STEREOSELECTIVE SYNTHESIS: STUDIES INVOLVING DIPOLE-STABILIZED CARBANIONS α TO NITROGEN

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For my girls

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ABSTRACT

Organolithiums are key reagents and intermediates in organic synthesis. An exciting and growing field is the use of organolithiums in enantioselective synthesis. The often complex nature of these compounds makes their implementation towards the synthesis of natural products or pharmaceutical targets a challenging yet rewarding endeavour. The ability of organolithiums to form carbon-carbon bonds in a stereoselective and predictable way is vital to their success in organic synthesis.

The first chapter in this thesis summarizes the current mechanistic understanding of asymmetric carbon-carbon bond formation adjacent to nitrogen. A brief literature review is presented to illustrate the different ways in which a stereoselective lithiation/substitution reaction at carbon can occur. A review of the application of dipole-stabilized carbanions α to nitrogen used in the stereoselective synthesis of natural products is presented.

The second chapter in this thesis describes a study of the use of *N*-Boc-3-pyrroline, and related compounds, as molecular scaffolds for the stereoselective synthesis of functionalized five-membered ring containing alkaloids. The asymmetric alkylation of *N*-Boc-3-pyrroline is possible for simple alkyl halides but only modest enantioselectivity can be obtained using chiral lithium amides or s-butyl lithium/(-)-sparteine as bases. More promising was the enantioselective alkylation of a protected 3-pyrroline building block **116**. The assignment for the stereochemistry of the alkylated product from **116** and benzaldehyde was achieved by NMR techniques and conformational analysis. The work done on the synthesis of enantiomerically pure castanospermine analogs is also presented.

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LIST OF ABBREVIATIONS

AcOEt	ethyl acetate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Cbx	4,4-dimethyl-2,2-cyclohexyl-1,3-oxazolidine-3-carbonyl (IUPAC: 4-aza-4-carbonyl-3,3-dimethyl-1-oxa-spiro[4.5]decane)
Cby	2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl
CI	chemical ionization
COSY	correlated spectroscopy
CSR	chiral shift reagent
δ	chemical shift
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DFC	dry flash column
DIBAL	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance Fourier transform infrared
ee	enantiomeric excess
EI	electron impact ionization
er	enantiomeric ratio
ES	electrospray
Et	ethyl
$Eu(hfc)_3$	europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]
$Eu(tfc)_3$	europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]
FTIR	Fourier transform infrared

GC	gas chromatography
h	hour(s)
hh	hexahydro
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
ipr	internal proton return
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Me	methyl
min	minute(s)
MS	mass spectrometry
MTBE	*tert*-butyl methyl ether
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
op	optical purity
Ph	phenyl
ppm	parts per million
PTLC	preparative thin layer chromatography
pyr	pyridine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*,-tetramethylethylenediamine
TMS	trimethylsilyl or tertramethylsilane
TOF	time of flight
TS	transition state

CHAPTER 1: INTRODUCTION

The attention given to asymmetric synthesis in organic chemistry has grown exponentially in the last century. The necessity for synthesis of enantiomerically pure compounds (EPC) has largely been due to the study of the interaction of organic molecules with biological systems. A search of the primary literature, albeit a non-comprehensive search, shows that accounts of asymmetric synthesis were only a handful a year up until the 1960's (Figure 1, A). The development of modern synthetic methodology has given way to thousands of such accounts every year. However, development of stereoselective deprotonation of C-H acids has generated less attention (Figure 1, B). It has been speculated that this hole in the literature has been due to a view that useful stereoselective syntheses are limited to reactions that produce or retain a sp^3-hybridized carbon atom.[1] Hodgson and Stent have recently summarized the current state of knowledge of organolithium-ligand combinations and lithium amides as used in asymmetric synthesis.[2] In 2002, Basu and Thayumanavan described the three conditions that can give rise to a stereoselective deprotonation reaction.[3] Stereoselectivity will only occur if: a) an asymmetric deprotonation gives a configurationally stable carbanion; b) a dynamic kinetic resolution occurs between a configurationally unstable lithium carbanion and the reacting electrophile; or c) a dynamic thermodynamic resolution occurs between a temperature dependent configurationally stable carbanion and the electrophile. An examination of these three possible mechanistic pathways, as they pertain to enantioselective synthesis by means of dipole-stabilized carbanions proximal to nitrogen and electrophilic incorporation, will be presented. Additionally, a look at the application of these techniques based on these observations will also be discussed.

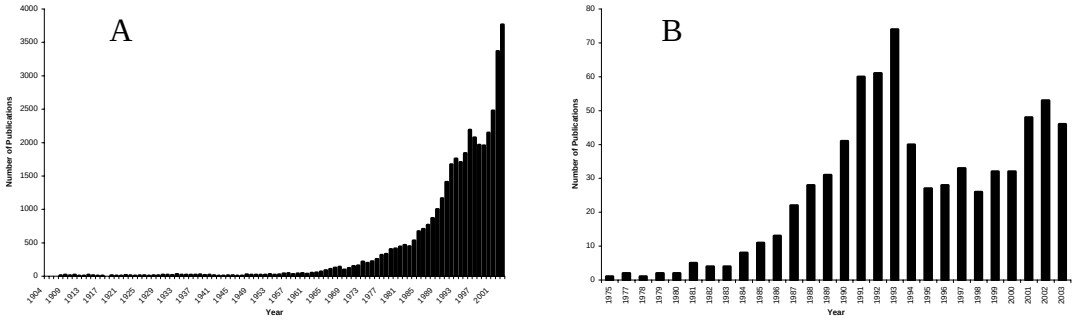
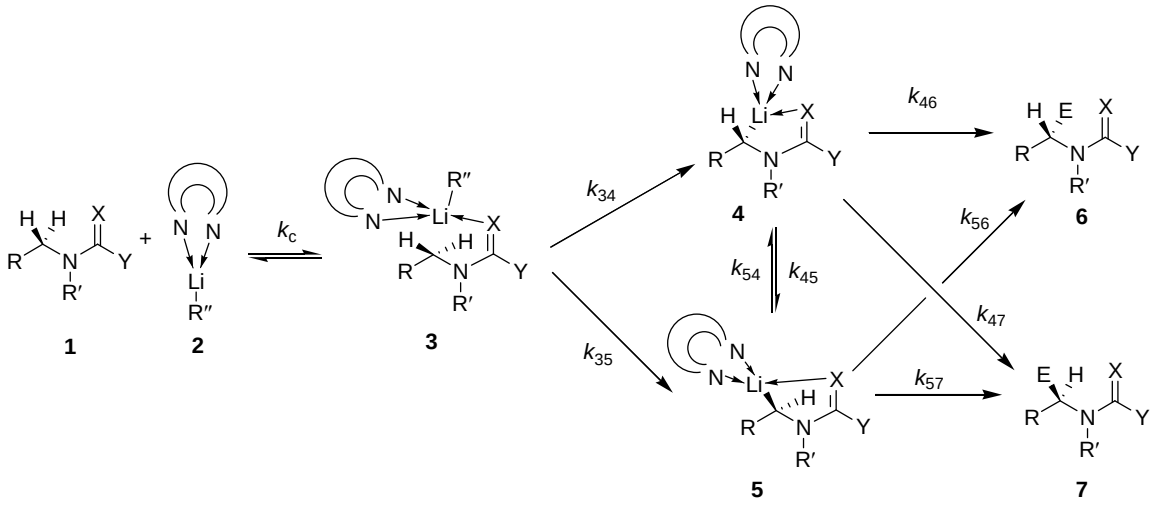


Figure 1. Histograms of the number of publications involving A) asymmetric synthesis during the last century and B) deprotonation reactions as a subset of A. (Data collected using SciFinder®).

A substrate of general structure **1** can be deprotonated, using an alkyllithium base in the presence of a tertiary amine (**2**), to give lithiated intermediates **4** and **5** (Scheme 1). The carbon-lithium bond is drawn as a covalent bond even though, according to some authors, it has a significant ionic character.[4] The bonding is typically presented this way because the carbanion has tetrahedral geometry and it facilitates discussion of stereochemistry. It is also important to realize that the aggregation state, and therefore the reactivity, of **3** are strongly influenced by temperature, solvent, salinity, and the structures of the alkyllithium and ligand.[5] If compound **1** is achiral, the two hydrogen groups in the prelithiation complex **3** are enantiotopic. When an achiral chelating amine (or other suitable ligand) is used, structures **4** and **5** are enantiomers. However, when a chiral ligand is used, structures **4** and **5** are diastereomers and can be formed at different rates (i.e. $k_{34} \neq k_{35}$). Furthermore, intermediates **4** and **5** can interconvert, depending on the configurational stability of the organolithium species. On addition of an electrophile (E^+), **4** will give **6,** and **5** will give **7,** if the electrophile attaches itself with retention of configuration. However, **4** will give **7,** and **5** will give **6**, if the electrophile adds with inversion of configuration. Since **6** and **7** are enantiomers when starting with achiral **1**, all these factors must be considered in an asymmetric synthesis of this nature. A successful stereoselective synthesis of **6** or **7** will have only one of these possible reaction paths dominating. It is also possible to synthesize **6** or **7** stereoselectively by employing groups R, R', or Y as chiral auxiliaries.[6, 7] Given a new substrate of general

structure **1**, can a chemist predict the stereochemical outcome of the deprotonation/substitution reaction?

Scheme 1

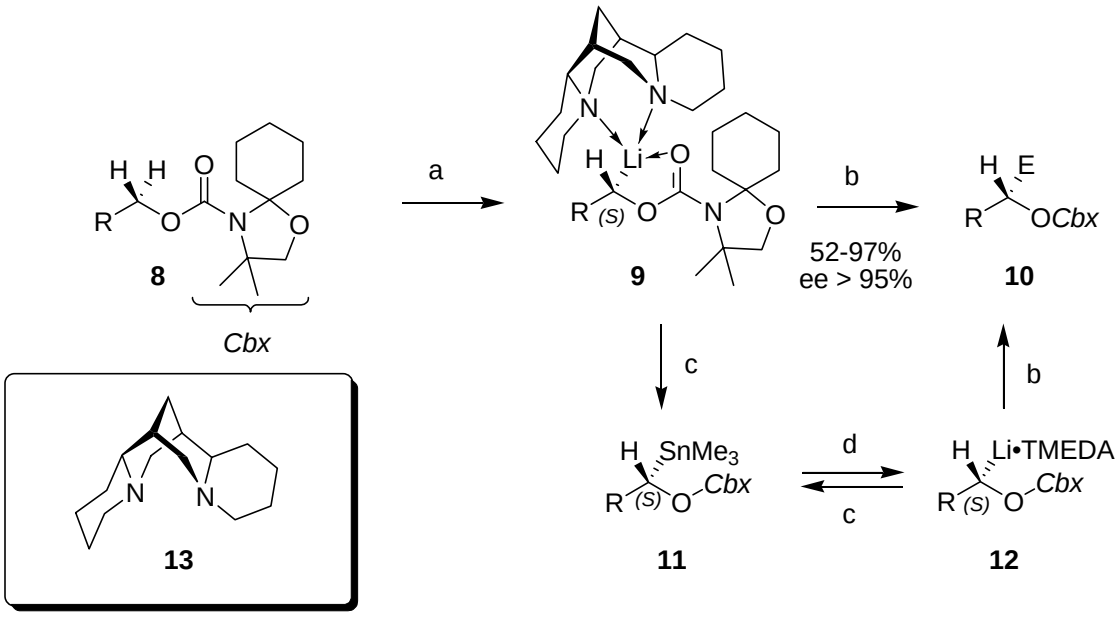


1.1 Asymmetric deprotonation by (-)-sparteine/alkyllithium

(-)-Sparteine **13** was first shown to induce modest stereoselectivity, in the asymmetric addition of alkyllithium and Grignard reagents to carbonyl groups, by Noyori in 1971.[8] In 1990, Hoppe published his seminal paper on asymmetric deprotonation of carbamates using sBuLi and sparteine.[9] This was the first account of a non-racemic organolithium of type **9** being formed by direct deprotonation where the R group was not a typical carbanion-stabilizing group (i.e. a group capable of allylic stabilization). Intermediate **9** was coupled with a few simple electrophiles in very high stereoselectivity (ee > 95%). It was known at that time that chiral stannanes of type **11** (the group attached to the oxygen need not be an oxazolidine-carbamate group) give configurationally stable organolithiums on transmetalation and react with electrophiles with retention of configuration.[10] The reaction sequence of **9** to **11** to **12** to **10** (E^+ = CO_2) gave the same configuration for **10** as did direct carbonylation of **9**. Furthermore, stannylation of **12** back to **11** occurred with retention of configuration. Removal of the Cbx group from **10**, where R = $(CH_2)_5CH_3$ and E^+ = CH_3I, gave (+)-(*S*)-2-octanol, thus

establishing the (*S*)-assignment for intermediate **9**. Therefore, compound **8** underwent an enantioselective deprotonation to give the configurationally stable "carbanion" intermediate. The potential utility of this new methodology comes from the ability to form a new carbon-carbon bond stereoselectively at a classically "unfunctionalized" site. The limitation that only the (-)-natural form of sparteine was available has been overcome recently, given way to the development of readily-accessible (+)-sparteine surrogates.[11, 12]

Scheme 2

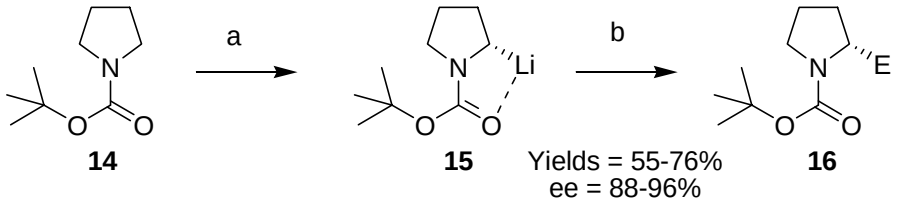


a) sBuLi / **13**, Et_2O, -78°C. b) E^+. c) $SnMe_3Cl$. d) nBuLi, TMEDA.

In 1991, Beak applied Hoppe's sBuLi/sparteine method to the enantioselective synthesis of 2-substituted *N*-Boc pyrrolidines **16** (Scheme 3).[13] Chemical yields of 55-76% and enantiomeric excesses (ee) of 88-96% were observed. Two possible mechanisms were considered to explain the high stereoselectivity: (i) an enantioselective deprotonation of **14**, $k_{34} \neq k_{35}$ (referring to Scheme 1), gave a configurationally stable intermediate which reacted exclusively with either retention or inversion during the electrophilic substitution (Figure 2) or (ii) complexation between racemic-**15** and sparteine (**13**) was lowering the energy of one of the two possible diastereomeric

transition state structures (TS_2; TS_3) on substitution. (There are actually four diastereomeric TS structures without assuming a stereoselective substitution mechanism.)

Scheme 3



a) sBuLi / **13**, Et_2O, -78°C. b) E^+.

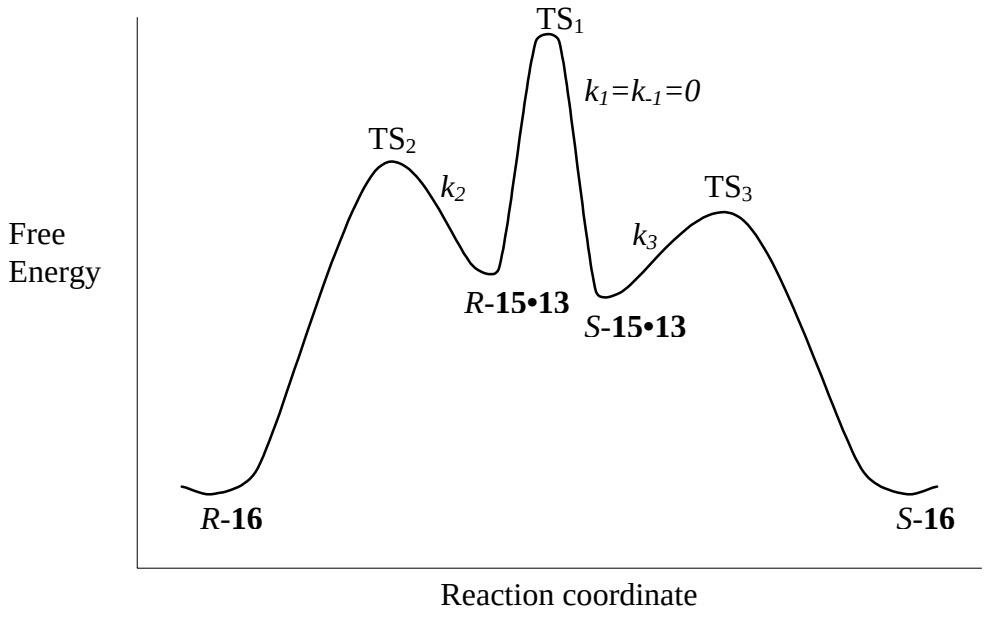
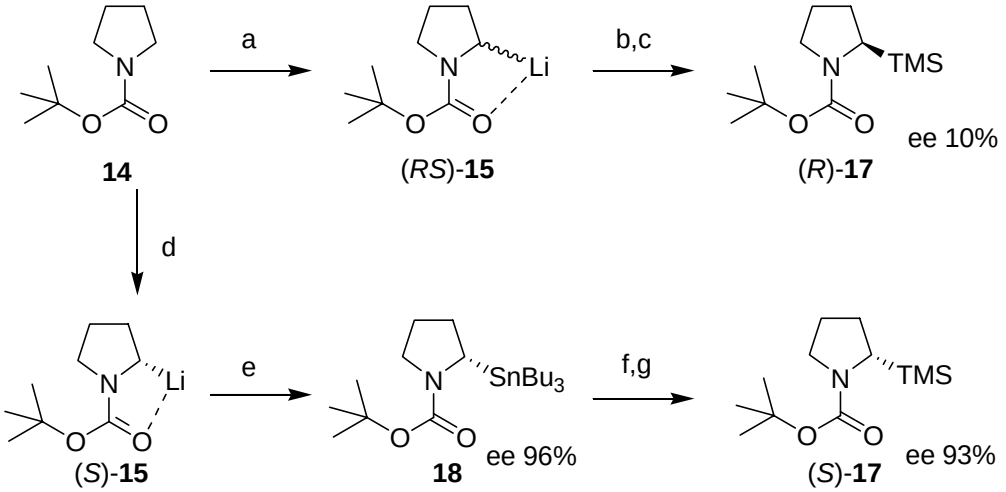


Figure 2. Qualitative free energy diagram representing asymmetric deprotonation /substitution of **14**.

In order to distinguish between the two possible mechanistic pathways, Beak performed the following experiments (Scheme 4):[14, 15] Reaction of sBuLi with excess **14** gave racemic **15**. Addition of TMSCl to (*R*,*S*)-**15**, followed by sparteine **13** gave **17** with a slight excess of the opposite enantiomer (ee 10%). Here an enantioselective

substitution was occurring with inversion of configuration. Alternatively, (*RS*)-**15** was generated by tin-lithium exchange of racemic **18** and reacted with TMSCl and **13**. The ee for this reaction was only 3% favouring the *S*-configuration. Chiral stannane **18** (ee 96%) underwent lithiodestannylation followed by substitution with TMSCl and the resulting product had retained its stereochemical information (ee 93%). Beak concluded that the enantio-determining step was the stereoselective deprotonation of **14** to give a configurationally stable organolithium intermediate and electrophilic substitution occurred with retention of configuration. Since the energy barrier for the conversion of *S*-**15** to *R*-**15** is large, the ratio *S*-**17** : *R*-**17** (enantiomeric ratio) will be determined by the diastereomeric ratio *S*-**15•13** : *R*-**15•13** (Figure 2).

Scheme 4



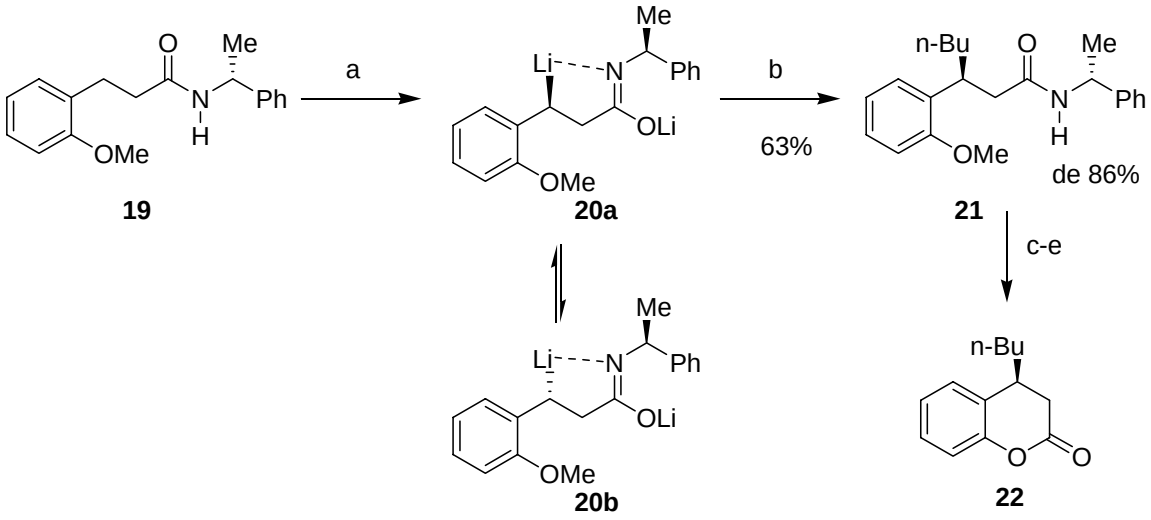
a) sBuLi, Et_2O, -78°C. b) TMSCl. c) (-)-sparteine **13**. d) sBuLi / **13**, Et_2O, -78°C. e) $SnBu_3Cl$. f) sBuLi. g) TMSCl.

1.2 Dynamic kinetic resolution

In Basu and Thayumanavan's 2002 review, the second mechanistic pathway presented that will result in a stereoselective lithiation/substitution reaction is a dynamic kinetic resolution.[3] This pathway closely parallels the classical Curtin-Hammett principle that the product distribution from conformational isomers is not simply

proportional to the conformer distribution ratio.[16] As an illustrative example, consider the stereoselective lithiation/substitution of **19** to give **21** (Scheme 5).[17] Optically pure amide **19** was treated with 2.2 equivalents sBuLi in the presence of TMEDA. Alkylation of **20** with nBuBr gave a 93:7 ratio of diastereomers. A dynamic kinetic resolution will be the dominant pathway as dilithiated intermediate **20** is not configurationally stable and undergoes rapid equilibrium (Figure 3). Tin-lithium exchange experiments and parallel reactions at different temperature were used to establish that **20** was configurationally labile. The observed stereoselectivity was due to the differences in energy between the two diastereomeric transition states ($\Delta\Delta G^{\ddagger}$). The stereoselective methodology was used to prepare enantiomerically pure (*S*)-4-butyldihydrocoumarin **22**.

Scheme 5



19 **20a** **20b** **21** **22**

a) sBuLi / TMEDA, EtO_2, -78°C. b) n-BuBr, -78°C → -10°C, dr = 93:7. c) PrepHPLC, dr > 99:1.
d) BBr_3, CH_2Cl_2. e) 15% HCl.

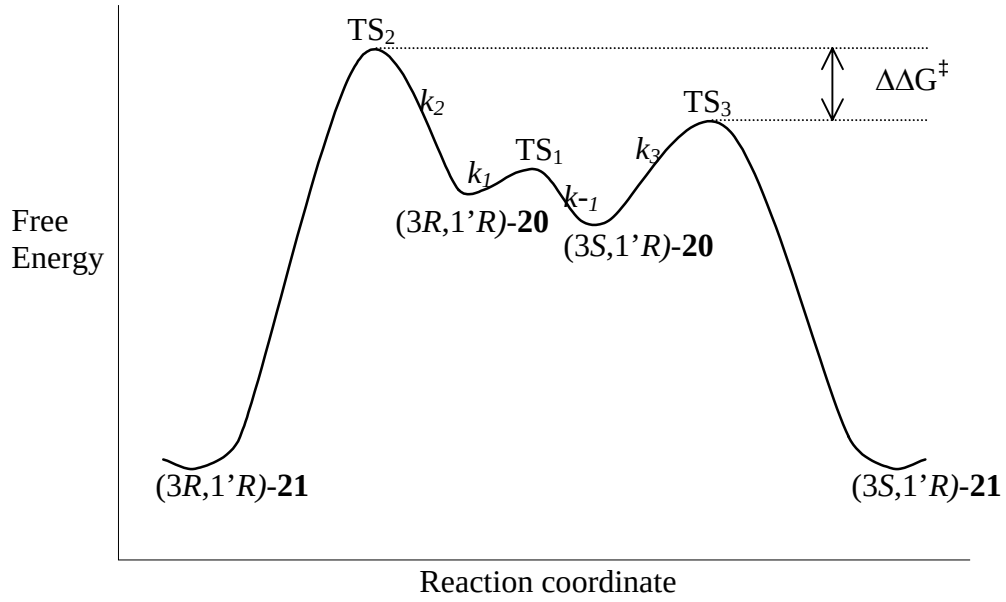


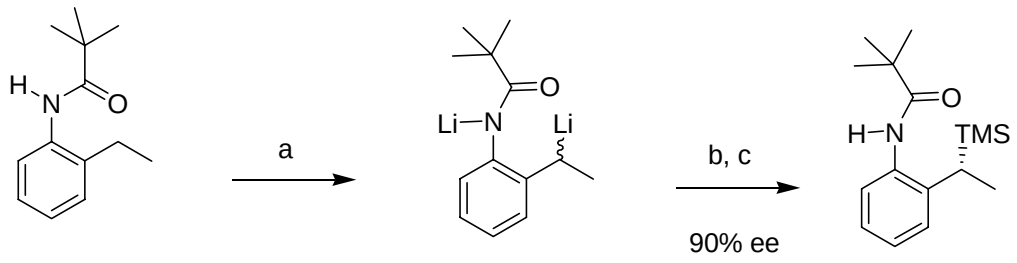
Figure 3. Qualitative free energy diagram representing dynamic kinetic resolution of **20**.

1.3 Dynamic thermodynamic resolution

In 2000, Beak *et al.* published an account of (and coined the term) dynamic thermodynamic resolution as a way of obtaining highly enantioenriched products.[18] As a prototypical example of a dynamic thermodynamic resolution they presented the silylation of *N*-pivaloylethylaniline **22** (Scheme 6). In 1996, Beak reported that the enantioselectivity of this reaction could be improved by allowing diastereomeric complex **23•13** to reach thermodynamic equilibrium at –25 °C followed by cooling the reaction to –78 °C before adding the electrophile.[19] Adding (-)-sparteine **13** and TMSCl to **23**, at –78 ºC, gave (*R*)-**24** in 52% yield and 21% ee, whereas, adding **13** to **23**, at –25 ºC (45 min), then cooling the reaction to –78 ºC gave (*R*)-**24** in 72% yield and 90% ee. At the higher temperature the population of the thermodynamically more stable (*R*)-**23•13** diastereomeric complex increased (Figure 4). Lowering the temperature to –78 °C resulted in lithiated intermediates that were configurationally stable on the time scale of the substitution reaction. As a result, highly enantioenriched substitution products were obtained by employing a warm-cool protocol to the formation of an organolithium/sparteine complex. Exploiting the dynamic kinetic resolution mechanism increased the stereoselectivity of this reaction further.[20] Compound **23** was stirred with

13 at –25 °C (45 min), cooled to –78 °C and reacted with 0.45 equivalents TMSCl. The reaction mixture was then warmed to –25 °C for another 45 min to re-populate the (*R*)-**23•13** complex. After cooling the reaction back to –78 °C and adding another 0.45 equivalents TMSCl, the final product **24** was obtained in 94% ee. Understanding the configurational stability of particular carbanion reactive intermediate is very important to obtaining highly stereoselective reactions.

Scheme 6



22 **23** **24**

a) sBuLi, MTBE, -25°C, 2h. b) sparteine, 45 min. c) -78°C then TMSCl, 30min.

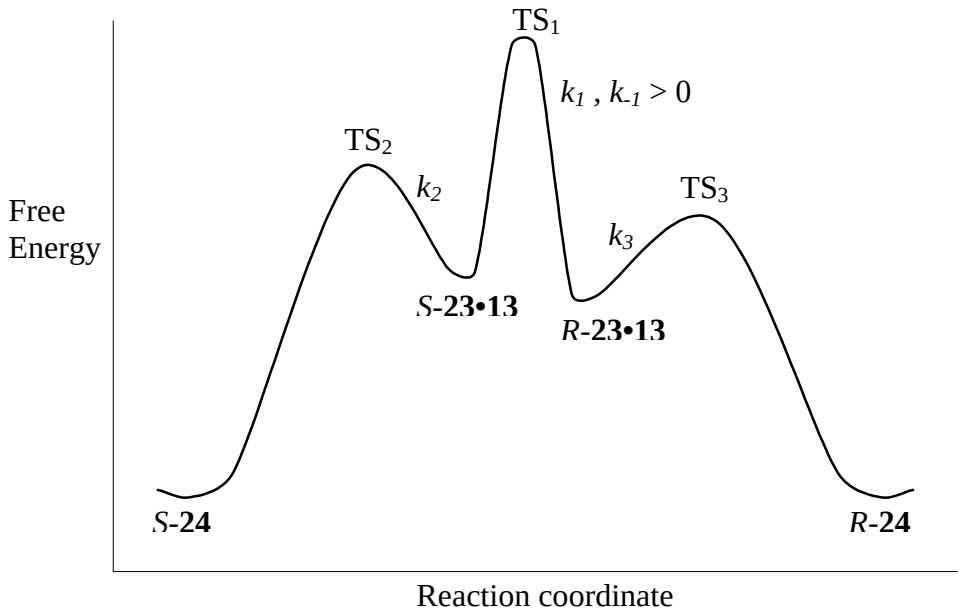
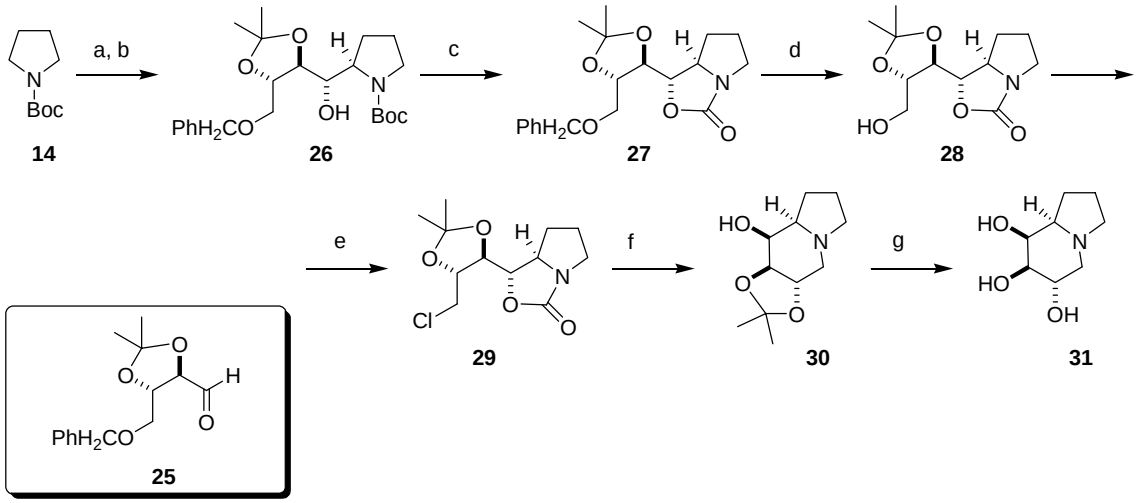


Figure 4. Qualitative free energy diagram representing dynamic thermodynamic resolution of **23**.

1.4 Applications of stereoselective deprotonation α to nitrogen

Many of the publications in the literature involving stereoselective reactions α- to or proximal to nitrogen are focused on developing synthetic methodology and theory. There are many fewer examples where this reaction was applied to the synthesis of targeted compounds. Our synthesis of analogs of the alkaloid castanospermine (compound **31**) is one of the few such examples (Scheme 7).[21] The key step in the synthesis was the coupling of lithiated *N*-Boc-pyrrolidine **14** to the tartaric acid-derived chiral building block **25**. Further discussion about this synthesis will be presented in the results and discussion section of this thesis.

Scheme 7

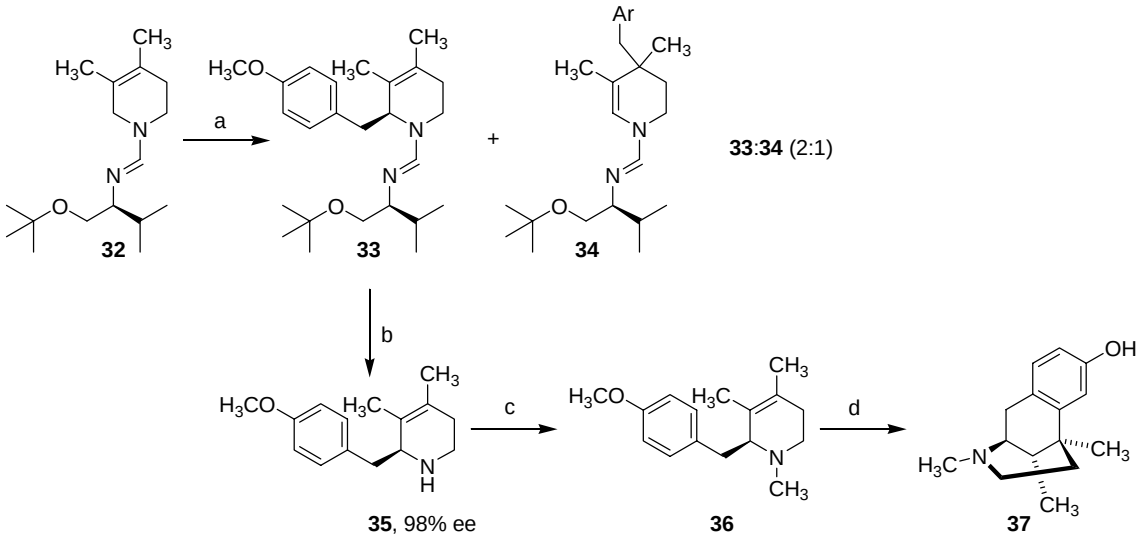


a) sBuLi / **13**, Et_2O, -78°C. b) **25** c) NaH, THF. d) H_2, Pd/C e) Ph_3P, CCl_4, K_2CO_3. f) NaOH, MeOH. g) TFA.

Meyers synthesized three natural products in the mid to late 1980's using methods in which a key step involved a stereoselective C-C bond formation α to a nitrogen atom. In 1985, his group reported the asymmetric synthesis of (+)-metazocine, a potent analgesic (Scheme 8).[6] Piperidine **32** was constructed, from 3,4-lutidine, to include the chiral formamidine auxiliary derived from L-valinol. Treatment of **32** with nBuLi, in THF at –78 °C, followed by 3 equivalents of *p*-methoxybenzyl chloride gave the α- and γ-alkylation products in a 2:1 ratio. Chromatographic separation of **33** from

its regio-isomer, followed by removal of the chiral auxiliary, gave amine **35** (96% ee) in 44% yield from **32**. Amine **35** was methylated by addition of ethylformate (40 °C, 12h) followed by lithium aluminium hydride reduction of the formamide. Cyclization and phenol deprotection of **36** gave (+)-metacozine **37**. It is interesting to note that Meyers reported that saturated piperidines and pyrrolidines, containing the valinol-derived auxiliary, could not be lithiated α to the nitrogen atom. Meyers extended this methodology to the asymmetric synthesis of (+)-morphinans in 1986 and (+)-anisomycin in 1987.[7, 22] Meyers' work is an example of asymmetric alkylation reactions and differ somewhat from Hoppe and Beak's stereoselective deprotonation methodology. In the sBuLi/sparteine deprotonation reaction the base is chiral and is therefore the species that induces stereoselectivity.

Scheme 8

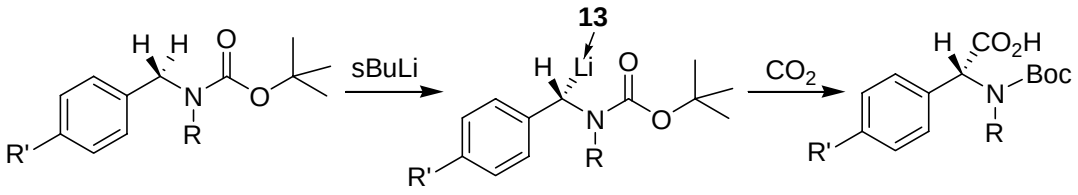


a) nBuLi, *p*-$MeOC_6H_5CH_2Cl$, -78 °C, THF. b) N_2H_4, HOAc, EtOH, 50 °C. c)EtO_2CH, $LiAlH_4$. d) 48% HBr, 135 °C.

As part of a program to develop unnatural amino acids for peptide synthesis, Voyer was the first to apply Beak's stereoselective deprotonation methodology to the synthesis of a target molecule. In 1995, Voyer reported the asymmetric synthesis of *N*-Boc-phenylsarcosine (Scheme 9).[23] Treatment of *N*,*N*,*N*-Boc-methylbenzylamine **38a** with sBuLi/(-)-sparteine **13**, followed by carboxylation, gave (-)-(*R*)-*N*,*N*-Boc-methyl phenylglycine **40a** in 55% yield and 78% ee when hexanes was the solvent. Lower

stereoselectivity (60% ee) was observed by switching to diethyl ether. In 1997, Voyer extended the methodology to the enantioselective synthesis of phenylglycines.[24] Reacting **38b** directly with sBuLi/**13** resulted in a racemic **40b** when trapped with CO_2. By protecting the nitrogen with a trimethylsilyl group, phenylglycines of type (*R*)-**40b** were obtained with moderate to high enantioselectivity (40-96% ee). Voyer continued to refine and perfect his phenylglycine synthesis in 1999 and 2001.[25]

Scheme 9



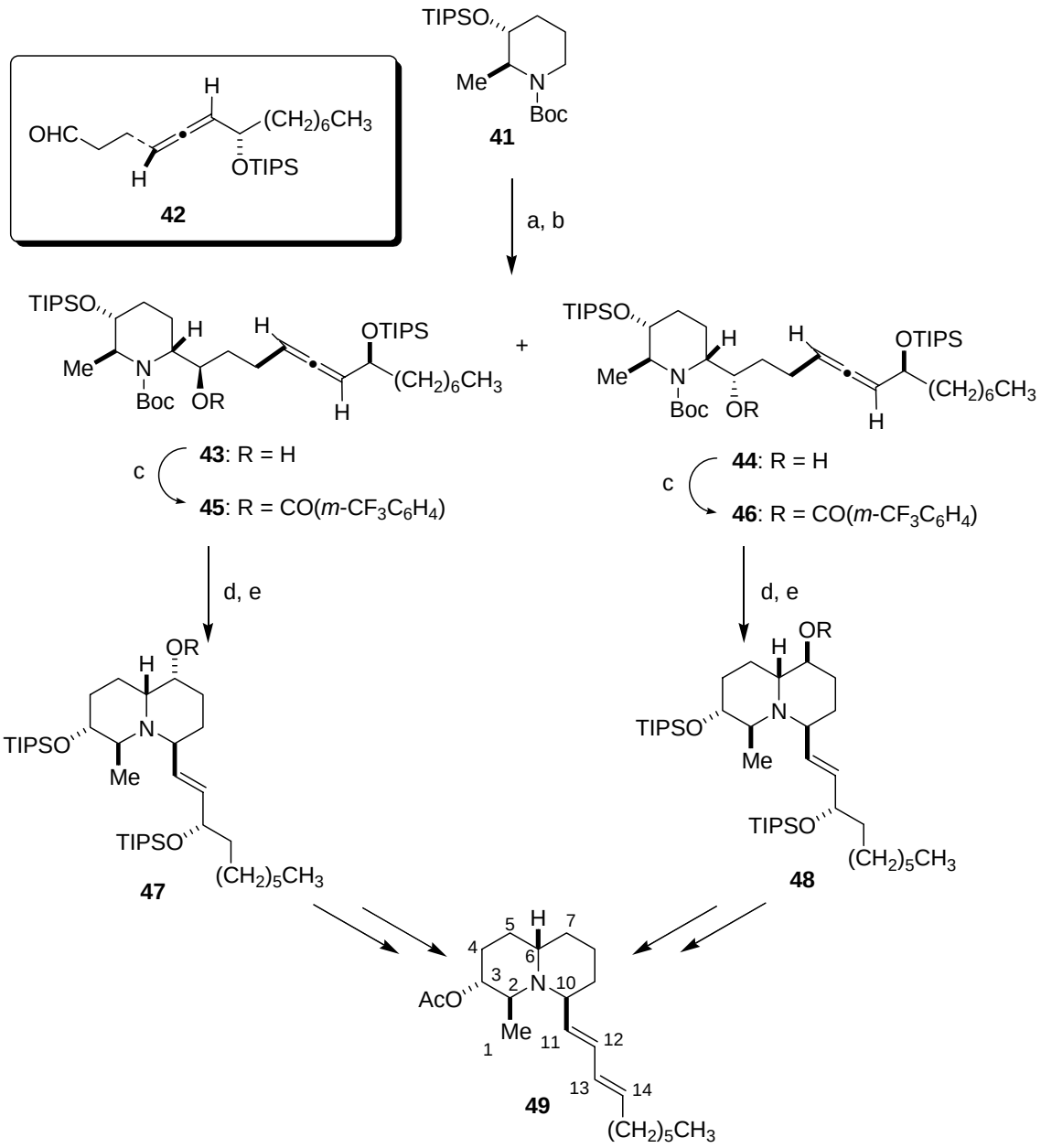
38a, R = Me
b, R = H
c, R = TMS

39a, R = Me
b, R = Li
c, R = TMS

40a, R = Me
b, R = H
c, R = TMS

In 1999, Cha utilized Beak's α-lithiation of *N*-Boc piperidines in the synthesis of quinolizidine alkaloid clavepictine A **49** (Scheme 10).[26] Piperidine **41** was lithiated with sBuLi/TMEDA and coupled aldehyde **42** to give only two diastereomers **43** and **44**. Beak's methodology was amenable to the synthesis of this natural product due the *trans* relationship between C-1 and C-7 (clavepictine numbering). After two protection/deprotection steps, the quinolizidine skeleton was constructed by a diastereoselective silver(I)-promoted cyclization reaction of the δ-amino allenes. Both diastereomers were cyclized to give the necessary C-1/C-11 *cis* relative stereochemistry. Deoxygenation and elimination steps were completed to converge both diastereomers to the synthesis of clavepictine A **49**.

Scheme 10

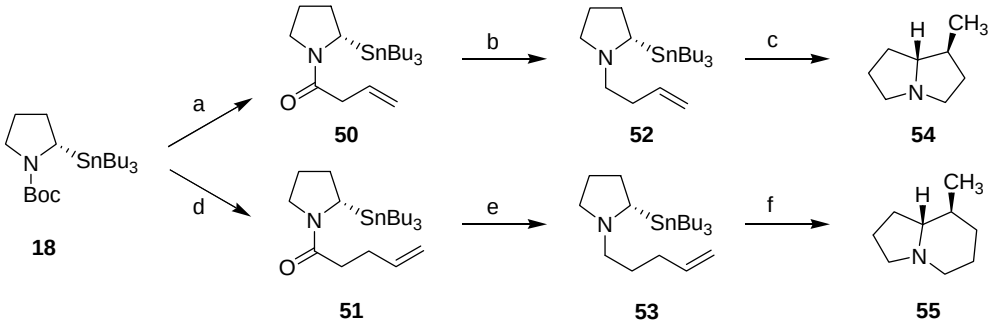


a) sBuLi, TMEDA. b) **42**. c) *m*-$CF_3C_6H_4COCl$, pyr, DCM. d) TMSOTf-lutidine. e) $AgNO_3$, acetone-H_2O.

In 2002, Coldham utilized Beak's preparation of chiral organotin **18** for the synthesis of enantiopure pyrrolizidine alkaloid (+)-pseudoheliotridane **54** and related chiral indolizidine **55** (Scheme 11).[27] Exchanging the Boc group in **18** with an alkyl chain containing a terminal alkene sets up an anionic cyclization after a tin-lithium

exchange reaction. The enantiopurity of **54** was assessed by the specific rotation of synthetic compound compared to the natural product.

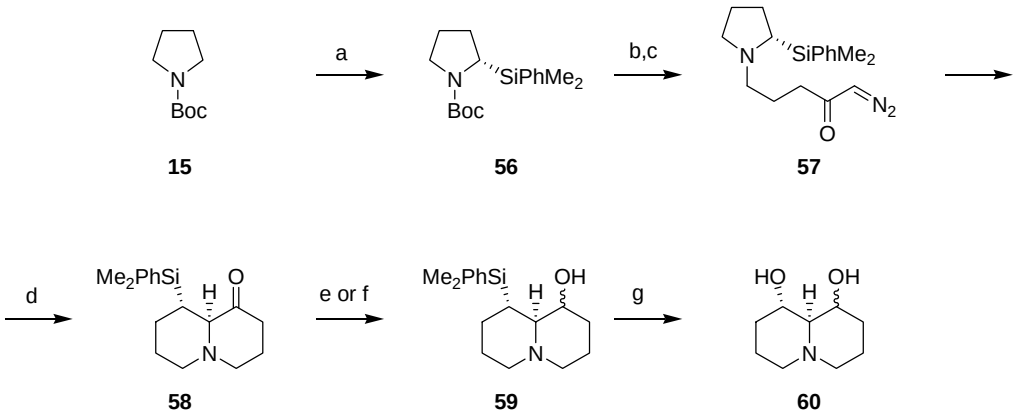
Scheme 11



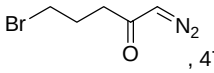
a) *B*-bromocatecholborane, DCM, RT, 30 min, then CH_2=$CHCH_2COCl$, 65%. b) AlH_3, Et_2O, 0 °C, 2 h, 89%. c) nBuLi, hexane/Et_2O 10:1, RT, 2 h, then MeOH, 90%. d) *B*-bromocatecholborane, DCM, RT, 30 min, then CH_2=$CHCH_2CH_2COCl$, 65%. e) $LiAlH_4$, Et_2O, 0 °C, 20 min, 90%.fc) nBuLi, hexane/Et_2O 4:1, RT, 6 h, then MeOH, 80%.

Also in 2002, West reported the synthesis of hydroxylated quinolizidines starting from Boc-pyrrolidine **14** (Scheme 12).[28] Stereoselectivity was controlled using sBuLi/sparteine, followed by silylation. Replacement of the Boc group with a diazoketone alkyl chain set up a Stevens rearrangement to form the bicyclic structure. Some of the enantiomeric excess was lost in the rearrangement reaction (Scheme 12, step d). Choice of reducing agents also allowed for control of the stereochemistry of the diols.

Scheme 12



a) sBuLi, sparteine, Et_2O, -78 °C, then $PhMe_2SiCl$, 92%, 85% ee. b) AcCl, EtOH, AcOEt. c)K_2CO_3, Et_3N, CH_3CN,



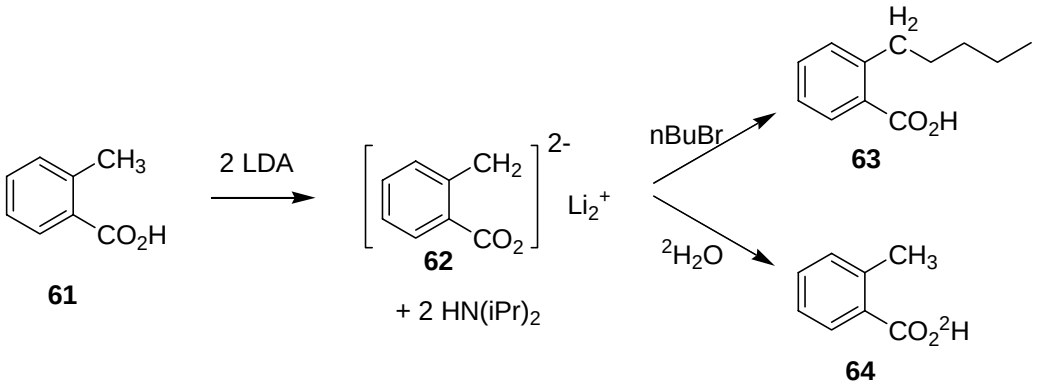
, 47%. d) $Cu(acac)_2$, toluene, 85 °C, 58%, 78% ee. e) DIBAl-H, DCM, -78 °C, 88% *cis*-diastereomer. f) $NaBH_4$, MeOH, 90% (4:1 *trans*-diastereomer). g) $Hg(O_2CCF_3)_2$, AcOOH, AcOH, TFA, DCM, 80%.

1.5 Internal proton return: A historical account

Problems encountered with attempts to alkylate Boc-3-pyrroline **14** (*vide infra*) gave way to an investigation into the possibility of internal proton return (ipr) being a factor. Ipr is the phenomenon in which the N-H proton, in amine-containing enolate solutions, reforms the α C-H bond on addition of an electrophile. Historically, studying this phenomenon has driven an evolving understanding of structure and reactivity in organolithium chemistry. In 1970, Creger reported the alkylation of 2-methylbenzoic acid, using 2 equivalents of LDA (0 °C in THF/heptane), and found "evidence for the formation of a molecular complex between the carbanionic species and diisopropylamine" (Scheme 13).[29] When the dianion was quenched with deuterium oxide, the methyl group showed no incorporation of deuterium. The proton source was the diisopropylamine. Creger concluded that the carbanion did form (i.e. LDA was a strong enough base) as evidenced by the formation of the alkylated product in good yield (69-73%). More importantly, protonation of the carbanion was proposed to have been due to the amine proton being in close proximity to the carbanionic species. If the amine was not associated with the carbanion, Creger concluded, some deuterium

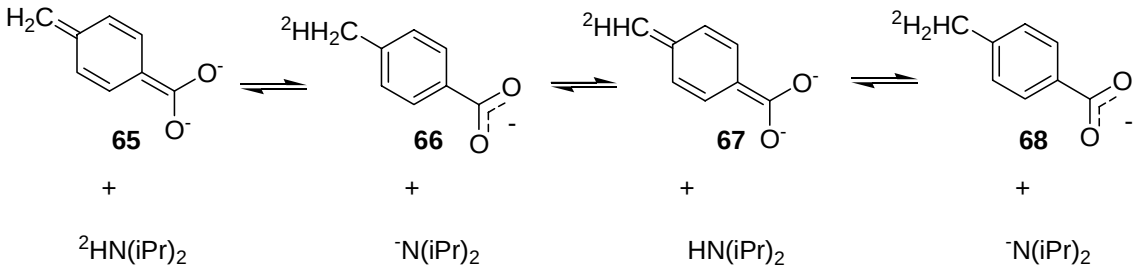
incorporation would be expected. In another experiment, the 2-methylbenzoic acid and LDA were placed under high vacuum to give a deep red gum. When re-dissolved in THF-d_8, the ^{1}H NMR spectrum showed a 1:1 ratio of 2-methylbenzoic acid to diisopropylamine. Had the amine been free in solution, the evacuation procedure would have removed it.

Scheme 13



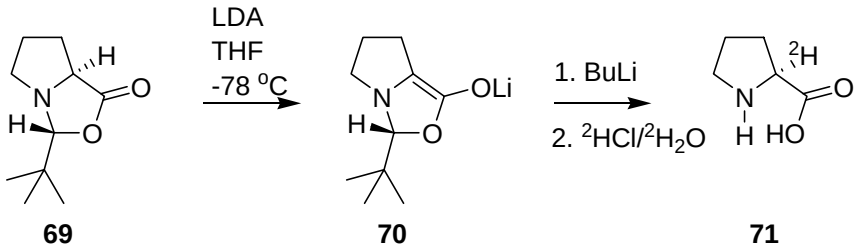
In 1972, Pfeffer and Silbert attempted to quantitatively measure the degree to which LDA could deprotonate aliphatic acids (at 25 °C).[30] By trapping the carbanion with CO_2 (at -10 °C) or with ^2H_2O, they tried to show the extent of metalation. These researchers found that adding hexamethylphosphoramide (HMPA) increased the yield of alkylation,[31] by solvating the reactive intermediate dianion, but did not change the extent of metalation. Alkylation cannot be used to determine the amount of carbanion formed because deprotonation and alkylation can occur simultaneously. For straight-chain aliphatic acids, deuteration and carbonylation occurred in 92-95%. They also repeated Creger's experiments and found that, in their hands, 2-methylbenzoic acid gave 25% carbonylation and 6% deuterium incorporation and 4-methylbenzoic acid gave 75% carbonylation and 32% deuterium incorporation. Furthermore, by introducing *N*-deuteriodiisopropylamine, after evacuating all volatiles from lithiated 4-methylbenzoic acid, they observed a 52% deuterium incorporation (Scheme 14). Mass spectral analysis showed that the distribution of deuterium atoms was 32% mono-deutero, 16% bis-deutero and 5% tris-deutero. Pfeffer concluded that a competitive proton-transference process was occurring.

Scheme 14



In 1983, Seebach encountered the ipr phenomenon when attempting to deuterate a chiral lithium enolate **70** (Scheme 15).[32] Quenching the enolate with excess ^{2}HOR resulted in the diisopropylamine proton being largely transferred back to the enolate (the product was less than 20% deuterated). The problem was overcome by adding an additional molar equivalent of butyllithium to the reaction to remove the amine proton. Under such conditions deuterium incorporation increased dramatically (the product was more than 95% deuterated). In 1985, Seebach determined that the lack of deuterium incorporation was not due to an isotope effect and that a hydrogen-bonded complex was responsible for the observed effects.[33, 34] Seebach and co-workers were able to grow crystals, among the first of this type, of unstable lithium ester and amide enolates. In the crystalline state, the lithium enolates exist as aggregates. Both dimers and tetramers were observed with lithium being tetracoordinated. Enolates that were crystallized as complexes with secondary amines gave only partial deuterium incorporation (25-60%) when quenched with $C^2H_3CO_2{}^2H/C^2H_3O^2H$. However, enolates crystallized with tertiary amines or THF gave almost complete deuterium incorporation (95%) when quenched in a similar manner.

Scheme 15

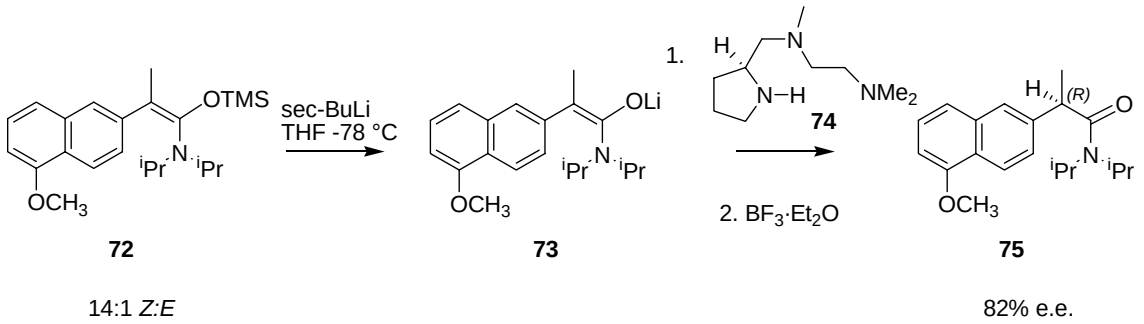


A 1988 review by Seebach summarizes the then recent explosion of research in the area of structure and reactivity of lithium enolates in both the crystalline state and in solution.[35] An important thought expressed at this time was that although lithium enolates exist in equilibrium as dimers, tetramers or higher aggregates these might not be the reactive species. The discussion can be generalized to other polar organometallic compounds as well. To further complicate things, autocatalysis by lithium halides has been shown to affect the supramolecular structure of the organolithium complexes during alkylation reactions.[36] However, it is generally agreed that the less aggregated enolate species are more reactive.[37]

1.5.1 Example of a synthetically useful internal proton return reaction

A discussion about internal proton return and secondary amine effects would not be complete without a brief account of the one example, in the literature, of the ipr phenomenon used in synthesis. Activation of the proton (of a chiral amine) towards transfer, which is complexed to an enolate with two enantiopic faces, could result in enantioselective protonation of the enolate. This differs from enantioselective protonation in which quenching is from an external chiral proton source.[38] The synthetic utility of the ipr process was first realized in 1991 by Vedejs.[39] Amide enolate **73**, generated under amine-free conditions, was complexed with a chiral tridentate amine (Scheme 16). Adding a Lewis acid to the amine-enolate complex resulted in the transfer of the amine proton to the α-carbon and recovery of a non-racemic amide. Trifluoroborane etherate gave the highest enantioselectivities (82% e.e.). Amine **74** was the source of the proton and protonation did not occur without adding the Lewis acid to the reaction mixture. In 1995, Vedejs published a full account of his earlier findings but could not improve the stereoselectivity of the reaction.[40] The utility of the enantioselective protonation reaction arises from the ability to resolve racemic carbonyl containing compounds, which can be transformed into enolates. The research of enantioselective protonation has taken off in the last 10 to 15 years; however, external protonation sources have been favoured.[41]

Scheme 16



72 **73** **74** **75**

14:1 *Z:E*

82% e.e.

1.6 Conclusions

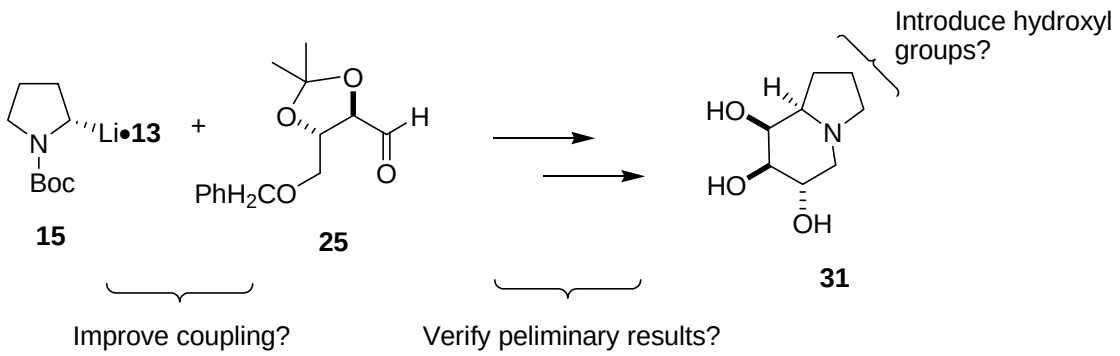
A brief literature review introducing the three possible mechanistic pathways for the stereoselective lithiation/substitution reaction at carbon proximal to nitrogen is presented in this chapter. A successful stereoselective pathway will either occur by i) a classical kinetic resolution (i.e. asymmetric deprotonation), ii) dynamic kinetic resolution, or iii) dynamic thermodynamic resolution. In order to identify which pathway is at work, a careful understanding of the configurational stabilities of the reactive carbanion intermediates is often necessary. It is difficult to generalize structural classes of compounds and draw a parallel with the three possible mechanisms. Variables such as temperature, solvent, and type of electrophile are so important that conditions that give high selectivity for one substrate may not work well for an apparently similar substrate. Therefore, each new structural template might require a methodology study to determine the feasibility of using that template for a planned targeted synthesis.

CHAPTER 2: RESULTS AND DISCUSSION

2.1 Introduction

Synthesis of alkaloid natural products have been and continues to be of interest to many chemists.[42] The high structural diversity, as well as, the often-dramatic biological activities of these compounds has made them popular targets for synthetic chemists. The strong basic properties of nitrogen-containing molecules can, on the other hand, make working with these compounds less desirable. Very polar molecules are not always compatible with the standard tools of a synthetic chemist. General strategies towards alkaloids should incorporate the standard solvents, reagents, and purification methods one would encounter in an organic chemistry lab. Our route to enantiomerically pure polyhydroxyindolizidines (1-deoxycastanospermine) couples Mukaiyama's chiral tartrate-derived reagents[43] with Hoppe[44] and Beak's[14] enantioselective sparteine-based deprotonation technology to give a short, direct route to these compounds (Scheme 17).[21] Described herein are my efforts to: i) introduce functionality on the five-membered ring of the indolizidine skeleton, ii) improve coupling of Mukaiyama's aldehyde to pyrrolidine, and iii) reproduce and verify preliminary results for the synthesis of 1-deoxycastanospermine.[45]

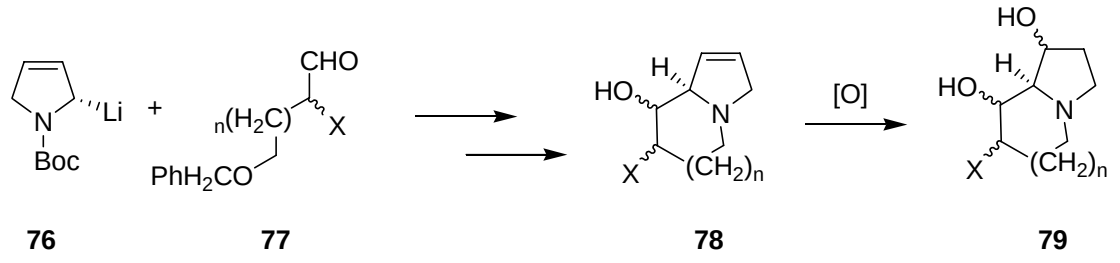
Scheme 17



2.2 Synthesis and reactions of *N*-Boc-3-pyrroline 85

Our study envisaged the stereoselective functionalization of the 3-pyrroline system via a deprotonation/alkylation sequence (Scheme 18). The situation is similar to the well-known enantioselective deprotonation of pyrrolidine developed by Beak (cf. the Introduction to this thesis) but the 3-pyrroline system is much less understood. Unlike pyrrolidine, pyrroline can be deprotonated by LDA[46] and I reasoned that chiral lithium amides could be used to functionalize 3-pyrroline stereoselectively. This would create a system complementary to Beak's pyrrolidine/sparteine combination.

Scheme 18

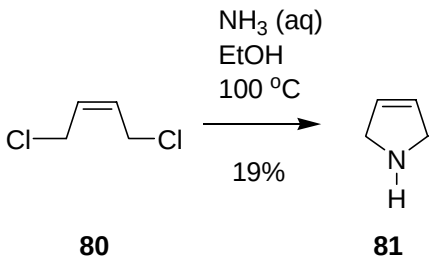


2.2.1 Synthesis of *N*-Boc-3-pyrroline 85

Multi-gram quantities of *N*-Boc-3-pyrroline **85** were required for my project. The free amine, 3-pyrroline **81**, is commercially available, however, it is sold as a mixture with 35% pyrrolidine. The commercial product was likely prepared by reduction of pyrrole with zinc / hydrochloric acid.[47] In order to avoid having to separate

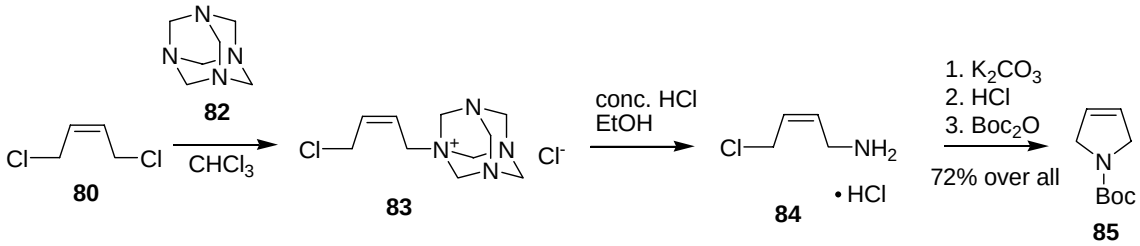
3-pyrroline from pyrrolidine on a large scale, alternate routes were considered. Palmer reported a synthesis of **81**, in 44% yield, by reaction of *cis*-1,4-dichloro-2-butene **80** with aqueous ammonia (Scheme 19).[48] In my hands, I observed a lower conversion of 19%. Therefore, it was decided that scaling up of this reaction was not promising.

Scheme 19



Another reported synthesis of **81**, developed by Brandänge in 1988, proved more amenable to large-scale synthesis from *cis*-1,4-dichloro-2-butene **80** (Scheme 20).[49] Substitution of one of the chlorides with hexamethylenetetramine **82** proceeded in quantitative yield. The crude salt **83** was converted to **84** by reaction with concentrated hydrochloric acid. Again, without purification, the crude salt **84** was cyclized under basic conditions. Brandänge reports isolating the free amine **81** in 74% yield from **80**. Given that I required carbamate **85** and not the amine, unpurified **84** was reacted with di-*tert*-butyldicarbonate plus two equivalents base to give **85** in 72% yield from **80**. A total of 33 g of *N*-Boc-3-pyrroline **85** were synthesized using this procedure. It should be noted that a high yielding synthesis of *N*-Boc-3-pyrroline from diallylamine utilizing Grubb's catalyst in a ring closing metathesis reaction has been reported recently.[50]

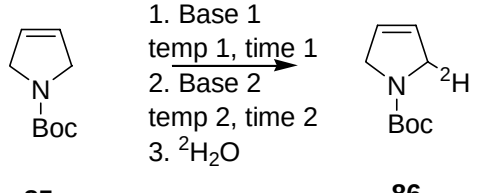
Scheme 20



2.2.2 Internal proton return in the *N*-Boc-3-pyrroline 85/lithium amide system

Deprotonation of pyrroline with LDA, followed by alkylation, is precedented,[46] however my initial results were disappointing. A short study aimed at optimizing the reaction conditions was then launched. The results are summarized in Table 1 (Scheme 21). To investigate the efficiency to which LDA was deprotonating *N*-Boc-3-pyrroline **85**, a simple experiment was tried and the presumed carbanion was trapped using deuterium oxide (Entry 1, Table 1). Surprisingly, the integration of the proton signals in the ^{1}H NMR spectrum showed no deuterium incorporation. This seemed to imply that either LDA is not a strong enough base to deprotonate Boc-3-pyrroline, or perhaps that the internal proton return occurred. Deprotonation of **85** with LDA followed by alkylation with n-butyl bromide gave the expected product **87** in 55 % yield - apparently the carbanion did form. However, the LiBr produced during the alkylation might have changed the aggregation of the lithium amide, and therefore the reactivity. An experiment that was not tried, but would answer this question, would be to react LDA with Boc-3-pyrroline, add LiBr to the reaction and then quench with deuterium oxide. To test for ipr, one equivalent of n-butyl lithium was added to "remove" diisopropylamine from the solution (Entry 2).[35] Quenching the carbanion with deuterium oxide again resulted in no deuterium incorporation. The reaction was also quenched with deuterium chloride/deuterium oxide (10% m/v) to no effect. In order to see if the reaction of LDA with Boc-3-pyrroline was happening too slowly at –78 °C, longer reaction times and warmer temperatures were tried (Entries 3 to 9). Again, no deuterium was incorporated and less material was being recovered. These entries (3 to 10) are not to be taken as reproducible results but as an account of the conditions tried to track down a systematic error in the experimental design.

Scheme 21



85 **86**

Table 1. Troubleshooting the deprotonation of *N*-Boc-3-pyrroline **85**.

	Conditions Step 1			Conditions Step 2				
Entry	Base 1	Temp 1 (ºC)	Time 1 (h)	Base 2	Temp 2 (ºC)	Time 2 (h)	Yield (%)	% ^{2}H
1	LDA	-78	0.5	-	-	-	86	0
2	LDA	-78	0.5	nBuLi	-78	0.5	89	0
3	LDA	-78	2.5	nBuLi	-78	0.5	79	0
4	LDA	0	2	-	-	-	40	0
5	LDA	0	2	nBuLi	0	0.5	0	0
6	LDA	-15	2	nBuLi	-15	0.5	10	0
7	LDA	-42	2	nBuLi	-42	0.5	25	0
8	LDA	-42	2	nBuLi	-78	0.5	75	0
9	LDA	-78	7	nBuLi	-78	0.5	80	0
10	nBuLi sparteine	-78	1	-	-	-	5	0
11	sBuLi sparteine	-78	0.25	-	-	-	90	>99
12	LDA	-78	0.5	sBuLi	-78	0.25	90	96

At this point, I decided to try and trap the carbanion of *N*-Boc-3-pyrroline **85** formed under secondary amine-free conditions. *N*-Boc-3-pyrroline was stirred with n-BuLi/(-)-sparteine **13**, at –78 °C, for just fifteen minutes followed by quenching with deuterium oxide (Table 1, Entry 10). This resulted in *ca.* 5% recovered Boc-3-pyrroline, which had no deuterium incorporation. It became apparent that the n-butyl lithium was destroying the *N*-Boc-3-pyrroline. When Beak and coworkers had investigated the deprotonation of *N*-Boc-pyrrolidine **14**, they found that nBuLi, sBuLi, and isopropyl lithium were all effective in generating carbanions from *N*-Boc-pyrrolidine in the presence of a chelating tertiary amine (i.e. TMEDA, or sparteine).[14] The researchers chose the sBuLi/(-)-sparteine system because it gave the highest enantioselectivity. It is assumed that the steric bulk of the *tert*-butyl group protects the carbonyl group of the carbamate from nucleophilic attack. However, this assumption does not appear to be

valid for *N*-Boc-3-pyrroline. Therefore, *N*-Boc-3-pyrroline was reacted with one equivalent of the bulkier sBuLi, in the presence of (-)-sparteine, and the resulting carbanion was trapped with deuterium oxide (Table 1, entry 11). The deuterated *N*-Boc-3-pyrroline was recovered in high yield (90%). Integration of the ^{1}H NMR spectrum showed that one deuterium atom had been incorporated at C-2. The ^{2}H-^{13}C coupling for C-2 in the ^{13}C NMR spectrum also supported this conclusion. From the intensities of the EI^{+}/MS molecular ion peaks, the deuterium composition was 3% undeuterated, 80% mono-deuterated and 17% bis-deuterated (Figure 5B). Either the rate of quenching the carbanion was competitive with proton transfer from the mono-deuterated product and the as yet unquenched carbanion, or a dianion had formed. If one could assume that the pyrroline was quantatively, or nearly quantatively deprotonated, then when you quench the reaction, there is really no more BuLi base in the system. Therefore, I would think that this is the most likely scenario – certainly the one with the most precedence.

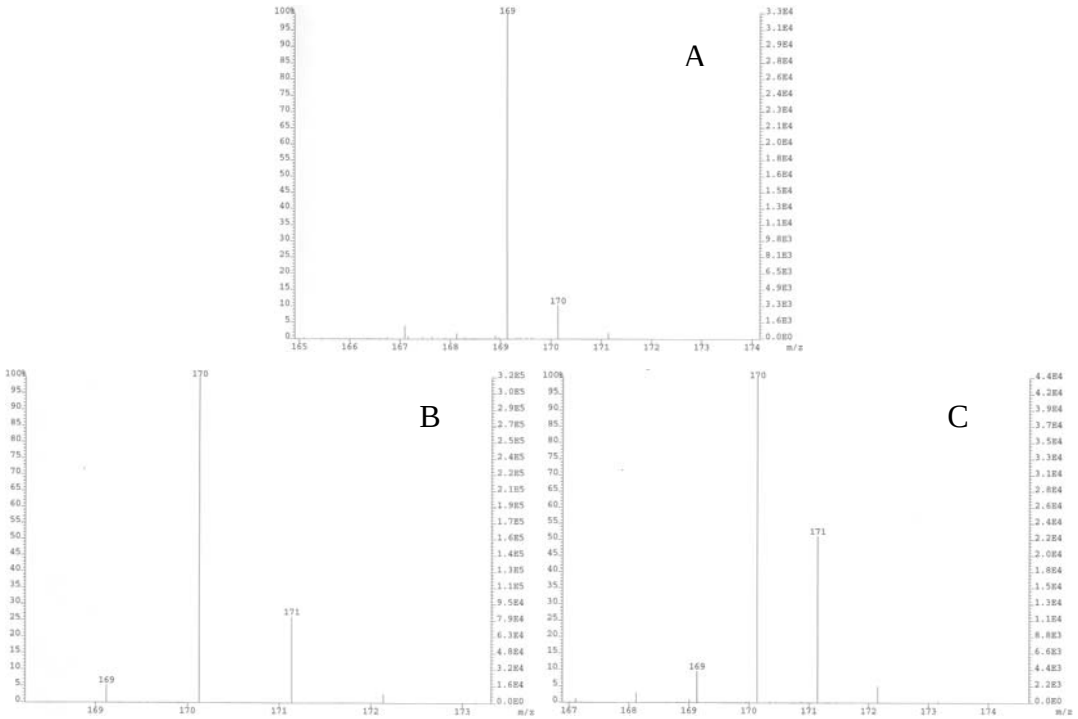


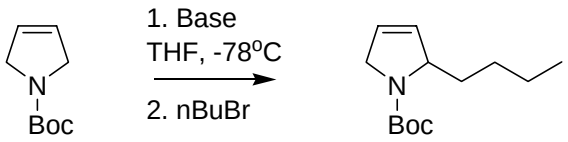
Figure 5. EI^{+}/MS molecular ions. A. *N*-Boc-3-pyrroline **85**. B. (2-^{2}H)-*N*-Boc-3-pyrroline **86** obtained from (-)-sparteine **13**/sBuLi. C. (2-^{2}H)-*N*-Boc-3-pyrroline **86** obtained from LDA plus a second equivalent sBuLi.

With the technical difficulties of generating a carbanion from *N*-Boc-3-pyrroline and trapping it with a deuteron cleared up, the internal proton return phenomenon was investigated. *N*-Boc-3-pyrroline was added to a solution of one equivalent of LDA (generated from diisopropylamine and nBuLi and kept at –78 °C). After 30 min, one equivalent of sec-butyl lithium was added to remove diisopropylamine from the solution. Subsequent quenching with deuterium oxide gave the expected Boc-3-pyrroline with one deuterium incorporated at C-2 (90% recovery, Table 1, entry 12). Again, the ^{1}H and ^{13}C NMR spectra looked good but the mass spectrum showed the deuterium composition was 6% undeuterated, 66% mono-deuterated and 28 % bis-deuterated (Figure 5C). Thus, using the approach elaborated by Seebach indicates that internal proton return does indeed occur in this system.[33] This appears to be the first example of ipr occurring for an organolithium intermediate outside of enolate chemistry. There is one report of ipr demonstrated for an organochromium(III) intermediate.[51]

2.2.3 Alkylation of *N*-Boc-3-pyrroline 85

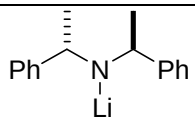
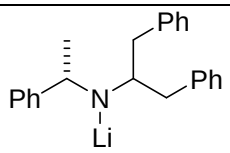
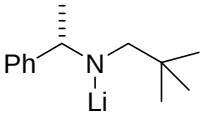
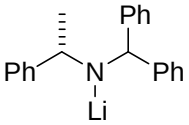
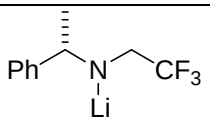
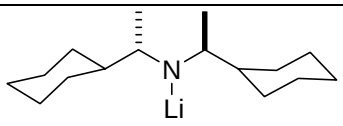
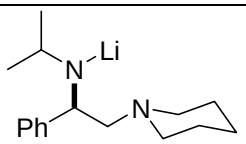
Enantioselective alkylation of *N*-Boc-3-pyrroline **85** was first attempted using chiral lithium amides (Scheme 22). The results are summarized in Table 2, entries 2 to 8. With the hindsight of the internal proton return experiments, the low yields may have been due to ipr. The alkylation of *N*-Boc-3-pyrroline, using LDA and n-butyl bromide, was reported in 1980 by Macdonald to proceed in 65% yield and in 1995 by Francke (70% yield).[46, 52] There is also a report of alkylation of *N*-methoxycarbonyl-3-pyrroline using LDA and nBuBr (58% yield) and 7-iodo-1,1,1-trimethoxyheptane (74% yield).[53] I was only able to achieve a 55% yield of the monoalkylated product **87**. Alkylation with iodomethane and methyl triflate gave only trace amounts of the alkylated product (visualized by TLC but not isolated). Alkylation with allyl bromide and benzyl bromide gave unstable products, which were never isolated after unsuccessful attempts at chromatography on silica gel. Monoalkylation with n-butyl bromide was attempted after one equivalent of sec-butyl lithium was added to remove the interfering proton (Scheme 23). However, only the dialkylated product **95** was observed.

Scheme 22

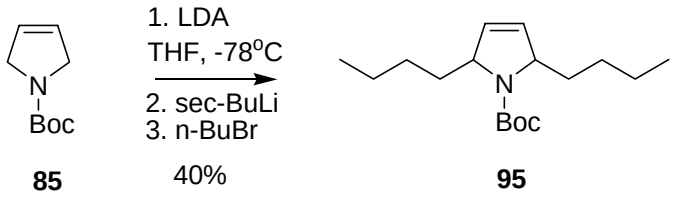


85 **87**

Table 2. Alkylation of *N*-Boc-3-pyrroline **85** using different bases at –78 °C.

Entry	Base	Yield (%)	ee (%)
1	LDA	55	-
2	 **88**	36	21
3	 **89**	37	19
4	 **90**	32	12
5	 **91**	NR	-
6	 **92**	NR	-
7	 **93**	NR	-
8	 **94**	NR	-
9	TMEDA/sBuLi	42	-
10	(-)-sparteine **13**/sBuLi	53	12

Scheme 23



85 40% **95**

The sparteine/alkyl lithium base was not explored initially due to problems with the stability of n-butyl lithium and *N*-Boc-3-pyrroline (*vide supra*). TMEDA/sec-butyl lithium and (-)-sparteine/sec-butyl lithium were found to give the desired alkylation product on reaction with n-butyl bromide (Table 2). However, (-)-sparteine/sBuLi still did not give any product when benzyl bromide was used.

Solvent can have a major role in the formation of carbanions and their subsequent reaction with electrophiles. The choice of solvent will influence the aggregation state of the organolithium compounds. The effect of some commonly used solvents, for the reaction of *N*-Boc-3-pyrroline with n-butyl bromide using chiral lithium amide **88**, were surveyed (Table 3). Tetrahydrofuran gave the best yield. Dimethoxyethane gave a lower yield than THF but displayed the same enantioselectivity. No alkylation product was observed in diethyl ether or toluene.

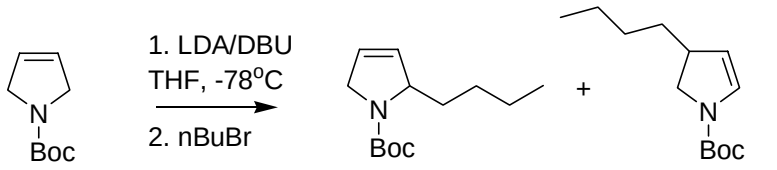
Table 3. Alkylation of *N*-Boc-3-pyrroline **85** in different solvents.

Entry	Solvent	Temp (°C)	Yield (%)	ee (%)
1	THF	-78	36	21
2	DME	-66	9	20
3	Et_2O	-78	NR	-
4	Toluene	-78	NR	-

Additives are commonly used in carbanion chemistry to effect selectivity and influence rate. The addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to lithium amides is believed to give more reactive aggregates.[54] The use of DBU and LDA had a slight improvement on the alkylation at C-2 (Table 4), however alkylation at C-4 was also observed (Scheme 24). Unfortunately, DBU did not improve the alkylation with

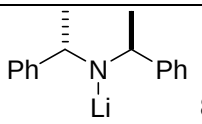
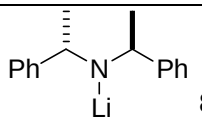
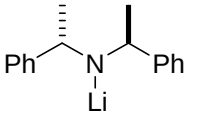
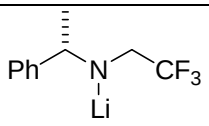
benzyl bromide or iodomethane to *N*-Boc-3-pyrroline. The addition of sparteine, TMEDA and HMPA to the chiral lithium amides, shown in Table 4, did not improve the outcome of the reaction.

Scheme 24



85 **87 -** 57% **96** - 13%

Table 4. Alkylation of *N*-Boc-3-pyrroline **85** in the presence of common additives.

Entry	Base	Additive	Yield (%)	ee (%)
1	LDA	DBU	57	-
2	 **88**	(-)-Sparteine	14	20
3	 **88**	TMEDA	42	20
4	 **88**	HMPA	13	21
5	 **92**	TMEDA	NR	-

N-Boc-3-pyrroline **85** was alkylated with n-butyl bromide in modest yield. Some stereoselectivity was observed when chiral lithium amides were used, however this was low. Modest stereoselectivity was also observed using (-)-sparteine/sBuLi. Electrophiles other then the simple alkyl halide did not add. Therefore, it does not seem likely that more complex electrophiles can be made to work. Unless better reaction conditions can be found, it is unlikely that *N*-Boc-3-pyrroline will be a useful scaffold for building complex structures. Future experiments could include an investigation into the configurational stability of lithiated *N*-Boc-3-pyrroline **76**. While modest

stereoselectivity was observed, experiments involving a warm-cool cycle of **76** could be explored to see if a dynamic thermodynamic resolution is possible for this system.[18]

2.2.3.1 Determining enantioselectivity of alkylation of *N*-Boc-3-pyrroline 85

The key principle in measuring the ratio of enantiomers in a non-racemic sample is to situate the enantiomers in a chiral environment and exploit some difference in the now diastereoisomeric species (such as complexes involving the chiral environment). All techniques are either chromatographic, i.e. HPLC and GC using chiral columns, or involve coupling the enantiomers, using covalent or non-covalent bonding, with an enantiomerically pure compound.[55] The use of so-called chiral shift reagents (CSR) in NMR is an example of the latter. Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] **97** [Eu(hfc)$_3$] and europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] **98** [Eu(tfc)$_3$] are commonly used optically active NMR shift reagents. Enantiomeric forms of these reagents are also available derived from (-)-camphor. To measure the ratio of enantiomers, a ^{1}H NMR spectrum of racemic Boc-2-butyl-3-pyrroline **87** ($CDCl_3$) was recorded with no CSR added (Figure 6). Small amounts of Eu(hfc)$_3$ were added and the ^{1}H NMR spectrum was recorded again. This procedure was repeated until two peaks were sufficiently separated. The CSR caused a noticeable separation of the one singlet, corresponding to the *tert*-butyl group protons, into two chemical shift non-equivalent signals. Integration of the peak areas gave a 1:1 ratio. The other proton signals were too broad to integrate. The non-racemic samples were treated in a similar manner and the enantiomeric excess (ee) was calculated using the following equation.

$$ee = \frac{|R - S|}{R + S} \times 100$$

2.2.3.2 Determining enantioselectivity of *N*-Boc-2-butyl-3-pyrroline 87

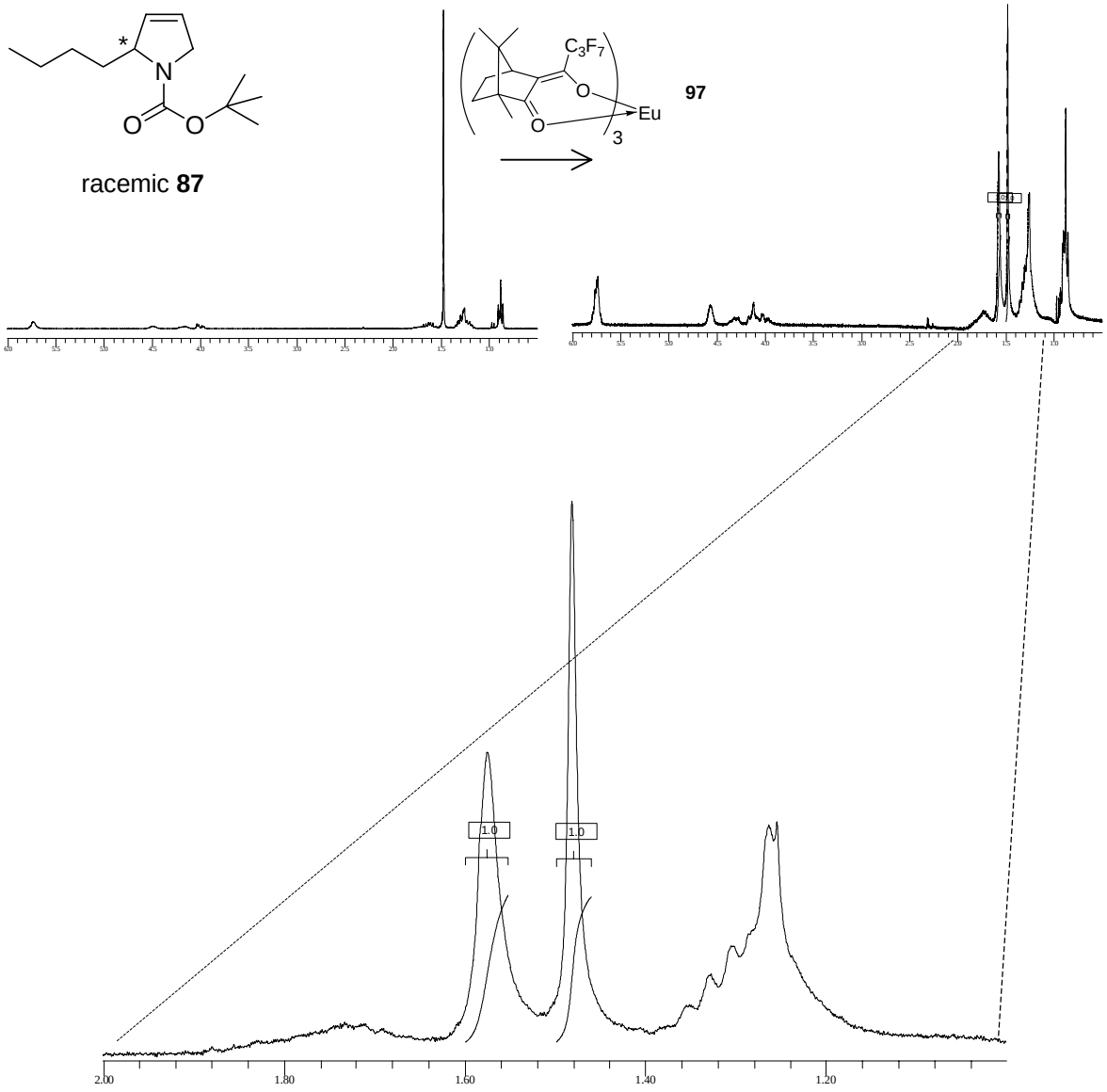


Figure 6. ^{1}H NMR spectra of racemic *N*-Boc-2-butyl-3-pyrroline **87** before and after adding CSR.

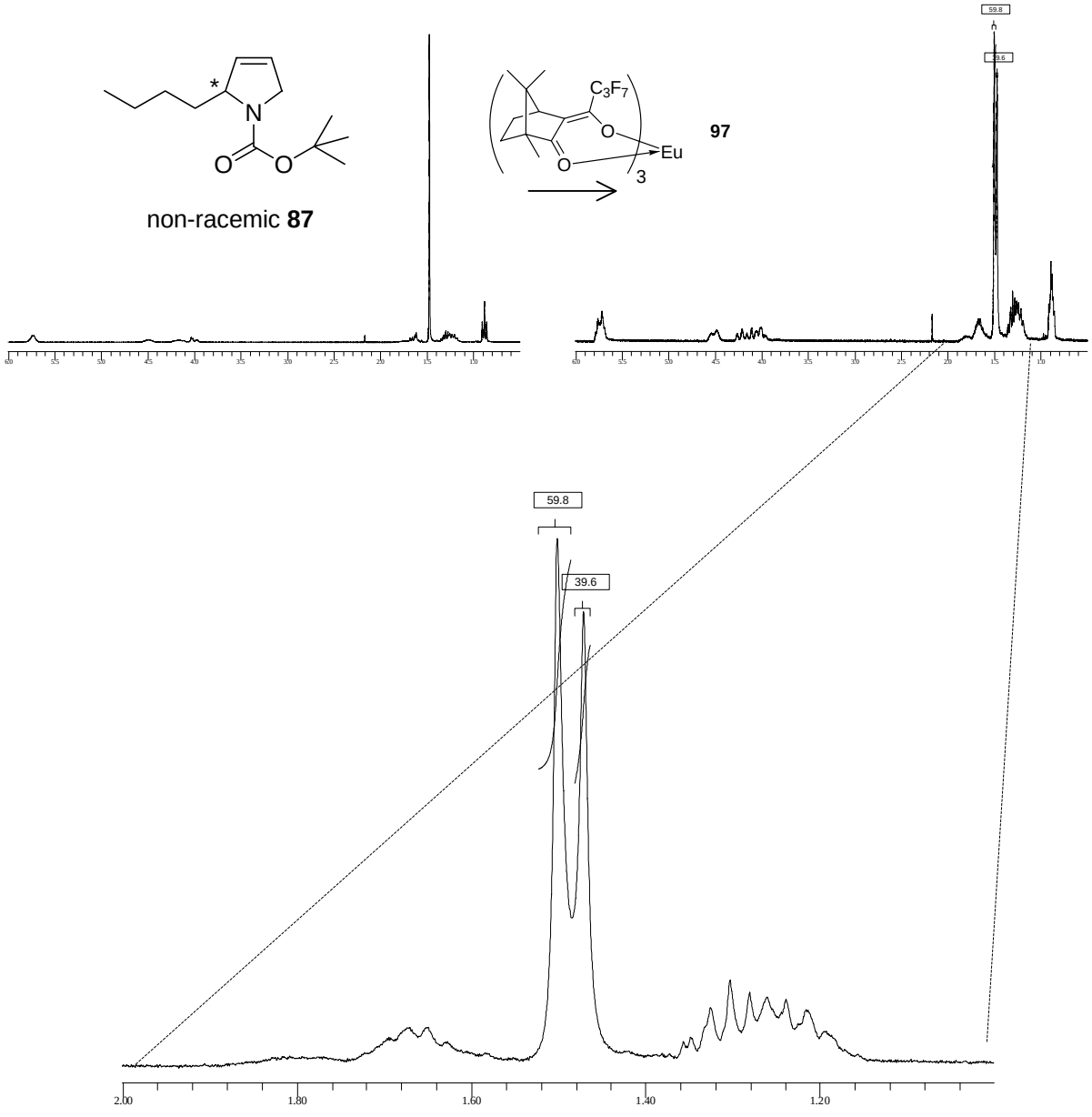


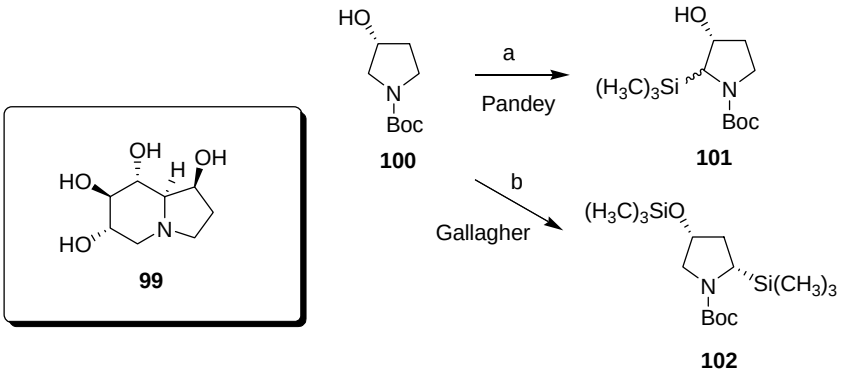
Figure 7. ^{1}H NMR spectra of non-racemic *N*-Boc-2-butyl-3-pyrroline **87** before and after adding CSR.

2.3 Additional exploratory studies involving heterocyclic scaffolds

2.3.1 *N*-Boc-3-hydroxypyrroline 100 and *N*-Boc-3,4-dihydroxypyrrolidine 106

My first strategy to explore a potential way to introduce the fourth hydroxyl group, as in castanospermine **99**, was to undertake the alkylation of N-Boc-3-hydroxypyrrolidine **100** (Scheme 25). In 1996, Pandey reported adding the trimethylsilyl group to the 2-position of **100** using deprotonation with sec-butyl lithium/TMEDA, followed by a reaction with trimethylsilyl chloride.[56] This looked like an interesting experiment and, since the details seemed sketchy, I decided to repeat it.

Scheme 25

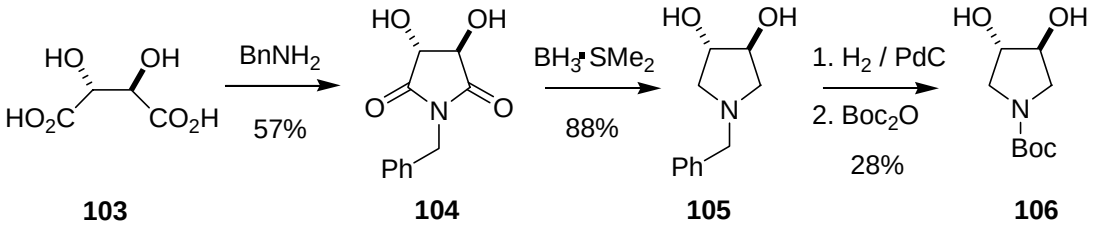


a) sBuLi, TMEDA, THF, -78 °C, then TMSCl. b) 2.2 eq sBuLi, TMEDA, THF, -78 °C to -46 °C, 2 h, cool to -78 °C, then TMSCl, 75%.

(*R*)-3-Pyrrolidinol hydrochloride was purchased and transformed into the corresponding Boc-derivative in 95% yield. The resulting (*R*)-N-Boc-3-hydroxypyrrolidine **100** was deprotonated using 2 equivalents of (-)-sparteine/sBuLi, at –78 °C, and the organolithium species was treated with a series of electrophiles (TMSCl, MeI, and PhCHO). Initially, only low yields were obtained. After checking the quality of all the reagents, it was determined that higher temperatures were needed to ensure that C-lithiation occurs. Furthermore, the regioselectivity was different than that reported by Pandey and coworkers and products functionalized at C-5 (starting material numbering) were obtained. Since the authors did not publish detailed procedures or spectral data, I

wrote to Dr. Pandey asking for the material. Dr. Pandey promptly responded and indicated that they had mistakenly assigned the position of silylation in their paper. They had, in 1998, published a correction to their previous paper based on the findings of Gallagher.[57] Gallagher was able to show, by X-ray crystallographic analysis, that silylation of N-Boc-3-hydroxypyrrolidine occurs at C-5 and proceeds with *cis* selectivity. In contrast, other electrophiles did give mixtures of *cis* and *trans* isomers. Therefore, N-Boc-3-hydroxypyrrolidine was not investigated further as a starting material towards castanospermine.

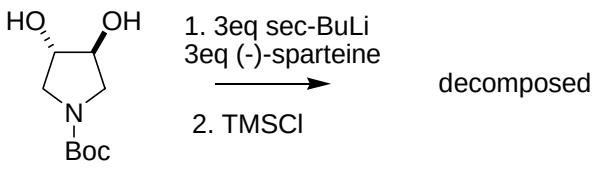
Scheme 26



103 **104** **105** **106**

A similar dihydroxypyrrolidine was briefly examined to explore the feasibility of deprotonating this molecule α to the nitrogen. *(3S,4S)*-N-Boc-3,4-dihydroxypyrrolidine **106** was synthesized from L-tartaric acid using a known procedure (Scheme 26).[58, 59] Reaction of **106** with 3 equivalents of sparteine/sec-butyl lithium for 7 hours, in THF at –78 °C, gave a white precipitate (Scheme 27). No silylated product was obtained on addition of TMSCl. Furthermore, no starting material could be isolated off the column. It was concluded that no further time was to be invested in this strategy.

Scheme 27

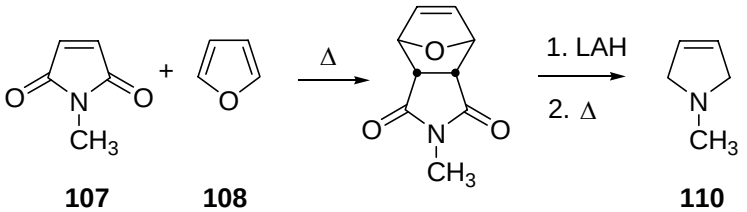


106

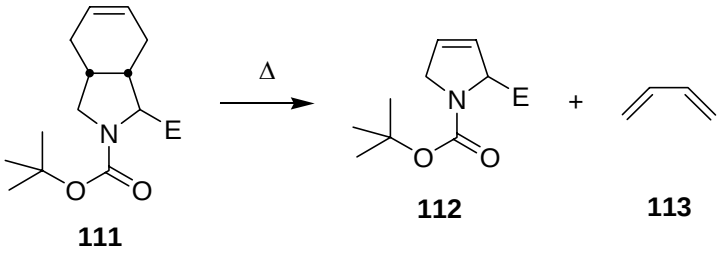
2.3.2 Protecting the double bond in *N*-Boc-3-pyrroline 85

The alkene functional group (carbon-carbon double bonds) is not, normally, a functional group that is thought about in the context of a protecting group strategy.[60] However, it is possible that protection of this group in 3-pyrroline might provide access to compounds that cannot be obtained by direct lithiation/alkylation. A literature survey indicated that in 1985, 1-methyl-3-pyrroline **110** was synthesized by using a Diels-Alder/retro-Diels-Alder protection/deprotection strategy (Scheme 28).[61] The Diels-Alder product from the reaction of N-methylmaleimide with furan gave an intermediate that survived the reduction of the imide functionality. Pyrolysis then gave 1-methyl-3-pyrroline **110** through a retro Diels-Alder reaction. The conditions for pyrolysis involved heating of the reduced Diels-Alder adduct **109** in silicone oil (250-300 °C) and collection of the 1-methyl-3-pyrroline and furan as they distilled over. My strategy would be to construct molecules similar to compound **111** and generate the double bond after the alkylation reaction (Scheme 29). If this strategy could be successfully applied to our synthesis of polyhydroxylindolizidines, then it would become possible to introduce the fourth hydroxyl group in castanospermine **99**.

Scheme 28

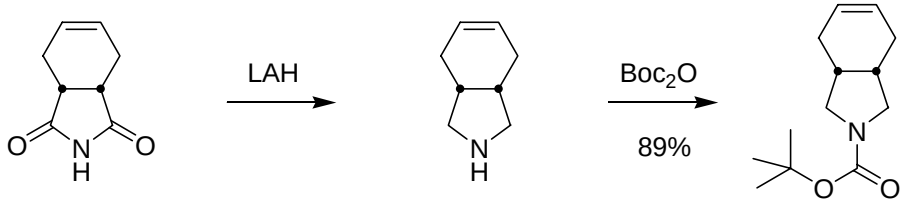


Scheme 29



A limitation of this strategy would be the necessity of only using functional groups that would withstand pyrolysis conditions. However, there are precedents of more-complex structures surviving this form of protection/deprotection. In 2001, Koomen used cyclopentadiene, through a hetero-Diels-Alder reaction, to protect the nitroso functional group of 2-nitrosoadenosine tetraacetate during methanolic removal of the acetate groups.[62] The removal of the cyclopentadienyl moiety from the triol-compound was facilitated by bubbling nitrogen gas through a DMF solution of the triol, heated to 95 °C. In 1998, Liu reported a retro-Diels-Alder approach to the natural product senecivernic acid.[63] In 1991, Rutledge used anthracene as both a protecting and stereodirecting group.[64] Also in this year, Warren employed furan to protect the double-bond geometry in a Horner-Wittig intermediate.[65] In addition, the retro-Diels-Alder reaction was reviewed in 1987 as it had been used in the synthesis on natural products.[66]

Scheme 30

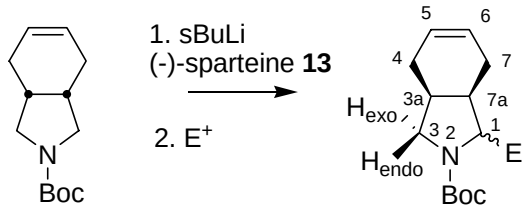


114 **115** **116**

The protected pyrroline building block: 1,3,3a,4,7,7a-hexaahydroisoindole-1-carboxylic acid, *tert*-butyl ester **116** (Boc-hh-isoindole) was synthesized in two steps from *cis*-1,2,3,6-tetrahydrophthalimide **114** using a known procedure (Scheme 30).[67] Tetrahydrophthalimide **114** is an attractive starting material as it retails for about $0.20 per gram. The imide was reduced with lithium aluminium hydride to give the corresponding amine **115**. The crude amine was then reacted with di-*tert*-butyl dicarbonate to give Boc-hh-isoindole **116** in 89% yield, after chromatography. Beak, *et al* has recently reported the enantioselective silylation of Boc-hh-isoindole **116** using (-)-sparteine/sec-butyl lithium and TMSCl.[67] They reported a yield of 48% for **118**, a diastereomeric ratio of 95:5 and an enantiomeric ratio of 73:27 (Table 5, entry 1). The

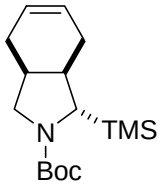
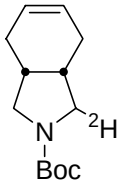
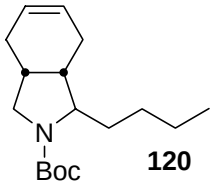
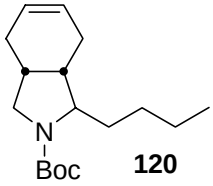
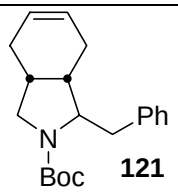
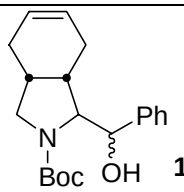
reaction gave the same absolute configuration as reported for Boc-pyrrolidine **14** and the *exo*-diastereomer was the major isomer. The absolute configuration was inferred from the X-ray structure of the *N*-Boc-octahydro-1-(TMS)-isoindole (converted to the *N*-tosylate) obtained under the same conditions. This reaction was only mentioned briefly and as a complementary method to the reported synthesis of trans 3,4-substituted pyrrolidines.

Scheme 31



116 **117**

Table 5. Electrophilic addition products of Boc-hh-isoindole **116**.

Entry	Electrophile	Product	Yield (%)	Stereoselectivity
1	TMSCl	 **118**	48[a]	95:5 dr[a] ee 46%[a]
2	$^{2}H_2O$	 **119**	88	ND[b]
2	n-BuBr	 **120**	13	ND[b]
3	n-BuI	 **120**	21	dr 1.1:1
4	$PhCH_2Br$	 **121**	68 (1.5:1 dr)	dr 1.5:1
5	PhCHO	 **122**	61 (3.8:1.3:1 dr)	dr 3.8:1.3:1 ee (major) 90%[c] ee (minor) 84%

[a] Data from reference [67]; [b] Not determined; [c] The major isomer was *(3aS,7aR)-exo-R* **125** (cf., section 2.3.2.1).

As a part of my project, the reaction reported by Beak was repeated and other electrophiles were also briefly studied. Boc-hh-isoindole **116** was deprotonated using sBuLi/sparteine and the resulting organolithium species was treated with a series of electrophiles (Table 5, Scheme 31). Trapping of the carbanion with deuterium oxide gave the mono-deuterated product in 88% yield and 79% deuterium incorporation. The

deuterium incorporation was measured by integration of the ^{1}H NMR spectrum. Alkylation with n-butyl bromide and n-butyl iodide was successful but proceeded in modest yields and showed almost no diastereoselectivity (1.1:1). The two diastereomers could not be chromatographically separated by either dry-flash-column (DFC) chromatography or by preparative thin layer chromatography (PTLC). As a result, the enantioselectivity was not determined. The two isomers were separated on a GC/MS and gave two peaks that had a molecular ion (M+H) of 280 (Figure 8). Reaction with benzyl bromide gave a reasonable yield for **121** (68%) and a somewhat better diastereoselectivity of 1.5:1. Again, DFC nor PTLC chromatography could not separate the two diastereomers, however, from Beak's work the exo-diastereomer is expected to be the major isomer. GC/MS showed two isomers with a molecular ion (M+H) of 314 (Figure 9).

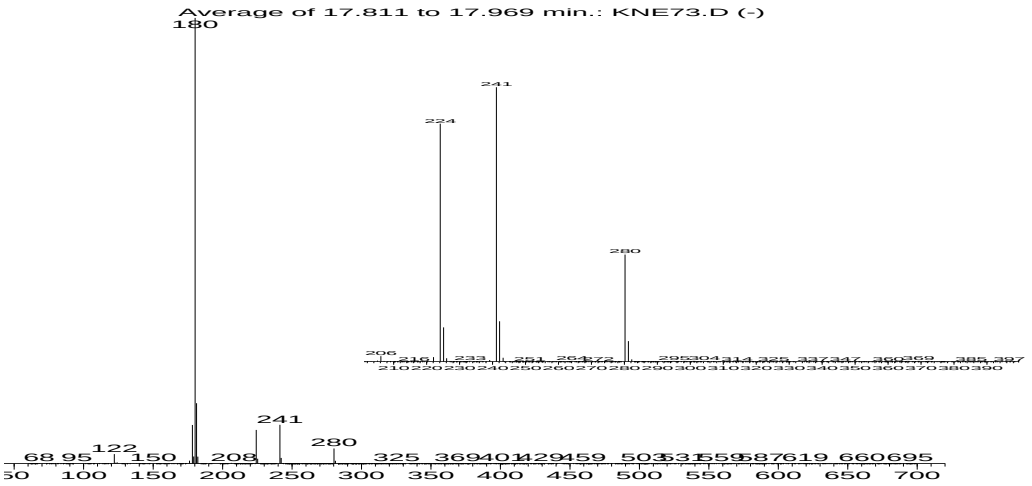


Figure 8. CI+ (NH_3)Mass spectrum of Boc-1-butyl-hh-isoindole **120** (major diastereomer shown).

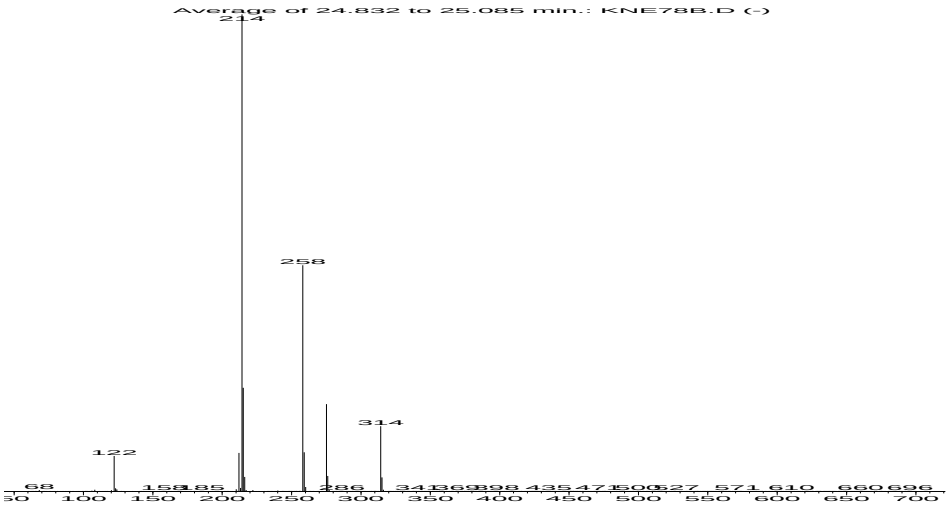


Figure 9. CI+ (NH_3) Mass spectrum of Boc-1-benzyl-hh-isoindole **121** (major diastereomer shown).

Addition of benzaldehyde to Boc-hh-isoindole **116** proceeded in good yield (61%) and reasonable diastereoselectivity (3.8:1.3:1 by ^{1}H NMR). The mixture of diastereomers, after chromatography, were derivatized as the TMS ethers and analyzed by GC/MS (using *N*,*O*-Bis(trimethylsilyl)trifluoroacetamide containing 10% TMSCl) (Figure 10). By GC/MS all four diastereomers could be seen. The four peaks at 25.04, 25.79, 27.33 and 27.60 min all contained the ions *m/z* = 402, 346 and 302 as the major ions formed. Two of the four diastereomers could be further purified (by PTLC) and subjected to full characterization. The infrared spectra for both isomers had strong, broad peaks at 3020 cm^{-1}, characteristic of the hydroxyl group. The major diastereomer (GC t_r = 25.04 min) had a negative optical rotation ($[\alpha]_D^{25}$ –12 (c 1.0, $CHCl_3$)) and the minor (GC t_r = 27.33 min) had a positive optical rotation ($[\alpha]_D^{25}$ +49 (c 0.32, $CHCl_3$)). The enantiomeric ratios for the major and one of the minor diastereomers was found to be 95:5 and 92:8, respectively. The enantiomeric ratios were measured in the ^{1}H NMR spectra using (+)-Eu(tfc)$_3$ as a chiral shift reagent. The racemic material was not prepared for comparison; however, three sets of diastereomeric resonance signals were integrated and compared for both diastereomers. The configurational assignment will be discussed in the next section.

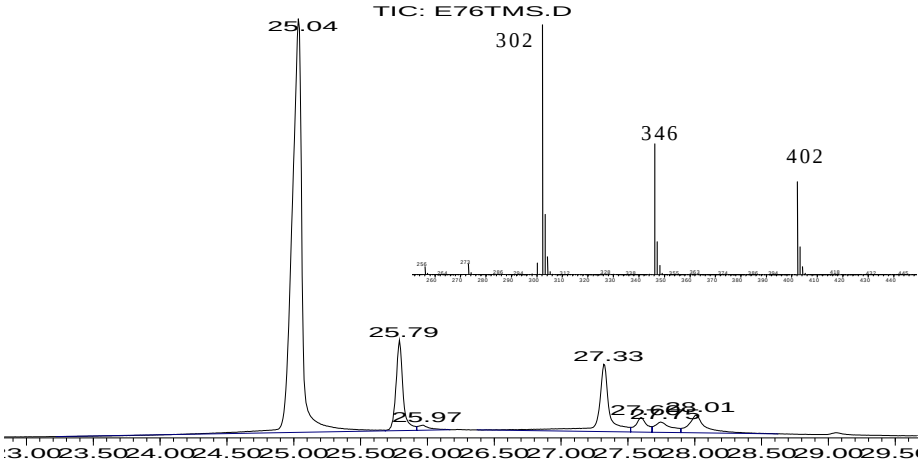


Figure 10. Gas chromatograph/ CI+ (NH_3) mass spectrum of Boc-1-(TMSO(phenyl)methyl)-hh-isoindole **122**.

Thus, enantioselective hydroxyalkylation of Boc-hh-isoindole **116** was accomplished and could be used for the synthesis of more complex structures that contain the isoindole skeleton. The configuration of the alkylated products is discussed in the next section. The pyrolysis of these compounds to give 2-substituted-3-pyrrolines has not been investigated as yet. It should be noted that other dienophiles could be screened to see if they would help or hinder the alkylation or the pyrolysis step.

2.3.2.1 Conformational analysis and assignment of relative configuration of 116

Eight stereoisomers are possible from the coupling of Boc-hh-isoindole **116** with benzaldehyde (Figure 11). Samples of the major diastereomer, from the reaction, and one of the two minor diastereomers were chromatographically separated and fully characterized. The third minor diastereomer could not be separated from the major isomer. The ^{1}H NMR spectrum, for the major isomer, can be fully assigned by referring to the 2D COSY spectrum (Figure 12). The benzylic signal, at 4.61 ppm, has a large coupling (J = 9 Hz) to the H_1 signal at 3.76 ppm. The H_1 signal has a very small coupling to the H_{7a} signal at 1.65 ppm. This small coupling was not evident by looking at the multiplicity of this peak. The two H_3 signals at 3.46 ppm and 3.20 ppm both have a large coupling to the H_{3a} signal at 2.51 ppm (J = 9 and 10 Hz respectively). A similar

correlation exists for the minor isomer (Figure 13). The benzylic signal, at 4.68 ppm, has a large coupling (J = 8.5 Hz) to the H_1 signal at 4.18 ppm. The H_1 signal shows a medium spin-coupling (J = 4 Hz) to H_{7a} at 1.82 ppm. Similarly, the two H_3 signals at 3.59 ppm and 3.21 ppm both have a large coupling to the H_{3a} signal (J = 7.5 and 10.5 Hz respectively). In the minor isomer, the coupling between H_{3a} and H_{7a} can be seen. In both diastereomers, the multiplets corresponding to the two H_4 signals and the two H_7 signals can also be assigned by referring to the COSY spectrum.

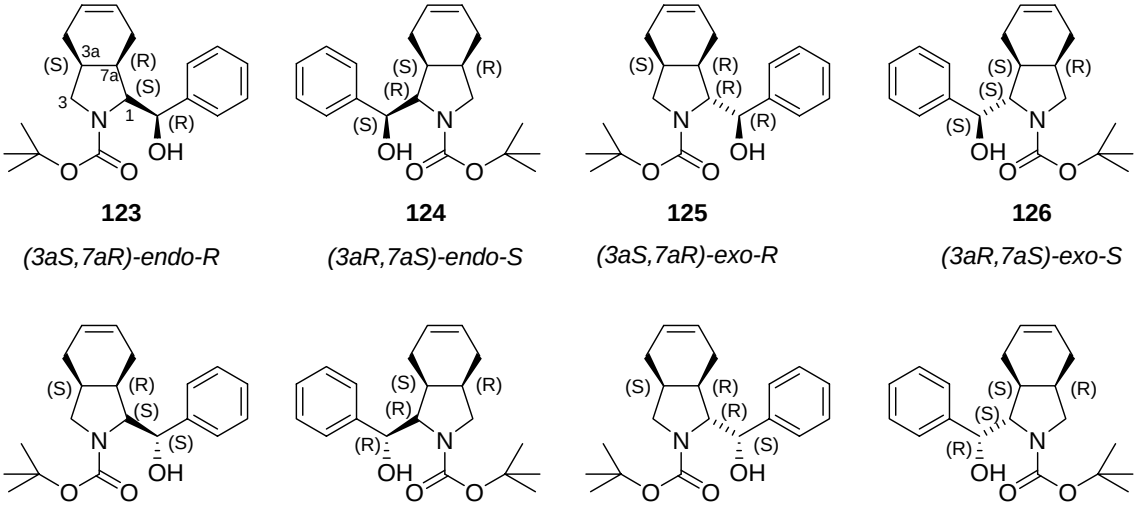


Figure 11. Possible stereoisomers of the product of addition of benzaldehyde to Boc-hh-isoindole **116**.

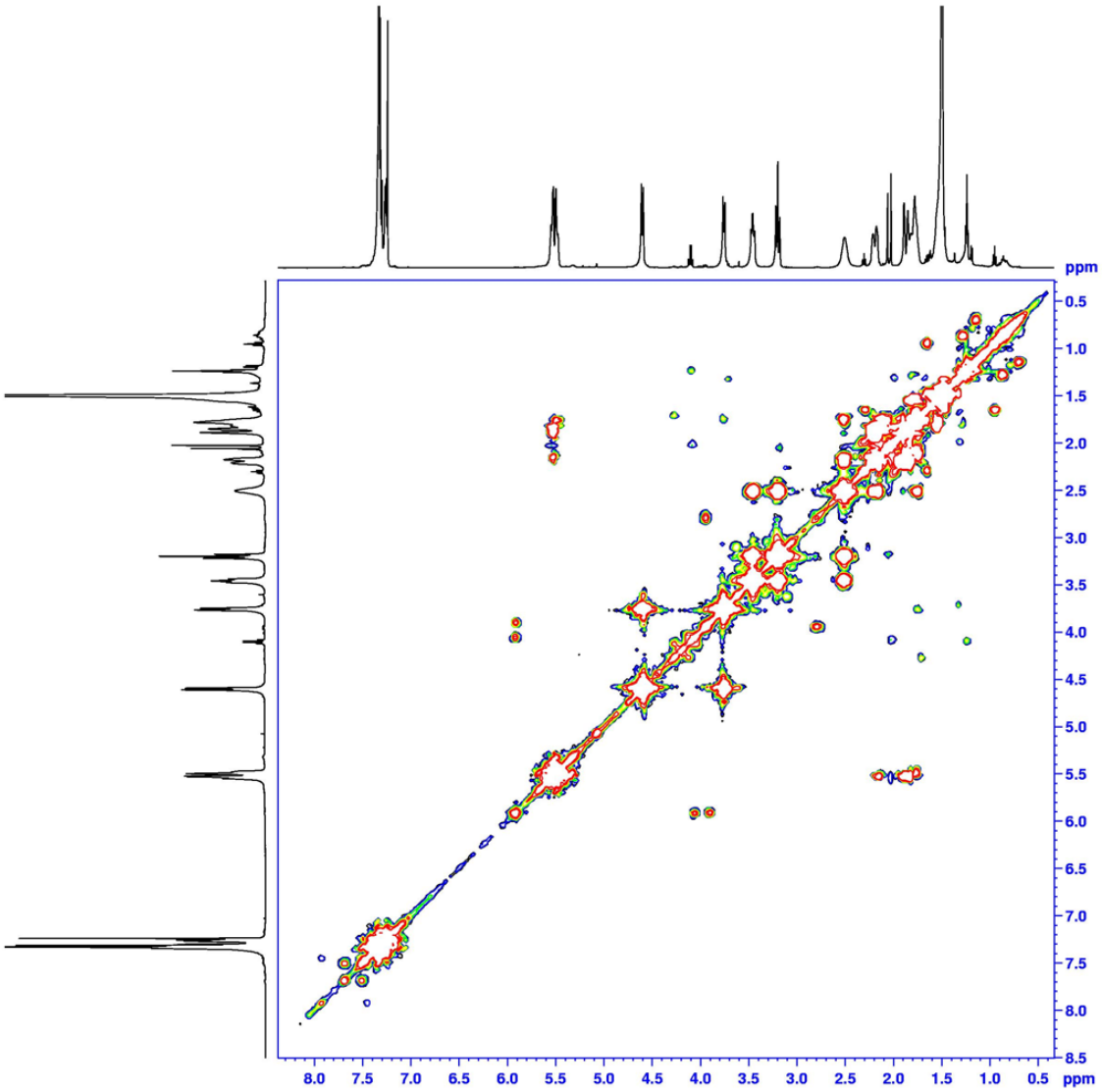


Figure 12. COSY spectrum of the major diastereomer from the coupling of Boc-hh-isoindole **116** with benzaldehyde.

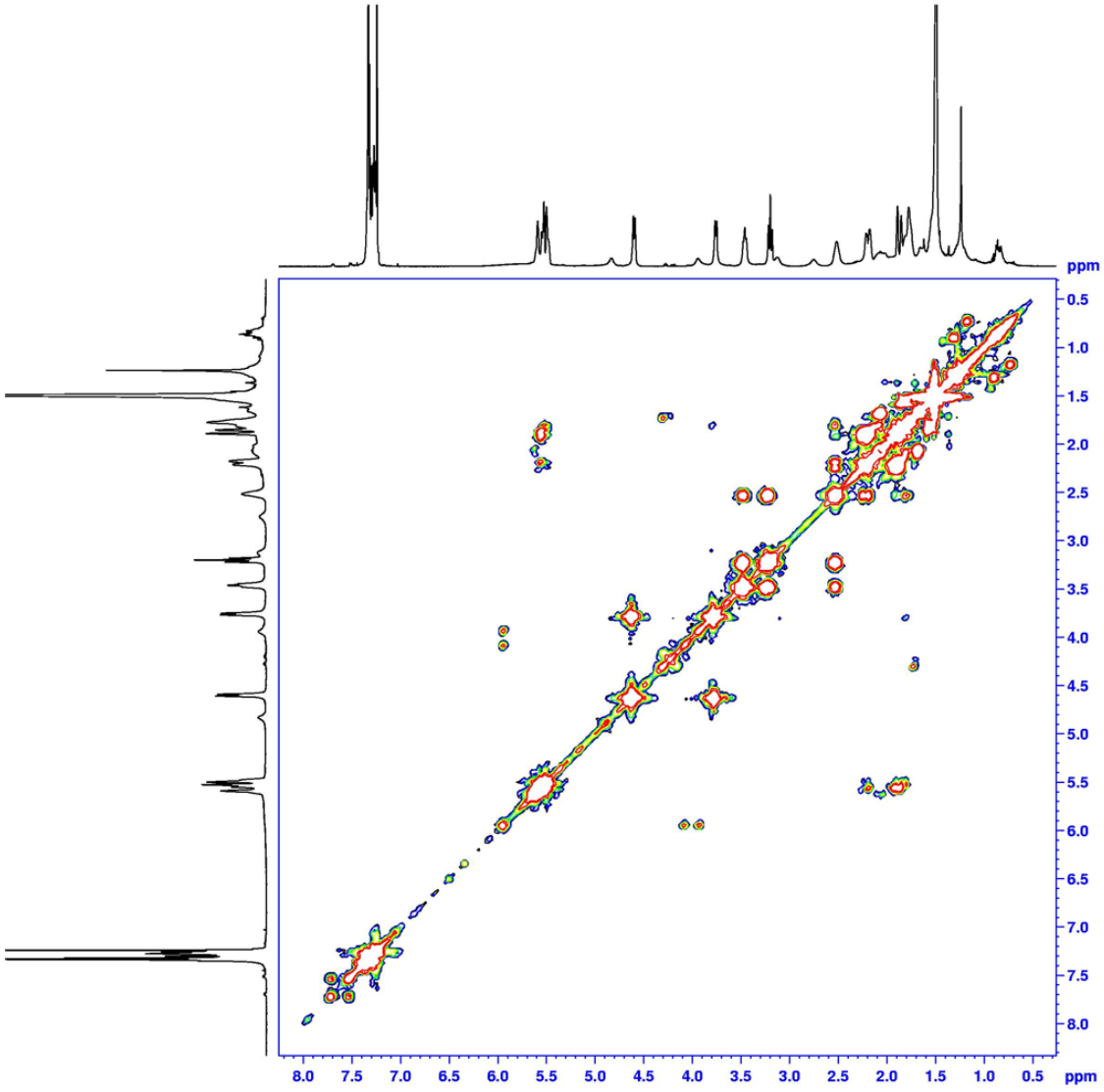


Figure 13. COSY spectrum of the minor diastereomer from the coupling of Boc-hh-isoindole **116** with benzaldehyde.

With the spin-systems assigned for both the major and minor diastereomers, the nuclear Overhauser effect (nOe) difference spectrometry was used to determine the relative configurations for the two molecules (Figures 14 and 15; note that the irradiated peak has been deleted for clarity). Irradiating the benzylic proton of the major diastereomer caused a 1.5% enhancement of the H_{7a} signal and a 1% enhancement of the H_{3a} signal (Figure 14). Therefore, the benzylic group must be on the exo-side of the molecule. Furthermore, irradiating the H_1 signal causes an enhancement of both the H_{7a} signal and one of the H_7 signals. This result is consistent with H_1 being on the endo-side of the curved molecule. Also, the exo-diastereomer allows for an almost 90° H_1-C_1-C_{7a}-H_{7a} dihedral angle, which is consistent with the very small spin coupling observed between the H_1 signal and the H_{7a} signal. The nOe difference spectrum also allows for the assignment of the H_{3exo} and the H_{3endo} signals in the ^{1}H NMR spectrum. Irradiating at 3.5 ppm caused an enhancement of the H_{7a} signal. Therefore, the signal at 3.46 ppm is due to the H_{3exo} as it would be closer in space to the H_{7a}.

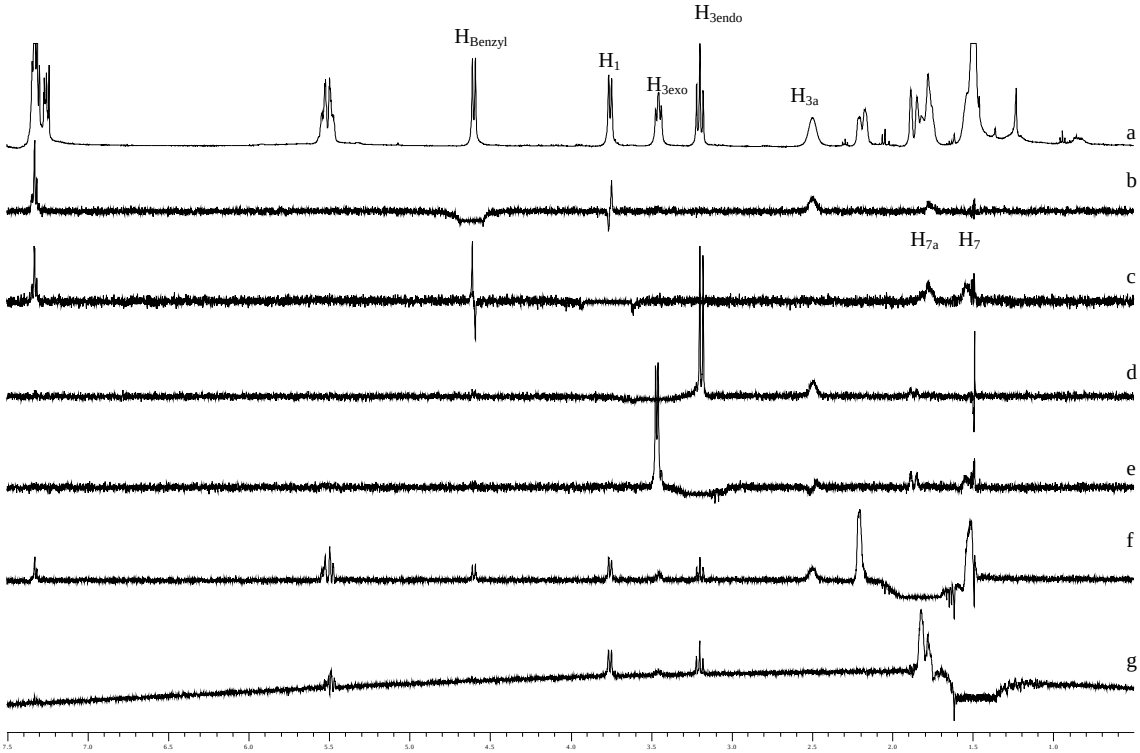


Figure 14. Nuclear Overhauser Effect (nOe) difference spectrometry for the major diastereomer from the coupling of Boc-hh-isoindole **116** with benzaldehyde. a) ^{1}H NMR spectrum, b) irradiation at 4.6 ppm, c) irradiation at 3.8 ppm, d) irradiation at 3.5 ppm, e) irradiation at 3.2 ppm, f) irradiation at 1.8 ppm, g) irradiation at 1.5 ppm.

The minor isomer does not show any significant enhancement of the H_{3a} and H_{7a} signals when irradiated at the benzylic proton (Figure 15). Also, irradiating the H_1 signal causes a small enhancement of the H_{3a} and H_{7a} signals, indicative of H_1 located on the same side of the ring as H_{7a}. The nOe experiments support the hypothesis that the minor diastereomer is the endo-diastereomer. Furthermore, the H_1 signal and the H_{7a} have a coupling constant of 4 Hz. A 4 Hz coupling constant is consistent with a 45° or 120° dihedral angle. A 45° H_1-C_1-C_{7a}-H_{7a} dihedral angle for the endo diastereomer represents a staggered conformation; as where a 120° H_1-C_1-C_{7a}-H_{7a} dihedral angle for the exo diastereomer represents an eclipsed conformation. Therefore, the 45° dihedral angle and consequently the endo diastereomer is a better fit for the data.

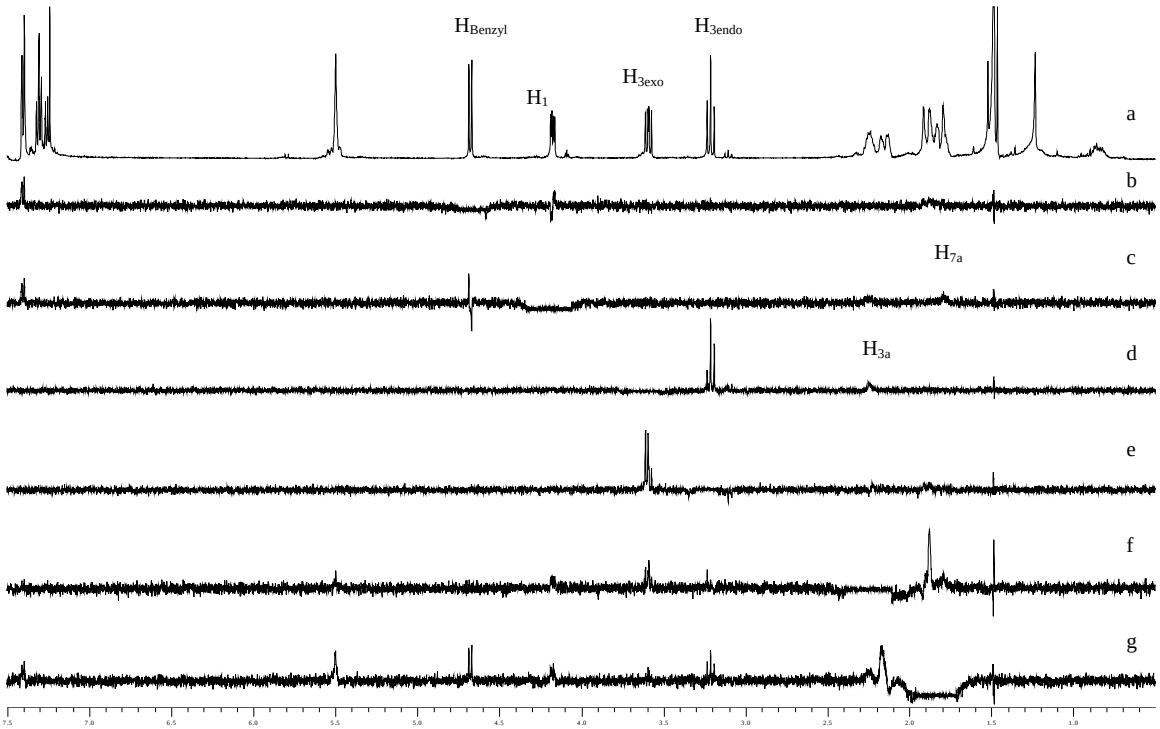


Figure 15. Nuclear Overhauser Effect (nOe) difference spectrometry for the minor diastereomer from the coupling of Boc-hh-isoindole **116** with benzaldehyde. a) ^{1}H NMR spectrum, b) irradiation at 4.7 ppm, c) irradiation at 4.2 ppm, d) irradiation at 3.6 ppm, e) irradiation at 3.2 ppm, f) irradiation at 2.2 ppm, g) irradiation at 1.8 ppm.

In order to assign the relative configuration of the hydroxyl group in compound **122**, the vicinal Karplus correlation between dihedral angle (ϕ) and coupling constant (J)

was used.[68] The four diastereomers were modeled using Chem3D Pro Molecular Modeling and Analysis software by Cambridgesoft. The assumption was made that the major conformer will have an internal hydrogen bond between the hydroxyl group and the carbonyl group. Conformational analysis about the C_1-C_{Bn} bond, followed by energy minimization (MM2 parameters), identified two conformational isomers for each of the four possible diastereomers in which an internal hydrogen bond was possible (Figures 16-19). The results of the conformational analysis are summarised in Table 6. For the exo-diastereomer (major), the *(3aS,7aR)-exo-R* molecular model gives one conformation in which ϕ = 179° (J = 10 Hz) for H_1-C_1-C_{Bn}-H_{Bn} and the other in which ϕ = -90° (J = 0 Hz). The *(3aS,7aR)-exo-S* molecular model gives one conformation in which ϕ = -56° (J = 2 Hz) and the other in which ϕ = 46° (J = 4.5 Hz) for H_1-C_1-C_{Bn}-H_{Bn}. The observed spin coupling has a magnitude of 9 Hz. Therefore, the preferred conformation of the major diastereomer should have the H_1 and H_{Bn} groups nearly anti-periplanar to each other. I would conclude that the major diastereomer has the *(3aS,7aR)-exo-R* **125** relative configuration. If this reaction follows the same enantioselectivity as reported by Beak, then this would also be the absolute configuration of the major isomer. The conformation in which J = 0 Hz must not be very populated. For the endo-diastereomer (minor), the *(3aS,7aR)-endo-R* **123** molecular model predicted a H_1-C_1-C_{Bn}-H_{Bn} dihedral angle of 57° (J = 2 Hz) for one conformer and 108° (J = 1 Hz) for the other. Whereas, the *(3aR,7aS)-endo-S* **127** molecular model predicted a H_1-C_1-C_{Bn}-H_{Bn} dihedral angle of 123° (J = 4 Hz) and 87° (J = 0 Hz). The observed coupling constant was 8.5 Hz. The conformational analysis data does not agree with either diastereomer, therefore the configuration of the minor diastereomer is unassigned.

Table 6. Conformational analysis of the four possible diastereomers arising from the coupling of Boc-hh-isoindole **116** with benzaldehyde.

	Diastereomer	Conf.	H---O dist. (Å)	H_1-C_1-C_{Bn}-H_{Bn} ϕ	Pred. $J_{1\text{-}Bn}$ (Hz)	H_1-C_1-C_{7a}-H_{7a} ϕ	Pred. $J_{1\text{-}7a}$ (Hz)
1	*(3aS,7aR)-endo-R*	a	1.92	56.5°	2	20.7°	7
2	*(3aS,7aR)-endo-R*	b	1.90	107.7°	1	2.1°	8
3	*(3aS,7aR)-endo-S*	a	1.92	122.5°	4	35.6°	6
4	*(3aS,7aR)-endo-S*	b	1.92	87.2°	0	10.2°	7.5
5	*(3aS,7aR)-exo-R*	a	1.90	178.7°	10	141.1°	7
6	*(3aS,7aR)-exo-R*	b	1.87	-90.7°	0	155.0°	8
7	*(3aS,7aR)-exo-S*	a	1.91	-55.6°	2	109.8°	2
8	*(3aS,7aR)-exo-S*	b	1.88	45.6°	4.5	148.9°	7

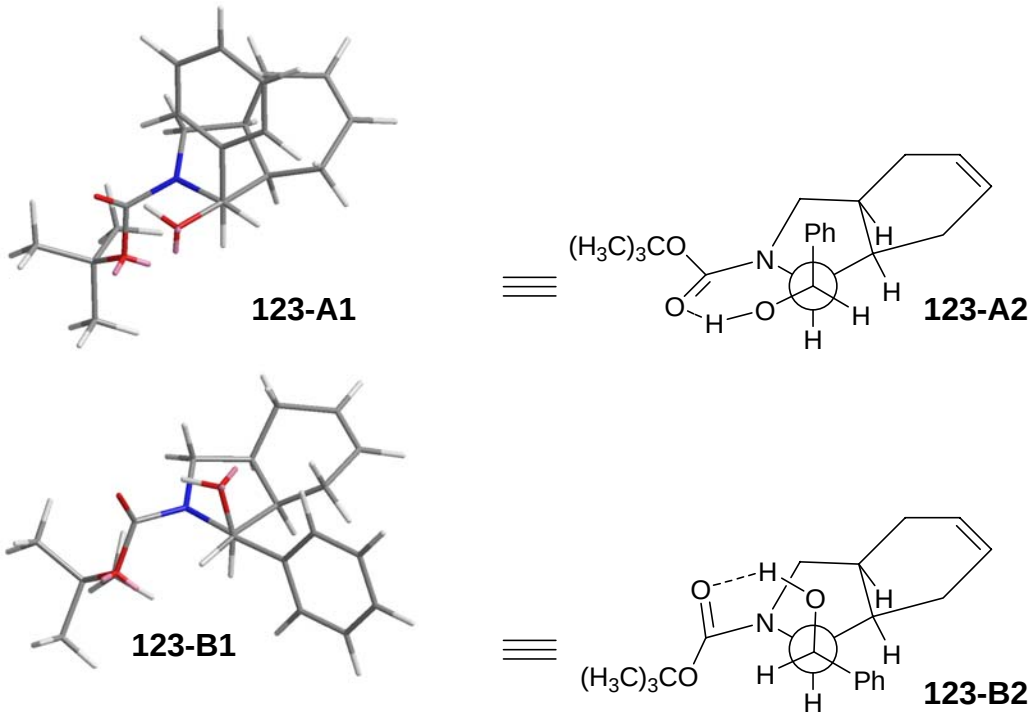


Figure 16. MM2-minimized models for [*(3aS,7aR)-endo-R*]-**123**.

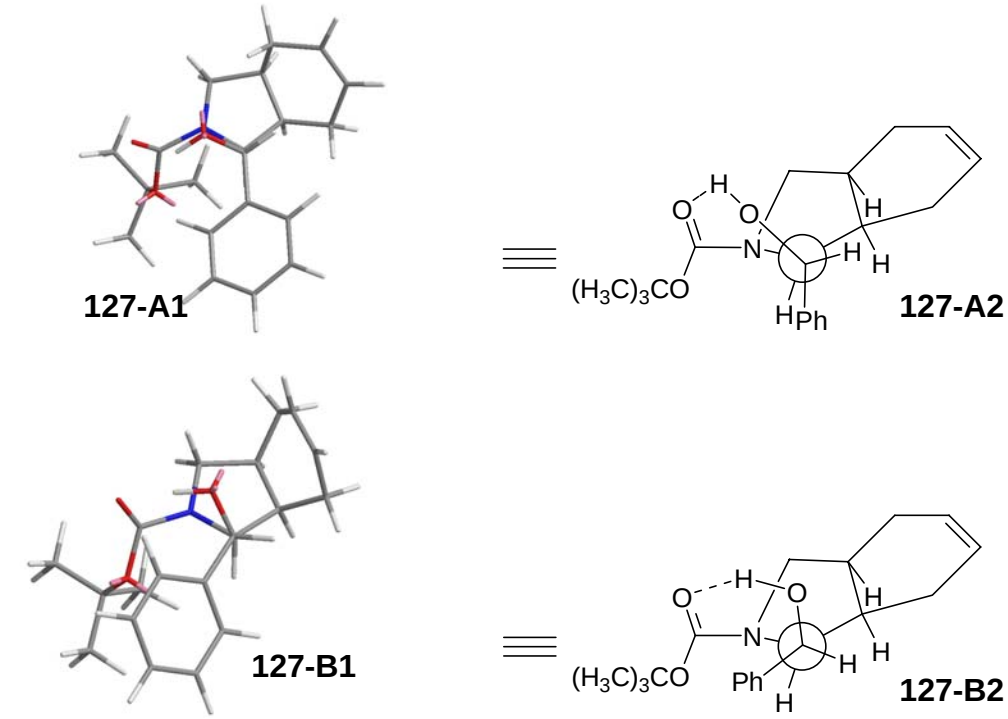


Figure 17. MM2-minimized models for [*(3aS,7aR)-endo-S*]-**127**.

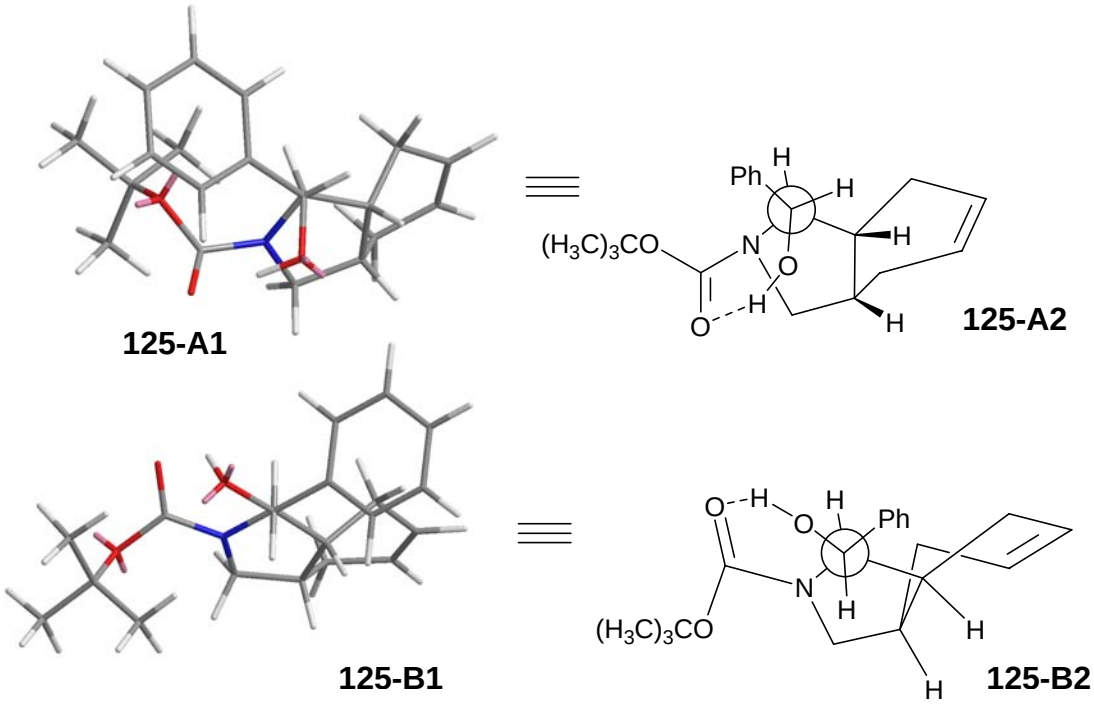


Figure 18. MM2-minimized models for [*(3aS,7aR)-exo-R*]-**125**.

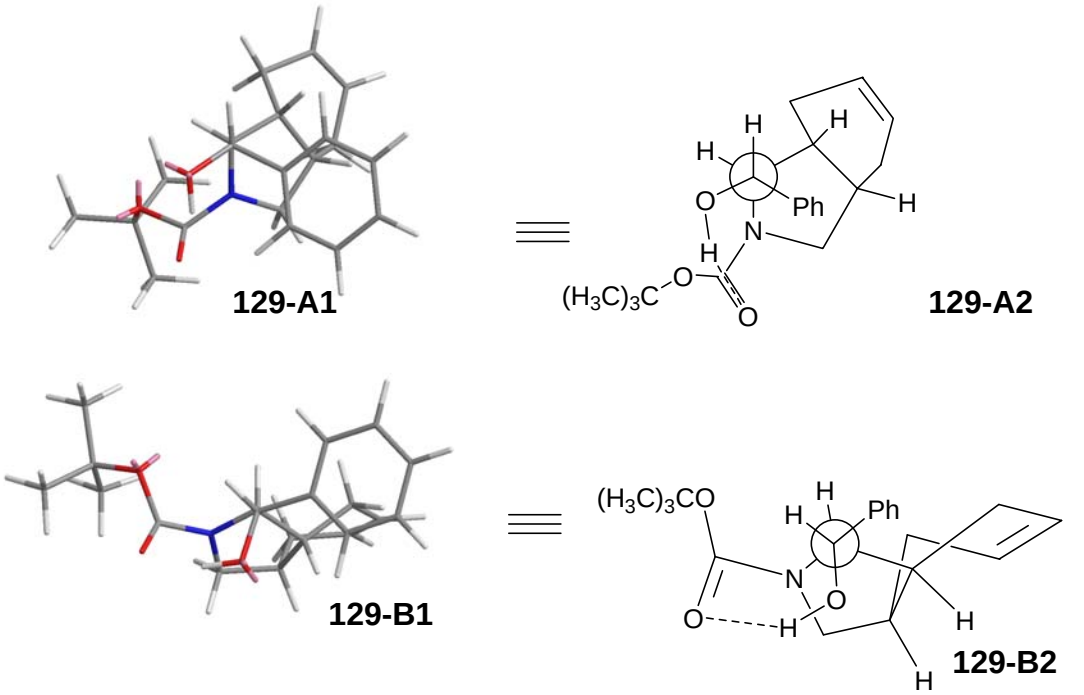


Figure 19. MM2-minimized models for [*(3aS,7aR)-exo-S*]-**129**.

2.4 Approaches to castanospermine

Castanospermine **99** is an alkaloid of the indolizidine group, which has interesting structure and biological properties, and the problem of total synthesis of this compound has attracted considerable attention.[69] The aim of this chapter is to present the results obtained during a study on synthesis of castanospermine analogues (like compound **31**) by our group and a relevant stereochemical investigation.[21, 45]

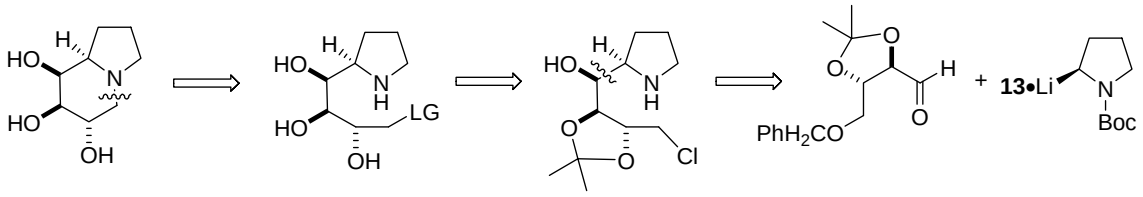
At this point a bit of background is required for the reader regarding the experimental results included in this section of the manuscript. Our group's study on the synthesis of castanospermine analogs was initially the M. Sc. project of J. Shao[45] and included contributions from Drs. Irving and Novak.[21] Shao had successfully synthesized three 1-deoxycastanospermine analogs through a combination of a known, but not commercially available, chiral aldehyde coupled with an enantioselective deprotonation step. However, these were only preliminary results and required verification before publishing. Furthermore, there existed in the literature a wrong assignment of configuration for these target compounds. Therefore, it was very important that the results be verified before contradicting the literature. The non-trivial synthesis of the chiral aldehyde is included here for completeness as I both repeated it both during an honours project at the B. Sc. level and during the initial stages of my graduate program. Furthermore, both enantiomers from this synthesis were required for i) experimentation with different approaches aimed at improving the key-coupling step in our castanospermine analog synthesis ii) verification of preliminary results and iii) potential synthesis of polyhydroxylindolizidines with functionality on the five-membered ring (*vide supra*).

2.4.1 Synthetic strategy

The retrosynthetic analysis of compound **31**, used for the development of a new synthesis of castanospermine analogs, is shown (Scheme 32). A disconnection at nitrogen reveals the six-membered ring could be formed by a S_N2 reaction between the nucleophilic amine in structure **131** and an appropriate leaving group. A second

disconnection reveals that all the necessary carbon atoms can be assembled with four stereogenic centers in place. Therefore, the indolizidine skeleton can be constructed by coupling the chiral configurationally stable organolithium intermediate **15** with Mukaiyama's aldehyde **25**.

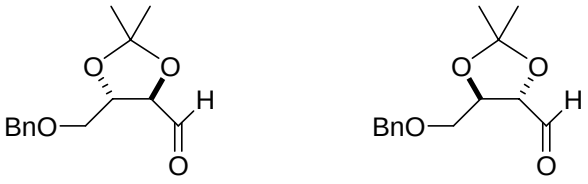
Scheme 32



31 **131** **132** **25** **15**

2.4.2 Synthesis of starting materials

Tartaric acid derivatives are common starting materials in organic synthesis.[70] Both enantiomers of tartaric acid are available in pure form and are relatively inexpensive. Tartaric acid comprises a four-carbon building block with two stereogenic centers. The naturally occurring L-(+)-isomer and it's D-(-)-enantiomer are chiral and possess C_2 symmetry. Therefore, in each case, a reaction at only one end of the molecule leads to only one product. Both enantiomers of Mukaiyama's aldehyde **25** and **133**, required for our synthesis, have been made and are available in large quantities (Figure 20).[43]



25 **133**

$[\alpha]_D^{25}$ = +16 (c 1.0, $CHCl_3$) $[\alpha]_D^{25}$ = -15 (c 1.1, $CHCl_3$)

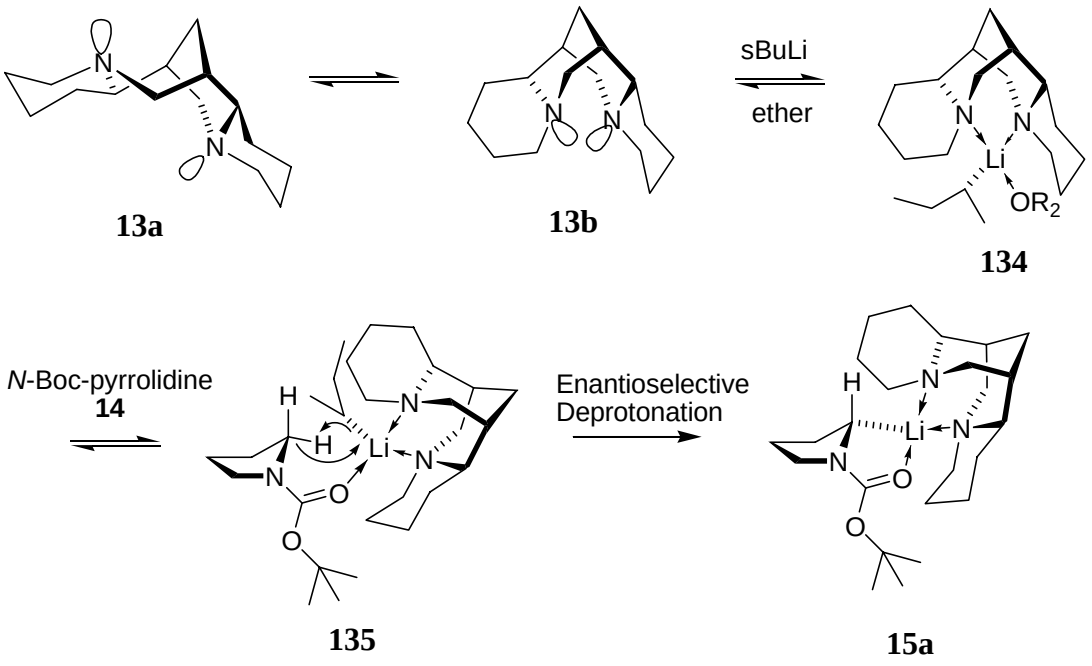
lit.[41] $[\alpha]_D^{25}$ = +16 (c 1.0, $CHCl_3$) lit.[41] $[\alpha]_D^{25}$ = -15 (c 1.1, $CHCl_3$)

Figure 20. Structures of L-tartaric acid derived "Mukaiyama aldehyde" **25** and its enantiomer **133**.

2.4.3 Investigation into deprotonation of *N*-Boc-pyrrolidine 14

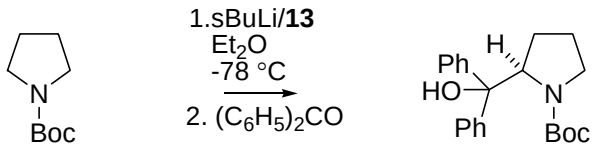
Beak and coworkers had investigated the enantioselective deprotonation of *N*-Boc-pyrrolidine 14, followed by coupling with several electrophiles, in detail.[14] These authors reported two methods for conducting the reaction. Procedure A calls for addition of sBuLi to a cooled (-78 °C) solution of (-)-sparteine **13** and *N*-Boc-pyrrolidine **14**, followed by a 4-hour reaction period, and then direct addition of the electrophile. Procedure B calls for a cooled (-78 °C) solution of s-BuLi and **13** to be added to a cooled (-78 °C) solution of **14**, followed by a 4-hour reaction period, and then addition of the electrophile. In procedure A, the alkyllithium base is added to a cooled solution of the C-H acid in the presence of the chiral ligand. In procedure B, the alkyllithium base is combined with the chiral ligand before addition of the C-H acid. The chiral species that, ultimately, leads to the chiral product is believed to form in the deprotonation step. Therefore, sBuLi must first coordinate to a sparteine molecule, ignoring for the moment the possibility of high aggregation, before it finds a *N*-Boc-pyrrolidine molecule. The formation of pre-lithiation complexes **134** and **135** is outlined in Scheme 33. Lithium cations are thought to form tetravalent complexes in this system.[71] The alkyl lithium must first coordinate with sparteine to give complex **134** (a solvent molecule occupies the fourth coordination site for lithium.). The lithium atom then complexes with the carbonyl oxygen of the carbamate in compound **14** to give complex **135**. Since sparteine is chiral, the two hydrogens α to the nitrogen in complex **135** are diastereotopic. Stereoselective deprotonation follows to give *N*-Boc-2-lithio-pyrrolidine/**13** complex **15a**. Therefore, procedure B looked more attractive as it allowed for complexation of sparteine/sBuLi prior to addition of **14**.

Scheme 33



The results of Beak using benzophenone as the electrophile for both procedures are listed in Table 7. Procedure B resulted in a higher enantioselectivity than A but required the transfer of a cooled solution (–78 °C) via a cannula. (Cannulation involves transfer of the solution through a thin needle by increasing the pressure in one of the vessels connected by the needle). It was uncertain as to how much warming of the solution could occur during transfer. Therefore, procedure B was modified slightly by adding N-Boc-pyrrolidine very slowly to a cooled solution (-78 °C) of (-)-sparteine **13** and sBuLi. The slow addition of **14** was assumed to minimize any warming of the solution. Using benzophenone as the electrophile, compound **136** was obtained with an optical purity (o.p.) of 86% and a yield of 95% (Scheme 34). The o.p. was calculated by measuring the specific rotation of our product and comparing it to the extrapolated specific rotation of the pure enantiomer. (Optically pure R-**136** gives a specific rotation of +146 and the measured value was +126.) Since a high o.p. was obtained using this modified procedure, the modified procedure was then followed using an aldehyde as an electrophile.

Scheme 34



14 **136**

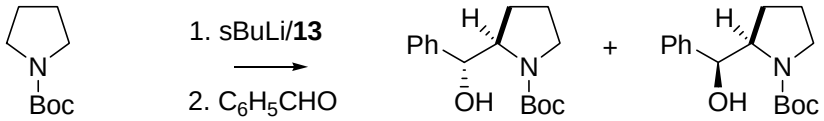
Table 7. Coupling of **14** with benzophenone using different experimental procedures.

Entry	Procedure[a]	Yield (%)	o.p. (%)
1	A[14]	45	83
2	B[14]	75	90
3	Modified B	95	86

a) A: addition of sBuLi to cooled (-78 °C) solution of **13** and **14**. B: cooled (-78 °C) solution of sBuLi and **13** added to a cooled (-78 °C) solution of **14**. Modified B: slow addition of **14** to cooled (-78 °C) s-BuLi/**13** solution**.**

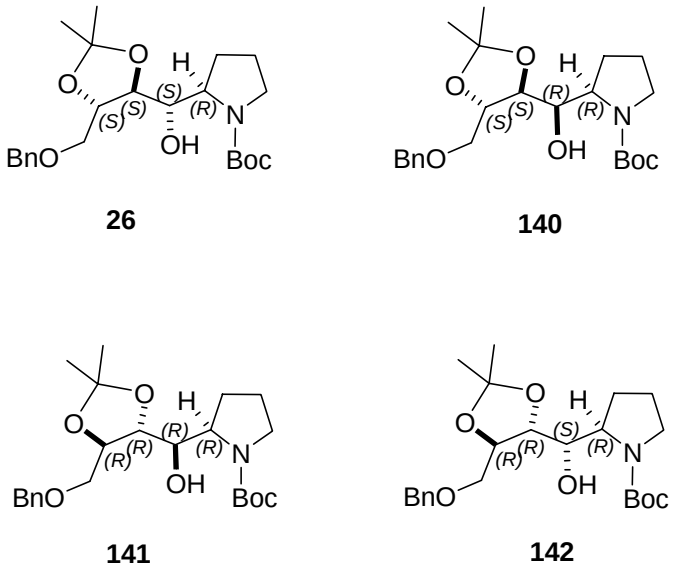
Beak had studied several electrophiles with the s-BuLi/sparteine system, however, aldehydes had not been studied. In our group, benzaldehyde and cyclohexanecarboxaldehyde were used as electrophiles previously before attempts were made to use aldehyde **25**.[45] I decided to repeat the experiments using benzaldehyde (Scheme 35) because the enantioselectivity of the reaction was easily determined by NMR using a chiral shift reagent. In the preliminary results, the *anti*-diastereomer **137** was obtained in 80% e.e. and 55% yield and the *syn*-diastereomer **138** was obtained in 81% e.e. and 27% yield. The diastereomer ratio (dr) for this reaction was 2:1. These results were obtained using Beak's coupling procedure A (*vide supra*). This reaction was repeated using the modified coupling procedure B. The dr was verified as 2:1 by gas chromatography of the crude reaction mixture. The *anti*-diastereomer **137** was obtained in 94% ee and 49% yield and the *syn*-diastereomer **138** were obtained in 91% e.e. and 28% yield. With these promising results I proceeded with the coupling reaction of *N*-Boc-pyrrolidine **14** with Mukaiyama's aldehyde **25**.

Scheme 35



14 **137** **138**

The coupling of *N*-Boc-pyrrolidine **14** with L-tartaric acid derived aldehyde **25** gave L-*anti*-R isomer **26** and L-*syn*-R isomer **140** (Figure 17). Coupling of **14** with D-tartaric acid derived aldehyde **133** gave D-*anti*-R isomer **142** and D-*syn*-R isomer **141**. The *anti* diastereomer was formed preferentially over the *syn* diastereomer for aldehyde **25**. The opposite diastereoselectivity was observed for aldehyde **133**.



26 **140**

141 **142**

Figure 17. Products of coupling of *N*-Boc-pyrrolidine **14** with tartrate derived aldehydes **25** and **133** using sBuLi/**13** as the base.

The previous results using coupling procedure A and the results using the modified procedure B are listed in Table 8. These results appear to confirm the preliminary results.[45] I have not characterized the minor product **140** due to difficulties in separating

it from the unreacted aldehyde **25**. Coupling of **14** with aldehyde **133** gave results similar to the previous results; however, the dr differed slightly.

Table 8: Results of coupling **14** with aldehyde **25** and **133**.

Entry	Procedure	Electrophile	Products	Yield (%)	dr
1	A	**25**	**26** / **140**	43 / 4.5	9:1
2	Modified B	**25**	**26** / **140**	43 / ~5	9:1
3	A	**133**	**141** / **142**	62 / 15	4:1
4	Modified B	**133**	**141** / **142**	55 / 20	3:1

The differences in diastereoselectivity between reactions using **25** and **133** as electrophiles can be rationalized by considering the matched and mismatched pair concept.[72] Consider the reaction between an enzyme and a chiral substrate. One enantiomer of the substrate often reacts preferentially with the enzyme. This seems intuitively acceptable because the 3-dimensional substrate must fit into the 3-dimensional active site of the enzyme. In non-enzymatic organic reactions, the same 3-dimensional interactions between two chiral reacting species apply. Aldehyde **133** gave lower diastereoselectivity with addition to the *N*-Boc-2-lithio-pyrrolidine/sparteine complex **15**. Presumably, the steric interactions that bias one face of the carbonyl group in **133** are smaller compared to aldehyde **25**. Alternatively, the difference in activation energies ($\Delta\Delta G^{\ddagger}$) when **25** reacts to give either the *anti* or the *syn* products is greater (i.e. the reaction is more selective) relative to $\Delta\Delta G^{\ddagger'}$ for analogous situation involving **133** (Figure 18). Aldehyde **25** and complex **15** are the matched pair and their reaction proceeds with higher selectivity.

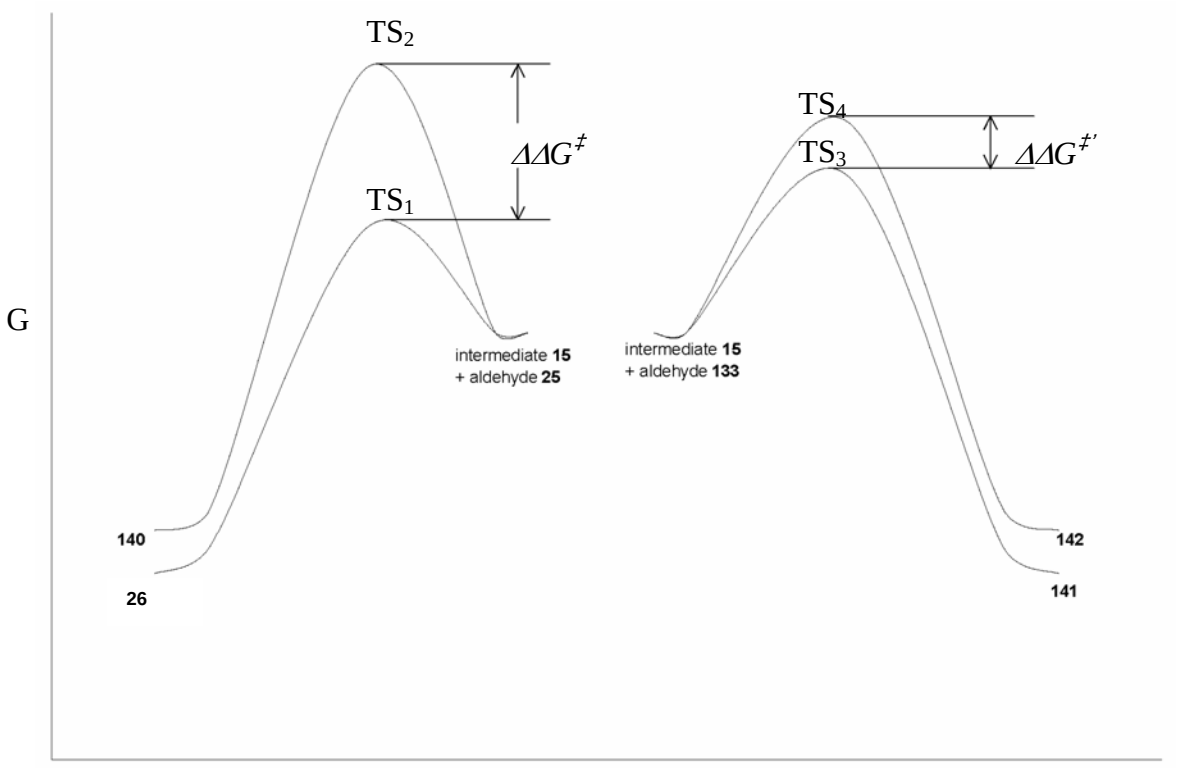


Figure 18. Qualitative free energy diagram representing the coupling of **15** with chiral aldehydes **25** and **133**.

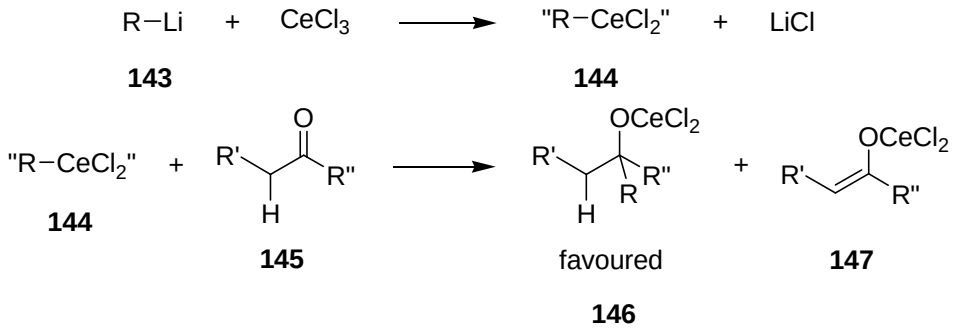
Nucleophilic addition of an achiral nucleophile to chiral aldehyde **25** can be expected to be diastereoselective. Consequently, is the double asymmetric induction necessary? In order to answer this question, *N*-Boc-pyrrolidine **14** was coupled to aldehyde **25** using TMEDA as the bidentate ligand instead of sparteine. The coupling reaction gave a mixture of three diastereomers in roughly equal amounts and an overall yield of 49%. Thus, the selectivity of the reaction is definitely greater when using sparteine (double stereodifferentiation) than when TMEDA was the ligand (simple stereoselection).

2.4.4 The organocerium reagent

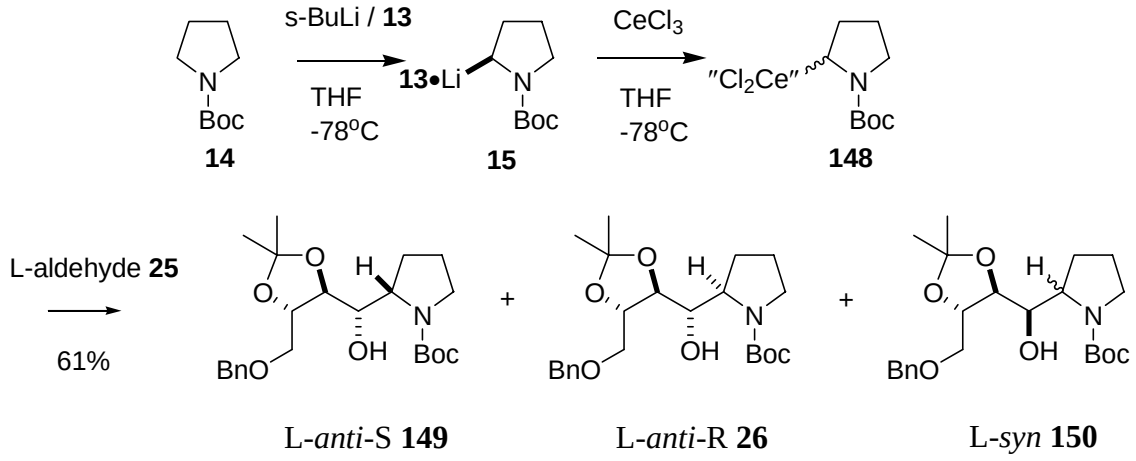
Organolithium compounds can behave either as strong nucleophiles or bases in reaction with electrophiles. Imamoto demonstrated that transmetalation of Li to Ce, by

treating the organolithium reagents with cerium(III) chloride, minimized the proton transfer reactions associated with high basicity of the organometallic species.[73] The reaction of an organolithium reagent with excess anhydrous $CeCl_3$ produces the corresponding organocerium compound. (This reaction also works well with Grignard reagents.) Addition of an easily enolizable ketone, to an organocerium reagent, usually gives the addition product and not the enolate, which would result from the competing proton transfer reaction (Scheme 36).

Scheme 36



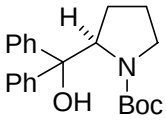
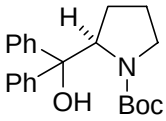
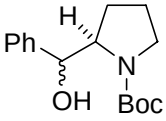
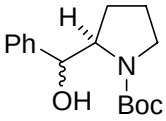
Scheme 37



The coupling reaction was studied to see what effect transmetalation using $CeCl_3$ would have. The first experiment involved coupling of the organocerium reagent **148**, derived from the organolithium species **15,** with L-aldehyde **25** (Scheme 37). Lithiation of *N*-Boc-pyrrolidine **14** was carried out in the usual manner. The organolithium compound was transferred to a cooled (-78 °C) suspension of cerium chloride. Addition

of aldehyde **25** gave a mixture of diastereomers.[73] The yield of this reaction did improve (61% compared to 48%). However, the diastereoselectivity of this reaction differed greatly from that of the organolithium compound. The opposite configuration, at the carbon α to the nitrogen, was observed for the major diastereomer. The ratio of L-*anti*-S **149** to L-*anti*-R **26** was 3.2:1. (As described above, the R isomer **26** was the major diastereomer formed through coupling of **25** directly with **15**.) The absolute configuration of **149** was easily determined because the enantiomer to **149**, the D-*anti*-R isomer, was previously characterized.[45] The *syn* diastereomers were formed in 7% yield. Since no literature precedent could be found regarding the configurational stability of organocerium reagents of this type, a brief study was launched and the organocerium intermediate **148** was coupled to different electrophiles. The results are summarized in Table 9.

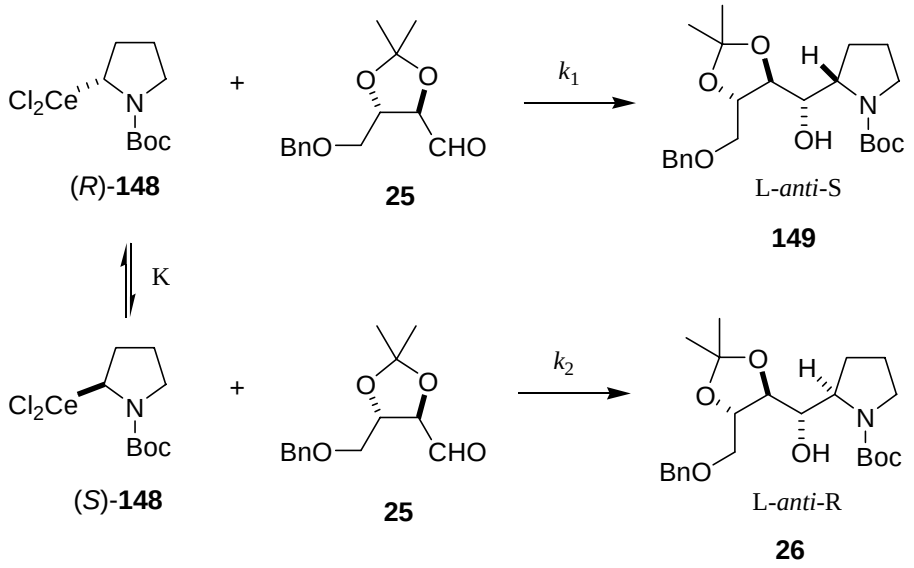
Table 9. Addition of electrophiles to nucleophiles **15** and **148**.

Entry	Electrophile	Nucleophile	Product	Yield (%)	o.p.
1	Ph_2CO	**15**	 **136**	95	86 %
2	Ph_2CO	**148**	 **136**	79	3 %
3	PhCHO	**15**	 **137/ 138** d.r. 2.5:1[a]	89	> 90 %
4	PhCHO	**148**	 **137/ 138** d.r. 4:1[a]	87	< 20 %[b]
5	L-aldehyde **25**	**15**	L-*anti*-R / L-*syn*-R (9:1)	49	NA
6	L-aldehyde **25**	**148**	L-*anti*-S / L-*anti*-R (3.2:1)	54% (+7%*syn*)	NA

a) Determined by gas chromatography. b) This value is an estimate based on the optical rotation of the mixture of diastereomers. I decided not to separate the two isomers due to the results of coupling to benzophenone.

Coupling of the organocerium reagent **148** with benzophenone and with benzaldehyde both low stereoselectivity in both cases compared to the corresponding organolithium reagent. The optical rotation of the products were measured and found to be close to zero. One interpretation suggests that racemization must occur after transmetalation. This implies that the organocerium species **148**, unlike the corresponding organolithium species **15**, is not configurationally stable under these conditions. The diastereoselectivity observed for coupling of **148** with **25** can be rationalized by considering the different rates of coupling to chiral aldehyde **25** (Scheme 38). Therefore, if $k_1 > k_2$ then diastereomer **149** will be formed in excess. This scenario would represent a dynamic kinetic resolution (cf. section 1.2).

Scheme 38



2.4.5 Acylsilane as an aldehyde equivalent

In an effort to increase the stereocontrol in our synthesis, the use of acylsilanes as electrophiles was explored for the sBuLi/sparteine *N*-Boc-pyrrolidine **14** system. This idea involves using a trimethylsilyl group as an achiral auxiliary in place of the aldehyde hydrogen of aldehyde **25**. The increased size of the trimethylsilyl group have been shown to enhance the diastereotopic face selectivity compared to the corresponding chiral aldehydes.[74] The predicted major and minor conformers, stabilized by chelation,

of aldehyde **25** and acylsilane **151** are shown in Figure 19. Addition of lithiated *N*-Boc-pyrrolidine **15** to acylsilane **151** would be expected to give the *anti*-diastereomer (Scheme 39). The trimethylsilyl group can then be removed by protiodesilylation, using fluoride anion, with retention of configuration.[74] High reaction yields are necessary since this approach would add several steps to the synthesis.

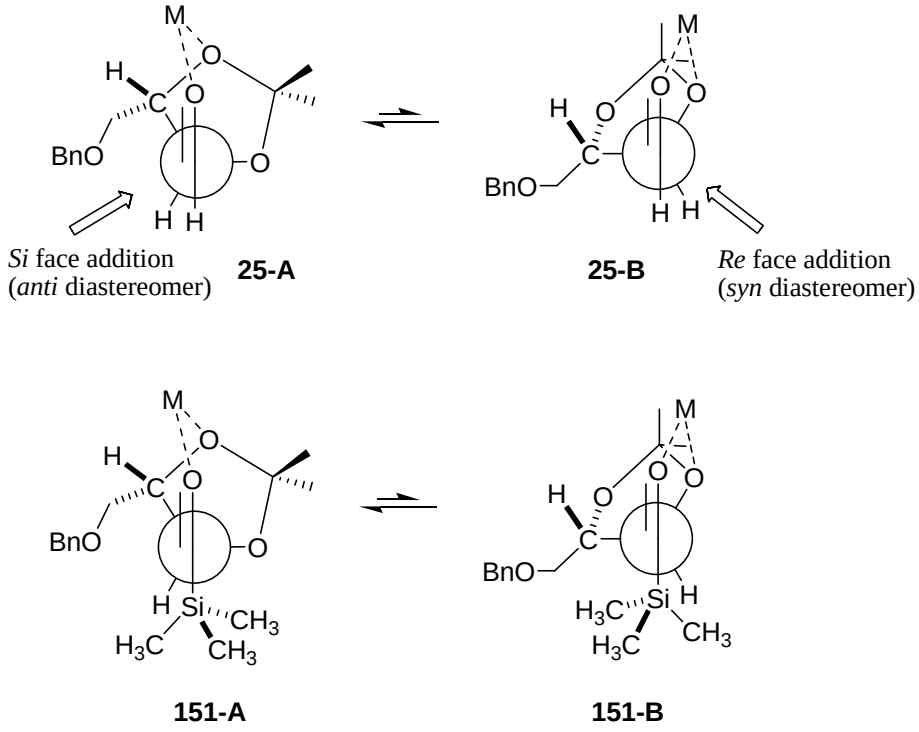
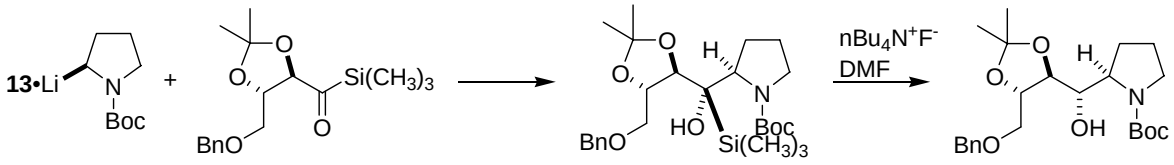


Figure 19. Conformers of aldehyde **25** and proposed acylsilane **151**.

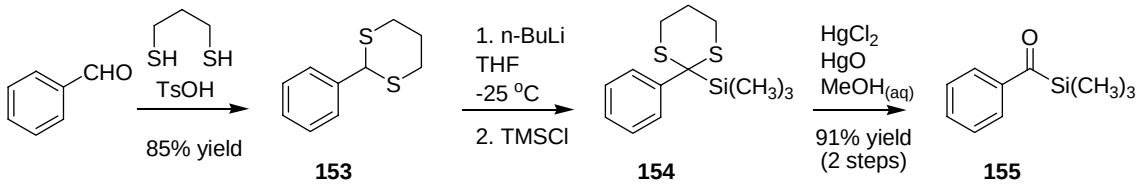
Scheme 39



Before attempting to study a complex acylsilane like **151** (assuming that it could be synthesized) in reaction with lithiated *N*-Boc-pyrrolidine **15**, the reaction conditions had to be optimized on a simple acylsilane. I have synthesized benzoyltrimethylsilane **155** following Corey's procedure (Scheme 40).[75] Benzaldehyde was refluxed with 1,3-

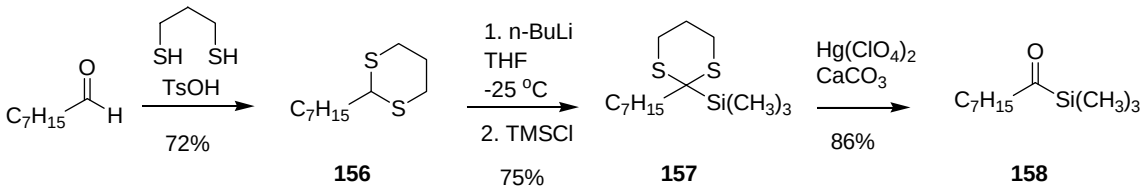
propanedithiol in the presence of an acid catalyst to give 2-phenyl-1,3-dithiane **153** (85% yield). Deprotonation of **153** with n-butyl lithium, followed by reaction with TMSCl gave 2-phenyl-2-(trimethylsilyl)-1,3-dithiane **154** in quantitative yield. Hydrolysis of the thioacetal group in **154** gave acylsilane **155** in 91% yield.

Scheme 40



Attempts to add acylsilane **155** to lithiated pyrrolidine failed. An unstable compound was visible using TLC, however, it rapidly decomposed and was not characterized. I suspected that the presence of the aromatic ring in **155** was causing the difficulties. Ohno had used acylsilanes that contained sp^3-hybridized carbon atoms alpha to the carbonyl group for the stereoselective addition of nucleophiles.[74] Therefore, acylsilane **158** was synthesized to determine whether a simple aliphatic acylsilane would couple to lithiated pyrrolidine. This reagent was made from octanal in the same manner as described for synthesis of **155**, however, the hydrolysis of the thioacetal group in **157** was accomplished using mercury perchlorate instead of mercury chloride and mercury oxide (Scheme 41).

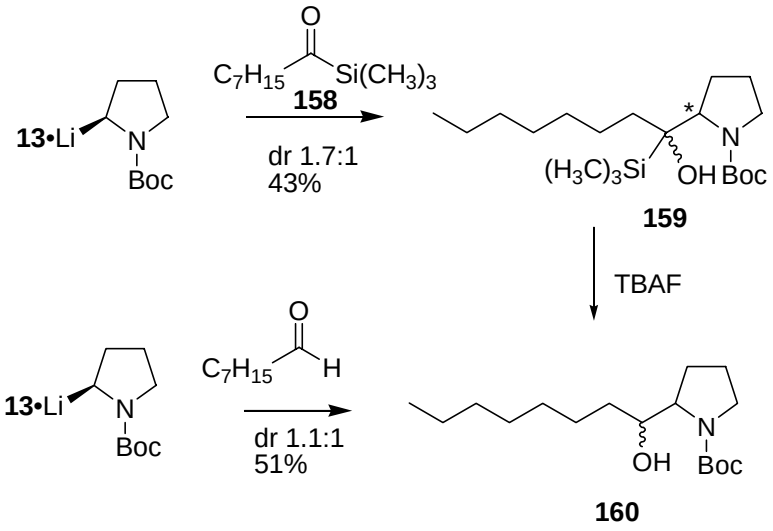
Scheme 41



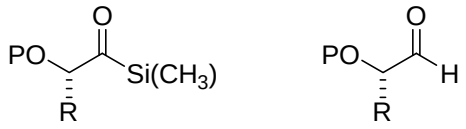
Acylsilane **158** was successfully coupled to the lithiated pyrrolidine **15** (Scheme 42). For comparison, octanal was also coupled to **15**. The yields have not been optimized. The diastereoselectivity observed using acylsilane **155** was higher than in reactions involving the aldehyde. However, the two diastereomers of compound **159**

could not be separated by chromatography. Fortunately, desilylation of the mixture of diastereomers gave the corresponding mixture of diastereomers **160**. The ^{1}H NMR spectra were identical to those obtained by direct coupling of octanal with **15**. This experiment demonstrated that, in principle, acylsilanes could be used as electrophiles in reactions with lithiated pyrrolidine (and, presumably, similar compounds).

Scheme 42



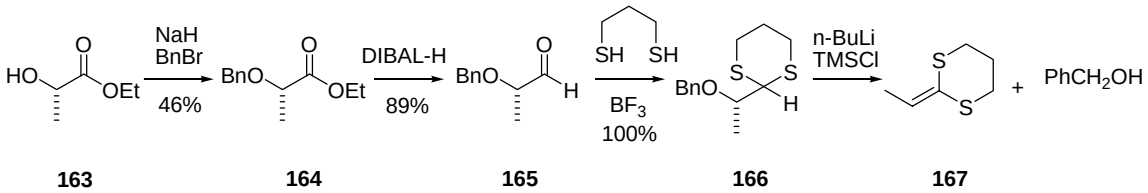
Having established the "proof of principle", the synthesis of a model chiral acylsilane was attempted next. An acylsilane of general structure **161** could be used to demonstrate the increase in selectivity expected, with respect to a similar aldehyde **162** (Figure 20). The synthesis of **161** proved difficult. Two approaches were attempted. First the dithiane route was employed using (S)-ethyl lactate **163** as the substrate (Scheme 43). The hydroxyl group in **163** was protected as the benzyl ether. The ester group was then successfully reduced directly to aldehyde **165** using DIBAL-H. The aldehyde group was transformed to the thioacetal group using boron trifluoride etherate as the catalyst. Silylation of **166**, however, was not possible, presumably due to a very facile elimination reaction.



161 **162**

Figure 20. General structure of model chiral acylsilane **161** and aldehyde **162**.

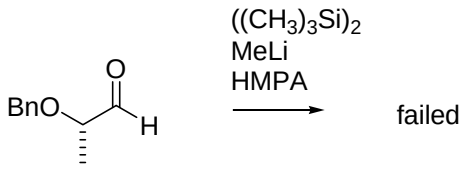
Scheme 43



163 **164** **165** **166** **167**

With the "umpolung approach"[76] (i.e. reversal of polarity) unsuccessful, silylation of aldehyde **165** was attempted directly. It is known that trimethylsilyllithium will add to aldehydes to give the corresponding α-hydroxysilanes. Swern oxidation has been shown to be a suitable method for oxidizing α-hydroxysilanes to acylsilanes. Trimethylsilyl lithium was generated *in situ* from hexamethyldisilane and methyl lithium in HMPA according to the method of Still.[77] Unfortunately, the addition of aldehyde **165** to the trimethylsilyl lithium solution did not give reproducible results and no α-hydroxysilane could be isolated (Scheme 44).

Scheme 44



165

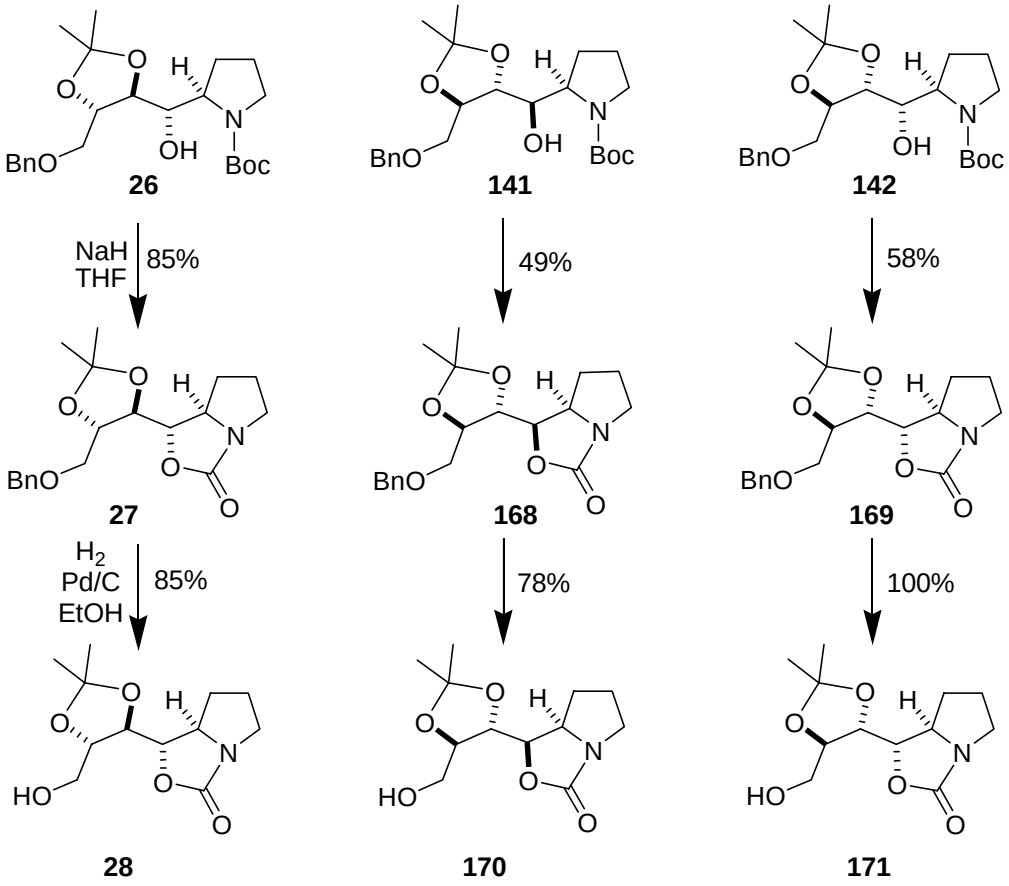
It was decided at this point to terminate the study involving acylsilanes. The objective of this project was to explore the use of an acylsilane as an electrophile for lithiated pyrrolidine, hoping for an improvement over the tartrate-derived aldehyde **25**. The synthesis of the selected acylsilane could, perhaps, be achieved by other known

approaches.[78] However, these syntheses are lengthy and therefore seemed counterproductive as means of improving the efficiency of the coupling reaction in our synthesis of chiral indolizidines.

2.4.6 Synthesis of 1-deoxycastanospermine isomers

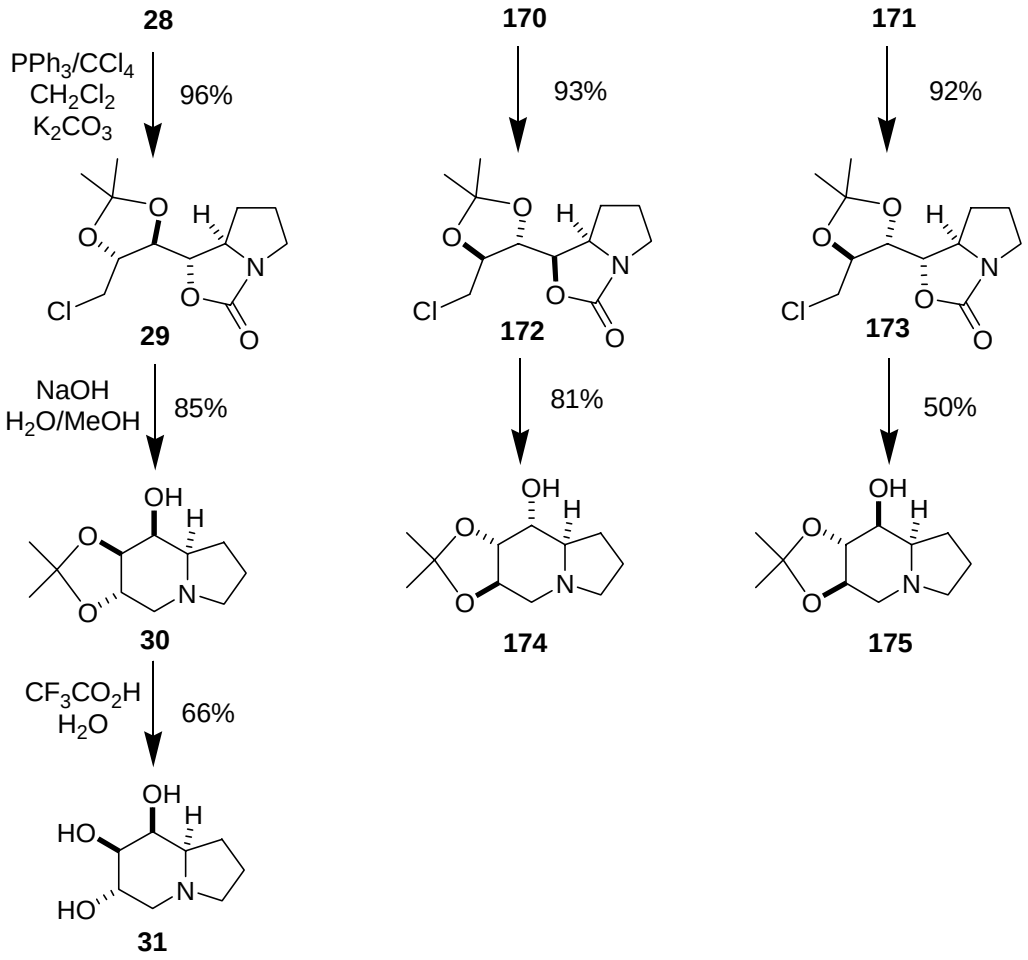
Following the crucial coupling reaction, five steps are required to complete the synthesis of the trihydroxyindolizidine compounds.[21,45] Sufficient amounts of diastereomers **26**, **141** and **142** were prepared and further transformed into their respective indolizidine isomers (Schemes 45 and 46). The Boc protecting group was not removed because the resulting free amine was difficult to purify. Instead, isomers **26**, **141** and **142** were treated with sodium hydride in THF (separately) to give cyclic carbamates **27**, **168** and **169** respectively. These compound have a strong odour and might have significant vapour pressures. The low yields may be due to loss of material when under high vacuum during solvent removal. Deprotection of the primary hydroxyl group gave the corresponding alcohols **28**, **170** and **171**. Removal of the benzyl groups in **28** and **170** were accomplished using hydrogen at medium pressure (50 psi) in the presence of a palladium catalyst. Only a small amount of **171** was made, therefore, hydrogenation was preformed under low pressure using a balloon as the source of hydrogen. The nearly quantitative yield of **171** may be due to the milder conditions.

Scheme 45



Alcohols **28**, **170** and **171** were then transformed into chlorides **29**, **172** and **173** (Scheme 46). These reactions occurred in high yields for all three isomers. Cyclization of the six-membered ring was accomplished by treating chlorides **29**, **172** and **173** with base in a water/methanol solution. This resulted in hydrolysis of the cyclic carbamate, followed by intermolecular nucleophilic displacement to give indolizidines **30**, **174** and **175**. The final step in the synthesis was removal of the acetonide group. Of the three isomers, only compound **30** was transformed into 8-epi-1-deoxycastanospermine **31**.

Scheme 46

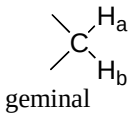
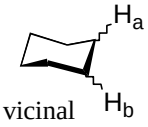


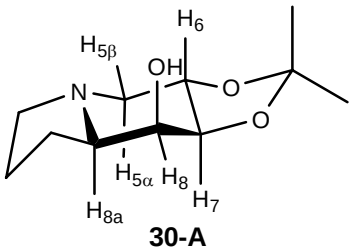
2.4.7 Assignment of absolute configuration of trihydroxyindolizidines 30, 31, 174 and 175

Assignments of configuration, at the four stereogenic centers, were based on the reported stereoselectivites of Beak and Mukaiyama. To verify these predicted assignments; proton spin-coupling constants were measured and assigned using homonuclear decoupling experiments. Typical proton spin-coupling constants are listed in Table 10. The magnitude of spin-coupling constants gives information regarding the orientation of neighbouring protons. Geminal protons typically have large couplings (12 – 15 Hz). Axial and equatorial vicinal protons of a cyclohexane type molecule, in a chair conformation, are also distinguishable. Axial-axial couplings are typically larger values, whereas, axial-equatorial and equatorial-equatorial couplings are typically

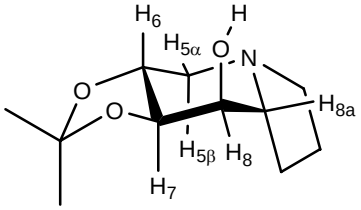
smaller values. If two chair conformations easily interconvert, then the coupling information is generally not retrievable. However, for molecules where one conformation is preferred energetically over the other, coupling constants can be used to assign the relative configuration of stereogenic centers in a chiral molecule.

Table 10. Typical proton-proton spin-coupling constants.[68]

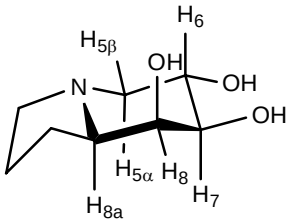
Type	J_{ab} (Hz)	J_{ab} Typical (Hz)
 geminal	0-30	12-15
 vicinal		
axial-axial	6-14	8-10
axial-equatorial	0-5	2-3
equatorial-equatorial	0-5	2-3



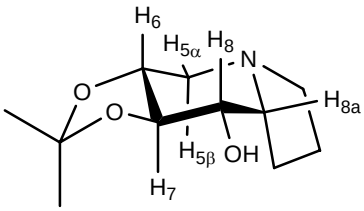
30-A



174-A



31-A



175-A

Figure 21. Conformational structures of indolizidine compounds.

The conformational structures for the four indolizidine compounds synthesized are shown in Figure 21. All measured proton spin-coupling constants support the predicted configurational assignments (Table 11). Axial-axial coupling constants were generally about 10 Hz and axial-equatorial/equatorial-equatorial coupling constants were 5 Hz or less. Furthermore, the opposite configuration at C-8 for isomers **174** and **175** is clearly shown by the spin coupling constants. The proton at C-8 in the *syn* isomer **174-A** is equatorial, therefore, the coupling of H_8 to axial H_7 was small (3.7 Hz). In the *anti* isomer **175-A,** the proton at C-8 is axial. Consequently, the coupling of H_8 to axial H_7 was large (9.0 Hz). The spin-coupling constants provide very good evidence that the assignment of configurations, based on the reported stereoselectivites of Beak and Mukaiyama, were correct.

Table 11. Measured proton spin-coupling constants for indolizidine compounds **30**, **31**, **174**, and **175**. (Coupling constants in Hz.)

Isomer	$J_{5\alpha\text{-}5\beta}$	$J_{5\alpha\text{-}6}$	$J_{5\beta\text{-}6}$	$J_{6\text{-}7}$	$J_{7\text{-}8}$	$J_{8\text{-}8a}$
30	9.5	9.8	4.2	9.8	2.3	2.3
174	9.6	5.6	9.6	9.7	3.7	3.7
175	9.5	5.2	9.6	9.6	9.0	6.0
31	11.5	11.5	5.3	9.6	2.5	< 1

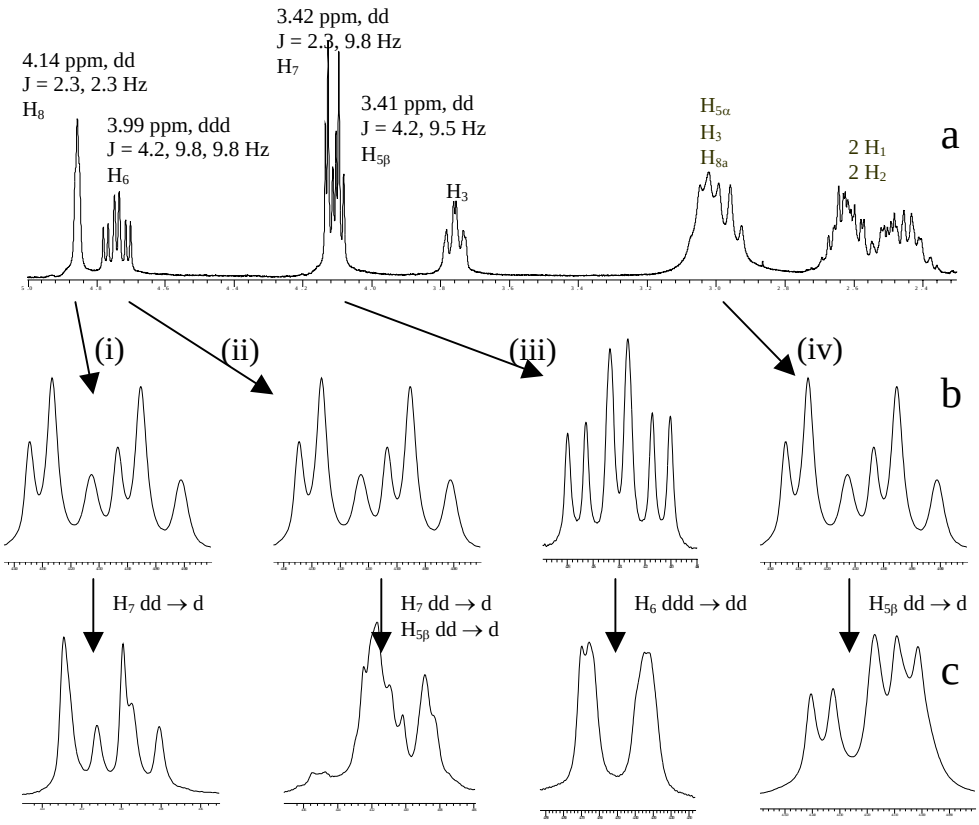


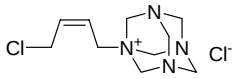
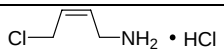
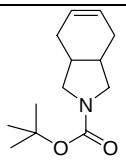
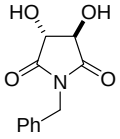
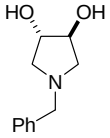
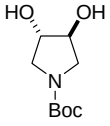
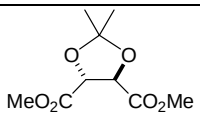
Figure 22. Homonuclear decoupling of indolizidine **30**. a) Normal ^{1}H NMR spectrum. b) Normal ^{1}H NMR spectrum expanded. c) Homonuclear decoupled spectrum irradiated at frequencies i, ii, iii and iv, respectively.

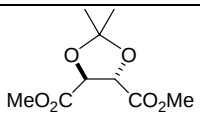
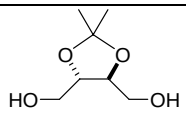
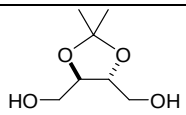
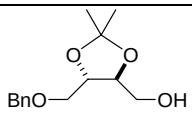
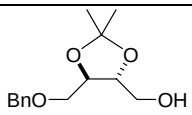
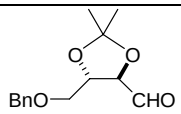
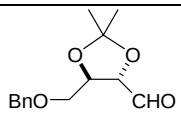
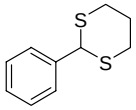
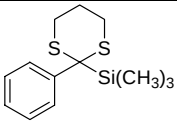
The ^{1}H NMR spectra showing the reduction in multiplicity (for selected signals) after the decoupling (for isomer **30**) are shown in Figure 22. Irradiation at H_8's frequency (4.14 ppm) has the effect of reducing the multiplicity of H_7 from a double doublet to a doublet (Figure 22 i). Decoupling of H_6 (3.99 ppm) produces a decrease in multiplicity for both H_7 and $H_{5\beta}$ (Figure 22 ii). Simultaneous decoupling of H_7 and $H_{5\beta}$ (3.40 ppm) reduces H_6 from a double double doublet to a doublet (Figure 22 iii). Finally, irradiation of the obscured $H_{5\alpha}$ signal (~3 ppm) allows for unambiguous assignment of the $H_{5\beta}$ resonance as the double doublet at 3.41 ppm, which was reduced to a doublet (Figure 22 iv).

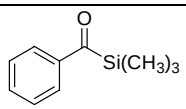
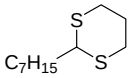
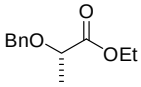
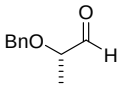
2.5 Summary of experiments previously described

A large portion of the work associated with preparing compounds necessary to carry out research described in this thesis involved repeating procedures that have been previously published. In all cases the spectral data of the compounds obtained matched the published spectra. In some cases, the experimental procedures were modified which resulted in better yields or avoided a polar intermediate (Table 12, entries 3, 7 and 17). As mentioned before (c.f., page 50), a portion of this thesis deals with a re-evaluation of the work done previously in our laboratory.[45] The following experiments were repeated (Table 13) and on the whole the yields were the same. The measured specific rotation differed for a few of the compounds (Table 13, entries 1, 2, 5, 12 and 16). However, the homonuclear decoupling experiments (c.f., pages 67-70), together with the knowledge of the known absolute configuration of the tartrate starting material, gave direct evidence of the absolute configuration of the synthesized compounds.

Table 12. Synthetic preparations of compounds, not commercially available, reported in this work that were previously described in the literature.

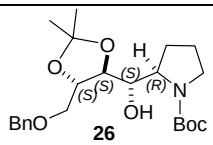
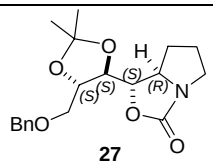
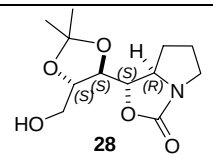
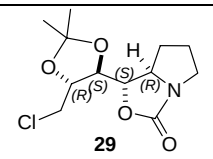
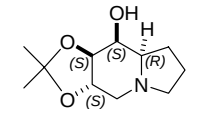
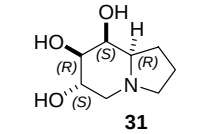
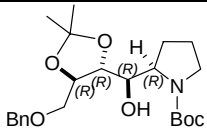
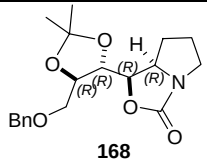
Entry	Synthetic Target	Reported Yield (%)	Observed Yield (%)	Page No.	Literature Reference
1	 **83**	99	100	76	49
2	 **84**	100	80	77	49
3	 **85**	74 (amine)	72	78	49*
4	 **116**	73	89	84	67
5	 **104**	73	57	91	59
6	 **105**	86	88	92	59
7	 **106**	86	28	93	58*
8	 **184**	88	95	94	82

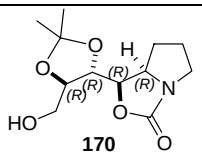
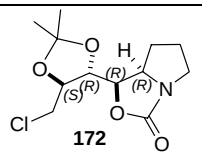
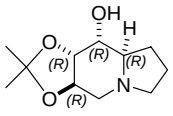
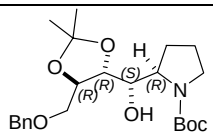
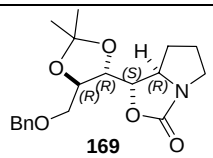
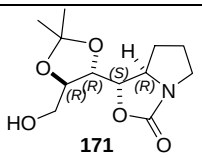
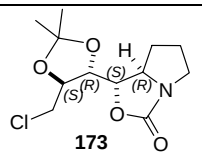
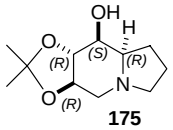
9	 **185**	96	58	95	82
10	 **186**	75	92	96	84
11	 **187**	95	80	96	84
12	 **188**	76	66	97	84
13	 **189**	79	62	97	84
14	 **25**	85	81	98	43
15	 **133**	not given	79	98	43
16	 **14**	NA	82	99	85
17	 **153**	73	85	108	87*
18	 **154**	90	91	109	75

19	 **155**	58	89	110	75
20	 **156**	80	72	111	88
21	 **164**	88	46	114	91
22	 **165**	78	89	115	91

* Procedure modified from reported method.

Table 13. Comparison of compounds obtained in this work with those reported in J. Shao's M. Sc. thesis (reference 45).

Entry	Synthetic Target	Reported Yield (%)	Reported $[\alpha]_D^{25}$	Observed Yield (%)	Observed $[\alpha]_D^{25}$
1	 **26**	43	-16.8 (c 1.8, $CHCl_3$)	43	+29 (c 1.0, $CHCl_3$)
2	 **27**	80	+34.4 (c 1.0, $CHCl_3$)	85	+15 (c 1.0, $CHCl_3$)
3	 **28**	88	+26.8 (c 1.1, $CHCl_3$)	85	+26 (c 1.0, $CHCl_3$)
4	 **29**	86	+24.8 (c 1.0, $CHCl_3$)	96	+26 (c 1.0, $CHCl_3$)
5	 **30**	83	+24.8 (c 1.0, $CHCl_3$)	85	+42 (c 1.1, $CHCl_3$)
6	 **31**	81	+32.2 (c 2.0, MeOH)	66	+32 (c 1.0, MeOH)
7	 **141**	62	+34.4 (c 1.42, $CHCl_3$)	55	+35 (c 1.0, $CHCl_3$)
8	 **168**	80	+34.4 (c 1.4, $CHCl_3$)	49	+37 (c 1.0, $CHCl_3$)

9	 **170**	81	+42.2 (c 1.0, $CHCl_3$)	78	+45 (c 0.88, $CHCl_3$)
10	 **172**	91	+34.0 (c 0.25, MeOH)	93	+34 (c 1.0, $CHCl_3$)
11	 **174**	78	-48.8 (c 1.2, $CHCl_3$)	81	-55 (c 0.9, $CHCl_3$)
12	 **142**	15	+3.2 (c 1.4, $CHCl_3$)	20	+47 (c 1.1, $CHCl_3$)
13	 **169**	67	+37 (c 1.1, $CHCl_3$)	58	+37 (c 1.0, $CHCl_3$)
14	 **171**	75	+55.1 (c 0.97, $CHCl_3$)	100	+47 (c 0.80, $CHCl_3$)
15	 **173**	87	+49.2 (c 1.0, $CHCl_3$)	92	+51 (c 1.0, $CHCl_3$)
16	 **175**	67	+9.1 (c 1.0, $CHCl_3$)	50	-14 (c 1.3, $CHCl_3$)

2.6 Conclusions and suggestion for future work

The initial work in this thesis concentrated on the verification of preliminary results for the new stereoselective synthesis of castanospermine analogs. Three polyhydroxylindolizidines were synthesized and their absolute configuration was determined (as depicted in structures **30**, **174** and **175**). 1-Deoxycastanospermine **31** was synthesized in six steps and 17% overall yield from *N*-Boc-pyrrolidine **14** and aldehyde **25**. The preliminary results for the synthesis of castanospermine analogue were verified.

Two strategies were unsuccessfully carried out with the goal of improving the yield and/or selectivity in the coupling of **25** to **14**. The use of an acylsilane in place of an aldehyde was shown to work, in principle, as an electrophile for intermediate **15**. The study, however, was concluded without the successful synthesis of an acylsilane analog of **25**. Attempts to improve the nucleophilicity of intermediate **15** through transmetalation with $CeCl_3$ were partially successful. The yield of the coupling reaction between **14** and **25** was increased from 49% to 61%. However, the stereoselectivity of this reaction decreased significantly.

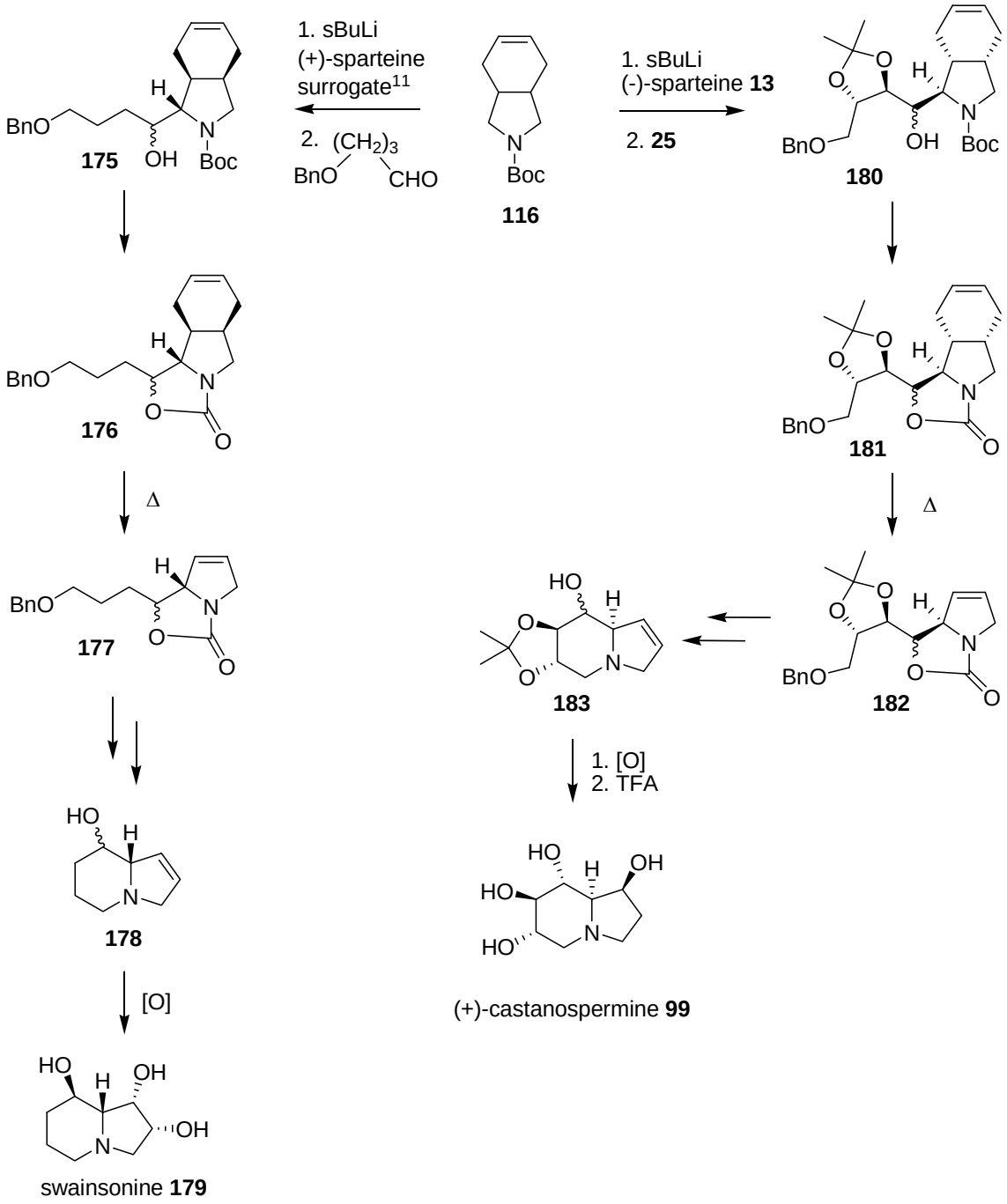
The third objective of this thesis was to introduce functionality to the five-membered ring of the indolizidine structure. This aspect was absent from the original synthetic plan and would allow for a much more flexible synthesis of castanospermine analogs. A methodology study on the stereoselective alkylation of *N*-Boc-3-pyrroline **85** was carried out and showed that only simple alkyl halides would add α to the nitrogen with any degree of reproducibility. Modest yields and modest stereoselectivity were obtained. The best result was obtained with chiral lithium amide **88** as the base and n-butyl bromide as the electrophile (36% yield, 21% ee). It was also shown, by deuterium labelling experiments, that internal proton return can be a factor in the deprotonation of **85** with lithium amide bases. This was the first time ipr was shown to occur in organolithium chemistry outside of enolate systems.

In order to avoid the problems associated with the alkylation of **85**, a study on the stereoselective alkylation of Boc-hh-isoindole **116** was initiated. Compound **116** was envisioned as a replacement for **85** in which the carbon-carbon double bond was

protected as a Diels-Alder adduct. Compound **116** was successfully reacted in a lithiation/substitution sequence to make alkylation products **120**, **121** and **122**. Using sparteine **13**/sBuLi as the base and benzaldehyde as the electrophile, **125** (the major diastereomer from **116**) was obtained in 90% ee. Further work on this study should include the pyrolysis step for compounds **120**, **121**, and **122**.

Assuming that the conditions for the retro-Diels-Alder step could be worked out, the total synthesis of the alkaloids (+)-castanospermine **99** and swainsonine **179** from **116** would be possible (Scheme 47). Coupling of aldehyde **25** with **116** using sBuLi/(-)-sparteine **13** should give the correct configuration at C-8a (as in **99**) for compound **180**. However, the newly formed hydroxyl group would probably give the wrong configuration (based on the coupling of **14** with **25**). The configuration at C-8 could be inverted (e.g. using the Mitsunobu reaction). Formation of the cyclic carbamate **181** would likely increase the chances the molecule would survive pyrolysis. Transformation of **182** to **183** should be straightforward. Finally, a survey of hydroxylation conditions for the correct regio- and the stereochemistry would give (+)-castanospermine **99**. Similarly, swainsonine **179** could be synthesized by a similar approach. Swainsonine has the opposite configuration at C-8a as castanospermine. Therefore a (+)-sparteine surrogate could be utilized.[11]

Scheme 47


1. sBuLi
(+)-sparteine
surrogate[11]
2. (CH2)3
BnO
CHO
116
1. sBuLi
(-)-sparteine 13
2. 25
175
176
177
178
179
180
181
182
183
Δ
[O]
1. [O]
2. TFA
swainsonine 179
(+)-castanospermine 99

CHAPTER 3: EXPERIMENTAL

3.1 General methods

All air sensitive reactions were carried out under dry nitrogen. Tetrahydrofuran, dimethoxyethane and diethyl ether were distilled under nitrogen from sodium and benzophenone. Dichloromethane, triethylamine, and diisopropylamine were distilled from calcium hydride. Dimethylsulfoxide and N,N-dimethylformamide were distilled from calcium hydride at reduced pressure. Alkyl lithium reagents were periodically titrated using 2,5-dimethoxybenzyl alcohol.

Gas chromatography (GC) was performed using Hewlett Packard 5890A instrument fitted with a methyl silicone gum column (HP-1, 5 m x 0.53 mm). Dry flash column (DFC) chromatography was carried out using Sigma silica gel Type H (10-40 μm).[79] Thin layer chromatography (TLC) was performed on precoated glass plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), by staining with iodine, or by immersing in a developing solution and charring on a hot plate. (The developing solution was prepared by dissolving concentrated sulfuric acid (50 g), cerium (IV) sulfate (10 g) and phosphomolybdic acid hydrate (40 g) in water (1 L)).

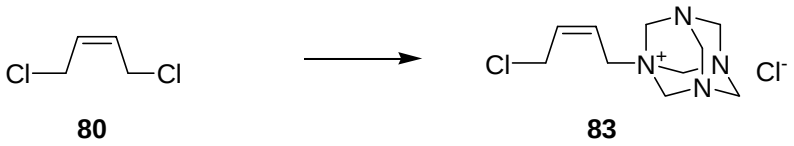
Concentrated phosphate buffer was prepared was prepared by dissolving sodium hydrogen phosphate (47 g) and sodium dihydrogen phosphate (32 g) in water (0.5 L).

Melting points and boiling points are uncorrected. Melting points were measured on a Gallencamp melting point apparatus.

Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AM-300 (300 MHz) or a Bruker 500 MHz spectrometer in chloroform-d solvent unless otherwise noted. Chemical shifts are reported in ppm of δ scale with TMS (δ = 0.0 ppm for ^{1}H NMR) or chloroform-d (δ = 77.0 ppm for ^{13}C NMR) as the internal standard. Infrared (IR) spectra were recorded on a Biorad FTS-40 Fourier transform interferometer using a diffuse reflectance cell (DRIFT). Only diagnostic peak frequencies are reported. Mass spectra were recorded on a VG Analytical retrofit of a single sectored, magnetic scanning MS-12 (low resolution) or a double speed VG 70-250-VSE (high resolution) and are reported as m/z ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV. Gas Chromatography/Mass Spectrometry (GC/MS) was performed on an Agilent Technologies 6890N Network GC System equipped with a 7683 Series Injector and a 5973 Network Mass Selective Detector. GC separations were carried out on a DB-5 (0.25 mm x 30 m x 0.25 μm) column using helium at flow of 0.5 mL/min. The oven was held at 125 °C for 1 min. and then raised to 300 °C at a rate of 5 °C/min. Optical rotations were measured on a Rudolph Instruments Digipol 781 Automatic Polarimeter (1 dm, 1 mL cell) at 589 nm; all concentrations are given in g/100 mL.

3.2 Synthesis of N-Boc-3-pyrroline 85

1-((2*Z*)-4-Chlorobut-2-enyl)-3,5,7-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decane; chloride 83[49]



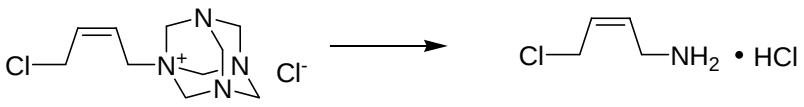
80 **83**

Hexamethylenetetramine **82** (20.0 g, 0.190 mol) was dissolved in chloroform (200 mL) at room temperature. To this solution was added (2-Z)-1,4-dichlorobut-2-ene **80** (15.0 mL, 0.140 mol). The reaction mixture was refluxed overnight and cooled to room temperature. The product was isolated by filtration and washed with dichloromethane (200 mL). The product **83** was a white solid and was used without any further purification (52 g, quantitative yield).

mp: 185-190 °C, dec. (lit.[49] 180-190 °C, dec.).

^{1}H NMR δ (D_2O)**:** 6.03 (dt, *J* = 10.6, 8.3 Hz, 1H); 5.46 (dt, *J* = 10.6, 8.3 Hz, 1H); 4.80 (s, 6H); 4.38 (d, *J* = 13 Hz, 3H); 4.23 (d, *J* = 13 Hz, 3H); 3.89 (d, *J* = 8.3 Hz, 2H); 3.34 (d, J = 8.3 Hz, 2H).

(2Z)-4-Chlorobut-2-enamine hydrochloride 84[49]

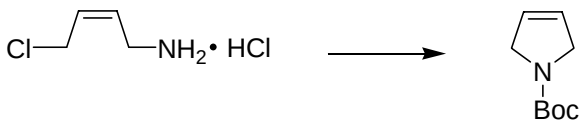


83 **84**

The starting material **83** (48.0 g, 0.180 mol) was added portion-wise into a refluxing solution of conc. HCl (63 mL) and ethanol (360 mL). The heating mantle was then removed and the reaction mixture was stirred at room temperature for 12 h. The resulting suspension was cooled to 0 °C for 2 h. Ammonium chloride was removed by filtration and the solvent was removed on a rotary evaporator. The residue was dissolved in ethanol and filtered to further remove ammonium chloride. The solvent was evaporated under vacuum to give the desired product **84** (20.5 g, 80%).

^{1}H NMR δ (D_2O)**:** 6.03 (dt, *J* = 10.6, 8.3 Hz, 1H); 5.46 (dt, *J* = 10.6, 8.3 Hz, 1H); 3.89 (d, *J* = 8.3 Hz, 2H); 3.34 (d, *J* = 8.3 Hz, 2H).

***N*-(*tert*-butoxycarbonyl)-3-pyrroline 85**[49]



84 **85**

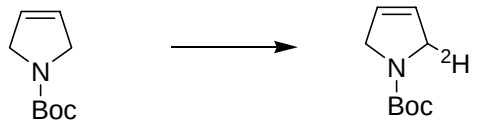
(*Z*)-4-Chlorobut-2-enamine hydrochloride **84** (20.5 g, 0.14 mol) was dissolved in ethanol (500 mL) and water (25 mL). K_2CO_3 (50 g, 0.36 mol) was added and the reaction mixture was refluxed for 2 h. The solution was allowed to cool to room temperature. The precipitated salts were filtered off and the mother liquor was acidified with 6 M hydrochloric acid (77 mL). The product was concentrated under reduced pressure. The unpurified amine hydrochloride (21.3 g) was taken up in methanol (150 mL) at room temperature. NaOH (12.8 g, 0.32 mol) in water (50 mL) was slowly added. Di-*tert*-butyl dicarbonate (45.8 g, 0.21 mol) in methanol (50 mL) was added dropwise, with stirring, over 1 hour. Within an hour an abundant amount of a white precipitate had formed. After stirring at room temperature for 24 h, the reaction mixture was then extracted with hexane (3 x 200 mL), and the organic layers were combined, dried ($MgSO_4$) and filtered through a pad of Celite. The solvent was removed and the crude product was purified by distillation (bp. 90 °C, 0.1 mmHg) to give N-(*tert*-butoxycarbonyl)-3-pyrroline **85** (17.6 g, 72%).

^{1}H NMR δ: 5.76 (s, 1H); 5,72 (s, 1H); 4.11 (s, 2H); 4.06 (s, 2H); 1.45 (s, 9H).

LRMS (EI^+) (relative intensity): 169 (5); 112 (21); 96 (25); 69 (16); 68 (47); 57 (100).

3.3 Reactions involving N-Boc-3-pyrroline

N-(*tert*-butoxycarbonyl)-2-deuterio-3-pyrroline 86



85 **86**

A: Sparteine/sec-BuLi

(-)-Sparteine (203 mg, 0.868 mmol) was dissolved in freshly distilled THF (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (1.1 mL, 0.83 M) was added drop wise and the solution was stirred for 15 min. *N*-Boc-3-pyrroline **85** (134 mg, 0.792 mmol) in THF (1 mL) was added slowly over 5 min and stirred at –78 °C for 15 min. The reaction was quenched with deuterium oxide (1 mL) and warmed to room temperature. Saturated ammonium chloride (10 mL) was added and the aqueous phase was extracted with hexane (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The recovered N-Boc-3-pyrroline (256 mg crude, 90% recovery est. by ^{1}H NMR) was analyzed by ^{1}H NMR and determined to have one deuterium (99%).

B: LDA

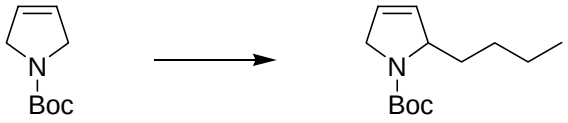
Lithium diisopropylamide was prepared by adding *n*BuLi (0.90 mL, 0.83 M) to an ice-cooled (0 °C) solution of diisopropylamine (0.11 mL, 0.75 mmol) in THF (10 mL). After 30 min., the LDA was cooled to –78 °C and *N*-Boc-3-pyrroline **85** (115 mg, 0.680 mmol) in THF (1 mL) was added. The reaction was stirred for 30 min., after which, a second portion of *sec*-BuLi (0.90 mL, 0.83 M) was added. The reaction was quenched with deuterium oxide (1 mL) and warmed to room temperature. Water (10 mL) was added and the aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The recovered N-Boc-3-pyrroline (104 mg, 90% recovery) was analyzed by ^{1}H NMR and determined to have one deuterium (96%).

^{1}H NMR δ: 5.74 (m, 2H); 4.06 (m, 3H); 1.43 (s, 9H).

^{13}C NMR δ: 154.3; 125.92; 125.81; 125.78; 125.68; 79.2; 53.1; 52.82; 52.78 (t, J = 22 Hz); 52.5 (t, J = 22 Hz); 28.5 (Rotational isomers).

LRMS (EI^{+}) (relative intensity): 170 (4); 113 (16); 97 (19); 70 (24); 69 (38); 57 (100).

***N*-(*tert*-butoxycarbonyl)-2-butyl-3-pyrroline 87[46]**



85 **87**

A: Chiral lithium amide

A suspension of (-)-bis-[(*S*)-α-methylbenzyl]amine hydrochloride (275 mg, 1.05 mmol), in tetrahydrofuran (5 mL), was cooled to –78 °C and n-butyl lithium (0.88 mL, 2.4 M) was slowly added. After 15 min, the lithium amide solution was warmed to 0 °C, held at this temperature for 30 min and cooled back to –78 °C. *N*-Boc-3-pyrroline **85** (169 mg, 1.00 mmol), in tetrahydrofuran (1 mL), was added to the chiral lithium amide over 20 min. The reaction was stirred for 15 min and n-butyl bromide (0.22 mL, 2.0 mmol) was added. The mixture was stirred at –78 °C for 20 min, warmed to 0 °C and quickly quenched with saturated sodium bicarbonate (5 mL). The aqueous phase was extracted with hexanes (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave non-racemic product **87** (82 mg, 36%), unreacted *N*-Boc-3-pyrroline **85** (49 mg, 29%) and the chiral amine (233 mg, 94%).

ee 21 % (+)-$Eu(hfc)_3$

B: LDA[46]

Lithium diisopropylamide was prepared by adding *n*-BuLi (0.46 mL, 2.4 M) to a cooled (-78 °C) solution of diisopropylamine (0.15 mL, 1.05 mmol) in THF (5 mL). The solution was warmed to 0 °C, held at this temperature for 30 min and cooled back to –78 °C. *N*-Boc-3-pyrroline **85** (169 mg, 1.0 mmol) in THF (1 mL) was added. The reaction was stirred for 15 min and n-butyl bromide (0.22 mL, 2.0 mmol) was added. The mixture was stirred at –78 °C for 15 min, warmed to 0 °C and quickly quenched with saturated sodium bicarbonate (5 mL). The aqueous phase was extracted with hexanes (3 x 25 mL). The organic phase was collected, washed with brine (5 mL), dried

($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **87** (124 mg, 55%).

C: LDA plus DBU additive

Lithium diisopropylamide (0.94 mmol) was prepared as above but with DBU (0.14 mL, 0.94 mmol). N-Boc-3-pyrroline (159 mg, 0.94 mmol) in THF (1 mL) was added and reacted with n-butyl bromide (0.50 mL, 4.7 mmol) was added. The reaction time and work-up were the same. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **87** (120 mg, 57%), the isomer 4-butyl-4,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester **96** (27 mg, 13%) and recovered starting material **85** (12 mg, 7%).

D: TMEDA/sec-BuLi

N,*N*,*N*,*N*-Tetramethylethylenediamine (0.15 mL, 0.98 mmol) was dissolved in freshly distilled THF (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (1.18 mL, 0.83 M) was added drop wise and the solution was stirred for 15 min. *N*-Boc-3-pyrroline **85** (150 mg, 0.89 mmol) in THF (1 mL) was added slowly over 5 min and stirred at –78 °C for 15 min. The reaction was stirred for 15 min and n-butyl bromide (0.48 mL, 4.5 mmol) was added. The mixture was stirred at –78 °C for 10 min, warmed to 0 °C for 15 min and quenched with water (5 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **87** (84 mg, 42%).

*E: Sparteine **13**/sec-BuLi*

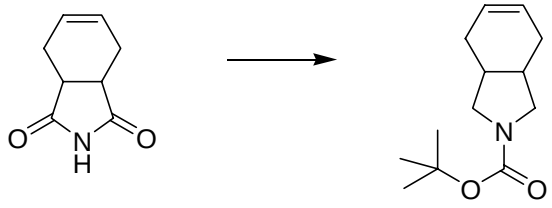
(-)-Sparteine **13** (252 mg, 1.08 mmol) was dissolved in freshly distilled THF (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (1.30 mL, 0.83 M) was added drop wise and the solution was stirred for 15 min. *N*-Boc-3-pyrroline **85** (166 mg, 0.982 mmol) in THF (1 mL) was added slowly over 5 min. The reaction was stirred for 15 min and n-butyl bromide (0.53 mL, 4.9 mmol) was added. The mixture was stirred at –78 °C for 10 min, warmed to 0 °C for 15 min and quenched with water (5 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and

concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **87** (116 mg, 53%).
ee 12% (+)-$Eu(tfc)_3$

^{1}H NMR δ: 5.70 (m, 2H); 4.47 (m, 1H); 4.15 (m, 1H); 3.97 (m, 1H); 1.72-1.51 (m, 2H); 1.45 (s, 9H); 1.35-1.11 (m, 4H); 0.86 (t, *J* = 7 Hz, 3H).

3.4 Other scaffolds

1,3,3a,4,7,7a-Hexahydroisoindole-2-carboxylic acid *tert*-butyl ester 116[67]

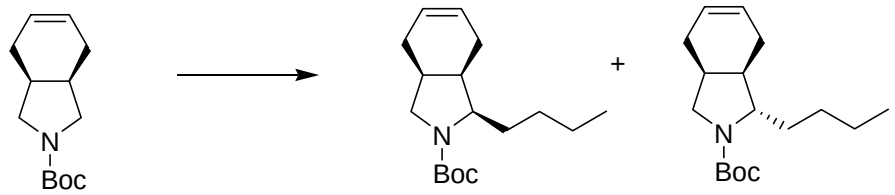


114 **116**

cis-1,2,3,6-Tetrahydropthalimide **114** (10.0 g, 66.1 mmol) was dissolved in dry tetrahydrofuran (150 mL) and added drop wise to a suspension of lithium aluminium hydride (6.27 g, 165 mmol) in THF (50 mL). The green mixture was refluxed for 24 h and then cooled to 0 °C. The reaction was quenched by slowly adding a saturated solution of sodium sulfate until all of the excess LAH was consumed. Excess solid sodium sulfate was added and the mixture was stirred for 30 min. The salts were filtered off and washed with THF. Concentration under reduced pressure gave the crude amine **115** (7.5 g). This oil was dissolved in dichloromethane (150 mL). Di-*tert*-butyl dicarbonate (14.4 g, 66.1 mmol) in dichloromethane (20 mL) was added drop wise. After 1 h, the solvent was removed under vacuum. DFC chromatography (95% hexane/5% AcOEt) followed by distillation (boiling range 108-116 °C, 0.25 torr) gave the desired product **116** (13.1 g, 89%).

^{1}H NMR δ: 5.61 (s, 2H); 3.39 (dd, *J* = 6.0, 10.5 Hz, 2H); 3.36 (dd, *J* = 6.5, 10.5 Hz); 3.14 (dd, *J* = 5.5, 10.5 Hz, 1H); 3.05 (dd, *J* = 6.5, 10.5 Hz); 2.22 (m, 4H); 1.88 (m, 2H); 1.43 (s, 9H).

1-Butyl-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylic acid *tert*-butyl ester 120



116 **120a** **120b**

(-)-Sparteine **13** (204 mg, 0.872 mmol) was dissolved in freshly distilled diethyl ether (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (0.67 mL, 1.3 M) was added drop wise and the solution was stirred for 15 min. The starting material **116** (162 mg, 0.725 mmol) in THF (2 mL) was added slowly over 1 h. The reaction was stirred for 4 h and n-butyl iodide (0.42 mL, 3.7 mmol) was added. The mixture was stirred at –78 °C over night (13 h), warmed to 0 °C for 15 min and quenched with water (10 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **120** (42 mg, 21%) as a mixture of diastereomers (1.1:1 by ^{1}H NMR) and unreacted starting material **116** (75 mg, 46%).

IR (DRIFT) (mixture of 2 diastereomers) ν_{max}: 2928; 1694 cm^{-1}.

Elemental analysis calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01; found: C, 73.29; H, 10.21; N, 4.81.

ee: ND.

HRMS (ES/TOF): calcd. for $C_{17}H_{30}NO_2$ $(M+H)^+$: 280.2271; found 280.2268.

Major Diastereomer:

^{1}H NMR δ: 5.62 (m, H_5 and H_6); 3.60 (ddd, J = 5, 9.5, 10 Hz, H_1); 3.36 (dd, J = 7, 8 Hz, H_3); 3.06 (dd, J = 9.5, 10 Hz, H_3); 2.82 (m, 1H); 2.41 (m, 1H); 2.18 (m, 2H); 1.94 (m, 2H); 1.65 (m, 1H); 1.44 (m, 9H); 1.28 (m, 4H), 0.87 (m, 3H).

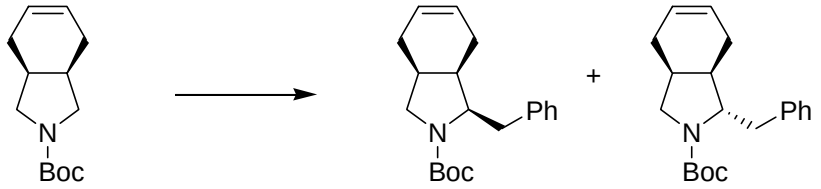
GC/MS (CI+, NH_3) (relative intensity)**:** 17.90 min; 280 (M+1) (3); 241 (9); 224 (8); 180 (100).

Minor Diastereomer:

^{1}H NMR δ: 5.68 (m, H_5 and H_6); 3.54 (ddd, *J* = 1, 7, 10 Hz, H_1); 3.34 (dd, *J* = 7.5, 8 Hz, H_3); 3.06 (dd, *J* = 9.5, 10 Hz, H_3); 2.41 (m, 2H); 2.18 (m, 2H); 1.94 (m, 2H); 1.65 (m, 1H); 1.43 (m, 9H); 1.28 (m, 4H), 0.87 (m, 3H).

GC/MS (CI+, NH_3) (relative intensity)**:** 19.24 min; 280 (M+1) (5); 241 (1); 224 (1); 180 (100).

1-Benzyl-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylic acid *tert*-butyl ester 121



116 **121a** **121b**

(-)-Sparteine **13** (267 mg, 1.14 mmol) was dissolved in freshly distilled diethyl ether (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (0.88 mL, 1.3 M) was added drop wise and the solution was stirred for 15 min. The starting material **116** (212 mg, 0.950 mmol) in THF (2 mL) was added slowly over 1 h. The reaction was stirred for 4 h and benzyl bromide (0.56 mL, 4.8 mmol) was added. The mixture was stirred at –78 °C for 1 h and quenched with water (10 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product **121** (201 mg, 68%) as a mixture of diastereomers (1.5:1 by ^1H NMR).

IR (DRIFT) (mixture of 2 diastereomers) ν_{max}: 3025; 2972; 2930; 1693; 1603 cm^{-1}.
Elemental analysis calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47; found: C, 76.34; H, 8.53; N, 4.39.
ee: ND.

Major Diastereomer:
^{1}H NMR δ: 7.22 (m, 5H); 5.56 (m, H_5 and H_6); 3.58 (dt, J = 9.5, 2 Hz, H_1); 3.37 (dd, J = 8, 10 Hz, H_3); 3.17 (dd, J = 10, 10 Hz, H_3); 3.07 (dd, J = 10, 14 Hz, H_{Bn}); 2.69 (dd, J = 10, 13 Hz, H_{Bn}); 2.42 (m, H_7); 2.21 (m, H_7); 1.95 (m, $2H_4$); 1.88 (m, H_{7a}); 1.68 (m, H_{3a}); 1.49 (s, 9H).
GC/MS: (CI+, CH_4) (relative intensity)**:** 25.16 min; 314 (M+1) (2); 298 (4); 286 (16); 258 (100); 240 (9); 214 (15); 197 (3); 166 (14).

GC/MS: (CI+, NH_3) (relative intensity)**:** 25.05 min; 314 (M+1) (14); 275 (18); 258 (47); 214 (100).

HRMS (ES/TOF): calcd. for $C_{20}H_{28}NO_2$ $(M+H)^+$: 314.2115; found 314.2153.

Minor Diastereomer:

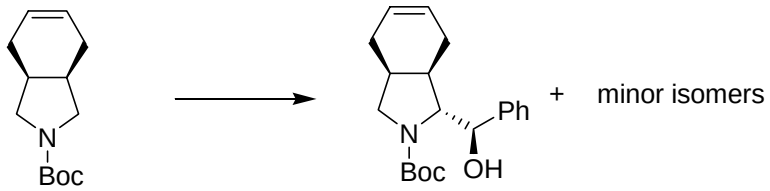
^{1}H NMR δ: 7.22 (m, 5H); 5.56 (m, H_5 and H_6); 3.71 (dt, *J* = 9.5, 2 Hz, H_1); 3.31 (dd, *J* = 8, 10 Hz, H_3); 3.14 (dd, *J* = 2.5, 12 Hz, H_3); 3.05 (dd, *J* = 3, 12 Hz, H_{Bn}); 2.65 (dd, *J* = 9.5, 13.5 Hz, H_{Bn}); 2.42 (m, H_7); 2.21 (m, H_7); 1.95 (m, $2H_4$); 1.88 (m, H_{7a}); 1.68 (m, H_{3a}); 1.47 (s, 9H).

GC/MS (CI+, CH_4) (relative intensity)**:** 27.16 min; 314 (M+1) (2); 298 (5); 286 (16); 258 (100); 240 (10); 214 (15); 197 (6); 166 (12).

GC/MS (CI+, NH_3) (relative intensity)**:** 27.08 min; 314 (M+1) (6); 275 (5); 258 (14); 214 (100).

HRMS (ES/TOF): calcd. for $C_{20}H_{28}NO_2$ $(M+H)^+$: 314.2115; found 314.2134.

(*1R,3aS,7aR*)-1-[(*R*)-Hydroxyphenylmethyl]-1,3,3a,4,7,7a-hexahydroisoindole-2-carboxylic acid *tert*-butyl ester 125



116 **125**

(-)-Sparteine **13** (250 mg, 1.07 mmol) was dissolved in freshly distilled diethyl ether (10 mL) and cooled to –78 °C. *sec*-Butyl lithium (0.80 mL, 1.07 M) was added dropwise and the solution was stirred for 15 min. The starting material **116** (199 mg, 0.891 mmol) in THF (2 mL) was added slowly over 1 h. The reaction was stirred for 4 h and benzaldehyde (0.11 mL, 1.1 mmol) was added. The mixture was stirred at –78 °C for 1 h and quenched with water (10 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (hexane/AcOEt polarity gradient) gave the product (178 mg, 61%) as a mixture of diastereomers (3.8:1.3:1 by ^{1}H NMR). An analytical sample was purified by PTLC.

GC/MS (CI+, NH_3) of alcohols **122** did give a molecular ion (M+1) of 330, however, substantial decomposition occurred on the column. Therefore, the alcohols were derivatized with *N,O*-Bis(trimethylsilyl)trifluoroacetamide containing 10% trimethylsilyl chloride and re-analyzed.[80]

Major Diastereomer: **125**

ee 90% (+)-Eu(tfc)$_3$.

IR (DRIFT) ν_{max}: 3373 (OH); 3026; 2972; 2839; 1655 cm^{-1}.

^{1}H NMR δ: 7.33 (m, 4H); 7.26 (m, 1H); 5.54 (ddd, *J* = 3, 10, 12.5 Hz, 1H); 5.49 (ddd, *J* = 2, 10, 12.5 Hz, 1H); 4.61 (d, *J* = 9 Hz, H_{Bn}); 3.76 (d, *J* = 9 Hz, H_1); 3.46 (dd, *J* = 9, 10 Hz, H_3); 3.20 (dd, *J* = 10, 10 Hz, H_3); 2.51 (m, H_{7a}); 2.19 (m, 1H); 1.87 (m, 1H); 1.78 (m, 2H); 1.55 (m, 1H); 1.49 (s, 9H).

^{13}C NMR δ: 158.8; 142.5; 128.4; 127.8; 127.1; 124.5; 124.1; 80.91; 78.8; 71.3; 50.8; 35.9; 32.5; 28.4; 25.5; 23.8.

$[\alpha]_D^{25}$ -12 (c 1.0, $CHCl_3$).

GC/MS (CI+, NH_3) (relative intensity)**:** 25.04 min; 402 (M+1) (37); 346 (52); 302 (100); 273 (4); 256 (3); 212 (4).

Elemental analysis calcd. for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25; found: C, 71.12; H, 6.11; N, 4.07.

HRMS (ES/TOF): calcd. for $C_{20}H_{28}NO_3$ $(M+H)^+$: 330.2064; found 330.2071.

2 Minor Diastereomers:

ee 84% (+)-Eu(tfc)$_3$.

IR (DRIFT) ν_{max}: 3297; 3023; 2926; 1668; 1406; 1365; 1154; 1122 cm^{-1}.

^{1}H NMR δ: 7.40 (d, *J* = 7.5 Hz, 2H); 7.31 (dd, *J* = 7, 7.5 Hz, 2H); 7.26 (d, *J* = 7 Hz, 1H); 5.50 (m, H_5 and H_6); 4.68 (d, *J* = 8.5 Hz, H_{Bn}); 4.18 (dd, *J* = 4, 8.5 Hz, H_1); 3.59 (dd, *J* = 7.5, 10.5 Hz, H_3); 3.21 (dd, *J* = 10.5, 10.5 Hz, H_3); 2.24 (m, 1H); 2.15 (m, 1H); 1.91 (m, 1H); 1.88 (m, 1H); 1.83 (m, 1H); 1.79 (m, 1H); 1.49 (s, 9H).

^{13}C NMR δ: 158.4; 142.6; 128.3; 127.9; 127.8; 124.7; 123.5; 80.9; 74.7; 70.8; 52.3; 37.1; 33.6; 28.5; 24.0; 20.6.

$[\alpha]_D^{25}$ +49 (c 0.32, $CHCl_3$).

GC/MS (CI+, NH_3) (relative intensity)**:** 27.33 min; 402 (M+1) (23); 346 (10); 302 (100); 273 (7); 256 (5); 212 (22).

Elemental analysis calcd. for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25; found: C, 73.21; H, 8.51; N, 3.98.

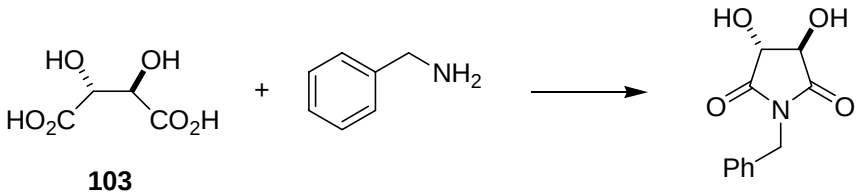
HRMS (ES/TOF): calcd. for $C_{20}H_{28}NO_3$ $(M+H)^+$: 330.2064; found 330.2075.

Unable to remove major diastereomer from this isomer.

GC/MS (CI+, NH_3) (relative intensity)**:** 25.79 min; 402 (M+1) (63); 346 (79); 302 (100); 273 (4); 256 (3); 212 (9).

HRMS (ES/TOF): calcd. for $C_{20}H_{28}NO_3$ $(M+H)^+$: 330.2064; found 330.2080.

1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione 104[58, 59]



103 **104**

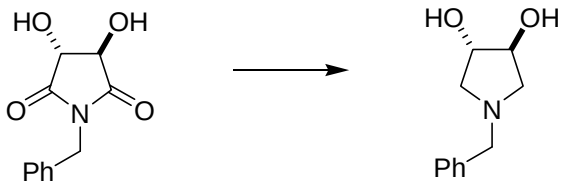
L-Tartaric acid **103** (4.00 g, 27.0 mmol) was placed in a 500 mL 3-neck flask equipped with a Dean-Stark trap. p-Xylene (125 mL, freshly distilled) was added and the solution was heated to boiling. Benzyl amine (2.9 mL, 27 mmol) was added over 15 min. The reaction was refluxed for 3 h until no more water could be collected (approx. 1 mL of water was collected). The flask was cooled in an ice bath (0 °C) and the yellow crystals were collected and washed with cold benzene. Recrystallization from water (65 mL) gave yellow needle-like crystals **104** (3.38 g, 57%).

mp: 197-199 ; lit. 196-198 °C.[59]

^{1}H NMR δ (D_2O)**:** 7.42 (m, 5H); 4.75 (s, 2H); 4.71 (s, 2H).

IR: 3287; 1709 cm^{-1}.

***(3S,4S)*-1-Benzylpyrrolidine-3,4-diol**[58, 59]



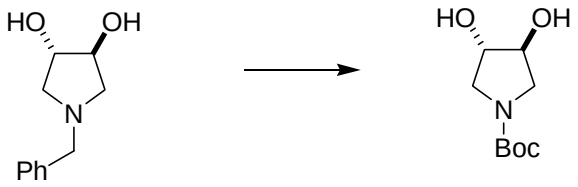
104 **105**

Compound **104** (2.08 g, 9.4 mmol) was dissolved in freshly distilled THF (40 mL) and cooled to 0 °C. Borane dimethylsulfide complex (4.70 mL, 10 M) was added and reaction was refluxed for 9 h.[81] The flask was cooled to 0 °C and the excess hydride was quenched with 6 M hydrochloric acid (3 mL). After stirring for 1 h, saturated sodium bicarbonate (5 mL) was added and the solvent was removed under vacuum. The residue was taken up in dichloromethane/methanol (20:1) and purified by DFC chromatography (methanol/dichloromethane gradient on alumina). The product amine **105** (1.59 g, 88%) was a light yellow wax.

$[\alpha]_D^{25}$ +6.7 (c 1.0, $CHCl_3$); lit. $[\alpha]_D^{20}$ +32.4 (c 4.2, MeOH).[59]

^{1}H NMR δ: 7.28 (m, 5H); 4.06 (app. t, *J* = 4 Hz, 2H); 3.65 (d, *J* = 13 Hz, 1H); 3.58 (d, *J* = 13 Hz, 1H); 3.20 (brs, OH); 2.93 (dd, *J* = 6, 10 Hz, 2H); 2.44 (dd, *J* = 4, 10 Hz, 2H).

3,4-Dihydroxypyrrolidine-1-carboxylic acid tert-butyl ester 106[58, 59]



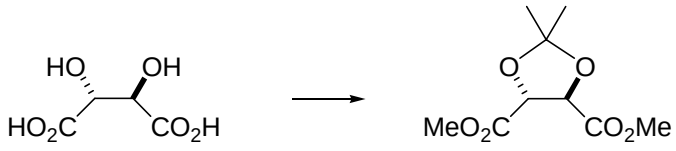
105 **106**

N-Benzyl amine **105** (500 mg, 2.26 mmol) was dissolved in ethanol (10 mL) and acetic acid (136 mg, 2.26 mmol). A catalytic amount of 10% palladium on activated carbon was added and the vessel was charged with hydrogen. The reaction was monitored using gas chromatography. The reaction was carried out with 50 psi hydrogen for 22 h followed by 200 psi hydrogen for 21 h. The catalyst was filtered off through Celite. The methanolic solution was basified with potassium hydroxide (127 mg, 2.26 mmol) and the solvent was removed under vacuum. The crude amine (433 mg) was dissolved in *tert*-butanol. Sodium hydride (200 mg, 5 mmol), in water (3 mL), and di-*tert*-butyl dicarbonate (1.09 g, 5 mmol), in *tert*-butanol, were added. The reaction was stirred overnight at ambient temperature. Water (5 mL) was added and extracted with hexanes (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. DFC chromatography (dichloromethane/methanol gradient) gave the Boc-protected amine **106** (129 mg, 28%).

^{1}H NMR δ: 4.04 (d, *J* = 3.5 Hz, 2H); 3.53 (td, *J* = 3.5, 12 Hz, 2H); 3.29 (d, *J* = 12 Hz, 2H); 1.47 (s, 9H).

3.5 Synthesis of starting materials for castanospermine analogs[21, 45]

Dimethyl 2,3-*O*-isopropylidene-L-tartrate 184[82]



103 **184**

L-Tartaric acid **103** (100.0 g, 0.666 mol), 2,2-dimethoxypropane (164 mL, 1.33 mol) and p-toluenesulfonic acid monohydrate (0.400 g) in methanol (40 mL) were refluxed for one hour. Another portion of 2,2-dimethoxypropane (83.0 mL, 0.670 mol) in cyclohexane (450 mL) was added to the mixture and refluxed for a further 1.5 hours. The methanol-cyclohexane azeotrope (observed bp 48-49 ^{o}C) was removed over 40 hours. A total of 510 mL of distillate was collected. The mixture was then cooled to 40 °C, an additional 2,2-dimethoxypropane (24.6 mL, 0.200 mol) was added and the mixture was refluxed for one hour. Fractional distillation then removed another portion of distillate (30 mL) over three hours (bp 49-50 °C). The bulk of the remaining solvent was removed by simple distillation (bp 76-77 °C) and all further solvent was removed *in vacuo*. The product was dissolved in diethyl ether (300 mL) and washed with saturated sodium bicarbonate solution (3x50 mL). To ensure no loss of product, the aqueous washes were extracted further with diethyl ether (2x50 mL). The organic phase was then dried with $MgSO_4$, filtered and the solvent was removed. The crude product was distilled to give the diester **184** (137.9 g, 95%).

bp 128-137 °C (0.1 mmHg).

R_f 0.4 (hexane/ethyl acetate 2:1).

$[\alpha]_D^{25}$ -63.2 (neat) .

$[\alpha]_D^{20}$ -63.6 (neat); lit $[\alpha]_D^{20}$ -53.7 (neat).[82]

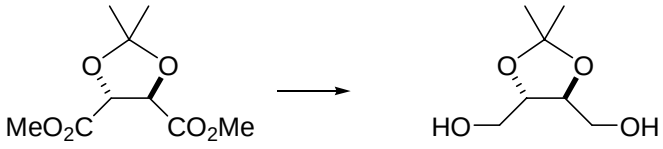
^{1}H NMR δ: 4.70 (s, 2H); 3.72 (s, 6H); 1.37 (s, 6H).

Dimethyl 2,3-*O*-isopropylidene-D-tartrate 185[82]

D-Tartaric acid (10.1 g, 0.0674 mol) was transformed into diester **185** (10.9 g, 58%) following the same procedure for the formation of **184**. The lower yield was due to failure to push the reaction to completion by adding more 2,2-dimethoxypropane and further removal of the azeotrope.

$[\alpha]_D^{25}$ +61.4 (neat); lit. $[\alpha]_D^{20}$ +53.0 (neat).[82]

***(4S,5S)*- 4,5-Bis(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane 186[83]**



184 **186**

Diester **184** (30.37 g, 0.139 mol) was dissolved in methanol (165 mL) and the temperature cooled to 0 °C. Dry sodium borohydride (11.61 g, 0.307 mol) was added portion wise over 1.5 h. After 10 min., the solution was allowed to stir for 8 h at room temperature. The solvent was then removed *in vacuo* and the gummy residue was partitioned between water (150 mL) and ethyl acetate (250 mL). The aqueous layer was extracted with ethyl acetate (2 x 250 mL). Sodium chloride was added to the aqueous layer until the solution was saturated. The aqueous layer was again extracted with ethyl acetate (2 x 300 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. Purification by DFC chromatography (hexane/AcOEt polarity gradient) gave the diol **186** (20.708 g, 92%).

$[\alpha]_D^{25}$ -1.6 (c 1.0, $CHCl_3$); lit. $[\alpha]_D^{20}$ +3.8 (c +3.7, $CHCl_3$).[84]

R_f 0.39 (DCM/MeOH 9:1).

^{1}H NMR δ: 4.08 (t, 2H); 3.91-3.85 (m, 2H); 3.68-3.62 (m, 4H); 1.33 (s, 6H).

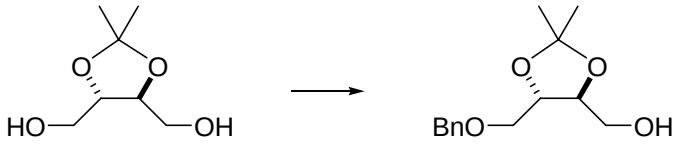
***(4R,5R)*-4,5-Bis(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane 187[83]**

Diester **185** (8.87 g, 0.041 mol) was reduced to diol **187** (5.28 g, 80%) following the same procedure used to prepare diol **186**.

$[\alpha]_D^{25}$ +1.8 (c 1.1, $CHCl_3$).

$[\alpha]_D^{25}$ -2.5 (c 5.2, $CHCl_3$).

***(4S,SR)*-4-Benzyloxymethyl-2,2-dimethyl--5-hydroxymethyl-1,3-dioxolane 188[84]**



186 **188**

Under a nitrogen atmosphere, DMF (130 mL) and sodium hydride (3.36 g, 0.140 mol) were mixed at 0 °C. A solution of diol **186** (15.06 g, 0.0929 mol) in DMF (40 mL) was added over 15 min. The ice-bath was removed and the mixture was allowed to stir for one hour at room temperature. The ice-bath was replaced and benzyl bromide (8.29 mL, 0.0697 mol) was added drop wise. The ice-bath was removed and the solution was allowed to stir overnight at room temperature. The DMF was removed by distillation under reduced pressure (bp 54-59 °C). The residue was dissolved in water (50 mL) and extracted with dichloromethane (2 x 100 mL). Sodium chloride was added to saturate the aqueous layer and it was further extracted with dichloromethane (3 x 100 mL). The organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by DFC chromatography (hexane/AcOEt polarity gradient) gave alcohol **188** (15.4 g, 66%).

$[\alpha]_D^{25}$ +9.0 (c 1.0, $CHCl_3$); lit. $[\alpha]_D^{25}$ +9 (c 0.99, $CHCl_3$).[84]

R_f 0.41 (hexane/ethyl acetate 1:1).

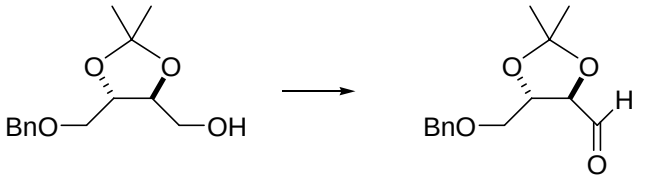
^{1}H NMR δ: 7.30 (m, 5H); 4.59 (s, 2H); 4.08-3.97 (m, 1H); 3.97-3.89 (m, 1H); 3.83-3.48 (m, 4H); 2.64 (br s, 1H); 1.41 (s, 6H).

***(4R,5R)*-2,2-Dimethyl-4-benzyloxymethyl-5-hydroxymethyl-1,3-dioxolane 189[84]**

Monobenzylation of diol **187** (5.14 g, 0.032 mol) provided alcohol **189** (4.92 g, 62%) using the same procedure for the synthesis of alcohol **188**.

$[\alpha]_D^{25}$ -9.2 (c 1.0, $CHCl_3$); lit. $[\alpha]_D^{25}$ -8 (c 0.975, $CHCl_3$).[84]

***(4R,5S)*-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 25[43]**



188 **25**

Under a nitrogen atmosphere, oxalyl chloride (4.15 mL, 47.6 mmol) and dichloromethane (80 mL) were cooled to –78 °C. DMSO (6.18 mL, 87.2 mmol) was added and the walls of the flask washed with dichloromethane (20 mL). The mixture was stirred for 5 min. Alcohol **188** (10.0 g, 39.6 mmol) in dichloromethane (20 mL) was added and the solution was allowed to stir at –78 °C for two hours. Triethylamine (27.9 mL, 200 mmol) in dichloromethane (20 mL) was then added and the temperature was raised to 0 °C over one hour. The mixture was then poured into a cold phosphate buffer (500 mL, pH = 7) and the product was extracted with diethyl ether (500 mL), washed with water (3 x 20 mL) and dried ($MgSO_4$). The crude product was purified by distillation (0.1 mmHg, temp. 146 – 152 °C) to give aldehyde **25** (8.02 g, 81%). The aldehyde will polymerize with time so it should be stored under nitrogen and refrigerated. The monomer can be regenerated by distillation.

$[\alpha]_D^{25}$ +16 (c 1.02, $CHCl_3$); lit. $[\alpha]_D^{21}$ +16.8 (c 1.10, $CHCl_3$).[43]

R_f 0.24 (hexane/ethyl acetate 1:1).

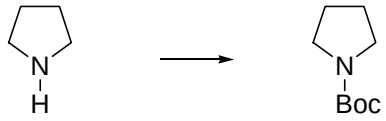
^{1}H NMR δ: 9.74 (br s, 1H); 7.39-7.17 (m, 5H); 4.59 (s, 2H); 4.22 (m, 2H), 3.65 (m, 2H); 1.50 (s, 3H); 1.41 (s, 3H).

***(4S,5R)*-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolane -4-carbaldehyde 133[43]**

Swern oxidation was used to transform alcohol **189** (4.83 g, 0.019 mol) to aldehyde **133** (3.79 g, 79%), as described for aldehyde **25**.

$[\alpha]_D^{25}$ –15 (c 1.10, $CHCl_3$).

***N*-(*tert*-Butoxycarbonyl)pyrrolidine 14**[85]



14

Pyrrolidine (1.556 g, 21.9 mmol) was added to a solution of sodium hydroxide (0.947 g, 24 mmol) in water (24 mL) at ambient temperature, and the solution was diluted with *tert*-butyl alcohol (16 mL). Di-*tert*-butyl dicarbonate (5.45 g, 25 mmol) in *tert*-butyl alcohol (5 mL) was added drop wise, with stirring, over 1 hour. Within an hour an abundant amount of a white precipitate had formed. After stirring at room temperature for 24 hours, the reaction mixture was then extracted with hexane (3 x 100 mL), and the organic layers were combined and dried ($MgSO_4$). The solvent was removed and the crude product was purified by distillation (bp. 101-102 °C, 0.1 mmHg) to give N-(*tert*-butoxycarbonyl)pyrrolidine **14** (3.05 g, 82%).

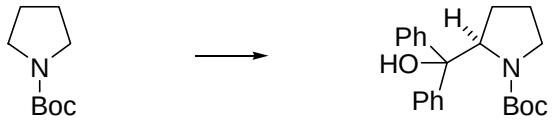
^{1}H NMR δ: 3.29 (m, 4H); 1.81 (m, 4H); 1.44 (s, 9H).

3.6 Enantioselective deprotonation using sBuLi / (-)-sparteine 13

*Procedure A. Electrophilic addition to N-Boc-pyrrolidine **14***[21]

Under a nitrogen atmosphere, (-)-sparteine **13** (0.305 g, 1.3 mmol) in diethyl ether (10 mL) was cooled to -78 ^{o}C. Next sBuLi (1.3 mmol) was added drop wise. N-(*tert*-butoxycarbonyl) pyrrolidine **14** (0.169 g, 1.0 mmol) in diethyl ether (0.7 mL) was added drop wise over 15 min. and the solution was allowed to stir for 4 hours at -78 ^{o}C. The electrophile (1.4 mmol) in diethyl ether (0.7 mL) was then added drop wise over 15 min. and the solution was allowed to stir for 15 min. at -78 ^{o}C. Acetic acid (0.115 mL) was added to quench the reaction and the reaction flask was allowed to warm up to room temperature for 15 min. Work up consisted of addition of saturated sodium chloride solution (10 mL) and extraction with diethyl ether (3 x 50 mL). The combined organic layers were washed with saturated sodium chloride (10 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to provide the crude product.

***(2R)*-2-(Diphenylhydroxy)methyl-*N*-(*tert*-butoxycarbonyl)pyrrolidine 136[14]**



14 **136**

Procedure A was followed for the deprotonation of **14**. Benzophenone (0.255 g, 1.4 mmol) was then added as the electrophile (one hour reaction time). Purification by DFC chromatography (hexane/AcOEt polarity gradient) gave the product **136** (0.334 g, 95%) as a white solid.

$[\alpha]_D^{25}$ +126 (c 3.60, $CHCl_3$); lit. $[\alpha]_D^{25}$ +132.1 (c 1.97, $CHCl_3$).[14]

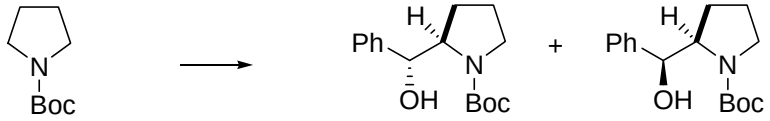
ee 86%.

mp 139-143 °C; lit. 146-148 °C.[14]

R_f 0.47 (hexane/ethyl acetate 4:1).

^{1}H NMR δ: 7.48-7.20 (m, 10 H); 4.89 (dd, *J* = 3.6, 8.8 Hz, 1H); 3.34 (m, 1H); 2.86 (m, 1H); 2.05 (m, 1H); 1.93 (m, 1H), 1.44 (s, 9H); 1.25 (m, 1H), 0.76 (m, 1H).

***(2R,1'R)*- and *(2R,1'S)*-2-(Hydroxyphenyl)methyl-*N*-(*tert*-butoxycarbonyl)pyrrolidine 137 and 138**[14, 45]



14 **137** **138**

Procedure A was followed for the deprotonation of **14**. Benzaldehyde (0.300 g, 2.8 mmol) was then added as the electrophile. Purification by DFC chromatography ((hexane:DCM 9:1)/AcOEt polarity gradient) gave the products **137** and **138** (0.470 g, 89%). The two diastereomers were separated by further DFC chromatography to give pure **137** (0.260 g, 49 %) and **138** (0.147 g, 28%).

Diastereoselectivity: 2:1 (gas chromatography).

Compound **137**:

$[\alpha]_D^{25}$ +12 (c 1.03, $CHCl_3$).

ee 94% (^{1}H NMR / $Eu(tfc)_3$ chiral shift reagent).

R_f 0.46 (DCM/hexane/AcOEt 7:4:2).

^{1}H NMR δ: 7.40-7.17 (m, 5H); 4.54 (d, *J* = 8.8 Hz 1H); 4.21-4.02 (m, 1H); 3.70-3.39 (m, 2H); 3.38- 3.28 (m, 1H); 1.78-1.64 (m, 2H); 1.51 (s, 9H); 1.49 (m, 1 H).

Compound **138**:

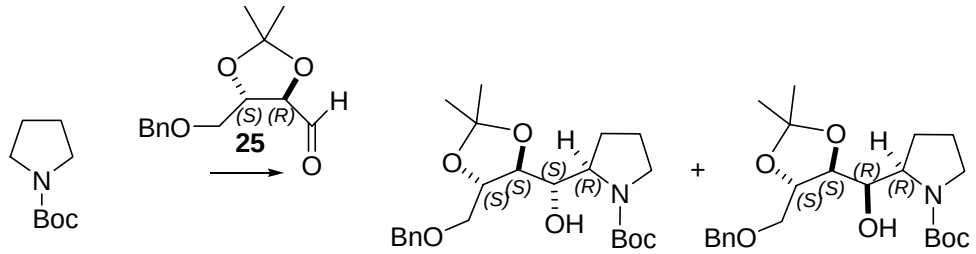
$[\alpha]_D^{25}$ +96.6 (c 1.02, $CHCl_3$).

ee 91% (^{1}H NMR / $Eu(tfc)_3$ chiral shift reagent).

R_f 0.37 (DCM/hexane/AcOEt 7:4:2).

^{1}H NMR δ: 7.39-7.16 (m, 5H); 4.93 (d, *J* = 1.9 Hz, 1H); 4.29-4.16 (m, 1H); 3.43-3.29 (m, 1H); 3.38- 3.05 (m, 1H); 3.02-2.89 (m, 1H); 1.89-1.76 (m, 2H); 1.51 (s, 9H); 1.41-1.23 (m, 1H).

***(2R,1'S,2'S,3'S)*- and *(2R,1'R,2'S,3'S)*-*N*-(*tert*-Butoxycarbonyl)-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 26 and 140**[21, 45]



Procedure A was followed for deprotonation of **14** (1.4 mmol). Aldehyde **25** (0.516 g, 2.1 mmol) was then added as the electrophile. Purification by DFC chromatography (DCM/hexane/AcOEt 7:2:4) gave the product **26** (0.251 g, 43%). Product **140** was not separated from the unreacted aldehyde **25**.

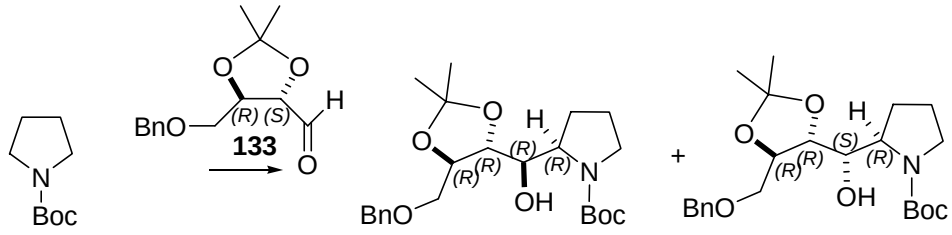
Compound **26**:

$[\alpha]_D^{25}$ +29 (c 1.0, $CHCl_3$).

R_f 0.72 (DCM/hexane/AcOEt 7:2:4).

^{1}H NMR δ: 7.34-7.16 (m, 5H); 5.10 (br s, 1H); 4.56 (s, 2H); 4.29 (m, 1H); 3.92-3.72 (m, 2H); 3.38 (dd, *J* = 8.0, 8.0 Hz, 1H); 3.59 (dd, *J* = 5.9, 10.1 Hz 1H); 3.43 (ddd, *J* = 5.1, 8.0, 8.0 Hz, 1H); 3.32 (m, 1H); 3.29 (dd, *J* = 5.1, 5.9 Hz); 2.50 (m, 1H); 1.89-1.67 (m, 3H); 1.43 (s, 9H); 1.35 (s, 3H); 1.32 (s, 3H).

***(2R,1'R,2'R,3'R)*- and *(2R,1'S,2'R,3'R)*-*N*-(*tert*-Butoxycarbonyl)-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 141 and 142[21, 45]**



Procedure A was followed for deprotonation of **14** (3.0 mmol). Aldehyde **133** (0.980 g, 3.9 mmol) was then added as the electrophile. Purification by DFC chromatography (DCM/hexane/AcOEt 7:2:4) gave the *anti* product **141** (0.702 g, 55%) and the *syn* product **142** (0.251 g, 20 %).

Compound **141**:

$[\alpha]_D^{25}$ +35 (c 1.0, $CHCl_3$).

R_f 0.54 (CH_2Cl_2/hexane/AcOEt 7:2:4).

^{1}H NMR δ: 7.36-7.20 (m, 5H); 4.56 (s, 2H); 4.17 (m, 1H); 4.02 (dd, *J* = 7.1, 7.1 Hz, 1H); 3.90 (d, *J* = 8.9 Hz, 1H); 3.69 (dd, *J* = 3.8, 10.1 Hz, 1H); 3.60 (m, 1H); 3.57 (dd, *J* = 5.7, 10.1 Hz, 1H); 3.51 (ddd, *J* = 5.1, 7.9, 10.9 Hz, 1H); 3.24 (ddd, *J* = 7.1, 7.1, 17.7 Hz, 1H); 2.10-1.84 (m, 3H); 1.65 (m, 1H); 1.42 (s, 9H); 1.36 (s, 6H).

Compound **142**:

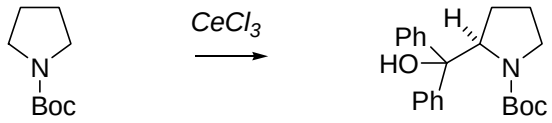
$[\alpha]_D^{25}$ +47 (c 1.1, $CHCl_3$).

R_f 0.63 (DCM/hexane/AcOEt 7:2:4).

^{1}H NMR δ: 7.44-7.22 (m, 5H); 4.69; (m, 1H); 4.56 (s, 2H); 4.40 (m, 1H); 4.30 (br s, 1H); 4.13 (m, 1H); 3.80 (d, J=8.3 Hz, 1H); 3.58 (m, 2H); 3.39 (m, 1H); 3.29 (m, 1H); 1.93 (m, 1H); 1.77 (m, 3H); 1.44 (s, 12H); 1.40 (s, 3H).

3.7 Cerium chloride transmetalation[73, 86]

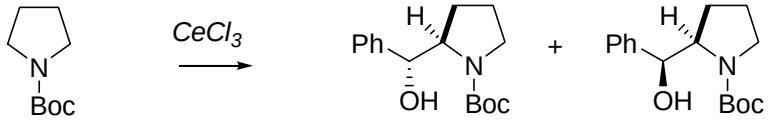
(2R)-2-(Diphenylhydroxy)methyl-*N*-(*tert*-butoxycarbonyl)pyrrolidine 136



14 **136**

$CeCl_3 \cdot 7H_2O$ (559 mg, 1.50 mmol) was placed in a 25 mL round bottom flask, with a magnetic stir bar, and dried (140 °C, 0.1 mmHg) for 8 h. The flask was cooled room temperature and the vacuum released to nitrogen. Dry tetrahydrofuran (5 mL) was added and the suspension was stirred over night at room temperature. In a second 25 mL round bottom flask, (-)-sparteine **13** (375 mg, 1.6 mmol) was dissolved in tetrahydrofuran (25 mL) and cooled to –78 °C. s-Butyl lithium (1.33 mL, 1.2 M) was slowly added and the solution was stirred for 15 min. *N*-Boc-Pyrrolidine **14** (253 mg, 1.5 mmol) in THF (1 mL) was slowly added over 15 min and the reaction was stirred at –78 °C for 4.5 h. The organolithium solution was then cannulated to the cooled (-78 °C) cerium chloride suspension. After 30 min, benzophenone (182 mg, 1.0 mmol) in THF (1mL) was added and reaction was stirred for 1 h. The reaction was quenched with acetic acid (1 mL) and washed with brine (5 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. DFC chromatography (hexane/AcOEt gradient) gave the product **136** (279 mg, 79%).

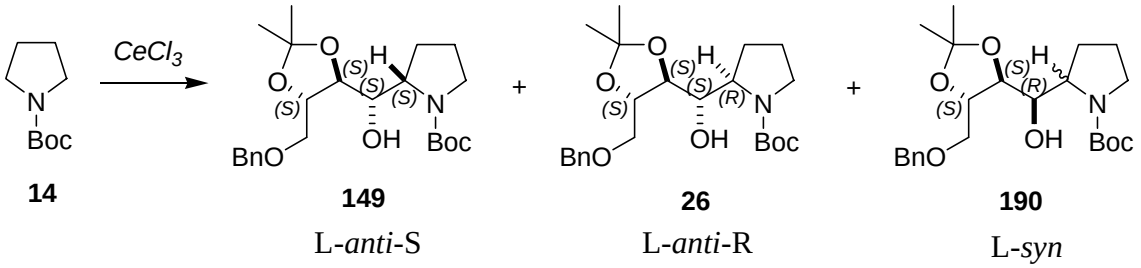
***(2R,1'R)*- and *(2R,1'S)*-*N*-(*tert*-butoxycarbonyl)-2-(hydroxyphenyl)methylpyrrolidine 137 and 138**



14 **137** **138**

$CeCl_3 \cdot 7H_2O$ (559 mg, 1.5 mmol) was placed in a 25 mL round bottom flask, with a magnetic stir bar, and dried (140 °C, 0.1 mmHg) for 2 h. The flask was cooled room temperature and the vacuum released to nitrogen. Dry tetrahydrofuran (5 mL) was added and the suspension was stirred for 4 h at room temperature. In a second 25 mL round bottom flask, (-)-sparteine **13** (375 mg, 1.6 mmol) was dissolved in tetrahydrofuran (25 mL) and cooled to –78 °C. s-Butyl lithium (1.33 mL, 1.2 M) was slowly added and the solution was stirred for 15 min. *N*-Boc-Pyrrolidine **14** (254 mg, 1.5 mmol) in THF (1 mL) was slowly added over 15 min and the reaction was stirred at –78 °C for 4 h. The organolithium solution was then cannulated to the cooled (-78 °C) cerium chloride suspension. After 30 min, benzaldehyde (116 mg, 1.1 mmol) in THF (1mL) was added and reaction was stirred for 1 h. The reaction was quenched with acetic acid (1 mL) and washed with brine (5 mL). The aqueous phase was extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. DFC chromatography (hexane/AcOEt gradient) gave the products (241 mg, 87%) as a 4:1 mixture of diastereomers.

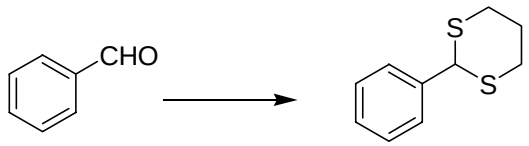
***(2S,1'S,2'S,3'S)*- and *(2R,1'S,2'S,3'S)*-*N*-(*tert*-Butoxycarbonyl)-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 149 and 26**



$CeCl_3 \cdot 7H_2O$ (1.7 g, 4.5 mmol) was placed in a 50 mL round bottom flask, with a magnetic stir bar, and dried (140 °C, 0.1 mmHg) for 2 h. The flask was cooled room temperature and the vacuum released to nitrogen. Dry tetrahydrofuran (15 mL) was added and the suspension was stirred over night at room temperature. In a second 25 mL round bottom flask, (-)-sparteine **13** (844 mg, 3.6 mmol) was dissolved in tetrahydrofuran (10 mL) and cooled to –78 °C. s-Butyl lithium (2.75 mL, 1.2 M) was slowly added and the solution was stirred for 15 min. *N*-Boc-Pyrrolidine **14** (512 mg, 3.0 mmol) in THF (3 mL) was slowly added over 15 min and the reaction was stirred at –78 °C for 4 h. The organolithium solution was then cannulated to the cooled (-78 °C) cerium chloride suspension. After 30 min, L-aldehyde **25** (753 mg, 3.0 mmol) in THF (3mL) was added and reaction was stirred for 3 h. The reaction was quenched with acetic acid (1 mL) and washed with brine (20 mL). The aqueous phase was extracted with diethyl ether (3 x 100 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. DFC chromatography (hexane/AcOEt gradient) gave the products (940 mg, 75%) as a mixture of diastereomers.

3.8 Acylsilane experiments

2-Phenyl-[1,3]dithiane 153[87]



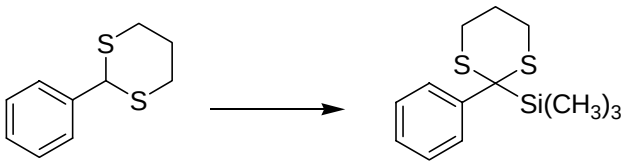
153

Benzaldehyde (5.0 g, 47 mmol) and 1,3-propanedithiol (5.66 mL, 56 mmol) were dissolved in benzene (25 mL). A catalytic amount of p-toluenesulfonic acid was added and reaction was refluxed for 7 h. A Dean-Stark trap was used to remove water during the reaction. The reaction was cooled to room temperature; water (15 mL) was added and extracted into dichloromethane (100 mL). The organic phase was washed with 0.5 M sodium hydroxide (2 x 20 mL), brine (20 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. Recrystallization from methanol gave 2-phenyl-[1,3]dithiane **153** (7.82 g, 85%).

mp: 68 °C; lit. 67-68 °C.[87]

^{1}H NMR δ: 7.47 (m, 2H); 7.33 (m, 3H); 5.17 (s, 1H); 3.07 (ddd, *J* = 3, 12, 14 Hz, 2H); 2.91 (ddd, *J* = 4, 4, 14 Hz, 2H); 2.18 (m, 1H); 1.93 (m, 1H).

Trimethyl-(2-phenyl-[1,3]dithian-2-yl)silane 154[75]



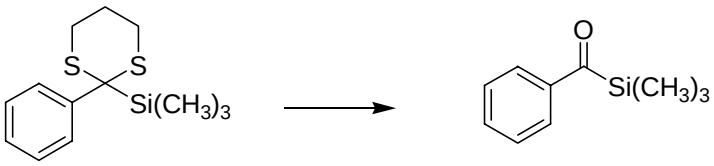
153 **154**

2-Phenyl-[1,3]dithiane **153** (1.00 g, 5.09 mmol) was dissolved in THF (25 mL) and cooled to –25 °C. n-Butyl lithium (2.43 mL, 2.2 M) was slowly added and the reaction was stirred at this temperature for 1.5 h. Trimethylsilyl chloride (0.71 mL, 5.6 mmol) was slowly added. The reaction was stirred at –25 °C for 15 min and then the temperature was raised to 0 °C for an additional 4 h. The reaction was quenched with water (0.2 mL) and concentrated under vacuum. The residue was taken up in diethyl ether (100 mL) and washed successively with 0.5 M sodium hydroxide (10 mL) and water (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product was a white crystalline material of sufficient purity **154** (1.19 g, 91%).

mp: 94 °C; lit. 94.4-94.8 °C.[75]

^{1}H NMR δ: 7.91 (dd, *J* = 1, 8 Hz, 2H); 7.37 (t, *J* = 8 Hz, 2H); 7.18 (t, *J* = 7 Hz, 1H); 2.77 (ddd, *J* = 3, 14, 14 Hz, 2H); 2.43 (ddd, *J* = 4, 4, 14 Hz, 2H); 2.03 (tq, *J* = 3, 14 Hz, 1H); 1.89 (m, 1H); 0.06 (s, 9H).

Phenyltrimethylsilanylmethanone 155[75]

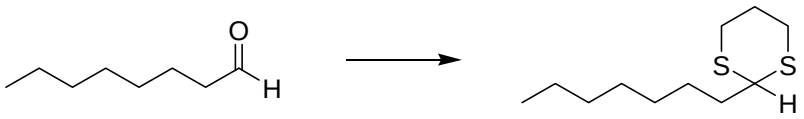


154 **155**

In a 100 mL round bottom flask, protected from the light, was added the starting material **154** (8.26 g, 32.0 mmol), methanol (50 mL, 10% water), $HgCl_2$ (19 g, 71 mmol) and yellow HgO (10.5 g, 48.0 mmol). The reaction was refluxed for 1.5 h and filtered through Celite. The Celite packing was washed with boiling methanol (100 mL). The filtrate was added to saturated ammonium chloride (25 mL) and extracted with 1:1 diethyl ether/n-pentane (100 mL). The organic phase was washed with saturated ammonium chloride (25 mL), water (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The flask was cooled in an ice bath to prevent the volatile product from distilling over with the pentane. Kugelrohr distillation (10 mmHg) gave the product **155** (5.09 g, 89%).

^{1}H NMR δ: 7.83 (m, 2H); 7.48 (m, 3H); 0.38 (s, 9H).

2-Heptyl-[1,3]dithiane156[88]

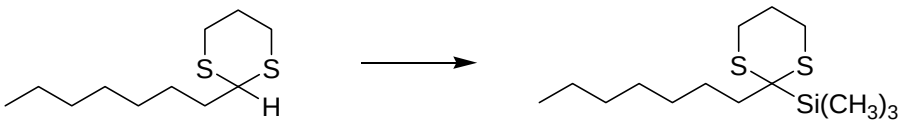


156

Octanal (5.0 g, 39 mmol) and 1,3-propanedithiol (3.9 mL, 39 mmol) were dissolved in tetrahydrofuran (50 mL). p-Toluenesulfonic acid was added and reaction was refluxed for 22 h. The reaction was cooled to room temperature; water (25 mL) was added and extracted into diethyl ether (200 mL). The organic phase was washed with 1.0 M sodium hydroxide (2 x 25 mL), brine (25 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. Distillation (170 °C, 0.1 mmHg) gave 2-heptyl-[1,3]dithiane **156** (6.13 g, 72%).

^{1}H NMR δ: 4.02 (t, *J* = 7 Hz, ½H); 3.72 (t, *J* = 7 Hz, ½H); 2.81 (m, 2H); 2.63 (m, 2H); 1.87 (m, 2H); 1.72 (m, 2H); 1.47 (m, 1H); 1.37 (m, 1H); 0.85 (m, 3H).

(2-Heptyl-[1,3]dithian-2-yl)trimethylsilane 157

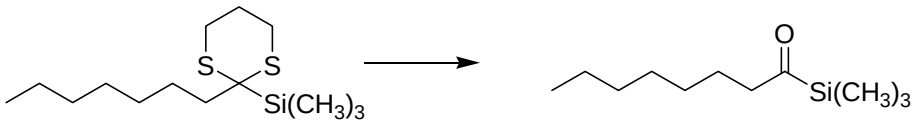


156 **157**

2-Heptyl-[1,3]dithiane **156** (5.87 g, 270 mmol) was dissolved in THF (50 mL) and cooled to –25 °C. n-Butyl lithium (11.3 mL, 2.5 M) was slowly added and the reaction was stirred at this temperature for 1 h. Trimethylsilyl chloride (3.8 mL, 30 mmol) was slowly added. The reaction was stirred at –25 °C for 30 min and then the temperature was raised to 0 °C for an additional 1.5 h. The reaction was quenched with water (2 mL) extracted with diethyl ether (200 mL) and washed successively with 0.5 M sodium hydroxide (2 x 25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. DFC chromatography gave the product **157** (5.83 g, 75%).

^{1}H NMR δ: 3.00 (ddd, *J* = 3, 10, 14 Hz, 2H); 2.40 (ddd, *J* = 4, 4, 14 Hz, 2H); 2.15 (m, 2H); 2.00 (m, 1H); 1.85 (m, 1H); 1.44 (m, 2H); 1.27 (m, 8H); 0.85 (m, 3H); 0.15 (s, 9H).
^{13}C NMR δ: 38.8; 37.3; 31.9; 30.1; 29.2; 27.7; 25.1; 23.4; 22.6; 14.0; -2.5.

1-Trimethylsilanyloctan-1-one[89]



157 **158**

(2-Heptyl-[1,3]dithian-2-yl)-trimethylsilane **157** (4.77 g, 16.4 mmol) was dissolved in 4:1 tetrahydrofuran/water (100 mL). Calcium carbonate (3.61 g, 36 mmol) and mercury perchlorate trihydrate[90] (13.4 g, 29.5 mmol) were added and the reaction was stirred at room temperature for 2.5 h. The solid material was filtered off and washed with hexanes (50 mL). Water (25 mL) was added and the aqueous phase was extracted with hexanes (2 x 100 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Distillation (140 °C, 20 mmHg) gave acylsilane **158** (2.82 g, 86%).

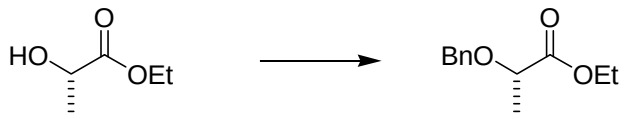
^{1}H NMR δ: 2.53 (t, *J* = 7.5 Hz, 2H); 1.45 (m, 2H); 1.21 (m, 8H); 0.82 (m, 3H); 0.14 (s, 9H).

^{13}C NMR δ: 48.5; 31.7; 29.3; 29.1; 22.5; 22.1; 14.0; -3.18.

LRMS (CI+, NH_3), *m/z* (relative intensity)**:** 201 (53); 157 (7); 144 (8); 129 (40); 90 (100); 77 (25); 73 (54); 60 (22).

HRMS (EI+) *m/z* calcd. for $C_{11}H_{24}OSi$: 200.1596; found: 200.1595.

Ethyl *(S)*-2-benzyloxypropionate 164[91]



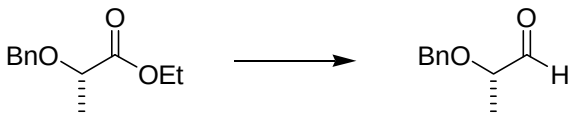
163 **164**

To a cooled (-20 °C) suspension of 80% sodium hydride (3.05 g, 102 mmol) in THF (75 mL) and DMF (50 mL), was added benzyl bromide (10.6 mL, 89 mmol). (S)-Ethyl lactate **163** (9.60 mL, 85 mmol) was added drop wise using a syringe pump. The reaction was monitored by TLC (hexane/AcOEt 1:1). The reaction was slowly warmed to room temperature and stirred over night. The mixture was slowly poured into water (50 mL) and extracted into n-pentane (500 mL). The organic phase was washed with water (2 x 25 mL) and brine (25 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. DFC chromatography (hexane/AcOEt gradient) gave ethyl (S)-2-benzyloxypropionate **164** (8.01 g, 46%).

$[\alpha]_D^{25}$ –78.2 (c 10.0, $CHCl_3$); lit. $[\alpha]_D$ –88.2 (c 10, $CHCl_3$)[91].

^{1}H NMR δ: 7.36 (m, 5H); 4.70 (d, *J* = 12 Hz, 1H); 4.45 (d, *J* = 12 Hz, 1H);4.21 (q, *J* = 7 Hz, 2H); 4.05 (q, *J* = 7, 1H); 1.44 (d, *J* = 7 Hz, 3H), 1.30 (t, *J* = 7 Hz, 3H).

***(S)*-2-Benzyloxypropanal 165[91]**



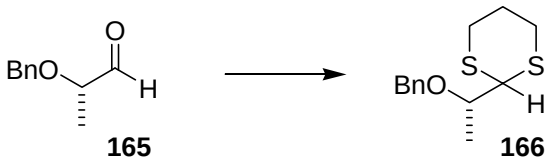
164 **165**

Ethyl *(S)*-2-benzyloxypropionate **164** (8.00 g, 38.4 mmol) was dissolved in freshly distilled diethyl ether (100 mL) and cooled to –78 °C. DIBAL-H (33.3 mL, 1.5 M) was added drop wise, over 8.5 h, using a syringe pump. After stirring for another hour, the reaction was quenched with saturated sodium sulfate (60 mL). The mixture was warmed to room temperature and poured into diethyl ether (400 mL). Celite (30 g) and aqueous potassium sodium tartrate (200 mL) were added and mixture was stirred for 1 h. This mixture was filtered through a pad of Celite and the salts were washed with diethyl ether. The organic phase was washed in succession with water (3 x 100 mL), saturated sodium bicarbonate (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Distillation (94-99 °C, 0.1 mmHg) gave 2-benzyloxypropanal **165** (5.58 g, 89%).

$[\alpha]_D^{25}$ –61.3 (c 1.1, $CHCl_3$); lit. $[\alpha]_D$ –49.6 (c 6.2, $CHCl_3$).[91]

^{1}H NMR δ: 9.65 (s, 1H); 7.34 (m, 5H); 4.64 (d, *J* = 12 Hz, 1H); 4.58 (d, *J* = 12 Hz, 1H); 3.87 (q, *J* = 7 Hz, 1H); 1.31 (d, *J* = 7 Hz, 3H).

***(S)*-2-(1-Benzyloxyethyl)-[1,3]dithiane 166**



165 **166**

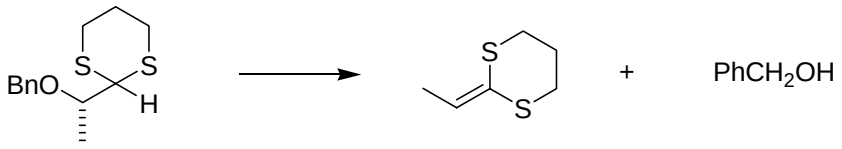
(S)-2-Benzyloxypropanal **165** (1.01 g, 4.85 mmol) was dissolved in chloroform (25 mL) at room temperature. 1,3-Propandithiol (0.51 mL, 5.09 mmol) and $BF_3 \cdot OEt_2$ (6 drops) were added and reaction was stirred for 1 h.[92] The reaction mixture was poured into diethyl ether (100 mL), washed with 1.0 M sodium hydroxide (2 x 10 mL), brine (10 mL), dried ($MgSO_4$), filtered through Celite and concentrated under vacuum. *(S)*-2-(1-Benzyloxyethyl)-[1,3]dithiane **166** was obtained in quantitative yield.

$[\alpha]_D^{25}$ –9.0 (c 1.8, $CHCl_3$).

^{1}H NMR δ: 7.33 (m, 5H); 4.62 (s, 2H); 4.28 (d, *J* = 5 Hz, 1H); 3.75 (dq, *J* = 5, 6.5 Hz, 1H); 2.88 (m, 4H); 1.90 (m, 2H); 1.35 (d, *J* = 6.5 Hz; 3H).

^{13}C NMR δ: 138.1; 128.3; 127.8; 127.6; 76.6; 71.2; 53.4; 30.3; 30.2; 26.2; 17.7.

2-Ethylidene-[1,3]dithiane 167



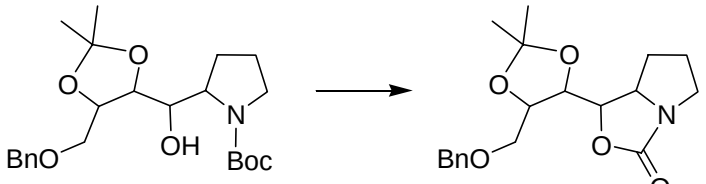
166 **167**

2-(1-Benzyloxy-ethyl)-[1,3]dithiane **166** (1.26 g, 4.95 mmol) was dissolved in THF (20 mL) and cooled to –25 °C. n-Butyl lithium (2.23 mL, 2.4 M) was slowly added and the reaction was stirred at this temperature for 1 h. Trimethylsilyl chloride (0.68 mL, 5.34 mmol) was slowly added. The reaction was stirred at –25 °C for 30 min and then the temperature was raised to 0 °C for an additional hour. The reaction was quenched with water (2 mL) extracted with diethyl ether (100 mL) and washed with 0.5 M sodium hydroxide (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. DFC chromatography gave 2-ethylidene-[1,3]dithiane[93] **167** (723 mg, 99.9%) and benzyl alcohol instead of the desired product.

^{1}H NMR δ: 5.98 (q, *J* = 7 Hz, 1H); 2.83 (m, 4H); 2.13 (m, 2H); 1.75 (d, *J* = 7 Hz, 3H).

3.9 Synthesis of castanospermine analogues

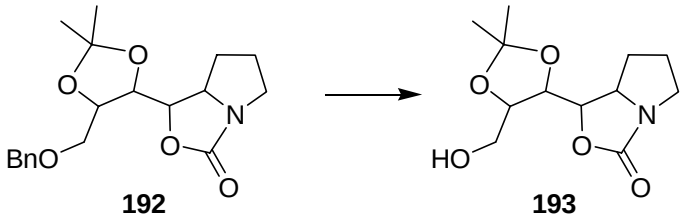
Procedure B. Intramolecular carbamate formation



191 **192**

Compound **191** was dissolved in tetrahydrofuran and heated. Sodium hydride was added to this hot solution and reaction was monitored by TLC. The solvent was then removed by evaporation and the residue was dissolved in diethyl ether. The organic phase was then washed with a small volume of water, dried with anhydrous $MgSO_4$ and evaporated at reduced pressure. Purification was accomplished using DFC chromatography (hexane/AcOEt polarity gradient).

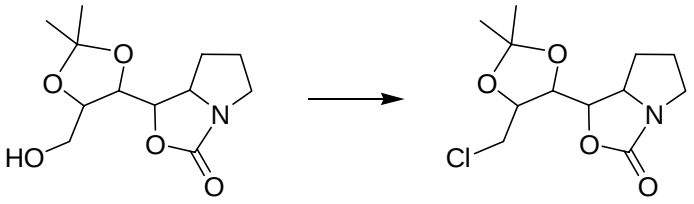
Procedure C. Removal of benzyl protecting group



192 **193**

A mixture of **192** and 10% Pd/C (180mg) in ethanol was shaken in a Parr hydrogenator under hydrogen (50 psi) at room temperature for 5 hours. The catalyst was filtered off and the solvent removed on a rotary evaporator. Purification was by DFC chromatography (hexane/AcOEt polarity gradient).

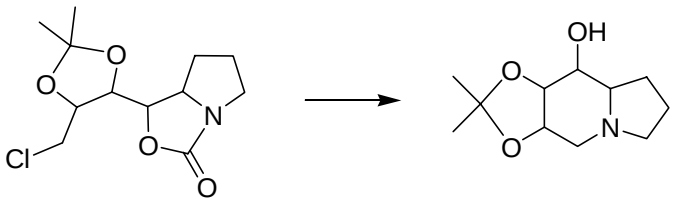
Procedure D. Alkyl chloride formation from an alcohol



193 **194**

Alcohol **193** (1 eq.) was dissolved in a 4:1 mixture of CCl_4/CH_2Cl_2 (0.05 M solution). Triphenylphosphine (2.5 eq.) and potassium carbonate (2 eq.) were added and the solution was refluxed for 4 hours. The solvent was then removed by evaporation and the residue dissolved in CH_2Cl_2. The organic phase was washed once with water and the this aqueous phase was extracted twice with CH_2Cl_2. The organic portions were collected, dried with anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. Purification was by DFC chromatography (hexane/AcOEt polarity gradient).

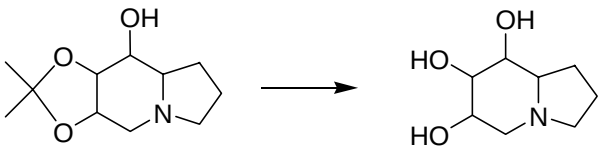
Procedure E. Cyclization via intramolecular displacement



194 **195**

Compound **194** (1 eq.) was dissolved in a 2:1 methanol/water solution (0.02 M concentration). Sodium hydroxide (3 eq.) was added and the solution was refluxed for fifteen hours. After the solution was cool, the solvent was removed by evaporation and the residue was dissolved in CH_2Cl_2. The organic phase was washed once with water and the aqueous phase was extracted twice with CH_2Cl_2. The organic portions were collected, dried with anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. Purification was by DFC chromatography (CH_2Cl_2/methanol polarity gradient).

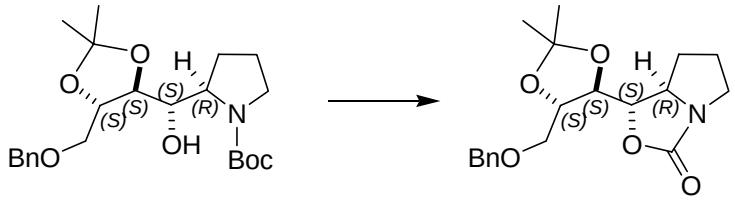
Procedure F. Removal of acetonide group



195 **196**

Compound **195** was dissolved in a trifluoroacetic acid/water solution. After stirring at room temperature for 50 hours, the solvent was evaporated under reduced pressure. The residue was dissolved in methanol and stirred with amberlyst A-27 basic resin for 2 hours. The solution was filtered and the solvent evaporated. Purification was by DFC chromatography.

***(2R,1'S,2'S,3'S)*-1,1'-*N,O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 26**[21, 45]



26 **27**

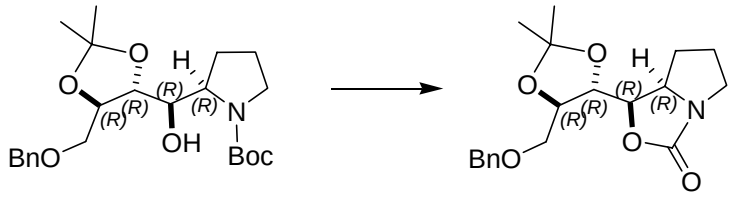
Following procedure B, compound **26** (0.635 g, 0.0015 mol) was reacted to give compound **27** (0.444 g, 85%). The reaction time was 30 minutes.

$[\alpha]_D^{25}$ +15 (c 1.0, $CHCl_3$).

R_f 0.37 (hexane/AcOEt 1:1).

^{1}H NMR δ: 7.38-7.23 (m, 5H); 4.57 (d, *J* = 12.0 Hz, 2H); 4.27 (dd, *J* = 3.7, 7.1 Hz, 1H); 4.11 (ddd, *J* = 3.5, 5.5, 7.4 Hz, 1H); 4.01 (ddd, *J* = <1, 7.4, 7.4 Hz, 1H); 3.82 (ddd, *J* = 4.0, 5.5, 9.4 Hz, 1H); 3.72 (dd, *J* = 3.4, 10.5 Hz, 1H); 3.63 (dd, *J* = 5.5, 10.4 Hz, 1H); 3.58 (dd, *J* = 7.4, 10.9); 3.13 (ddd, *J* = 4.9, 8.9, 8.9 Hz, 1H); 2.05 (m, 2H); 1.89 (m, 1H); 1.45 (m, 1H); 1.42 (s, 3H); 1.40 (s, 3H).

***(2R,1'R,2'R,3'R)*-1,1'-*N,O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 168**[21, 45]



141 **168**

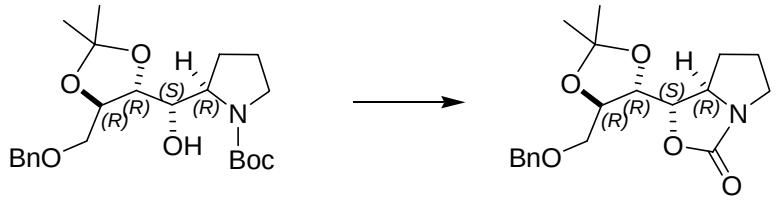
Following procedure B, compound **141** (0.187 g, 0.44 mmol) was reacted to give compound **168** (0.075 g, 49%). The reaction time was 2 hours 15 minutes.

$[\alpha]_D^{25}$ +37 (c 1.0, $CHCl_3$).

R_f 0.46 (hexane/AcOEt 1:1).

^{1}H NMR δ: 7.40-7.18 (m, 5H); 4.58 (d, *J* = 6.1 Hz, 2H); 4.55 (m, 1H); 4.20 (ddd, *J* = 2.4, 7.4, 7.4 Hz, 1H); 3.90 (m, 2H); 3.76 (dd, *J* = 1.6, 10.7 Hz, 1H); 3.60 (dd, *J* = 5.1, 10.9 Hz, 1H); 3.57 (m, 1H); 3.18 (ddd, *J* = 3.2, 9.6, 9.6 Hz, 1H); 2.04 (m, 2H); 1.92 (m, 1H); 1.46 (m, 1H); 1.42 (s, 3H); 1.39 (s, 3H).

***(2R,1'S,2'R,3'R)*-1,1'-*N*,*O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-benzyloxybutyl)pyrrolidine 169**[21, 45]



142 **169**

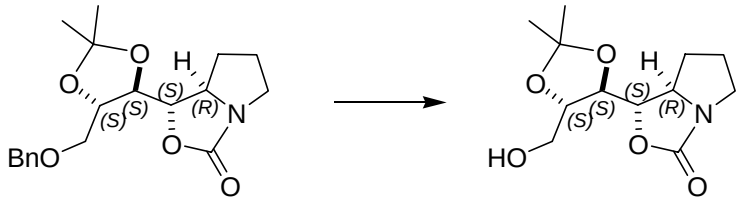
Following procedure B, compound **142** (0.095 g, 0.23 mmol) was reacted to give compound **169** (0.046 g, 58%). The reaction time was 30 minutes.

$[\alpha]_D^{25}$ +37 (c 1.0, $CHCl_3$).

R_f 0.35 (hexane/AcOEt 1:1).

^{1}H NMR δ: 7.38-7.24 (m, 5H); 4.56 (s, 2H); 4.32 (dd, *J* = 2.4, 3.7 Hz, 1H); 4.28 (ddd, *J* = 5.1, 8.1, 10.2 Hz, 1H); 4.01 (dd, *J* = 2.3, 8.1 Hz, 1H); 3.82 (ddd, *J* = 3.8, 5.7, 9.5 Hz, 1H); 3.68 (dd, *J* = 4.8, 10.2 Hz, 1H); 3.59 (dd, *J* = 5.6, 10.0 Hz, 1H); 3.57 (ddd, *J* = 7.9, 7.9,12.5 Hz, 1H); 3.18 (ddd, *J* = 4.8, 10.2 Hz, 1H); 2.02 (m, 2H); 1.98 (m, 1H); 1.43 (m, 1H); 1.42 (s, 3H); 1.41 (s, 3H).

***(2R,1'S,2'S,3'S)*-1,1'-*N,O*-Carbonyl-2-(1',2',3',4'-tetrahydroxy-2',3'-*O*-isopropylidenebutyl)pyrrolidine 28**[21, 45]



27 **28**

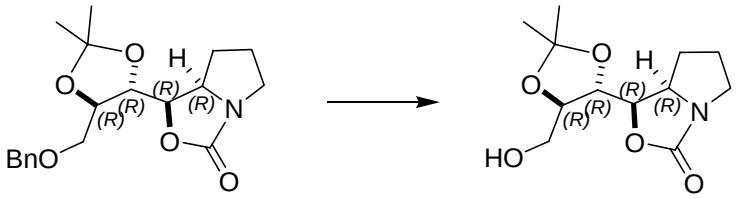
The benzyl protecting group in **27** (0.444 g, 1.3 mmol) was removed using procedure C. Deprotection gave compound **28** (0.285 g, 85%).

$[\alpha]_D^{25}$ +26 (c 1.0, $CHCl_3$).

R_f 0.25 (hexane/AcOEt 1:4).

^{1}H NMR δ: 4.23 (m, 1H); 3.98 (m, 2H); 3.82 (dd, *J* = 4.0, 9.4 Hz, 1H); 3.80 (dd, *J* = 3.5, 9.9 Hz, 1H); 3.65 (br d, *J* = 11.4 Hz, 1H); 3.49 (ddd, *J* = 7.8, 7.8, 11.3 Hz, 1H); 3.10 (ddd, *J* = 4.2, 9.0, 13.2 Hz, 1H); 2.69 (br s, 1H); 2.02 (m, 2H); 1.86 (m, 1H); 1.42 (m, 1H); 1.36 (s, 3H); 1.34 (s, 3H).

***(2R,1'R,2'S,3'R)*-1,1'-*N*,*O*-Carbonyl-2-(1',2',3',4'-tetrahydroxy-2',3'-*O*-isopropylidenebutyl)pyrrolidine 170**[21, 45]



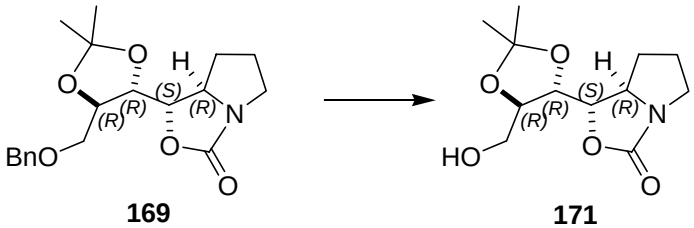
The benzyl protecting group in **168** (0.075 g, 0.22 mmol) was removed using procedure C. Deprotection gave compound **170** (0.044 g, 78%).

$[\alpha]_D^{25}$ +45 (c 0.88, $CHCl_3$).

R_f 0.39 (hexane/AcOEt 1:4).

^{1}H NMR δ: 4.54 (dd, *J* = 7.6, 9.5 Hz, 1H); 4.10 (ddd, *J* = 3.1, 4.0, 7.3 Hz, 1H); 3.94 (dd, *J* = 7.6, 9.5 Hz, 1H); 3.92 (m, 1H); 3.88 (dd, *J* = 2.9, 12.2 Hz, 1H); 3.70 (dd, *J* = 4.1, 12.2 Hz, 1H); 3.56 (ddd, *J* = 7.6, 7.6, 11.5 Hz, 1H); 3.17 (ddd, *J* = 3.4, 9.3, 12.7 Hz, 1H); 2.13 (br s, 1H); 2.06 (m, 1H); 1.89 (m, 2H); 1.50 (m, 1H); 1.41 (s, 3H); 1.38 (s, 3H).

***(2R,1'S,2'S,3'R)*-1,1'-*N,O*-Carbonyl-2-(1',2',3',4'-tetrahydroxy-2',3'-*O*-isopropylidenebutyl)pyrrolidine 171**[21, 45]



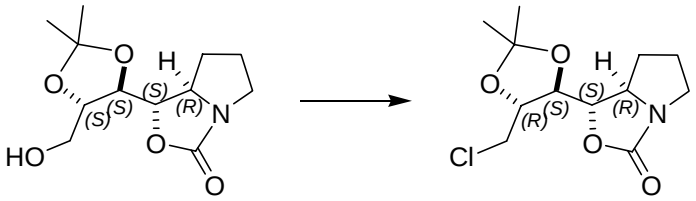
The benzyl protecting group in **169** (0.046 g, 0.13 mmol) was removed using a modified procedure C. Hydrogen was delivered *via* a balloon to flask containing **169** and the catalyst. Deprotection gave compound **171** (0.035 g, 100%).

$[\alpha]_D^{25}$ +47 (c 0.80, $CHCl_3$).

R_f 0.36 (hexane/AcOEt 1:4).

^{1}H NMR δ: 4.35 (dd, *J* = 1.8, 3.4 Hz, 1H); 4.19 (ddd, *J* = 3.7, 3.7, 7.9 Hz, 1H); 4.09 (dd, *J* = 1.5, 8.2 Hz, 1H); 3.84 (ddd, *J* = 3.9, 5.5, 12.9 Hz, 1H); 3.81 (dd, *J* = 4.0, 10.1 Hz, 1H); 3.69 (dd, *J* = 3.5, 12.0 Hz, 1H); 3.55 (ddd, *J* = 7.7, 7.7, 15.8 Hz, 1H); 3.19 (ddd, *J* = 3.8, 9.1, 12.9 Hz, 1H); 2.53 (br s, 1H); 2.08 (m, 2H); 1.89 (m, 1H); 1.47 (m, 1H); 1.41 (s, 3H); 1.40 (s, 3H).

***(2R,1'S,2'S,3'R)*-1,1'-*N,O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-chlorobutyl)pyrrolidine 29**[21, 45]



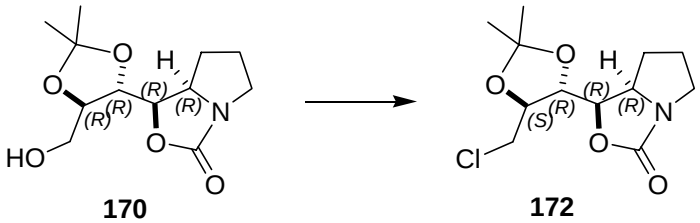
The hydroxy group in **28** (0.235 g, 0.91 mmol) was substituted for chlorine using procedure D. The substitution reaction gave compound **29** (0.241 g, 96%).

$[\alpha]_D^{25}$ +26 (c 0.90, $CHCl_3$).

R_f 0.35 (hexane/AcOEt 1:1).

^{1}H NMR δ: 4.25 (dd, *J* = 3.6, 8.1 Hz, 1H); 4.18 (dd, *J* = 3.9, 5.2, 9.1 Hz, 1H); 4.01 (dd, *J* = 7.1, 8.0 Hz, 1H); 3.83 (ddd, *J* = 3.7, 5.8, 9.5 Hz, 1H); 3.78 (dd, *J* = 3.8, 12.1 Hz, 1H); 3.64 (dd, *J* = 5.3, 11.9 Hz, 1H); 3.61 (ddd, *J* = 6.8, 6.8, 14.6 Hz, 1H); 3.16 (ddd, *J* = 4.2, 9.1, 13.2 Hz, 1H); 2.09 (m, 2H); 1.93 (m, 1H); 1.49 (m, 1H); 1.43 (s, 3H); 1.40 (s, 3H).

***(2R,1'R,2'R,3'S)*-1,1'-*N*,*O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-chlorobutyl)pyrrolidine 172[21, 45]**



The hydroxy group in **170** (0.042 g, 0.16 mmol) was substituted for chlorine using procedure D. The substitution reaction gave compound **172** (0.041 g, 93%) as a white solid.

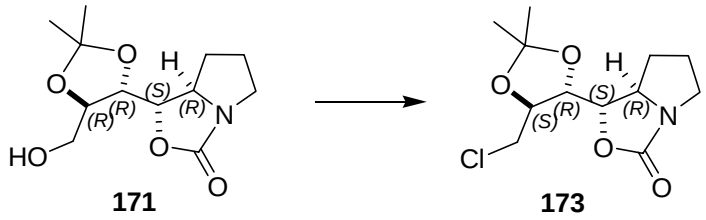
mp: 72-73 ^{o}C.

$[\alpha]_D^{25}$ +34 (c 1.0, $CHCl_3$).

R_f 0.46 (hexane/AcOEt 1:1).

^{1}H NMR δ: 4.55 (dd, *J* = 7.5, 9.5 Hz, 1H); 4.25 (ddd, *J* = 3.1, 5.3, 7.0 Hz, 1H); 3.94 (dd, *J* = 7.0, 9.6 Hz, 1H); 3.91 (ddd, *J* = 5.2, 7.5, 11.6 Hz, 1H); 3.83 (dd, *J* = 3.1, 12.0 Hz, 1H); 3.64 (dd, *J* = 5.3, 12.0 Hz, 1H); 3.57 (ddd, *J* = 7.5, 7.5, 11.1 Hz, 1H); 3.18 (ddd, *J* = 3.4, 9.3, 11.3, 1H); 2.08 (m, 1H); 1.90 (m, 2H); 1.58 (m, 1H); 1.43 (s, 3H); 1.39 (s, 3H).

***(2R,1'S,2'R,3'S)*-1,1'-*N,O*-Carbonyl-2-(1',2',3'-trihydroxy-2',3'-*O*-isopropylidene-4'-chlorobutyl)pyrrolidine 173**[21, 45]



The hydroxy group in **171** (0.035 g, 0.13 mmol) was substituted for chlorine using procedure D. The substitution reaction gave compound **173** (0.033 g, 92%) as a white solid.

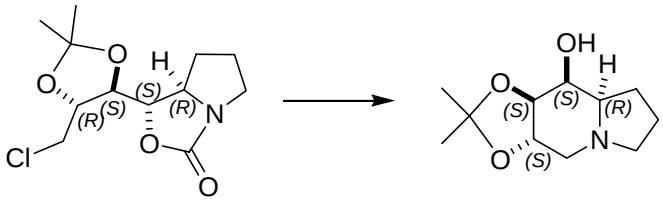
mp: 99-100 ^{o}C.

$[\alpha]_D^{25}$ +51 (c 1.0, $CHCl_3$).

R_f 0.29 (hexane/AcOEt).

^{1}H NMR δ: 4.41 (dd, *J* = 1.9, 3.6 Hz, 1H); 4.35 (ddd, *J* = 4.4, 6.6, 7.3 Hz, 1H); 4.07 (dd, *J* = 1.9, 7.5 Hz, 1H); 3.85 (ddd, *J* = 3.7, 5.7, 9.5 Hz, 1H); 3.70 (dd, *J* = 4.4, 11.5 Hz, 1H); 3.62 (dd, *J* = 6.4, 11.6 Hz, 1H); 3.58 (ddd, *J* = 7.9, 7.9, 11.3 Hz, 1H); 3.21 (ddd, *J* = 4.0, 9.1, 13.0 Hz, 1H); 2.04 (m, 2H); 1.91 (m, 1H); 1.48 (m, 1H); 1.43 (s, 3H); 1.42 (s, 3H).

***(6S,7S,8S,8aR)*-6,7-*O*-Isopropylidene-6,7,8- trihydroxyindolizidine 30**[21, 45]



29 **30**

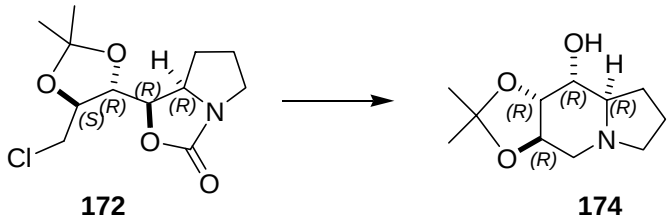
Following procedure E, compound **29** (0.045 g, 0.16 mmol) was reacted to give indolizidine **30** (0.029 g, 85%) as a white solid.

$[\alpha]_D^{25}$ +41 (c 1.1, $CHCl_3$).

R_f 0.39 (DCM/7% MeOH).

^{1}H NMR δ: 4.14 (dd, *J* = 2.3, 2.3 Hz, H_8); 3.99 (ddd, *J* = 4.2, 9.8, 9.8 Hz, H_6); 3.42 (dd, *J* = 2.3, 9.8 Hz, H_7); 3.41 (dd, *J* = 4.2, 9.5 Hz, H_5); 3.04 (ddd, *J* = 2.1, 6.3, 8.3 Hz, 1H); 2.29 (m, 3H); 1.91 (m, 2H); 1.76 (m, 2H); 1.52 (s, 3H); 1.46 (s, 3H).

***(6R,7R,8R,8aR)*-6,7-*O*-Isopropylidene-6,7,8-trihydroxyindolizidine 174**[21, 45]



172 **174**

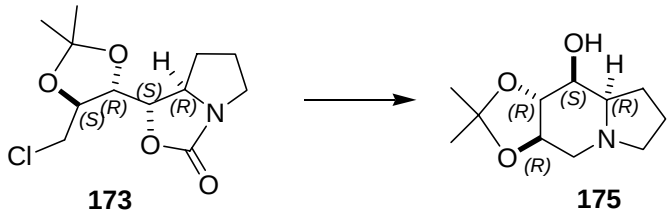
Following procedure E, compound **172** (0.040 g, 0.15 mmol) was reacted to give indolizidine **174** (0.026 g, 81%) as a white solid.

$[\alpha]_D^{25}$ -55 (c 0.9, $CHCl_3$).

R_f 0.09 (DCM/7% MeOH).

^{1}H NMR δ: 4.22 (dd, *J* = 3.7, 3.7 Hz, 1H); 4.13 (ddd, *J* = 5.6, 9.6, 9.7 Hz, 1H); 3.73 (dd, *J* = 3.7, 9.7 Hz, 1H); 3.46 (br s, 1H); 3.00 (dd, *J* = 5.6, 9.3 Hz, 1H); 2.98 (m, 1H); 2.95 (ddd, *J* = 2.2, 8.2, 11.1 Hz, 1H); 2.76 (dd, *J* = 9.6, 9.6 Hz, 1H); 2.62 (ddd, *J* = 9.0, 9.0, 11.1 Hz, 1H); 1.94 (m, 2H); 1.73 (m, 1H); 1.50 (m, 1H); 1.44 (s, 6H).

***(6R,7R,8S,8aR)*-6,7-*O*-Isopropylidene-6,7,8- trihydroxyindolizidine 175**[21, 45]



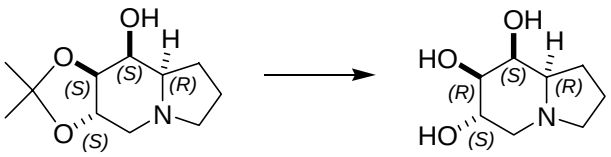
Following procedure E, compound **173** (0.033 g, 0.15 mmol) was reacted to give indolizidine **175** (0.013 g, 50%) as a white solid.

$[\alpha]_D^{25}$ -14 (c 1.3, $CHCl_3$).

R_f 0.42 (DCM/30% MeOH).

^{1}H NMR δ: 4.02 (dd, *J* = 6.0, 9.0 Hz, H_8); 3.73 (dd, *J* = 9.0, 9.6 Hz, H_7); 3.62 (ddd, *J* = 5.2, 9.6, 9.6 Hz, H_6); 3.42 (br s, 1H); 3.15 (ddd, *J* = 6.0, 6.4, 9.8 Hz, H_{8a}); 2.97 (ddd, *J* = 1.9, 7.9, 10.8 Hz, H_3); 2.85 (dd, *J* = 5.2, 9.5 Hz, $H_{5\beta}$); 2.72 (dd, *J* = 9.5, 9.6 Hz, $H_{5\alpha}$); 2.63 (ddd, *J* = 2.4, 9.0, 10.8 Hz, H_3); 1.90 (m, 2H); 1.71 (m, 2H); 1.35 (s, 6H).

***(6S,7R,8S,8aR)*-6,7,8-Trihydroxyindolizidine**[21, 45]



30 **31**

The acetonide group in **30** (0.024 g, 0.11 mmol) was removed following procedure F. Deprotection gave indolizidine **31** (0.013 g, 66%).

$[\alpha]_D^{25}$ +32 (c 1.0, MeOH).

^{1}H NMR (D_2O) δ: 4.07 (dd, *J* = <1, 2.5 Hz, H_8); 3.89 (ddd, *J* = 5.3, 9.6, 10.9 Hz, H_6); 3.54 (dd, J = 3.1, 9.4 Hz, H_7); 3.50 (ddd, *J* = 5.3, 11.9 Hz, $H_{5\beta}$); 3.39 (ddd, *J* = 3.0, 8.1, 11.1 Hz, H_3); 3.23 (ddd, *J* = 1.5, 5.6, 10.9 Hz, H_{8a}); 2.92 (ddd, *J* = 8.5, 8.5, 11.1 Hz, H_3); 2.67 (dd, *J* = 11.5, 11.5 Hz, $H_{5\alpha}$); 1.92 (m, 4H).

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