t, *J* 7.2 Hz, CH_3), 4.15 (2H, q, *J* 7.2 Hz, OCH_2), 4.91 (1H, s, H-2), 7.20-7.40 (10H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 13.7 (CH_3), 58.0 (OCH_2), 61.8 (C-2), 128.3, 128.8, 132.6, 133.0 (Ar), 168.2 (CO).

2,2-Bis(phenylsulfanyl)ethanoic acid **2.4**[128]



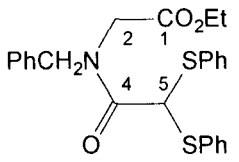
2.4

To a suspension of potassium hydroxide (1.3 g, 23.4 mmol, 1.5 eq) in methanol (100 ml) and water (25 ml) was added thioacetal ester **2.8** (5.0 g, 15.6 mmol) and the mixture was stirred for 18h at room temperature. The reaction mixture was concentrated under reduced pressure and the solution was extracted with dichloromethane (3 x 100 ml). The aqueous phase was acidified and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield carboxylic

acid **2.4**, which was pure enough by ^{1}H NMR and tlc to proceed to the next step (3.7 g, 13.5 mmol, 80%).

δ_H ($CDCl_3$, 400 MHz) 4.86 (1H, s, H-2), 7.20-7.60 (10H, m, Ar), 10.96 (1H, s(br), OH); δ_c ($CDCl_3$, 75.5 MHz) 58.2 (C-2), 128.9, 129.1, 132.2, 133.5 (Ar), 174.7 (CO).

Ethyl 3-aza-*N*-benzyl-4-oxo-5,5-bis(phenylsulfanyl)pentanoate **2.10a/b**



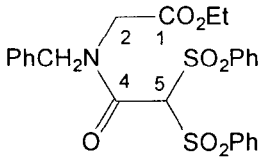
2.10a/b

To a solution of amine ester **2.9** (1.7 g, 9.1 mmol) in dry dichloromethane (100 ml) at 0°C, were added carboxylic acid **2.4** (3.0 g, 11.0 mmol, 1.2 eq) and dicyclohexylcarbodiimide (2.4 g, 12.0 mmol, 1.3 eq) successively. The reaction mixture was stirred at room temperature for 18h. The reaction mixture was filtered through Celite®, rinsed thoroughly with dichloromethane (300 ml) and the filtrate was concentrated under reduced pressure to give a residue (5.1 g), which was purified on silica-gel (200 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 1 : 4) as eluent to yield amide **2.10a/b** (4.0 g, 8.8 mmol, 90%) as a mixture of s-*cis* and s-*trans* amide rotamers (2:1) which was recrystallised (ethyl acetate / hexane).

M.p. 67-69°C (From ethyl acetate / hexane); (Found: C, 66.60; H, 5.54; N, 2.69; S, 14.22. $C_{25}H_{25}NO_3S_2$ requires C, 66.49; H, 5.58; N, 3.10; S, 14.20%.); (Found $[M+H]^+$ 452.1363, $C_{25}H_{26}NO_3S_2$ requires 452.1354.); υ_{max} /cm^{-1} 3059, 3030 (C-H, arom), 2983, 2937, 2906, 2872 (C-H aliph), 2604 (C-S), 1742 (C=O ester), 1654 (C=O amide), 1024 (C-O ester);
Major- δ_H ($CDCl_3$, 300 MHz) 1.27 (3H, t, *J* 7.2 Hz, CH_3), 4.08 (2H, s, H-2), 4.20 (2H, q, *J* 7.2 Hz, OCH_2), 4.63 (2H, s, Bn), 5.08 (1H, s, H-5), 7.10-7.60 (15H, m, aromatics); δ_c ($CDCl_3$, 75.5 MHz) 14.1 (CH_3), 48.0 (C-2), 52.6 (C-Bn), 58.9 (C-5), 61.1 (OCH_2), 126.7, 127.9, 128.6, 128.9, 132.5, 133.6, 134.0, 135.6 (Ar), 167.6 (CO ester), 168.7 (CO amide).
Minor- δ_H ($CDCl_3$, 300 MHz) 1.21 (3H, t, *J* 7.1 Hz, CH_3), 4.06 (2H, s, H-2), 4.13 (2H, q, *J* 7.2 Hz, OCH_2), 4.67 (2H, s, Bn), 5.12 (1H, s, H-5), 7.10-7.60 (15H, m, Ar); δ_c ($CDCl_3$, 75.5 MHz)

14.0 (CH_3), 48.6 (C-2), 50.5 (C-Bn), 59.0 (C-5), 61.6 (OCH_2), 126.7, 127.7, 128.6, 128.9, 132.4, 133.6, 134.0, 136.0 (Ar), 167.6 (CO ester), 168.7 (CO amide).

Ethyl 3-aza-*N*-benzyl-4-oxo-5,5-bis(phenylsulfonyl)pentanoate **2.11a/b**



2.11a/b

To a solution of amide **2.10a/b** (4.0 g, 8.9 mmol) in dry dichloromethane (150 ml) at 0°C, was added *meta*-chloroperbenzoic acid (10.8 g, 53 mmol, 6 eq). The reaction mixture was stirred at room temperature for 18h before being quenched with saturated aqueous sodium carbonate and the solution extracted with dichloromethane (3 x 200 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a residue (6.5 g), which was chromatographed on silica-gel (160 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 1 : 1) as eluent to yield sulfone **2.11a/b** (3.8 g, 7.3 mmol, 82 %), as a mixture of s-*cis* and s-*trans* rotamers (7:2) which was recrystallized (ethyl acetate / hexane).

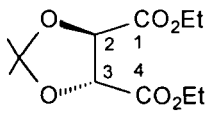
M.p 122-123°C; (from Ethyl Acetate / Hexane); Found: C, 58.28; H, 4.83; N, 2.73; S, 12.43. $C_{25}H_{25}NO_7S_2$ requires C, 58.24; H, 4.89; N, 2.72; S, 12.44%; ($[M+H]^+$ Found 516.1150, $C_{25}H_{26}NO_7S_2$ requires 516.1150.); υ_{max} /cm^{-1} 3064, 3031 (C-H arom), 2984, 2940, 2907, (C-H aliph), 2606 C-S, 1745 (C=O ester), 1667 (C=O amide), 1345 (S=O);

Major- δ_H ($CDCl_3$, 400 MHz) 1.29 (3H, t, *J* 7.1 Hz, CH_3), 4.12 (2H, s, H-2), 4.23 (2H, q, *J* 7.1 Hz, OCH_2), 4.79 (2H, s, Bn), 5.71 (1H, s, H-5) 7.05-7.75 (11H, m, Ar), 7.84 (4H, dd *J* 1.2, 8.6 Hz, *ortho*-SO_2Ph); δ_c ($CDCl_3$, 100.6 MHz) 14.1 (CH_3), 49.1 (C-2), 52.9 (C-Bn), 61.5 (OCH_2), 83.7 (C-5), 126.7, 128.4, 128.6, 128.6, 129.4, 130.7, 134.8, 137.0 (Ar), 159.8 (CO ester), 167.9 (CO amide);

Minor- δ_H ($CDCl_3$, 400 MHz) 1.25 (3H, t, *J* 7.2 Hz, CH_3), 4.13 (2H, s, H-2), 4.16 (2H, q, *J* 7.2 Hz, OCH_2), 4.59 (2H, s, Bn), 5.89 (1H, s, H-5), 7.05-7.75 (11H, m, Ar), 8.00 (4H, dd *J*, 1.2, 8.6 Hz, *ortho*-SO_2Ph); δ_c ($CDCl_3$, 100.6 MHz) 13.9 (CH_3), 49.3 (C-2), 51.1 (C-Bn), 62.1 (OCH_2),

84.4 (C-5), 126.7, 128.4, 128.6, 128.6, 129.4, 130.7, 134.9, 137.0 (Ar), 159.8 (CO ester), 167.7 (CO amide).

Diethyl 2,3-*O*-isopropylidene L-tartrate **2.64**[69]

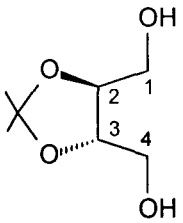


2.64

A solution of L-diethyl tartrate **2.20** (20.0 g, 97.0 mmol), 2,2-dimethoxypropane (14.0 ml, 116.0 mmol, 1.2 eq) and a catalytic amount of *para*-toluenesulfonic acid (10mg) in dry tetrahydrofuran (150 ml) was refluxed for 6h and the methanol removed via distillation. The reaction mixture was concentrated under reduced pressure and aqueous sodium carbonate added (100 ml). The solution was extracted with ethyl acetate (3 x 250 ml). The organic layers were combined, dried over magnesium sulfate and concentrated to give a residue (19.0 g), which was purified via vacuum distillation (b.p. 140°C, 1 mm Hg) to give ketal **2.64** (17.4 g, 71.0 mmol, 73%).

δ_H ($CDCl_3$, 300 MHz) 1.28 (6H, t, *J* 7.05 Hz, CH_3), 1.46 (6H, s, CH_3), 4.24 (4H, q, *J* 7.1 Hz, OCH_2), 4.73 (2H, s, H-2,3); δ_c ($CDCl_3$, 75.5 MHz) 14.0 (CH_3), 26.3 (CH_3 Ketal), 61.8 (OCH_2), 77.1 (C-2,3), 113.7 (ketal), 169.6 (*C*O).

2,3-*O*-Isopropylidene-L-threitol **2.65**[69]



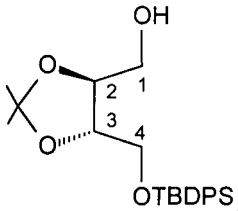
2.65

To a solution of ketal **2.64** (17.4 g, 71.0 mmol) at 0°C in dry tetrahydrofuran (300 ml), was added lithium aluminum hydride (6.2 g, 163.0 mmol, 2.3 mol eq) portion-wise. The reaction mixture was stirred at room temperature for 4h and subsequently quenched with a solution of water (10 ml) / triethylamine (30 ml) / tetrahydrofuran (100 ml) at 0°C. The suspension was stirred at room temperature for a further 40 minutes. The reaction mixture was then filtered

through Celite® and rinsed thoroughly with tetrahydrofuran (400 ml). The filtrate was concentrated under reduced pressure to give a residue (10 g), which was chromatographed on silica-gel (120 g) with ethyl acetate / petroleum ether mixtures (1 : 1 to 1: 0) as eluent to give diol **2.65** (8.0 g, 50.0 mmol, 71%).

δ_H ($CDCl_3$, 400MHz) 1.43 (6H, s, CH_3), 2.05 (2H, s(br), OH), 3.70 (2H, ddd, *J* 11.6, 2.8, 1.4 Hz, H-1,4), 3.77 (2H, ddd, *J* 11.6, 2.8, 1.4 Hz, H-1,4), 4.00 (2H, t, 2.8 Hz, H-2,3); δ_C ($CDCl_3$, 100.6 MHz) 26.8 (CH_3), 62.2 (C-1,4), 78.4 (C-2,3), 109.2 (Ketal).

4-*O*-(*tert*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threitol **2.66**[70]



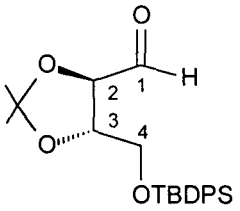
2.66

To a solution of diol **2.65** (6.3 g, 39.0 mmol) at 0°C in dry tetrahydrofuran (300 ml), was added *n*-butyllithium (1.6M in hexane, 24.6 ml, 39.0 mmol, 1 eq) drop-wise via a syringe. The reaction mixture was stirred at 0°C for 40 minutes, *tert*-butyldiphenylsilyl chloride (TBDPSCl) (10.1 ml, 39.0 mmol, 1 eq) was then added drop-wise and the reaction mixture stirred for a further hour at 0°C followed by 18h at room temperature. The reaction mixture was quenched with aqueous sodium hydrogen carbonate (150 ml) and then concentrated under reduced pressure. The solution was extracted with dichloromethane (3 x 150 ml) followed by ethyl acetate (2 x 150 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to yield a residue (16.5 g), which was chromatographed on silica-gel (140 g) with ethyl acetate / petroleum ether (1 : 9) until all the *tert*-butyldiphenylsilyl alcohol had eluted, followed by ethyl acetate / petroleum ether (3 : 7), as eluent to afford silyl ether **2.66** (12.8 g, 32.0 mmol, 82%).

δ_H ($CDCl_3$, 400 MHz) 1.08 (9H, s, *t*-Bu), 1.40 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.16 (1H, dd, *J* 8.0, 5.0 Hz, OH), 3.67 (1H, m, H-1), 3.76 (1H, dd, *J* 10.5, 6.2 Hz, H-4), 3.82 (1H, m, H-1), 3.84 (1H, dd, *J* 10.5, 4.0 Hz, H-4), 3.99 (1H, m, H-3), 4.09 (1H, m, H-2), 7.35-7.50 (6H, m, Ar),

7.65-7.75 (4H, m, Ar); δ_C ($CDCl_3$, 100 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 27.0 (CH_3), 27.1 (CH_3), 62.6 (C-1), 64.2 (C-4), 77.5 (C-3), 79.6 (C-2), 109.2 (ketal), 127.8, 127.8, 129.8, 129.9, 132.9, 133.0, 135.6, 135.6 (Ar).

4-*O*-(*tert*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-L-threose **2.63**[70]

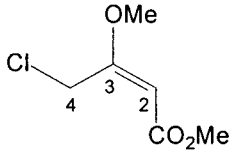


2.63

To a solution of dimethyl sulfoxide (2.7 ml, 38.0 mmol, 3 eq) in dry dichloromethane (50 ml) at -78°C, was added oxalyl chloride (2.2 ml, 25.0 mmol, 2 eq) drop-wise via a syringe. The reaction mixture was stirred for 10 minutes at -78°C. The alcohol **2.66** (5.0 g, 13 mmol) in dry dichloromethane (20 ml) was then added to the mixture drop-wise, followed by triethylamine (8.8 ml, 63.0 mmol, 5 eq) after a further 20 minutes. The mixture was allowed to warm to 0°C, upon which the mixture was quenched with saturated aqueous sodium carbonate (150 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were dried over magnesium sulfate and concentrated to yield a residue (7.2 g), which was chromatographed on silica-gel (120 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 1 : 1) as eluent to yield **2.63** (4.8 g, 12 mmol, 95%).

δ_H (300 MHz, $CDCl_3$) 1.08 (9H, s, *t*-Bu), 1.43 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.86 (2H, m, H-4), 4.20 (1H, m, H-3), 4.44 (H, dt, *J* 7.0, 1.5 Hz, H-2), 7.34-7.48 (6H, m, Ar), 7.68-7.74 (4H, m, Ar), 9.80 (H, t, *J* 1.5 Hz, H-1); δ_C ($CDCl_3$, 75.5 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 27.0 (CH_3), 27.1 (CH_3), 63.5 (C-4), 77.5 (C-3), 81.9 (C-2), 111.5 (ketal), 127.8, 127.8, 129.8, 129.9, 132.9, 133.0, 135.6, 135.6 (Ar), 200.7 (C-1).

Methyl 4-chloro-3-methoxy-(*E*)-2-butenoate **2.29**[93]

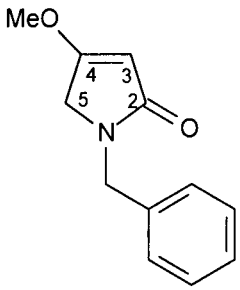


2.29

To a solution of absolute methanol (24.0 ml, 0.60 mol, 3 eq), at -10 to -5°C, was added thionyl chloride (16.0 ml, 0.22 mol, 1.1 eq) drop-wise over 30 minutes via a pressure-compensating dropping funnel. This was followed by the slow addition of ethyl 4-chloroacetoacetate (27.0 ml, 0.20 mol) via the dropping funnel. The reaction mixture was stirred for 18h at room temperature and concentrated. *p*-Toluene sulfonic acid (200 mg) was added and the reaction mixture was heated at reflux for 3h and the methanol removed via distillation. The product was isolated from the crude mixture via vacuum distillation (b.p. 70-80°C, 5 mm Hg, lit[91] 95-97°C, 18 mm Hg) to give methyl 4-chloro-3-methoxy-(*E*)-2-butenoate **2.29** (28.2 g, 17.0 mmol, 85%).

δ_H ($CDCl_3$, 300 MHz) 3.67 (6H, s, OCH_3), 4.61 (2H, s, H-4), 5.10 (1H, s, H-2); δ_c ($CDCl_3$, 75.5 MHz) 39.3 (C-4), 51.2 (OCH_3), 56.0 (OCH_3), 93.2 (C-2), 166.7 (C-3), 168.7 (CO).

1-Benzyl-4-methoxy-3-pyrrolin-2-one **2.28**[89,90]



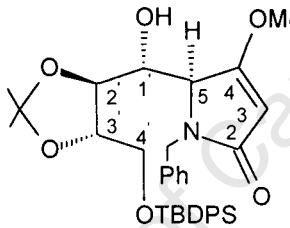
2.28

To a solution of benzylamine (8.0 ml, 72.0 mmol, 1.2 eq) in dry acetonitrile (100 ml) at 0°C, was added Hünig's base (9.6 ml, 90.0 mmol, 1.5 eq) drop-wise via a syringe followed by methyl 4-chloro-3-methoxy-(*E*)-2-butenoate **2.29** (8.2 ml, 60.0 mmol). The reaction mixture was heated with stirring at 60°C for 18 hrs. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (150 ml) and extracted with ethyl acetate (3 x 250 ml).

The combined organic extracts were dried over magnesium sulfate and concentrated to yield a residue (16 g), which was chromatographed on silica-gel (200 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 7 : 3) as eluent to yield the pyrrolinone **2.28** (10.0 g, 49 mmol, 82%).

M.p. 43-45°C (From ethyl acetate-hexane); δ_H ($CDCl_3$, 300 MHz) 3.68 (2H, s, H-5), 3.74 (3H, s, OCH_3), 4.55 (2H, s, Bn), 5.05 (1H, s, H-3), 7.10-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 45.3 (CH_2Ph), 49.9 (C-5), 58.0 (OCH_3), 94.1 (C-3), 127.4, 127.9, 128.7, 137.3 (Ar), 172.1 (C-4), 173.4 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*, 1-Benzyl-5-[4-*tert*-butyldiphenylsilyloxy-1-hydroxy-2,3-*O*-isopropylidene]-butyl-4-methoxy-3-pyrrolin-2-one **2.67**

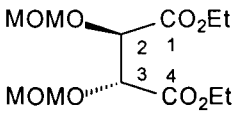


2.67

To a solution of pyrrolinone **2.28** (300 mg, 1.5 mmol, 1.5 eq) in dry tetrahydrofuran (5 ml) at -78°C, was added *n*-butyllithium (1.55 M in hexane, 1.45 ml, 2.2 mmol) drop-wise via a syringe. The reaction mixture was stirred for 30 minutes at -78°C. Trimethylsilyl chloride (0.57 ml, 4.5 mmol) was then added drop-wise and the reaction mixture was stirred for a further 30 minutes at -78°C. Aldehyde **2.63** (400 mg, 1.0 mmol) in dry tetrahydrofuran (4 ml) was added drop-wise, followed by tin (IV) chloride (1M in dichloromethane, 2 ml, 2.0 mmol, 2 eq) drop-wise. The reaction mixture was stirred vigorously and allowed to warm slowly up to -20°C over 3 hours. The reaction mixture was stirred for 18 hrs at -20°C. The reaction mixture was quenched with cold saturated aqueous sodium bicarbonate (30 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (50 ml) and dried over magnesium sulfate. The organic layer was concentrated under reduced pressure to yield a residue (900 mg), which was chromatographed on silica-gel (65 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 1 : 1) as eluent to give a mixture of diastereomers **2.67** in a ratio 2:1 (300 mg, 0.50 mmol, 50%) and unreacted aldehyde **2.63** (125 mg, 0.31 mmol, 32%).

Major-δ_H ($CDCl_3$, 400 MHz) 1.07 (9H, s, *t*-Bu), 1.26 (3H, s, CH_3), 1.32 (3H, s, CH_3), 3.27 (1H, d, *J* 2.4 Hz, OH), 3.71 (3H, s, OCH_3), 3.73 (1H, dd, *J* 10.4, 5.6 Hz H-4'), 3.83 (1H, dd *J* 10.4, 4.2 Hz, H-4'), 3.97 (1H, m, H-1'), 4.03 (1H, m, H-3'), 4.23 (3H, m, H-2', H-5 and Bn), 5.10 (1H, s, H-3), 5.13 (1H, d, *J* 16.8 Hz, Bn), 7.20-7.35 (5H, m, Ar), 7.38-7.45 (6H, m, Ar), 7.65-7.75 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.7 ($(CH_3)_3$), 27.0 (CH_3), 27.0 (CH_3), 44.0 (C-Bn), 58.1 (OCH_3), 62.0 (C-5), 64.6 (C-4'), 71.6 (C-1'), 76.9 (C-3'), 81.7 (C-2'), 95.2 (C-3), 109.6 (ketal), 127.5, 127.7, 127.7, 128.2, 128.2, 128.7, 129.9, 132.7, 132.7, 135.6, 135.6, 137.7 (Ar) 173.0 (C-4), 174.4 (C-2).

Diethyl-2,3-di-*O*-methoxymethyltartrate **2.71**[88]

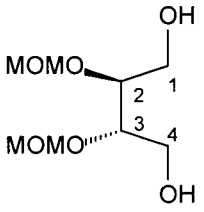


2.71

Dimethoxymethane (70 ml, 0.79 mol, 8 eq) was added to a solution of L-diethyl tartrate **2.20** (20.0 g, 97.0 mmol) in dry dichloromethane (250 ml). The reaction mixture was cooled to 0°C and phosphorus pentoxide (35g, 234.3 mmol) was added portion-wise at ten minute intervals until the reaction had gone to completion (tlc). The reaction mixture was poured into cold saturated aqueous sodium carbonate (250 ml) and the solid residue in the flask was washed with dichloromethane (4 x 50 ml), which was combined with the original organic layer. The compound was extracted into dichloromethane (3 x 250 ml), which was washed with brine (250 ml), dried over magnesium sulfate and concentrated to yield an oil **2.71** (26.0 g, 87 mmol, 91%), which was pure enough by ^{1}H NMR to proceed to the next step.

δ_H ($CDCl_3$, 300 MHz) 1.29 (6H, t, *J* 7.2 Hz, CH_3), 3.33 (6H, s, OCH_3), 4.22 (4H, m, CH_2), 4.65 (2H, d, J_{AB} 7.2 Hz, OCH_2O), 4.66 (2H, s, H-2,3), 4.76 (2H, d, J_{AB} 7.2 Hz, OCH_2O); δ_C ($CDCl_3$, 75.5 MHz) 14.1 (CH_3), 56.2 (OCH_3), 61.4 (CH_2), 75.7 (C-2,3), 96.5 (OCH_2O), 168.9 (CO).

2,3-Di-*O*-methoxymethyl-L-threitol **2.72**[88]

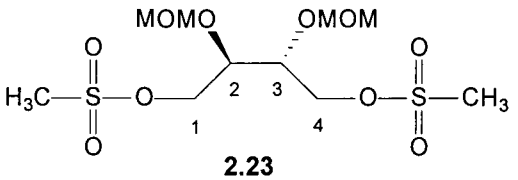


2.72

To a solution of lithium aluminum hydride (6.7 g, 176.0 mmol, 2 mol eq) in dry tetrahydrofuran (200 ml) at -20°C, was added MOM ether **2.71** (26.0 g, 88 mmol) in dry tetrahydrofuran (150 ml) drop-wise over 30 minutes via a pressure-compensating dropping funnel. The reaction mixture was stirred for 4 hours from –20°C to room temperature. The reaction mixture was quenched with saturated sodium sulfate (10 ml) at 0°C and left stirring until a white solid precipitated out of the solution. The reaction mixture was filtered through Celite® and rinsed with methanol / dichloromethane (1 : 4, 4 x 200 ml). The filtrate was concentrated under reduced pressure to give a residue (22.0 g), which was purified on silica-gel (200 g) with ethyl acetate / petroleum ether mixtures (1 : 1 to 1 : 0) as eluent to give diol **2.72** (14.5 g, 69.0 mmol, 78%) as a solid which was recrystallised from ethyl acetate.

M.p. 59-61°C (lit[86] 60-62°C); δ_H ($CDCl_3$, 400 MHz) 2.88 (2H, s(br), OH), 3.40 (6H, s, OCH_3), 3.70-3.78 (6H, m, H-1,4, H-2,3), 4.69 (2H, d, J_{AB} 6.8 Hz, OCH_2O), 4.74 (2H, d, J_{AB} 6.8 Hz, OCH_2O); δ_C ($CDCl_3$, 100.6 MHz) 55.8 (OCH_3), 61.7 (C-1,4), 80.1 (C-2,3), 97.3 (OCH_2O).

1,4-Di-*O*-methanesulfonyl-2,3-di-*O*-methoxymethyl-L-threitol **2.23**[88]



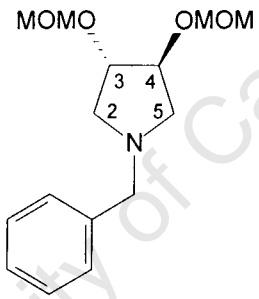
2.23

To a solution of mesyl chloride (7.4 ml, 95.0 mmol, 4 eq) in dry dichloromethane (100 ml) at 0°C, were added diol **2.72** (5.0 g, 24.0 mmol) and triethylamine (13.3 ml, 95.0 mmol, 4 eq) in dry dichloromethane (50 ml) slowly via a pressure-compensating dropping funnel. The reaction mixture was stirred for an hour at 0°C. The reaction mixture was poured into an ice / water mixture and the product extracted with dichloromethane (3 x 200 ml). The combined

organic layers were washed with brine (2 x 150 ml) followed by water (100 ml). The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure to give a residue (8.5 g), which was chromatographed using silica-gel (100 g) using ethyl acetate / petroleum ether mixtures (1 : 1 to 3 : 2) as eluent to give dimesylate **2.23** (7.5 g, 20.0 mmol, 88%).

δ_H ($CDCl_3$, 300 MHz) 3.04 (6H, s, SO_2CH_3), 3.40 (6H, s, OCH_3), 4.10 (2H, m, H-2,3), 4.32 (2H dd, *J* 10.8, 5.2 Hz, H-1,4), 4.44 (2H, dd, *J* 10.8, 4.0 Hz, H-1,4), 4.71 (2H, d, J_{AB} 6.8 Hz, OCH_2O), 4.74 (2H, d, J_{AB} 6.8 Hz, OCH_2O); δ_C ($CDCl_3$, 100.6 MHz) 37.5 (SO_2CH_3), 56.1 (OCH_3), 67.8 (C-1,4), 74.9 (C-2,3), 97.4 (OCH_2O).

(3*S*, 4*S*)-1-Benzyl-3,4-bis-methoxymethoxy-pyrrolidine **2.24**[88]



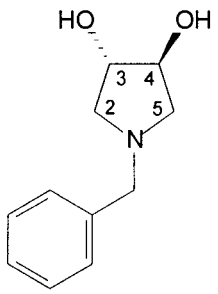
2.24

A solution of dimesylate **2.23** (6.5 g, 18.0 mmol) in benzylamine (50 ml) was heated with stirring at 60°C for 24h. The excess benzylamine was recovered by vacuum distillation. The product was dissolved in ethyl acetate (250 ml) and washed with brine (3 x 100 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue (9.5 g), which was chromatographed on silica-gel (150 g) using ethyl acetate / petroleum ether mixtures (1 : 9 to 2 : 3) as eluent to give pyrrolidine **2.24** (4.4 g, 16.0 mmol, 87%).

δ_H ($CDCl_3$, 400 MHz) 2.54 (2H, dd, *J* 9.9, 4.6 Hz, H-2,5), 2.92 (2H, dd, *J* 9.9, 6.0 Hz, H-2,5), 3.34 (6H, s, OCH_3), 3.58 (1H, d, J_{AB} 12.8 Hz, Bn), 3.65 (1H, d, J_{AB} 12.8 Hz, Bn), 4.15 (2H, m, H-3,4), 4.62 (2H, d, J_{AB} 6.8 Hz, OCH_2O), 4.69 (2H, d, J_{AB} 6.8 Hz, OCH_2O), 7.20-7.40 (5H, m,

Ar); δ_C ($CDCl_3$, 100.6 MHz) 55.3 (OCH_3), 58.6 (C-2,5), 60.2 (CH_2Ph), 81.5 (C-3,4), 95.6 (OCH_2O), 126.9, 128.1, 128.7, 138.3 (Ar).

(3*S*, 4*S*)-1-Benzyl-3,4-dihydroxypyrrolidine **2.25**[139]

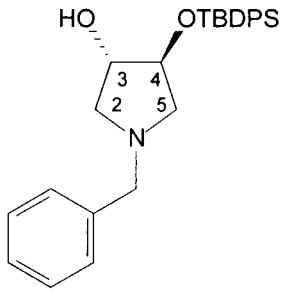


2.25

A solution of pyrrolidine **2.24** (4.4 g, 16.0 mmol) in tetrahydrofuran / hydrochloric acid (2 M), (1 : 1, 20 ml) was heated with stirring at 60°C for 18h. The reaction mixture was quenched with solid sodium carbonate until pH 10 was obtained. The reaction mixture was concentrated under reduced pressure. Toluene was added to the residue and the mixture was concentrated again under reduced pressure. This process was repeated a further two times. Dichloromethane (100 ml) was added and the solution was filtered through Celite® and the residue rinsed with dichloromethane / acetonitrile (1 : 1, 3 x 100 ml). The filtrate was concentrated under reduced pressure and re-dissolved in dichloromethane (100 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give diol **2.25** (3.0 g, 15.5 mmol, 97%).

δ_H ($CDCl_3$, 400 MHz) 2.41 (2H, dd, *J* 10.3, 4.0 Hz, H-2,5), 2.87 (2H, dd, *J* 10.3, 5.8 Hz, H-2,5), 3.51 (1H, d, J_{AB} 12.4 Hz, Bn), 3.59 (1H, d, J_{AB} 12.4 Hz, Bn), 4.03 (2H, t, *J* 4.6 Hz, H-3,4), 4.60 (2H, s(br), OH), 7.20-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 60.0 (C-2,5), 60.3 (C-Bn), 78.0 (C-3,4),127.3, 128.3, 129.2, 137.2 (Ar).

(3*S*, 4*S*)-1-Benzyl-4-*tert*-butyldiphenylsilyloxy-3-hydroxypyrrolidine **2.26**

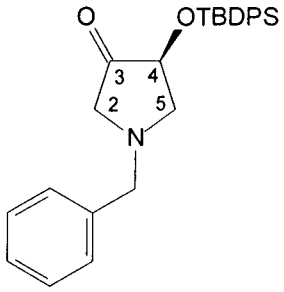


2.26

To a solution of diol **2.25** (1.00 g, 5.0 mmol) in dry acetonitrile (30 ml) at 0°C, were added imidazole (0.42 g, 6.2 mmol, 1.2 eq) and *tert*-butyldiphenylsilyl chloride (1.4 ml, 5.5 mmol, 1.1 eq). The reaction mixture was stirred at room temperature for 18h. The reaction mixture was quenched with water (50 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine (100 ml) and dried over magnesium sulfate. The organic layer was concentrated under reduced pressure to give a residue (2.5 g). The residue was chromatographed on silica-gel (100 g) using ethyl acetate / petroleum ether mixtures (1 : 9 to 2 : 3) as eluent to give silyl ether **2.26** (0.60 g, 1.4 mmol, 30%).

$[\alpha]_D$ + 13.1 (*c* 0.75, CH_2Cl_2); $[M+H]^+$ (Found 432.2332, $C_{27}H_{34}NO_2Si$ requires 432.2359.); υ_{max} /cm^{-1} 3414 (O-H), 3070, 3052, 3031 (C-H arom), 2998, 2932, 2896 (C-H aliph); δ_H ($CDCl_3$, 300 MHz) 1.07 (9H, s, *t*-Bu), 2.40 (1H, s(br), OH), 2.40 (1H, dd, *J* 10.1, 4.2 Hz, H-2), 2.65 (1H, dd, *J* 10.0, 2.3 Hz, H-5), 2.76 (1H, dd, *J* 10.0, 5.4 Hz, H-5), 3.04 (1H, dd, *J* 10.1, 6.5 Hz, H-2), 3.60 (1H, d, J_{AB} 13.0 Hz, Bn), 3.68 (1H, d, J_{AB} 13.0 Hz, Bn), 4.09 (1H, m, H-4), 4.20 (1H, m, H-3), 7.20-7.30 (5H, m, Ar), 7.40-7.50 (6H, m, Ar), 7.60-7.80 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.1 (Si-C), 26.9 ($(CH_3)_3$), 59.8 (C-5), 60.1 (C-Bn), 61.1 (C-2), 78.7 (C-4), 80.1 (C-3), 127.0, 127.7, 127.8, 128.2, 128.7, 129.7, 129.8, 133.8, 133.9, 135.6, 135.7, 138.3 (Ar).

(4*S*)-1-Benzyl-4-*tert*-butyldiphenylsilyloxy-pyrrolidin-3-one **2.27**

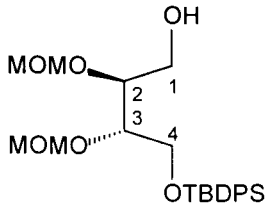


2.27

To a solution of dimethyl sulfoxide (0.1 ml, 1.4 mmol, 2.4 eq) in dry dichloromethane (10 ml) at -78°C, was added oxalyl chloride (0.07 ml, 0.83 mmol, 1.4 eq) drop-wise via a syringe. The reaction mixture was stirred for 10 minutes at -78°C. The alcohol **2.26** (0.25 g, 0.58 mmol) in dry dichloromethane (3 ml) was then added to the mixture drop-wise, followed by triethylamine (0.44 ml, 3.2 mmol, 5.5 eq) after a further 20 minutes. The reaction mixture was allowed to warm to 0°C upon which the reaction was quenched with saturated aqueous sodium carbonate (20 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (381 mg), which was chromatographed on silica-gel (30g) with ethyl acetate / petroleum ether (1 : 39), followed by ethyl acetate / petroleum ether (1 : 19) and finally ethyl acetate / petroleum ether (1 : 9) as eluent to yield ketone **2.27** (0.17 g, 0.4 mmol, 70%).

$[\alpha]_D$ + 3.5 (*c* 0.75, CH_2Cl_2); $[M+H]^+$ (Found 430.2189, $C_{27}H_{32}NO_2Si$ requires 430.2202.); υ_{max} /cm^{-1} 3071, (C-H arom), 2960.02, 2931.05, 2891.97, 2857, 2796, (C-H aliph), 1771 (CO), 1112 (C-O); δ_H ($CDCl_3$, 400 MHz) 1.16 (9H, s, *t*-Bu), 2.56 (1H, t, *J* 6.5 Hz, H-5), 2.74 (1H, d, *J* 13.2 Hz, H-2), 3.26 (1H, t, *J* 6.5 Hz, H-5), 3.32 (1H, d, *J* 13.2 Hz, H-2), 3.54 (1H, d, *J* 9.6 Hz, Bn), 3.76 (1H, d, *J* 9.6 Hz, Bn), 4.36 (1H, t, *J* 6.5 Hz, H-4), 7.20-7.35 (5H, m, Ar), 7.40-7.60 (6H, m, Ar) 7.70-7.87 (4H, m, Ar); δ_c ($CDCl_3$, 75.5 MHz) 19.2 (Si-C), 26.7 ($(CH_3)_3$), 58.2 (C-5), 59.5 (C-2), 60.3 (CH_2Ph), 74.6 (C-4), 127.4, 127.6, 127.6, 127.7, 128.3, 128.6, 129.8, 132.6, 133.5, 135.6, 135.9, 136.9 (Ar), 211.4 (C-3).

4-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-di-methoxymethyl-L-threitol **2.73**

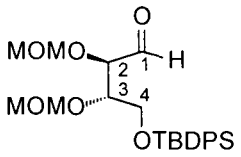


2.73

To a solution of diol **2.72** (6.0 g, 28.5 mmol) at 0°C in dry tetrahydrofuran (300 ml), was added *n*-butyllithium (1.6M in hexane, 17.9 ml, 28.5 mmol, 1 eq) drop-wise via a syringe. The reaction mixture was stirred at 0°C for 40 minutes. *tert*-Butyldiphenylsilyl chloride (7.5 ml, 28.5 mmol, 1 eq) was then added drop-wise and the reaction mixture was stirred for a further hour at 0°C followed by 18h at room temperature. The reaction mixture was quenched with aqueous sodium hydrogen carbonate (200 ml) and was concentrated under reduced pressure. The solution was extracted with dichloromethane (3 x 200 ml) and with ethyl acetate (2 x 200 ml). The combined organic layers were dried over magnesium sulfate and concentrated to yield a residue (16.5 g), which was chromatographed on silica-gel (140 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 3 : 2), as eluent to yield silyl ether **2.73** (12.0 g, 26.9 mmol, 94%).

$[\alpha]_D$ +1.5 (*c* 1.5, CH_2Cl_2); ($[M+H]^+$ Found 448.2300, $C_{24}H_{36}O_6Si$ requires 448.2281.); υ_{max} /cm^{-1} 3466 (O-H), 3071, 3054 (C-H arom), 2985, 2954, 2933, 2892, 2859, 2826, (C-H aliph),1149, 1112 (C-O ether); δ_H ($CDCl_3$, 400 MHz) 1.06 (9H, s, *t*-Bu), 3.10 (1H, t, *J* 6.8 Hz, OH), 3.34 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.70-3.90 (6H, m, H-1,4 and H-2,3), 4.61 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.64 (1H, d, J_{AB} 7.0 Hz, OCH_2O), 4.68 (1H, d, J_{AB} 7.0 Hz, OCH_2O), 4.68 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 7.40 (6H, m, Ar), 7.66 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.1 (Si-C), 26.8 ($(CH_3)_3$), 55.8 (OCH_3), 55.9 (OCH_3), 62.7 (C-1, C-4), 63.0 (C-1, C-4), 78.1 (C-2, C-3), 80.5 (C-2, C-3), 97.2 (OCH_2O), 97.7 (OCH_2O), 127.7, 127.7, 129.8, 129.8, 133.1, 133.2, 135.5, 135.5 (Ar);

4-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-di-methoxymethyl-L-threose **2.74**

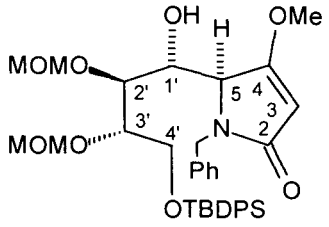


2.74

To a solution of dimethyl sulfoxide (1.6 ml, 22 mmol, 3 eq) in dry dichloromethane (30 ml) at -78°C, was added oxalyl chloride (1.3 ml, 14.8 mmol, 2 eq) drop-wise via a syringe. The reaction mixture was stirred for 10 minutes at -78°C. The alcohol **2.73** (3.3 g, 7.4 mmol) in dry dichloromethane (10 ml) was then added to the mixture drop-wise, followed by triethylamine (5.2 ml, 37 mmol, 5 eq) after a further 20 minutes. The reaction mixture was allowed to warm to 0°C, upon which the reaction was quenched with sodium carbonate (100 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (4 g), which was chromatographed on silica-gel (80 g) with ethyl acetate / petroleum ether mixtures (1 : 9 to 1 : 1) as eluent to yield aldehyde **2.74** (3.0 g, 6.7 mmol, 90%).

$[\alpha]_D$ +9.5 (*c* 0.75, CH_2Cl_2); ($[M+H]^+$ Found 447.2224, $C_{24}H_{35}O_6Si$ requires 447.2203.); υ_{max} /cm^{-1} 3070, 3054 (C-H arom), 2986, 2957, 2933, 2894, 2859, 2827 (C-H aliph), 2742 (C-H aldehyde), 1733 (C=O aldehyde), 1152, 1112 (C-O ether); δ_H ($CDCl_3$, 300 MHz) 1.05 (9H, s, *t*-Bu), 3.23 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.81 (2H, d, *J* 6.5 Hz, H-4), 4.07 (1H, td, *J* 6.5, 3.2 Hz, H-3), 4.27 (1H, dd, *J* 3.2, 0.8 Hz, H-2), 4.52 (1H, d, *J* 6.8 Hz, OCH_2O), 4.58 (1H, d, *J* 6.8 Hz, OCH_2O), 4.73 (1H, d, *J* 6.9 Hz, OCH_2O), 4.78 (1H, d, *J* 6.9 Hz, OCH_2O) 7.30-7.50 (6H, m, Ar), 7.60-7.70 (4H, m, Ar), 9.80 (1H, d, *J* 0.8 Hz, H-1); δ_C ($CDCl_3$, 100.6 MHz) 19.1 (Si-C), 26.8 ($(CH_3)_3$), 55.8 (OCH_3), 56.2 (OCH_3), 61.8 (C-4), 77.4 (C-3), 81.4 (C-2), 96.7 (OCH_2O), 97.5 (OCH_2O) 127.8, 127.8, 129.9, 129.9, 132.9, 133.0, 135.6, 135.6 (Ar), 202.1 (C-1).

1'*R*, 2'*S*, 3'*S*, 5*S*, 1-Benzyl-5-[4'-*tert*-butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-methoxy-3-pyrrolin-2-one **2.75**



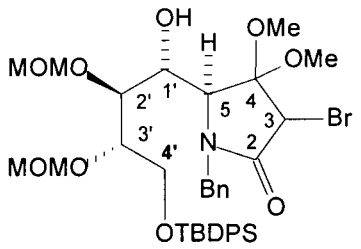
2.75

To a solution of pyrrolinone **2.28** (0.32 g, 1.55 mmol) in dry tetrahydrofuran (5 ml) at -78°C, was added *n*-butyllithium (1.6 M in hexane, 1.45 ml, 2.3 mmol) drop-wise via a syringe. The reaction mixture was stirred for 30 minutes at -78°C. Trimethylsilyl chloride (0.59 ml, 4.7 mmol) was then added drop-wise and the reaction mixture was stirred for a further 30 minutes at -78°C. Aldehyde **2.74** (0.50 g, 1.1 mmol) in dry tetrahydrofuran (4 ml) was added, followed by tin (IV) chloride (1M in dichloromethane, 2 ml, 2.0 mmol) drop-wise. The reaction mixture was stirred vigorously, warmed up to -20°C over 3 hours, and stirred for 18 hrs at -20°C. The reaction mixture was quenched with cold saturated sodium bicarbonate (30 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine (50 ml) and dried over magnesium sulfate, before being concentrated under reduced pressure to yield a residue (0.90 g), which was chromatographed on silica-gel (65 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 6 : 4) as eluent to give diastereomer **2.75** (0.41 g, 0.63 mmol, 57%), a mixture of diastereomers **2.76** (0.23 g, 0.36 mmol, 33%), and unreacted aldehyde **2.74** (0.025 g, 0.06 mmol, 5%).

M.p. 114-115°C (from ethyl acetate-hexane); $[\alpha]_D$ +6.35 (*c* 2.0, CH_2Cl_2); (Found: C, 66.65; H, 7.29; N, 2.15%. $C_{36}H_{47}NO_8Si$ requires C, 66.54; H, 7.29; N, 2.16%); ($[M+H]^+$ Found 650.3120, $C_{36}H_{48}NO_8Si$ requires 650.3149.); $\upsilon_{max}(CH_2Cl_2)$ / cm^{-1} 3400 (OH), 1683 (C=O), 1635 (C=C); δ_H ($CDCl_3$, 400 MHz) 1.06 (9H, s, *t*-Bu), 3.04 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.61 (1H, s, OH), 3.69 (3H, s, OCH_3), 3.74-3.86 (3H, m, H-3', H-4'), 4.01 (1H, dd, *J* 7.3, 1.5 Hz, H-2'), 4.09 (1H, d, *J* 1.5 Hz, H-5), 4.13 (1H, d, *J* 17.2 Hz, Bn), 4.14 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.19 (1H, dd, *J* 7.3, 1.5 Hz, H-1'), 4.25 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.68 (2H, s, OCH_2O), 5.17 (1H, d, *J* 17.2 Hz, Bn), 5.20 (1H, s, H-3), 7.20-7.70 (15H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C),

26.8 ($(CH_3)_3$), 43.3 (C-Bn), 55.5 (OCH_3), 56.3 (OCH_3), 58.1 (OCH_3), 60.8 (C-5), 62.3 (C-4'), 68.2 (C-1'), 77.9 (C-3'), 80.5 (C-2'), 95.7 (C-3), 96.8 (OCH_2O), 99.2 (OCH_2O), 127.2, 127.7, 127.8, 127.9, 128.6, 129.8, 129.9, 133.1, 133.1, 135.4, 135.5, 137.9 (Ar), 171.9 (C-4), 173.4 (C-2);

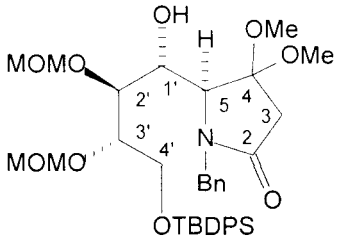
1'*R*, 2'*S*, 3'*S*, 5*S*, 1-Benzyl-3-bromo-5-[4'-*tert*-butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.152.**



2.152

To a solution of **2.75** (2.30 g, 3.5 mmol) in methanol (60 ml) at -20°C, bromine (1 M in dichloromethane, 6 ml, 6 mmol ,1.7 eq) was added. The reaction mixture was stirred for 30 minutes at -20°C. The reaction mixture was quenched with saturated sodium carbonate (100 ml) at -20°C and concentrated under reduced pressure. The product was extracted with ethyl acetate (3 x 200 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a residue, which was chromatographed on silica-gel (100 g) with ethyl acetate as an eluant to give **2.152** as an oil (2.6 g, 3.4 mmol, 98 %). The compound wasn't characterized but taken through the next step.

1'*R*, 2'*S*, 3'*S*, 5*S*, 1-Benzyl-5-[4'-*tert*-butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.135**



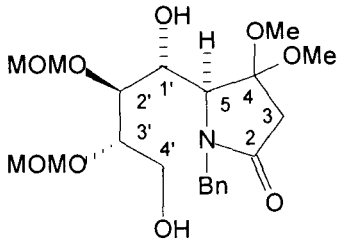
2.135

To a solution of bromide **2.152** (2.6 g, 3.4 mmol) in tetrahydrofuran / aqueous ammonium chloride / methanol (2 : 2 : 1), (75 ml), was added zinc powder (1.1 g, 17.1 mmol, 5 eq). The reaction mixture was stirred at room temperature for 30 minutes, before being filtered through Celite® and thoroughly rinsed with ethyl acetate (200 ml). Saturated sodium bicarbonate (100 ml) was added to the filtrate, which was concentrated under reduced pressure and then extracted with ethyl acetate (3 x 200 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield an oil (2.1 g). The crude product was purified on silica-gel (60 g) using ethyl acetate / petroleum ether (8 : 2) as eluent to give **2.135** (1.9 g, 2.8 mmol, 81%).

M.p. 131-132°C (from ethyl acetate-hexane); $[\alpha]_D$ +7.5 (c 2.0, CH_2Cl_2); (Found: C, 65.26; H, 7.75; N, 2.09%, $C_{37}H_{51}NO_9Si$ requires C, 65.17; H, 7.54; N, 2.05%); ($[M+H]^+$ Found 682.3434, $C_{37}H_{52}NO_9Si$ requires 682.3411.); υ_{max} /cm^{-1} 3418 (O-H), 3069, 3051, 3029 (C-H arom), 2934, 2893, 2857 (C-H aliph), 1696 (C=O amide), 1150, 1132, 1112 (C-O ether); δ_H ($CDCl_3$, 300 MHz) 1.05 (9H, s, *t*-Bu), 2.48 (1H, d, *J* 15.6 Hz, H-3), 2.97 (3H, s, OCH_3), 2.99 (1H, d, *J* 15.6 Hz, H-3), 3.04 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 3.62 (1H, d, *J* 2.4 Hz, OH), 3.66 (1H, d, *J* 1.6 Hz, H-5) 3.70-3.86 (3H, m, H-3', H-4'), 3.93 (1H, d, *J* 15.8 Hz, Bn), 4.03 (1H, m, H-1'), 4.13 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.23 (1H, dd, *J* 7.4 and 1.4 Hz, H-2'), 4.29 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.71 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.75 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 5.30 (1H, d, *J* 15.8 Hz, Bn), 7.20-7.30 (5H, m, Ar), 7.30-7.50 (6H, m, Ar), 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 42.1 (C-3), 43.4 (C-Bn), 48.2 (OCH_3), 50.9 (OCH_3), 55.3 (OCH_3), 56.4 (OCH_3), 60.0 (C-5), 62.3 (C-4'), 69.4 (C-1'), 78.0 (C-

78.0 (C-3'), 82.1 (C-2'), 96.8 (OCH_2O), 99.3 (OCH_2O), 105.0 (C-4), 127.3, 127.5, 127.7, 127.7, 128.5, 129.8, 129.9, 133.2, 133.2, 135.4, 135.4, 136.7 (Ar), 172.5 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*-1-Benzyl-5-[1',4'-dihydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.136**

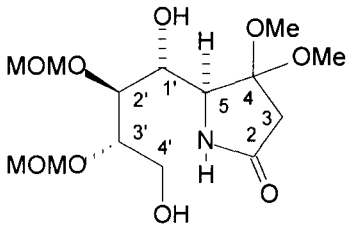


2.136

To a solution of **2.135** (1.2 g, 1.77 mmol) in tetrahydrofuran (80 ml) at -20°C, was added tetrabutylammonium fluoride (3 ml, 1M in tetrahydrofuran, 3 mmol, 1.7 eq). The reaction mixture was stirred for 3 hrs at 0°C and then concentrated under reduced pressure to give a residue (1.4 g), which was purified directly on silica-gel (60g) using ethyl acetate followed by methanol / ethyl acetate (1 : 9) as eluent to give diol **2.136** (0.65 g, 1.46 mmol, 83%).

M.p. 92-94°C (from ethyl acetate-hexane); (Found: C, 57.17; H, 7.51; N, 3.16%. $C_{21}H_{33}NO_9$ requires C, 56.87; H, 7.50; N, 3.16%); Found $[M+H]^+$ 444.2233 $C_{21}H_{34}NO_9$ requires 444.2233; $[\alpha]_D$ –15.2 (c 1.0, CH_2Cl_2); υ_{max} /cm^{-1} 3423 (O-H), 3087, 3057, 3031 (C-H arom), 2943, 2897, 2834 (C-H aliph), 1677 (C=O), 1148, 1134, 1104 (C-O ether); δ_H ($CDCl_3$, 400 MHz) 2.43 (1H, d, J_{AB} 15.4 Hz, H-3), 2.92 (1H, d, J_{AB} 15.4 Hz, H-3), 2.97 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.45 (2H, s(br), OH), 3.55-3.72 (4H, m, H-3', H-4', H-5), 3.83 (1H, d, *J* 15.6 Hz, Bn), 4.01 (2H, m, H-1', H-2'), 4.18 (1H, d, J_{AB} 7.2 Hz, OCH_2O), 4.24 (1H, d, J_{AB} 7.2 Hz, OCH_2O), 4.66 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.78 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 5.24 (1H, d, *J* 15.6 Hz, Bn), 7.20-7.30 (5H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 41.9 (C-3), 43.4 (C-Bn), 48.2 (OCH_3), 50.8 (OCH_3), 55.5 (OCH_3), 56.2 (OCH_3), 59.9 (C-5), 62.2 (C-4'), 69.4 (C-1'), 81.0 (C-3'), 81.1 (C-2'), 96.8 (OCH_2O), 98.8 (OCH_2O), 104.7 (C-4), 127.4, 127.6, 128.5, 136.2 (Ar), 172.4 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[1'4'-dihydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.129**

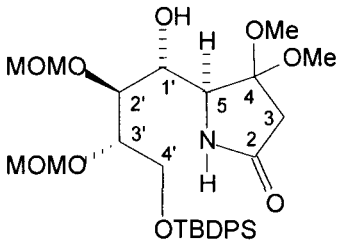


2.129

A solution of **2.136** (0.21 g, 0.47 mmol) and *tert*-butanol (1ml) in dry tetrahydrofuran (3 ml) was added to pre-dried liquid ammonia (12 ml) at -78°C. Sodium (0.20 g, 8.6 mmol) was added in several pieces with vigorous stirring. The reaction mixture was stirred for two hours at -70°C, upon which a solution of methanol / acetic acid (5 : 1, 24 ml) was added. The mixture was allowed to warm to room temperature with stirring. The mixture was concentrated under reduced pressure to give a solid, which was purified on silica-gel (30g) using petroleum ether, followed by ethyl acetate / petroleum ether (1 : 1), followed by ethyl acetate and finally methanol / ethyl acetate (1 : 9) to give **2.129** (0.16 g, 0.44 mmol, 95%).

$[\alpha]_D$ -87.5 (*c* 1.0, CH_2Cl_2); ($[M+H]^+$ Found 354.1783, $C_{14}H_{27}NO_9$ requires 354.1764.); υ_{max} /cm^{-1} 3385 (O-H and N-H), 3054, 2946, 2898, 2837 (C-H aliph), 1697 (C=O), 1134 (C-O); δ_H ($CDCl_3$, 400 MHz) 2.39 (1H, d, J_{AB} 16.2 Hz, H-3), 2.63 (1H, d, J_{AB} 16.2 Hz, H-3), 3.24 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.60 (2H, s(br), OH), 3.66 (1H, dd, *J* 12.6 and 4.2 Hz, H-4'), 3.72-3.84 (4H, m, H-1', H-3', H-4', H-5), 3.88 (1H, m, H-2'), 4.62 (1H, d, *J* 6.4 Hz, OCH_2O), 4.66 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.70 (1H, d, J_{AB} 6.6 Hz, OCH_2O) 4.85 (1H, d, *J* 6.4 Hz, OCH_2O), 6.77 (1H, s, NH); δ_C ($CDCl_3$, 100.6 MHz) 40.1 (C-3), 48.7 (OCH_3), 51.1 (OCH_3), 55.6 (OCH_3), 55.8 (OCH_3), 57.9 (C-5), 61.6 (C-4'), 69.8 (C-1'), 78.0 (C-3'), 80.9 (C-2'), 97.1 (OCH_2O), 98.5 (OCH_2O), 107.0 (C-4), 172.6 (C-2);

1'*R*, 2'*S*, 3'*S*, 5*S*-5-[4'-*tert*-Butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.122a**

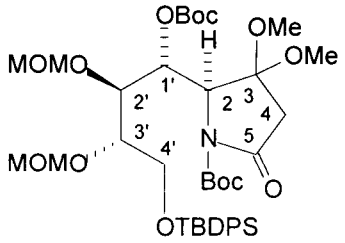


2.122a

To a solution of diol **2.129** (1.00 g, 2.8 mmol) in acetonitrile (25 ml) at 0°C, were added imidazole (375 mg, 5.5 mmol, 2 eq), *tert*-butyldiphenylsilyl chloride (1.4 ml, 5.5 mmol, 2 eq) and triethylamine (2.1 ml). The reaction mixture was left to stir at room temperature and monitored by TLC. Every two hours an extra 2 equivalents of imidazole and *tert*-butyldiphenylsilyl chloride were added (x 10) until the reaction had gone to completion. The reaction was quenched with sodium hydrogen carbonate (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give an oil (2 g). The crude product was purified on silca-gel (60 g) using ethyl acetate / hexane (8 : 2) as eluent to give **2.122a** (1.5 g, 2.6 mmol, 93%).

M.p. 92-94°C (from ethyl acetate-hexane); $[\alpha]_D$ –24.7 (c 2.0, CH_2Cl_2); (Found: C, 60.97; H, 7.41; N, 2.56%. $C_{30}H_{45}NO_9Si$ requires C, 60.89; H, 7.66; N, 2.37%); $[M+H]^+$ Found 592.2912, $C_{50}H_{46}NO_9$ requires 592.2942; υ_{max} /cm^{-1} 3532 (N-H), 3352 (O-H), 3070, 3053, (C-H arom), 2935, 2893, 2858 (C-H aliph), 1713 (C=O), 1113, 1067 (C-O ether); δ_H ($CDCl_3$, 300 MHz) 1.06 (9H, s, *t*-Bu), 2.44 (1H, d, *J* 16.4 Hz, H-3), 2.55 (1H, d, *J* 16.4 Hz, H-3), 3.27 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.40 (1H, s, OH), 3.43 (3H, s, OCH_3), 3.84-4.03 (6H, m, H-1', H-2', H-3', H-4' and H-5), 4.65 (2H, s, OCH_2O), 4.66 (1H, d, J_{AB} 6.2 Hz, OCH_2O), 4.96 (1H, d, J_{AB} 6.2 Hz, OCH_2O), 6.75 (1H, s(br), NH), 7.30-7.50 (6H, m, Ar), 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.2 (Si-C), 26.7 ($(CH_3)_3$), 40.3 (C-3), 48.8 (OCH_3), 51.2 (OCH_3), 55.7 (OCH_3), 56.0 (OCH_3), 58.0 (C-5), 63.61 (C-4'), 70.1 (C-1'), 78.7 (C-3'), 79.0 (C-2'), 96.7 (OCH_2O), 99.0 (OCH_2O), 107.1 (C-4), 127.7, 127.7, 129.7, 129.7, 133.8, 133.3, 135.5, 135.6 (Ar), 172.10 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butoxycarbonyloxy-4'-*tert*-butyldiphenyl-silyloxy-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-5-oxo-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.138**

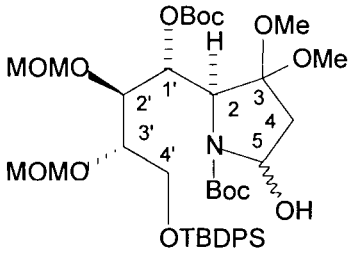


2.138

To a solution of lactam **2.122a** (1.50 g, 2.5 mmol) in dry tetrahydrofuran (305 ml), were added di-*tert*-butyl dicarbonate (2.20 g, 10 mmol, 4 eq) and dimethylaminopyridine (0.17 g, 1.4 mmol, 0.5 eq). The reaction mixture was stirred at room temperature for 16h, after which it was concentrated under reduced pressure to yield an oil. The crude product was purified on silica-gel (100 g) using ethyl acetate / hexane (3 : 7) as eluent to give **2.138** (1.60 g, 2.0 mmol, 80%).

M.p. 158-159°C (from ethyl acetate-petroleum ether); $[\alpha]_D$ + 2.3 (*c* 3, $CHCl_3$), (Found: C, 60.44; H, 7.70; N, 1.36%. $C_{40}H_{61}NO_{13}Si$ requires C, 60.66; H, 7.76; N, 1.77%); ($[M+Na]^+$ Found 814.3819, $C_{40}H_{61}NO_{13}SiNa$ requires 814.3810.); υ_{max} /cm^{-1} 3072 (C-H arom), 2979 2958, 2935, 2892, 2857 (C-H aliph), 1752 (O-C=O), 1716 (N-Boc-C=O), 1635 (C=O amide), 1133, 1106 (C-O ether); δ_H ($CDCl_3$, 400 MHz) 1.07 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.50 (9H, s, *t*-Bu), 2.49 (1H, d, *J* 16.2 Hz, H-4), 3.02 (1H, d, *J* 16.2 Hz, H-4), 3.24 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.94 (1H, dd, *J* 9.8, 6.2 Hz, H-4'), 4.00 (1H, td, *J* 6.2, 1.9 Hz, H-3'), 4.10 (1H, dd, *J* 9.8, 6.2 Hz, H-4'), 4.45 (1H, dd, *J* 9.0, 1.9 Hz, H-2'), 4.64 (1H, d, *J* 2.0 Hz, H-2), 4.70 (1H, d, *J* 6.6 Hz, OCH_2O), 4.70 (2H, s, OCH_2O), 4.84 (1H, d, *J* 6.6 Hz, OCH_2O), 5.41 (1H, d, *J* 9.0, 2.0 Hz, H-1'), 7.30-7.50 (6H, m, Ar) 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.9 ($SiC(CH_3)_3$), 27.7 ($OCO_2C(CH_3)_3$), 28.0 ($OCO_2C(CH_3)_3$), 43.6 (C-4), 48.7 (OCH_3), 51.0 (OCH_3), 55.7 (OCH_3), 56.1 (OCH_3), 59.9 (C-2), 63.1 (C-4'), 76.0 (C-1'), 77.2 (C-2'), 77.5 (C-3'), 82.6 ($OC(CH_3)_3$), 83.3 ($OC(CH_3)_3$), 96.7 (OCH_2O), 98.3 (OCH_2O), 102.6 (C-3), 127.6, 127.7, 129.7, 129.7, 133.4, 133.5, 135.5, 135.5 (Ar), 149.7 (CO Boc), 153.2 (CO Boc), 169.2 (C-5);

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butoxycarbonyloxy-4'-(*tert*-butyl-diphenylsilyloxy)-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-5-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.139**

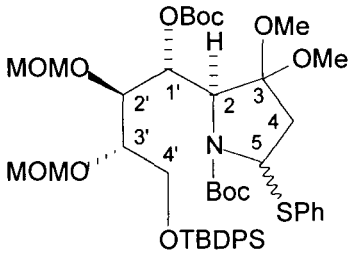


2.139

To a solution of carbamate **2.138** (0.70 g, 0.88 mmol) in dry tetrahydrofuran (50 ml) at -78°C was added DIBAL (1.5 M in toluene, 2.35 ml, 3.5 mmol, 4 eq) drop-wise. The reaction mixture was stirred over two hours between -60°C and -50°C. The reaction mixture was quenched with a saturated solution of sodium acetate at -78°C and a mixture of ammonium chloride and ethyl acetate (1 : 3) was added. The mixture was allowed to warm to room temperature after which the mixture was filtered through Celite® and the filtrate extracted three times with ethyl acetate and washed with ammonium chloride. The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure to yield an oil (0.80 g). The crude product was purified on silica-gel (50 g) using ethyl acetate / petroleum ether (3 : 7) as an eluent to give lactol **2.139** (0.60 g, 0.76 mmol, 86%).

M.p. 118-119°C (from Ethyl Acetate / Petroleum Ether); $[\alpha]_D$ -3.1 (*c* 3, $CHCl_3$), $[M+Na]^+$ Found 816.3928 $C_{40}H_{63}NO_{13}SiNa$ requires 816.3966; υ_{max} /cm^{-1} 3445 (O-H), 2978 (C-H arom), 2858 (C-H aliph), 1749 (C=O), 1634 (C=O), 1108 (C-O). The ^1H and ^{13}C NMR spectra were too complex to analyze.

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butoxycarbonyloxy-4'-(*tert*-butyl-diphenylsilyloxy)-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-5-phenylthio-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.140**

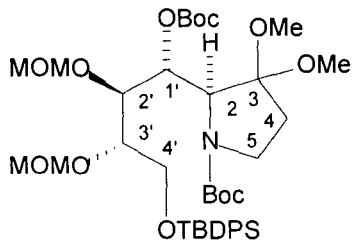


2.140

To a solution of lactol **2.139** (0.57 g, 0.72 mmol) in dry tetrahydrofuran (25 ml) at -78°C were added thiophenol (0.11 ml, 1.08 mmol, 1.5 eq) and BF_3.etherate (0.14 ml, 1.08 mmol, 1.5 eq). The reaction was stirred for 2 hours between -60°C and -50°C. The reaction mixture was quenched with aqueous sodium carbonate and extracted with ethyl acetate (3 x 75 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a crude oil (0.72 g), which was purified on silica-gel (50g) using ethyl acetate/ petroleum ether (1:9) followed by ethyl acetate / petroleum ether (1 : 4) as eluents to yield α-thiocarbamate **2.140** (0.58 g, 0.66 mmol, 91%) as a mixture of diastereomers:

Major-**2.140** δ_H ($CDCl_3$, 400 MHz) 1.08 (9H, s, *t*-Bu), 1.26 (9H, s, *t*-Bu), 1.43 (9H, s, *t*-Bu), 2.55 (1H, d, *J* 12.5 Hz, H-4), 2.99 (1H, dd, *J* 12.5 Hz, 8.2 Hz, H-4), 3.29 (6H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.90-4.20 (3H, m, H-3', H-4'), 4.40-4.50 (2H, m, H-2', H-2), 4.66 (1H, d, *J* 6.4 Hz, OCH_2O), 4.69 (1H, m, *J* 6.4 Hz, OCH_2O), 4.81 (1H, d, *J* 7.0 Hz, OCH_2O), 4.90 (1H, d, *J* 7.0 Hz, OCH_2O), 5.11 (1H, d, *J* 8.0 Hz, H-5), 5.43 (1H, d, *J* 8.8 Hz, H-1'), 7.12-7.19 (2H, m, Ar), 7.22-7.30 (3H, m, Ar), 7.32-7.44 (6H, m, Ar), 7.64-7.74 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.9 ($(CH_3)_3$), 27.9 ($OCO_2C(CH_3)_3$), 28.0 ($OCO_2C(CH_3)_3$), 44.3 (C-4), 49.0 (OCH_3), 50.7 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 59.3 (C-2), 63.4 (C-4'), 66.3 (C-5), 75.4 (C-1'), 76.2 (C-2'), 77.7 (C-3'), 80.7 ($OC(CH_3)_3$), 81.4 ($OC(CH_3)_3$), 97.3 (OCH_2O), 98.1 (OCH_2O), 107.8 (C-3), 126.2, 127.6, 128.8, 129.7, 129.8, 129.9 130.3, 132.3, 133.7, 133.7, 135.6, 138.5 (Ar), 152.7 (CO), 153.2 (CO).

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butoxycarbonyloxy-4'-(tert-butyl-diphenyl-silyloxy)-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.141**



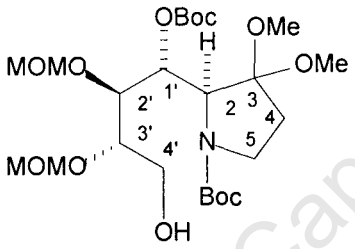
2.141

To a solution of lactol **2.140** (400 mg, 0.51 mmol) in dry dichloromethane (20 ml) at -78°C, were added triethylsilane (0.16 ml, 1.02 mmol, 2 eq) and borontrifluoride etherate (0.13 ml, 1.02 mmol, 2 eq). The reaction mixture was stirred for 1hr at -78°C. Triethylamine (0.21 ml, 1.53 mmol, 3 eq) was added followed by saturated sodium carbonate and the reaction mixture was allowed to warm up to room temperature with stirring. The crude product was extracted three times with ethyl acetate and the combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (750 mg). The product was purified on silica-gel (40 g) using ethyl acetate / petroleum ether (1 : 4) as eluent to give **2.141** (360 mg, 0.46 mmol, 91%) as an oil.

$[M+H]^+$ Found 778.4216, $C_{40}H_{64}NO_9Si$ requires 778.4198; υ_{max} /cm^{-1} 3072, 3051 (C-H arom), 2963, 2933, 2895, 2857 (C-H aliph), 1750 (O-C=O), 1697 (N-C=O), 1162, 1109 (C-O);
Major-δ_H ($CDCl_3$, 400 MHz) 1.06 (9H, s, *t*-Bu), 1.40 (9H, s, *t*-Bu), 1.43 (9H, s, *t*-Bu), 2.02 (1H, m, H-4), 2.32 (1H, m, H-4), 3.19 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 3.28 (3H, s, OCH_3) 3.32 (2H, m, H-5), 3.35 (3H, s, OCH_3), 3.99 (3H, m, H-3', H-4'), 4.27 (1H, d, *J* 3.2 Hz, H-2), 4.53 (1H, t, *J* 8.0 Hz, H-2'), 4.72 (4H, m, OCH_2O), 5.30 (1H, dd, *J* 8.0, 3.2 Hz, H-1'), 7.30-7.50 (6H, m, Ar) 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 27.7 ($OCO_2C(CH_3)_3$), 28.4 ($OCO_2C(CH_3)_3$), 32.8 (C-4), 43.6 (C-5), 49.1 (OCH_3), 50.5 (OCH_3), 55.8 (OCH_3), 56.0 (OCH_3), 57.4 (C-2), 63.7 (C-4'), 76.6 (C-1'), 77.5 (C-3'), 78.2 (C-2'), 79.2 ($OC(CH_3)_3$), 81.3 ($OC(CH_3)_3$), 97.4 (OCH_2O), 98.4 (OCH_2O), 108.4 (C-3), 127.6, 127.7, 129.7, 129.7, 133.4, 133.5, 135.5, 135.5 (Ar), 149.7 (CO), 153.2 (CO).
Minor-δ_H ($CDCl_3$, 400 MHz) 1.06 (9H, s, *t*-Bu), 1.44 (9H, s, *t*-Bu), 1.50 (9H, s, *t*-Bu), 2.02 (1H, m, H-4), 2.32 (1H, m, H-4), 3.19 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.32

(2H, m, H-5), 3.35 (3H, s, OCH_3), 3.99 (3H, m, H-3', H-4'), 4.19 (1H, d, *J* 3.2 Hz, H-2), 4.33 (1H, t, *J* 8.0 Hz, H-2'), 4.72 (3H, m, OCH_2O), 4.89 (1H, d, *J* 6.4 Hz, OCH_2O), 5.38 (1H, dd, *J* 8.0, 3.2 Hz, H-1'), 7.30-7.50 (6H, m, Ar) 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 27.8 ($OCO_2C(CH_3)_3$), 28.4 ($OCO_2C(CH_3)_3$), 32.0 (C-4) 43.6 (C-5), 48.5 (OCH_3), 50.5 (OCH_3), 55.4 (OCH_3), 56.1 (OCH_3), 58.0 (C-2), 63.5 (C-4'), 76.8 (C-1'), 77.6 (C-3'), 78.2 (C-2'), 80.3 ($OC(CH_3)_3$), 81.7 ($OC(CH_3)_3$), 96.4 (OCH_2O), 98.6 (OCH_2O), 109.0 (C-3), 127.6, 127.7, 129.7, 129.7, 133.4, 133.5, 135.5, 135.5 (Ar), 149.7 (CO), 153.2 (CO).

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butyloxycarbonyloxy-4'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.146**



2.146

To a solution of amine **2.141** (600 mg, 0.77 mmol) in tetrahydrofuran (20 ml) at -20°C was added tetrabutylammonium fluoride (1.16 ml, 1.16 mmol, 1.5 eq). The reaction mixture was allowed to warm up to 10°C and stirred for five days at 10°C. The reaction mixture was quenched with ammonium chloride and extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated to yield a residue. The residue was purified on silica-gel (50 g), using ethyl acetate / petroleum ether mixtures (2 : 3 to 1 : 1) to yield **2.146** (335 mg, 0.62 mmol, 81%).

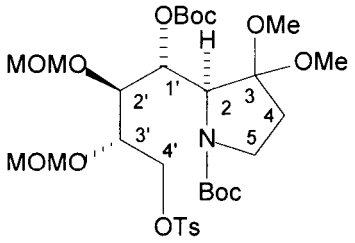
M.p. 128-130°C (from Ethyl Acetate / Hexane); $[\alpha]_D$ -4.2 (*c* 3 CH_2Cl_2); (Found: C, 53.52; H 8.39; N, 2.46%. $C_{24}H_{45}NO_{12}$ requires C, 53.42; H, 8.41; N, 2.60%.); [M+H] 540.2997, $C_{24}H_{46}NO_{12}$ requires 540.3020; υ_{max} /cm^{-1} 3475 (O-H), 2976, 2944, 2898, 2837 (C-H aliph), 1750 (O-C=O), 1697 (N-C=O), 1163, 1108 (C-O);

Major- δ_H ($CDCl_3$, 400 MHz) 1.42 (9H, s, *t*-Bu), 1.45 (9H, s, *t*-Bu),1.74 (1H, s, OH), 2.01 (1H, m, H-4), 2.62 (1H, m, H-4), 3.22 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.31 (2H, m, H-5), 3.39 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.81 (3H, m, H-3' H-4'), 4.21 (1H, d, *J* 2.4 Hz, H-2), 4.28

(1H, t, *J* 8.0 Hz, H-2'), 4.59 (1H, d, *J* 6.9 Hz, OCH_2O), 4.80 (3H, m, OCH_2O), 5.40 (1H, m, H-1'); δ_C ($CDCl_3$, 100.6 MHz) 27.8 ($OCO_2C(CH_3)_3$), 28.4 ($OCO_2C(CH_3)_3$), 33.0 (C-4), 43.7 (C-5), 48.9 (OCH_3), 50.5 (OCH_3), 55.9 (OCH_3), 56.2 (OCH_3), 57.3 (C-2), 62.5 (C-4'), 76.0 (C-1'), 77.0 (C-2'), 79.5 (C-3'), 81.0 ($OC(CH_3)_3$), 81.5 ($OC(CH_3)_3$), 97.6 (OCH_2O), 98.4 (OCH_2O), 108.4 (C-3),153.1 (CO), 154.2 (CO);

Minor- δ_H ($CDCl_3$, 400 MHz) 1.44 (9H, s, *t*-Bu), 1.50 (9H, s, *t*-Bu), 2.01 (1H, m, H-4), 2.62 (1H, m, H-4), 3.20 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.31 (2H, m, H-5), 3.41 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.81 (3H, m, H-3', H-4'), 4.08 (1H, d, *J* 1.8 Hz, H-2), 4.28 (1H, t, *J* 8.0 Hz, H-2'), 4.70 (1H, d, *J* 6.9 Hz, OCH_2O), 4.80 (3H, m, OCH_2O), 5.40 (1H, m, H-1'); δ_C ($CDCl_3$, 100.6 MHz) 27.8 ($OCO_2C(CH_3)_3$), 28.5 ($OCO_2C(CH_3)_3$), 32.0 (C-4), 43.7 (C-5), 48.6 (OCH_3), 50.5 (OCH_3), 55.9 (OCH_3), 56.4 (OCH_3), 57.7 (C-2), 62.6 (C-4'), 76.0 (C-1'), 78.0 (C-2'), 80.4 (C-3'), 80.7 ($OC(CH_3)_3$), 81.9 ($OC(CH_3)_3$), 97.0 (OCH_2O), 98.6 (OCH_2O), 108.9 (C-3), 153.0 (CO), 154.2 (CO).

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-(*tert*-Butoxycarbonyloxy)-2',3'-bis-methoxymethoxy-4'-(*p*-toluene-sulfonyloxy)]-butyl-3,3-dimethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.148**



2.148

To a solution of alcohol **2.146** (60 mg, 0.12 mmol) in dry dichloromethane (0 ml) at 0°C, were added tosyl chloride (30 mg, 0.18 mmol, 1.5 eq), triethylamine (0.04 ml, 0.24 mmol, 2 eq) and DMAP (a catalytic amount). The reaction mixture was stirred at room temperature. Every 4 hrs, an extra 1.5 equivalents of tosyl chloride and 2 equivalents of triethylamine were added until the reaction had gone to completion (48 hrs). The reaction mixture was poured over an ice/water mixture and the crude product was extracted with ethyl acetate (3 x 20 ml). The combined organic layers were dried over magnesium sulfate and concentrated to yield a residue, which was purified on silica-gel (5 g) using ethyl acetate / petroleum ether (2 : 3) as eluent to yield **2.148** (75 mg, 100%, 0.12 mmol) as a 2:1 mixture of *N*-Boc rotamers by ^{1}H NMR.

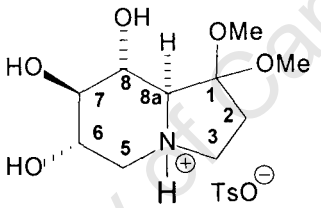
M.p. 135-136°C (from ethyl acetate / petroleum ether); $[\alpha]_D$ +0.8 (*c* 1.5 CH_2Cl_2); (Found: C, 53.61; H, 7.43; N, 1.90; S, 4.47%. $C_{31}H_{51}NO_{14}S$ requires C, 53.67; H, 7.41; N, 2.02; S, 4.62%.); ($[M+H]^+$ Found 694.3110, $C_{31}H_{52}NO_{14}S$ requires 694.3109.); υ_{max} /cm^{-1} 2976, 2898, 2828 (C-H aliph), 1749 (O-C=O), 1690 (N-C=O), 1367 (S=O), 1162, 1108 (C-O).

Major- δ_H ($CDCl_3$, 400 MHz) 1.41 (9H, s, *t*-Bu), 1.43 (9H, s, *t*-Bu), 1.96 (1H, m, H-4), 2.24 (1H, m, H-4), 2.40 (3H, s, CH_3), 3.17 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 3.25 (2H, m, H-5), 3.25 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 4.11 (2H, m, H-2', H-3'), 4.21 (1H, d, *J* 4.2 Hz, H-2), 4.25-.4.40 (2H, m, H-4'), 4.56 (1H, m, OCH_2O), 4.62-4.74 (3H, m, OCH_2O) 5.14 (1H, dd, *J* 4.2, 7.6 Hz, H-1'), 7.29 (2H, d, *J* 7.8 Hz, Ar), 7.81 (2H, d, *J* 7.8 Hz, Ar); δ_C ($CDCl_3$, 100.6 MHz) 21.6 (CH_3), 27.8 ($OCO_2C(CH_3)_3$), 28.4 ($OCO_2C(CH_3)_3$), 32.6 (C-4), 43.6 (C-5), 48.9 (OCH_3), 50.5 (OCH_3), 56.0 (OCH_3), 56.0 (OCH_3), 57.2 (C-2), 70.0 (C-4'), 74.7 (C-1'), 75.4 (C-2'), 76.0 (C-

3'), 79.5 ($OC(CH_3)_3$), 81.7 ($OC(CH_3)_3$), 96.8 (OCH_2O), 98.4 (OCH_2O), 108.2 (C-3),127.9, 128.1, 129.7, 133.2 (Ar), 153.1 (CO), 154.2 (CO);

Minor- δ_H ($CDCl_3$, 400 MHz) 1.41 (9H, s, *t*-Bu), 1.53 (9H, s, *t*-Bu), 1.96 (1H, m, H-4), 2.21 (1H, m, H-4), 2.40 (3H, s, CH_3), 3.17 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 3.25 (2H, m, H-5), 3.25 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 4.11 (2H, m, H-2', H-3'), 4.25-.4.40 (3H, m, H-4', H-2), 4.54 (1H, m, OCH_2O), 4.62-4.74 (3H, m, OCH_2O) 5.22 (1H, m, H-1'), 7.31 (2H, d, *J* 7.8 Hz, Ar), 7.77 (2H, d, *J* 7.8 Hz, Ar); δ_C ($CDCl_3$, 100.6 MHz) 21.6 (CH_3), 27.8 ($OCO_2C(CH_3)_3$), 28.4 ($OCO_2C(CH_3)_3$), 32.0 (C-4), 43.6 (C-5), 48.9 (OCH_3), 50.5 (OCH_3), 56.0 (OCH_3), 56.0 (OCH_3), 57.9 (C-2), 69.2 (C-4'), 74.7 (C-1'), 75.4 (C-2'), 76.0 (C-3'), 79.5 ($OC(CH_3)_3$), 81.7 ($OC(CH_3)_3$), 96.6 (OCH_2O), 98.5 (OCH_2O), 108.8 (C-3), 127.9, 128.1, 129.7, 133.2 (Ar), 153.1 (CO), 154.2 (CO);

6*S*, 7*S*, 8*R*, 8a*S* 1,1-Dimethoxy-octahydro-indolizidine-6,7,8-triol **2.149**



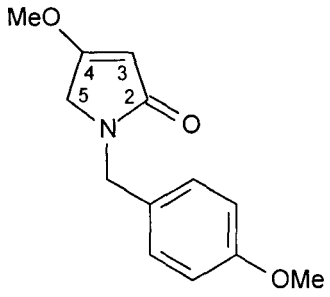
2.149

A solution of tosylate **2.148** (40 mg, 0.06 mmol) in dry dichloromethane and trifluoroacetic acid (0.75 ml : 0.25 ml), (3 :1) was stirred at 0°C for 2 hrs. The excess dichloromethane and trifluoroacetic acid were removed under vacuum for 45 minutes. The residue was dissolved in dry dichloromethane and cooled to 0°C and diisopropylethylamine was added. The reaction mixture was stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo* and redissolved in methanol. Potassium carbonate was added and the mixture was stirred for 30 minutes. The mixture was filtered through Celite and the Celite rinsed thoroughly with methanol. The filtrate was concentrated to yield a residue (50 mg), which was purified on silica-gel (10g) using ethyl acetate, followed by methanol / ethyl acetate (9 : 1 to 4 : 1) with three drops of ammonia to yield **2.149** as a tosylate salt(13 mg, 0.039 mmol, 64%).

δ_H (CD_3OD, 400 MHz) 1.90 (1H, m, H-2), 2.10 (1H, m, H-2), 2.35 (3H, s, CH_3), 3.05 (1H, m, H-3), 3.15 (1H, m, H-3) 3.35 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.57 (1H, d, *J* 6.4 Hz, H-8a),

3.88 (1H, d, *J* 9.6 Hz, H-5), 4.04 (1H, dd, *J* 9.6 and 3.4 Hz, H-5), 4.32 (1H, d, *J* 3.4 Hz, H-6), 4.55 (1H, d, *J* 3.6 Hz, H-7), 4.68 (1H, dd, *J* 6.4 and 3.6 Hz, H-8); δ_C (CD_3OD, 100.6 MHz) 21.3 (Ts(CH_3)), 34.6 (C-2), C-3, OCH_3 under CD_3OD, 51.6 (OCH_3), 70.0 (C-8a), 75.8 (C-6), 77.0 (C-5), 83.5 (C-8), 91.8 (C-7),122.1 (C-1), 127.0, 129.8, 141.7, 143.6 (Ar).

4-Methoxy-1-(4-methoxybenzyl)-3-pyrrolin-2-one **2.86**

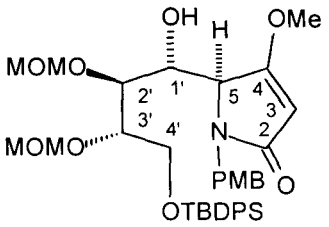


2.86

To a solution of *para*-methoxybenzylamine (4.8 ml, 36 mmol, 1.2 eq) in dry acetonitrile (70 ml) at 0°C, was added Hünig's base (7.7 ml, 46 mmol, 1.5 eq) drop-wise via a syringe followed by methyl 4-chloro-3-methoxy-(*E*)-2-butenoate **2.29** (4.1 ml, 30 mmol). The reaction mixture was heated with stirring at 60°C for 18 hrs. The reaction was quenched with saturated sodium hydrogen carbonate (150 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (6 g), which was chromatographed on silica-gel (120 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 7 : 3) as eluent to yield **2.86** (4.7 g, 20 mmol, 67%).

M.p. 73-74°C (from ethyl acetate-hexane); (Found: C, 66.82; H, 6.42; N, 5.65%. $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00%); ($[M+H]^+$ Found 234.1128, $C_{13}H_{16}NO_3$ requires 234.1130.); υ_{max} /cm^{-1} 2929, 2838 (C-H arom), 1671 (C=O), 1624 (C=C), 1115 (C-O); δ_H ($CDCl_3$, 300 MHz) 3.68 (2H, s, H-5), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.48 (2H, s, Bn), 5.06 (1H, s, H-3), 6.83 (2H, d, J_{AB} 8.7 Hz, Ar), 7.14 (2H, d, J_{AB} 8.7 Hz, Ar). δ_C ($CDCl_3$, 75.5 MHz) 44.7 (Bn), 49.7 (C-5), 55.2 (OCH_3), 58.0 (OCH_3), 94.2 (C-3), 114.1, 129.2, 129.5, 159.0 (Ar), 172.0 (C-4), 173.3 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-*tert*-butyldiphenylsilyloxy-1-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-methoxy-1-(4''-methoxybenzyl)-3-pyrrolin-2-one **2.89**



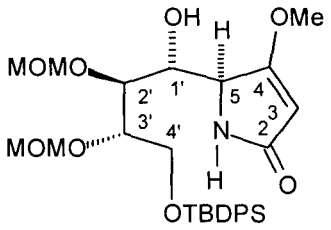
2.89

To a solution of pyrrolinone **2.86** (0.39 g, 1.7 mmol) in dry tetrahydrofuran (5.0 ml) at -78°C, was added *n*-butyllithium (1.6 M in hexane, 1.6 ml, 2.5 mmol, 1.5 eq) drop-wise via a syringe. The reaction mixture was stirred for 30 minutes. Trimethylsilyl chloride (0.64 ml, 5.0 mmol, 3 eq) was added drop-wise and the reaction mixture was stirred for a further 30 minutes. Aldehyde **2.74** (0.55 g, 1.2 mmol) in dry tetrahydrofuran (4.0 ml) was added drop-wise followed by tin (IV) chloride (1M in dichloromethane, 2 ml, 2.0 mmol) drop-wise. The reaction mixture was stirred vigorously and allowed to warm up to -20°C over three hours, after which it was stirred at -20°C for 18 hours. The reaction mixture was quenched with cold saturated sodium hydrogen carbonate (30 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with brine (50 ml) and dried over magnesium sulfate. The organic layer was concentrated under reduced pressure to yield a residue (1.2 g), which was chromatographed on silica-gel (65 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 7 : 3) as eluent to give diastereomer **2.89** (0.52 g, 0.76 mmol, 63%), mixed diastereomers **2.90** (0.20 g, 0.29 mmol, 24%), and unreacted aldehyde **2.74** (0.06 g, 0.13 mmol, 11%).

Major- **2.89** M.p. 107-108°C (from ethyl acetate-hexane); $[\alpha]_D$ = +6.67 (c 3.0, CH_2Cl_2); (Found: C, 65.52; H, 7.36; N, 2.10%. $C_{37}H_{49}NO_9Si$ requires C, 65.37; H, 7.26; N, 2.06%.); ($[M+H]^+$ Found 680.3280, $C_{37}H_{50}NO_9Si$ requires 680.3255.); υ_{max}/cm^{-1} 3053 (OH), 2933 (CH), 1678 (C=O), 1628 (C=C); δ_H ($CDCl_3$, 300 MHz) 1.06 (9H, s, *t*-Bu), 3.08 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.75-3.90 (3H, m, H-3', H-4'), 3.99 (1H, dd, *J* 7.1, 1.8 Hz, H-2'), 4.08 (1H, d, *J* 2.0 Hz, H-5), 4.08 (1H, d, *J* 15.3 Hz, Bn), 4.19 (1H, dd, *J* 7.1, 2.0 Hz H-1'), 4.22 (1H, d, *J* 6.5 Hz, OCH_2O), 4.34 (1H, d, *J* 6.5 Hz OCH_2O), 4.68 (2H, s, OCH_2O) 5.10 (1H, d, *J* 15.3 Hz, Bn), 5.20 (1H, s, H-3), 6.79 (2H, d, *J* 8.7 Hz, PMB),

7.17 (2H, d, *J* 8.7 Hz, PMB), 7.30-7.50 (6H, m, Ar), 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 42.8 (C-Bn), 55.2 (OCH_3), 55.5 (OCH_3), 56.3 (OCH_3), 58.1 (OCH_3), 60.9 (C-5), 62.4 (C-4'), 68.3 (C-1'), 77.9 (C-3'), 80.9 (C-2'), 95.7 (C-3), 96.8 (OCH_2O), 99.2 (OCH_2O), 114.0 (PMB), 127.7, 127.8, 129.2, 129.8, 129.9, 130.0, 133.0, 133.1, 135.4, 135.5 (Ar), 158.9 (PMB), 171.9 (C-4), 173.3 (C-2)

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-*tert*-Butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-methoxy-3-pyrrolin-2-one **2.116**



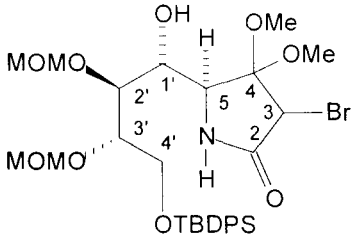
2.116

To a solution of **2.89** (1.00 g, 1.5 mmol) in acetonitrile / water (9 : 1), (70 ml) at -20°C, was added ceric ammonium nitrate (CAN) (3.4 g, 6.0 mmol, 4 eq). The reaction mixture was allowed to warm up to room temperature and stirred for a further 3 hours. The reaction mixture was quenched with cold saturated sodium bicarbonate (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (1.3 g). The residue was chromatographed on silica-gel (60 g) with ethyl acetate (500 ml) followed by methanol / ethyl acetate (1 : 9) as eluent to yield **2.116** (0.69 g, 1.2 mmol, 82%).

$[\alpha]_D$ –2.75 (c 2.0, CH_2Cl_2); ($[M+H]^+$ Found 560.2678, $C_{29}H_{42}NO_8Si$ requires 560.2680.); υ_{max} /cm^{-1} 3330 (O-H, N-H), 3071, 3051, 3014 (C-H arom), 2934, 2892, 2824 (C-H aliph), 1671 (C=O), 1622 (C=C), 1153,1110 (C-O); δ_H ($CDCl_3$, 400 MHz) 1.05 (9H, s, *t*-Bu), 3.10 (1H, d, *J* 2.8 Hz, OH), 3.29 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.81 (2H, m, H-4'), 4.05 (3H, m, H-2', H-3' and H-5), 4.27 (1H, dd, *J* 6.8, 1.6 Hz, H-1'), 4.61 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.66 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.67 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.86 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 5.07 (1H, s, H-3), 6.10 (1H, s (br), NH), 7.35-7.45 (6H, m, Ar), 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 55.8 (OCH_3), 56.2 (OCH_3), 58.7 (OCH_3), 58.8 (C-5), 63.3 (C-4'), 71.7 (C-1'), 78.4 (C-3'), 78.9 (C-2'), 94.8 (C-3), 96.7

(OCH_2O), 98.9 (OCH_2O), 127.7, 127.7, 129.8, 129.8, 133.1, 133.1, 135.6, 135.6 (Ar), 173.5 (C-4), 177.5 (C-2).

1'*R*, 2'*S*, 3'*S*, 5*S*, 3-Bromo-5-[4'-*tert*-butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.120**

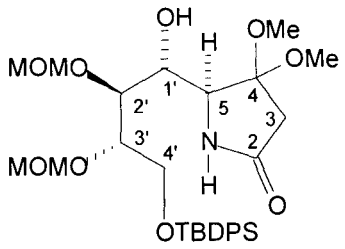


2.120

To a solution of lactam **2.116** (0.60 g, 1.1 mmol) in methanol at -20°C, was added bromine (1 M in dichloromethane, 1.5 ml, 1.5 mmol, 1.5 eq). The reaction mixture was stirred at -20°C for 30 minutes and then quenched with cold saturated sodium carbonate (50 ml) at -20°C and concentrated under reduced pressure. The product was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give an oil (0.90 g). The crude mixture was purified on silica-gel (65 g) using ethyl acetate as eluent to give bromide **2.120** (0.70 g, 1.0 mmol, 91%), as a 4 : 1 mixture of diastereomers.

Major: **2.120** $[\alpha]_D$ –5.75 (c 2.0, CH_2Cl_2); ($[M+H]^+$ Found 670.2026, $C_{30}H_{45}NO_9SiBr^{79}$ requires 670.2047.); υ_{max} /cm^{-1} 3526 (N-H), 3406 (O-H), 3071, 3051 (C-H arom), 2950, 2933, 2892, 2857, 2824 (C-H aliph), 1726 (C=O), 1114 (C-O), 614 (C-Br); δ_H ($CDCl_3$, 400 MHz) 1.06 (9H, s, *t*-Bu), 3.23 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.78-4.01 (5H, m, H-2', H-3', H-4' and H-5), 4.02 (1H, s, H-3), 4.52 (1H, m, H-1'), 4.54 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.58 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.68 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.93 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 7.02 (1H, s (br), NH), 7.30-7.50 (6H, m, Ar), 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.9 ($(CH_3)_3$), 45.1 (C-3), 50.5 (OCH_3), 51.3 (OCH_3), 55.7 (OCH_3), 55.9 (OCH_3), 57.5 (C-5), 63.3 (C-4'), 69.2 (C-1'), 78.3 (C-3'), 78.4 (C-2'), 96.4 (OCH_2O), 99.0 (OCH_2O), 105.4 (C-4), 127.7, 127.8, 129.7, 129.7, 133.4, 133.5, 135.6, 135.7 (Ar), 170.2 (C-2).

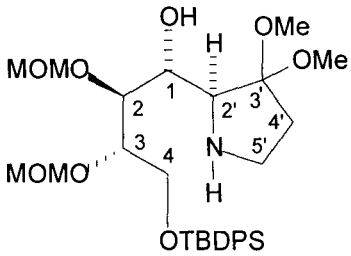
1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-*tert*-Butyldiphenylsilyloxy-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-pyrrolidin-2-one **2.122b**



2.122b

To a solution of bromide **2.120** (0.70 g, 1.0 mmol) in tetrahydrofuran / aqueous ammonium chloride / methanol (2 : 2 : 1, 50 ml), was added zinc powder (0.34 g, 5.0 mmol, 5 eq). The reaction mixture was stirred at room temperature for 30 minutes, before being filtered through Celite® and the precipitate thoroughly rinsed with ethyl acetate. Saturated sodium bicarbonate (50 ml) was added to the filtrate and the whole concentrated under reduced pressure. The product was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield an oil (0.67 g), which was purified on silica-gel (55g) using ethyl acetate as the eluent to give ketal **2.122b** (0.52 g, 0.92 mmol, 90%) with identical spectroscopic and analytical data as **2.122a** from before.

1*R*, 2*S*, 3*S*, 2'*S*, 4-(*tert*-Butyldiphenylsilyloxy)-1-(3',3'-dimethoxypyrrolidin-2'-yl)-2,3-bis-methoxymethoxybutan-1-ol **2.123**



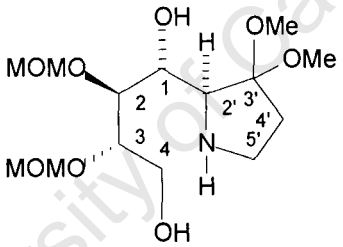
2.123

To a solution of ketal **2.122** (0.48 g, 0.81 mmol) in dry diethyl ether at 0°C was added lithium aluminium hydride (4 mol eq) portion-wise. The reaction was stirred for 18 hours at room temperature and then for a further 3 hours at reflux. The reaction mixture was quenched by

slow addition of a tetrahydrofuran / triethylamine / water mixture (9 : 1 : 1) at 0°C. The mixture was then filtered through Celite® and the precipitate thoroughly rinsed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to give a residue, which was purified on silica-gel (20 g) using ethyl acetate to elute unreacted starting material followed by methanol : ethyl acetate (1 : 9) with two drops of ammonia solution as eluents to give amine **2.123** (0.21 g, 0.36 mmol, 44%).

δ_H ($CDCl_3$, 300 MHz) 1.06 (9H, s, *t*-Bu), 1.66-1.70 (1H, m, H-4'), 1.80-2.00 (2H, m, H-4', N-H), 2.95 (2H, m, H-5'), 3.27 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.36 (1H, s, OH), 3.42 (3H, s, OCH_3), 3.66-3.71 (2H, m, H-1, 2'), 3.90 (2H, t, *J* 3.4 Hz, H-4), 4.00 (1H, m, H-2), 4.14 (1H, dd, *J* 1.1, 7.7 Hz, H-3), 4.68 (1H, d, *J* 6.7 Hz, OCH_2O), 4.72 (2H, s, OCH_2O), 4.90 (1H, d, *J* 6.7 Hz, OCH_2O), 7.30-7.50 (6H, m, Ar), 7.60-7.80 (4H, m, Ar).

1*R*, 2*S*, 3*S*, 5'*S*, 1-(3',3'-Dimethoxypyrrolidin-2'-yl)-2,3-bis-methoxymethoxybutane-1,4-diol **2.124**



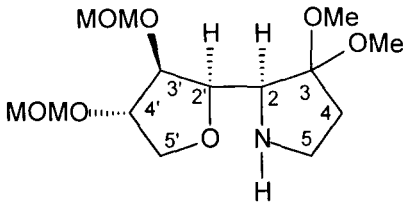
2.124

To a solution of amine **2.123** (200 mg, 0.35 mmol) in tetrahydrofuran at -20°C, was added tetrabutylammonium fluoride (0.5 ml, 1 M in tetrahydrofuran, 0.5mmol, 1.5 eq). The reaction mixture was stirred for 6 hrs at 0°C. The reaction mixture was concentrated under reduced pressure to give a residue (280 mg) which was purified on silica-gel (20 g), using ethyl acetate followed by methanol / ethyl acetate (1:20 to 1:30) with two drops of ammonia solution (1 : 20) as eluent to give diol **2.124** (80 mg, 0.23 mmol, 70%).

δ_H ($CDCl_3$, 400MHz) 1.90 (2H, m, H-4'), 2.90 (2H, m, H-5'), 3.10 (2H, s(br), NH), 3.24 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.38 (1H, d, *J* 2.1 Hz, H-2') 3.40 (1H, s, OCH_3), 3.60 (1H, s, OH), 3.65 (H, dd, *J* 9.6, 2.1 Hz, H-1), 3.75 (2H, m, H-4), 3.86 (1H, m, H-2), 3.97 (1H, m, H-3), 4.67 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.71 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.73

(1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.81 (1H, d, J_{AB} 6.8Hz, OCH_2O); δ_C ($CDCl_3$, 100.6 MHz) 35.3 (C-4'), 43.2 (C-5'), 48.6 (OCH_3), 50.7 (OCH_3), 55.6 (OCH_3), 56.0 (OCH_3), 59.7 (C-2'), 61.4 (C-4), 71.3 (C-1), 78.1 (C-3), 80.6 (C-2), 97.0 (OCH_2O), 98.5 (OCH_2O), 112.3 (C-3).

2*S*, 2'*R*, 3'*S*, 4'*S*, 3,3-Dimethoxy-2-(3',4'-bis-methoxymethyltetrahydrofuran-2'-yl)-pyrrolidine **2.127**

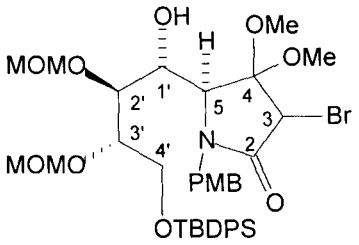


2.127

To a solution of diol **2.124** (80 mg, 0.23 mmol) in dry pyridine (3 ml), were added triphenylphosphine (0.15 g, 0.58 mmol, 2.5 eq) and carbon tetrabromide (0.05 g, 0.35 mmol, 1.5 eq). The reaction mixture was stirred for 18 hours shielded from light at room temperature. Toluene was then added to the reaction mixture to azeotrope off the pyridine and the mixture was concentrated under reduced pressure to give a residue which was purified on silica-gel using ethyl acetate, followed by methanol / ethyl acetate with two drops of ammonia solution (1 : 20 to 3 : 20) to give indolizidine **2.127** (50 mg, 0.15 mmol, 65%).

δ_H ($CDCl_3$, 400 MHz) 2.00-2.15 (2H, m, H-4), 3.10-3.25 (1H, m, H-5), 3.27 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.32-3.41 (1H, m, H-5), 3.35 (3H, s, OCH_3), 3.42 (3H, s, OCH_3), 3.75 (1H, d, *J* 7.5 Hz, H-2), 3.82 (1H, dd, *J* 9.9 and 1.5 Hz, H-5'), 4.17 (1H, dd, *J* 7.5 and 3.6 Hz, H-2'), 4.22 (1H, dd, *J* 9.9 and 4.2 Hz , H-5'), 4.33 (1H, d, *J* 4.2, 1.5 Hz, H-4'), 4.35 (1H, d, *J* 3.6 Hz, H-3'), 4.64 (1H, d, *J* 6.8 Hz, OCH_2O), 4.68 (1H, d, *J* 6.8 Hz, OCH_2O), 4.82 (1H, d, *J* 6.4 Hz, OCH_2O), 4.84 (1H, d, *J* 6.4 Hz, OCH_2O); δ_C($CDCl_3$, 100.6 MHz) 34.9 (C-4), 43.5 (C-5), 49.6 (OCH_3), 50.5 (OCH_3), 55.6 (OCH_3), 56.4 (OCH_3), 61.8 (C-2), 72.0 (C-5'), 77.8 (C-2'), 79.8 (C-4'), 83.4 (C-3'), 95.7 (OCH_2O), 97.3 (OCH_2O), 109.2 (C-1).

1'*R*, 2'*S*, 3'*S*, 5*S*, 3-Bromo-5-[4'-(*tert*-butyldiphenylsilyloxy)-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-1-(4-methoxybenzyl)pyrrolidin-2-one **2.131**



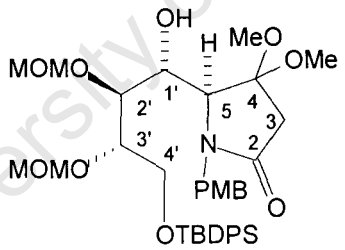
2.131

To a solution of **2.89** (1.00 g, 1.5 mmol) in methanol (30 ml) at -20°C, was added bromine (1 M in dichloromethane, 2 ml, 2 mmol, 1.4 eq). The reaction mixture was stirred for 30 minutes at -20°C, before being quenched with aqueous sodium carbonate (50 ml) at -20°C and concentrated under reduced pressure. The product was extracted with ethyl acetate (3 x 100 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give **2.131** as an oil (1.3 g). The crude mixture was purified on silica-gel (60 g) using ethyl acetate / petroleum ether (7 : 3) as eluent to give 2 diastereomers **2.131a** and **2.131b** which were separated.

2.131a (0.50 g, 0.63 mmol, 40%); $[\alpha]_D$ +1.2 (c 0.75 CH_2Cl_2); $[M+H]^+$ Found 790.2640 $C_{38}H_{53}NO_{10}SiBr$ requires 790.2622; υ_{max} /cm^{-1} 3418 (O-H), 3071, 3050 (C-H arom), 2996, 2935, 2893, 2857 (C-H aliph), 1713 (C=O), 1111 (C-O), 621 (C-Br); δ_H ($CDCl_3$, 400 MHz) 1.07 (9H, s, *t*-Bu), 2.85 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.46 (1H, d, *J* 4.0 Hz, OH), 3.61 (1H, m, 4'), 3.76 (4H, s, H-5, OCH_3), 3.89 (1H, dd, *J* 2.8, 7.4 Hz, H-4'), 3.99 (2H, d, *J* 14.8 Hz, Bn), 3.95-4.06 (2H, m, H-2', H-3'), 4.12 (1H, s, H-3), 4.52 (1H, m, H-1'), 4.59 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.72 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.75 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.81 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 5.19 (1H, d, *J* 14.8 Hz, Bn), 6.80 (2H, d, *J* 8.5 Hz, PMB), 7.20 (2H, d, *J* 8.5 Hz, PMB), 7.30-7.45 (6H, m, Ar), 7.65-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.2 (Si-C), 26.9 ($(CH_3)_3$), 45.2 (C-3), 45.2 (C-Bn), 49.9 (OCH_3), 51.1 (OCH_3), 55.2 (OCH_3), 55.7 (OCH_3), 56.5 (OCH_3), 60.5 (C-5), 63.8 (C-4'), 68.4 (C-1'), 77.5 (C-3'), 78.7 (C-2'), 97.3 (OCH_2O), 97.4 (OCH_2O), 104.1 (C-4), 113.8 (PMB), 127.7, 128.0, 129.7, 129.7, 133.5, 133.5, 135.3, 135.4, 135.6, 135.6 (Ar), 159.2 (PMB), 173.3 (CO).

2.131b (0.66 g, 55%, 0.84 mmol); $[\alpha]_D$ –33.82 (c 2, CH_2Cl_2); $[M+H]^+$ (Found 790.2640 $C_{38}H_{53}NO_{10}SiBr$ requires 790.2622); υ_{max} /cm^{-1} 3418 (O-H), 3071, 3050 (C-H arom), 2996, 2935, 2893, 2857 (C-H aliph), 1713 (C=O lactam), 1111 (C-O ether), 621 (C-Br); δ_H ($CDCl_3$, 400 MHz) 1.05 (9H, s, *t*-Bu), 3.01 (3H, s, OCH_3), 3.11 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.78-3.88 (4H, m, H-3', H-4', H-5), 3.91 (2H, d, *J* 15.6 Hz, Bn), 3.98 (1H, dt, *J* 7.9, 2.0 Hz, H-1'), 4.14 (1H, s, H-3), 4.16 (1H, d J_{AB} 6.4 Hz, OCH_2O), 4.22 (1H, dd, *J* 7.9, 1.8 Hz, H-2'), 4.31 (1H, d, J_{AB} 6.4 Hz, OCH_2O), 4.69 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.73 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 5.10 (1H, d, *J* 15.6 Hz, Bn), 6.81 (2H, d, *J* 8.6 Hz, PMB), 7.15 (2H, d, *J* 8.6 Hz, PMB), 7.32-7.46 (6H, m, Ar), 7.58-7.66 (4H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 19.2 (Si-C), 26.8 ($(CH_3)_3$), 43.8 (C-Bn), 45.2 (C-3) 49.0 (OCH_3), 51.6 (OCH_3), 52.0 (OCH_3), 55.2 (OCH_3), 55.2 (C-3), 56.4 (OCH_3), 59.4 (C-5), 62.1 (C-4'), 69.3 (C-1'), 77.6 (C-3'), 82.8 (C-2'), 96.6 (OCH_2O), 99.5 (OCH_2O), 102.7 (C-4), 114.0 (PMB), 127.8, 127.9, 129.0, 129.5, 129.9, 133.1, 135.3, 135.4, 135.5, 135.6 (Ar), 159.1 (PMB), 168.6 (CO).

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-(*tert*-butyldiphenylsilyloxy)-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4,4-dimethoxy-1-(4-methoxybenzyl)pyrrolidin-2-one **2.132**

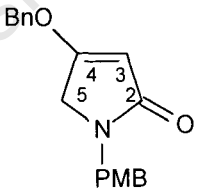


2.132

To a solution of bromide **2.131** (0.66 g, 0.63 mmol) in tetrahydrofuran / aqueous ammonium chloride / methanol (2 : 2 : 1, 25 ml), was added zinc powder (0.30 mg, 3.15 mmol, 5 eq). The reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was filtered through Celite® and thoroughly rinsed with ethyl acetate (150 ml). Saturated sodium bicarbonate (50 ml) was added to the filtrate and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 100 ml), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to yield an oil (0.40 g). The crude product was purified on silica-gel (30 g) using ethyl acetate : petroleum ether mixtures (8 : 2 to 9 : 1) as eluent to give **2.132** (0.39 g, 0.54 mmol, 77%).

M.p. 123-124°C (from ethyl acetate-hexane); $[\alpha]_D$ +2.0 (*c* 2.0, CH_2Cl_2); (Found: C, 63.81; H, 7.43; N; 1.91%. $C_{38}H_{53}NO_9Si$ requires C, 64.11; H, 7.50; N, 1.97%); (Found $[M+H]^+$ 712.3517 $C_{38}H_{54}NO_9Si$ requires 712.3512.); υ_{max} /cm^{-1} 3373 (O-H), 3089, 3070, 3051, 3030,(C-H arom), 2999, 2954, 2931, 2894, 2856, 2823 (C-H aliph), 1686 (C=O lactam), 1140, 1113, 1103 (C-O ether); δ_H ($CDCl_3$, 400 MHz) 1.05 (9H, s, *t*-Bu), 2.45 (1H, d, *J* 15.0 Hz, H-3), 3.00 (1H, d, *J* 15.0 Hz, H-3), 3.02 (3H, s, OCH_3), 3.03 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.56 (1H, d, *J* 2.7 Hz, OH), 3.64 (1H, d, 2.5 Hz, H-5), 3.76 (3H, s, OCH_3), 3.81 (3H, m, H-3', H-4'), 3.87 (1H, d, *J* 15.6 Hz, Bn), 4.02 (1H, dt, *J* 7.2, 2.5 Hz, H-1'), 4.20 (1H, d, *J* 6.6 Hz, OCH_2O) 4.21 (1H, m, H-2'), 4.37 (1H, d, *J* 6.6 Hz, OCH_2O), 4.71 (1H, d, *J* 6.8 Hz, OCH_2O), 4.75 (1H, d, *J* 6.8 Hz, OCH_2O), 5.13 (1H, d, *J* 15.6 Hz, Bn), 6.81 (2H, d, *J* 8.8 Hz, PMB), 7.16 (1H, d, 8.8 Hz, PMB), 7.30-7.50 (6H, m, Ar) 7.60-7.70 (4H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.1 (Si-C), 26.7 ($(CH_3)_3$), 42.1 (C-3), 42.9 (C-Bn), 48.2 (OCH_3), 50.8 (OCH_3), 55.2 (OCH_3), 55.3 (OCH_3), 56.4 (OCH_3), 59.9 (C-5), 62.4 (C-4'), 69.4 (C-1'), 78.0 (C-3'), 81.8 (C-2'), 96.8 (OCH_2O), 99.2 (OCH_2O), 105.0 (C-4), 113.8 (PMB), 127.7, 127.7, 128.6, 128.8, 129.8, 129.8, 133.2, 133.2, 135.3, 135.4 (Ar), 158.9 (PMB), 172.2 (CO).

4-Benzyloxy-1-(4-methoxybenzyl)-3-pyrrolin-2-one **2.91**

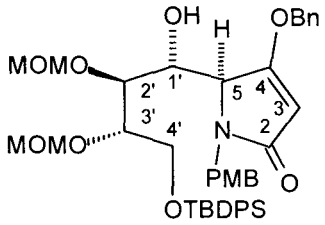


2.91

To a solution of pyrrolinone **2.86** (4.00 g, 17.0 mmol) in dry benzyl alcohol (32 ml), was added a catalytic amount of *p*-toluenesulfonic acid (10 mg). The reaction mixture was heated at 80°C under reduced pressure (20 mm Hg) for five hours. The reaction mixture was quenched with aqueous sodium bicarbonate (100 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The excess benzyl alcohol was removed via vacuum distillation to yield a residue. The residue was chromatographed on silica-gel (100 g) with ethyl acetate / petroleum ether mixtures (6 : 4 to 8 : 2) as eluents to yield pyrrolin-2-one **2.91** (3.4 g, 11 mmol, 65%).

M.p. 108-109°C (from ethyl acetate); (Found: C, 74.10; H, 6.20; N, 4.53%. $C_{19}H_{19}NO_3$ requires C, 73.77, H, 6.19; N, 4.53%); Found $[M+H]^+$ 310.1443 $C_{19}H_{20}N0_3$ requires 310.1443; $\upsilon_{max}(CH_2Cl_2)cm^{-1}$ 1678 (C=O), 1626 (C=C); δ_H ($CDCl_3$, 300 MHz) 3.75 (2H, s, H-5), 3.79 (3H, s, OCH_3), 4.50 (2H, s, NBn), 4.94 (2H, s, OBn), 5.16 (1H, s, H-3), 6.85 (2H, d, *J* 8.7 Hz, PMB), 7.17 (2H, d, *J* 8.7 Hz, PMB), 7.30-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 44.8 (NBn), 50.0 (C-5), 55.3 (OCH_3), 73.0 (OBn), 95.4 (C-3), 114.1 (PMB), 127.9, 128.7, 128.7, 129.3, 129.5, 134.7, 159.06 (PMB), 172.0 (C-4), 172.1 (C-2)

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-(*tert*-Butyldiphenylsilyloxy)-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-benzyloxy-1-(4''-methoxybenzyl)-3-pyrrolin-2-one **2.94**



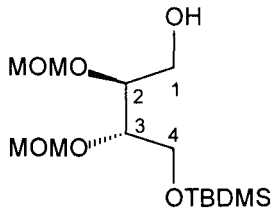
2.94

To a solution of pyrrolinone **2.91** (1.64 g, 5.3 mmol, 1.5 eq) in dry tetrahydrofuran (17.5 ml) at -78°C, was added *n*-butyllithium (1.6 M in hexane, 4.96 ml, 7.9 mmol, 2.25 eq) drop-wise via a syringe. The reaction mixture was stirred for 30 minutes at -78°C. Trimethylsilyl chloride (2.02 ml, 15.9 mmol, 4.5 eq) was added drop-wise and the reaction mixture was stirred for a further 30 minutes. Aldehyde **2.74** (1.57 g, 3.5 mmol) in dry tetrahydrofuran (14 ml) was added drop-wise, followed by tin (IV) choride (1M in dichloromethane, 7 ml, 7.0 mmol, 2 eq) which was also added drop-wise. The reaction mixture was stirred vigorously and allowed to warm to -20°C over three hours. The reaction mixture was stirred at -20°C for 18 hours. The reaction mixture was quenched with cold aqueous saturated sodium hydrogen carbonate (150 ml) and extracted with ethyl acetate (3 x 200 ml). The combined organic layer was washed with brine (200 ml) and dried over magnesium sulfate. The organic layer was concentrated under reduced pressure to yield a residue (3.50 g), which was chromatographed on silica-gel (65 g) with ethyl acetate / petroleum ether mixtures (3 : 7 to 6 : 4) as eluent to give pure diastereomer **2.94** (1.66 g, 2.2 mmol, 63%), mixed diastereomers **2.95** (0.66 g, 0.87 mmol, 25 %) and unreacted aldehyde **2.75** (0.19 g, 0.42 mmol, 12%).

2.94 M.p. 109-110°C (from ethyl acetate-hexane); $[\alpha]_D$ +17.83 (*c* 2.3, CH_2Cl_2); (Found: C, 68.32; H, 6.83; N, 1.85%. $C_{43}H_{53}NO_9Si$ requires C, 68.51; H, 7.07; N, 1.85%.); Found $[M+H]^+$ 756.3576, $C_{43}H_{54}NO_9Si$ requires 756.3568; υ_{max}/cm^{-1} 3053 (OH), 2933 (CH), 1678 (C=O), 1628 (C=C); δ_H ($CDCl_3$, 300 MHz) 1.03 (9H, s, *t*-Bu), 3.12 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.74 (3H, s, OCH_3 (PMB)), 3.76-3.89 (3H, m, H-4', H-3'), 3.92 (1H, dd, *J* 6.0 and 2.1 Hz, H-2'), 4.18 (1H, d, *J* 16.2 Hz, NBn), 4.20-4.25 (2H, m, H-5, H-1'), 4.35 (1H, d, J_{AB} 6.5 Hz, OCH_2O), 4.47 (1H, d, J_{AB} 6.5 Hz, OCH_2O), 4.60 (1H, d, J_{AB} 6.9 Hz, OCH_2O), 4.63 (1H, d, J_{AB}

6.9 Hz, OCH_2O), 4.92 (2H, s, OBn), 4.96 (1H, d, *J* 16.2 Hz, NBn), 5.20 (1H, s, H-3), 6.78 (2H, d, J_{AB} 8.7 Hz, PMB), 7.17 (2H, d, J_{AB} 8.7 Hz, PMB) 7.20-7.80 (15H, m, Ar); δ_C ($CDCl_3$, 75.5 MHz) 19.1 (Si-C), 26.8 ($(CH_3)_3$), 43.4 (Bn), 55.2 (OCH_3), 55.5 (OCH_3), 56.2 (OCH_3), 61.9 (C-5), 63.2 (C-4'), 68.7 (C-1'), 73.1 (OBn), 77.9 (C-3'), 78.4 (C-2'), 96.7 (C-3), 96.8 (OCH_2O), 98.9 (OCH_2O), 113.9 (PMB), 127.5, 127.7, 127.7, 128.6, 128.7, 129.3, 129.3, 129.8, 130.0, 133.0, 133.1, 134.6, 135.4, 135.5 (Ar), 158.8 (PMB), 172.1 (C-4), 172.1 (CO).

4-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-di-methoxymethyl-L-threitol **2.153**[112]



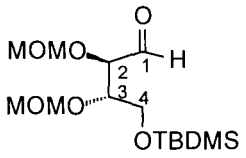
2.153

To a solution of **2.72** (5.00 g, 23.8 mmol) at 0°C in dry tetrahydrofuran (300 ml), was added *n*-butyllithium (1.6 M in hexane, 14.8 ml, 23.8 mmol, 1 eq) drop-wise via a syringe. The reaction mixture was stirred at 0°C for 40 minutes. *tert*-Butyldimethylsilyl chloride (TBDMSCl) (3.59 g, 23.8 mmol, 1 eq) was then added drop-wise and the reaction mixture was stirred for a further hour at 0°C followed by 18 h at room temperature. The reaction mixture was quenched with aqueous sodium hydrogen carbonate (200 ml) and was concentrated under reduced pressure. The solution was extracted with dichloromethane (3 x 200 ml) and then with ethyl acetate (2 x 200 ml). The combined organic layers were dried over magnesium sulfate and concentrated to yield a residue (7.82 g), which was chromatographed on silica-gel (100 g) with ethyl acetate / petroleum ether (1 : 9) until all the *tert*-butyldimethylsilyl alcohol was eluted, followed by ethyl acetate / petroleum ether (3 : 7) as eluent to yield silyl ether **2.153** (7.20 g, 22.2 mmol, 93%).

δ_H ($CDCl_3$, 400 MHz) 0.04 (6H, s, CH_3), 0.87 (9H, s, *t*-Bu), 3.18 (1H, t, *J* 6.4 Hz, OH), 3.38 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.60-3.80 (6H, m, H-1,4 and H-2,3), 4.64 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.67 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.73 (1H, d, J_{AB} 6.8 Hz, OCH_2O), 4.74 (1H, d, J_{AB} 6.8 Hz, OCH_2O); δ_C ($CDCl_3$, 100.6 MHz) –5.6 (CH_3), -5.6 (CH_3), 18.1 (Si-C), 25.8 ($(CH_3)_3$),

55.7 (OCH_3), 55.8 (OCH_3), 62.1 (C-4), 62.5 (C-1), 78.4 (C-3), 80.4 (C-2), 97.2 (OCH_2O), 97.6 (OCH_2O).

4-O-(*tert*-Butyldimethylsilyl)-2,3-O-di-methoxymethyl-L-threitose **2.104**[112]

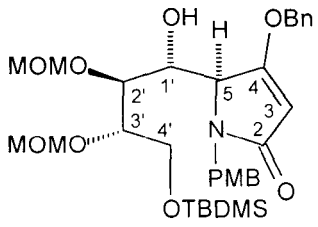


2.104

To a solution of dimethyl sulfoxide (1.97 ml, 27.7 mmol, 3 eq) in dry dichloromethane (30 ml) at -78°C, was added oxalyl chloride (1.61 ml, 18.5 mmol, 2 eq) drop-wise via a syringe. The reaction mixture was stirred for 10 minutes at -78°C. The alcohol **2.150** (3 g, 9.2 mmol) in dry dichloromethane (10 ml) was then added to the reaction mixture drop-wise. Triethylamine (6.4 ml, 46.2 mmol, 5 eq) was added after a further 20 minutes drop-wise. The reaction mixture was allowed to warm to 0°C upon which the reaction was quenched with aqueous sodium carbonate (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was dried over magnesium sulfate and concentrated to yield a residue (3.5 g), which was chromatographed on silica-gel (65 g) with ethyl acetate / petroleum ether (1 : 9) until the dimethyl sulfide was eluted, followed by ethyl acetate / petroleum ether (1 : 1) as eluent to yield **2.104** (2.7 g, 8.3 mmol, 90%).

δ_H ($CDCl_3$, 300 MHz) 0.03 (3H, s, CH_3), 0.04 (3H, s, CH_3), 0.86 (9H, s, *t*-Bu), 3.30 (3H, OCH_3), 3.41 (3H, s, OCH_3), 3.73-3.76 (2H, m, H-4), 3.98-4.03 (1H, m, H-3), 4.16 (1H, dd, *J* 3.3, 1.2 Hz, H-2), 4.58 (1H, d, J_{AB} 6.9 Hz, OCH_2O), 4.67 (1H, d, J_{AB} 6.9 Hz, OCH_2O), 4.72 (1H, d, *J* 6.6 Hz, OCH_2O), 4.78 (1H, d, *J* 6.6 Hz, OCH_2O) 9.80 (1H, d, *J* 1.2 Hz, H-1); δ_C ($CDCl_3$, 75.5 MHz) –5.6 (CH_3), -5.6 (CH_3), 18.1 (Si-C), 25.8 ((CH_3)$_3$), 55.7 (OCH_3), 56.1 (OCH_3), 60.9 (C-4), 77.9 (C-3), 81.2 (C-2), 96.8 (OCH_2O), 97.5 (OCH_2O), 202.0 (C-1).

1'*S*, 2'*S*, 3'*S*, 5*R*, 5-[4'(*tert*-Butyldimethylsilyloxy)-1'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-benzyloxy-1-(4''-methoxybenzyl)-3-pyrrolin-2-one **2.105**



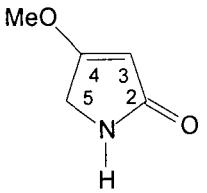
2.105

To a solution of pyrrolinone **2.91** (2.00 g, 6.5 mmol, 1.5 eq) in dry tetrahydrofuran (21.5 ml) at -78°C, was added *n*-butyllithium (1.6 M in hexane, 8.1 ml, 12.9 mmol, 3 eq) drop-wise via a syringe. The reaction mixture was stirred for 30 minutes. Trimethylsilyl chloride (2.5 ml, 19.41 mmol, 4.5 eq) was added drop-wise and the reaction mixture was stirred for a further 30 minutes. Aldehyde **2.104** (1.40 g, 4.3 mmol) in dry tetrahydrofuran (17.2 ml) was added drop-wise, followed by tin (IV) chloride (1 M in dichloromethane, 8.6 ml, 8.6 mmol, 2 eq) drop-wise. The reaction mixture was stirred vigorously and allowed to warm to -20°C over three hours. The reaction mixture was stirred at -20°C for 18 hours. The reaction mixture was quenched with cold aqueous sodium hydrogen carbonate (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was washed with brine (100 ml) and dried over magnesium sulfate. The organic layer was concentrated under reduced pressure to yield a residue (3.86 g), which was chromatographed on silica-gel (100 g) with ethyl acetate / hexane (3 : 7) (200 ml) to elute the unreacted aldehyde followed by ethyl acetate / hexane (6 : 4) until all the products had eluted to give pure diastereomer **2.105** (1.55 g, 2.45 mmol, 57%), mixed diastereomers **2.106** (0.61 g, 0.96 mmol, 22%), and unreacted aldehyde **2.104** (0.25 g, 0.78 mmol, 18%).

$[\alpha]_D$ +14.75 (*c* 2.0, CH_2Cl_2); Found $[M+H]^+$ 632.3278, $C_{33}H_{50}NO_9Si$ requires 632.3255 3399 (O-H), 2998, 2956, 2856 (C-H Aliph), 1648 (C=O), 1096 (C-O); δ_H ($CDCl_3$, 400 MHz) 0.03 (6H, s, CH_3), 0.87 (9H, s, *t*-Bu), 3.20 (3H, s, OCH_3), 3.40 (3H, s, OCH_3), 3.59 (1H, s(br), OH), 3.66-3.75 (2H, m, H-3', H-4'), 3.77 (3H, s, OCH_3) 3.78 (2H, m, H-2', H-4'), 4.19 (1H, d, J_{AB} 15.4 Hz, NBn), 4.22 (1H, d, *J* 2.0 Hz, H-5), 4.27 (1H, m, H-1'), 4.38 (1H d, J_{AB} 6.6 Hz, OCH_2O), 4.48 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.65 (1H, d, J_{AB} 6.6 Hz, OCH_2O), 4.71 (1H, d, J_{AB} 6.6 Hz,

OCH_2O), 4.96 (2H, s, OBn), 5.07 (1H, d, J_{AB} 15.4 Hz, NBn), 5.22 (1H, s, H-3), 6.82 (2H, d, J_{AB} 8.6 Hz, PMB), 7.23 (2H, d, J_{AB} 8.6 Hz, PMB); δ_c ($CDCl_3$, 100.6 MHz) –5.5 (CH_3), -5.5 (CH_3), 18.2 (Si-C), 25.8 ((CH_3)$_3$), 43.4 (NBn), 55.2 (OCH_3), 55.6 (OCH_3), 56.3 (OCH_3), 61.9 (C-5), 62.31 (C-4'), 68.5 (C-1'), 73.1 (OBn), 78.0 (C-3'), 78.6 (C-2'), 96.6 (C-3), 96.6 (OCH_2O), 99.1 (OCH_2O), 114.0 (PMB), 127.6, 128.7, 128.7, 129.4, 130.1, 134.7 (Ar), 158.9 (PMB), 172.1 (C-4), 172.2 (CO).

4-Methoxy-3-pyrrolin-2-one **2.31**[93]

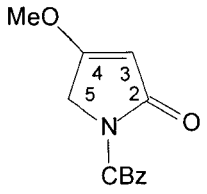


2.31

To a solution of aqueous ammonia (10%, 13.8 ml, 81 mmol) at 60°C, was added methyl 4-chloro-3-methoxy-(*E*)-2-butenoate **2.29** (3 ml, 22.08 mmol) drop-wise via a pressure compensating dropping funnel over an hour. The reaction mixture was then heated at 60°C with stirring for a further 3h. The reaction mixture was cooled to room temperature and the solution thoroughly extracted with dichloromethane (6 x 200 ml). The combined organic layers were combined, dried over magnesium sulfate and concentrated under reduced pressure to give a solid, which was recrystallized from toluene to give **2.31** (2.0 g, 17.6 mmol, 80%).

δ_H ($CDCl_3$, 300 MHz) 3.77 (3H, s, OCH_3), 3.88 (2H, s, H-5), 5.03 (1H, s, H-3), 6.90 (1H, s (br), NH); δ_C ($CDCl_3$, 100.6 MHz) 46.7 (C-5), 58.2 (OCH_3), 94.2 (C-3), 175.7 (C-4), 175.9 (CO).

4-Methoxy-3-pyrrolin-2-one-1-carboxylic acid benzyl ester **2.83**

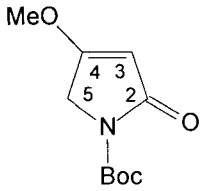


2.83

To a solution of pyrrolinone **2.31** (0.80 g, 7.08 mmol) in dry tetrahydrofuran (50 ml) at 0°C, was added sodium hydride (60% in oil, 0.38 g, 21.2 mmol, 3 eq) and the reaction mixture stirred at 0°C for 10 minutes. Benzyl chloroformate (1.1 ml, 7.8 mmol, 1.1 eq) was added at 0°C and the reaction mixture stirred at room temperature for 3h. The reaction mixture was quenched with aqueous ammonium chloride (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue (2.92 g), which was chromatographed on silica-gel (70 g) using ethyl acetate / petroleum ether (7 : 3) as eluant to give **2.83** (1.1 g, 3.54 mmol, 50%).

M.p. 128-129°C (from ethyl acetate); (Found: C, 63.15; H, 5.00; N; 5.61%. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.30; N, 5.66%); (Found $[M+H]^+$ 248.0922, $C_{13}H_{13}NO_4$ requires 248.0922.); ν_{max}/cm^{-1} 3056 (C-H arom), 2986, 2943, 2898, 2870, 2856 (C-H aliph), 1781 (O-C=O), 1735 (N-C=O), 1633 (C=C), 1331; δ_H ($CDCl_3$, 300 MHz) 3.83 (3H, s, OCH_3), 4.23 (2H, s, H-5), 5.11 (1H, s, H-4), 5.29 (2H, s, Bn), 7.30-7.50 (5H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 49.1 (C-5), 58.6 (OCH_3), 67.7 (Bn), 94.7 (C-3), 128.1, 128.3, 128.5, 135.5 (Ar), 150.6 (CO_{Carb}), 168.5 (C-4), 174.9 (CO_{lact}).

4-Methoxy-3-pyrrolin-2-one-1-carboxylic acid *tert*-butyl ester **2.82**

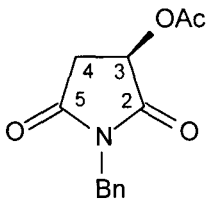


2.82

To a solution of pyrrolinone **2.31** (1.00 g, 8.8 mmol) in dry acetonitrile (50 ml) at room temperature, was added di-*tert*-butyl dicarbonate (2.03 ml, 8.8 mmol, 1 eq) followed by 4-dimethylaminopyridine (0.10 g, 0.88 mmol, 0.1 eq). The reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated under reduced pressure to give a residue (1.89 g), which was chromatographed on silica-gel (65 g) using ethyl acetate / petroleum ether (7 : 3) as eluent to give **2.82** (1.58 g, 7.4 mmol, 84%).

M.p. 94-95°C (from ethyl acetate); (Found: C, 56.54; H, 7.36; N; 6.52%. $C_{10}H_{15}NO_4$ requires C, 56.33; H, 7.09; N, 6.57%); (Found $[M+H]^+$ 214.1079, $C_{10}H_{16}NO_4$ requires 214.1079.); ν_{max} (CH_2Cl_2) / cm^{-1} 3041, 3005, 2985, 2940, 2911, 2877, 2826 (C-H aliph), 1779 (O-C=O), 1682 (C=O lactam), 1626 (C=C); δ_H ($CDCl_3$, 400 MHz) 1.50 (9H, s, *t*-Bu), 3.80 (3H, s, OCH_3), 4.14 (2H, s, H-5), 5.06 (1H, s, H-3), δ_C ($CDCl_3$, 100.6 MHz) 28.0 ($OCO_2C(CH_3)_3$), 49.1 (C-5), 58.4 (OCH_3), 82.5 ($OC(CH_3)_3$), 94.9 (C-3),149.3 (CO_{carb}), 168.9 (C-4), 174.5 (CO_{lact}).

3*R*, *N*-Benzyl-3-acetoxy-pyrrolidin-2,5-dione **2.97**[109]

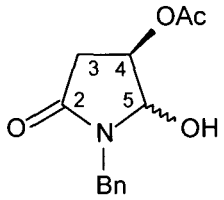


2.97

A solution of L-Malic acid **2.96** (5.00 g, 37 mmol) in acetyl chloride (30 ml) was refluxed for 2 hrs. The excess acetyl chloride was removed *in vacuo* and the residue dried under high vacuum for 1 hr. The residue was then dissolved in tetrahydrofuran (50 ml) and benzylamine (4.9 ml, 44.8 mmol 1.2 eq) was added and the mixture stirred at room temperature for 18 hrs. The mixture was then concentrated and redissolved in acetyl chloride (50 ml) which was refluxed for a further 24 hrs, upon which the solution was concentrated and dissolved in ethyl acetate (200 ml). This was then washed with saturated sodium carbonate and dried over magnesium sulfate. Finally the organic layer was reduced *in vacuo* and the residue purified on silica-gel (160 g) using ethyl acetate / petroleum ether mixtures (1 : 4 to 3 : 7) as eluent to give **2.97** (7.70 g, 31 mmol, 84%).

δ_H ($CDCl_3$, 400 MHz) 2.12 (3H, s, OAc), 2.63 (1H, dd, *J* 4.6 and 18.2 Hz, H-4), 3.11 (1H, dd, *J* 8.6 and 18.2 Hz, H-4), 4.63 (1H, d, J_{AB} 14.0 Hz, Bn), 4.68 (1H, d, J_{AB} 14.0 Hz, Bn), 5.41 (1H, dd, *J* 4.6 and 8.6 Hz, H-3) 7.20-7.40 (5, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 20.3 (CH_3), 35.6 (C-4), 42.5 (Bn), 67.4 (C-3), 128.0, 128.6, 128.7, 135.1 (Ar), 169.6 (C=O), 172.8 (C=O), 173.1 (C=O).

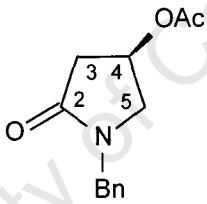
4*R*, *N*-Benzyl-4-acetoxy-5-hydroxy-pyrrolidin-2-one **2.98**[109]



2.98

To a solution of pyrrolinone **2.97** (3.70 g, 16 mmol) in ethanol (100 ml) at -30°C, was added sodium borohydride (3.00 g, 80 mmol, 5 eq) portion-wise. The reaction mixture was stirred at -20°C for 2.5 h until the reaction had gone to completion. The mixture was quenched with cold saturated sodium hydrogen carbonate (100 ml) and extracted with ethyl acetate (3 x 200 ml). The organic layer was dried over magnesium sulfate and concentrated to yield a white solid **2.98** (3.60 g, 14.4 mmol, 96%).

4*R*, *N*-Benzyl-4-acetoxy-pyrrolidin-2-one **2.99**[110]



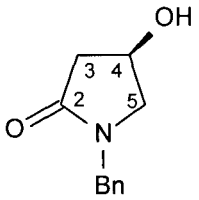
2.99

To a solution of α-hydroxylactam **2.98** (1.00 g, 4.0 mmol) in dry dichloromethane (20 ml), was added trifluoroacetic anhydride (0.67 ml, 4.7 mmol, 1.2 eq). The reaction mixture was stirred at room temperature for an hour, upon which it concentrated. The residue was dissolved in trifluoroacetic acid (5 ml) and cooled to 0°C, upon which triethylsilane (0.8 ml, 5.0 mmol, 1.25 eq) was added. The reaction mixture was stirred for an hour at 0°C, after which it was concentrated and purified on silica-gel (30 g) using ethyl acetate / petroleum ether (1 : 1) as eluent to give pyrrolidinone **61** as an oil (0.70 g, 2.90 mmol, 74%).

δ_H ($CDCl_3$, 300 MHz) 2.02 (3H, s, CH_3), 2.55 (1H, dd, *J* 2.4, 17.4 Hz, H-4), 2.82 (1H, dd, *J* 7.5, 17.4 Hz, H-4), 3.23 (1H, dd, *J* 2.4, 11.4 Hz, H-2), 3.61 (1H, dd, *J* 5.7, 11.4 Hz, H-2), 4.45 (1H, d, J_{AB} 14.7 Hz, Bn), 4.51 (1H, d, J_{AB} 14.7 Hz, Bn), 5.21-5.29 (1H, m, H-3), 7.20-7.37 (5H, m,

Ar); δ_C ($CDCl_3$, 100.6 MHz) 20.9 (CH_3), 37.8 (C-4), 46.3 (Bn), 52.9 (C-2), 66.8 (C-3), 127.8, 128.1, 128.8, 135.7 (Ar), 170.5 (C=O), 171.9 (C=O).

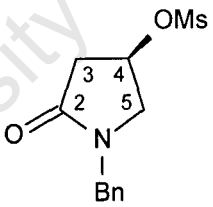
4*R*, *N*-Benzyl- 4-hydroxy-pyrrolidin-2-one **2.100**



2.100

To a solution of potassium hydroxide (0.25 g, 4.4 mmol, 1.5 eq) in methanol (20 ml), was added pyrrolidinone **2.99** (0.70 g, 2.9 mmol). The reaction mixture was stirred at room temperature for 30 minutes, upon which it was concentrated, 1 M HCl (20 ml) added and the product was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried over magnesium sulfate and reduced *in vacuo* to give lactam **2.100** (0.55 g, 2.9 mmol, 100%).

4*R*, *N*-Benzyl-4-methanesulfonyloxy-pyrrolidin-2-one **2.101**

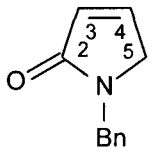


2.101

To a solution of lactam **2.100** (0.55 g, 2.9 mmol) in dry dichloromethane (20 ml) at 0°C, was added triethylamine (0.8 ml, 5.8 mmol, 2 eq), followed by mesyl chloride (0.45 ml, 5.8 mmol, 2 eq) and a catalytic amount of 4-dimethylaminopyridine (10 mg). The reaction mixture was stirred for an hour, upon which it was added to iced-water. The product was extracted with dichloromethane (3 x 100 ml) and the combined organic layers dried over magnesium sulfate. Concentration gave an oil, which was purified on silica-gel (20 g) using ethyl acetate / petroleum ether (1 : 1) as eluent to give mesylate **2.101** (0.71 g, 2.6 mmol, 90%).

δ_H ($CDCl_3$, 400 MHz) 2.71 (1H, dd, *J* 17.7, 2.7 Hz, H-5), 2.87 (1H, dd, *J* 17.7, 6.6 Hz, H-5), 2.99 (3H, s, SCH_3) 3.50 (1H, dd, *J* 12.0, 1.5 Hz, H-3), 3.64 (1H, dd, *J* 12.0, 5.4, H-3), 4.87 (2H, s, Bn), 5.27 (1H, m, H-4), 7.20-7.40 (5H, m, Ar);

N-Benzyl-3-pyrrolin-2-one **2.95**[111]



2.95

To a solution of mesylate **2.101** (0.71 g, 2.6 mmol) in dry tetrahydrofuran (20 ml), was added triethylamine (0.72 ml, 5.2 mmol, 2 eq) and the reaction mixture refluxed for 24 h. The reaction mixture was quenched with saturated sodium hydrogen carbonate (20 ml). The product extracted with ethyl acetate (3 x 100 ml) and the extract dried over magnesium sulfate. Concentration gave a residue, which was purified on silica-gel (30 g) to give **2.95** (0.31 g, 1.8 mmol, 70 %).

δ_H ($CDCl_3$, 400 MHz) 3.87 (2H, t, *J* 2.0 Hz, H-5), 4.63 (2H, s, Bn), 6.22 (1H, dt, *J* 6.0, 2.0 Hz, H-3), 7.04 (1H, dt, *J* 6.0, 2.0 Hz, H-4), 7.20-7.40 (5H, m, Ar); δ_C ($CDCl_3$, 100.6 MHz) 46.0 (Bn), 52.3 (C-5), 110.8 (C-3), 127.6, 127.9, 128.0, 128.8 (Ar), 142.8 (C-4), 170 (C-2).

3.3 Crystal structure determination of **2.89** and **2.146**

A single crystal of **2.89** and **2.146** were covered in a small amount of paratone oil and mounted on a glass fibre. X-ray single crystal intensity data were collected on a Nonius Kappa-CCD diffractometer using graphite monochromated MoKα radiation. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). The strategy for the data collections was evaluated using the Bruker Nonius "Collect" program. Data were scaled and reduced using DENZO-SMN software.[130]

Both structures were solved by direct methods and refined employing full-matrix least-squares with the program SHELXL-97[131] refining on F^2. Packing diagrams were produced using the

program PovRay and graphic interface X-seed. All non-H atoms were refined anisotropically. ALL hydrogen atoms except the hydroxyl hydrogens were placed geometrically and were refined using a riding model, with C–H = 0.95 – 1.00 Å and U_{iso} = 1.2 -1.5 x U_{eq}(C). The hydroxyl hydrogens were located in the difference electron density maps and refined with simple bond length constraints. Both structures were refined successfully with R = 0.0415 for **2.89** and R = 0.0472 for **2.146**.

1'*R*, 2'*S*, 3'*S*, 5*S*, 5-[4'-*tert*-butyldiphenylsilyloxy-1-hydroxy-2',3'-bis-methoxymethoxy]-butyl-4-methoxy-1-(4''-methoxybenzyl)-3-pyrrolin-2-one **2.89**

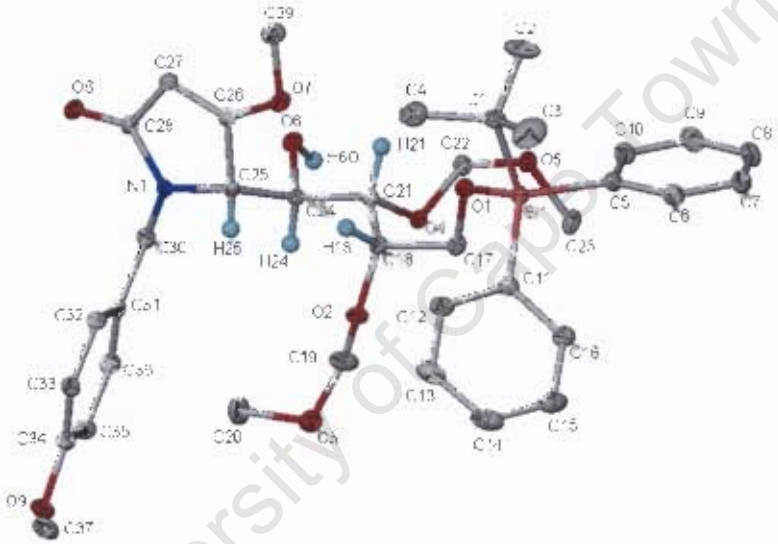


Figure 3.1 X-ray structure of **2.89**

Molecular structure of **2.89** with probability level = 40% showing atomic labels. All hydrogen atoms except the hydroxyl hydrogen H6O and the hydrogens on the chiral centres, e.g. H18, H21, H24 and H25, are omitted for clarity.

Table 3.1. Crystal data and structure refinement for **2.89**.

Empirical formula	C37 H49 N O9 Si
Formula weight	679.86
Temperature	153(2) K

Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 8.20690(10) Å alpha = 90 deg.
	b = 15.76910(10) Å beta = 90 deg.
	c = 27.8258(3) Å gamma = 90 deg.
Volume	3601.09(6) A^3
Z, Calculated density	4, 1.254 Mg/m^3
Absorption coefficient	0.120 mm^{-1}
F(000)	1456
Crystal size	0.30 x 0.20 x 0.20 mm
Theta range for data collection	2.93 to 27.51 deg.
Limiting indices	-10<=h<=10, -20<=k<=20, -35<=l<=36
Reflections collected / unique	8224 / 8224 [R(int) = 0.0000]
Completeness to theta = 27.51	99.1 %
Absorption correction	None
Max. and min. transmission	0.9764 and 0.9650
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8224 / 1 / 445
Goodness-of-fit on F^2	1.051
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.0949
R indices (all data)	R1 = 0.0559, wR2 = 0.1009
Absolute structure parameter	-0.07(10)
Extinction coefficient	0.0146(13)
Largest diff. peak and hole	0.544 and -0.387 $e.A^{-3}$

Table 3.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **2.89**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	4921(1)	3087(1)	1929(1)	25(1)
O(4)	8170(1)	2062(1)	3501(1)	24(1)
O(6)	6465(2)	2162(1)	4375(1)	27(1)
O(5)	7647(2)	963(1)	2963(1)	31(1)
O(1)	5354(2)	2935(1)	2501(1)	29(1)
O(2)	8345(2)	3827(1)	3311(1)	30(1)
O(8)	4214(2)	3689(1)	5427(1)	42(1)
O(7)	3386(2)	3251(1)	3757(1)	30(1)
C(32)	7430(2)	5396(1)	4822(1)	27(1)
O(3)	9556(2)	5133(1)	3286(1)	48(1)
C(25)	5736(2)	3602(1)	4245(1)	22(1)
N(1)	5859(2)	3767(1)	4762(1)	25(1)
C(26)	3940(2)	3411(1)	4199(1)	22(1)
C(21)	6806(2)	2622(1)	3557(1)	21(1)
C(1)	2623(2)	3183(1)	1898(1)	35(1)
C(17)	6983(2)	3024(1)	2677(1)	28(1)
C(30)	7378(2)	3835(1)	5030(1)	28(1)
C(12)	5683(2)	4846(1)	1951(1)	38(1)
C(24)	6855(2)	2878(1)	4089(1)	21(1)
C(36)	9793(2)	4775(1)	5172(1)	30(1)
C(22)	7795(2)	1192(1)	3446(1)	28(1)
C(35)	10592(2)	5544(1)	5150(1)	33(1)
O(9)	10712(2)	6985(1)	4934(1)	40(1)
C(33)	8226(2)	6177(1)	4796(1)	29(1)
C(28)	4415(2)	3638(1)	4986(1)	29(1)
C(11)	5998(2)	4071(1)	1723(1)	28(1)
C(5)	5588(2)	2138(1)	1574(1)	28(1)
C(31)	8197(2)	4687(1)	5000(1)	24(1)
C(10)	5989(2)	1390(1)	1814(1)	34(1)
C(6)	5627(3)	2119(1)	1071(1)	36(1)
C(29)	1652(2)	3085(2)	3729(1)	39(1)
C(27)	3191(2)	3439(1)	4621(1)	28(1)
C(23)	9190(3)	964(2)	2725(1)	39(1)
C(18)	6923(2)	3343(1)	3195(1)	23(1)
C(9)	6411(3)	661(1)	1568(1)	44(1)
C(34)	9812(2)	6247(1)	4955(1)	29(1)
C(37)	10154(3)	7608(1)	4600(1)	46(1)
C(19)	8352(3)	4648(1)	3091(1)	45(1)
C(8)	6466(3)	664(2)	1075(1)	46(1)

C(7)	6067(3)	1395(2)	823(1)	44(1)
C(16)	7131(3)	4090(1)	1345(1)	37(1)
C(15)	7876(3)	4838(2)	1204(1)	48(1)
C(20)	9221(4)	5405(2)	3760(1)	53(1)
C(14)	7524(3)	5581(2)	1427(1)	49(1)
C(3)	2140(3)	3558(2)	1409(1)	70(1)
C(13)	6430(3)	5594(1)	1805(1)	48(1)
C(4)	1979(3)	3760(2)	2294(1)	57(1)
C(2)	1867(3)	2308(2)	1956(1)	73(1)

Table 3.3 Selected bond lengths for **2.89**

Bonds	Length (Å)	Bonds	Length (Å)
Si(1)-C(5)	1.8756(19)	O(4)-C(22)	1.415(2)
O(4)-C(21)	1.434(2)	C(21)-C(24)	1.533(2)
C(21)-H(21)	1.0000	C(21)-C(18)	1.521(2)
N(1)-C(28)	1.354(2)	N(1)-C(30)	1.457(2)
C(25)-N(1)	1.466(2)	C(25)-H(25)	1.0000
C(25)-C(24)	1.529(2)	O(6)-C(24)	1.418(2)
O(6)-H(6O)	0.9798(10)	C(24)-H(24)	1.0000
O(2)-C(19)	1.432(2)	O(8)-C(28)	1.242(2)
O(7)-C(26)	1.336(2)	C(32)-C(31)	1.375(3)

Table 3.4 Selected torsion angles fo **2.89**

Bonds	Angle(°)	Bonds	Angle(°)
O(1)-Si(1)-C(5)	109.27(8)	C(24)-C(25)-H(25)	109.9
C(28)-N(1)-C(30)	121.60(14)	C(28)-N(1)-C(25)	111.38(15)
C(30)-N(1)-C(25)	125.13(14)	O (4)-C(21)-C(24)	104.23(13)
C(18)-C(21)-C(24)	116.11(14)	C(24)-C(21)-H(21)	108.8
N(1)-C(30)-C(31)	114.77(15)	O(6)-C(24)-C(21)	109.04(13)
C(25)-C(24)-C(21)	117.05(14)	O(6)-C(24)-H(24)	107.6
C(25)-C(24)-H(24)	107.6	C(21)-C(24)-H(24)	107.6

C(21)-C(18)-C(17)	112.39(15)	C(21)-C(18)-H(18)	108.6
C(17)-C(18)-H(18)	108.6	C(32)-C(31)-C(30)	122.83(16)
C(18)-O(2)-C(19)	112.95(14)	C(19)-O(3)-C(20)	113.57(19)
N(1)-C(25)-C(26)	100.67(13)	N(1)-C(25)-C(24)	111.71(14)

1'*R*, 2'*S*, 3'*S*, 5*S*, 2-[1'-*tert*-Butyloxycarbonyloxy-4'-hydroxy-2',3'-bis-methoxymethoxy]-butyl-3,3-dimethoxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester **2.146.**

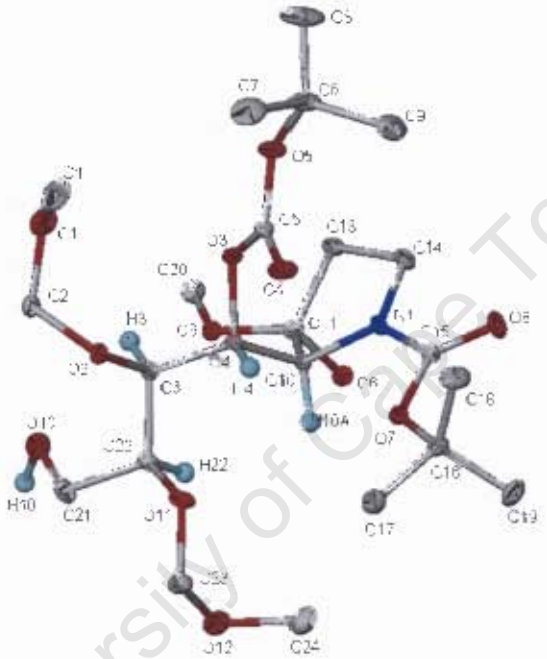


Figure 3.2 X-ray structure of 2.146

Molecular structure of **2.146** with probability level = 30% showing atomic labels. All hydrogen atoms except the hydroxyl hydrogen H10 and the hydrogens on the chiral centres, e.g. H3, H4, H10A and H22, are omitted for clarity.

Table 3.5 Crystal data and structure refinement for **2.146**

Empirical formula	C24 H45 N O12
Formula weight	539.61
Temperature	113(2) K
Wavelength	0.71073 Å

Crystal system, space group	Orthorhombic, P212121
Unit cell dimensions	a = 10.18130(10)Å alpha = 90 deg. b = 14.2352(2) Å beta = 90 deg. c = 19.8503(3) Å gamma = 90 deg.
Volume	2876.96(7) $Å^3$
Z, Calculated density	4, 1.246 Mg/m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	1168
Crystal size	0.32 x 0.25 x 0.22 mm
Theta range for data collection	3.49 to 25.67 deg.
Limiting indices	-12<=h<=12, -17<=k<=17, -24<=l<=24
Reflections collected / unique	5453 / 5453 [R(int) = 0.0000]
Completeness to theta = 25.67	99.5 %
Max. and min. transmission	0.9785 and 0.9689
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5453 / 1 / 349
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1270
R indices (all data)	R1 = 0.0527, wR2 = 0.1316
Absolute structure parameter	-0.1(9)
Extinction coefficient	0.0070(16)
Largest diff. peak and hole	1.360 and -0.333 e.$Å^{-3}$

Table 3.6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **2.146**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2236(2)	451(2)	2487(1)	46(1)
O(2)	3895(2)	-690(1)	2291(1)	21(1)
O(3)	4985(2)	499(1)	3277(1)	20(1)
O(4)	4836(2)	-644(1)	4071(1)	30(1)
O(5)	4176(2)	858(1)	4243(1)	30(1)
O(6)	8762(2)	1409(1)	2377(1)	25(1)
O(7)	7973(2)	-1071(1)	3720(1)	23(1)
O(8)	8646(2)	-16(1)	4513(1)	38(1)
O(9)	6598(2)	1422(1)	2002(1)	21(1)
O(10)	5094(2)	-7(2)	753(1)	41(1)
O(11)	6221(2)	-1673(1)	2046(1)	28(1)
O(12)	8094(2)	-2103(2)	1408(1)	41(1)
N(1)	7659(2)	455(1)	3555(1)	22(1)
C(1)	1609(3)	-19(3)	3043(2)	60(1)
C(2)	2791(2)	-207(2)	2044(1)	27(1)
C(3)	5129(2)	-220(2)	2180(1)	19(1)
C(4)	5791(2)	-108(2)	2865(1)	18(1)
C(5)	4676(2)	151(2)	3891(1)	21(1)
C(6)	3696(3)	675(2)	4940(1)	37(1)
C(7)	2612(4)	-48(3)	4923(2)	53(1)
C(8)	3190(5)	1637(2)	5142(2)	62(1)
C(9)	4838(4)	386(3)	5377(1)	54(1)
C(10)	7192(2)	303(2)	2862(1)	18(1)
C(11)	7416(2)	1300(2)	2557(1)	21(1)
C(12)	9185(3)	873(2)	1804(1)	29(1)
C(13)	7197(3)	1966(2)	3143(1)	25(1)
C(14)	7800(3)	1450(2)	3740(1)	28(1)
C(15)	8140(2)	-212(2)	3974(1)	24(1)
C(16)	8199(2)	-1914(2)	4141(1)	25(1)
C(17)	7635(3)	-2690(2)	3702(2)	34(1)
C(18)	7443(3)	-1849(2)	4798(1)	40(1)
C(19)	9657(3)	-2043(2)	4252(2)	42(1)
C(20)	6552(3)	2351(2)	1730(1)	29(1)
C(21)	5328(3)	-917(2)	1017(1)	33(1)
C(22)	5975(3)	-805(2)	1704(1)	23(1)
C(23)	6877(3)	-2372(2)	1680(1)	33(1)
C(24)	9102(3)	-2057(2)	1905(2)	44(1)

Table 3.7 Selected Bond lengths for **2.146**

Bond	Length (Å)	Bond	Length (Å)
O(8)-C(15)	1.219(3)	N(1)-C(15)	1.354(3)
N(1)-C(14)	1.470(3)	N(1)-C(10)	1.470(3)
C(4)-C(10)	1.542(3)	C(4)-H(4)	1.0000
C(3)-C(4)	1.525(3)	C(3)-C(22)	1.526(3)
C(3)-H(3)	1.0000	C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800	C(1)-H(1C)	0.9800
C(14)-H(14A)	0.9900	C(14)-H(14B)	0.9900
C(10)-C(11)	1.560(3)	C(10)-H(10A)	1.0000
C(21)-C(22)	1.522(3)	C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900	C(22)-H(22)	1.0000

Table 3.8 Selected torsion angles for **2.146**

Bond	Angle(°)	Bond	Angle (°)
C (5)-O(3)-C(4)	115.03(17)	C(5)-O(5)-C(6)	118.89(19)
C(15)-N(1)-C(14)	119.12(19)	C(15)-N(1)-C(10)	126.06(19)
C(14)-N(1)-C(10)	113.98(18)	O(2)-C(3)-C(4)	107.33(17)
O(2)-C(3)-C(22)	109.50(18)	C(4)-C(3)-C(22)	111.13(19)
O(2)-C(3)-H(3)	109.6	C(4)-C(3)-H(3)	109.6
C(22)-C(3)-H(3)	109.6	O(3)-C(4)-C(3)	108.43(17)
O(3)-C(4)-C(10)	107.53(17)	C(3)-C(4)-C(10)	116.47(18)
O(3)-C(4)-H(4)	108.0	C(3)-C(4)-H(4)	108.0
C(10)-C(4)-H(4)	108.0	O(4)-C(5)-O(5)	127.6(2)
O(4)-C(5)-O(3)	125.7(2)	O(5)-C(5)-O(3)	106.66(19)
O(2)-C(3)-C(4)	107.33(17)	O(2)-C(3)-C(22)	109.50(18)
C(4)-C(3)-C(22)	111.13(19)	O(2)-C(3)-H(3)	109.6
C(4)-C(3)-H(3)	109.6	C(22)-C(3)-H(3)	109.6

O(3)-C(4)-C(3)	108.43(17)	O(3)-C(4)-C(10)	107.53(17)
C(3)-C(4)-C(10)	116.47(18)	O(3)-C(4)-H(4)	108.0
C(3)-C(4)-H(4)	108.0	C(10)-C(4)-H(4)	108.0
O(4)-C(5)-O(5)	127.6(2)	O(4)-C(5)-O(3)	125.7(2)
O(5)-C(5)-O(3)	106.66(19)	N(1)-C(14)-C(13)	103.40(18)
N(1)-C(14)-H(14A)	111.1	C(13)-C(14)-H(14A)	111.1
N(1)-C(14)-H(14B)	111.1	C(13)-C(14)-H(14B)	111.1
O(8)-C(15)-O(7)	126.6(2)	O(8)-C(15)-N(1)	122.1(2)
O(7)-C(15)-N(1)	111.30(19)	C(21)-O(10)-H(10)	110(2)
C(23)-O(11)-C(22)	116.77(19)		

Chapter 4: References

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