Total synthesis of 1-Deoxy-6, 7, 8a-*epi*-Castanospermine, (+)-Epiquinamide, (+)-CP-99,994 and Orthogonal *N*-Deacetylation and *N*-Cbz Deprotection

A thesis

Submitted in partial fulfillment of the requirements

Of the degree of

Doctor of Philosophy

By

Prakash R. Sultane

ID: 20083025

INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH, PUNE

2014

This Thesis is dedicated to...

My grandmother, Brother

And

My beloved family

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH (IISER), PUNE
(An Autonomous Institution, Ministry of Human Resource Development, Govt. of India)
900 NCL Innovation Park, Dr. Homi Bhabha Road, Pune 411008

Dr. Ramakrishna G. Bhat
Associate Professor
Department of Chemistry,
IISER Pune

CERTIFICATE

Certified that the work incorporated in the thesis entitled "***Total synthesis of 1-Deoxy-6, 7, 8a-epi-Castanospermine, (+)-Epiquinamide, (+)-CP-99,994 and Orthogonal N-Deacetylation and N-Cbz Deprotection***" submitted by **Mr. Prakash R. Sultane** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 28th Feb. 2014, Pune

Dr. Ramakrishna G. Bhat
(Research Supervisor)

rgb@iiserpune.ac.in • Ph: +91-20-25908092 • Fax: +91-20-25898022

DECLARATION

I declare that, this written submission represents my ideas in my own words and where others' ideas have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea / data / fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date: 28th Feb. 2014, Pune

Mr. Prakash R Sultane

ID: 20083025

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Prakash R. Sultane

CONTENTS

ABBREVIATIONS

Ac	Acyl
Ar	Aryl
Bn	Benzyl
^{t}Boc	tert-butoxycarbonyl
bs	broad singlet
Calcd.	Calculated
Cat.	Catalytic
Cbz	benzyloxycarbonyl
d	doublet
DCC	N,N’-dicyclohexylcarbodiimide
HOBt	Hydroxybenzotriazole
DCM	dichloromethane
dd	doublet of doublet
DMAP	N,N'-dimethylaminopyridine
DMSO	dimethylsulfoxide
ESI	electrospray ionisation
EtOAc	ethyl acetate
g	gram
h	hour
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infra red
J	Spin coupling constant
LDA	Lithium diisopropylamide
m	multiplet
m/z	mass/charge
Me	methyl
mg	milligram
min	minute
mL	milliliters

mmol	millimole
MOM	Methoxymethyl
mol	mole
mp	melting point
NMR	Nuclear Magnetic Resonance
MALDI-TOF/TOF	Matrix-Assisted Laser Desorption /Ionization – Time of Flight
NMO	N-Methylmorpholine N-Oxide
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
COSY	Correlation spectroscopy
Ph	phenyl
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
t	triplet
m	multiplet
td	triplet of doublet
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
PG	Protecting group
R_f	Retention factor
MeOH	Methanol
HCl	Hydrochloric acid
LAH	Lithium aluminium hydride
IBX	2-Iodoxybenzoic acid
n-BuLi	n-butyl lithium
₹	Indian rupee

SYNOPSIS

The thesis entitled "***Total synthesis of 1-Deoxy-6, 7, 8a-epi-Castanospermine, (+)-Epiquinamide, (+)-CP-99,994 and Orthogonal N-Deacetylation and N-Cbz Deprotection***" comprises of three main chapters.

Chapter I: ***Total synthesis of 1-Deoxy-6, 7, 8a-epi-Castanospermine and formal synthesis of Pumiliotoxin 251D***

This chapter presents a brief overview on the importance and the synthesis of (+)-castanospermine **1** followed by the total synthesis of 1-deoxy-6, 7, 8a-*epi*-castanospermine and formal synthesis of pumiliotoxin 251D. Our synthesis employs cross metathesis approach for building a key intermediate and this has been utilized effectively in constructing indolizidine skeleton for the total synthesis of 1-deoxy-6,7,8a-*epi*-castanospermine and also for the bicyclic framework of pumiliotoxin 251D. The naturally occurring (+)-castanospermine **1** and their analogues **2**, **3** and **4** have been reported to exhibit glycosidase inhibition (Fig.1).

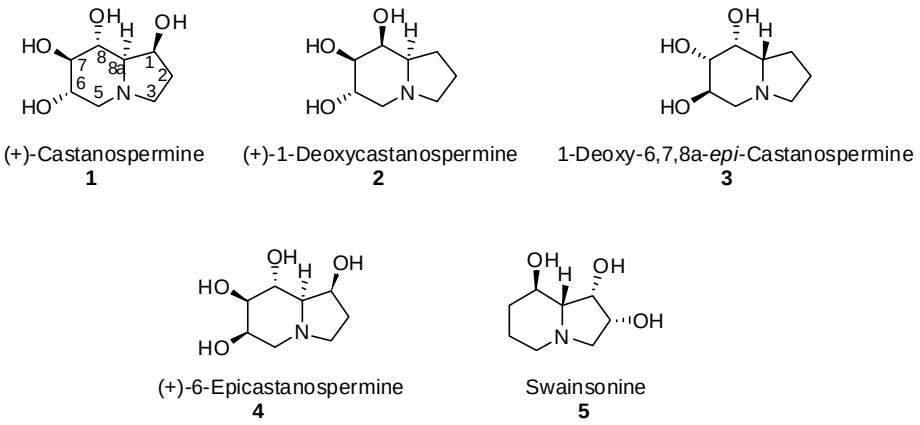
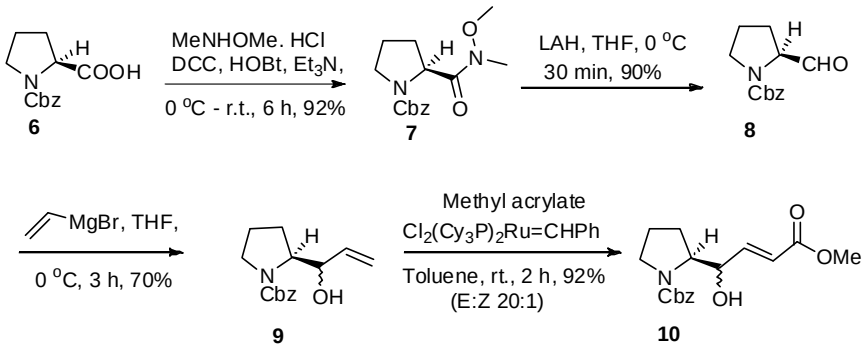


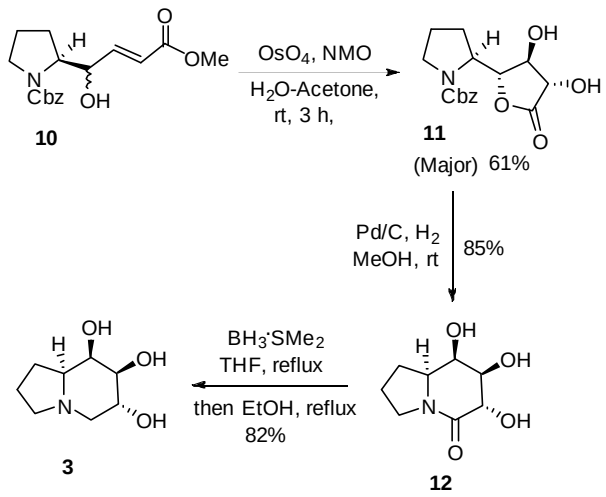
Figure 1 (+)-Castanospermine and its analogues

We started our synthesis by coupling N-Cbz proline **6** with *N,O*-dimethylhydroxylamine hydrochloride using DCC and HOBt to afford the corresponding Weinreb amide **7**. This on treatment with lithium aluminium hydride (LAH) in THF at 0 ^{o}C furnished the corresponding aldehyde **8** in very good yield (90%). The addition of vinyl magnesium bromide to aldehyde **8** afforded a diastereomeric mixture of the corresponding alcohol **9.**



Scheme 1 Synthesis of key intermediate **10**

The cross metathesis of **9** with methyl acrylate was performed using Grubbs' second generation catalyst in toluene at room temperature to afford predominantly the desired *E*-isomer **10** (E/Z 20:1) in excellent yield (92%). This alkene **10** when treated with catalytic amount of OsO_4, NMO (Upjohn dihydroxylation) in acetone–water mixture provided the corresponding lactone **11** as a major product.



Scheme 2 Synthesis of 1-deoxy-*epi*-castanospermine

Single crystal X-ray diffraction analysis unambiguously proved the structure and established stereochemistry of all hydroxyl groups in lactone **11** (Fig 2). Further, pure lactone **11** upon hydrogenolysis using H_2, Pd/C afforded the bicyclic lactam **12**. Finally, bicyclic lactam on reduction with BH_3·DMS complex in THF gave the desired final compound 1-deoxy-*epi*-castanospermine **3** in 82% yield.

Pumiliotoxin 251D (**5)**, was isolated from the Ecuadorian frog *Dendrobates tricolor*, was the first alkaloid of this class whose structure was unambiguously determined.

Pumiliotoxin 251D has shown ability to activate voltage dependent sodium channels, therefore displaying in some cases cardiotonic and myotonic activity.

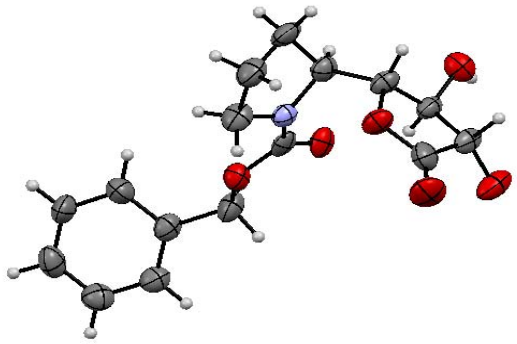


Figure 2. Molecular structure of lactone **11** by X-ray analysis (ORTEP diagram; ellipsoids are drawn at 50% probability).

Earlier syntheses of pumiliotoxin 251D were carried out successfully by utilizing the indolizidine bicyclic frameworks **12–14** as key intermediates (Fig 3).

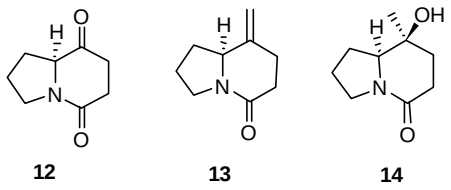
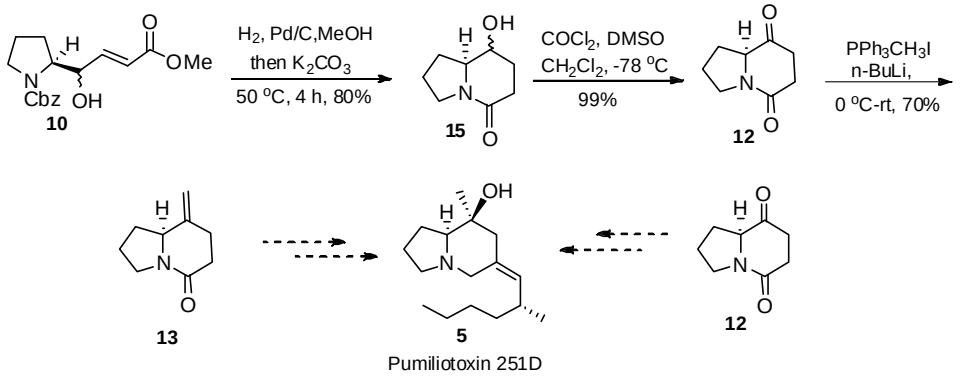


Figure 3. Key intermediates of Pumiliotoxin 251D

We envisioned that olefin **10** can be effectively utilized for the easy access of indolizidine bicyclic frameworks **12**, **13**. In this regard, unsaturated ester **10** on treatment with Pd/C, H_2 in MeOH, followed by the addition of K_2CO_3 gave the corresponding alcohol **15** in 80% yield. It is important to note that the sequence of transformations such as deprotection of benzyloxycarbonyl (Cbz) group, reduction of double bond, and facile cyclization occurred in one pot.

Subsequently, alcohol **15** upon Swern oxidation, afforded the indolizidinedione **12** in almost quantitative yield 99% and in an over yield of 42% in 6 steps. This approach is the shortest route to access the optically pure indolizidine frameworks. Finally, when compound **12** was subjected to Wittig olefination afforded the optically pure bicyclic lactam **13** in 70% yield.



Scheme 3. Formal synthesis of Pumiliotoxin 251D

Chapter 2: Chiral Pool Approach to cis-2, 3-Disubstituted Piperidines, (+)-CP-99,994 and (+)-Epiquinamide

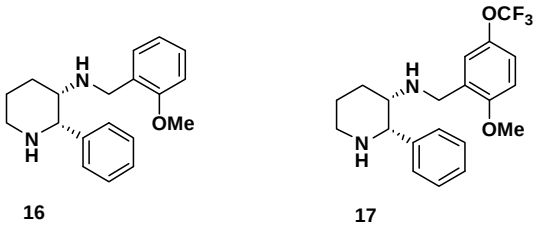
This chapter has been divided in to two sections. Section-A presents an efficient stereoselective approach to *cis*-2,3-disubstituted piperidines via the reduction of N-acyliminium ion intermediate using a novel pathway. Application of this methodology is exemplified by the enantioselective total synthesis of (+)-(2*S*, 3*S*)-CP-99,994. Section-B presents the synthetic studies towards the total synthesis of (+)-epiquinamide.

Section-A: *Enantioselective synthesis of cis-2, 3-disubstituted Piperidines: Total synthesis of CP-99,994*

This section briefly states the importance of (+)-(2*S*, 3*S*)-CP-99,994 and outlines the recent synthetic procedures on the functionalized piperidines. In this section simple and efficient stereoselective approach for the synthesis of *cis*-2,3-disubstituted piperidines has been described. Application of this methodology has been further exemplified by the enantioselective total synthesis of (+)-(2*S*,3*S*)-CP-99,994.

Piperidine motifs are also very important pharmacophores for many molecules in clinical and preclinical trials. In particular 2-aryl-3-amino piperidines are present in many bioactive molecules and drugs. Some of the compounds derived from this general structure are well known as substance P (SP) receptor antagonists. For example molecules such as (+)-(2*S*,3*S*)-CP-99,994 (**16**), (+)-(2*S*,3*S*)-CP-122,721 (**17**) are known to be non-peptide antagonists of neurokinin-1 (NK-1) substance P receptor (Fig. 4).

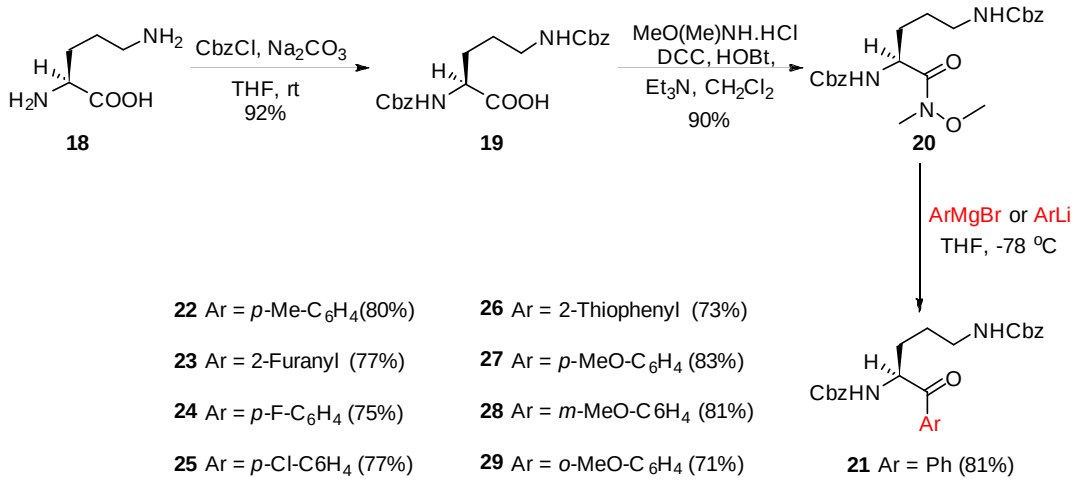
Enantiopure ketones were prepared starting from L-ornithine via the addition of different Grignard reagents to Weinreb amide **20**.



16 **17**

Figure 4 Antagonists of neurokinin-1 (NK-1) substance P receptor

We envisioned that 2, 3-disubstituted piperidines can be built by intramolecular cyclization of diaminoarylketones via N-acyliminium ion intermediate which could eventually be reduced by silyl hydrides.



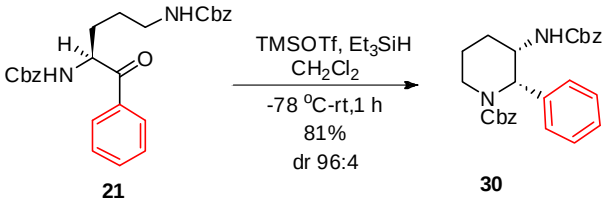
18 **19** **20**

22 Ar = *p*-Me-C$_6$H$_4$(80%)
23 Ar = 2-Furanyl (77%)
24 Ar = *p*-F-C$_6$H$_4$ (75%)
25 Ar = *p*-Cl-C6H$_4$ (77%)
26 Ar = 2-Thiophenyl (73%)
27 Ar = *p*-MeO-C$_6$H$_4$ (83%)
28 Ar = *m*-MeO-C 6H$_4$ (81%)
29 Ar = *o*-MeO-C $_6$H$_4$ (71%)

21 Ar = Ph (81%)

Scheme 4. Synthesis of enantiopure aminoketone

In order to explore this new possibility, we subsequently treated the diaminophenylketone **21** with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at -78 ^oC to afford the 2,3-disubstituted piperidine derivative **30** in very good yield with high diastereomeric ratio (Scheme 5).



21 **30**

Scheme 5. Cyclization of amino ketone **21**

Diastereomeric ratio was determined by ^{1}H-NMR. The *cis* relationship of the substituents at C-2 and C-3 in compound **30** was deduced from the $J_{2\text{-}3}$ coupling constant (J = 6.4 Hz), NOE and NOESY studies. Further, single crystal X-ray analysis of **30** was unambiguously confirmed the *cis* relationship between the two substituents.

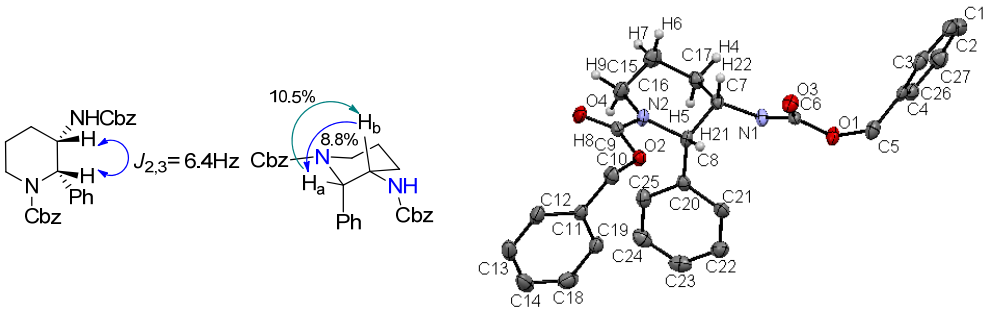


Figure 5. NOE and X-ray single crystal structure of compound **30** (ORTEP diagram, ellipsoid drawn at 50% probability)

Encouraged by this initial success we planned to synthesize different 2, 3-*cis*-piperidines to demonstrate the synthetic utility of this approach. Strength of the approach lies in the fact that diverse organolithium or Grignard reagents can be effectively utilized to prepare different diaminoketone derivatives. Diaminoketones (**22-29**) upon treatment with trimethylsilyl triflate (TMSOTf) (1 equiv.) and triethylsilane (Et_3SiH) (1 equiv.) in CH_2Cl_2 at -78 ^{o}C afforded the corresponding 2, 3-disubstituted piperidine derivatives (**31-38**) in very good yields (up to 83%) and diastereoselectivity (*dr* up to 96:4). The stereochemistry of the piperidine derivatives **31-38** was assigned by the analogy.

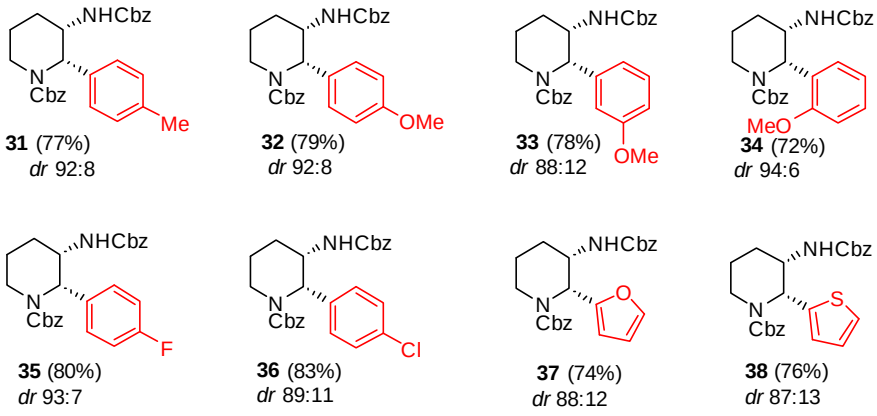
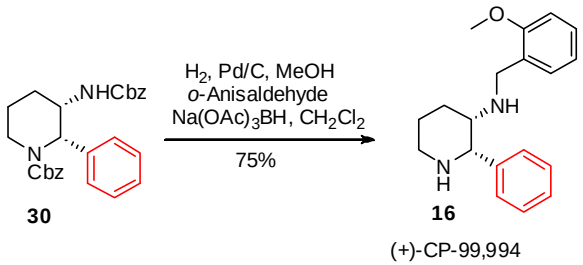


Figure 6. cis-2, 3-disubstituted piperidine derivatives

After successfully synthesizing different 2*S*, 3*S*-*cis*-piperidines, we employed this methodology for the concise enantioselective synthesis of (+)-CP-99,994 (**16**) by subjecting compound **30** for hydrogenolysis followed reductive amination with *o*-anisaldehyde.



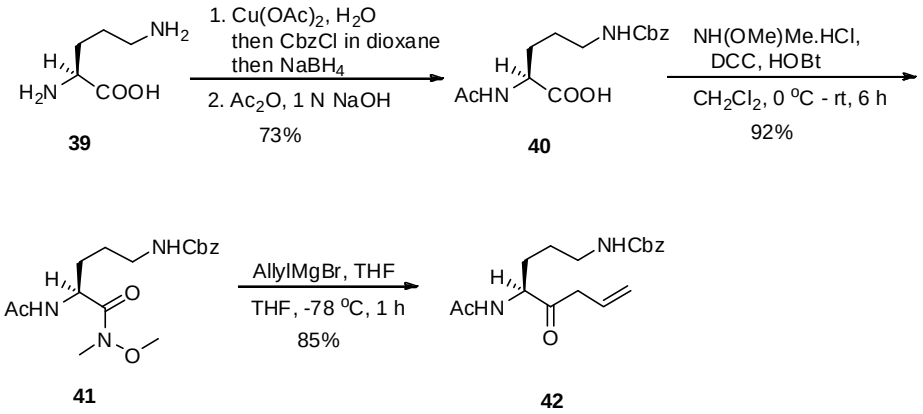
Scheme 6. Synthesis of (+)-CP-99,994

We described a novel approach for the wide and easy access of 2, 3-disubstituted piperidine derivatives and in particular synthesis of various congeners of (+)-CP-99,994 to test the biological activity against NK1-receptor.

Section-B: ***Total synthesis of (+)-Epiquinamide***

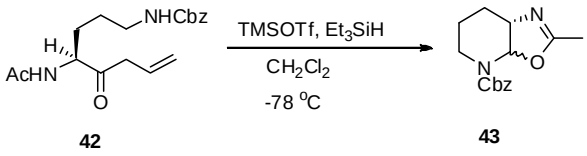
This section briefly outlines the importance and selected syntheses of (+)-epiquinamide in literature. Total synthesis of (+)-epiquinamide starting from inexpensive and commercially available starting material L-ornithine has been described.

Epiquinamide **47** was isolated along with epibatidine from the poison frog *Epipedobates tricolor* by Daly and co-workers in 2003 and it has potent and selective agonistic activities against β2 nicotinic receptors. Our ongoing research in nitrogen containing heterocycles, directed out interest for the total synthesis of (+)-epiquinamide.



Scheme 7. Preparation of amino ketone

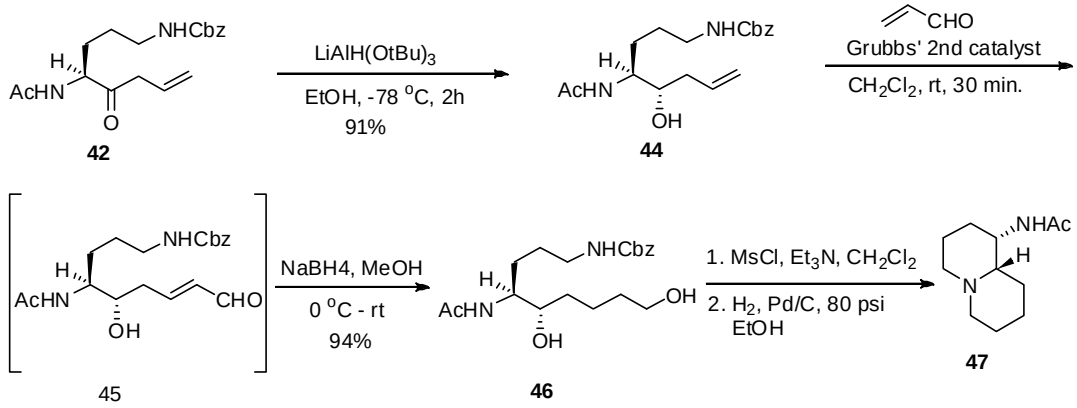
Our synthesis started with the protection of commercially available L-ornithine **39** (Scheme 7). The protection was achieved in two steps. At first, δ-amine in L-ornithine was protected by Cbz-Cl by making copper complex. Further, α-amine in L-N^{δ}-Cbz-ornithine was acetylated using acetic anhydride under alkaline condition to afford L-N^{δ}-Cbz-N^{α}-acetyl ornithine **40** in 73% yield. The free carboxylic group in **40** was converted into the corresponding Weinreb amide **41** in excellent yield (92%). This on treatment with allylmagnesium bromide afforded the corresponding ketone **42**. Having suitably placed N-Cbz and keto groups we planned to explore the reductive cyclization methodology. Amino ketone **42** when treated with TMSOTf and triethyl silane in dichloromethane at -78 ^{o}C afforded the unexpected compound which was relatively unstable and could not be purified. Based on the mass spectrum of the crude compound we surmised that possible side product as **43**. We believed that neighboring group participation (NGP) of *N*-acetyl group might have afforded compound **42** (Scheme 8).



42 **43**

Scheme 8 Attempted cyclization of ketone **42** and NGP of acetyl group

Having obtained ally ketone **268** in hand, we sought an alternative plan to achieve the target (+)-epiquinamide (Scheme 9). Homoallyl ketone was stereosectively reduced to amino alcohol **44**; as exclusively one isomer using LiAlH(O^{t}Bu)$_3$ in EtOH at -78 ^{o}C in 91% yield.



42 **44** **47**

45 **46**

Scheme 9 Total synthesis of (+)-Epiquinamide

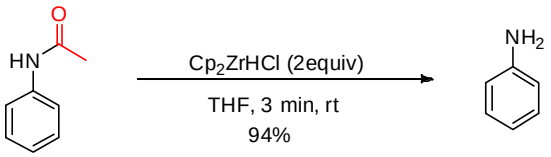
The cross metathesis of alcohol **44** with acrolein using Grubbs' second generation catalyst afforded aldehyde **45** which was immediately reduced with $NaBH_4$ in MeOH to afford diol **46**.This diol was dimesylated followed by the treatment of dimesylated compound with 10% Pd/C, H_2 at 80 psi provided desired product (+)-epiquinamide **47** in 65% yield over two steps (Scheme 9) . Spectral data of (+)-epiquinamide **47** were in a close agreement with the literature value. Specific rotation of compound **47** was in accordance with reported value.

Chapter 3: Convenient N-decetylation and N-Cbz Deprotection under mild conditions

In this chapter we present a convenient and practical approach for the deprotection of N-acetyl (N-Ac) and N-benzyloxycarbonyl (N-Cbz) groups. This chapter is subdivided into two sections. Section A describes the use of Schwartz reagent for the efficient and facile N-deacetylation. Detailed studies on N-deacetylation on various N-acetyl amines have been carried out for generality. Section B presents a novel method for the orthogonal deprotection of N-Cbz as well as for bezyl ester hydrogenolysis using $NaBH_4$ and Pd/C. For the wider applicability of the approach, gram scale deprotection have been demonstrated.

Section A: *Orthogonal N-deacetylation under mild conditions using Schwartz reagent*

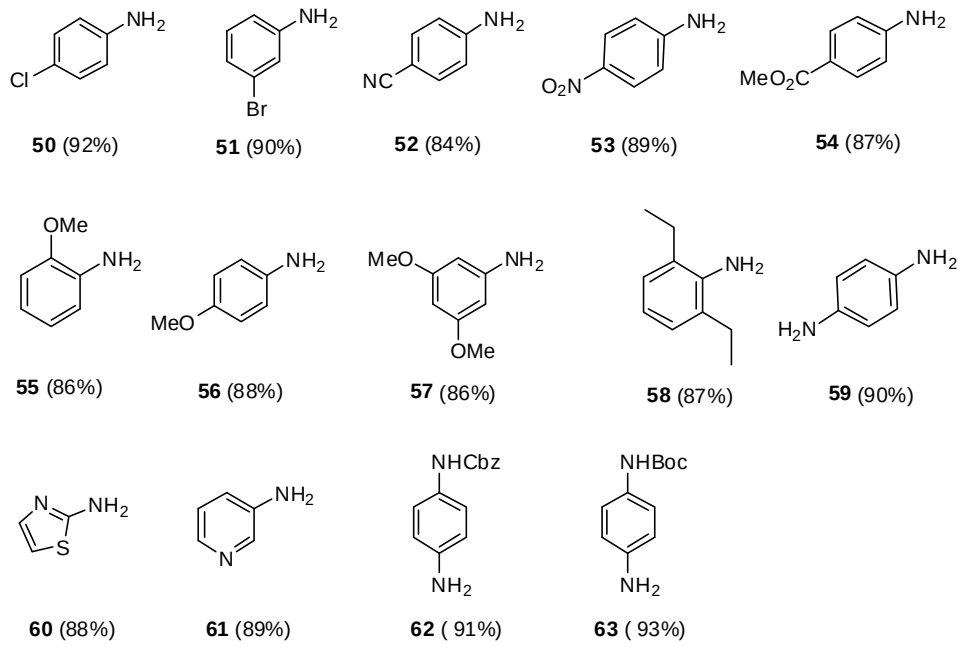
This section begins with the literature overview on the available methods of N-deacetylation and presents a mild and efficient chemoselective *N*-deacetylation using the Schwartz reagent at room temperature. In spite of the wide utility of acetyl protection for amines in organic synthesis, acetyl deprotection (*N*-deacetylation) is practically limited to the traditional harsh deprotecting conditions using strong basic and acidic conditions. In order to explore the utility of Schwartz reagent for the N-deacetylation we started our study by the preparation of *N*-acetyl amines. As a model reaction acetanilide **48** was treated with Schwartz reagent in anhydrous THF at room temperature. Interestingly, the initial turbid reaction mixture changed into a clear solution in a very short time (3 min) followed by quenching the reaction with water afforded aniline **49** in excellent yield.



48 **49**

Scheme 10 Model reaction for N-deacetylation

Encouraged by the initial result different N-acetylated amines were examined for the *N*-deacetylation. Under the optimized condition *N*-deacetylation occurred in very rapid time affording corresponding amines (**50-72)** in excellent yields. Electron withdrawing and donating moieties and streic factor did not have any impact on the rate of the reaction and yields.



50 (92%) **51** (90%) **52** (84%) **53** (89%) **54** (87%)

55 (86%) **56** (88%) **57** (86%) **58** (87%) **59** (90%)

60 (88%) **61** (89%) **62** (91%) **63** (93%)

Figure 7. Aromatic and Heteroaromatic amines from N-deacetylation

In order to have generality of this approach N-acetylated aliphatic amines were subjected to optimized deprotection conditions using Schwartz reagent. All the aliphatic substrates underwent facile N-deacetylation by affording corresponding aliphatic amines (**64-68**) in excellent yields in rapid time. It is very important to note that the deprotection conditions did not induce any epimerization at chiral amino centre of compounds (**69-71)**. It is also glad to note that deprotection worked efficiently with the amino acid derivative without any epimerization.

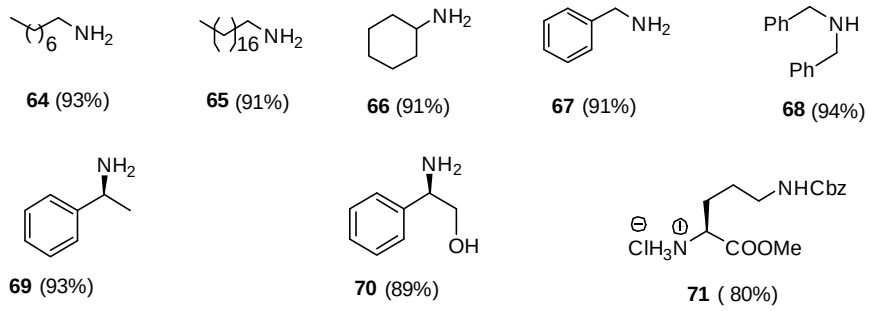
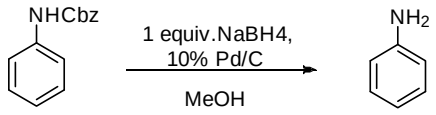


Figure 8. Aliphatic amines from N-deacetylation

Further competitive N-deacetylation was carried out in presence of other protecting groups such as Boc, Fmoc, Cbz, Ts. Under N-deacetylation condition other protecting groups were stable. We presented a facile and rapid method for *N*-deacetylation. The protocol may provide an advantage to remove acetyl group at any convenient stage of the natural product synthesis.

Section B: *Orthogonal deprotection of N-Cbz and deprotection of Benzyl esters*

This section begins with the literature overview on the available methods of deprotection of N-benzyloxycarbonyl (Cbz) group. This section presents novel protocol for the N-Cbz deprotection and benzyl ester hydrogenolysis using $NaBH_4$-Pd/C system in ethanol at room temperature. For the practical utility method has been demonstrated on gram scale. In our initial experiment on compound **72** using 10% Pd/C and $NaBH_4$ (1 equiv) in MeOH at room temperature afforded the aniline **49** in excellent yield (98%) in rapid time (5 min).



Scheme 11 Model reaction

Encouraged by the initial result different N-Cbz substrates were prepared and examined for the *N*-Cbz deprotection. Substrates under deprotection conditions afforded the corresponding amines (**50-59, 63, 73-76**) in excellent yields (Fig 9). Electron withdrawing and donating moieties did not have any significant impact on the reaction time and yields.

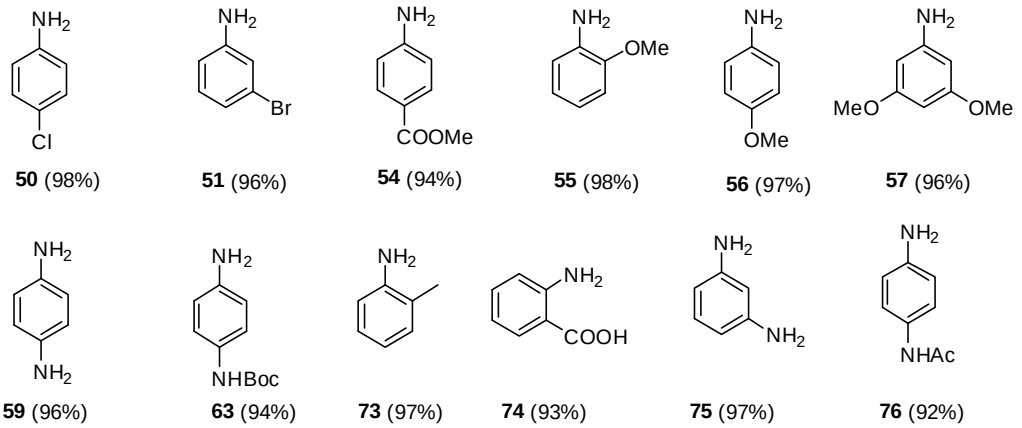


Figure 9 Aromatic amines

N-Cbz aliphatic amines under optimized reaction conditions afforded the corresponding aliphatic amines (**64-68**) in excellent yields (Fig 10). Furthermore, reaction conditions enabled the deprotection of N-Cbz chiral amines without any epimerization (**69-70, 77**) (Fig. 10).

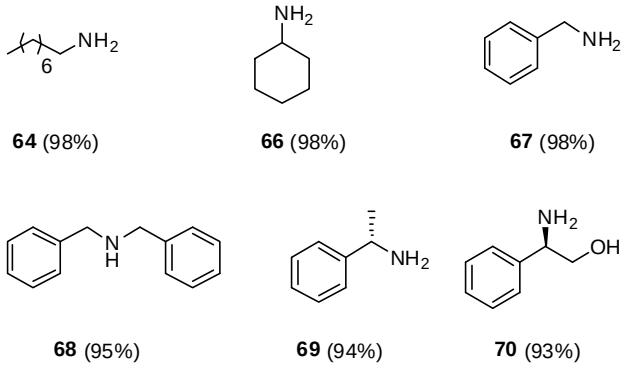
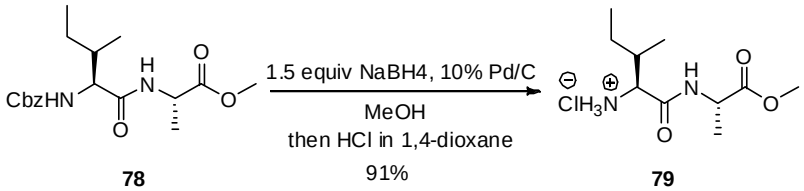


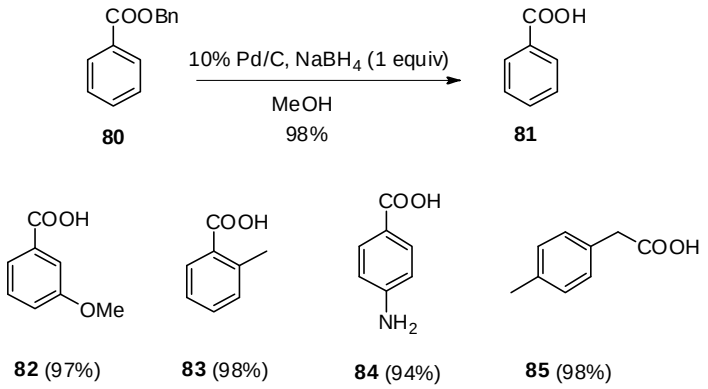
Figure 10 Aliphatic and Chiral Amines

Application of this methodology has been demonstrated for the dipeptide **78** to afford optically pure dipeptide (**79**) (Scheme 11). Interestingly, we did not observe catalytic poisoning of catalyst by amines.



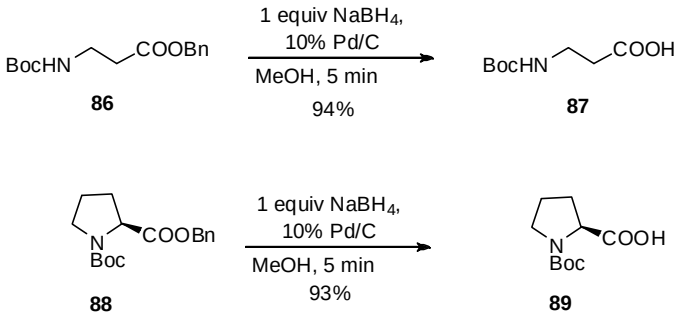
Scheme 11 Application to peptide

Similarly, hydrogenolysis of benzyl esters was successfully achieved using 10% Pd/C and $NaBH_4$ (1 equiv.) in methanol at room temperature.



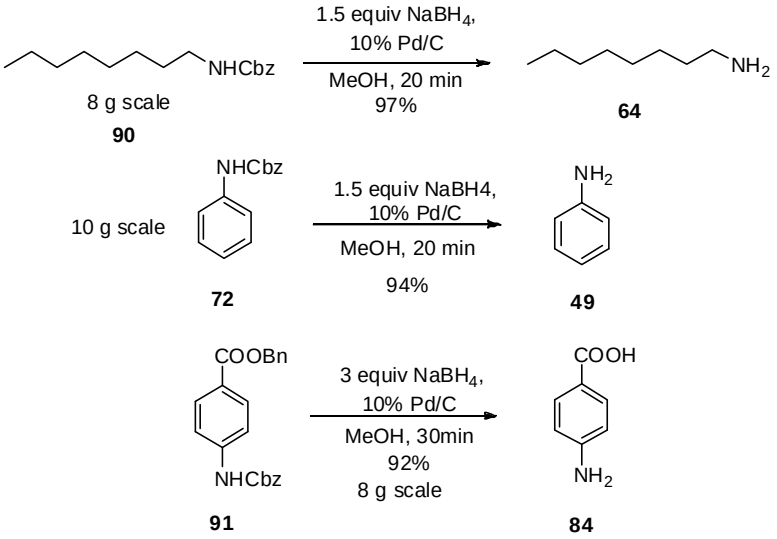
Scheme 12 Hydrogenolysis of benzylester

Different bezyl esters when subjected to the optimized reaction conditions (1 equiv. $NaBH_4$ and 10% Pd/C) in methanol afforded the corresponding carboxylic acids (**81-85**) in excellent yields (Scheme 12). Similarly, amino acid benzyl esters (**86** and **88**) when treated with 1 equiv. of $NaBH_4$ and 10% Pd/C in methanol at room temperature afforded the free carboxylic acids (**87** and **89**) in excellent yields in rapid time (5 min).We did not observe any epimerization of **89** during hydrogenolysis. .



Scheme 12 Hydrogenolysis of amino acid benzylester

For the practical utility, we demonstrated the Cbz and Bn ester depotection on a gram scale (Scheme 13).



Scheme 13 Gram scale reaction

(*Numbers of substrates and products in the synopsis are different from those in thesis*)

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List of Publications

1. Total synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine and formal synthesis of pumiliotoxin-251D

   Prakash R. Sultane; Amar R. Mohite; Ramakrishna G. Bhat, *Tetrahedron Lett.,* **2012**, *53*, 5856-5858.(http://dx.doi.org/10.1016/j.tetlet.2012.08.061)

2. Stereoselective Approach to *cis*-2, 3-Disubstituted Piperidines *via* Reduction of *N*-acyliminium ion interemediate: Enantioselective Synthesis of (+)-(2*S*, 3*S*)-CP 99, 994

   Prakash R. Sultane; Ramakrishna G. Bhat, *J. Org. Chem.*, **2012**, *77*, 11349–11354 (DOI 10.1021/jo302181k). Highlighted in Organic Chemistry Portal (URL:http://www.organic-chemistry.org/Highlights/2013/22April.shtm)

3. $BF_3 \cdot Et_2O$ and trifluoroacetic acid/triethyl amine-mediated synthesis of functionalized piperidines

   Amar R. Mohite, **Prakash R. Sultane**; Ramakrishna G. Bhat, *Tetrahedron Lett.,* **2012**, *53*, 30-35(http://dx.doi.org/10.1016/j.tetlet.2011.10.072) Highlighted in *ChemInform* DOI: 10.1002/chin.201217154

4. Chemoselctive N-Deacetylation under mild conditions

   Prakash R. Sultane, Trimbak Mete**,** Ramakrishna G. Bhat., *Org. Biomol. Chem.,* **2014**, *12*, 261 – 264

5. Total synthesis of (+)-Epiquinamide

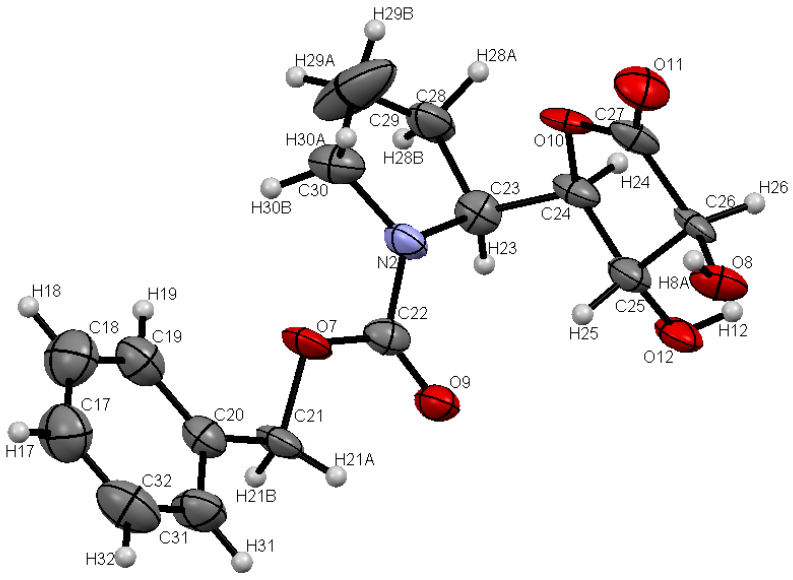
   Prakash R. Sultane, Digvijay Porwal**,** Ramakrishna G. Bhat, *Manuscript is ready*

6. Deprotection of Cbz and benzyl ester under mild conditions.

   Prakash R. Sultane, Trimbak Mete**,** Ramakrishna G. Bhat, *Communicated*

Chapter 1

Total Synthesis of 1-Deoxy-6, 7, 8a-*epi*-Castanospermine and Formal synthesis of Pumiliotoxin 251D



X-ray crystal structure of lactone 98

O N E

Total synthesis of 1-Deoxy-6,7,8a-*epi*-Castanospermine, and Formal synthesis of Pumiliotoxin 251D

1

In this chapter a concise and efficient synthesis of (6R,7S,8R,8aS)-6,7,8-trihydroxyindolizidine (1-deoxy-6,7,8a-epi-castanospermine) has been described. The synthesis employs cross metathesis in building a key intermediate and this intermediate has been used effectively in constructing indolizidine skeleton for the total synthesis of 1-deoxy-6,7,8a-epi-castanospermine. Similarly, this key intermediate has also been utilized in constructing the bicyclic framework of pumiliotoxin 251D. Synthetic studies have been discussed in detail in Section A and Section B. It is interesting to note that indolizidine skeleton has been constructed in one pot following the sequence of transformations such as deprotection of Cbz group, reduction of double bond and cyclization.

Section A

Total synthesis of 1-Deoxy-6,7,8a-*epi*-Castanospermine

1A. 1 Introduction to (+)-Castanospermine and its Analogues

Polyhydroxylated alkaloids are family of natural products that usually include aza heterocyclic core and exhibit potent inhibitory activity towards glycosidases. (+)-Castanospermine **1** belongs to a family of naturally occurring polyhydroxylated indolizidine alkaloids (Figure 1.1). (+)-Castanospermine **1** was first isolated in 1981 from the seeds of the Moreton Bay chestnut Castanospermum australe by Hohenschutz and co-workers[1] and from the dry pods of Alexa leiopetala.[2] In the original report, the absolute stereochemistry of (+)-castanospermine **1** was arbitrarily chosen as one enantiomer,[2-3] however, the total synthesis by Ganem and Bernotas[4] unambiguously established the absolute stereochemistry as depicted in Fig.1.1.

The naturally occurring (+)-castanospermine **1** and its analogues **2**, **3** have been reported to exhibit glycosidase inhibition activity.[5]

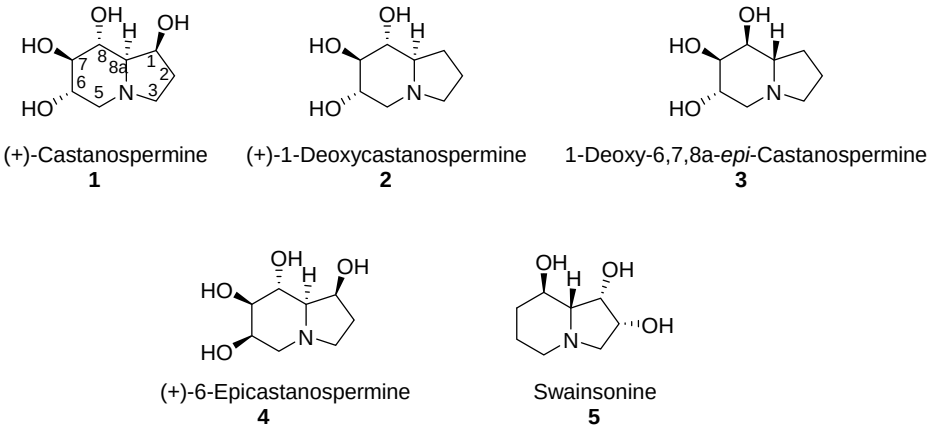


Figure 1.1 (+)-Castanospermine and its analogues: Potent glycosidase Inhibitors

1A. 2 Biological activity of (+)-Castanospermine and its analogues

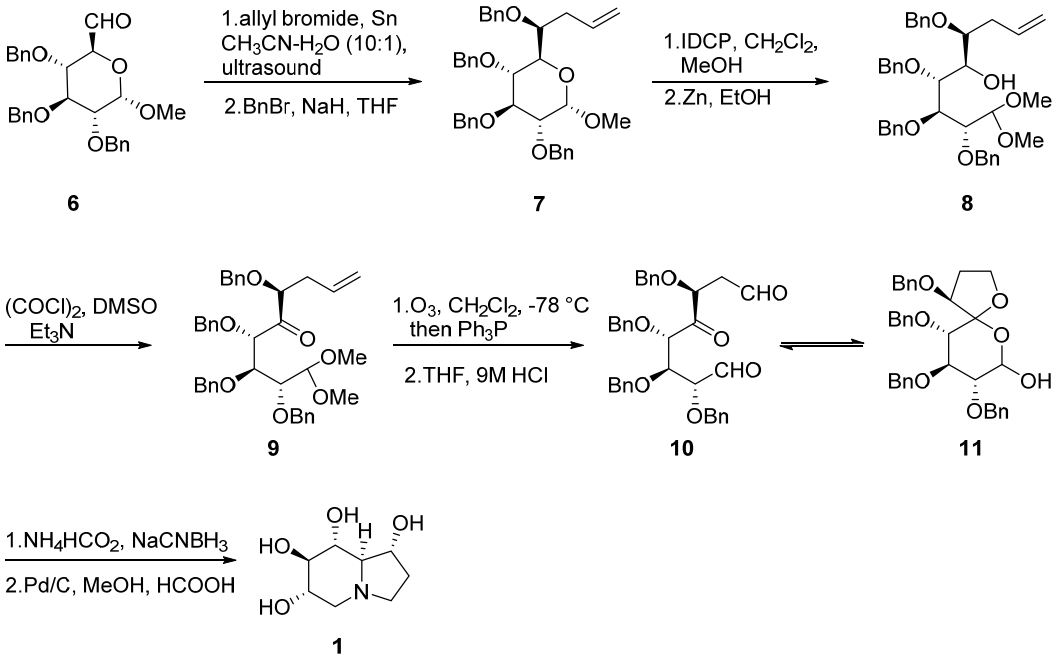
Glycosidases are class of enzymes and they are involved in catalyzing the hydrolysis of glycosidic bonds. The hydrolysis of glycosidic bonds is of prime importance, since many fundamental processes are governed by carbohydrate-mediated information, *viz.* quality control of protein folding, signalling pathways, and modulation of cell-cell adhesion.[6] (+)-Castanospermine **1** and its analogues are regarded as potential antiviral, antitumor, anti-inflammatory and immunomodulating agents. Further studies on (+)-castanospermine **1** have been demonstrated the potential use of **1**, in the treatment of various cancer types,[7] and diabetes.[8] Recent in vitro as well as in vivo studies have also shown that (+)-castanospermine **1** and its analogues **2-4** are potent inhibitors of dengue virus. Importantly, Diamond and co-workers[9] demonstrated that (+)-castanospermine **1** prevented mortality in mice infected with dengue virus, and also inhibited the all four serotypes of dengue viruses. It is believed that (+)-castanospermine **1** inhibits the viral infection by disrupting the folding of several viral proteins of structural importance. This has been ascribed to the ability of (+)-castanospermine to prevent removal of terminal glucose residues on *N*-linked oligosaccharides, which may interrupt the interaction with protein folding enzymes.

1A. 3 Reported Synthesis of (+)-Castanospermine

Many interesting biological properties of (+)-castanospermine and its analogues attracted the attention of many organic chemists. These molecules have been the subject of synthesis. Some of the selected and important syntheses for (+)-castanospermine and its analogue:1-deoxy-6,7,8a-*epi*-castanospermine have been discussed.

1A. 3. 1 Synthesis by Mootoo et al.

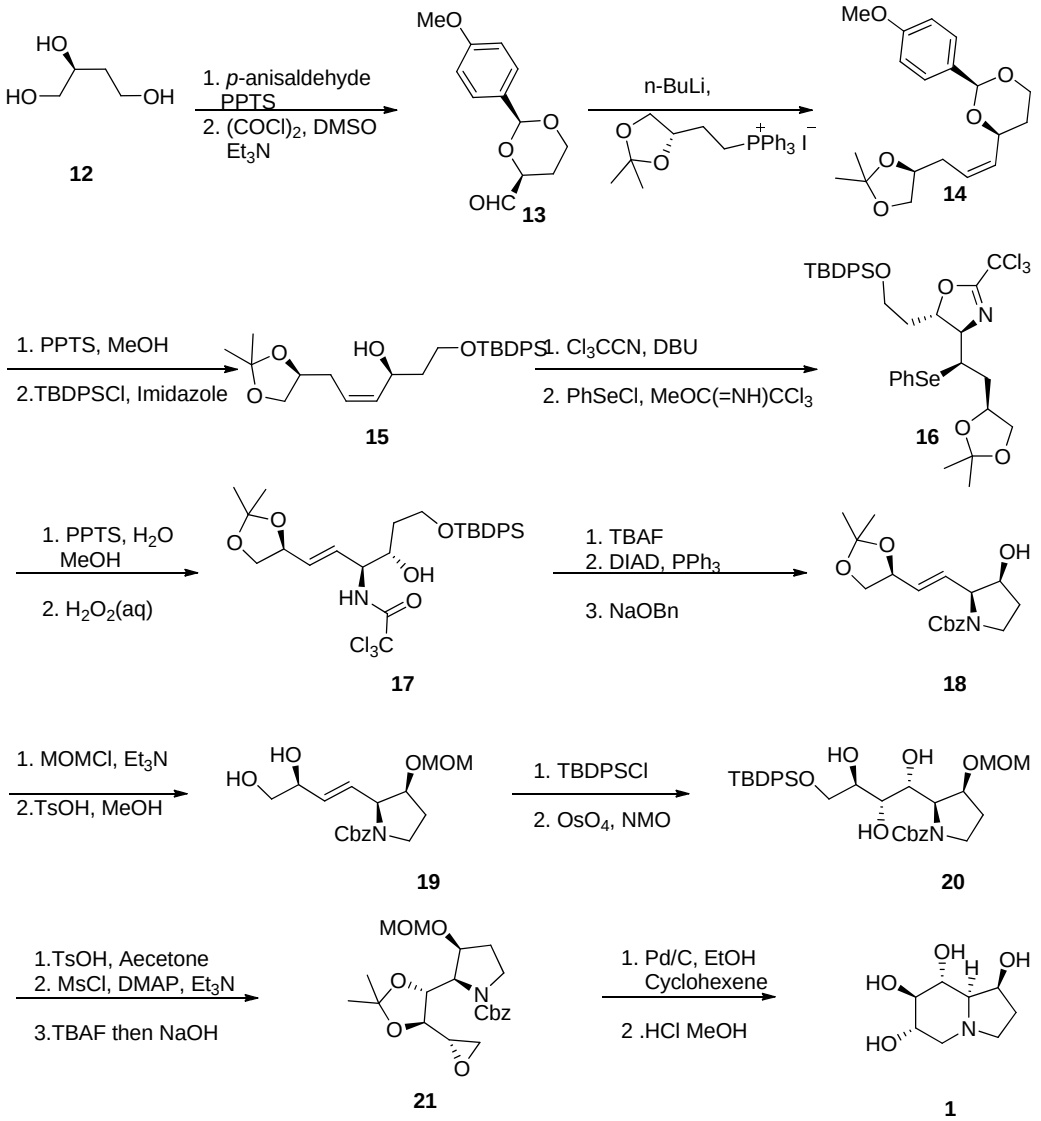
Mootoo and co-workers[10] described the total synthesis of castanospermine **1** based on the triple reductive amination approach. Their synthesis began with the known aldehyde **6** that was obtained in four steps from methyl α-D-glucopyranoside. Allylation of aldehyde **6** under Whitesides reaction condition using allyl bromide and tin metal followed by the protection of resulting alcohol with benzyl bromide afforded the desired allylated pyranoside **7** (Scheme 1.1). The conversion of pyranoside **7** to the requisite tricarbonyl intermediate **10** was achieved in sequence of reactions. Treatment of compound **7** with iodonium dicollidine perchlorate (IDCP) followed by sequence of reactions gave a mixture of lactol isomer **11** and *bis*-aldehyde **10**.



Scheme 1.1: Total Synthesis of (+)-Castanospermine published by Mootoo *et al.*

This upon treatment with 1.5 equiv of ammonium formate and sodium cyanoborohydride in anhydrous methanol followed by hydrogenolysis afforded the target compound (+)-castanospermine **1** (overall yield 22% starting from aldehyde **6** over nine steps) (Scheme 1.1). However, the stereocenters at C(6), C(7), and C(8) were all derived from methyl α-D-glucopyranoside, while the stereocenter at C(1) was created using a tin-mediated allylation under Barbier conditions and stereocentre at C(8a) was obtained via reductive amination where hydride was delivered preferentially via α-face on bicyclic iminium ion intermediate.

1A. 3. 2 Synthesis by Kang et al.



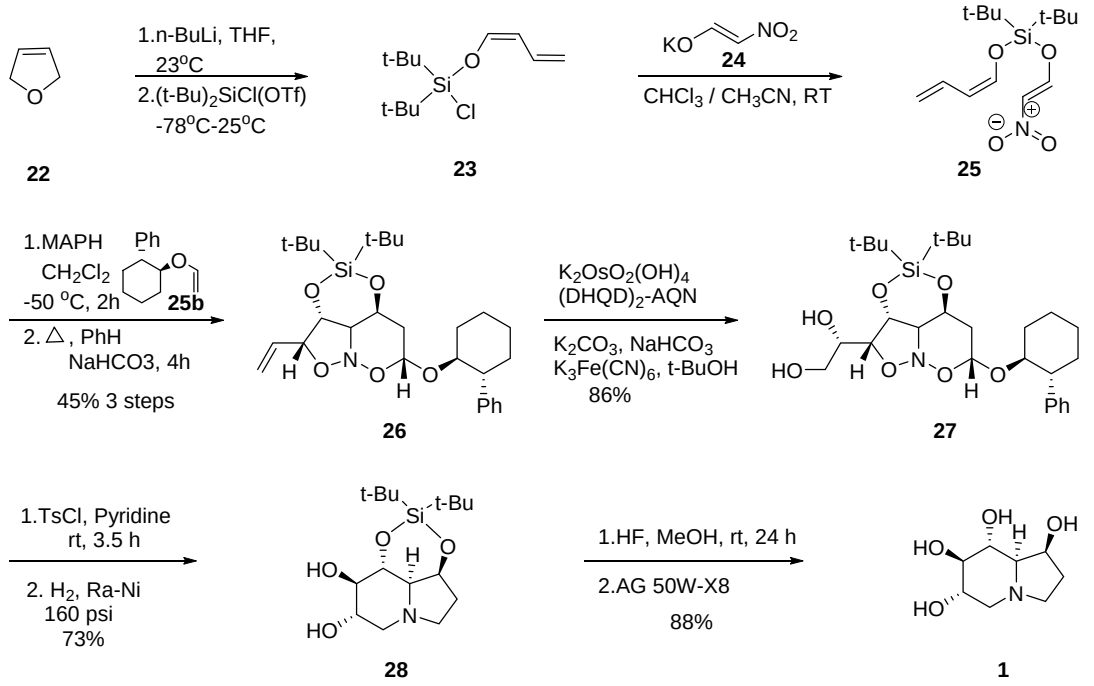
Scheme 1.2 Total Synthesis of (+)-Castanospermine by Kang *et al.*

In 1998, Kang et al. reported[11] the total synthesis of castanospermine. Unlike other carbohydrate based chiral pool approaches, they started the synthesis from the commercially available triol **12**, (also **12** can be synthesized in one step from L-(−)-malic acid) (Scheme 1.2). Triol **12** was treated with *p*-anisaldehyde in presence of PPTS followed by Swern oxidation to afford the corresponding aldehyde **13**. Further Wittig olefination of **13** with Wittig salt afforded the corresponding olefin **14**. Chemoselective hydrolysis of *p*-methoxybenzylidene group was achieved using PPTS in methanol. Subsequent regioselective silylether formation, treatment with 2, 2, 2-trichloacetimdate, and phenylselenyl chloride-mediated cyclization favoured the construction of *trans*-oxazoline **16** (*trans:cis* = 15:1). Resulting trichloroacetate was subjected for partial hydrolysis using PPTS in aqueous MeOH followed by the oxidative elimination of selenyl group using H_2O_2 in THF afforded *trans*-olefin **17**. Further desilylation, Mitsunobu cyclization, and treatment with NaOBn afforded the corresponding pyrrolidine derivative **18**. Further, protecting group manipulations followed by the diastereoselective dihydroxylation gave triol **20** in high yield along with minor amounts of the isomeric triol (15:1 ratio) (Scheme 1.3). The observed diastereoselectivity was in accordance with selectivity models proposed by Kishi[12] and Stork.[13] Triol **20** was subjected to protecting group manipulation to afford the desired dioxolane **21**. Finally, the removal Cbz group induced 6-endocyclization over 5-exocyclization and followed by the removal of MOM group afforded the castanospermine **1**.

1A. 3. 3 Synthesis by Denmark et al.

In 1999, Denmark and co-workers[14] disclosed the total synthesis of four polyhroxylated alkaloids:(+)-castanospermine, (+)-6-epicastanospermine, (+)-australine, and (+)-3-epiaustraline (Scheme 1.3). The key step in their synthesis was the tandem asymmetric [4 + 2]/[3 + 2] cycloaddition of nitroalkenes as a general method to synthesize pyrrolidine- and pyrrolizidine-containing compounds which they had investigated. Synthesis began with the rapid ring opening of 2, 5-dihydrofuran **22** in presence of n-BuLi at -23^{o}C. Silylation of resulting alkoxide with di-*tert*-butylchlorosilyl triflate followed by the chloride displacement with potassium nitro acetaldehyde **24** gave nitroalkene derivative **25**. However, compound **25** was found to be intrinsically unstable and in addition, it was labile under all conventional methods of purification.

Storage under N_2 for more than a day at room temperature resulted in loss of the nitroalkene fragment. In addition, distillation, chromatography (silica gel, Et_3N treated silica gel, basic and neutral alumina plugs) and cold chromatography (basic and neutral alumina plug, -60 °C) promoted the nitroalkene fragmentation.



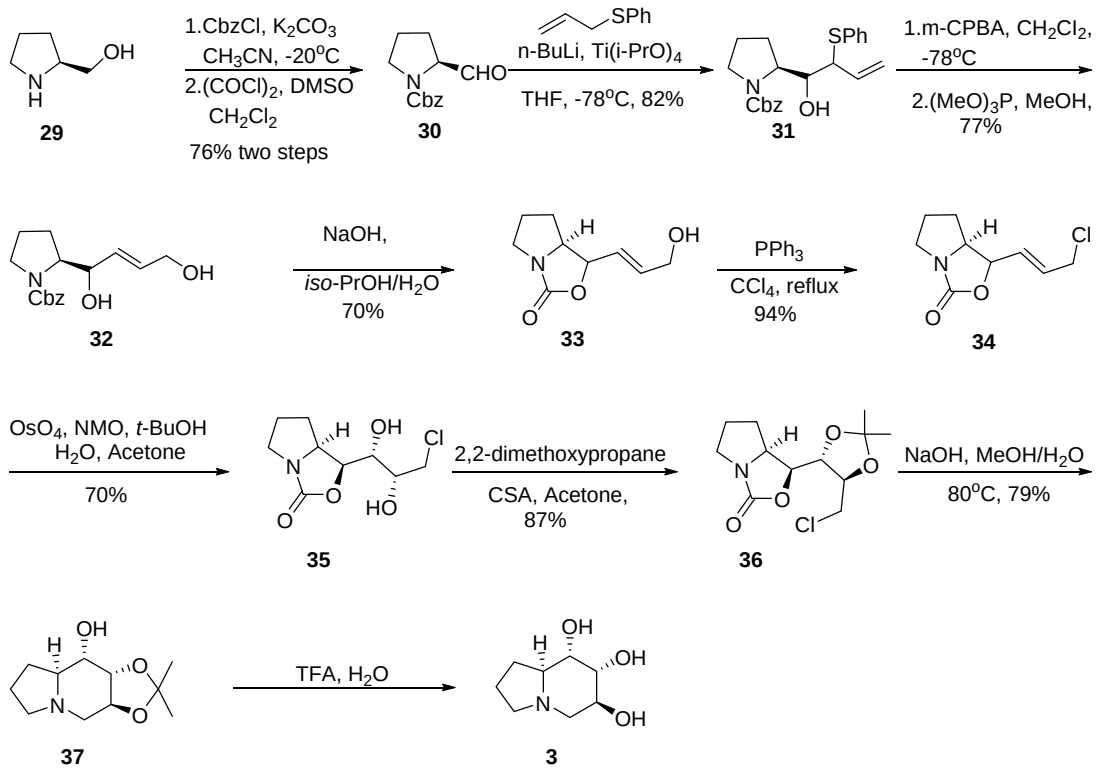
Scheme 1.3 Denmark's approach

However, they were able to purify the nitroalkene through celite filtration. Extensive studies on the crucial [4+2]/[3+2] cycloaddition using various Lewis acids revealed that methylaluminum bis(2,6-diphenyloxide) (MAPh) promoted highly selective Diels-Alder reaction of nitroalkene and **25b** to give desired alkene **26**. Finally, hydroxylated stereocenter was introduced using Sharpless asymmetric dihydroxylation of resulting alkene **26** in presence of an anthraquinone ligand $(DHQD)_2$-AQN in 86% yield. The enantiomeric purity of (1*S*, 2*S*) diol **27** was determined by CSP SFC analysis to be 99.9% ee. Selective tosylation of the primary alcohol in diol **27** was achieved using *p*-toluenesulfonyl chloride in pyridine as a solvent. Bicyclic indolizidine structure was achieved by the catalytic hydrogenolysis using Raney-Ni and H_2 (160 psi, 36 h) in MeOH. This unmasked tosylates led to cyclization. Finally, the treatment of **28** with HF in MeOH led to the smooth deprotection of di-*tert*-butylsilylene group to afford the fluoride salt of compound **1**. The free base of compound **1** was obtained by the cation exchange chromatography.

1A. 4 Reported Synthesis of Castanospermine isomers:

1A. 4. 1 Synthesis by Chan et al.

In 1992 Chan and co-workers[15] reported the total synthesis of four different isomers of castanospermine from a common precursor (Scheme 1.4). Addition of anion of allyl phenyl sulfide to aldehyde, followed by an allylic sulfide rearrangement and a subsequent nucleophilic cyclization were the key steps in the synthesis. Synthesis commenced with the Cbz protection of L-prolinol **29** followed by Swern oxidation affording the corresponding aldehyde **30**. Further, the reaction of **30** with allyl phenyl sulfide in presence of $Ti(^{i}OPr)_4$ and n-BuLi gave a diastereomeric mixture of **31 (**only two out of the four possible isomers in a ratio of 2:1).



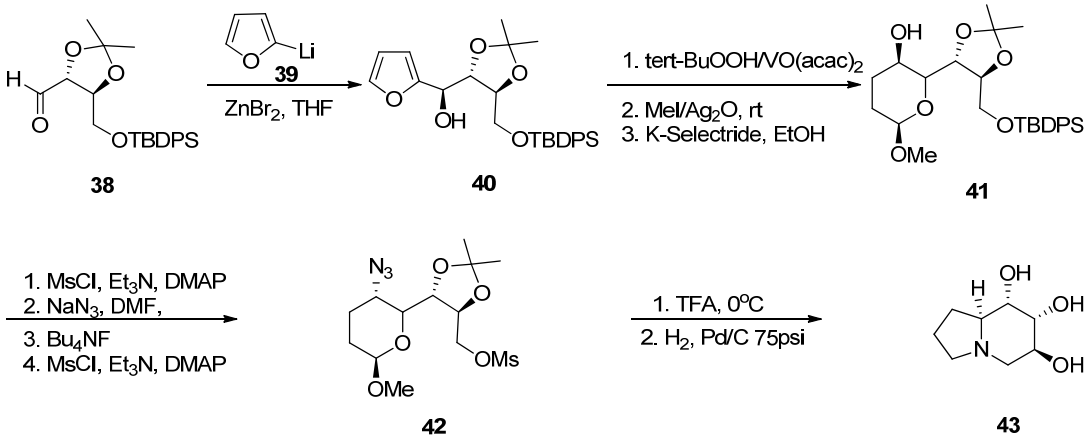
Scheme 1.4 Total synthesis of *8-epi*-Castanospermine by Chan *et al.*

Compound **31** under reaction conditions underwent sulfoxide rearrangement followed by the cyclization to afford the cyclic carbamate **33**. This on treatment with tri-phenyl phosphine in carbon tetrachloride afforded the chloro derivative **34** further the subsequent dihydroxylation furnished the diol **35** in 3:1 ratio. Diol **35** was protected with 2, 2-

dimethoxypropane and the resulting cyclic carbamate **36** was hydrolyzed to afford corresponding amino alcohol intermediate. This was cyclized in situ to give bicyclic amine **37.** Finally, the deprotection of dioxolane afforded the isomer of castanospermine **2**. Coupling constants and extensive 2D NMR studies determined the stereochemistry of **2**.

1A. 4. 2 Synthesis by Martin et al.

In 1995 Martin and co-workers[16] reported the total synthesis of l-deoxy-8,8a-di-*epi*-castanospermine (Scheme 1.5). Martin's synthesis started with the stereoselective addition of 2-furyllithium **39** to the silyl-protected aldehyde **38** in presence of $ZnBr_2$ to give furyl carbinol **40**.



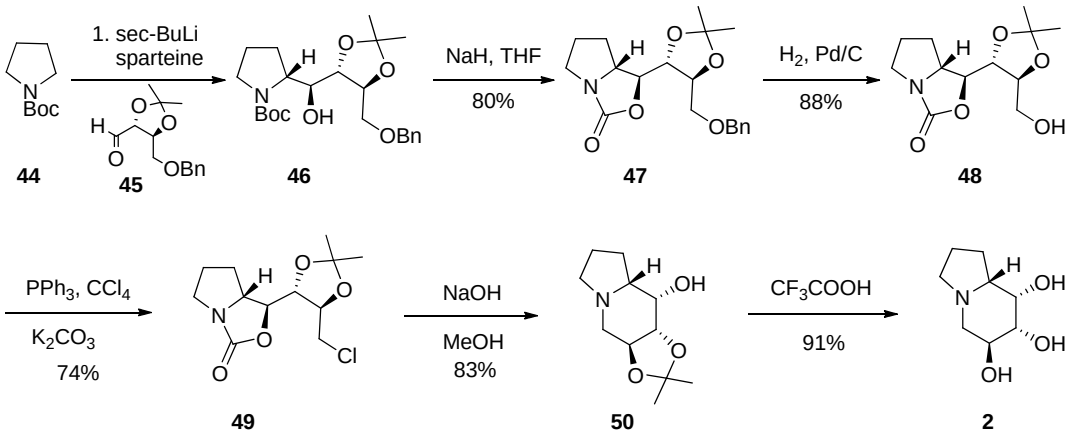
Scheme 1.5 Total synthesis of 8-*epi*-Castanospermine by Martin *et al.*

This upon series of transformations by viz. oxidation, methylation of the anomeric hydroxyl group and the reduction of hydropyranone afforded the corresponding alcohol **41**. Further, protecting group manipulation and installation of azido group gave compound **42**. Finally, treatment of azide **42** with TFA followed hydrogenation using Pd/C under H_2 afforded l-deoxy-8,8a-di-*epi*-castanospermine **43**. However, we noticed that ^{1}H and ^{13}C NMR data of **43** did not match with the data reported by Chan et al.

1A. 4. 3 Synthesis by Majewski et al.

In 1998, Majewski *et al.* reported[17] the total synthesis of diastereoisomers of 8-*epi*-1-deoxycastanospermine **2**. The reaction of lithiated *N*-Boc-pyrrolidine with aldehyde **45** derived from L-tartaric acid afforded the corresponding alcohol **46** in 9:1 ratio. This on

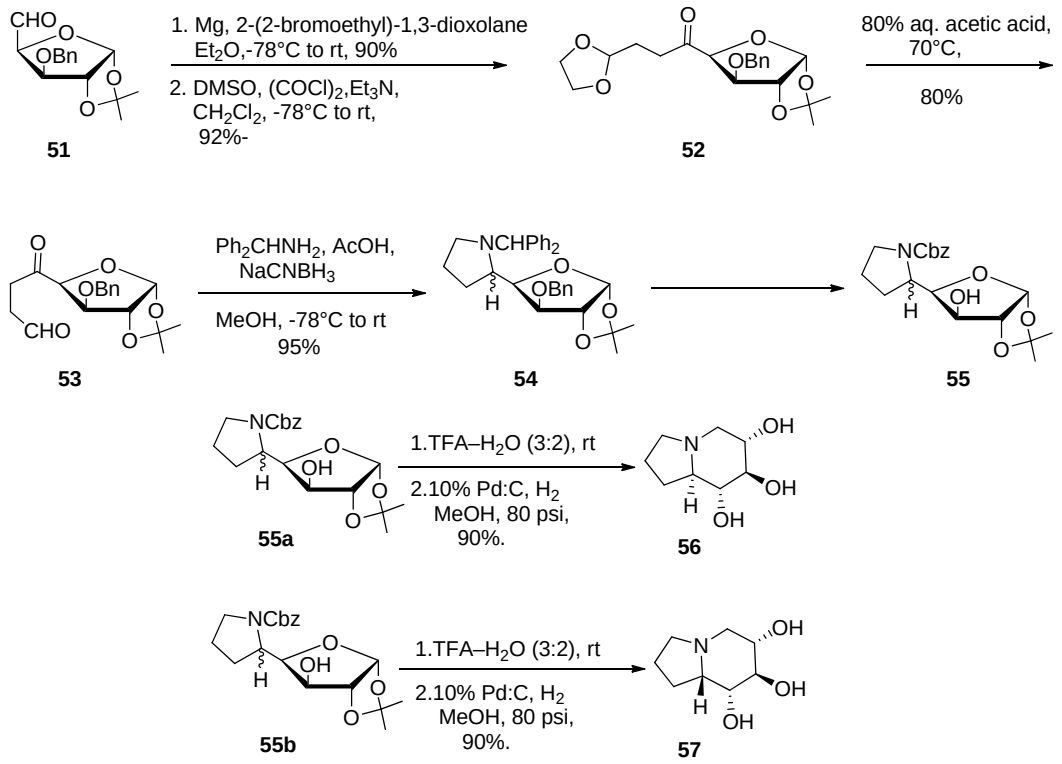
treatment with NaH in THF resulted into cyclic carbamate **47**. This upon hydrogenolysis followed by treating with Ph_3P in CCl_4 gave the chloro-derivative **49** through the formation of alcohol **48.** Under alkaline hydrolytic conditions compound **49** underwent hydrolysis followed by the concomitant cyclization afforded compound **50**. Finally, removal of isopropylidene protecting group furnished the 8-*epi*-1-deoxycastanospermine.



Scheme 1.6 Total Synthesis of Majewski's approach

1A. 4. 4 Synthesis by Dhavale et al.

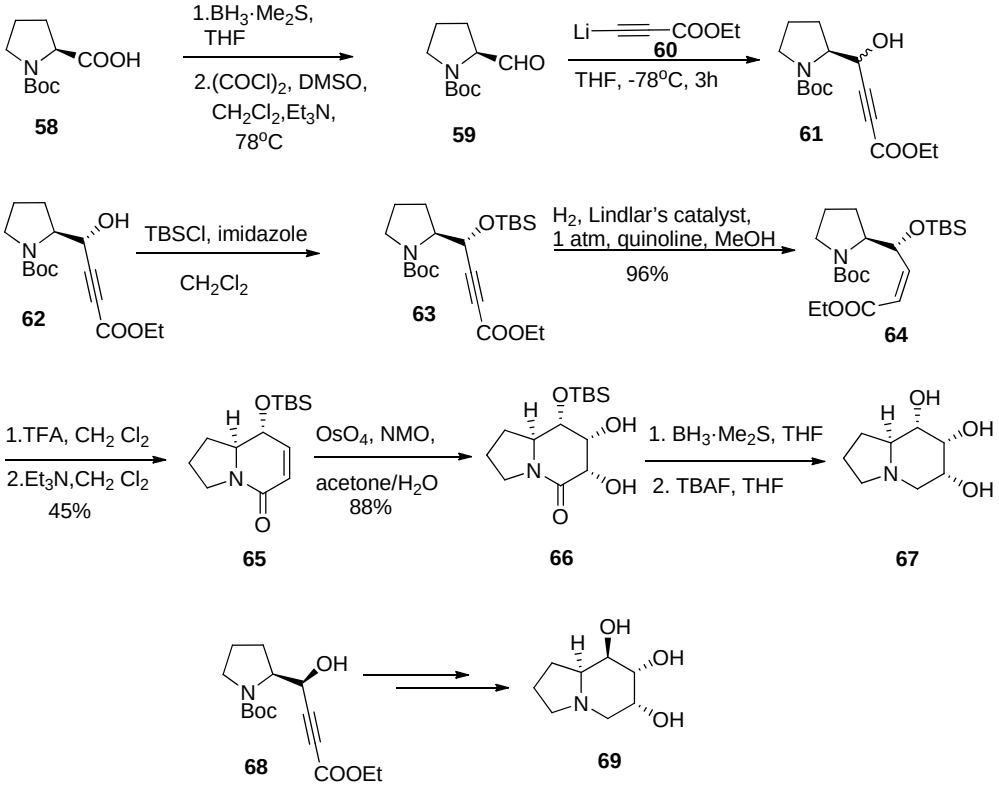
In 2001, Dhavale and co-workers[18] reported the total synthesis of 1-deoxy-castanospermine and 1-deoxy-8a-*epi*-castanospermine (Scheme 1.7). Synthesis started with the addition of Grignard reagent (prepared from magnesium and 2-(2-bromoethyl)-1, 3-dioxolane in THF) to *α-D-xylo*-pentodialdose **51** to afford a mixture of C5-carbinols. This upon Swern oxidation gave the corresponding ketone **52**. This on treatment with acetic acid in methanol afforded keto-aldehyde **53**. This upon reaction with amino diphenylmethane and sodium cyanoborohydride in methanol gave an inseparable diastereomeric mixture of **54**. Further, hydrogenolysis followed by the protection of resultant free amine with CbzCl gave separable mixture of **55a** and **55b**. Removal of the isopropylidene and Cbz protecting groups in **55a** and **55b** using TFA followed by Pd/C, H_2 furnished the 1-deoxy-castanospermine **56** and 1-deoxy-8a-*epi*-castanospermine **57** respectively.



Scheme 1.7 Total Synthesis of 1-deoxy-castanospermine and 1-deoxy-8a-*epi*-castanospermine by Dhavale *et al.*

1A. 4. 5 Synthesis by Ding et al.

In 2003, Ding *et al*. achieved[19] the total synthesis of two isomers of 1-deoxycastanospermine (Scheme 1.8). Addition of ethyl lithiopropiolate to aldehyde derived from *N*-Boc-L-proline, cyclization to construct indolizidine skeleton and asymmetric dihydroxylation were the key steps involved in total synthesis. Synthesis commenced with the reduction of Boc-L-proline **58** followed by Swern oxidation of the resulting alcohol to aldehyde **59**. The addition of ethyl propiolate **60** to aldehyde **59** afforded a separable mixture of alcohols **62** and **68** in a combined yield of 80%. The alcohol **62** was silylated with TBSCl followed by partial reduction of triple bond using Lindlar's catalyst afforded the alkene **64**. The deprotection Boc group followed by the addition of Et_3N led to the intramolecular cyclization to furnish lactam **65.** The dihydroxylation of key intermediate **65** using OsO_4/NMO provided diol **66.** *Syn*-dihydroxylation of **65** was occurred from the face of the double bond in *syn* relationship to *8a*-H with an *exo* approach.



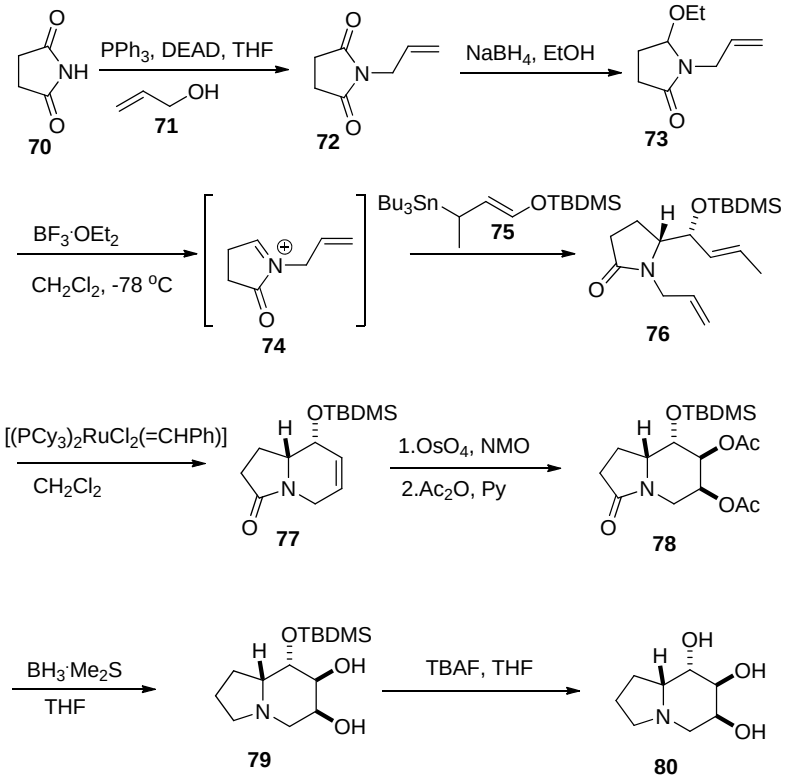
Scheme 1.8 Total synthesis of 1-deoxy-6, 8a-*epi*-Castanospermine by Ding *et al.*

The reduction of lactam in **66** and deprotection of TBS group afforded the desired trihydroxyindolizidines **67**. Similarly, trihydroxyindolizidine isomer **69** was prepared from alcohol **68.**

1A. 4. 6 Synthesis by Quintard et al.

In 2004, Quintard and co-workers[20] reported the total synthesis of 1-deoxy-6,8a-di-*epi*-castanospermine by the addition of γ-siloxyallyltributylstannanes to an iminium ion (Scheme 1.9). The key step of the synthesis was the allylstannation of the N-allyliminium intermediate followed by ring closing metathesis. An ethoxy amide **73** was prepared by the alkylation of succinimide **70** using allyl alcohol **71** under Mitsunobu reaction conditions followed by reduction of *N*-allylsuccinimide **72** using $NaBH_4$ in ethanol. *α*-ethoxy amide **73** was treated with γ-siloxyallyltributylstannanes **75** in the presence of $BF_3{\cdot}OEt_2$ followed by ring closing metathesis using Grubbs' catalyst to give indolizinone **77**. Indolizinone **77** upon dihydroxylatation followed by acetylation afforded the corresponding lactam **78**. This on treatment with $BH_3{\cdot}Me_2S$ in THF, resulted in the

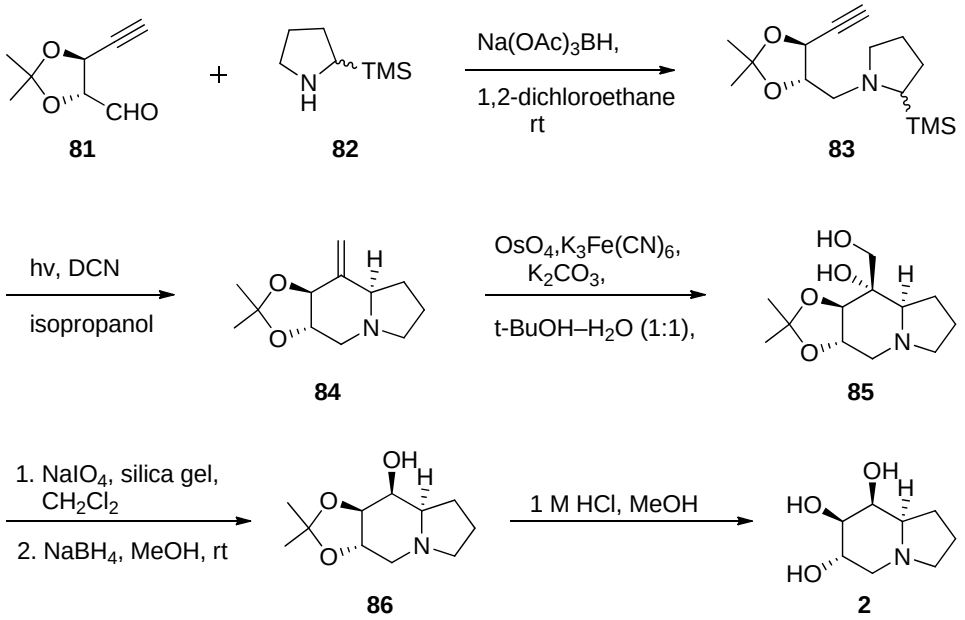
reduction of amide bond as well as deprotection of acetyl groups to afford indolizidine 7**9**. Finally, removal of TBDMS group using TBAF afforded 1-deoxy-6,8a-di-*epi*-castanospermine **80**.



Scheme 1.9 Quintard's approach for racemic1-deoxy-6,8a-di-*epi*-castanospermine

1A. 4. 7 Synthesis by Pandey et al.

In 2007, Pandey and co-workers[21] utilized photoinduced electron transfer (PET) provoked amine radical cyclization for the synthesis of 1-deoxy-8-*epi*-castanospermine (Scheme 1.10) . The synthesis commenced with the reductive amination of amine **82** with aldehyde derivative **81** to afford acetylene tethered amine **83**. This was converted into alkene **84** by using photoinduced electron transfer (PET) cyclization a protocol well established by Pandey *et al.*[22] Dihydroxylation of alkene **84** using OsO_4 furnished the corresponding diol **85**. This upon periodate oxidation conditions afforded the corresponding ketone, which on sodium borohydride reduction gave **86** in 82% yield as single diastereomer. Finally, acetonide deprotection afforded 1-deoxy-8-*epi*-castanospermine **2** in 95% yield.



Scheme 1.10 Pandey's approach for 1-deoxy-8-*epi*-Castanospermine

1A. 5 Rationale of Present work and Synthetic Planning

1A. 5. 1 Introduction

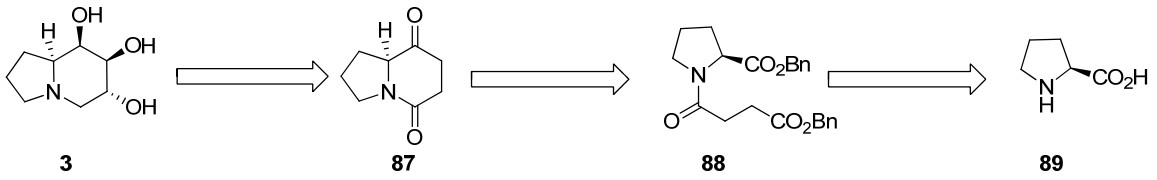
The naturally occurring aza fused bicyclic alkaloids containing indolizidine ring systems are very important core structures and they are prevalent in biologically active compounds isolated from fungi, bacteria, higher plants, vertebrates, and higher invertebrates.[23] Due to their significant biological activity and complexity in the structure, the development of new and efficient strategies for the construction of aza-heterocycles is challenging and demanding in organic synthesis. As described in the introduction the naturally occurring polyhydroxylated indolizidine alkaloids such as (+)-castanospermine **1** and their analogues **2-4** have been reported to exhibit glycosidase inhibition activity[5] and have attracted attention of synthetic organic chemists community. As ongoing projets in our laboratory we have been focussing on the synthesis of useful and bioactive aza heterocycles. Though there are few reports of racemic and enantioselective synthesis of 1-deoxy-8a-*epi*-castanospermine isomers, however interestingly, there are discrepancies in the reported assignments and characterization of these isomers.[15-16,21] This prompted us to synthesize 1-deoxy-6,7,8a-*epi*-castanospermine **3** to evaluate the correct structure**.** In the

absence of any authentic NMR spectra as these are ring modified analogues of natural product catanospermine, and lack of any single crystal structure evidence in the literature made it difficult to decide correct data.

Hence, we became interested in synthesis of this isomer and obtaining its crystal data so as to resolve the ambiguity. Available literature knowledge on the synthetic approaches towards this molecule and some of the analogues proved useful in designing a strategy, but this also constrained our synthetic routes to achieve the target. However, we supposed that growing a single crystal of the target molecule is very essential for the current study.

1A. 5. 2 Attempted Synthesis by Dieckmann Condensation

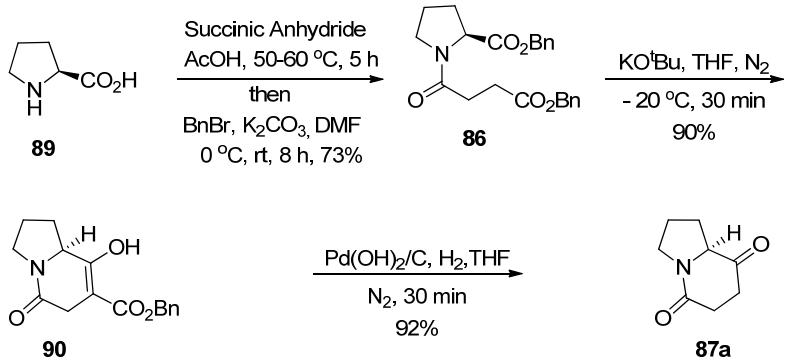
In our retrosynthetic analysis, we reasoned that the indolizidine ring system could be attained by *N*-succinylation of amino acid proline, which in turn provides number of carbon atoms that are required. This also masks secondary amino group of proline as a protecting group. Thus we believed that it would be a protecting group free synthesis.



3 **87** **88** **89**

Scheme 1.11 Retrosynthetic analysis

In order to execute our strategy we subjected commercially available and less expensive L-proline **89 (**Scheme 1.12) for *N*-succinylation using succinic anhydride in glacial acetic acid following the reported procedure to furnish *N*-succinyl proline in good yield. Further, *N*-succinyl proline was esterified by treating with benzyl bromide under alkaline conditions to afford dibenzyl ester **88**. This was then subjected to Dieckman condensation using sodium hydride in anhydrous THF at 0 ^{o}C to afford enol-ester **90** in low yield. Further we modified this strategy by carrying out the intramolecular Dieckman condensation under sonochemical condition, which led to significant enhancement in the yield and reaction rate. It was clearly evident from ^{1}H and ^{13}C NMR spectra that compound **90** solely existed in enolic form rather than its keto form or as mixture.



Scheme 1.12 Dieckmann cyclisation

Sr. No.	Base	Yield for **90**	Specific rotation for (**87a)**
1	NaH	95%	$[\alpha]^{25}_{D}$ -7.6 (*c* 1, $CHCl_3$)
2	LDA	74%	$[\alpha]^{25}_{D}$ -10 (*c* 1, $CHCl_3$)
3	tert-BuOK	92%	$[\alpha]^{25}_{D}$ -60 (*c* 1, $CHCl_3$)
4	Sodium tert-pentoxide	95%	$[\alpha]^{25}_{D}$ -80 (*c* 1, $CHCl_3$)
5	KHMDS	90%	$[\alpha]^{25}_{D}$ -13 (*c* 1, $CHCl_3$)
6	LiTMP(Lithium tetramethyl piperdine)	92%	$[\alpha]^{25}_{D}$ -19 (*c* 1, $CHCl_3$)

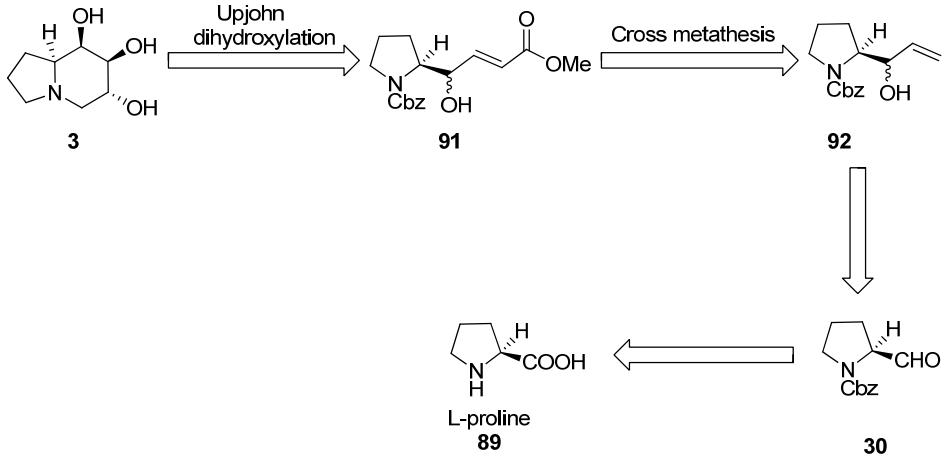
Table 1.1 Observed specific rotation of **87a** synthesized by Dieckman cyclization using bulky bases followed by decarboxylation

Further owing to the presence of dibenzyl ester, compound **90** was subjected to beta keto decarboxylation using catalytic amount of $Pd(OH)_2/H_2$ in THF under atmospheric pressure to afford bicyclic core **87a** (Scheme 1.12).

Unfortunately, observed specific rotation of compound **87a** was -7.6 (lit. -245, *c* 1.56 $CHCl_3$)[42] which signified that stereochemistry was not conserved in the molecule during transformation. We believed that use of bulky bases may avoid racemization. We then used different bulky bases like potassium tertiary butoxide, KHMDS, and even sodium *tert*-pentoxide to carry out Dieckmannn condensation. Unfortunately in all cases **87a** was partially racemized. (See table-1.1).

1A. 5. 3 Cross Metathesis Approach and Synthetic Planning:

While not succeeding in our initial attempt we sought an alternative route for the desired target molecule. Retrosynthetic point of view our approach was to synthesize bicyclic frame work using Grubbs' cross metathesis. Retrosynthetic strategy for the synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine **3** is presented in Scheme 1.13. As per our retrosynthetic plan (scheme 1.13), castanospermine **3** could be obtained from alkene **91** *via* dihdroxylation followed by cyclization. The alkene **91** in turn could be obtained from alcohol **92** through ring closing metathesis using methyl acrylate. Precursor alcohol could be easily accessed via addition of vinyl magnesium bromide on aldehyde **30**, which could further be obtained from commercially available L-proline.

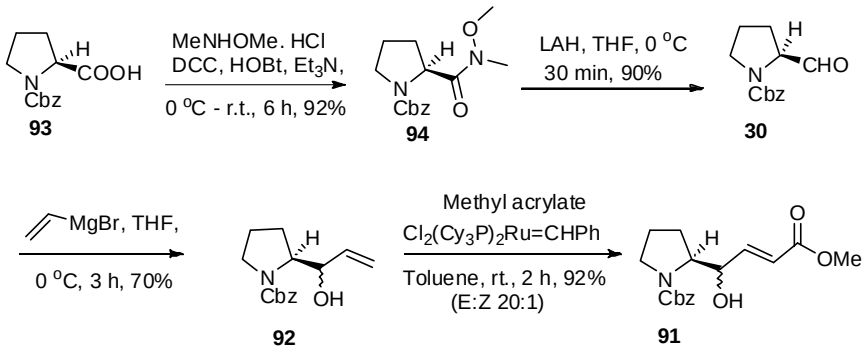


Scheme 1.13 Retrosynthetic plan based on Cross metathesis approach

1A. 5. 4 Results and Discussion:

Our initial effort focussed on the synthesis of a key olefin intermediate **91**. In order to achieve the target as per the plan we started our synthetic studies using *N*-Cbz-L-proline **93** (Scheme 1.14). This was coupled with *N, O*-dimethylhydroxylamine hydrochloride using DCC and HOBt to form the corresponding Weinreb amide 94 in 92% yield. Treatment of Weinreb amide **94** with lithium aluminium hydride (LAH) in THF at 0 ^{o}C furnished the corresponding aldehyde **30** in 90% yield. As anticipated, ^{1}H spectrum of the aldehyde showed the presence two singlets at 9.59(1H) and 9.48(1H) indicating that aldehyde existed in 1:1 mixture of rotamers. The addition of vinyl magnesium bromide to

L-proline aldehyde **30** afforded a diastereomeric mixture of the corresponding alcohol **92** in 70% yield.



Scheme 1.14 Synthesis of key intermediate **102**

It is important to note that Grignard's reaction did not proceed at lower temperature (-78 °C). However, Grignard addition was spontaneous at 0 °C to room temperature to afford corresponding alcohol **92**. The mixture of alcohol isomers could not be separated using silica gel column chromatography. However, we decided to proceed for olefin cross metathesis in the next step. The use of olefin metathesis to assemble heterocyclic systems from acyclic or cyclic diolefins has increased enormously in the last decade, as a result of the alkylidene ruthenium and molybdenum catalysts[24] developed by Grubbs, Schrock, and Hoveyda. Some of the catalysts for the metathesis have been shown in Figure 1.2.

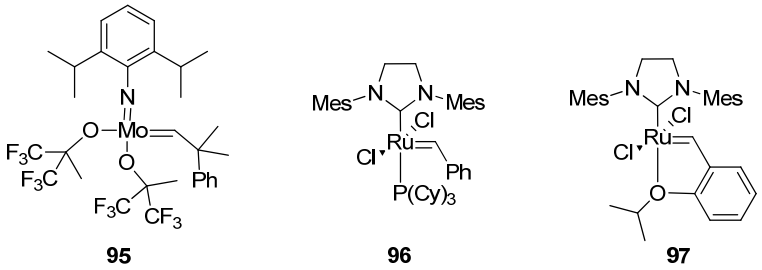
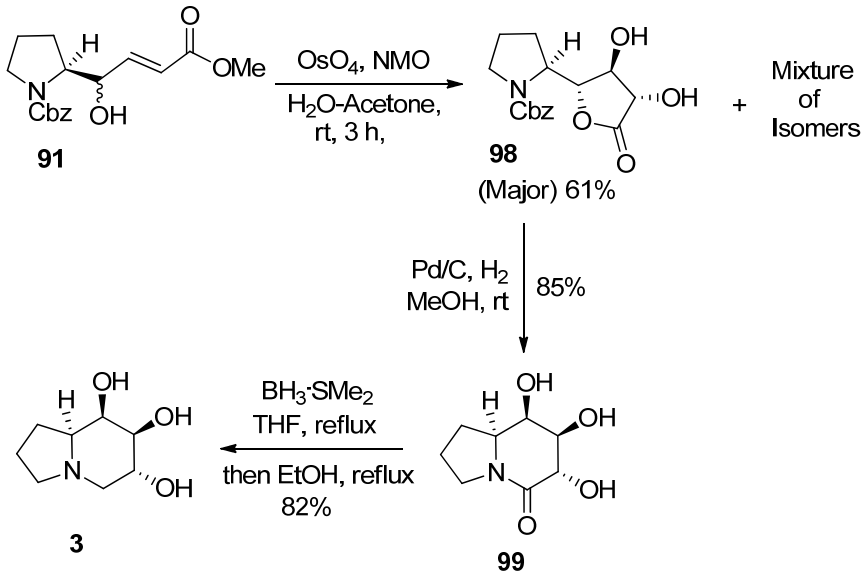


Figure 1.2 Schrock, Grubbs' and Hoveyda catalysts

Thus encouraged by the ease with which olefins were prepared, we applied olefin cross metathesis to synthesize the key intermediate **91** (Scheme 1.15). Initially, we treated alkene **92** with methyl acrylate in presence of Grubbs' first generation catalyst in DCM as well as toluene at refluxing condition, but we could not observe any product formation, rather staring material was recovered. Later, in another attempt, alkene **92** was treated with excess methyl acrylate in presence of Grubbs' second generation catalyst **96** in DCM at

room temperature. However, reaction did afford expected product but in very poor yield(40%). Under refluxing condition reaction led to the formation mixture of side products along with expected product. Interestingly, we observed that Grubbs' cross metathesis of **92** with methyl acrylate worked very well in toluene at room temperature affording expected *E*-isomer **91** predominantly (*E:Z* 20:1) in excellent yield (92%). After successfully synthesizing the key intermediate **91**, our next task was to install two hydroxyl groups with the expected stereochemistry required for the target castanospermine analogue. Alkene **91** was treated with AD-mix *α*, but unfortunately the reaction did not proceed and starting material was recovered back. We surmised that free hydroxyl groups in alkene **91** may have interfered in the reaction. Later, we decided to protect the hydroxyl group for the facile Sharpless asymmetric dihydroxylation. Unfortunately, protection did not proceed smoothly, but gave complex mixture of products. However, the reaction of alkene **91** with catalytic amount OsO_4, NMO (Upjohn dihydroxylation)[25] in acetone–water mixture furnished the lactone **98** as a white solid in 60% yield.



Scheme 1.15 Synthesis of 1-deoxy-6, 7, 8a-*epi*-castanospermine

The formation of lactone was evidenced by its ^{13}C spectrum which showed the presence of lactone carbonyl at δ 173.6. This was further ascertained by the presence intense band at 1771 cm^{-1} in IR spectrum. Finally, the molecular structure of **98** was confirmed by single-crystal X-ray analysis (Fig.1.3). This gave the exclusive evidence for the stereochemistry of newly installed hydroxyl groups. The lactone **98** upon hydrogenolysis

using H_2, Pd/C afforded the bicyclic lactam **99**. Finally, bicyclic lactam on reduction with BH_3·DMS complex[26] in THF gave the desired final compound 1-deoxy-di-*epi*-castanospermine **3** in 82% yield.

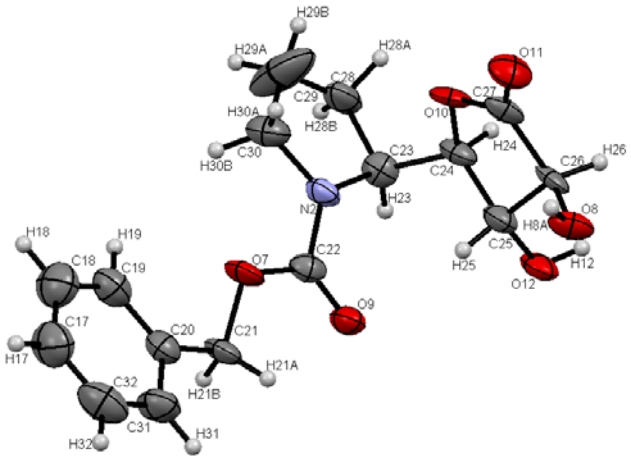


Figure 1.3 Molecular structure of lactone **98** by X-ray analysis (ORTEP diagram; ellipsoids are drawn at 50% probability).

It is also important to note that in contrast to the usual practice[26] we successfully reduced the amide bond without protecting any of the hydroxyl groups, thus minimizing the extra two steps in the route. After completion of reaction it was refluxed with EtOH to avoid the formation of amine-borane complex. Thus, synthesis of (6*R*,7*S*,8*R*,8a*S)*-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **3** was accomplished in total of 7 steps in an overall yield of 23%.

It was observed that the ^{1}H and ^{13}C-NMR data (Table 1.2) for compound **3** did not match with the spectral data reported by Chan et al.[15] while the data of its enantiomer reported by Martin et al.[16] and Pandey et al.[21] were in a close agreement with spectral data of **3** obtained by us**.** Specific rotation of compound **3** was in a close accordance with that of its enantiomer **2** (for **2**, obs: $[\alpha]^{25}_D$ = -30, *c* 0.5, MeOH; its enantiomer $[\alpha]^{27}_D$ = +26.1, *c* 0.45, MeOH).[21] Our stereochemical assignment was further supported by single crystal X-ray analysis of compound **98.**

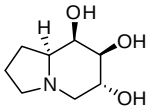
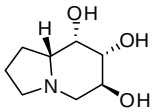
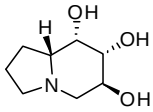
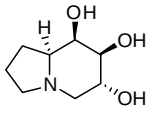
Structure	^{1}H and ^{13}C-NMR Comparison
 **3**	mp: 147-149 ^{o}C; $[\alpha]_D^{25}$ = -30 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 3.87 – 3.78 (m, 2H), 3.28 (dd, 1H, *J* = 9.3, 3.3 Hz), 3.15 (dd, 1H, *J* = 10.6, 5.3 Hz), 3.06 – 2.98 (m, 1H), 2.23 – 2.13 (m, 2H), 1.99 –1.67 (m, 5H); ^{13}C-NMR (100 MHz, CD_3OD) δ: 77.9, 69.7, 69.2, 67.9, 57.6, 54.5, 25.2, 22.9. Data obtained by us
	^{1}H NMR (300 MHz, CD_3OD) δ 3.85-3.76 (complex m, 2 H), 3.25 (dd, *J* = 9.4, 3.2 Hz, 1 H), 3.13 (dd, J = 10.5, 5.2 Hz, 1 H), 3.02-2.97 (m, 1 H), 2.18-2.09 (complex m, 2 H), 1.89 (t, J = 10.5 Hz, 1 H), 1.90- 1.67 (complex m, 4 H); ^{13}C NMR (125 MHz, CD_3OD) δ 78.0, 69.9, 69.4, 67.8, 57.7, 54.6, 25.3, 23.0 By Martin *et al. J. Org. Chem*. **1995**, *60*, 276-278
	mp: 149–151 ^{o}C, $[\alpha]_D^{27}$ +26.1 (c 0.45, MeOH), ^{1}H NMR (500 MHz, D2O) 1.99–2.30 [4H, m, C(1)H2–C(2)H2], 2.94 (1H, t, *J* = 11.5 Hz, 5a-H), 3.14–3.23 (1H, m, 3a-H), 3.53 (1H, ddd,*J* = 1.0, 6.6, 11.6 Hz, 8a-H), 3.67 (1H, ddd, *J* = 3.0, 8.3, 11.4 Hz, 3b-H), 3.74 (1H, dd, *J* = 5.3, 9.8 Hz, 5b-H), 3.76 (1H, dd, *J* = 3.0, 9.5 Hz, 7a-H), 4.10 (1H, ddd, *J* = 5.4, 7.7, 11.4 Hz, 6b-H), 4.27 (1H, dd, J = 1.0, 3.0 Hz, 8a-H); ^{13}C-NMR (125 MHz, D2O) 22.2 (CH2), 24.3 (CH2), 53.9 (CH2), 54.3(CH2), 66.8 (CH), 67.8 (CH), 69.6 (CH), 75.0 (CH) By Pandey *et al. Tetrahedron* **2007**, *63*, 4756–4761
 **3**	$[\alpha]_D^{20}$ = -17.3 (c 0.86 in MeOH, 'H NMR (CD_3OD) δ 4.52-4.20 (m, 3 H), 3.90-3.55 (m, 2 H), 3.48-3.10 (m, 3 H), 2.65 (m, 1 H), 2.55-2.10 (m, 3 H); ^{13}C NMR (CD30D) 6 73.4, 72.7, 71.9, 66.0, 66.3, 55.1, 29.6, 22. By Chan *et al. J. Org. Chem.* **1992**, *57*, 3078-3085

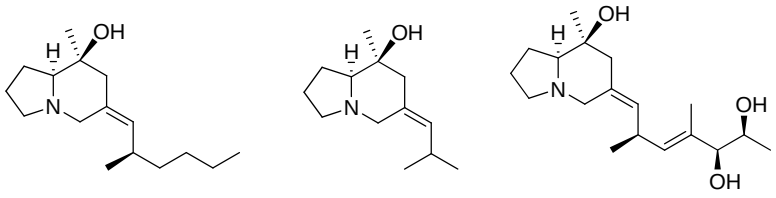
Table 1.2 ^{1}H and ^{13} NMR Comparison Chart of Compound **3** and its enantiomer

Section B

Formal synthesis of Pumiliotoxin 251D

1B. 1 Introduction to Pumiliotoxin251D

The pumiliotoxins are family of natural products and were first isolated in 1970's from the *Dendrobates pumilio* frogs in South America.[27] There are over thirty known pumiliotoxins, and all of them consist of a common indolizidine framework, displaying a tertiary alcohol at C8 position and an exocyclic double bond. However, it is very interesting to note that only one difference in the pumiliotoxin family occurs at the alkylidene appendage. These alkaloids are reported to serve in chemical defense against predators and have high pharmacological activity on nerve and muscle.[28] Cardiotonic and myotonic[29] properties have been exhibited for several species. Interaction with the charge-dependent ion channels of certain nerve cells influences signal transduction by induction of the opening of Na ion channels.[28]



Pumiliotoxin 251D **100** | Pumiliotoxin 209F **101** | Pumiliotoxin 323A **102**

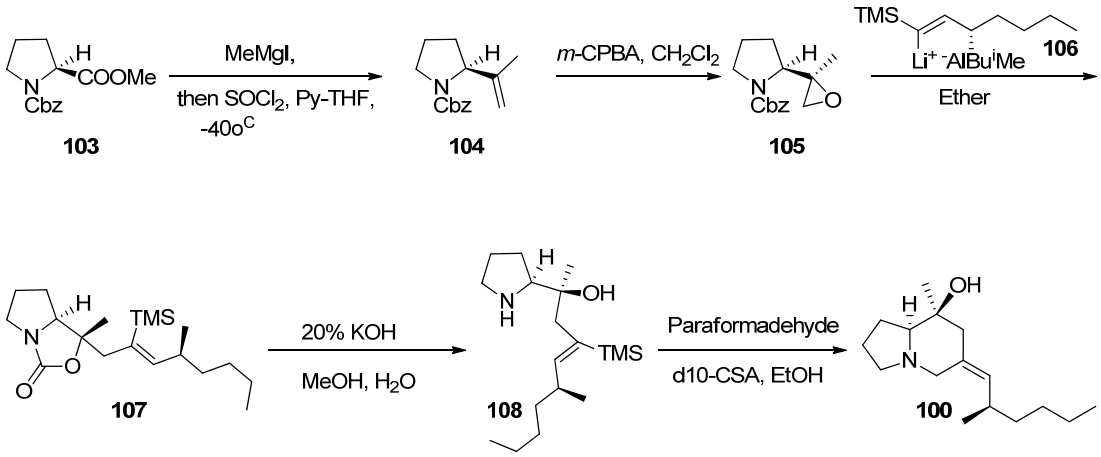
Figure 1.4 Representative pumiliotoxins

One of the simplest members, pumiliotoxin 251D (**100)**, isolated from the Ecuadorian frog *Dendrobates tricolor*, was the first alkaloid of this class whose structure was unambiguously determined.[27b] The interesting structures and biological properties of these alkaloids, coupled with the fact that for all practical purposes these compounds are essentially unavailable from the natural source, make them ideal targets for synthesis and for developing new synthetic methodologies. As such several total synthesis and formal synthesis of pumiliotoxin 251D have been reported. Some of the very important syntheses have been discussed below.

1B. 2 Reported Synthesis of Pumiliotoxin 251 D

1B. 2. 1 Synthesis by Overman et al.

In 1981, Overman and co-workers[30] reported the first total synthesis of pumiliotoxin 251D (Sheme 1.16). The synthetic strategy relied on an iminium ion-vinylsilane cyclization step to construct the indolizidine framework.



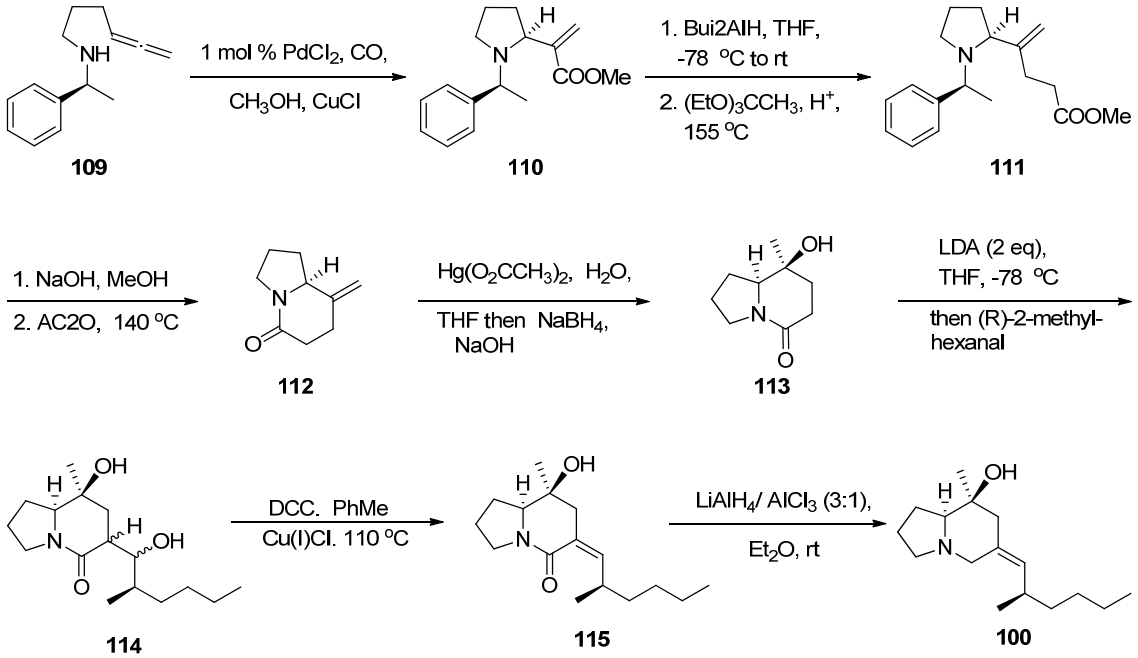
Scheme 1.16 Synthesis of pumiliotoxin 251D

The enantiospecific total synthesis of pumiliotoxin 251D was achieved in 10 steps starting from ester **103**. Synthesis started with the conversion of ester **103** into alkene **104** using sequential addition of MeMgI followed by dehydration of the resulting alcohol using $SOCl_2$ in pyridine-THF. The resulting alkene **104** when treated with *m*-chloro perbenzoic acid afforded epoxide **105** in 1:1 ratio. Epoxide (mixture of isomers) **105**, when treated with silylvinyl alanate **106** under refluxing conditions gave bicyclic carbamates **107** which upon hydrolysis using methanolic KOH solution afforded amino alcohol **108**. This on treatment with paraformaldehyde and *d*-10-camphor sulfonic acid under refluxing conditions in ethanol afforded the target molecule pumiliotoxin 251D.

1B. 2. 2 Synthesis by Gallagher et al.

In 1991, Gallagher *et al.* disclosed[31] the total synthesis of pumiliotoxin 251D, starting from allene derivative **109** (Scheme 1.17) . Pd (II) catalyzed the electrophilic cyclization of allene **109**, affording the pyrrolidine derivative was the one of the key steps**.**

Synthesis started with the electrophilic intramolecular cyclization of 2-substituted pyrrolidine **109** under carbomethoxylation conditions using $PdCl_2$, CO and $CuCl_2$ in methanol to afford the corresponding unsaturated etser **110**. Further, the reduction of **110** to allylic alcohol followed by the Claisen rearrangement effected the homologation to ester **111**.



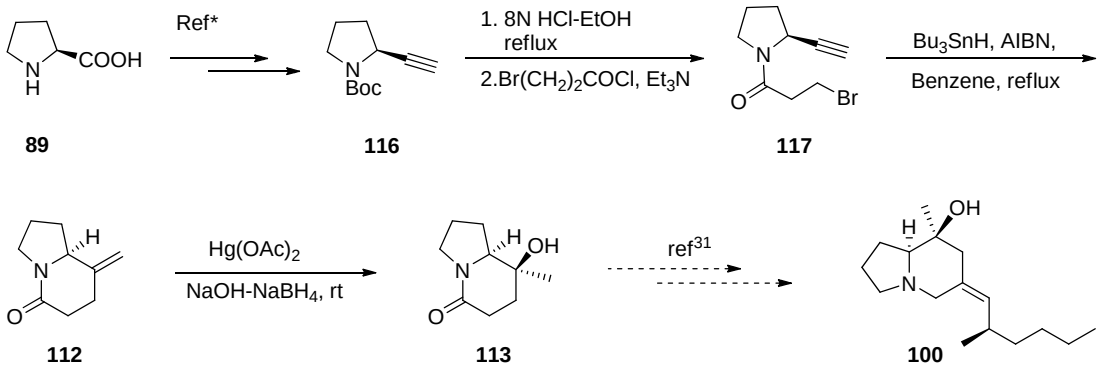
Scheme 1.17 Allene-Based Electrophile-Mediated Cyclization by Gallagher et *al.*

Hydrolysis of ester **111** and treatment of resultant carboxylate salt with acetic anhydride directly furnished the bicyclic lactam **112** as a single enantiomer in 76% yield. Lactam **112** was a crucial intermediate in this synthesis since it provided the necessary functional elements with a bicyclic framework required for the remaining transformations. Alkene moiety in 1**12** was converted smoothly into the tertiary alcohol **113** via oxymercuration reaction in 95% yield. Finally, it was very important to incorporate the (*Z*)-alkylidene unit at C-6 position stereoselectively. Previously, this problem had been elegantly solved by both Overman[32] and Trost[33] within the context of these indolizidine alkaloids. Gallagher and co-workers focused on aldol reaction involving lactam to establish the basic carbon framework of the side chain and the use of a stereospecific elimination step to control alkene geometry. Lactam **113** was treated with 2 equiv of LDA followed by the addition of (*R*)-2-methyl- hexanal provided diol **114**. This was subjected

for the stereospecific *syn* elimination using DCC and Cu(I)Cl to afford (*Z*)-**115**. Finally, the 1, 2-reduction of the unsaturated lactam moiety of **115** was achieved by using $LiAlH_4/AlC1_3$ to afford pumiliotoxin 251D in 67% isolated yield. The total synthesis of pumiliotoxin 251D **100** was achieved in total of 9 steps with an overall yield of 6.3%.

1B. 2. 3 Synthesis by Cossy et al.

In 1996, Cossy and co-workers[34] reported the formal synthesis of pumiliotoxin 251D (Scheme 1.18). Synthesis again relied on the bicyclic lactam intermediate **113**, and this was also the key intermediate in the Gallagher's total synthesis of pumiliotoxin 251D. The key feature of Cossy's approach was chemically and photo chemically induced radical cyclization of bromo derivative **117**.

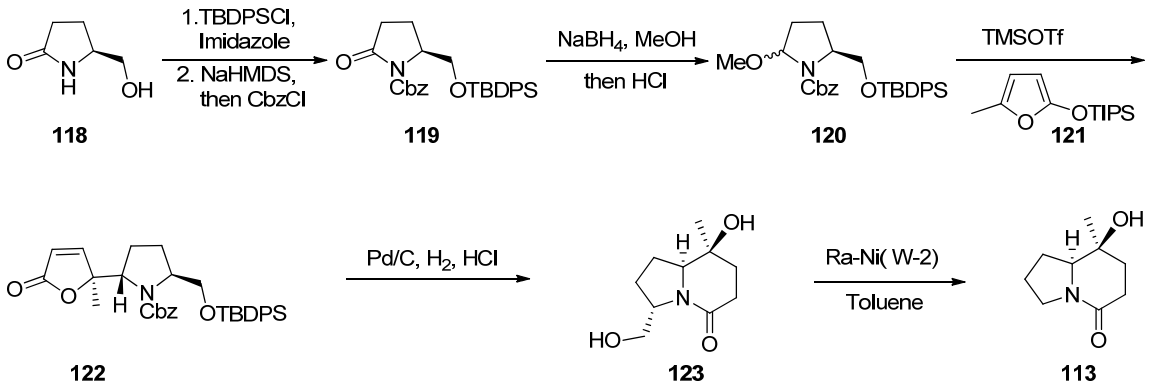


Scheme 1.18 Formal Synthesis of pumiliotoxin 251D by photo chemically induced radical cyclization approach

Commercially available L-proline was converted into the corresponding 2-alkyne pyrrolidine[35] derivative **116.** Deprotection of Boc group followed by the treatment with 3-bromopropionyl chloride and triethyl amine gave the corresponding bromoderivative **117**. This was treated with Bu_3SnH in presence of AIBN under refluxing conditions to furnish the desired bicyclic lactam **112** in 40% yield. Finally, the reductive hydroxymercuration of lactam **112** provided the desired key intermediate **113** in 95% yield. Cossy and co-workers achieved the formal synthesis of pumiliotoxin 251D in total 12 steps and was the shortest enantioselective synthesis reported at that time.

1B. 2. 4 Synthesis by Martin et al.

In 1999, Martin and co-workers[36] disclosed the formal synthesis of pumiliotoxin 251D employing vinylogous Mannich reaction approach (Scheme 1.19). Amide **118** was converted into methoxy pyrrolidine derivative **120** via protection of alcohol and amine moieties followed by the amide reduction. Methoxy pyrrolidine derivative **120** was treated with furan derivative **121** in presence of TMSOTf to afford the corresponding lactone substituted derivative **122** which upon reduction and global deprotection afforded the bicyclic lactam **123:** a required indolizidine framework. Finally, refluxing a mixture of bicyclic lactam **123** and Raney nickel (W-2) in toluene afforded key intermediate bicyclic lactam **113** which was utilized for the synthesis of pumiliotoxin 251D by others.

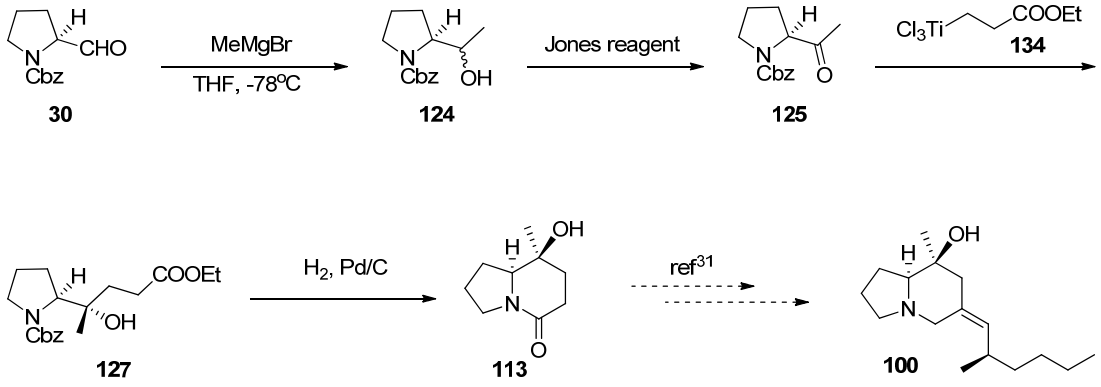


Scheme 1.19 Formal Synthesis by Martin *et al.*

1B. 2. 5 Synthesis by Barret et al.

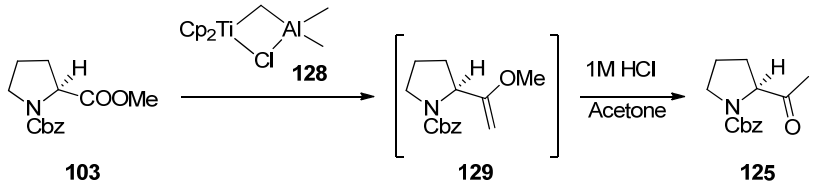
In 1999, Barret and co-workers[37] achieved a formal synthesis of pumiliotoxin 251D, via a highly diastereoselective addition of a titanium homoenolate to an L-proline derivative (Scheme 1.20). Synthesis commenced with the addition of MeMgBr to L-prolinal **30** followed by the oxidation of resulting secondary alcohol **124** to ketone **125** using Jones reagent. Reaction of the titanium homoenolate **126**, prepared in situ from titanium tetrachloride and 1-ethoxy-1-(trimethylsilyloxy)cyclopropane following the procedure of Nakamura and Kuwaijma[38] with ketone **125** gave hydroxyl ester **127** in 49% yield as a single diastereoisomer. Finally, compound **127** under hydrogenolytic conditions

afforded the bicyclic lactam **113,** a precursor of pumiliotoxin 251 D. This formal synthesis was achieved in 19% overall yield and in seven steps from L-proline.



Scheme 1.20 Barret's approach

Alternatively the synthesis of ketone **125** was achieved using different route. Cbz-protected proline methyl ester **103** was treated with the Tebbe's reagent **128** afforded a mixture of enol ether **129** and ketone **125** (Scheme 1.21). Hydrolysis of this mixture in acetone with a catalytic amount of 1 M HCl gave exclusively ketone **125**. Following this approach the formal synthesis was achieved in 41% overall yield and in six steps from L-proline.

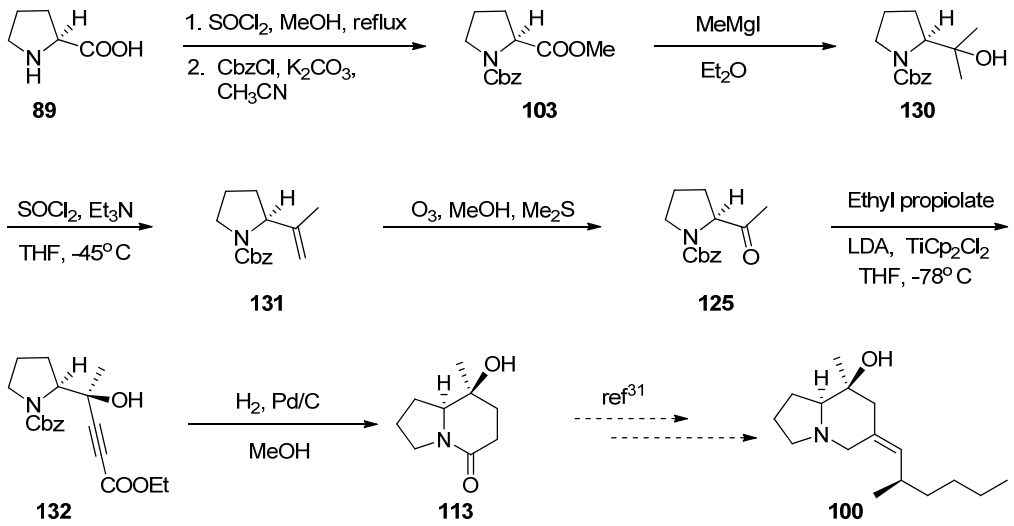


Scheme 1.21 Tebbe's reagent approach for the ketone **125**

1B. 2. 6 Synthesis by Ding et al.

In 2000, Ding *et al.* developed[39] an efficient enantioselective formal synthesis of pumiliotoxin 251D in good yield by using a Lewis acid (cat.) promoted diastereoselective addition of ethyl lithiopropiolate to ketone **125** derived from L-proline (Scheme 1.22). Synthesis commenced with the esterification of L-proline followed by the Cbz protection of amine to afford N-Cbz L-Proline methyl ester **103**. This on treatment with MeMgI followed by dehydration of resulting tertiary alcohol **130** using $SOCl_2$ and Et_3N afforded

an alkene substituted pyrrolidine derivative **131**. Compound **131** upon ozonolysis with O_3 in MeOH afforded the corresponding ketone **125**.



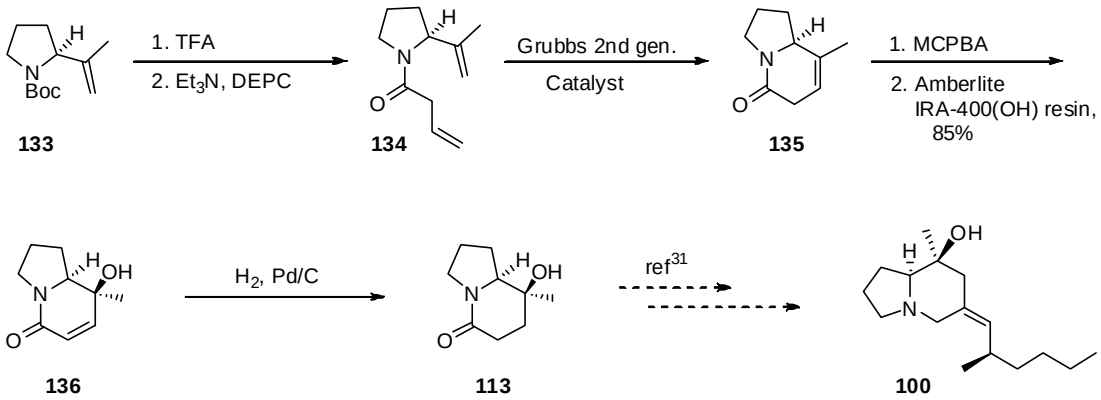
Scheme 1.22 $TiCp_2Cl_2$ mediated formal synthesis of pumiliotoxin 251D by Ding *et al.*

After extensive experiments, Ding and co-workers arrived to the conclusion that $TiCp_2Cl_2$ was a good choice for the addition of ethyl lithiopropiolate to the ketone **125** which resulted into the formation of hydroxyl alkyne ester **132** in 7.5:1 ratio. Finally, under hydrogenolytic conditions compound **132** afforded the bicyclic lactam **113**: highly sought precursor of pumiliotoxin 251D. By synthesizing compound **113** Ding and co-workers achieved the formal synthesis of pumiliotoxin 251D starting from L-proline in six steps with high diastereoselectivity and an overall yield of 18.2%.

1B. 2. 7 Synthesis by Stevenson et al.

In 2004, Stevenson and co-workers reported[40] the formal synthesis of pumiliotoxin 251D utilizing ring closing metathesis (RCM) strategy (Scheme 1.23). Synthesis commenced with the Boc deprotection of earlier known intermediate **133** using TFA followed by coupling of resulting amine with 3-butenoic acid to afford rotameric tertiary amide **134**. Stevenson *et al.* modified the earlier method of Paolucci.[41] Having obtained a suitable olefin substrate, ring closing metathesis was planned to construct the bicyclic framework. Compound **134** was treated with Grubbs' second generation catalyst in DCM to afford the desired product **135** in 88% yield. Compound **135** was converted into tertiary

alcohol **136** over two steps. Epoxidation of alkene using m-CPBA followed by the treatment with strongly basic ion exchange resin:Amberlite IRA-400(OH).



Scheme 1.23 Stevenson's approach

The resin acted as base in the epoxide ring opening and also as a scavenger for unreacted m-CPBA and its by-products. Finally, hydrogenation of alkene **136** over Pd/C catalyst and H_2 afforded the key intermediate bicyclic lactam **113**, thereby completed the formal asymmetric synthesis of pumiliotoxin 251D.

1B. 3 Present work and Objective

Synthetic organic chemists focused their attention on the total synthesis as well as formal synthesis of pumiliotoxin 251D (**100**) due to its interesting biological properties. As described earlier in the introduction most of the literature methods reveal that the alkaloid pumiliotoxin 251D (**100)** has been previously synthesized by using some of the common indolizidine bicyclic frameworks[31,42] (**87, 112, and 133**) as key intermediates (Figure 1.5).

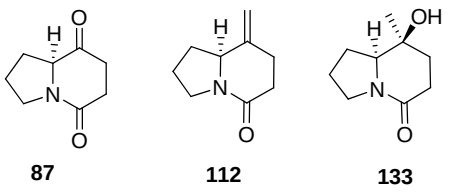
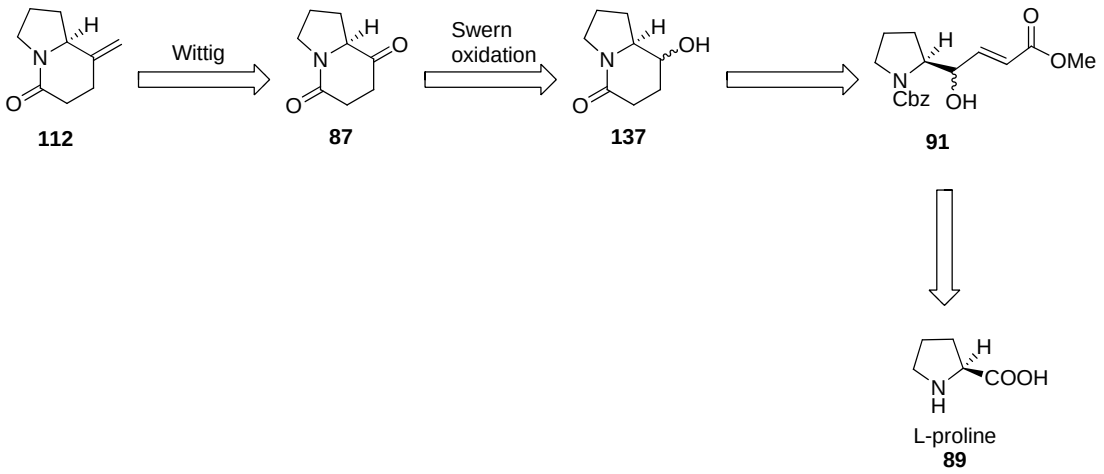


Figure 1.5. Key intermediates of Pumiliotoxin 251D

Structures of these intermediates encouraged us to believe that unsaturated ester intermediate **91** utilized in the synthesis of castanospermine isomer **3** (Scheme 1.15) in our

earlier approach can be employed effectively for the synthesis of the **87** and **112**. For the wider synthetic applications, we planned to synthesize key intermediates (**87** and **112**) from a common intermediate.

1B. 4 Retrosynthetic Analysis



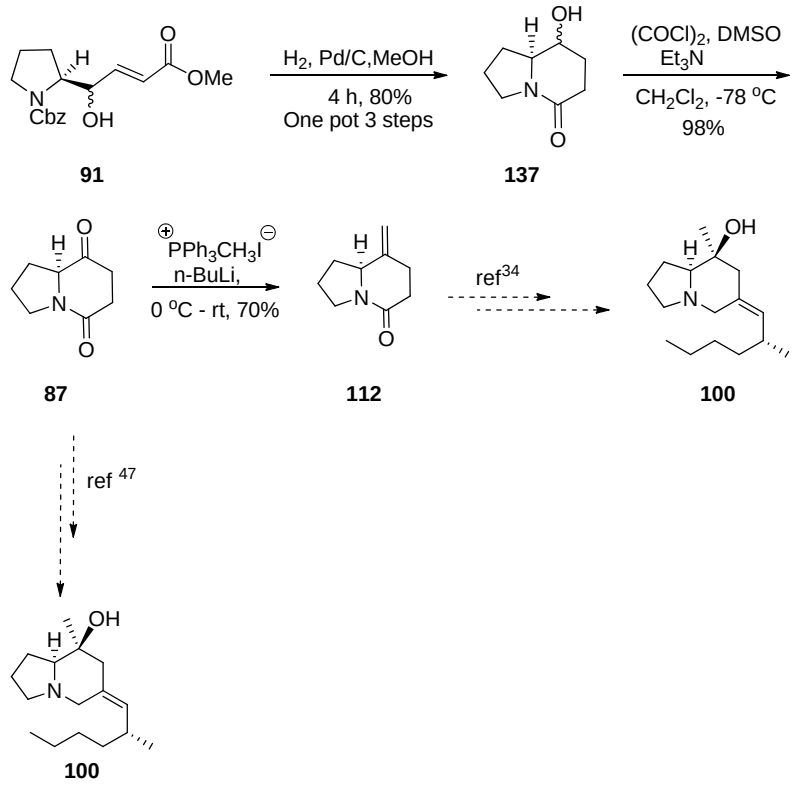
112 **87** **137** **91** **89**

Scheme 1.24 Retrosynthetic strategy towards key intermediates of pumiliotoxin 251 D

Retrosynthetic analysis is outlined in the scheme 1.24 as shown below. Bicyclic lactam **112** was the key intermediate in the total synthesis of pumiliotoxin 251D reported by Gallagher *et al.* We envisioned that this intermediate could be accessed through Wittig reaction of ketone **87** and this ketone could be easily prepared starting from unsaturated ester **91** via deprotection of Cbz group followd by in situ cyclization. Unsaturated ester **91** could be prepared starting from L-proline as explored in the total synthesis of castanospermine analogue **3** (Scheme 1.15). Earlier, strategy for synthesizing **91** has already been optimized and explored. Having compound **91** ready in hand, we planned to execute the synthesis of key intermediates.

1B. 5 Results and Discussion

Synthesis of unsaturated ester **91** was successfully achieved in the total synthesis of *epi*-castanospermine analogue (see Scheme 1.15). As planned we started the synthesis by treating the unsaturated ester **91** with catalytic Pd/C under the atmosphere of H_2 in MeOH followed by the treatment with K_2CO_3, to give the corresponding alcohol **137** in 80% yield



Scheme 1.25 Formal synthesis of pumiliotoxin 251D using cross metathesis approach

It was striking to note that series of transformations such as reduction of double bond, deprotection of Cbz and cyclization occurred in one pot.

Initial attempt to oxidize secondary hydroxyl group in **137** using IBX in EtOAc gave desired ketone **87** in very low yield. However, when alcohol **137** was treated with oxalyl chloride, DMSO and triethyl amine in DCM (Swern oxidation) provided bicyclic indolizidine dione **87** in almost quantitative yield (99%). Thus compound **87** was obtained in an overall yield of 42% in 6 steps starting from *N*-Cbz-proline **93**. Spectral data of compound **87** were in a close agreement with reported values.[42] Compound **87** obtained was optically pure as it's specific rotation was in accordance with the literature value (obs: $[\alpha]_D^{20}$ = -243, *c* 1.56, $CHCl_3$ lit.[42] $[\alpha]_D^{20}$ = -245, *c* 1.56, $CHCl_3$).

Finally, the ketone **87** when subjected to Wittig olefination (Ph_3PCH_3I/n-BuLi) provided the bicyclic lactam **112** in 70% yield. Spectral data of compound **112** were in a close agreement with reported values. Specific rotation of **112** was in accordance with the reported value (obs: $[\alpha]_D^{20}$ = -99.6, *c* 1.2, $CHCl_3$; lit.[31] $[\alpha]_D^{20}$ = -98.3 *c* 1.2, $CHCl_3$).

Bicyclic lactams **87** and **112** have been explored earlier as key intermediates for the synthesis of pumiliotoxin 251D,[31,42] but it is evident from the literature that **112** is more

viable and efficient precursor of pumiliotoxin 251D than **87**. Because the conversion of bicyclic lacatm **87** to the corresponding tertiary alcohol **121** was diastereoselectively poor (1:1.9).[42a] While the conversion of bicyclic lactam **112** to the corresponding tertiary alcohol **121** was higly diastereoselective (10:1).[31,34]

1B. 6 Conclusions

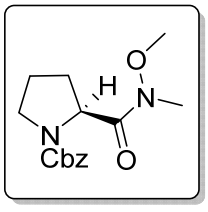
In conclusion we have achieved the formal synthesis of (+)-pumiliotoxin 251D in total of 6 or 7 steps starting from **98** in an overall 30% yield. Unsaturated ester **102** resulting from cross metathesis was used as a common key intermediate for this formal synthesis pumiliotoxin 251D.

We have also described the a concise and convenient total synthesis of (6R,7S,8R, 8aS)-6,7,8-trihydroxyindolizidine **3**. Our procedure required a total of 7 steps starting from N-Cbz-L-Proline **93** and proceeded in overall 23% yield. X-ray analysis of compound **98** established its unambiguous structural determination, which in turn confirmed the configurational structure of **3**.

1B. 7 Experimental Section:

General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. THF, CH_2Cl_2, MeOH, EtOAc, Pet. Ether, and Chloroform were purified and dried by using regular procedures using "Purification of Laboratory Chemicals" by Perrin and stored over activated 4 Å molecular sieves. Chromatographic purification of compounds was achieved with 100-200 mesh size silica gel. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and CD_3OD. Chemical shifts in ^1H NMR spectra are reported as δ in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard, *J*- values are given in Hz. ^{13}C NMR are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane and relative to the signal of chloroform-d. ^{13}C-NMR spectra were recorded with complete proton decoupling. ^1H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad, dt, doublet of triplet), number of protons, and coupling constant in hertz (Hz). Mass samples were analyzed by High-resolution mass spectrometry using ESI TOF and MALDI TOF/TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr disc and reported in cm^{-1}. Optical rotations were measured on a polarimeter. X-ray analysis was carried out using Single crystal X-ray diffractometer. All melting points were measured in open glass capillary and values are uncorrected.

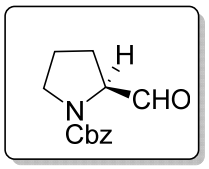
(*S*)-Benzyl 2-[methoxy(methyl)carbamoyl]pyrrolidine-1-carboxylate (Weinreb amide) (**94):**



To a cooled and stirred reaction mixture of *N*-benzyloxycarbonyl proline **93 (**10 g, 40.11 mmol) in CH_2Cl_2 (50 ml), were added *N,O*-dimethylhydroxyl amine hydrochloride(4.7 g, 48.13 mmol), Et_3N (11 mL, 80 mmol), HOBt (5.42 g, 40.11 mmol) and DCC (8.27 g, 40.11 mmol) at 0 ^oC. Reaction mixture was stirred at 0 °C for 30 min and then allowed to stir at room temperature for 6 h. The precipitate thus formed was removed by filtration and the residue was washed with EtOAc. The filtrate was diluted with additional EtOAc, washed

with saturated aqueous $NaHCO_3$, water, 5% HCl, and brine solution. The organic solvent was dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated in *vacuo* to give crude product, which was purified by column chromatography over silica gel eluting with EtOAc:Pet.Ether (3:7) to give Weinreb amide **94** (10.78 g, 92% yield). R_f = 0.3 (EtOAc: Pet.Ether, 1:1); $[\alpha]_D^{25}$ = -3.3 (*c* 1, $CHCl_3$); IR (Neat) cm^{-1}: 1706, 1670,; ^1H NMR (400 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) δ 7.41 – 7.27 (m, 10H), 5.21-5.03 (m, 4H), 4.78 (d, 1H, *J* = 8.31 Hz), 4.66 (d, 1H, *J* = 8.4 Hz,), 3.81 (s, 3H), 3.73 – 3.62 (m, 2H), 3.60 – 3.48 (m, 2H), 3.40 (s, 3H), 3.22 (s, 3H), 3.10 (s, 3H), 2.27 – 2.14 (m, 2H), 2.04 (m, 2H), 1.96 –1.80 (m, 4H)., ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of rotamers) *δ*: 173.2, 173.0, 155.0, 154.3, 136.8, 136.6, 128.5, 128.3, 127.8, 67.2, 66.9, 61.3, 60.8, 56.9, 56.6, 47.2, 47.7, 32.2, 32.1, 30.6,29.7, 24.3, 23.5; HRMS Calcd for $C_{15}H_{20}N_2O_4Na$ $(M + Na)^+$: 315.1321, found 315.1323.

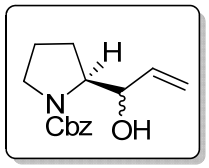
(*S*)-Benzyl 2-formylpyrrolidine-1-carboxylate (*N*-benzyloxycarbonyl Prolinal) (30):



To a stirred solution of Weinreb amide **94** (5 g, 17.10 mmol) in anhydrous THF (25 mL) at 0 ^oC was added lithium aluminium hydride (0.78 g , 20.52 mmol) and the reaction mixture was stirred for 30 min at same temperature. After completion, the reaction mixture was quenched with 10% HCl and the resulting aqueous mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), and was evaporated under reduced pressure and the resulting residue was purified by column chromatography over silica gel eluting with EtOAc:Pet.Ether (2:8) to give **30** (3.6 g, 90 % yield).

R_f = 0.5 (EtOAc: Pet.Ether, 1:1); $[\alpha]_D^{25}$ = -62 (*c* 1, $CHCl_3$) IR (Neat) cm^{-1}: 1735, 1700; ^1H NMR (400 MHz, $CDCl_3$) (reported as ~1:1 mixture of rotamers) *δ*: 9.48 + 9.59 (2s, 1H), 7.28-7.38 (m, 5H) , 5.13-5.17 (2d, 2H), 4.18-4.35 (2m, 1H), 3.50-3.62 (m, 2H), 1.81-2.20 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) (mixture of rotamers) *δ*: 200.1, 155.4, 154.5, 136.5, 136.3, 128.6, 128.2, 128.0, 67.4, 67.3, 65.3, 64.9, 47.3, 46.8, 27.9, 26.7, 24.6, 23.8; HRMS Calcd for $C_{13}H_{15}NO_3Na$ $(M + Na)^+$: 256.0950, found 256.0940.

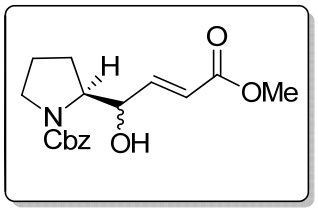
(*S*)-Benzyl 2-(1-hydroxyallylpyrrolidine-1-carboxylate (92):



To a stirred solution of aldehyde **30** (2.6 g, 11.15 mmol) in anhydrous THF (26 mL) at 0 ^{o}C was added vinyl magnesium bromide (15.6 Ml of 1M solution in THF) and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with saturated NH_4Cl and the resulting aqueous mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), and evaporated under reduced pressure, purified by column chromatography over silica gel eluting with EtOAc:Pet.Ether (3:7) to give the compound **92** as a colourless oil (2 g, 70% yield).

R_f = 0.3 (EtOAc: Pet.Ether, 1:1); $[\alpha]_D^{25}$ = -131.3 (*c* 2, $CHCl_3$), IR ($CHCl_3$) cm^{-1}: 3411, 1698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.38 (m, 5H), 5.76-5.86 (m, 1H), 4.87 (d, 1H, *J* = 3.1 Hz,), 3.86-4.32 (m, 2H), 3.25-3.70 (m, 2H), 1.65-2.01 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.2, 138.1, 136.5, 128.6, 128.3, 128.2, 128.1, 128.0, 117.3, 117.0, 75.6, 67.6, 67.4, 63.3, 63.1, 48.0, 47.4, 31.1, 28.4, 28.0, 24.1; HRMS Calcd. for $C_{15}H_{19}NO_3Na$ $(M + Na)^+$: 284.1263, found 284.1263.

(*S*)-*E*-Benzyl 2-(1-hydroxy-4-methoxy-4-oxobut-2-en-1-yl) pyrrolidine-1-carboxylate (191):

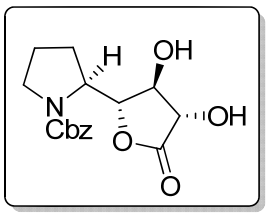


To a solution of allylic alcohol **92 (**1.7 g, 7.3 mmol) in anhydrous toluene (40 mL) and methyl acrylate (5.2 ml, 58.4 mmol) was added the Grubbs' second-generation catalyst (3 mol%). After stirring at room temperature for 2 h, the reaction mixture was exposed to air for 1.5 h, treated with Et_3N (10 drops), and then filtered through a Celite bed and the filtrate concentrated under reduced pressure and the resulting residue was purified by column chromatography over silica gel eluting with EtOAc: Pet.Ether (3:7) to afford the compound **91** as a colourless oil (1.91 g, 92% yield).

R_f = 0.15 (EtOAc: Pet.Ether, 2:8); $[\alpha]_D^{25}$ = -65.23 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) cm^{-1} : 3422, 1719, 1701. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.31-7.38 (m, 10H), 6.90+6.94 (2d, 2H, *J* = 5.2 Hz,), 6.21+6.17 (2d, 2H, 5.2 Hz), 5.14 + 5.16 (2s, 4H), 5.04 (d, 2H, *J* = 2.7 Hz,), 4.29+4.5(2bs, 2H), 3.9-4.1(m, 2H), 3.74 (d, 6H, *J* = 2.0 Hz). 3.55-3.62 (m, 2H), 3.28-3.44 (m, 2H), 1.73-2.02 (m, 8H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (mixture

of rotamers) 166.9, 158.0, 147.0, 136.3, 128.6, 128.3, 128.1, 122.2, 76.8, 67.7, 63.0, 51.7, 47.9, 28.1, 24.2; HRMS Calcd for $C_{17}H_{21}NO_5Na$ $(M + Na)^+$: 342.1317, found 342.1316.

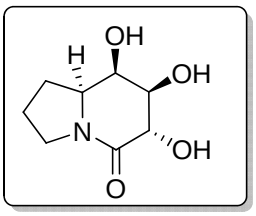
(*S*)-Benzyl-2-((2*R*, 3*S*, 4*S*)-3,4-dihydroxy-5-oxotetrahydrofuran-2-yl) pyrrolidine-1-carboxylate (98):



OsO_4 (0.035 g, 0.13 mmol) was added to a stirred solution of alkene **91** (0.6 g, 1.88 mmol) in acetone (24 mL) and H_2O (6 mL), followed by a solution of NMO (0.88 mL, 50% aqueous solution, 3.76 mmol) at 0 ^oC stirred for 3 h maintaining same temperature. Then excess solvent was evaporated in *in vacuo* and aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine, dried over anhydrous sodium sulfate, concentrated in *vacuo* to give crude product which was purified by column chromatography over silica gel eluting with EtOAc: Pet.Ether (1:1) to give the desired diol **98** (0.37 g, 61% yield).

R_f = 0.3 (EtOAc: Pet.Ether, 1:1); $[\alpha]_D^{25}$ = -66.2 (*c* 1, $CHCl_3$); IR (KBr) 3457, 3369, 1771, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.21 (dd, 2H, 12.3 Hz), 4.5 (dd, 1H, *J* = 9.7, 3.7 Hz,), 4.43 (d, 1H, *J* = 4.2 Hz,), 4.36 (dd, 1H, *J* = 6.4, 4.1 Hz,), 4.16 (dt, 1H, *J* = 9.3, 4.2 Hz,), 4.07 (dd, 1H, *J* = 9.0, 2.4 Hz,), 3.73 (d, 1H, *J* = 4.0 Hz,), 3.52 – 3.34 (m, 2H), 2.25 –1.82 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.6, 157.8, 136.1, 128.7, 128.4, 128.0, 82.7, 74.8, 73.3, 67.9, 55.8, 47.5, 28.1, 24.4; HRMS Calcd. for $C_{16}H_{19}NO_6Na$ $(M + Na)^+$: 344.1110, found 344.1111.

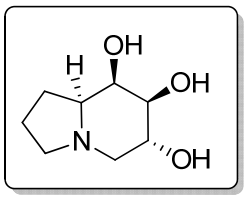
(6*S*, 7*R*, 8*R*, 8a*S*)-6, 7, 8-Trihydroxyhexahydroindolizin-5(1H)-one (99):



To a solution of diol **98 (**0.4 g, 1.24 mmol**)** in MeOH (15 mL), Pd/C (0.1 g) was added, and the solution was stirred vigorously under hydrogen atmosphere for 4 h. After completion of the reaction, reaction mixture was filtered through a Celite bed and to the filtrate, K_2CO_3 (0.26 g, 2.5 mmol) was added and resulting reaction mixture was heated at 50 ^oC for 1 h. Then mixture was filtered and concentrated under reduced pressure to give crude product, which was purified by column chromatography over silica gel eluting with MeOH:DCM (1:9) to give bicyclic lactam **99** as a colourless oil (0.15 g, 85% yield).

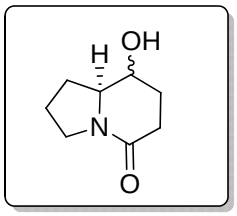
R_f = 0.3 (MeOH:DCM, 2:8) $[\alpha]_D^{25}$ = -98.6 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 4.11 – 4.04 (m, 2H), 3.81 (dd, 1H, *J* = 9.2, 2.3 Hz), 3.69 – 3.61 (m, 1H), 3.42 (dd, 2H, *J* = 9.3, 4.6 Hz), 2.06 – 1.95 (m, 2H), 1.92 –1.83 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD) δ 170.8, 75.4, 72.1, 69.8, 61.7, 46.2, 27.7, 23.3; HRMS Calcd for $C_8H_{13}NO_4$ Na $(M + Na)^+$: 210.0742, found 210.0742.

(6*R*, 7*S*, 8*R*, 8a*S*)-Octahydroindolizine-6, 7, 8-triol (3):



To a solution of lactam **99** (0.06 g, 0.32 mmol) in dry THF (5 mL), a solution of BH_3·Me_2S (0.12 mL, 1.28 mmol) was added under argon atmosphere. The reaction mixture was kept at room temperature for 4 h and then refluxed for 1 h. The excess of reducing agent was quenched by careful addition of EtOH (1 mL) at 0 °C. The solvent was evaporated and the residue was dissolved in EtOH (5 mL) and refluxed for 2 h. After which reaction mixture was cooled to room temperature and concentrated under reduced pressure to give the crude product which was purified by column chromatography over silica gel eluting with MeOH:DCM (2:8) to furnish the desired product **3** (0.045 g, 82%). R_f = 0.3 (MeOH:DCM, 3:7), mp: 147-149 ^{o}C; $[\alpha]_D^{25}$ = -30 (*c* 0.5, MeOH) , IR (KBr) cm^{-1}: 3395 ^{1}H NMR (400 MHz, CD_3OD) δ 3.87 – 3.78 (m, 2H), 3.28 (dd, 1H, *J* = 9.3, 3.3 Hz,), 3.15 (dd, 1H, *J* = 10.6, 5.3 Hz), 3.06 – 2.98 (m, 1H), 2.23 – 2.13 (m, 2H), 1.99 –1.67 (m, 5H). ^{13}C-NMR (100 MHz, CD_3OD) δ: 77.9, 69.7, 69.2, 67.9, 57.6, 54.5, 25.2, 22.9. HRMS Calcd for $C_8H_{16}NO_3$ $(M + H)^+$: 174.1130, found 174.1143.

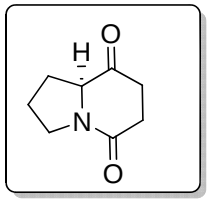
(*S*)-8-hydroxyhexahydroindolizin-5(*1H*)-one (137):



To a solution of ester **91 (**0.8 g, 2.5 mmol**)** in MeOH (25 mL), Pd/C (0.2 g) was added, and the solution was stirred vigorously under hydrogen atmosphere for 2 h. The reaction mixture was filtered through a Celite bed, and to the filtrate K_2CO_3 (0.69 g) was added, and it was heated at 50 ^{o}C for 3 h. Then the reaction mixture was filtered and concentrated under reduced pressure to give crude product which was purified by column chromatography over silica gel eluting with MeOH: DCM (1:9) to give compound **137** as colourless oil (1.31 g, 80% yield).R_f = 0.5 (MeOH: CH_2Cl_2, 1:1); $[\alpha]_D^{25}$ = -36.3 (*c* 1, $CHCl_3$); IR ($CHCl_3$) cm^{-1}: 3397 (br), 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.13 (bs, 1H), 3.46-3.56 (m, 3 H), 2.32-2.51 (m, 2 H), 2.04-2.13 (m, 2 H), 1.7-2.0 (m, 5

H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 63.9, 62.6, 45.4, 28.5 , 27.7, 26.1, 22.1, HRMS Calcd. for $C_8H_{13}NO_2Na$ $(M + Na)^+$: 178.0844, found 178.0841.

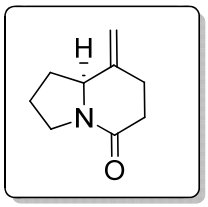
(*S*)-Hexahydroindolizine-5, 8-dione (87):



To a freshly distilled oxalyl chloride (0.22 mL, 2.56 mmol) in anhydrous CH_2Cl_2 (7 mL) at -78 °C under argon atmosphere, was added DMSO (0.18 mL, 2.64 mmol) in anhydrous CH_2Cl_2 (2 mL) drop-wise and the internal temperature was maintained below -78 °C. After stirring for 1 h at about -78 °C, hydroxyindolizidinone **137** (0.2 g, 1.28 mmol) in anhydrous CH_2Cl_2 (10 mL) was added slowly. Then Et_3N (0.88 mL) was introduced slowly at about -78 °C. The cooling bath was removed and the mixture was stirred for 1 h until the temperature reached 20 °C. The solvent was removed under reduced pressure and the residue was suspended in EtOAc. The white precipitate of $Et_3N{\cdot}HCl$ was filtered off and purified by column chromatography over silica gel eluting with EtOAc:Pet.Ether (1:1). Solvent was evaporated below 30 °C, to obtain hexahydroindolizinedione **87** as colourless oil (0.195 g, 99% yield).

R_f = 0.3 (EtOAc:Pet.Ether, 1:1) $[\alpha]_D^{20}$ = -243 (*c* 1.56, $CHCl_3$) (*c* 1, $CHCl_3$); IR (Neat) cm^{-1}: 2980, 1731, 1651, 1455, 1178; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (t, 1H, *J* = 7.9 Hz), 3.68 – 3.50 (m, 2H), 2.84 – 2.50 (m, 4H), 2.33 – 2.22 (m, 1H), 2.11 – 2.00 (m, 1H), 1.96 – 1.84 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.3, 169.1, 64.8, 45.4, 34.8, 30.8, 29.7, 27.8, 23.0; HRMS Calcd for $C_8H_{12}NO_2$ $(M + H)^+$: 154.0868, found 154.0864.

(*S*)-8-Methylelehexahydroindolizin-5(1*H*)-one (120):



To a stirred suspension of methyl triphenylphosphonium iodide (0.52 g, 13.07 mmol) in anhydrous THF (4 mL) at 0 ^oC was added n-BuLi (5.8 mL, 11.61 mmol, 2 M in hexane) with stirring for 45 min., The reaction mixture was then gradually warmed to room temperature. To this reaction mixture was added dropwise a solution of ketone **87** (0.1 g, 0.65 mmol) in anhydrous THF (3 mL). The resulting reaction mixture was stirred for 24 h at room temperature. After which, the reaction mixture was quenched by saturated aqueous NH_4Cl solution, extracted with CH_2Cl_2 dried over anhydrous sodium sulfate and concentrated in *vacuo*. The crude product was purified by column chromatography over

silica gel eluting with EtOAc:Pet.Ether (8:2) to give the desired product **112** as a colourless oil (0.069 g, 70% yield).

R_f = 0.5 (EtOAc:Pet Ether 1:1) $[\alpha]^{20}_D$ -99.6 (*c* 1.2, $CHCl_3$); IR (film) 1625; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H) 4.92 (s, 1H), 4.01-3.97 **(**m 1H), 3.67-3.44 (m, 2H,), 2.52-2.36 (m, 4H), 2.12 (m, 1H,), 2.05-1.63 (m, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 143.0, 108.9, 60.6, 44.5, 32.2, 30.6, 29.1, 22.0 : HRMS Calcd for $C_9H_{15}NO$ $(M + H)^+$: 152.1075, found 152.1079

1B. 8 Appendix I: ^{1}H and ^{13}C spectral data of representative compounds

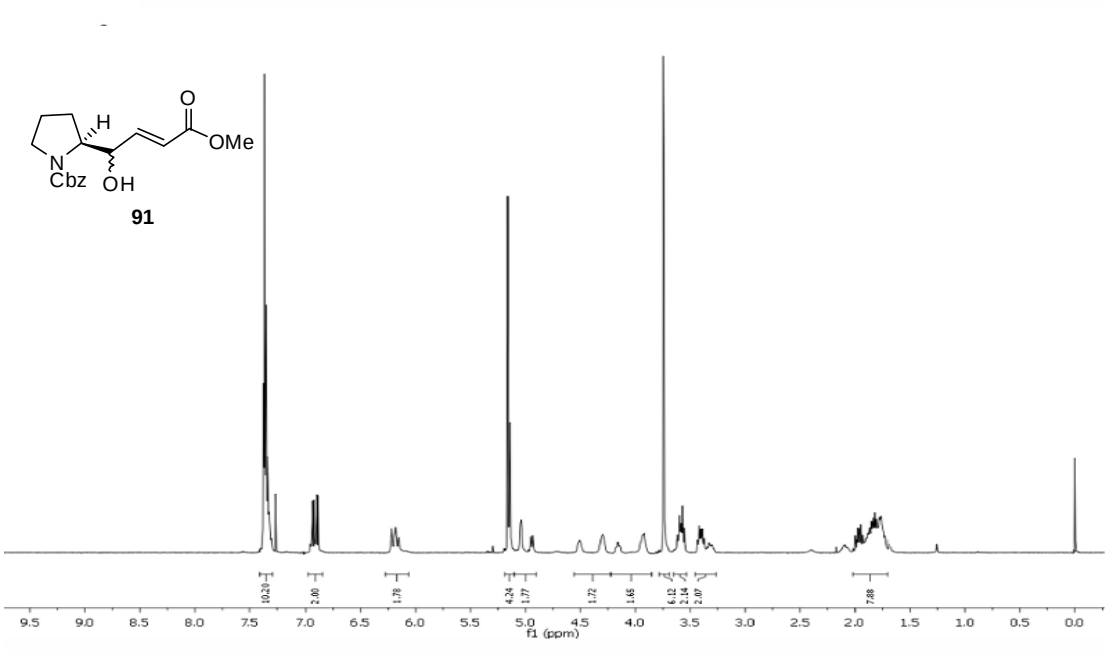


Fig AI.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **91**

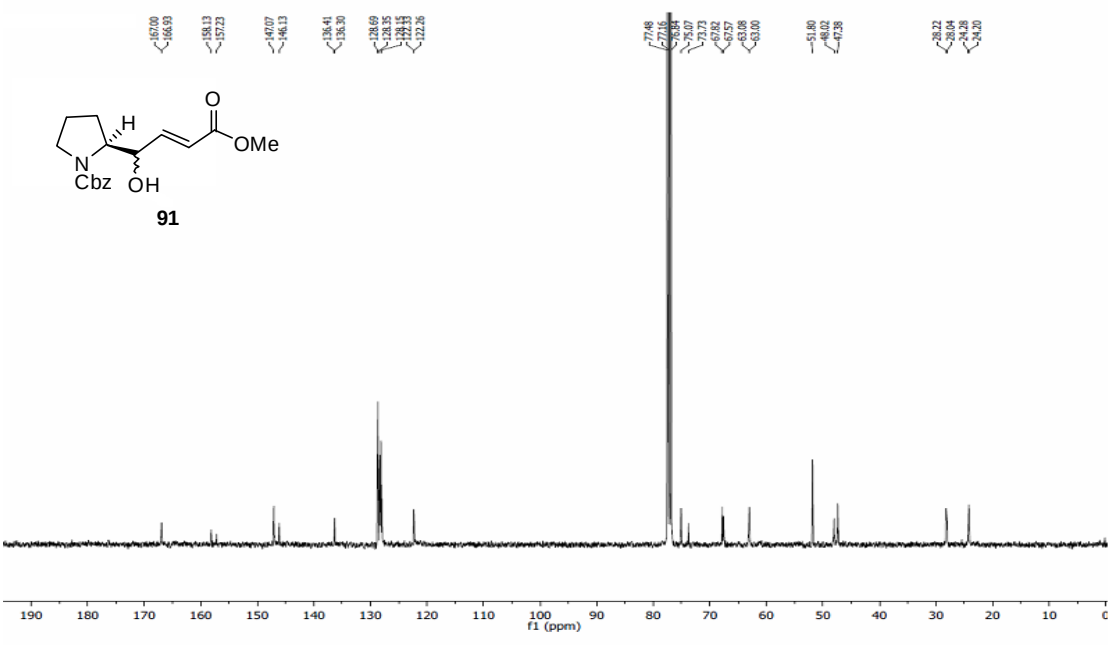


Fig AI.2: ^{13}C NMR (100MHz, $CDCl_3$) spectrum of compound **91**

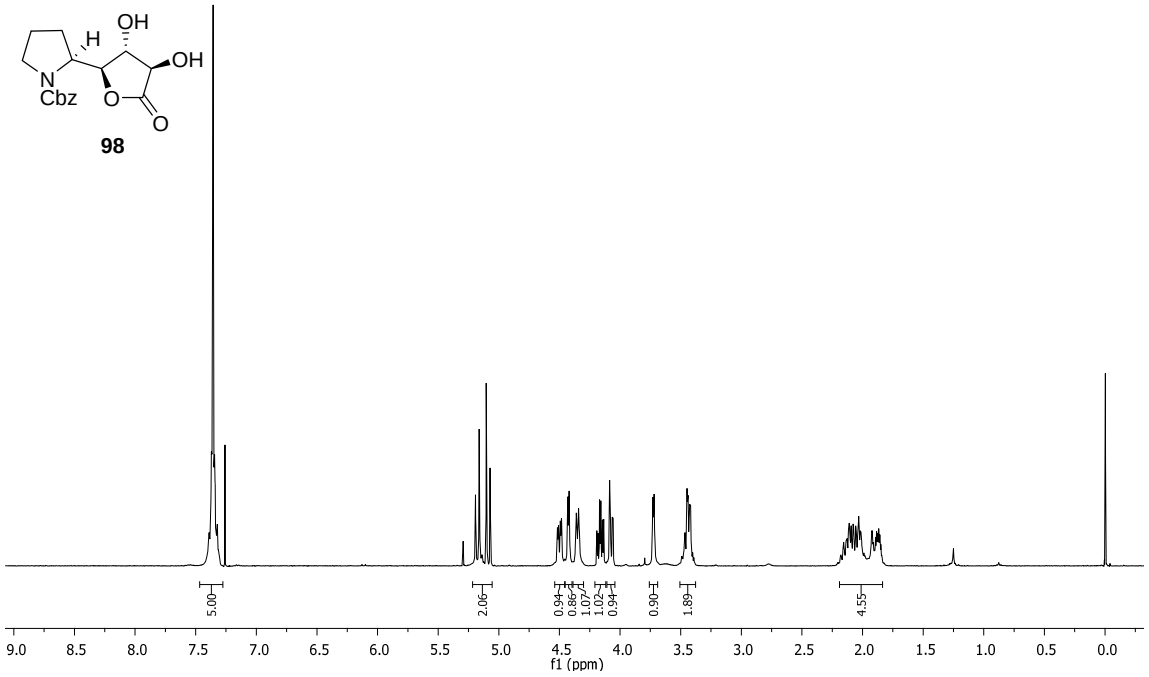


Fig AI.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **98**

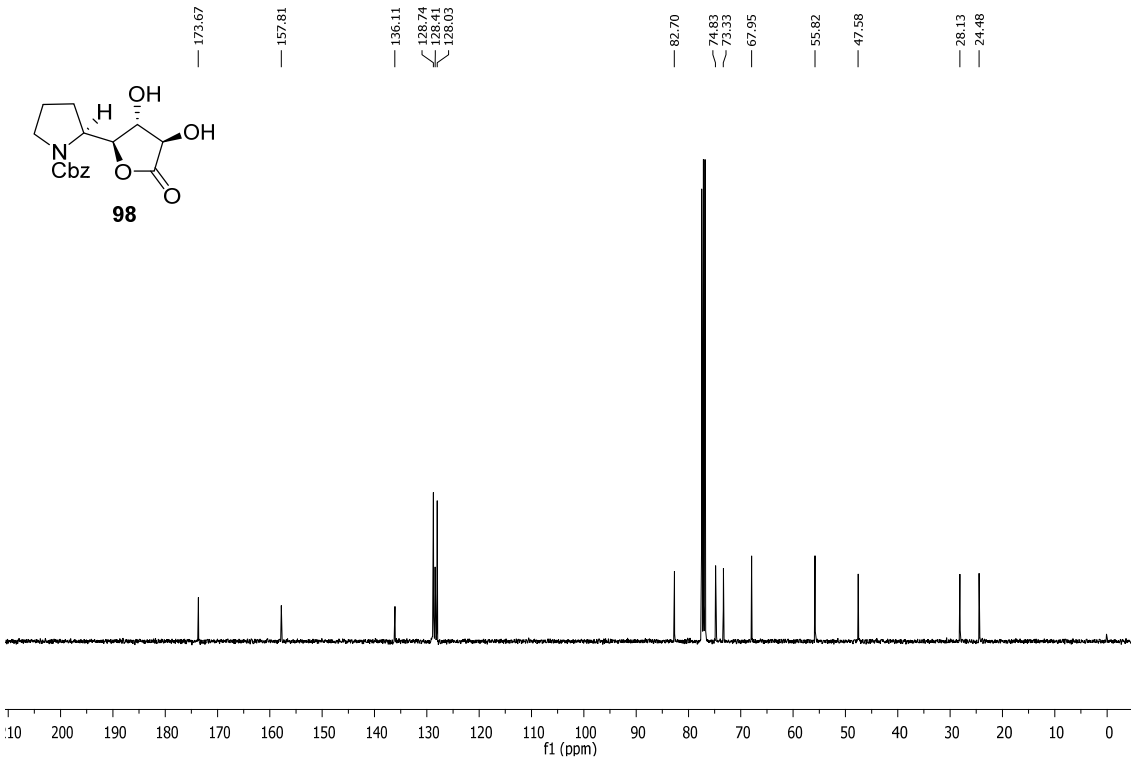


Fig AI.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **98**

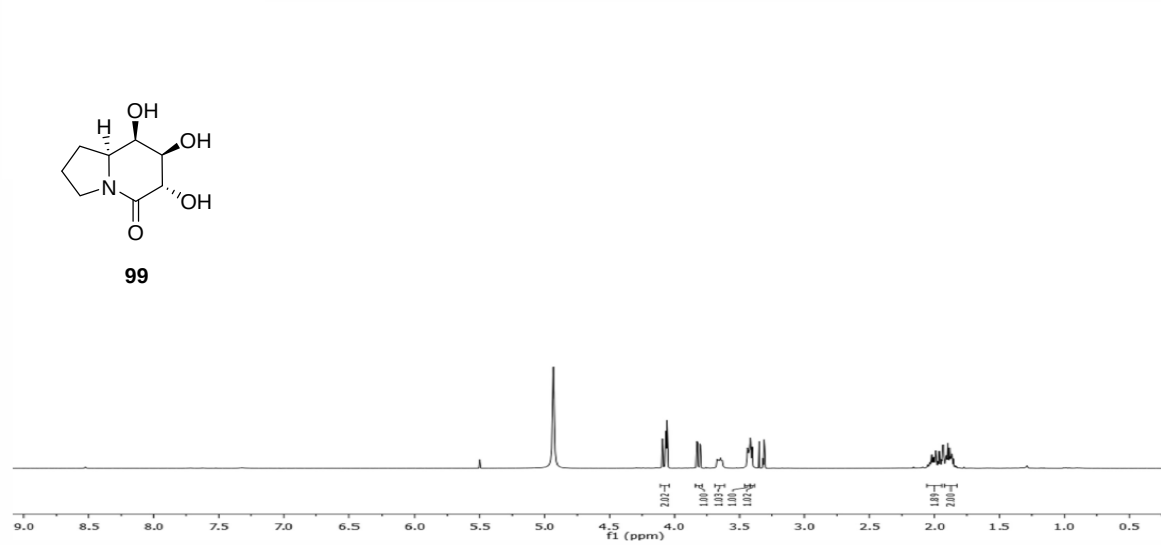


Fig AI.5: ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **99**

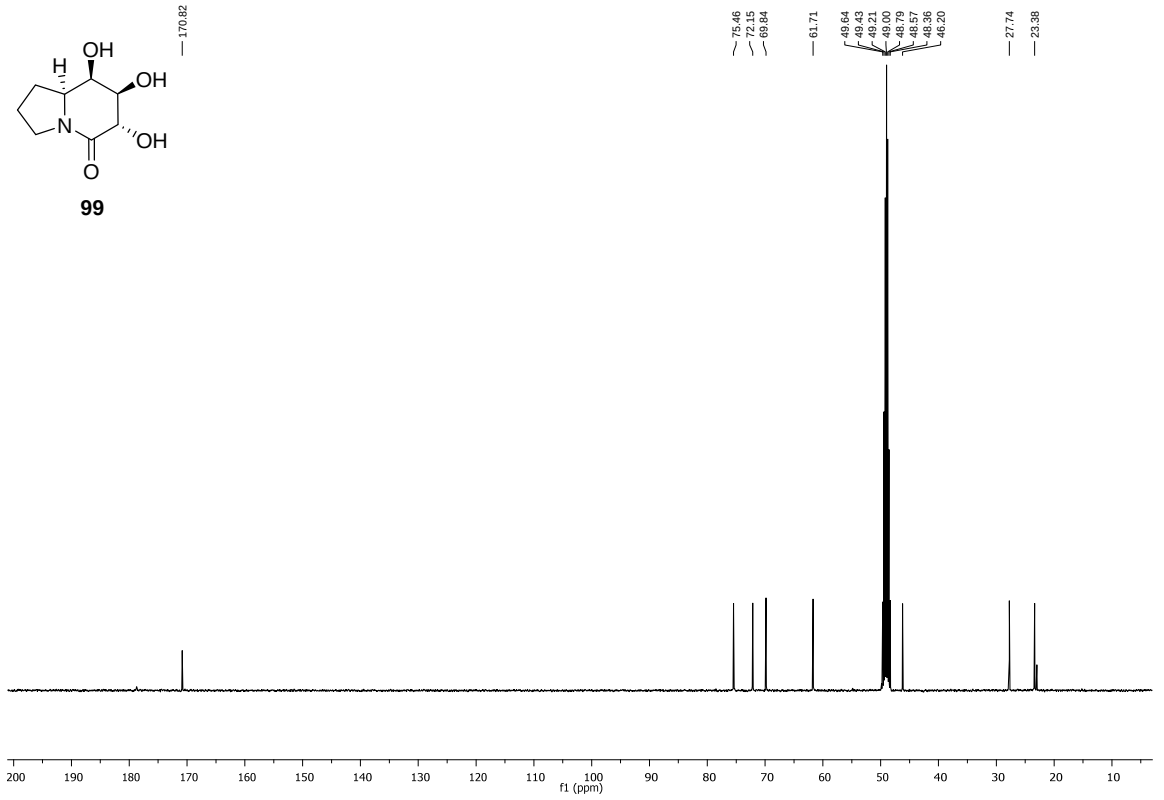


Fig AI.6: ^{13}C NMR (100 MHz, MeOH-d_4) spectrum of compound **99**

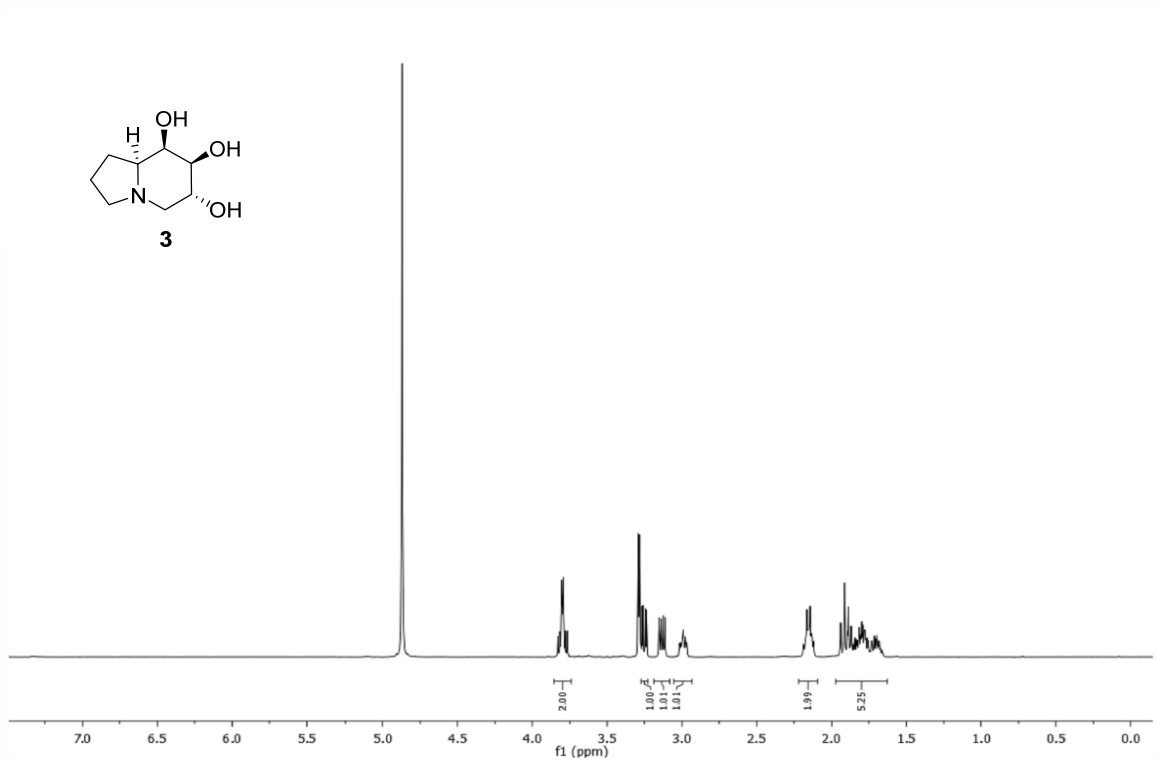


Fig AI.7: ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **3**

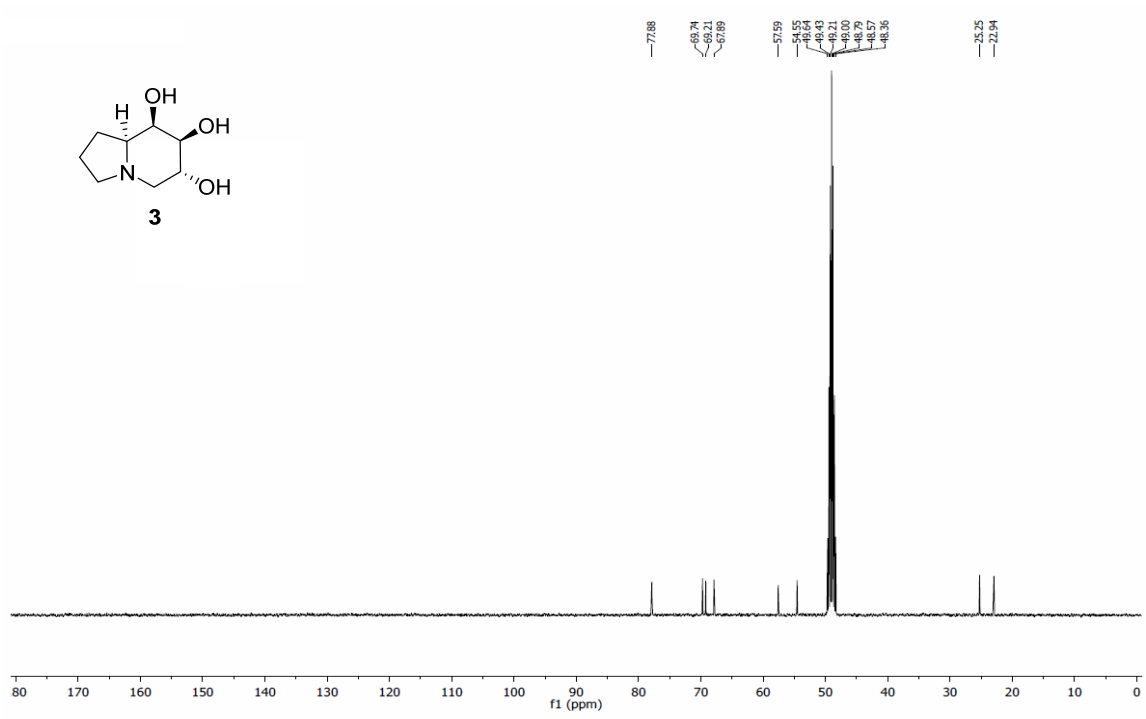
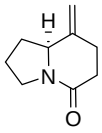


Fig AI.8: ^{13}C NMR (100 MHz, MeOH-d_4) spectrum of compound **3**



112

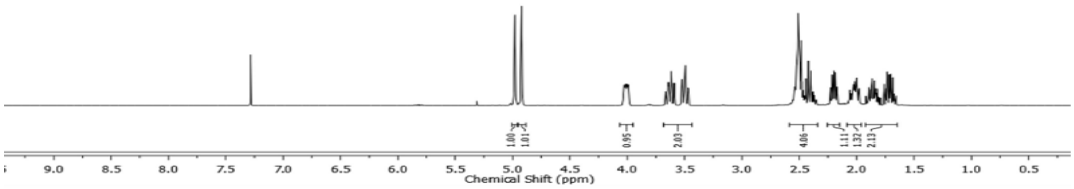
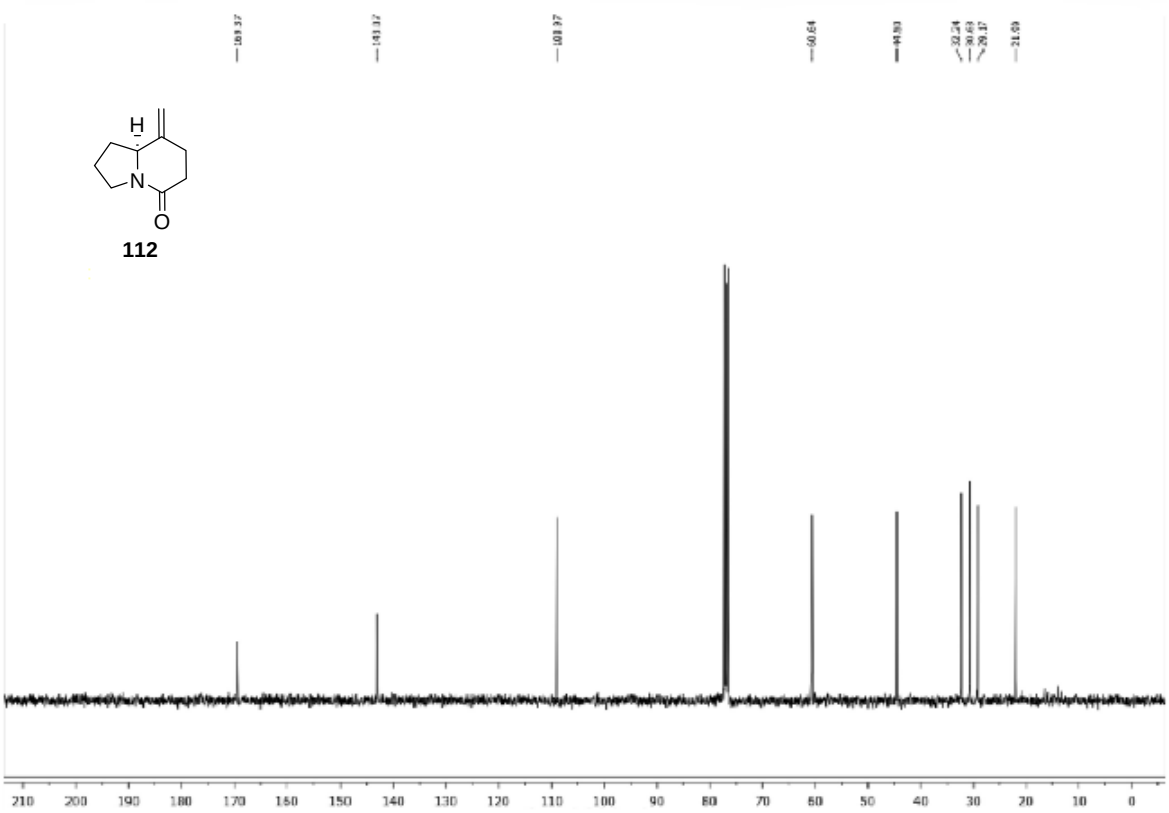


Fig AI.9: ^{13}C NMR (400 MHz, MeOH-d_4) spectrum of compound **112**



112

Fig AI.10: ^{13}C NMR (100 MHz, MeOH-d_4) spectrum of compound **112**

1B. 9 References

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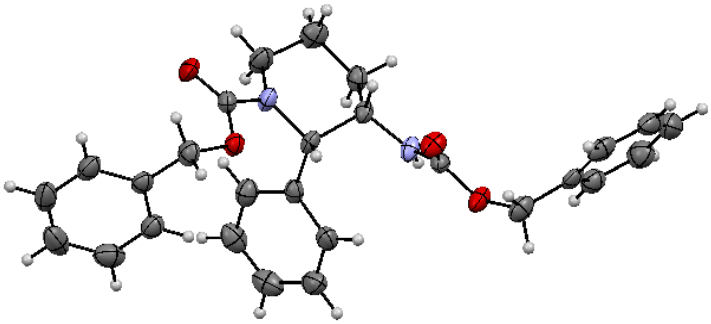
Chapter 2

Chiral Pool Approach to *cis*-2, 3-Disubstituted Piperidines, (+)-CP-99,994 and (+)-Epiquinamide



2, 3-*cis*-disubstituted piperidine

(X-ray Crystal structure)

Chiral Pool Approach to cis-2, 3-Disubstituted Piperidines, (+)-CP-99,994 and (+)-Epiquinamide

2

In this chapter novel synthesis of (+)-(2S, 3S)-CP-99, 994, a neurokinin-1 (NK1) receptor antagonist as well as natural product (+)-epiquinamide have been described starting from L-ornithine. This chapter has been divided into two sections. Section-A presents an efficient stereoselective approach to cis-2,3-disubstituted piperidines via the reduction of N-acyliminium ion intermediate using a novel pathway. Application of this methodology is exemplified by the enantioselective total synthesis of (+)-(2S, 3S)-CP-99,994. Section-B describes the synthetic studies towards the total synthesis of (+)-Epiquinamide.

Section A

Enantioselective synthesis of cis-2, 3-disubstituted Piperidines: Total synthesis of CP-99,994

2A. 1 Introduction

The piperidine ring system is widely distributed in many natural products and un-natural compounds[1] and some of these compounds exhibit a wide range of biological activities.[2] Hence there is a considerable interest in the synthesis and biological evaluations in these types of compounds. In particular, 2, 3-disubstituted piperidines have attracted much attention because they are found in various ring forms and exhibit a broad range of biological activities.[3] Some of the biologically important piperidine derivatives are shown in figure 1.

One of the earliest examples of piperidine ring containing molecule is quinine **143** and was extracted from the bark of the cinchona tree, *Cinchona officinalis*. This has been

for many centuries for the treatment of malaria[4]. Seroxat **142** is an antidepressant[5] synthetic drug, marketed by the pharmaceutical company GlaxoSmithKline and this has been listed in the top 100 best selling drugs with sales of over $1 billion.

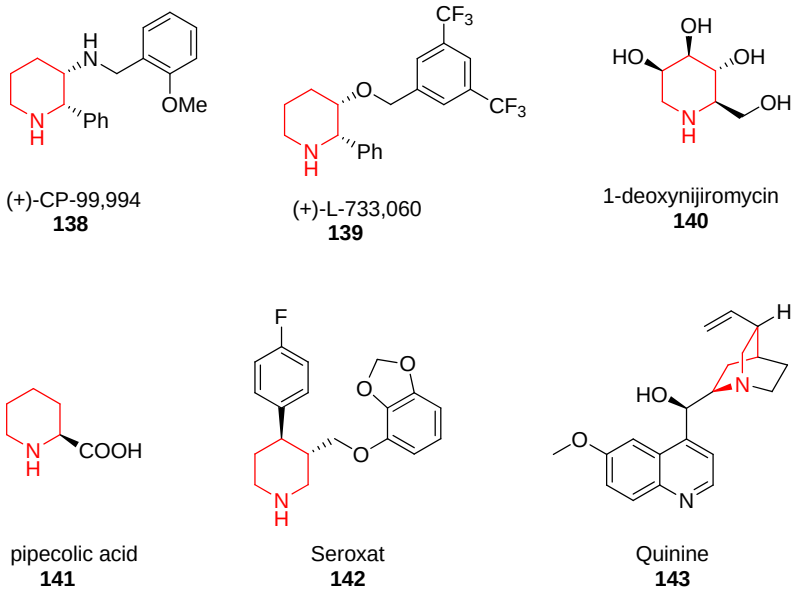


Figure 2.1 Bioactive compounds containing piperidine ring

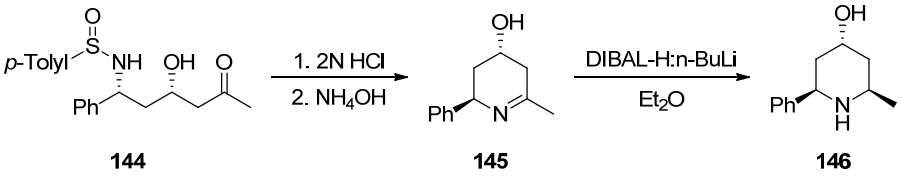
This interesting biological profile of such piperidine motifs, has attracted the attention of synthetic organic and medicinal chemists

2A. 2 Selected Syntheses of Piperidine Derivatives

Numerous synthetic methods have been developed to construct substituted piperidine derivatives. Reductive amination, Mannich reaction, intramolecular Michael addition, ring closing metathesis (RCM), radical cyclization, Diels-Alder cycloaddition, and nucleophilic addition to pyridinium salts are among the popular methods. Some recent examples and types of cyclization are discussed below.

2A. 2. 1 Reductive Amination approach by Davis et al.

In 2003, Davis and co-workers[6] constructed the piperidine via reductive amination using "ate" complex of DIBAL-H and n-BuLi. Chiral Sulfinamide has been successfully utilized as a chiral auxiliary for the construction of substituted piperidine. Chiral sulfinamide derivative **144** has been used to construct the piperdine ring.



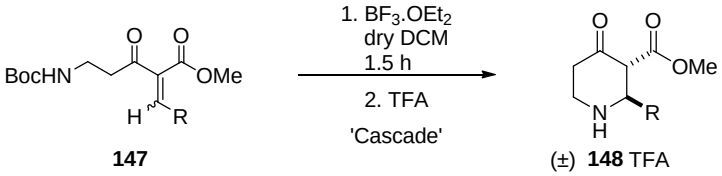
144 145 146

Scheme 2.1 Davis sulfinamide based approach for piperidine

Sulfinamide group was removed using 2 N HCl followed by the addition of NH_4OH afforded the corresponding cyclic imine **145**. This upon reduction using DIBAL-H and n-BuLi afforded *cis*-2, 6-disubstituted piperidine **146**.

2A. 2. 2 Aza-Michael addition approach by Bhat et al.

Recently in 2012, our research group[7] demonstrated the utility of intramolecular aza-Michael addition for the construction of trans-2, 3-substituted piperidines. Unsaturated β-keto ester **147** was prepared starting from β-alanine. Compound **147** when treated with TFA followed by triethyl amine to afford *trans*-2,3-disubstituted piperidinones. Deprotection of Boc group and base catalyzed aza-Michael addition took place in pot in a cascade manner.

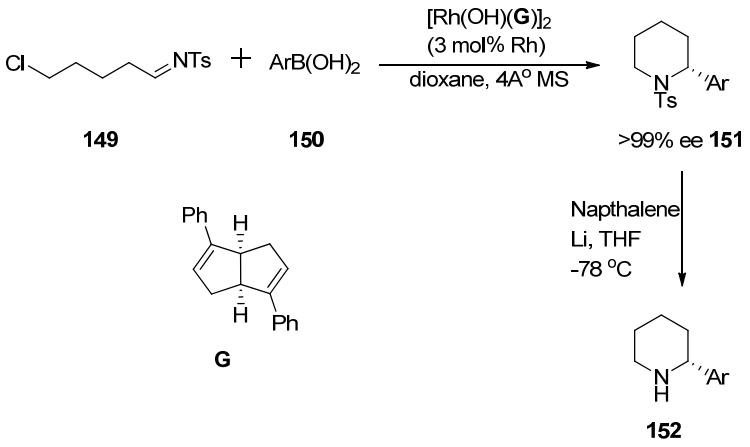


147 (±) **148** TFA

Scheme 2. 3 Cascade type reaction to piperidines

2A. 2. 3 Mannich Reaction approach by Lin

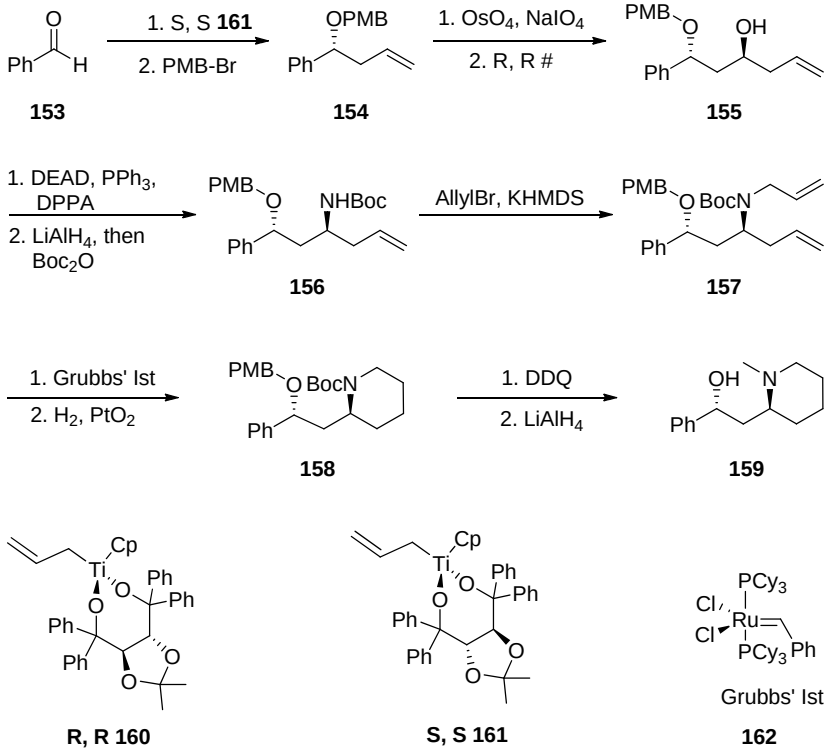
In 2011, Lin and co-workers[8] developed a rhodium-catalyzed asymmetric addition of aryl boronic acids to aliphatic *N*-tosylimines using chiral rhodium-diene complex as catalyst for the synthesis of substituted piperidine. N-tosylimines **149** was reacted with representative aryl boronic acids **150**, followed by the treatment with base affording corresponding 2-aryl piperidines **151** in high yields (73-84%) with excellent enantioselectivity (>99% ee) in one pot. The tosyl group in each resulting product was removed by using naphthalene/Li.



Scheme 2.4 Mannich reaction based approach

2A. 2. 4 Ring closing metathesis (RCM) approach by Cossy et al.

Cossy and co-workers[9] used RCM approach for the synthesis of the (+)-sedamine. Allylation of benzaldehyde was carried out using chiral allyl tin complex followed by PMB protection of resulting alcohol to afford alkene **154**. Dihydroxylation of alkene **154** followed by the oxidative cleavage with $NaIO_4$ followed by allylation afforded alcohol **155**.

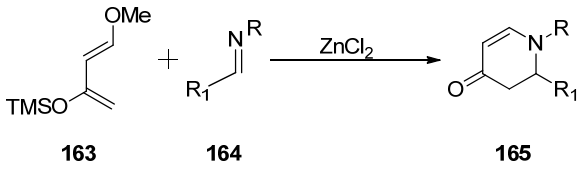


Scheme 2.5 RCM approach for piperidine

The secondary hydroxyl group was converted in to azide under Mitsunobu reaction condition. Further reduction of azide to amine followed by Boc protection afforded the desired compound **156**. N-alkylation of Boc protected amine **156** using allyl bromide and KHMDS provided olefin **157** suitable for metathesis. This, on treatment with Grubbs' first generation catalyst underwent RCM to afford 3,4-dehydropiperidine and this was reduced using H_2/PtO_2 to afford piperidine derivative **158**. PMB deprotection of **158** followed by reaction with $LiAlH_4$ in THF gave (+)-sedamine **159**.

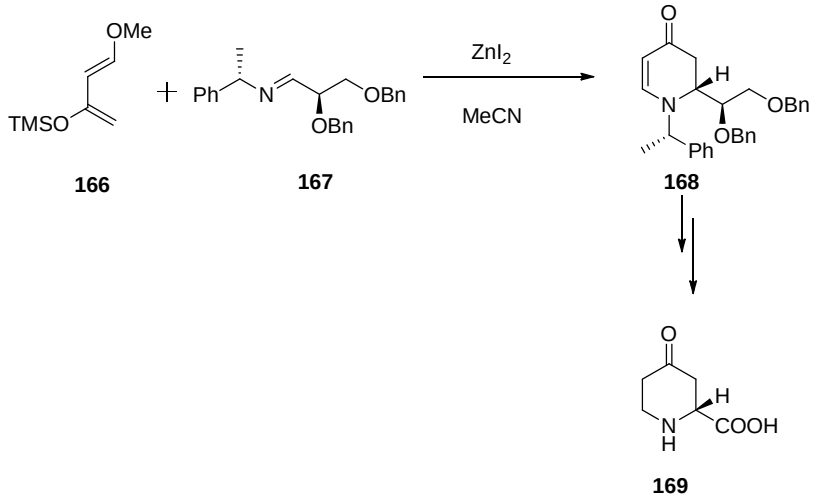
2A. 2. 5 Diels-Alder cycloadditon approach by Danishefsky et al.

In the early 80s, Danishefsky *et al*. reported the first general cycloadditions[10] between un-activated imines **164** and the Danishefsky's diene **163** catalyzed by $ZnCl_2$ to form piperidine derivatives **165**.



Scheme 2.6 Danishefsky's aza Diels-Alder cycloaddition approach

This methodology was later used in the synthesis of different alkaloids. For example Diaz-de-Villegas and co-workers[11] used an asymmetric Diels-Alder cycloaddition approach for the synthesis of (*R*)-4-oxopipecolic acid **169**.

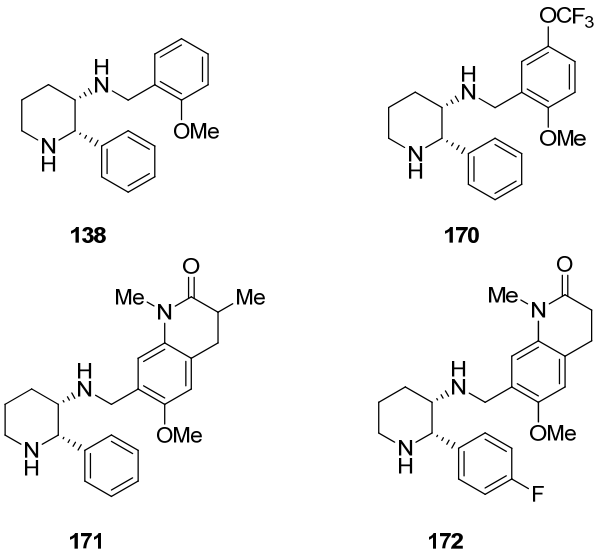


Scheme 2.7 Diels-Alder cycloaddition approach for the synthesis of (*R*)-4-oxopipecolic acid

Reaction of Danishefsky's diene **166** with the chiral imine **167** in presence of a catalytic amount of ZnI_2 afforded the piperidinone **168** as a single diastereomer in good yield. This piperidinone was further converted into (*R*)-4-oxopipecolic acid **169**.

2A. 3 Introduction to CP-99, 994

Substance P (SP) belongs to the tachykinin family of peptides. It shows important biological activities involving binding to the neurokinin-1 (NK1) receptor SP.[12] The release of SP is related to the transmission of pain and the induction of neurogenic inflammatory responses.[13] Therefore, the SP antagonist could act as remedy for a wide range of diseases like arthritis, asthma, and migraines. 2-aryl-3-amino piperidines are present in many bioactive molecules and drugs. Some of the compounds derived from this general structure are well known as substance P (SP) receptor antagonists. For example molecules such as (+)-(2*S*, 3*S*)-CP-99,994 (**138**),[14] (+)-(2*S*, 3*S*)-CP-122,721 (**170**)[15] are known to be non-peptide antagonists of neurokinin-1 (NK-1) substance P receptor. Likewise **171** and **172** have also shown the ability to antagonize the action of substance P. (+)-(2*S*, 3*S*)-CP-99,994 is a non-peptide neurokinin-1 receptor antagonist and was developed by *Pfizer Inc*.,[14] and has shown to possess potent antiemetic activity. It is important to note that *cis* relationship between the two substituents on the piperidine ring and most importantly 2*S*, 3*S* configurations are necessary for high affinity binding to human NK-1 receptor.



138 170

171 172

Figure 2.3 CP-99,994 and its congeners

Hence the development of new enantioselective synthetic approaches to functionalized piperidines is still stimulating and useful. Due to its biological importance total synthesis of (+)-CP-99,994 has been a subject of study. Some of the important total and formal syntheses of (+)-CP-99,994 have been discussed below.

2A. 4 Selected Syntheses of CP-99,994

2A. 4. 1 First development of CP-99,994 by Pfizer

In 1992 *Pfizer Inc*. discovered a potent Substance P antagonist CP-99,994.[14] After extensive screening studies they came up with the few lead structures (**138**, **173-175**, See Fig 2.4).

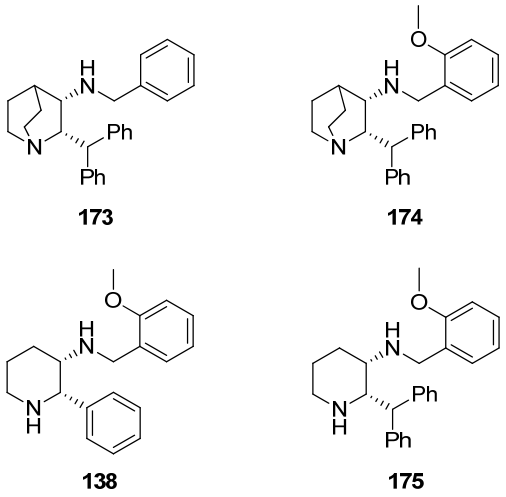
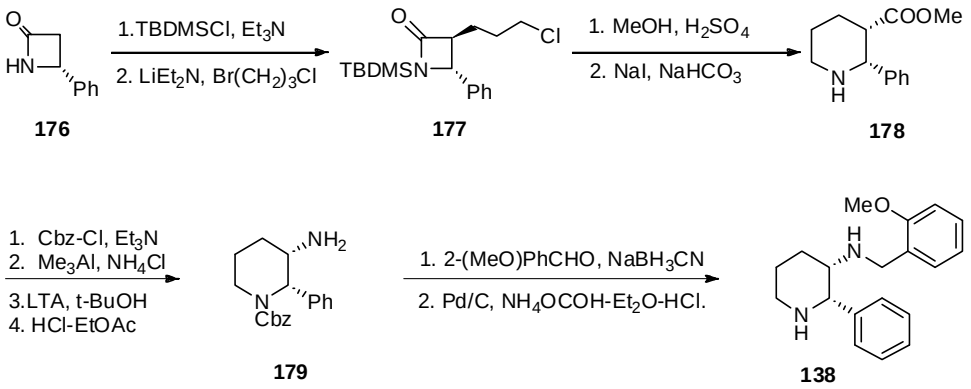


Figure 2.4 Substance P receptor antagonists

Among them compound **138** was considered as an initial lead molecule and was the most potent SP antagonist. Pfizer also discovered the importance of (+)-(2S, 3S) stereochemistry in **138** for the necessary biological activity.

The enantiospecific synthesis of **138** [(+)-(2*S*, 3*S*)-CP-99,994] started with the N-protection of lactam **176** using tert-butyldimethylsilyl chloride (TBDMSCl) and Et_3N afforded N-protected lactam. This on treatment with 1-bromo-3-chloro propane in the presence of base $LiEt_2N$ gave the corresponding chloro derivative **177**. Subsequent deprotection of the TBDMS group followed by the hydrolysis of the β lactam furnished the piperidine derivative **178**. Resulting piperidine **178** was protected with Cbz group followed by the conversion of ester group into the carboxamide using trimethylaluminum and ammonium chloride. Oxidation of carboxamide using lead tetra acetate (LTA)

followed by acidification with HCl afforded amine **179**. Reaction of **179** with *o*-methoxybenzaldehyde followed by deprotection of Cbz group provided (+)-(*2S, 3S*)-**138**.

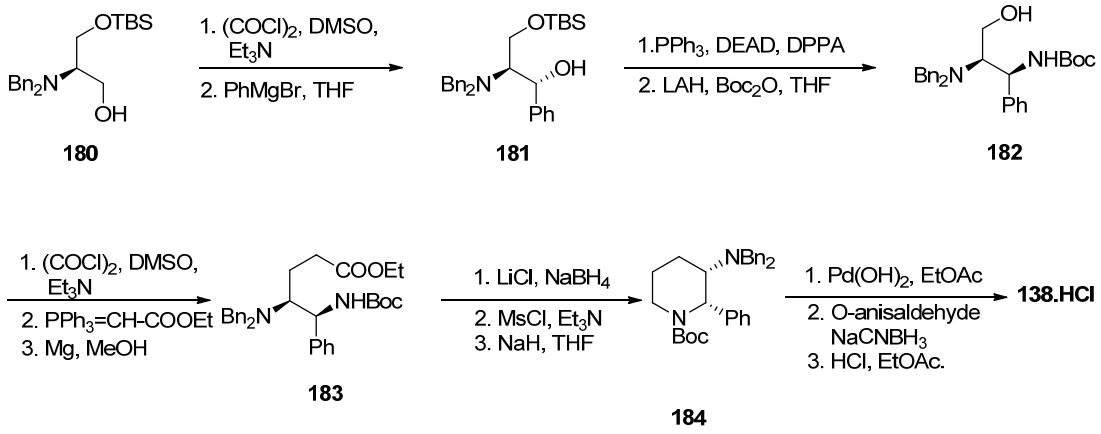


176 **177** **178** **179** **138**

Scheme 2. 8 Total synthesis of (+)-CP-99, 994

2A. 4. 2 Synthesis by Chandrasekhar et al.

In 1999, Chandrasekhar *et al*. described[16] the stereoselective synthesis of (+)-CP-99,994 starting from L-serine. Synthesis commenced with the Swern oxidation of N-dibenzyl serinol **180** followed by the addition of phenylmagnesium bromide to afford alcohol **181**. This was converted into azide under Mitsunobu condition. Azide upon one-pot reduction and simultaneous deprotection of the O-silyl ether using $LiAlH_4$ followed by the addition of $(Boc)_2O$ gave the protected diamino alcohol **182**. This, when subjected to one-pot Swern oxidation and Wittig olefination followed by the reduction of resulting double bond provided the corresponding ester **183**.

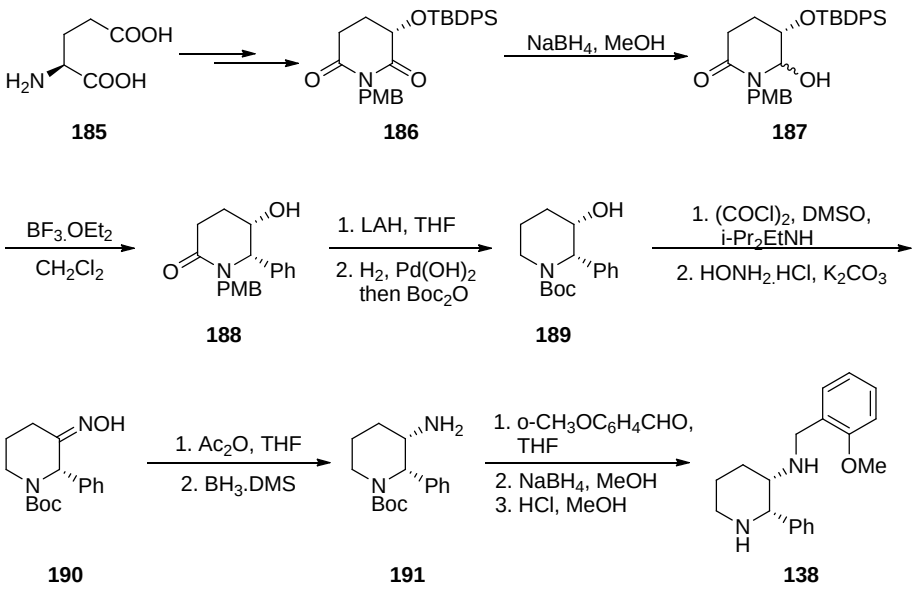


180 **181** **182** **183** **184**

Scheme 2.9 Chandrasekhar's approach

Ester was reduced to alcohol and subsequent mesylation followed by the treatment with NaH gave the 2,3-disubstituted piperidine **184**. Debenzylation followed by the reductive amination and removal of Boc group provided the desired product (+)-CP-99,994 as a hydrochloride salt **138**.

2A. 4. 3 Synthesis by Huang et al.

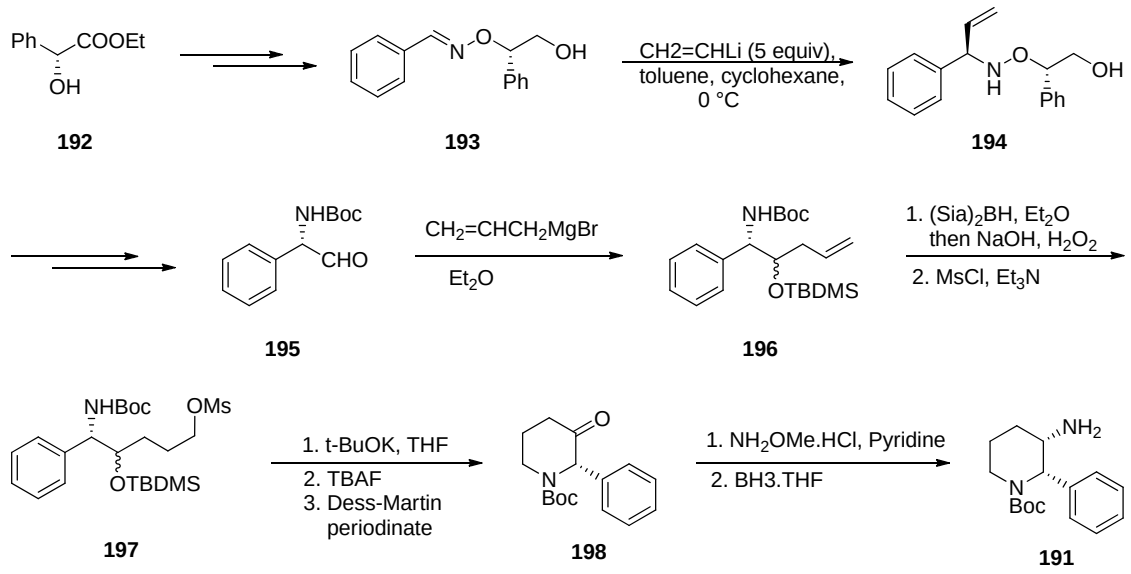


Scheme 2.10 Huang's approach for (+)-CP-99, 994

In 2003, Huang and co-workers[17] disclosed the total synthesis of (+)-CP-99,994 starting form L-glutamic acid derived (3*S*)- piperidinol. The key step of the synthesis was Lewis acid catalyzed Si (TBDMS) to C2 phenyl group migration. Synthesis commenced by the conversion of L-glutamic acid **185** to (3*S*) – (S)-protected glutarimide **186** over five steps. This upon treatment with $NaBH_4$ afforded hydroxyl lacatm **187**. Interestingly, **187** in presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, provided compound **188** by the smooth phenyl migration from the Si (TBDMS group). Reduction of a amide followed by the deprotection of PMB group afforded free amine which was trapped in situ by Boc_2O to give (2*S*, 3*S*)-3-Piperidinol **189**. This when subjected to Swern oxidation conditions followed by the reaction with hydroxylamine hydrochloride afforded the corresponding oxime **190**. Acylation of oxime followed by the reduction of resulting compound using $BH_3{\cdot}SMe_2$ afforded (2*S*, 3*S*)-3-aminopiperidine **191**. Under reductive alkylation conditions followed by Boc deprotection compound **191** furnished the optically pure (+)-CP-99,994 (**138**).

2A. 4. 4 Synthesis by Kibayashi et al.

In 2004, Kibayashi and co-workers[18] developed an efficient methodology for the preparation of (*R*)- and (*S*)-1-(aryl) ethylamines via diastereoselective addition of organolithium reagents to the (*E*)-arylaldehyde oxime ethers bearing a (1*S*)-2-hydroxy-1 phenylethyl or (2*R*)-1-hydroxy-2-phenylethyl group as a chiral auxiliary, both derived from a single precursor, methyl (*R*)-mandelate. They applied this methodology for the synthesis of (+)-CP-99,994.

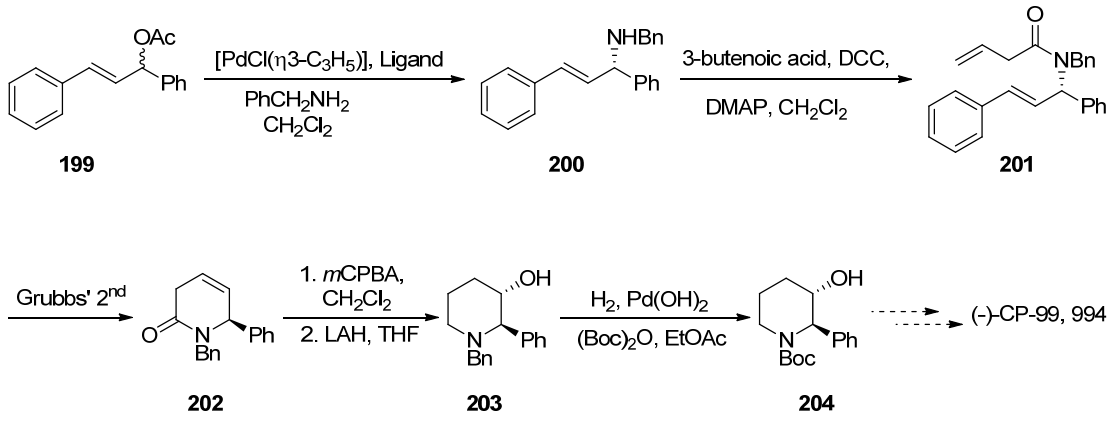


Scheme 2.11 Mandelate auxiliary approach by Kibayashi

Synthesis began with the preparation of oxime **193** from (*R*)-mandelate **192**. Addition of vinyl lithium to oxime **193** gave the corresponding alkene **194**. This was converted into aldehyde **195**. This on allylation followed by TBDMS protection of resulting secondary alcohol afforded compound **196**. Hydroboration of alkene **196** using disiamylborane followed by hydrogen peroxide basic workup gave the primary alcohol. Further, mesylation of this resulting alcohol under basic condition afforded the mesylate **197**. This on treatment with *t*-BuOK in THF provided the piperdine core which upon subsequent TBDMS deprotection and Swern oxidation gave the ketone **198**. Upon treatment with the methyloxyamine hydrochloride under basic condition resulted into oxime. Which upon reduction gave the amino derivative **191** a basic core of CP-99, 994 (**138**). Reductive amination of **198** with *o*-methoxy benzaldehyde and subsequent Boc deprotection afforded (+)-CP-99, 994 (**138**).

2A. 4. 5 Synthesis by Nakano et al.

In 2005, Nakano *et al.* disclosed[13] practical catalytic asymmetric synthesis of (-)-CP-99,994. Pd-catalyzed asymmetric allylic amination and the ring-closing metathesis were the key features of this synthesis



Scheme 2.12 Ring Closing Metathesis approach by Nakano *et al*.

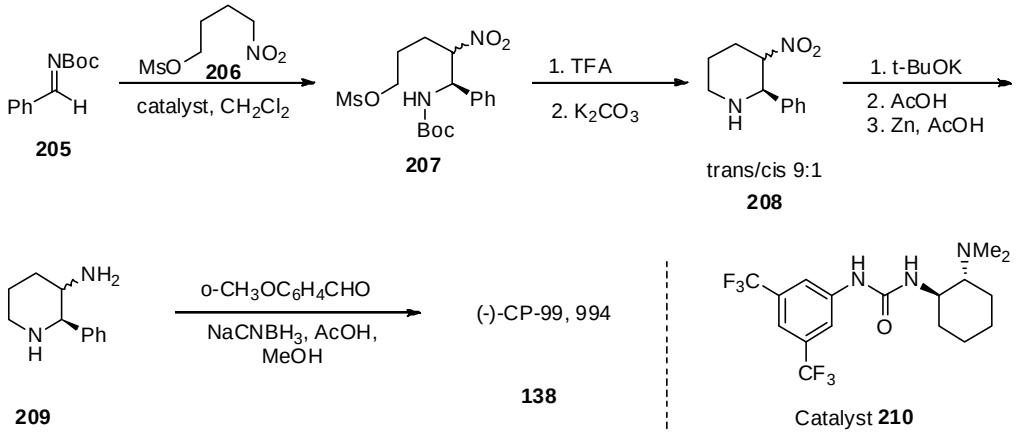
Synthesis commenced by the highly enantioselective Pd-catalyzed asymmetric allylic amination[19] of allylacetate **199** using polymer-supported phosphinooxathiane ligand to afford secondary amine **200**. DCC coupling of secondary amine **200** and 3-butenoic acid gave the corresponding diene **201**. Ring closing metathesis (RCM) of **201** was explored using Grubbs' second generation catalyst to provide piperidinone **202**. Epoxidation of the double bond in **202** using *m*-CPBA followed by the treatment with LAH afforded trans-*N*-Bn-hydroxyphenyl piperidine **203**. Benzyl group was deprotected by $H_2/Pd(OH)_2$ and the resulting free amine was trapped in situ by Boc_2O to give alcohol **204**. Finally, alcohol **204** was converted into the desired product (-)-CP-99,994 by sequential oxidation of alcohol, reductive amination and deprotection of Boc group.

2A. 4. 6 Synthesis by Takemoto et al.

In 2006, Takemoto and co-workers[19] utilized bifunctional thiourea catalyzed aza-Henry reaction of nitroalkanes with N-Boc-imines for the total synthesis of (-)-CP-99, 994.

Synthesis began with the bifunctional thiourea catalyzed aza-Henry reaction of nitroalkanes **206** with N-Boc-imine **205** to afford mesylate **207**. Deprotection of Boc group followed by the base treatment provided disubstituted piperidine derivative **208** (*trans*/*cis* isomer in 9/1 mixture). This on treatment with *t*-BuOK in THF and AcOH

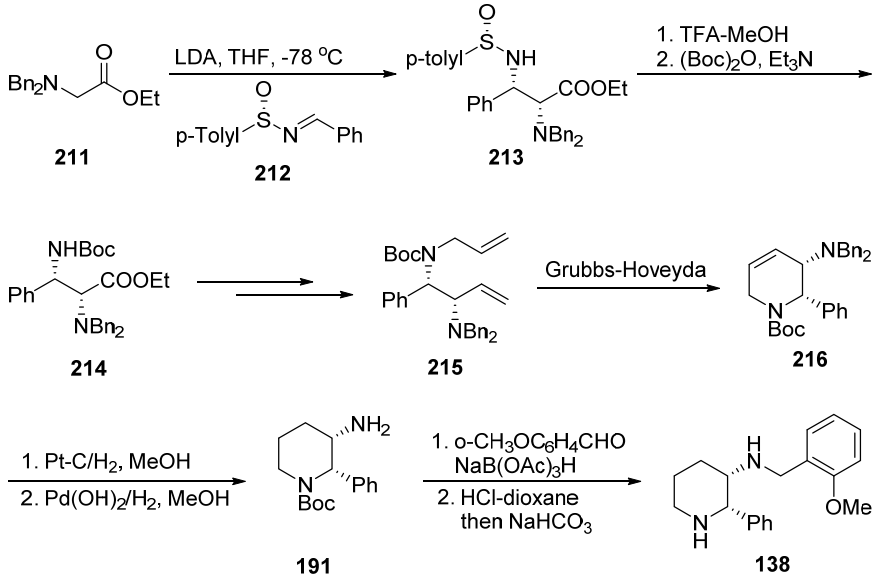
afforded the desired *cis*-isomer **208** as a major product which on treatment with Zn in AcOH resulted in the reduction to give amine **209**. Finally, reductive amination afforded (-)-CP-99,994.



Scheme 2.13 Thiourea catalyzed Henry reaction approach by Takemoto *et al.*

2A. 4. 7 Synthesis by Davis et al.

In 2007, Davis and co-workers described[20] the asymmetric synthesis of (+)-CP-99,994 using sulfinimide based approach. Synthesis started with the reaction of lithium enolate of ethyl (dibenzylamino) acetate **211** with sulfinimine **212** to afford 1, 2-diamine **213**. Deprotection of *N*-sulfinyl group with TFA followed by Boc protection gave the *N*-Boc protected diamine **214**. Diene, **215** was obtained from N-Boc protected diamine **214** in 4 steps.



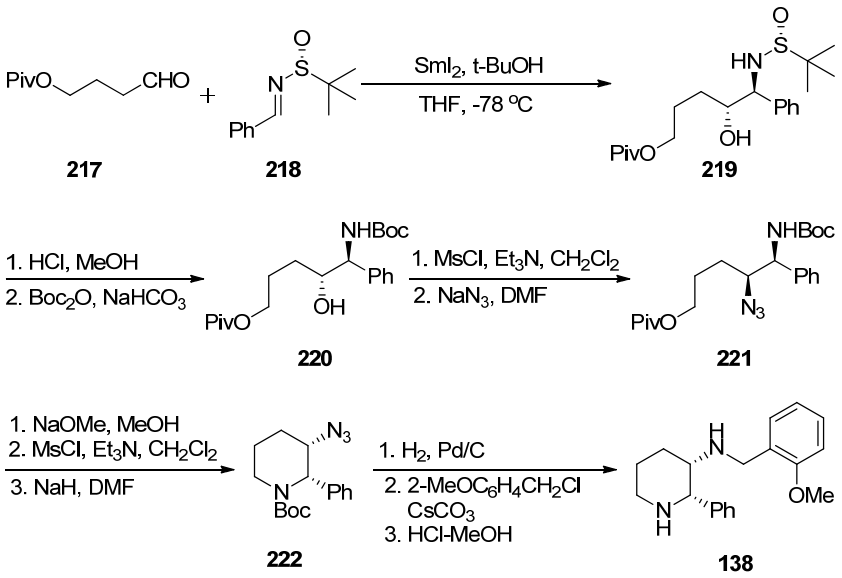
Scheme 2.14 Davis's sufinimide approach

Aminated diene **215** underwent ring closing metathesis (RCM) using Grubbs–Hoveyda catalyst to give amino tetrahydropyridine **216**. The double bond in the tetrahydropyridine **216** was selectively reduced with Pt/C, H_2 followed by the deprotection of N-dibenzyl with Pearlman's catalyst afforded free amine **191**. Reductive amination of *o*-anisaldehyde with **191** followed by removal of Boc group provided CP-(+)-99,994.

2A. 4. 8 Synthesis by Lin et al.

In 2008, Lin *et al*. reported[21] the total synthesis of CP-(+)-99,994 from anti-1,2-amino alcohol which was obtained through SmI_2 mediated coupling of sulfinimine and aldehyde. 1, 2-Amino alcohols are important and ubiquitous structural features in natural products and therapeutically important agents possessing a wide variety of biological activities. Lin and co-workers developed strategy to make 1, 2-amino alcohols and utilized them successfully in the total synthesis of CP-(-)-99,994.

Synthesis started with the key transformation involving SmI_2 mediated coupling of (R)-phenyl N-tert-butanesulfinyl imine **218** with 4-pivaloxybutanal **217** to afford 1, 2-amino alcohol **219**. N-sulfinyl group was removed with TFA followed by protection of resulting free amine with Boc_2O gave the corresponding Boc protected 1, 2 amino alcohol **220**.



Scheme 2.15 SmI_2 mediated coupling approach for (+)-CP-99, 994

This upon mesylation of the hydroxyl group using MsCl under alkaline condition followed by subsequent azide displacement provided azido derivative **221**. Deprotection of

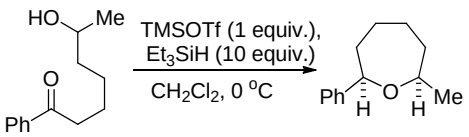
pivaloyl group (Piv) using NaOMe resulted alcohol. Which upon mesylation followed by the treatment with NaH afforded the ring closure to give 2,3-disubstituted piperidine **222**. The azide was reduced using hydrogenation followed by monoalkylation of resulting amine with 2-methoxy benzylbromide afforded protected (+)-CP-99,994 derivative. Finally, deprotection of Boc group provided the desired (+)-CP-99, 994.

2A. 5 Objectives of Present work and Synthetic Planning

Based on the literature proceeding as discussed above (2*S*, 3*S*)-(+)-CP-99,994 has been subject of synthetic studies and it has been synthesized by different methods. However, most of the methods available in the literature have usually adopted longer routes either by employing achiral or by using expensive starting materials. However, there are only handful approaches for the construction of 2-aryl-3-amino piperidines with diverse aryl groups at C-2 position, while controlling the stereochemistry of C-2 and C-3 positions. Hence the development of new shorter enantioselective synthetic approaches to functionalized piperidines is still stimulating and useful. With this initiative and also in connection with the our program devoted to the synthesis of functionalized piperidines[7] herein, we describe a highly practical and short approach for the enantioselective synthesis of *cis*-2,3-disubsituted piperidines and, concise and efficient asymmetric synthesis of (2*S*, 3*S*)-(+)-CP-99,994 (**138**) relying on diastereoselective reduction of diamino ketones.

2A. 5. 1 Background

Earlier in 1989, Nicolaou and co-workers[22] reported the synthesis of diastereopure oxepane **224** by the reductive condensation of hydroxyl ketone **223** with excess Et_3SiH and TMSOTf in high yields. In turn, this work was inspired by an elegant method reported by Olah and co-workers.[23]



223 **224**

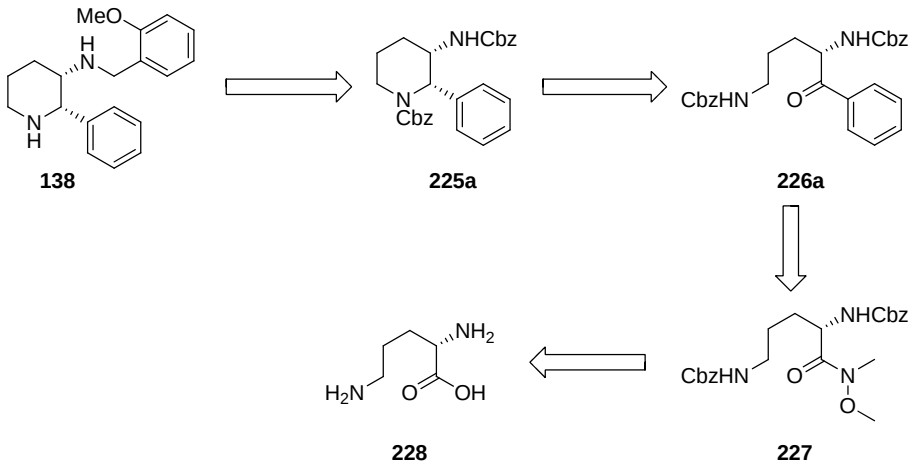
Scheme 2.16 Nicolaou's approach for the synthesis of oxepanes

In spite of the application of this stereoselective and high yielding approach to oxa-heterocycles, interestingly, we learnt from the literature that this approach has not been

extended to aza heterocycles. We envisioned that starting material with amino and keto moieties at suitable positions would lead to piperidine derivatives.

2A. 5. 2 Retrosynthetic Strategy

According to the retrosynthetic plan we envisaged that **138** could be easily synthesized form the key intermediate **225a** by the deprotection of Cbz group followed by the reductive amination.



138 **225a** **226a** **227** **228**

Scheme 2.17 Disconnection approach to piperidine

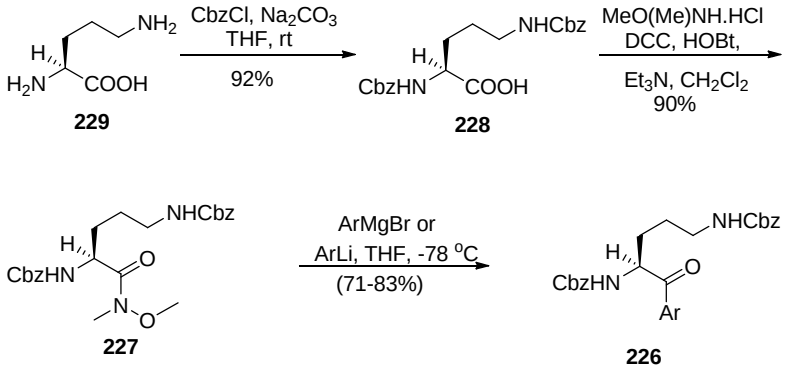
The key to this route lies in the formation of of N-acyliminium ion intermediate and reduction of this intermediate to give *cis*-2,3-disubstituted piperidine. In turn, amino ketone **226a** can be prepared from Weinreb amide **227** which could be accessed from commercially available L-ornithine **228**.

2A. 6 Result and discussion

In order to execute the our strategy we began our synthesis by preparing N*(α)*,N*(δ)*-bis-Cbz-ornithine **228**, starting from L-ornithine **229** and benzyl chloroformate in presence of Na_2CO_3 in THF-H_2O. following the reported procedure.[24]. The free carboxylic group in **228** was coupled with *N,O*- methyl hydroxyl amine hydrochloride[25] using DCC, HOBt and Et_3N to provide the corresponding Weinreb amide **227**.

Weinreb amide **227** on treatment with freshly prepared different arylmagnesium bromides[26] (5 equiv.) or/and aryl lithium[27] (5 equiv.) in THF at -78 ^oC to room temperature afforded the anticipated diamino ketones **226a-226i** in very good yields (71-

83%) in 30-60 minutes. These diamino ketones were purified by silica gel column chromatography. However, we observed that upon completion of the reaction, if stirred for longer time duration, reaction mixture resulted into decomposed products. In order to avoid any decomposition of products, Grignard reagents were added carefully and progress of the reaction was confirmed by TLC in time interval. Once, starting materials were disappeared, the reaction mixture was quenched with dilute HCl.



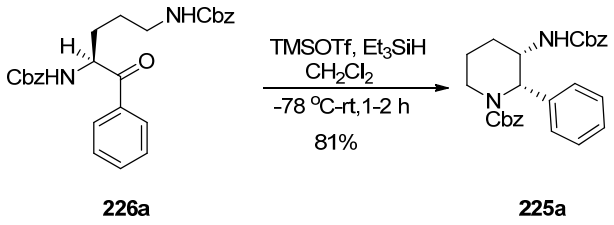
229 **228** **227** **226**

Entry	Product Ar	Yield (%)
226a	Ph	81
226b	*p*-Me-C_6H_4	80
226c	*2*-Furanyl	77
226d	*p*-F-C_6H_4	75
226e	*p*-Cl-C_6H_4	77
226f	*2*-Thiophenyl	73
226g	*p*-MeO-C_6H_4	83
226h	*m*-MeO-C6H_4	81
226i	*o*-MeO-C_6H_4	71

Scheme 2.18 Synthesis of enantiopure diamino ketones

We believed that that 2, 3-disubstituted piperidines can be built by intramolecular cyclization of diaminoarylketones *via* N-acyliminium ion intermediate which could be reduced in situ by silyl hydrides. In order to explore this possibility, we treated the diaminoarylketone **226a** with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at -78 ^oC to room tempearture for an hour. We were very glad to isolate the corresponding piperidine derivative **225a** in very good yield (81%). We

observed that optimization of the reaction temperature to −78 °C gave the high yield with excellent diastereoselectivity (96:4). We observed that intramolecular cyclization of diaminoarylketones was highly diastereoselctive by affording *cis*-2,3-disubstituted piperidine **225a** in 96:4 *dr*.



Scheme 2.19 Intramolecular cyclization of diaminoarylketone

Diastereomeric ratio was determined by ^{1}H-NMR. *Cis*-relationship of the substituents at C-2 and C-3 in compound **225a** was unambiguously deduced from the $J_{2\text{-}3}$ coupling constant. $J_{2\text{-}3}$ = 6.4 Hz suggested that the relation between substituents at C-2 and C-3 are *cis*. Further this was supported by single-crystal X-ray analysis of compound **225a** (Figure 2.6).

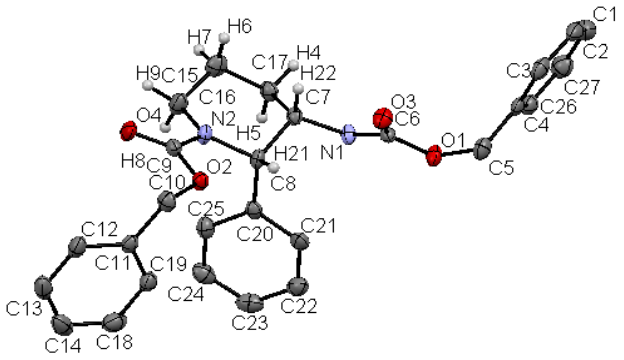


Figure 2.6 X-ray single crystal structure of compound **225a** (ORTEP diagram, ellipsoid drawn at 50% probability; aromatic hydrogens and hydrogens at C5, C10, N1, are omitted for clarity)

Relative stereochemistry at C-2 and C-3 substituent was further determined by NOE and NOESY studies (Figure 2.7). When proton at C-2 was irradiated, 10.5 % enhancement observed for proton at C-3. Also, when proton at C-3 was irradiated, 8.8% enhancement for the proton at C-2 was observed. This clearly, suggested that protons at C-2 and C-3 protons are *cis* to each other. As, C-3 stereocenter was already fixed in the starting material this NOE contact observation along with X-ray data unambiguously

confirmed the *cis* stereochemistry in (*2S, 3S*)-274. NOESY spectra also supported the *cis* geometry of protons at C-2 and C-3 protons.

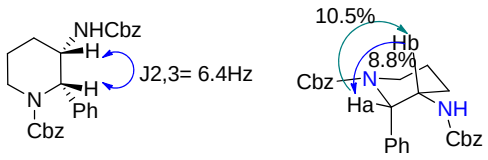


Figure 2.7 NOE studies of compound **225a**

Encouraged by this initial success we planned to synthesize various 2, 3-*cis*-piperidines to demonstrate the synthetic utility of this approach. Having already obtained few different amino ketones we planned to subject them the optimized reaction conditions. Amino ketones (**266-273**), when treated with TMSOTf and Et_3SiH in CH_2Cl_2 afforded the corresponding *cis*-2, 3- piperidines **225b-225i** in good yields (up to 83%, see Table 2.1). The stereochemistry of the piperidine derivatives **225b-225i** was assigned by the analogy. All aromatic and hetero-aromatic amino ketones underwent facile cyclization in high diastereomeric ratio (*dr* upto 96:4). However, there was no significant effect on yields and rate of the reaction due to the substituents on aromatic ring was observed.

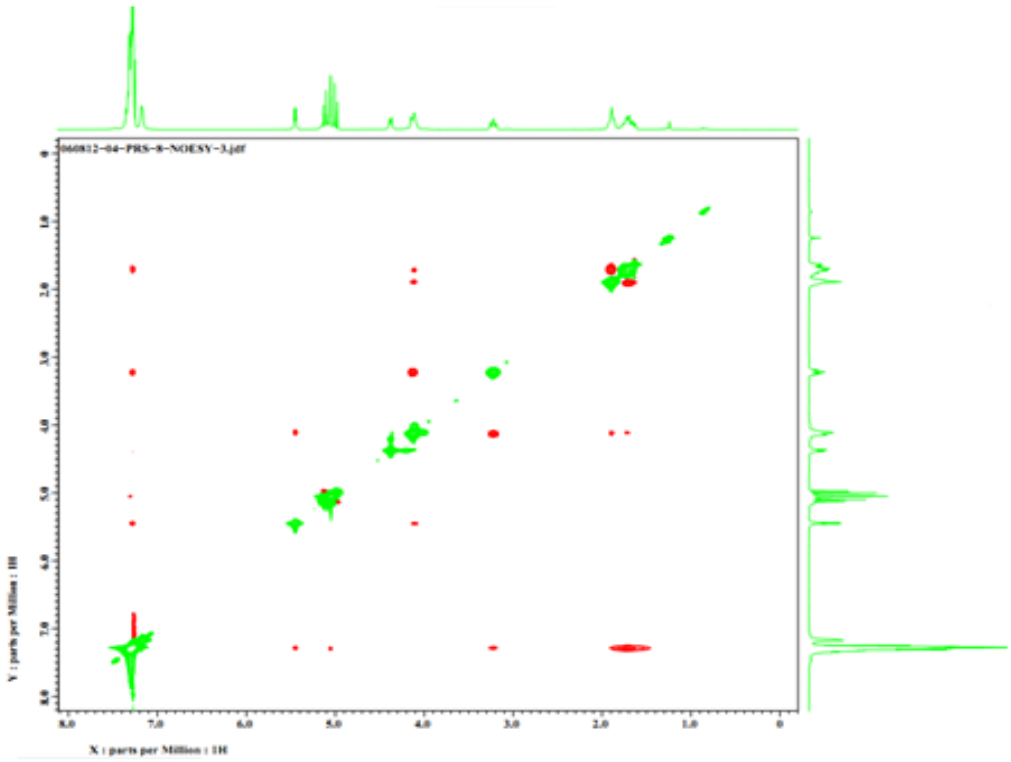


Figure 2.8 NOESY spectrum for compound **225a**

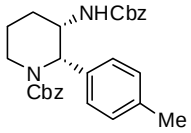
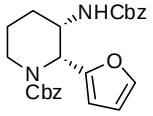
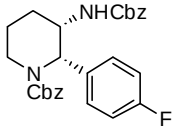
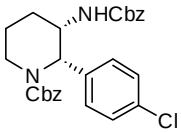
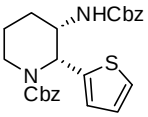
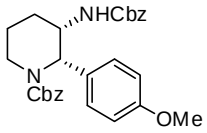
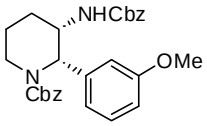
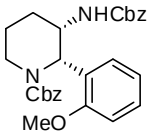
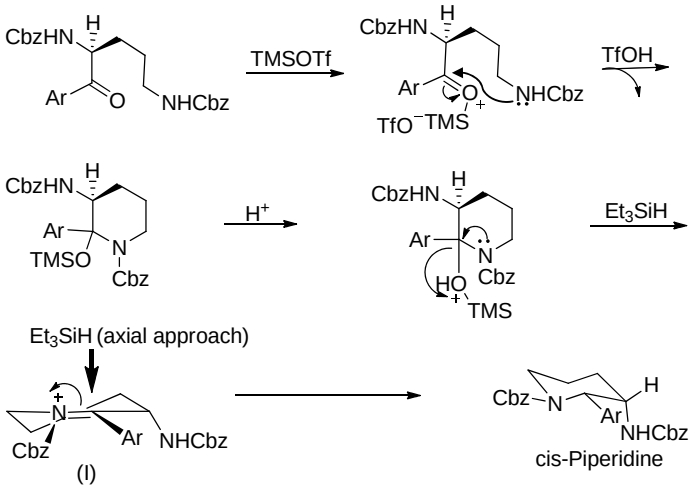
Entry	Product	yields	dr
225b		77%	92:8
225c		74%	88:12
225d		80%	93:7
225e		83%	89:11
225f		76%	87:13
225g		79%	92:8
225h		78%	88:12
225i		72%	94:6

Table 2.1 Substrate scope for intramolecular cyclization

2A. 6. 1 Plausible Mechanism

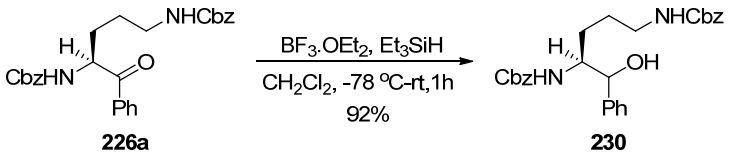
High diastereoselctivity leading to *cis*-2,3-disubstituted piperidines could be explained by the plausible mechanistic pathway as shown in Scheme 2.20. Carbonyl group of the enantiopure diaminoketone gets activated by TMSOTf, which in turn facilitates the intramolecular cyclization by the nucleophilic attack of secondary amine to give a planar N-acyliminum ion intermediate (I). The axial approach of Et_3SiH to (I), affording the *cis*

diastereomer, is certainly favored because of the higher stability of the resulting chair like transition state.



Scheme 2.20 Plausible mechanism for the stereoselective synthesis of piperidines via N-acyliminium ion.

It is interesting to note that reaction of diamino ketone **226a** and Et_3SiH in presence of $BF_3{\cdot}OEt_2$ afforded amino alcohol **230** as an exclusive product in excellent yield (92%). Attempts to synthesize the expected product **225a** by increasing the amount of $BF_3{\cdot}Et_2O$ along with varying the reaction temperature (-78 ^oC, 0 ^oC and rt) exclusively led to the formation of amino alcohol **230**. We also changed the mode of addition by adding Et_3SiH followed by $BF_3{\cdot}Et_2O$, but diaminoarylketone resulted in the formation of amino alcohol **230**.

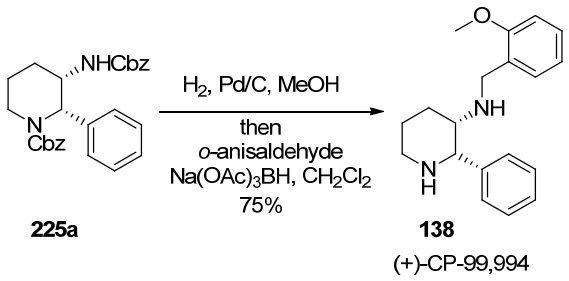


Scheme 2.21 Reaction of **226a** with $BF_3{\cdot}OEt_2$ and Et_3SiH.

2A. 6. 2 Synthesis of 2S, 3S-(+)-CP-99,994

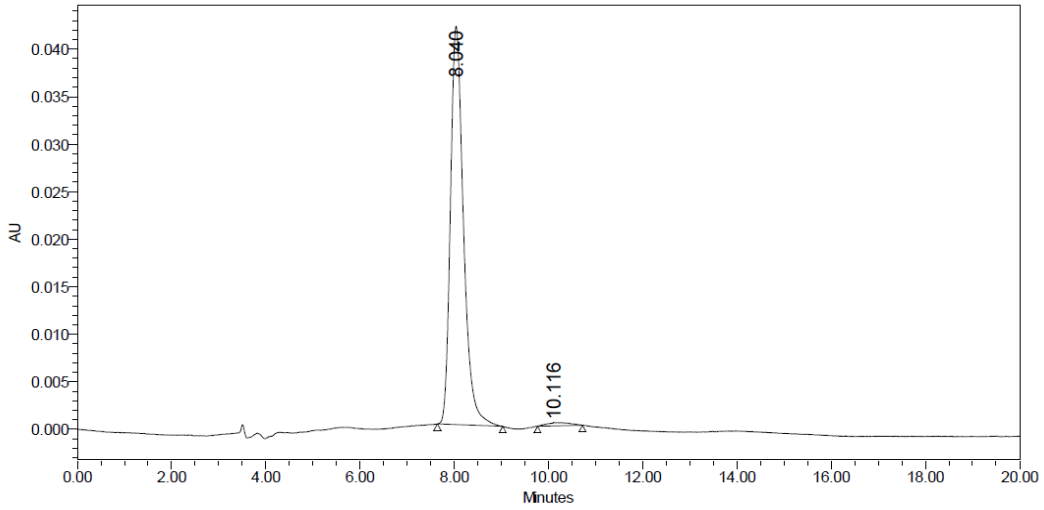
After successful synthesis of *cis*-2, 3-piperdines we planned to extend this novel approach for the synthesis of 2*S*, 3*S*-(+)-CP-99,994. Having already synthesized the piperidine derivative **225a** (see Scheme 2.19), a basic core of (+)-CP-99,994 (200), we planned to utilize the pure **225a** (by crystallography) in the synthesis of **138**.

Accordingly, piperidine derivative **225a** was converted into its corresponding free amine derivative using H_2, Pd/C in methanol. After completion of reaction, the reaction mixture was filtered through celite and subsequently treated with *o*-anisaldehyde followed by the addition of $Na(OAc)_3BH$ to afford (+)-CP-99,994 in good yield (75%).



225a **138**
(+)-CP-99,994

Scheme 2.22 Completion of total synthesis of (+)-CP-99,994



	RT	Area	% Area	Height
1	8.040	806080	98.57	41922
2	10.116	11681	1.43	349

Fig 2.9 HPLC Chiralpak IC, n-Hexane/2-propanol 10:90, 290 nm; Retention Time *t* major = 8.04 min, *t*minor = 10.11 min; *ee*= 96%

^1H, ^{13}C and specific rotation of compound **138** were in accordance with the reported data of (+)-CP-99,994 in the literature.[28] Further, enantiopurity of the (+)-CP-99,994 was confirmed by HPLC using chiral column. We believed that enatiomeric ratio has been maintained in the transformation.

2A. 7 Conclusions

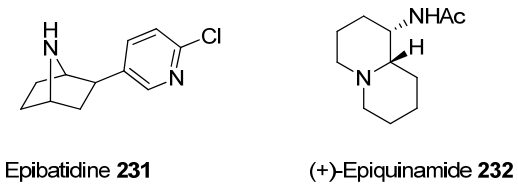
In conclusion we have described a highly efficient and useful approach for constructing *cis*-2-aryl 3-amino piperidines with an option of introducing diverse aryl groups at C-2 position. This also gives an easy access to condense different aldehydes at C-3 amine functionality without compromising the stereochemistry. The method described herein, opens a wide and easy access to synthesize piperidine derivatives and in particular synthesis of various congeners of (+)-CP-99,994 to test the biological activity against NK1-receptor. The application of this method is further exemplified by the short and concise enantioselective synthesis of (+)-CP-99,994.

Section B

Total synthesis of (+)-Epiquinamide

2B. 1 Introduction

Aza fused alkaloids isolated from frogs have attracted much attention due to their useful and interesting biological activities especially in the field of neurology. Epiquinamide **232** was isolated along with epibatidine **231** (Fig 2.9) from the poison frog *Epipedobates tricolor* by Daly and co-workers[29] in 2003. Epiquinamide is a novel structural class of nicotinic agonists, and selective β2 nicotinicreceptors.[30] Epiquinamide is believed to be a potential lead molecule for the development of new therapeutics for neuronal receptors. However, further biological studies have slowed down due to the limited availability of the natural product epiqinamide.



Epibatidine **231** (+)-Epiquinamide **232**

Figure 2.9 Structure of (+)-Epiquinamide

Natural availability of this alkaloid is significantly lower[29] (240 μg from 183 frogs). Hence, there is a need for the development of new practical synthetic strategies for the synthesis of epiquinamide. Available studies have confirmed the relative stereochemistry of the natural product **232** as (1R*, 10R*)-1-acetamidoquinolizidine. Few research groups have achieved total synthesis of epiquinamide using various strategies, however, synthesis of epiquinamide via more practical pathway with fewer synthetic steps are still challenging and useful.

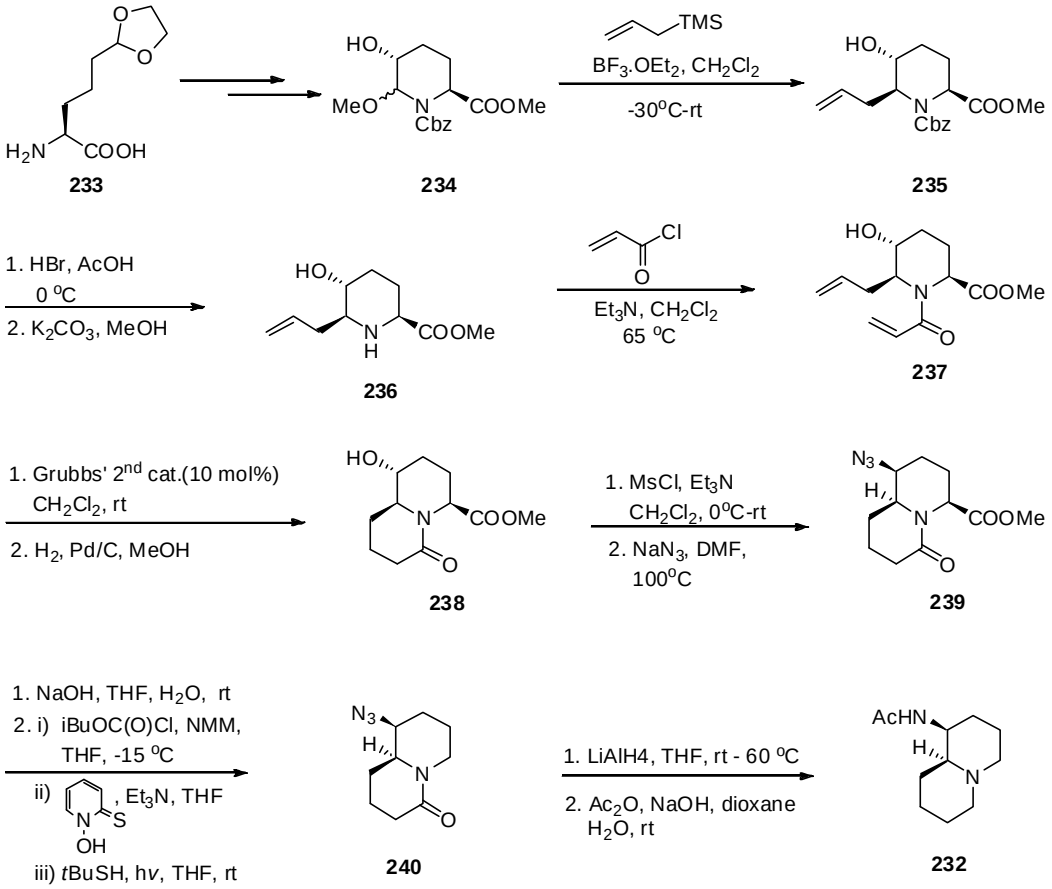
2B. 2 Selected Total Synthesis of (+)-Epiquinamide

Some of the important synthesis of (+)-epiquinamide have been outlined in this section.

2B. 2. 1 Synthesis by Blaauw et al.

In 2005, Blaauw and co-workers[31] described the total synthesis of (+)-epiquinamide **232** starting from the L-allysine ethylene acetal which is derived from the corresponding

unnatural amino acid amide. Key steps in the synthetic strategy were a highly diastereoselective N-acyliminium ion allylation and a ring-closing metathesis reaction.

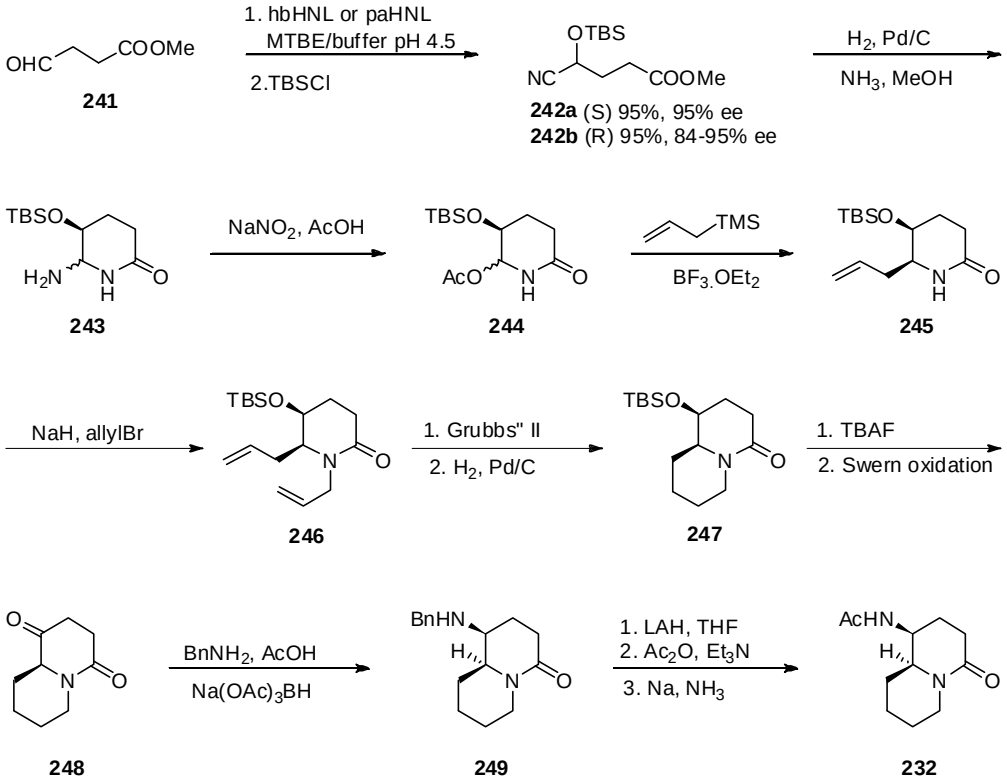


Scheme 2.23 Blaauw's approach

Ester **234** was prepared from L-allysine ethylene acetal **233** in 94% yield over 4 steps. Treatment of *N, O*-acetal with $BF_3{\cdot}OEt_2$ in the presence of allyltrimethylsilane afforded (*2S, 5R, 6S*)-configured product **235** as a single isolated product via a highly diastereoselective N-acyliminium ion intermediate. Deprotection of Cbz group followed by the reaction of acryloyl chloride with resulting free amine provided **237**. Treatment of **237** with Grubbs' second generation catalyst, followed by hydrogenation of resulting double bond afforded the bicyclic lactam **238**. Hydroxyl group in **238** was mesylated using MsCl and Et_3N followed by the reaction with sodium azide in DMF at 100 °C to afford azido derivative **239**. Azide was reduced to amine using $LiAlH_4$ in THF followed by N-acetylation using Ac_2O in DCM to afford the desired (+)-epiquinamide. They achieved enantiomerically pure epiquinamide in total of 15 steps with an overall yield of 15.5%, from readily available L-allysine ethylene acetal.

2B. 2. 2 Synthesis by Rutjes et al.

In 2008, Rutjes and co-workers[32] reported the total synthesis of (+)-epiquinamide. Synthesis involved few key steps such as chemoenzymatic formation of an enantiomerically pure cyanohydrin, reductive cyclization to the corresponding cyclic *N, N*-acetal.



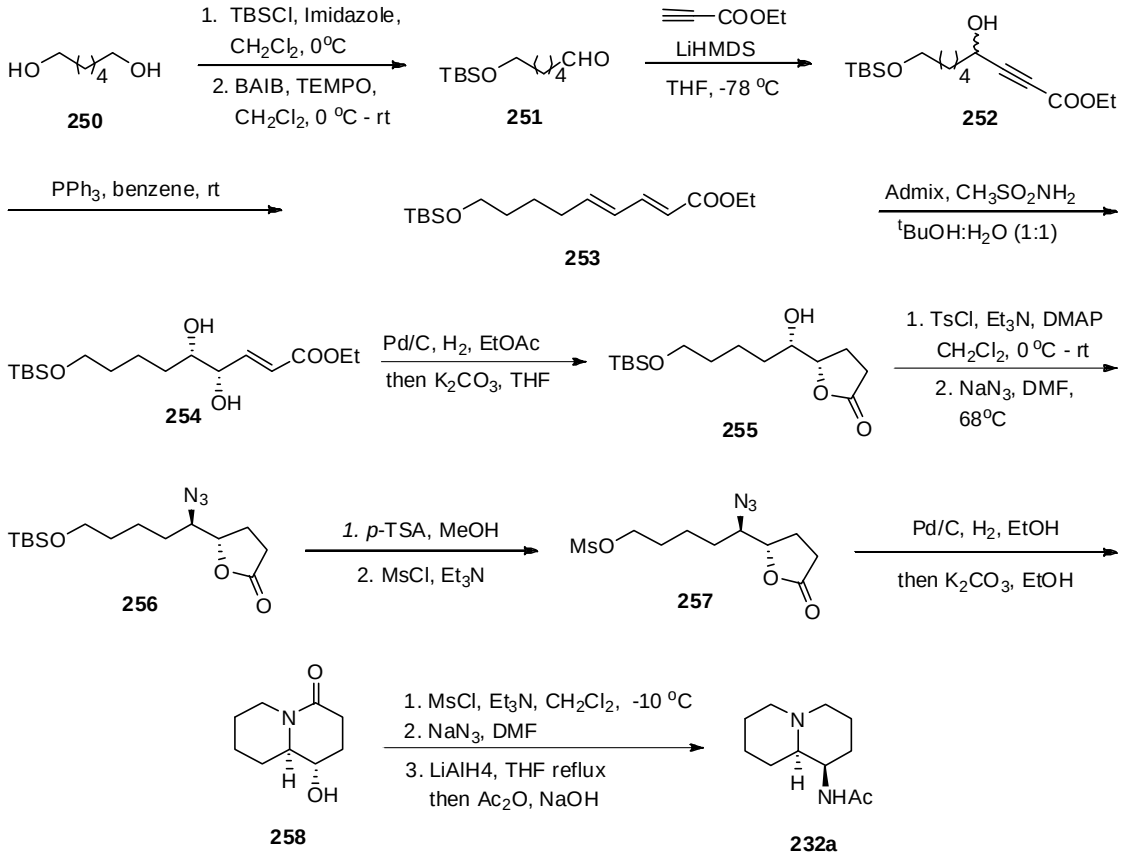
Scheme 2.24 Rutjes's approach

Synthesis started with the transformation of succinic semialdehyde **241** into both enantiomeric forms of the corresponding cyanohydrins **242** using crude cell lysates from rubber tree and almond-containing hydroxynitrile lyases. Chemoezymatic addition of HCN provided both cyanohydrins in excellent yields and very good enantioselectivity (95% ee) using an (*S*)-selective HNL from *Heveca brasiliensis*(*Hb*HNL) and an (*R*)-selective HNL from *Prunus amygdalus* (*Pa*HNL). TBS protected (*S*)-cyanohydrin **242** under reductive amination conditions provided the corresponding *N, N*-acetal **243** as a 2:1 mixture of *cis/trans*-isomers. This was treated with $NaNO_2$ in neat acetic acid to provide *N,O*-acetal **244** a suitable precursor for N-acyliminium ion. *N, O*-acetal **244** was treated with allyltrimethylsilane in presence of $BF_3{\cdot}OEt_2$ to give compound **245** (4.2:1 mixture of *cis*/*trans*-isomers). *Cis* isomer **245** was treated with NaH and allyl bromide to furnish

compound **246**, which was transformed into the bicyclic lactam **247** via RCM followed by hydrogenation. Deprotection of the TBS ether, followed by Swern oxidation, gave the bicyclic ketone **248**. Reductive amination of ketone **248** with benzyl amine provided the desired compound **249** in 70% *ee*. Lacatm **303** was reduced using LAH followed by the acetylation of secondary amine and benzyl deprotection to afford the final product (+)-epiquinamide **232** in 70% *ee*.

2B. 2. 3 Synthesis by Chandrasekhar et al.

In 2009, Chandrasekhar and co-workers[33] disclosed the total synthesis of (-)-epiquinimide **232a** which involved hydroxy propiolate rearrangement to conjugated diene and Sharpless asymmetric dihydroxylation.



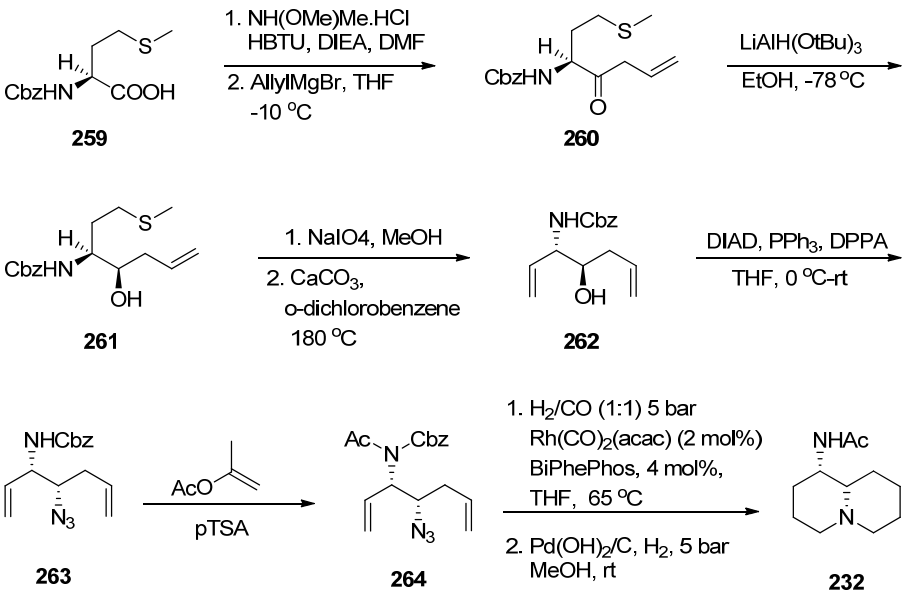
Scheme 2.25 Chandrasekhar's approach

Synthesis started with the conversion of diol **250** to aldehyde **251**. The lithiated ethyl propiolate was added to aldehyde **251** to afford hydroxy ethyl propiolate **252**.This was ready for an 'allene'-type rearrangement in the presence of PPh_3. The hydroxy ethyl propiolate **252** was treated with PPh_3 in benzene under refluxing condition to provide

diene ester **253**. Resulting diene when subjected to Sharpless asymmetric dihydroxylation using AD-mix-α to give the corresponding diol **254** enantioselctively. Alkene **254** was hydrogenated using Pd/C and H_2 followed by the treatment with K_2CO_3 in THF to afford lactone **255**. Hydroxyl group in **255** was converted into azide **256** via tosylation followed by addition of NaN_3. Deprotection of TBS group followed by mesylation and subsequent azide reduction provided the hydroxyl quinolizinone **258**. Finally, hydroxyl quinolizinone was converted into the desired product (-)-epiquinimide **232a**.

2B. 2. 4 Synthesis by Mann et al.

In 2009, Mann and co-workers[34] reported the total synthesis of (+)-epiquinamide using hydroformylation of a bis-homoallylic azide followed by a tandem catalytic hydrogenation/reductive bis-amination



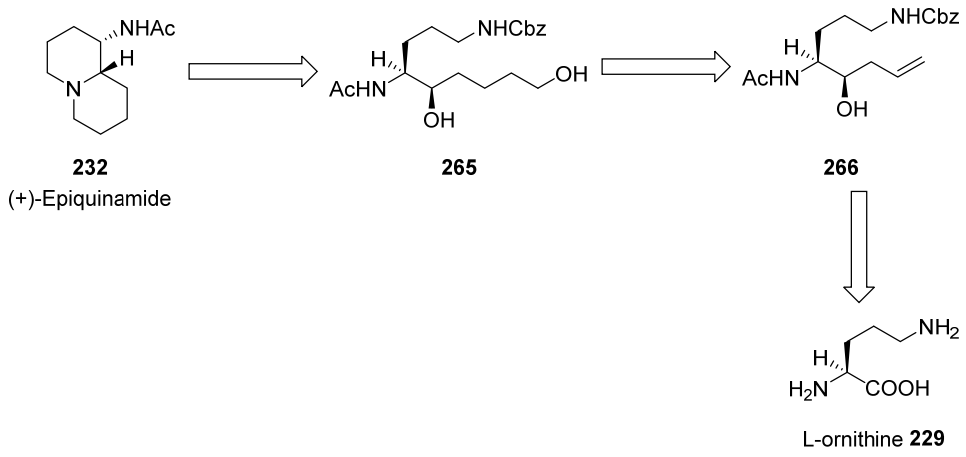
Scheme 2.26 Mann's approach

Synthesis began with the conversion of Cbz-L-methionine **259** to Weinreb amide using standard coupling conditions and subsequent treatment with allylmagnesium chloride afforded the corresponding homoallylic ketone **260** in excellent yield. The desired *anti* amino alcohol **261** was obtained by treating ketone **260** with tris-*tert*-butoxy lithium aluminium hydride in high diastereoselectivity. Oxidation of the sulfide was achieved quantitatively with sodium *meta*-periodate which under thermal treatment of *o*-

dichlorobenzene in the presence of calcium carbonate provided alkene **262**. Secondary alcohol was converted into azide under Mitsunobu reaction conditions. Acetylation of Cbz protected amine was achieved by using isopropenylacetate as solvent under mild acidic conditions using *p*-TSA to afford the desired N-Cbz, N-acetylated product **264**. Finally, compound **264** under hydroformylation conditions gave azido-bis-*δ,δ′*-aldehyde. This when subjected to hydrogenation in the presence of Pearlman's catalyst provided the desired product (+)-epiquinamide **232**.

2B. 3 Present work and Synthetic Planning

As an ongoing research work on aza heterocycles in our laboratory we became interested in the synthesis of (+)-epiquinamide due to its potential bioactivity. As depicted in the retrosynthetic analysis (scheme 2.27), we envisaged that (+)-epiquinamide could be constructed from the amino diol **265**. We believed that diol **265** would be a key intermediate for providing the bicyclic framework *via* mesylation followed by the deprotection of protected amine. Diol **265** could be obtained from L-ornithine derived allylic alcohol **266** using Grubbs' cross metathesis with acrolein followed by reduction. In turn, allylic alcohol **266** could be obtained from commercially available and less expensive L-ornithine **229** *via* Weinreb amide intermediate.



232 (+)-Epiquinamide

265

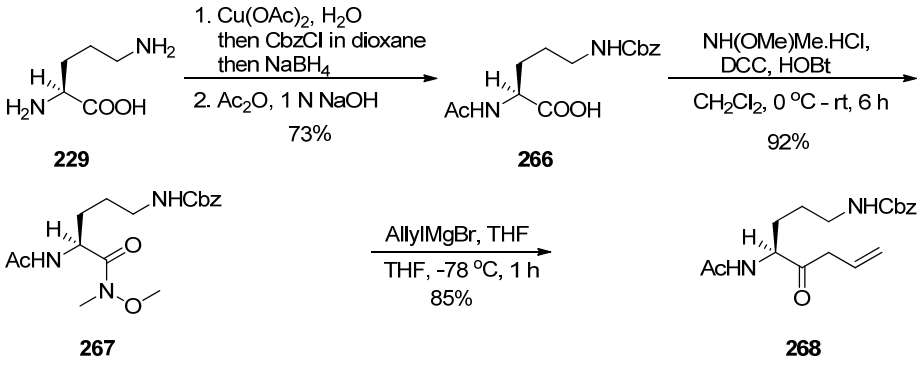
266

L-ornithine **229**

Scheme 2.27 Retrosynthetic Strategy of (+) – epiquinamide

2B. 4 Results and Discussion

Our synthesis started with the protection of commercially available L-ornithine **229**. The protection was achieved in two steps. At first, *δ*-amine in L-ornithine was protected by CbzCl by making copper complex[35] formation using Cu (II) acetate in water. The reaction mixture was stirred 45 min at room temperature followed by the addition of CbzCl in dioxane. After the completion of the reaction copper complex formed was broken down by addition of $NaBH_4$. The resultant black precipitate was filtered off[36] to give the $^{\delta}$N-Cbz protected L-ornithine in quantitative yield. Further, L-N^{δ}-Cbz-ornithine was obtained by precipitating clear filtrate using 10% HCl. α-amine in the L-N^{δ}-Cbz-ornithine was acetylated using acetic anhydride under alkaline condition to afford L- N^{δ}-Cbz-N^{α}-acetyl ornithine **266** in 73% yield. Further, free carboxylic group in **266** was coupled with NH(OMe)Me.HCl using DCC and HOBt in DCM to give the corresponding Weinreb amide **267** in excellent yield.

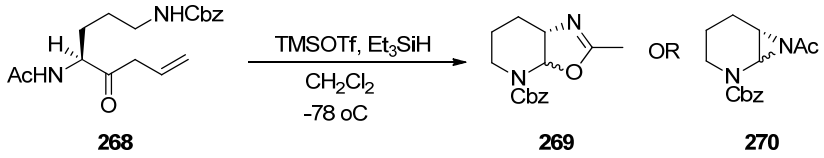


Scheme 2.28 Synthesis of intermediate

This on treatment with the freshly prepared allylmagnesium bromide in THF at -78 ^{o}C to afford the homoallyl ketone **268** in 85% yield. Our next task was to construct the appropriate skeleton for the cylization. We planned to execute the method explored by us previously for the construction of 2, 3-disubstituted piperidines (See Section 2A.6). We believed that ketone **268** is suitable precursor for the reductive cyclization.

Accordingly, ketone **268** was treated with TMSOTf and triethyl silane in dichloromethane at -78 ^{o}C for 1 h. However, interestingly under this optimized reaction condition we obtained an unexpected product which was inseparable and unstable for characterization. Based on the mass spectrum of the sample taken from reaction mixture, we surmised that

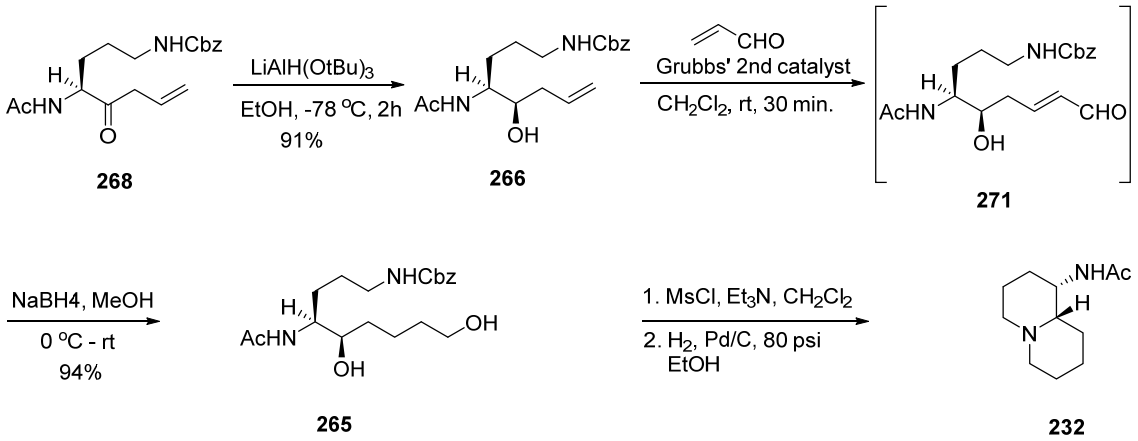
the undesired product may be either compound **269** or **270**. We firmly believed that N-acetyl group might have participated in the neighbouring group participation during the reaction. Difficulty in isolation of this undesired product limited the further exploration of this reaction and product.



268 **269** **270**

Scheme 2.29 Reductive Cyclization attempt

Having ally ketone **268** in hand, we sought an alternative plan to achieve the target (+)-epiquinamide.



268 **266** **271**

265 **232**

Scheme 2.30 Total synthesis of (+)-Epiquinamide

We planned that it would be possible to make bicyclic system in one step by the nucleophilic attack of amine on the two leaving groups simultaneously. In this regard, homoallyl ketone **268** was treated with $LiAlH(OtBu)_3$ in EtOH[37] at -78 °C to afford exclusively single isomer of amino alcohol **266** in 91% yield via stereoselective reduction. The formation of amino alcohol and diastereomeric ratio was confirmed by its ^1H NMR. Having obtained the homoallylic system we planned to explore the cross metathesis strategy. Reaction of amino alcohol **266** with acrolein in presence of Grubbs' first generation catalyst in CH_2Cl_2 at room temperature for 5 h did not proceed. Even, the

refluxing condition did not change the course of the reaction, and we recovered the starting material.

Then we switched to the Grubbs' second generation catalyst for the cross metathesis approach. Amino alcohol **266**, when treated with acrolein using Grubbs' second generation catalyst[38] in CH_2Cl_2 at room temperature afforded the corresponding aldehyde **271**. This aldehyde was immediately reduced with $NaBH_4$ in MeOH to afford diol **265** in 94% yield over two steps. Both the hydroxyl groups in **265** was mesylated using MsCl and Et_3N in DCM to give dimesylated compound. Further diemsyl compound when treated with with 10% Pd/C, H_2 in EtOH at 80 psi provided desired product (+)-epiquinamide **232** in 65% yield over two steps. Initial attempt of hydrogenolysis at atmospheric pressure did not proceed. High pressure reaction was carried out using H-Cube hydrogenator set up. ^1H and ^{13}C data of the compound **232** are in close agreement with the literature value.[39] Specific rotation of compound **232** was in accordance with the reported value $[\alpha]_D^{20}$ = +19.9 (*c* 1, $CHCl_3$) (Lit.[39] $[\alpha]_D^{20}$ = +21 (*c* 1, $CHCl_3$)

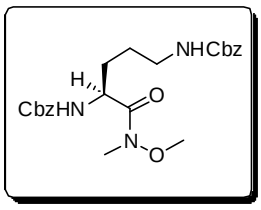
2B. 5 Conlusions

In conclusion, the total synthesis of (+)-epiquinamide was achieved in total 8 steps form the less expensive and commercially available starting material L-ornithine. The strategy involved Grubbs' cross metathesis approach and one pot Cbz deprotection followed by in situ cyclization as key steps.

2B. 6 Experimental Section

General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High resolution mass spectrometry using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in open glass capillary and values are uncorrected.

Weinreb amide (227)



To a cooled and stirred reaction mixture of (*S*)-*N*,*N*-dibenzyloxycarbonylornithin[14] **228** (20 g, 50 mmol), Et_3N(17.4 mL, 125 mmol), HOBt (6.75 g, 50 mmol) followed by DCC (12.37 g, 40.11 mmol) in CH_2Cl_2 (70 mL) were added at 0 ^{o}C and the reaction mixture was stirred for 30 min while maintaining 0 ^{o}C and then allowed to stir at room temperature for 6 h. The precipitate which formed was removed by filtration and the filter cake (residue) was washed with EtOAc. The filtrate was diluted with additional EtOAc, washed with saturated aqueous $NaHCO_3$, water, 5% HCl, and brine solution. The solution was dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated in *vacuo* to give weinreb amide which was purified over silica gel using column chromatography (EtOAc:Pet.Ether, 3:7) to furnish pure weinerb amide **227** as a white solid (20.34 g, 90% yield).

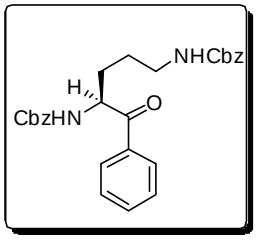
R_f = 0.3 Pet. Ether:EtOAc (50:50); $[\alpha]_D^{25}$ = - 4 (*c* 1, $CHCl_3$), mp = 69-71 ^{o}C; IR(cm^{-1}): 3340, 1690; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 10H), 6.01 (bs, 1H), 5.38 (bs, 1H), 5.21–4.92 (m, 4H), 4.70 (s, 1H), 3.69 (s, 3H), 3.13 (m, 5H), 1.82–1.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.43, 156.34, 156.15, 136.56, 136.25, 128.33, 127.96,

127.92, 127.85, 66.61, 66.33, 61.41, 50.54, 40.42, 31.83, 29.61, 25.62; HRMS (ESI) Calcd. for $C_{23}H_{29}N_3O_6Na$ $(M+Na)^+$:466.1954 found, 466.1954.

General procedure A for the preparation of ketones (226) from weinreb amide (227):

To a solution of Weinreb amide **7 (**0.221 g**,** 0.5 mmol) in 2 mL of dry THF at –78 °C was added freshly prepared arylmagnesium bromide (2 mmol, 4 equiv.) and the solution was allowed to warm to 0 °C. After the completion of the reaction (monitored by TLC), 1N HCl (5 mL) was added. The resultant mixture was then extracted with EtOAc (3 X 20 mL) and the combined organic layers were washed with saturated brine solution (2 X 20 mL), filtered and concentrated to give crude ketone which was purified over silica gel using column chromatography (EtOAc:Pet.Ether, 3:7) to furnish desired ketone (**226a-226i**).

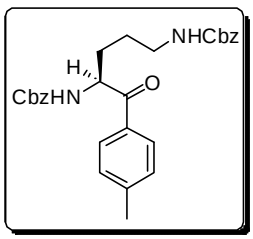
(*S*)-N, N' dibenzyl (5-oxo-5-phenylpentane-1,4-diyl)dicarbamate (226a):



The title compound **226a** was synthesized according to the general procedure A for ketones from weinreb amide **227** and phenylmagnesium bromide. Product was isolated as a white solid (0.185 g, 81% yield)

R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +24 (*c* 1, $CHCl_3$), mp = 101-103 ^oC; IR (cm^{-1}): 3320, 1676, 1545. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.25 (m, 10H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 5.16 – 4.99 (m, 4H), 4.77 (s, 1H), 3.24-3.10 (m, 2H), 1.98-1.88 (m, 1H), 1.75 – 1.40 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.60, 156.50, 156.24, 136.62, 136.37, 134.29, 134.15, 129.11, 128.76, 128.68, 128.64, 128.33, 128.23, 127.76, 127.11, 67.16, 66.79, 65.48, 55.20, 40.73, 31.04, 25.60 HRMS (ESI): Calcd.for $C_{27}H_{28}N_2O_5Na$ $(M+Na)^+$: 483.1896 found, 483.1896

(*S*)- N, N' dibenzyl 5-oxo-5-(p-tolyl)pentane-1,4-diyldicarbamate (226b):

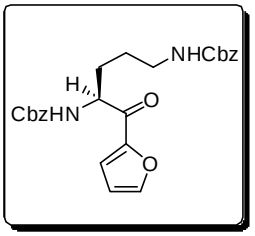


The title compound **226b** was synthesized according to the general procedure A for ketone from weinreb amide **227** and *p*-methylphenylmagnesium bromide. Product was isolated as white solid. (0.19 g, 80% yield)

R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +49 (*c* 1, $CHCl_3$), mp = 83-85 ^oC, IR (cm^{-1}) 3326, 1704, 1689, 1531. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* =

7.9 Hz, 2H), 7.40 – 7.18 (m, 12H), 5.83 (d, *J* = 7.6 Hz, 1H), 5.38-5.30 (m, 1H), 5.09 and 5.04 (2s, 4H), 4.79 (s, 1H), 3.17-3.11 (m, 2H), 2.4(s, 3H), 1.96-1.87 (m, 1H), 1.74 – 1.51 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 198.08, 156.47, 156.21, 145.19, 136.64, 136.39, 131.71, 129.79, 128.88, 128.74, 128.65, 128.62, 128.29, 128.20, 67.09, 66.75, 55.06, 40.76, 31.23, 25.54, 21.86. HRMS (ESI) Calcd.for $C_{28}H_{31}N_2O_5$ $(M+H)^+$:475.2233 found, 475.2237.

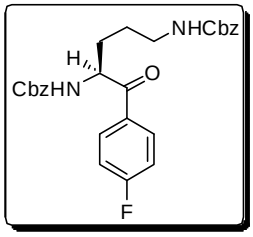
(S)- N, N' dibenzyl (5-(furan-2-yl)--5-oxopentane-1,4-diyl)dicarbamate (226c):



To a stirred solution of furan (0.81 g, 12 mmol) in dry THF at -78 ^oC was added n-BuLi (5.3 mL, 8.57 mmol, 1.6 M solution in hexane) and the reaction mixture was stirred for 30 minutes maintaining the temperature. The resulting reaction mixture was transferred to solution of Weinreb amide **227** (0.76 g, 1.71 mmol) in THF at -78^oC *via* cannula. After which the reaction mixture was allowed to warm to room temperature. After complete consumption of weinreb amide **227**, the reaction mixture was quenched with 1N HCl. The resultant mixture was then extracted with EtOAc (3 X 20 mL) and the combined organic layers were washed with brine solution (saturated NaCl) (1 X 40 mL), filtered and concentrated to give the corresponding crude ketone which was purified over silica gel using column chromatography (EtOAc:Pet.Ether, 3:7) to furnish desired furanyl ketone **226c** as a dark grey solid (0.17 g, 77% yield).

R_f = 0.5 Pet. Ether:EtOAc (50:50), mp = 94-96 ^oC; IR(cm^{-1}) 3330, 1706, 1692, 1546.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.40–7.20 (m, 11H), 6.50 (s, 1H), 5.89 (d, *J* = 7.8 Hz, 1H), 5.05 (m, 6H), 3.27–2.92 (m, 2H), 1.89 (s, 1H), 1.60 (dq, *J* = 7.5, 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.19, 156.47, 156.08, 150.59, 147.42, 136.56, 136.23, 128.46, 128.12, 128.02, 119.32, 112.68, 66.94, 66.54, 55.51, 40.47, 30.34, 25.69; HRMS(ESI): Calcd. for $C_{25}H_{26}N_2O_6Na$ $(M+Na)^+$: 473.1689 found 473.1684.

(*S*)- N, N' dibenzyl 5-(4-fluorophenyl)-5-oxopentane-1,4-diyldicarbamate (226d):

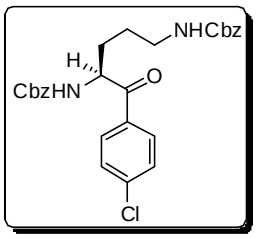


The title compound **8d** was synthesized according to the general procedure A for ketones from weinreb amide **227** and *p*-fluorophenylmagnesium bromide. Product was isolated as a white solid (0.178 g, 75%).

R_f = 0.5 Pet. Ether: EtOAc (50:50); $[\alpha]_D^{25}$ = +28.1 (*c* 1, $CHCl_3$), mp

= 95-96 °C; IR (cm^{-1}) 3370, 1706, 1677, 1516 ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.32 (m, 10H), 7.14 (t, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 5.1 (s, 2H), 5.0 (s, 2H), 4.76 (bs, 1H), 3.17 (bs, 2H), 1.93 (m, 1H), 1.58 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.13, 167.49, 164.93, 156.50, 156.19, 136.55, 136.26, 131.50, 131.41, 130.70, 128.58, 128.55, 128.25, 128.12, 116.31, 116.09, 67.09, 66.68, 55.00, 40.56, 30.68, 25.61. HRMS (ESI): Calcd. for $C_{27}H_{27}N_2O_5FNa$ $(M+Na)^+$: 501.1802 found, 501.1797.

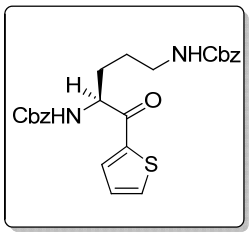
(S)- N, N' dibenzyl (5-(4-chlorophenyl)-5-oxopentane-1,4-diyl)dicarbamate(226e):



The title compound **226e** was synthesized according to the general procedure A for ketones from weinreb amide **227** and *p*-chlorophenylmagnesium bromide. Product was isolated as a white solid (0.19 g, 77% yield).

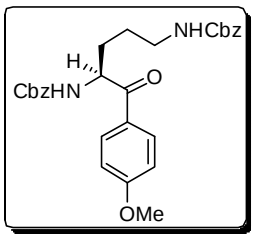
R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +22.8 (*c* 1, $CHCl_3$), mp = 99-101 °C; IR(cm^{-1}) 3335, 1677, 1656, 1531. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 10H), 5.73 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 4.76 (bs, 1H), 3.17 (bm, 2H), 1.92 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.51, 156.51, 156.20, 140.71, 136.57, 136.27, 132.62, 130.17, 129.48, 128.70, 128.67, 128.38, 128.25, 67.25, 66.84, 55.13, 40.66, 34.07, 30.90, 25.66; HRMS (ESI): Calcd. for $C_{27}H_{28}N_2ClO_5$ $(M+H)^+$: 495.1686 found, 495.1684.

(S)- N, N' dibenzyl 5-oxo-5-(thiophene-2-yl)pentane-1,4-diyldicarbamate (226f):



The title compound **226f** was synthesized according to the general procedure A for ketones from weinreb amide **227** and 2-thiophenemagnesium bromide. Product was isolated as a white solid (0.17 g, 73% yield). R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +26 (*c* 1, $CHCl_3$), mp = 98-99 °C; IR(cm^{-1}) 1685, 1667, 1515. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.71 (d, *J* = 4.6 Hz, 1H), 7.41–7.28 (m, 10H), 7.20–7.12 (m, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 5.28–5.13 (m, 1H), 5.10 and 5.07 (2s, 4H), 4.85 (m, 1H), 3.20 (bm, 3H), 2.05–1.92 (m, 1H), 1.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.29, 156.53, 156.11, 141.29, 136.62, 136.29, 135.36, 133.44, 128.67, 128.65, 128.34, 128.23, 67.20, 66.80, 56.12, 40.70, 31.57, 25.81; HRMS (ESI) Calcd.for $C_{25}H_{26}N_2O_5SNa$ $(M+Na)^+$:489.1460 found 489.1463.

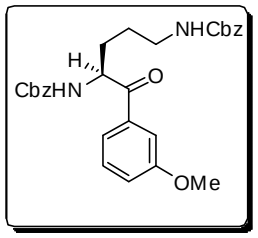
(*S*)- N, N' dibenzyl 5-(4-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (226g):



The title compound **226g** was synthesized according to the general procedure A for ketones from weinreb amide **227** and *p*-methoxyphenylmagnesium bromide. Product was isolated as a colorless oil (0.2 g, 83%). R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +28.4 (*c* 1, $CHCl_3$); IR(cm^{-1}) 3320, 1706, 1646, 1531. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.41–7.27 (m, 10H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.83 (d, *J* = 7.8 Hz, 1H), 5.31 (bm, 1H), 5.1 and 5.0 (2s, 4H), 4.79 (bs, 1H), 3.86 (s, 3H), 3.16 (bm, 2H), 2.02–1.84 (m, 1H), 1.69–1.52 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.83, 164.37, 1546.48, 156.2, 136.42, 131.1, 128.67, 128.65, 128.31, 128.22, 127.0, 114.3, 67.1, 66.7, 55.7, 54.7, 40.8, 31.4, 22.5; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_6Na$ $(M+Na)^+$: 513.2002 found 513.1993.

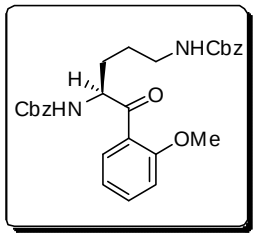
(*S*)- N, N' dibenzyl 5-(3-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (226h):

The title compound **226h** was synthesized according to the general procedure A for ketones from weinreb amide **227** and *meta*-methoxyphenylmagnesium bromide. Product was isolated as colorless oil (0.198 g, 81%) R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +22.8 (*c* 1, $CHCl_3$), IR(cm^{-1}) 3340, 1692, 1666, 1517. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51



(d, *J* = 7.4 Hz, 1H), 7.45 (s, 1H), 7.41 – 7.26 (m, 11H), 7.13 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.82 (d, *J* = 7.8 Hz, 1H), 5.41 – 5.27 (m, 1H), 5.1 and 5.07 (2s, 4H), 4.81 (s, 1H), 3.83 (s, 3H), 3.16 (m, 2H), 1.94 (m, 1H), 1.66–1.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.43, 160.15, 156.47, 156.18, 136.62, 136.35, 135.63, 130.09, 128.67, 128.63, 128.32, 128.22, 121.26, 120.72, 112.86, 67.15, 66.77, 55.61, 55.32, 40.73, 31.08, 25.59.HRMS (ESI): Calcd. for $C_{28}H_{3O}N_2O_6Na$ $(M+Na)^+$: 513.2002 found 513.1992.

(*S*)- N, N' dibenzyl 5-(2-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (226i):



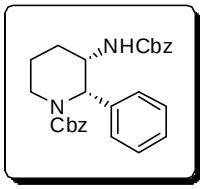
The title compound **226i** was synthesized according to the general procedure for ketones from weinreb amide **227** and *ortho*-methoxyphenylmagnesium bromide. Product was isolated as white solid (0.173 g, 71%). R_f = 0.5 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = +10 (*c* 1, $CHCl_3$), mp= 97-99 ^oC; IR(cm^{-1}) 1706, 1680, 1560; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.3 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.37 – 7.26 (m,

10H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 5.44 (m, 1H), 5.07 (2s , 4H), 4.80 (s, 1H), 3.89 (s, 3H), 3.14 (s, 2H), 1.90 (m, 1H), 1.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.52, 158.78, 156.37, 134.85, 131.45, 128.66, 128.24, 124.92, 121.22, 111.88, 66.99, 66.72, 59.49, 55.85, 40.86, 30.28, 29.84, 25.84 HRMS (ESI): Calcd.for $C_{28}H_{30}N_2O_6Na$ $(M+Na)^+$: 513.2002 found 513.2003.

General procedure B for Cyclization:

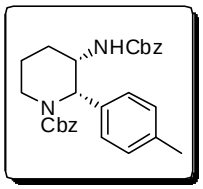
To a stirred solution of ketone (**226a-226i**) (0.5 mmol) in CH_2Cl_2 (1 mL) at -78 °C were added successively Et_3SiH (0.6 mmol), TMSOTf (0.6 mmol), and the reaction mixture was stirred for 30 min maintaining the temperature. After which the reaction mixture was allowed to warm to room temperature. After complete consumption of starting material (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, and dried over anhydrous Na_2SO_4 and concentrated to give cyclized product (2, 3-disubstituted piperidine) which was purified over silica gel using column chromatography (EtOAc:Pet.Ether, 2:8) to furnish 2, 3-disubstituted piperidine derivative (**225a-225i**).

(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-phenylpiperidine-1-carboxylate (225a):



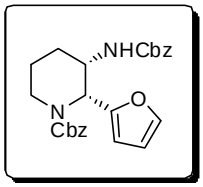
Synthesized according to the general procedure B. Product was isolated as white solid (0.18 g, 81% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$= -2 (*c* 1, $CHCl_3$), mp = 127-129 ^oC; IR (cm^{-1}): 3390, 1691.1518. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 13H), 7.17 (bm, 2H), 5.44 (d, *J* = 6.4 Hz, 1H), 5.21–4.90 (m, 4H), 4.35 (d, *J* = 9.1 Hz, 1H), 4.21–4.04 (m, 2H), 3.22 (m, 1H), 1.93-1.85 (m, 2H), 1.81–1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.86, 155.47, 138.36, 136.65, 136.43, 129.24, 128.66, 128.51, 128.33, 127.98, 127.85, 67.42, 66.92, 57.43, 50.17, 40.52, 26.14, 24.13; HRMS (ESI): Calcd. for $C_{27}H_{29}N_2O_4$ $(M+H)^+$:445.2127 found 445.2128.

(2S,3S)-benzyl 3-(benzyloxycarbonylamino)-2-(*p*-tolyl)piperidine-1-carboxylate (225b):



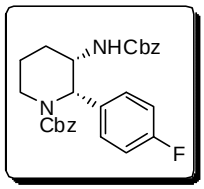
Synthesized according to the general procedure B. Product was isolated as colorless oil (0.176 g, 77% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -4.1 (*c* 1, $CHCl_3$); IR(cm^{-1}): 3329, 1695, 1516. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.25 (m, 8H), 7.19 (m, 4H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 6.3 Hz, 1H), 5.20 – 4.93 (m, 4H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.12 (m, 2H), 3.20 (t, *J* = 12.9 Hz, 1H), 2.32 (s, 3H), 1.89 (d, 2H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.81, 155.46, 137.61, 136.70, 136.46, 135.17, 129.38, 129.21, 128.65, 128.49, 128.32, 127.96, 127.86, 77.48, 77.16, 76.84, 67.38, 66.89, 57.16, 50.16, 40.38, 26.24, 24.17, 21.14. HRMS (ESI) Calcd.for $C_{28}H_{31}N_2O_4$ $(M+Na)^+$: 459.2284 found, 459.2285

(*2R,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(furan-2-yl)piperidine-1-carboxylate (225c):



Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.160 g, 74% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -19.6 (*c* 1, $CHCl_3$); IR(cm^{-1}): 3326, 1694, 1516. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.27 (m, 10H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.16 (bs, 1H), 5.45 (bs, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 5.21-5.01 (m, 4H), 4.39 (s, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 2.92 (t, *J* = 12 Hz , 1H), 1.84 – 1.75 (m, 2H), 1.67 – 1.59 (m, 2H), 1.56 – 1.47 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.59, 151.0, 142.19, 136.34, 128.71, 128.62, 128.41, 110.48, 107.69, 67.55, 67.06, 54.61, 46.99, 40.20, 24.59, 19.73; HRMS (ESI): Calcd. For $C_{25}H_{26}N_2O_5Na$ $(M+Na)^+$: 457.1739 found 457.1742.

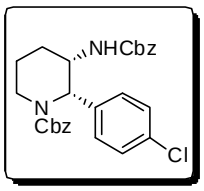
(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(4-fluorophenyl)piperidine-1-carboxylate (225d):



Synthesized according to the general procedure B. Product was isolated as a white solid (0.184 g, 80% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -2.1 (*c* 1, $CHCl_3$), mp= 139-141 ^oC; IR(cm^{-1}) 3322, 1692, 1656, 1529; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.23 (m, 13H), 6.95 (t, *J* = 8.6 Hz, 2H), 5.46 (d, *J* = 6.4 Hz, 1H), 5.21–4.94 (m, 4H), 4.32 (d, *J* = 8.6 Hz, 1H), 4.13 (d, *J* = 11.9 Hz, 2H), 3.20 (t, *J* = 14.7 Hz, 1H), 1.98-1.87 (m, 2H), 1.86 – 1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.82, 155.42, 136.57, 136.38, 130.85, 130.77, 128.70,

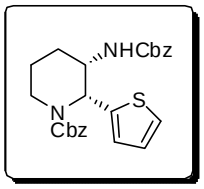
128.55, 128.42, 128.09, 127.94, 115.66, 115.45, 67.50, 66.99, 56.76, 50.12, 40.41, 26.00, 24.05; HRMS (ESI) Calcd. for $C_{27}H_{28}FN_2O_4$ $(M+H)^+$: 463.2033 found 463.2037.

(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(4-chlorophenyl)piperidine-1-carboxylate (225e):



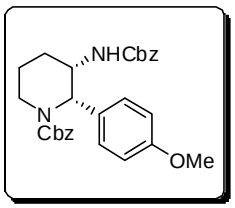
Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.198 g, 83% yield).
R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -4.6 (*c* 1, $CHCl_3$); IR(cm^{-1}): 3341, 1694, 1646, 1530; ^{1}HNMR: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 10H), 7.20 (d, *J* = 2.7 Hz, 3H), 7.17 (s, 2H), 5.43 (d, *J* = 6.5 Hz, 1H), 5.16 – 4.87 (m, 4H), 4.33 (d, *J* = 8.8 Hz, 1H), 4.15-4.04 (m, 2H), 3.22-3.14 (m, 1H), 1.91-1.83 (m, 2H),1.78-1.68 (m, 1H), 1.67-157 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 155.82, 155.40, 137.00, 136.49, 136.33, 133.80, 130.44, 128.69, 128.77, 128.53, 128.42, 128.37, 128.09, 127.92, 127.84, 67.52, 67.52, 67.00, 56.84, 50.06, 40.56, 25.89, 23.98; HRMS (ESI): Calcd. for $C_{27}H_{28}ClN_2O_4$ $(M+H)^+$: 479.1738 found, 497.1746.

(2R,3S)-Benzyl 3-(benzyloxycarbonylamino)-2-(thiophen-2-yl) piperidine-1 carboxylate (225f)



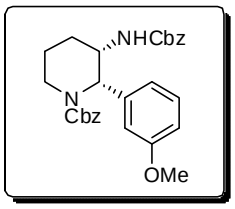
Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.17 g, 76% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$= -16.7 (*c* 1, $CHCl_3$); IR(cm^{-1}): 3390, 1694, 1518; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 10H), 6.98 – 6.92 (m, 1H), 5.63 (s, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 5.18 – 5.03 (m, 4H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.18 – 3.99 (m, 2H), 3.08 – 2.92 (m, 2H), 1.94 – 1.77 (m, 2H), 1.68 – 1.56 (m, 1H), 1.52-1.47(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.29, 155.62, 141.55, 136.46, 136.32, 128.73, 128.65, 128.43, 128.22, 127.94, 127.20, 125.09, 124.92, 67.74, 67.10, 56.23, 48.89, 39.68, 24.01, 19.73.HRMS (ESI) Calcd. for $C_{25}H_{26}N_2O_4SNa(M+Na)^+$: 473.1511 found, 473.1511.

(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(4-methoxyphenyl)piperidine-1-carboxylate (225g):



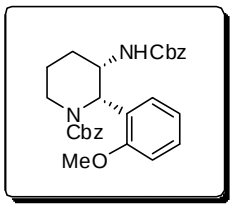
Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.187 g, 79% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -24.1 (*c* 1, $CHCl_3$); IR(cm^{-1}) 3329, 1695, 1516. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.24 (m, 10H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.44 (s, 1H), 5.30 (m, 1H), 5.20–5.05 (m, 4H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.20–4.09 (m, 1H), 3.80 (s, 3H), 2.89 (t, *J* = 11.3 Hz, 1H), 1.73 -1.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.69, 156.87, 155.78, 136.62, 136.40, 129.01, 128.72, 128.63, 128.40, 128.14, 127.83, 127.57, 114.31, 67.04, 58.20, 55.42, 48.05, 39.88, 23.69, 19.83. HRMS (ESI) Calcd.for $C_{28}H_{31}N_2O_5$ $(M+H)^+$: 475.2233 found, 475.2237.

(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(3-methoxyphenyl)piperidine-1-carboxylate (225h):



Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.184 g, 78% yield). R_f = 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -10 (*c* 1, $CHCl_3$), IR(cm^{-1}): 3331, 1692, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 9H), 7.20 (s, 2H), 6.86 (m, 3H), 5.42 (d, *J* = 5.8 Hz, 1H), 5.18 – 4.95 (m, 4H), 4.44 (d, *J* = 8.8 Hz, 1H), 4.18 – 4.05 (m, 2H), 3.69 (s, 3H), 3.28 – 3.17 (m, 1H), 1.98 – 1.83 (m, 2H), 1.83 – 1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.66, 155.84, 155.48, 139.84, 136.63, 136.40, 129.64, 128.66, 128.57, 128.51, 128.32, 128.20, 127.99, 127.90, 121.31, 115.37, 113.11, 67.44, 66.92, 57.40, 55.24, 50.07, 40.48, 26.17, 24.10. HRMS (ESI): Calcd. for $C_{28}H_{31}N_2O_5Na$ $(M+Na)^+$: 497.2052 found, 497.2051.

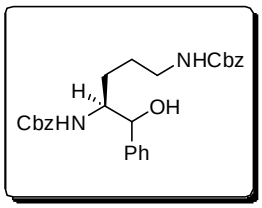
(*2S,3S*)-benzyl 3-(benzyloxycarbonylamino)-2-(2-methoxyphenyl)piperidine-1-carboxylate (225i):



Synthesized according to the general procedure B. Product was isolated in 72% yield as colorless viscous oil (0.17g, 72% yield). R_f= 0.6 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = + 2.6 (*c* 1, $CHCl_3$), IR(cm^{-1}): 3428, 1695, 1413; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.33(m, 5H), 7.25-7.21(m, 4H), 7.16-7.08(m, 3H), 6.91-6.85 (m, 2H), 5.43 (d, *J* = 2.5 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 5.11-5.06 (m, 4H), 4.5 (bs, 1H),4.28-4.21(m, 1H) , 3.8(s,

3H), 3.35-3.28(m, 1H), 1.80-1.71(m, 2H), 1.64-1.58(m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.95, 156.71, 145.16, 136.56, 131.09, 130.43, 128.62, 128.43, 128.22, 127.87, 127.55, 126.90, 120.44, 110.90, 67.28, 66.75, 56.56, 55.40, 41.52, 41.26, 23.98, 19.21. HRMS(ESI): Calcd. for $C_{28}H_{31}N_2O_5Na$ $(M+Na)^+$: 497.2052 found, 497.2045.

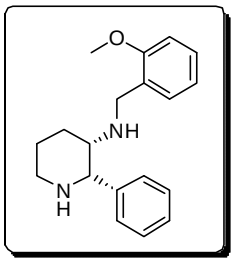
Synthesis of 1, 2-amino alcohol (230):



$BF_3{\cdot}OEt_2$ (0.192 mL, 1.53 mmol) was added to a solution of Et_3SiH (0.6 g, 5.1 mmol) in CH_2Cl_2 (2 mL) at room temperature. The solution was stirred for 5 min, and then transferred *via* cannula to a stirred solution of ketone **226a** (0.2 g, 0.51 mmol) in CH_2Cl_2 (5 mL) at -78 ^oC. The reaction mixture was stirred at -78 ^oC for 1 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 1 h. The reaction mixture was re-cooled to -78^oC and poured into a mixture of saturated aqueous $NaHCO_3$. The organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid **230** (0.184 g, 92% yield).

R_f = 0.4 Pet. Ether:EtOAc (50:50), $[\alpha]_D^{25}$ = -27.8 (*c* 1, $CHCl_3$); mp=116-117 ^oC; IR(cm^{-1}) 3290, 1686, 1545; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 – 7.07 (m, 16H), 7.04 (d, *J* = 9.2 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 5.06 – 4.76 (m, 4H), 4.45 (t, *J* = 5.5 Hz, 1H), 3.52 (m, 1H), 2.90 (m, 2H), 1.63 – 1.11 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.07, 155.81, 143.68, 137.41, 137.32, 128.37, 128.29, 127.75, 127.69, 127.56, 127.26, 126.71, 126.54, 74.69, 65.13, 64.82, 56.78, 40.48, 26.55, 26.39 HRMS (ESI): Calcd. for $C_{27}H_{30}N_2O_5Na$ $(M+Na)^+$:485.2052 found 485.2055.

Asymmetric synthesis of (+)-CP-99,994

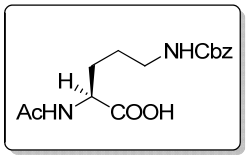


A mixture of **225a** (0.4 g, 0.87 mmol), and Pd/C (10%, 0.100 g), in MeOH (5 mL) was stirred under an atmosphere of H_2 at rt for 6 h. The crude mixture was filtered through a pad of celite and the filtrate was concentrated under vacuum to give crude diamine. To a solution of the crude diamine in CH_2Cl_2 (5 mL) and 2-methoxybenzaldehyde (0.118 g, 0.87 mmol) was added $NaBH(OAc)_3$ (0.276 g, 1.30 mmol) and the resulting mixture was stirred under an argon atmosphere for 20 h at room temperature. Saturated aqueous Na_2CO_3 solution (10 mL) was added and the organic layer was dried over

Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a mixture of $CHCl_3$/MeOH (80:20) as eluent to give **138** (0.21 g, 75%) as a pale yellow oil.

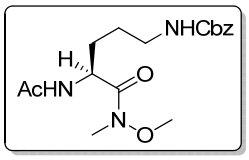
R_f = 0.6 Pet. DCM:MeOH (20:80), $[\alpha]_D^{25}$= +66.7 (*c* 1, $CHCl_3$); IR(cm^{-1}): 3328, 2923, 1465.[Lit.[7d] $[\alpha]_D^{25}$= +67.2 (1, $CHCl_3$)] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.21 (m, 5H), 7.16 (td, *J* = 7.9, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.81 (td, *J* = 7.3, 0.8 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 3.91 (d, *J* = 2.2 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.43(s, 3H), 3.34–3.27 (m, 1H), 2.87–2.82 (m, 2H), 2.6 (bs, 2H), 2.14 (d, *J* = 12.5 Hz, 1H), 2.06-1.92(m, 1H), 1.65-1.57(m, 1H), 1.43 (d, *J* = 13.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 141.5, 129.9, 128.4, 128.2, 127.5, 127, 126.4, 120.2, 109.9, 63.8, 54.9, 54.7, 47.6, 46.8, 27.9, 20.0 HRMS (ESI): Calcd. for $C_{19}H_{25}N_2O$ $(M+H)^+$: 297.1967 found, 297.1969.

(S)-2-acetamido-5-(((benzyloxy) carbonyl) amino) pentanoic acid (266):



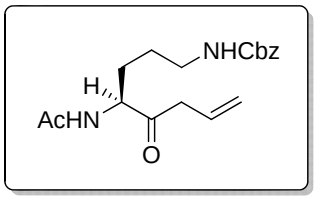
L-Ornithine hydrochloride **229** (20, 118.6mmol) and copper (II) acetate (11.84, 59.3mmol) were dissolved in 90 mL of 10% aq. sodium carbonate, and the solution was vigorously stirred for 45 minutes. To the stirred solution were added 200 mL of water and 200 mL of 1,4-dioxane, followed by slow addition of a solution of CbzCl (18.56mL, 130.47mmol) in 100 mL of 1,4-dioxane. After 6 hr, $NaBH_4$ (5.38g, 142.33mmol) was added slowely after 15 min, the copper (I) oxide precipitate formed was filtered. The clear, colorless filtrate was neutralized with dilute HCl in cold condition. L- N^{δ}-Cbz ornithine was precipitated and was filtered and washed with water. L- N^{δ}-Cbz ornithine was dissolved in 1N NaOH and to this solution acetic anhydride (14.52 g, 142.33mmol) was added and raction mixture was stirred for 3 hr at rt. Ethyl acetate was added and aqueous layer was extracted with EtOAc washed with brine, dried over anhydrous sodium sulphate and evaporated in vaccuo to afford L- N^{δ}-Cbz-N^{α}-acyl ornithine **266**. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.38 – 7.23 (m, 5H), 5.08 (s, 2H), 4.27 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.98 (s, 3H), 1.91 – 1.79 (m, 1H), 1.72 – 1.60 (m, 1H), 1.62 – 1.49 (m, *J* = 14.3, 7.0 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 173.0, 158.9, 138.4, 129, 128.92, 128.7, 67.3, 55.2,41.5, 30.7, 27.4, 22.6. HRMS (ESI) Calcd.for $C_{15}H_{20}N_2O_5Na$ $(M+Na)^+$: 331.1269 found, 331.1266

(S)-benzyl (4-acetamido-5-(methoxy(methyl)amino)-5-oxopentyl)carbamate (267):



To a cooled and stirred reaction mixture of (*S*)-*N*, *N*-dibenzyloxycarbonylornithin **266** (20 g, 50 mmol), Et_3N (17.4 mL, 125 mmol), HOBt (6.75 g, 50 mmol) followed by DCC (12.37 g, 40.11 mmol) in CH_2Cl_2 (70 mL) were added at 0 ^oC and the reaction mixture was stirred for 30 min while maintaining 0 ^oC and then allowed to stir at room temperature for 6 h. The precipitate which formed was removed by filtration and the filter cake (residue) was washed with EtOAc. The filtrate was diluted with additional EtOAc, washed with saturated aqueous $NaHCO_3$, water, 5% HCl, and brine solution. The solution was dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated in *vacuo* to give weinreb amide which was purified over silica gel using column chromatography (EtOAc:Pet.Ether, 3:7) to furnish pure Weinerb amide **267** as a white solid (20.34 g**,** 92% yield). $[\alpha]_D^{25}$ = -2.9 (*c* 1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.60 – 6.40 (m, 1H), 5.14 – 4.96 (m, 4H), 3.73 (s, 3H), 3.27 – 3.09 (m, 5H), 1.99 (s, 3H), 1.80 – 1.68 (m, 1H), 1.64 – 1.43 (m, 3H).^{13}C NMR (101 MHz $CDCl_3$) δ 172.5, 170.3, 156.6, 136.7, 128.6, 128.2, 128.2, 66.7, 61.8, 48.8, 40.8, 32.1, 30.2, 25.8, 23.3. HRMS (ESI) Calcd.for $C_{17}H_{25}N_3O_5Na$ $(M+Na)^+$: 374.1691 found, 374.1692.

(S)-benzyl (4-acetamido-5-oxooct-7-en-1-yl) carbamate (268):

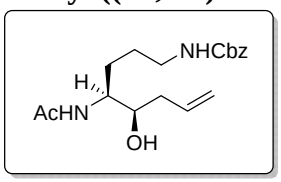


To a three necked oven dried round bottom flask was added freshly activated Mg (9.68 g, 398.65 mmol), dry Et_2O (50 mL) and a pinch of Iodine under Argon atmoshpere. Allyl bromide (24.15 mL, 284.5 mmol) in Et_2O (50 mL) was added to this solution drop-wise over 50 minuite. Rate of addition of allyl bromide was controlled in such a way that temperature of the solution remains below 30 ^oC. After addition solution was sirred for 1 hr. In another round bottom flask Et_2O was added to weinreb amide **267** (20 g, 56.95 mmol) under argon and cooled to -78^oC. Allyl magnesium bromide solution was transferred to this solution via cannula and cooling bath was removed and reaction mixture stirred for 30 minuite. Upon cooling to 0 ^oC 1 N HCl was added and aqueous layer was extracted with Et_2O (3 X 50 ml), washed with brine, dried over anhydrous sodium sulphate and evaporated in vaccuo to afford ketone **268**.

$[\alpha]_D^{25}$ = +33 (*c* 1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 7.10 – 6.95 (m,0. 3H), 6.45 – 6.31 (m, 1H), 6.19 (d, 0. 4H), 5.94 – 5.82 (m, 0.6H), 5.23 – 5.15 (m,

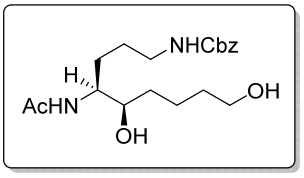
1H), 5.15 – 5.07 (m, *J* = 17.8 Hz, 2.46H), 4.97 – 4.86 (m, *J* = 12.1 Hz, 1H), 4.76 – 4.63 (m, *J* = 6.0 Hz, 1H), 3.29 – 3.16 (m, 3H), 2.01 (s, 3H), 1.95 – 1.86 (m, 2H), 1.60 – 1.42 (m, *J* = 21.3, 14.1 Hz, 3H). HRMS (ESI) Calcd. for $C_{18}H_{24}N_2O_4Na$ $(M+Na)^+$: 355.1634 found, 355.1636

Benzyl ((4S, 5S)-4-acetamido-5-hydroxyoct-7-en-1-yl)carbamate (266):



To a solution of ketone **268** (10 g, 30.10 mmol) in ethanol (60 ml) was added lithium tri-*tert* butoxyaluminohydride (16.81g, 66.22 mmol) at –78 ^oC. After the reaction mixture was stirred at the same temperature for 1hr, 1N HCl was added. The resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude products. Column chromatography on silica gel gave alcohol **266** as a white solid in 91% yield. Mp= 141-145 ^oC , $[\alpha]_D^{25}$ = -14 (*c* 1, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, *J* = 10.4, 4.5 Hz, 5H), 6.01 (d, *J* = 8.7 Hz, 0.2H), 5.81 (dt, *J* = 16.8, 7.1 Hz, 0.8H), 5.13 (dd, *J* = 19.0, 6.4 Hz, 3H), 4.96 (s, 1H), 3.93 (d, *J* = 8.8 Hz, 1H), 3.71 – 3.58 (m, 1H), 3.32 – 3.14 (m, 2H), 2.60 (s, 1H), 2.27 – 2.10 (m, 1H), 2.01 (s, 3H), 1.75 – 1.31 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 156.8, 136.7, 134.7, 128.7, 128.3, 128.2, 118.5, 73.49, 66.8, 53.8, 40.9, 38.4, 29.8, 27.1, 25.8, 23.5. HRMS (ESI) Calcd.for $C_{18}H_{26}N_2O_4Na$ $(M+Na)^+$: 357.1790 found, 357.1794

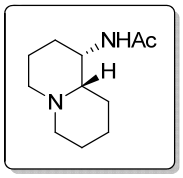
Benzyl ((4S, 5S)-4-acetamido-5, 9-dihydroxynonyl)carbamate (265):



To a solution of alcohol **266** (3 g, 8.97 mmol) in anhydrous CH_2Cl_2 (20 mL) and acroleine (4.76ml, 71.81 mmol) was added the Grubbs second-generation catalyst (0.228g, 0.27mmol). After being stirred at room temperature for 1 h, reaction mixture was filtered through a pad of celite. The filtrate was concentrated under reduced pressure to afford aldehyde. Crude aldehyde was dissolved in Methanol and $NaBH_4$ (4.07g, 10.7mmol) was added at 0^oC and reaction mixture stirred at rt for 30 minutes. Water was added to reaction mixture and excess solvent was evaporated in vaccuo. Then EtOAc was added and aqueous layer was extracted with EtOAc washed with brine, dried over anhydrous sodium sulphate and evaporated in vaccuo to afford diol **265** in 94% yield. MP= 149-151^oC, $[\alpha]_D^{25}$ = -7.2 (*c* 1, MeOH), ^1H NMR (400 MHz, MeOH-d_4) δ 7.38 – 7.24

(m, 5H), 5.03 (d, *J* = 24.6 Hz, 2H), 3.80 – 3.71 (m, 1H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.46 (s, 1H), 3.12 (t, *J* = 6.6 Hz, 2H), 1.96 (s, 3H), 1.74 – 1.63 (m, 1H), 1.63 – 1.34 (m, 10H); ^{13}C NMR (101 MHz, MeOH-d_4) δ 186.5, 160.96, 149.7, 149.0, 148.8, 81.2, 72.0, 66.5, 56.8, 40.0, 30.8, 29.9, 26.4, 22.5, 22.3, 17.1, 16.3; HRMS (ESI) Calcd. for $C_{19}H_{31}N_2O_5$ $(M+H)^+$: 367.2232 found, 367.2239

(+)-Epiquinamide (232):



MsCl (0.15 mL, 1.8 mmol) was added to a solution of diol **265** (0.412 g, 0.9 mmol) and Et_3N (0.5 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) at -10 °C. The mixture was stirred at this temperature for 0.5 h, then quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with water and dried over MgSO4. Solvents were removed under reduced pressure..Residue was again dissolved in EtOH and this solution was run through H-Cube using 10 % Pd/C and 100 psi. After completion of reaction, excess solvent was evaporated in *vaccuo* and resulting residue was purified using 90:10 CHCl3: MeOH and few drops of ammonia to furnished white solid in 76% yield. Mp = 127-129 ^oC, $[\alpha]_D^{20}$= +19.9 (*c* 1, $CHCl_3$) (Lit.[39] $[\alpha]_D^{20}$= +21 (*c* 1, $CHCl_3$) ^{1}H NMR(400 MHz, $CDCl_3$) δ6.22 (br s, 1H), 4.1 (br d, J = 6.9 Hz, 1H), 3.1 (t, J = 10.4 Hz, 2H), 2.08-1.98 (m, 6H), 1.8-1.75 (m, 3H), 1.7-1.4(m, 7H); ^{13}C NMR(100 MHz, $CDCl_3$) δ169.7 , 64.8, 56.7, 56.1, 48.1, 29.8, 29.3, 24.3, 23.5, 23.2, 19.6; HRMS (ESI) Calcd.for $C_{11}H_{21}N_2O$ $[M+H]^+$: 197.1648, found 197.1646.

2B. 7 Appendix II: ^{1}H and ^{13}C spectral data of representative compounds

Compound No.	*Fig AI.X*	*data*	*page No.*
227	Fig AII.1 and AII.2	^{1}H-^{13}C	94
226a	Fig AII.3 and AII.4	^{1}H-^{13}C	95
225a	Fig AII.5 and AI.6	^{1}H-^{13}C	96
138	Fig AII.7 and AI.8	^{1}H-^{13}C	97
267	Fig AII.9 and AII.10	^{1}H-^{13}C	98
265	Fig AII.11 and AII.12	^{1}H-^{13}C	99
232	Fig AII.13 and AII.14	^{1}H-^{13}C	100

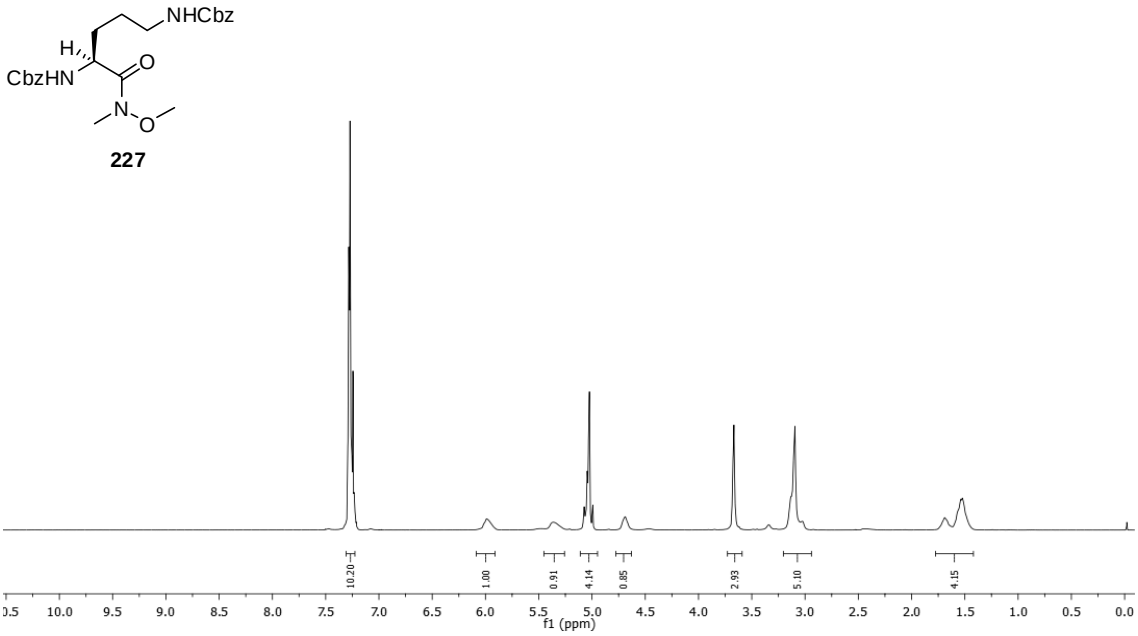


Fig AII.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **227**

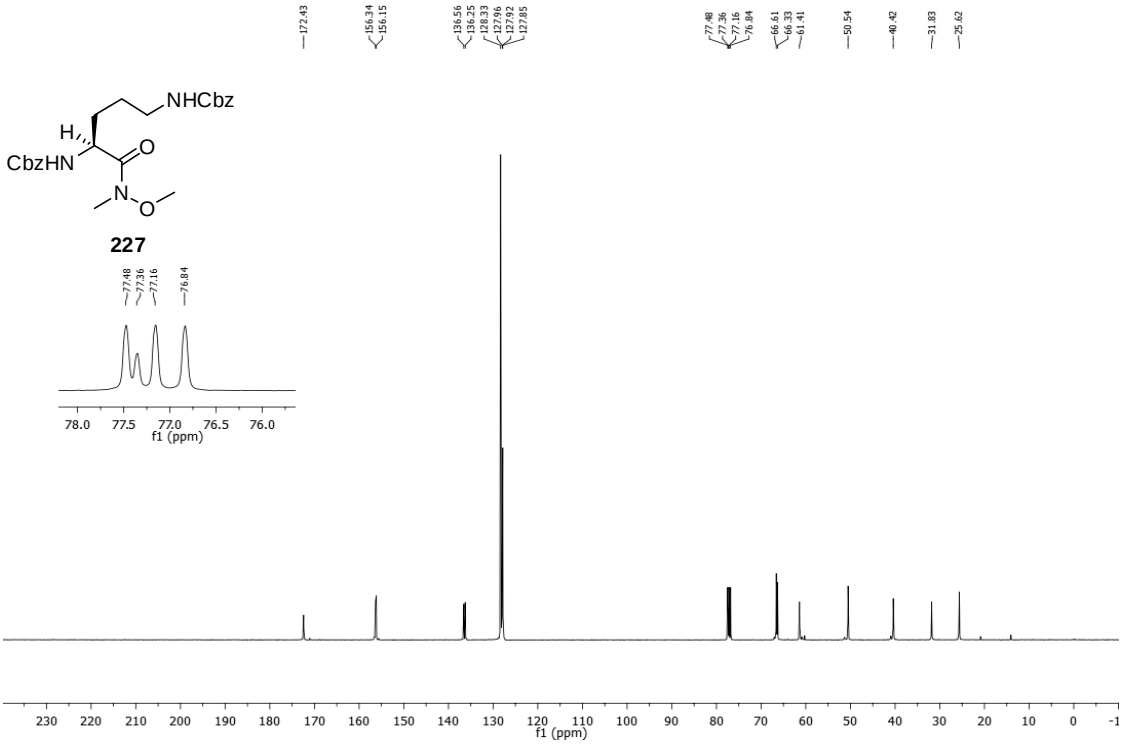


Fig AII.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **227**

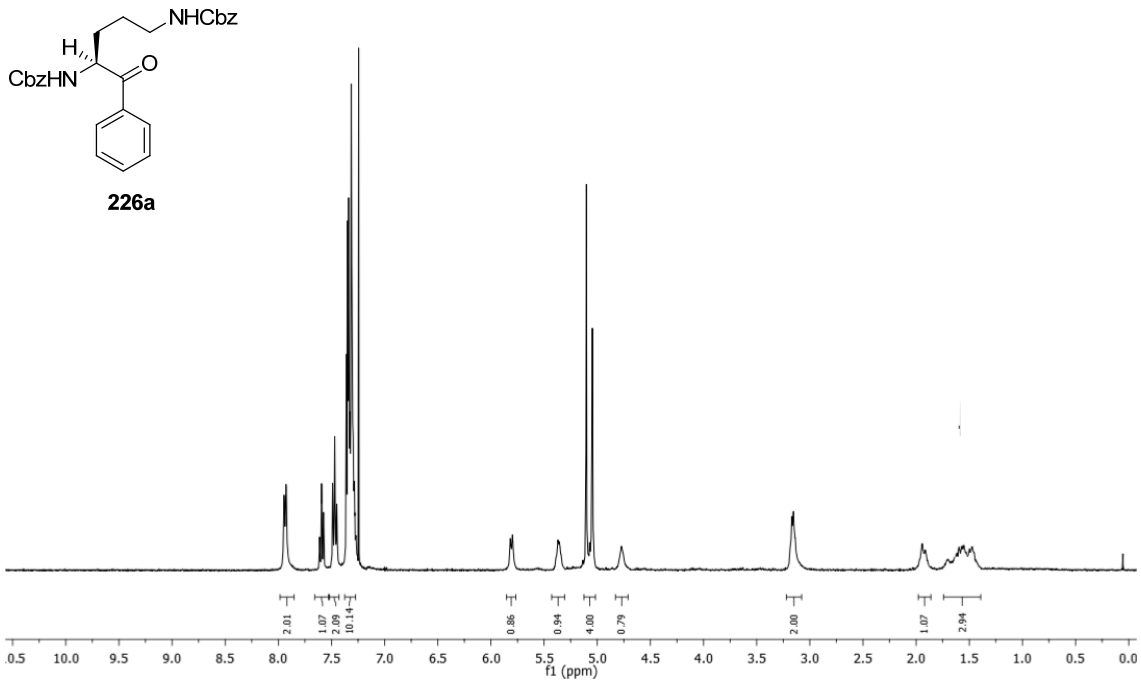


Fig AII.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **226a**

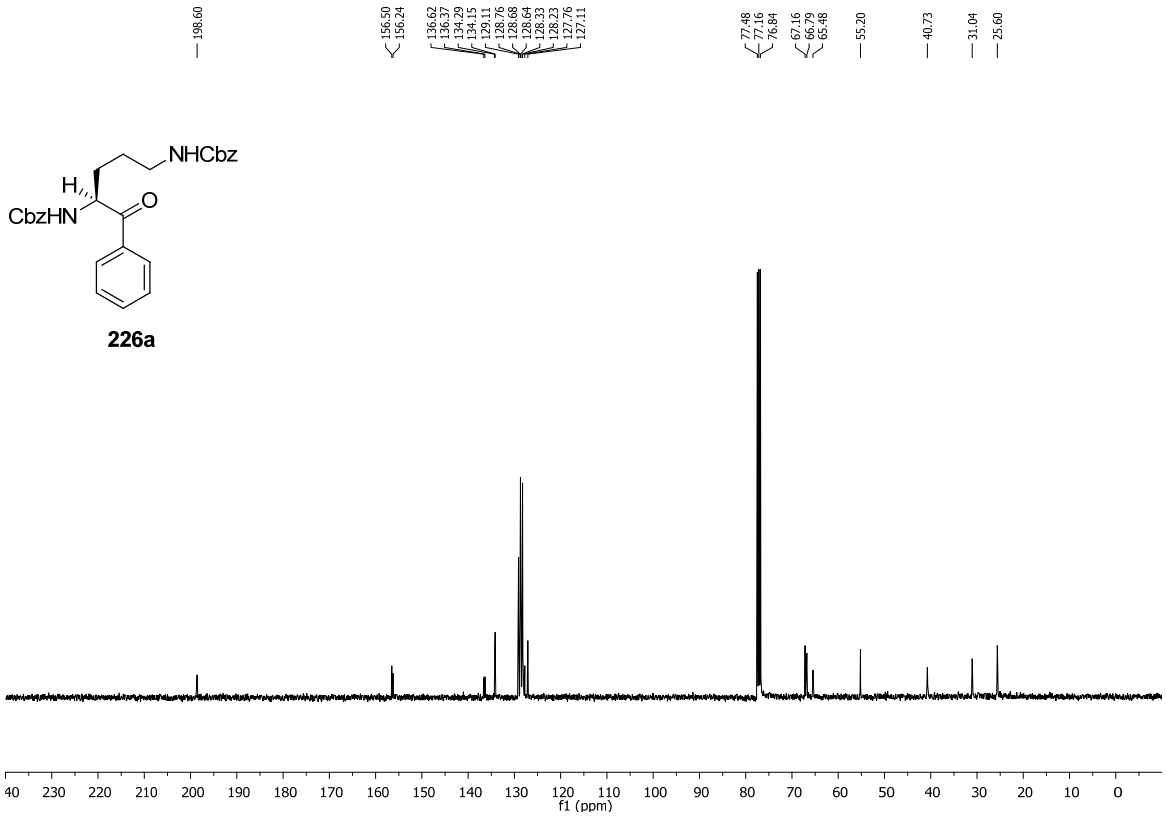


Fig AII.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **226a**

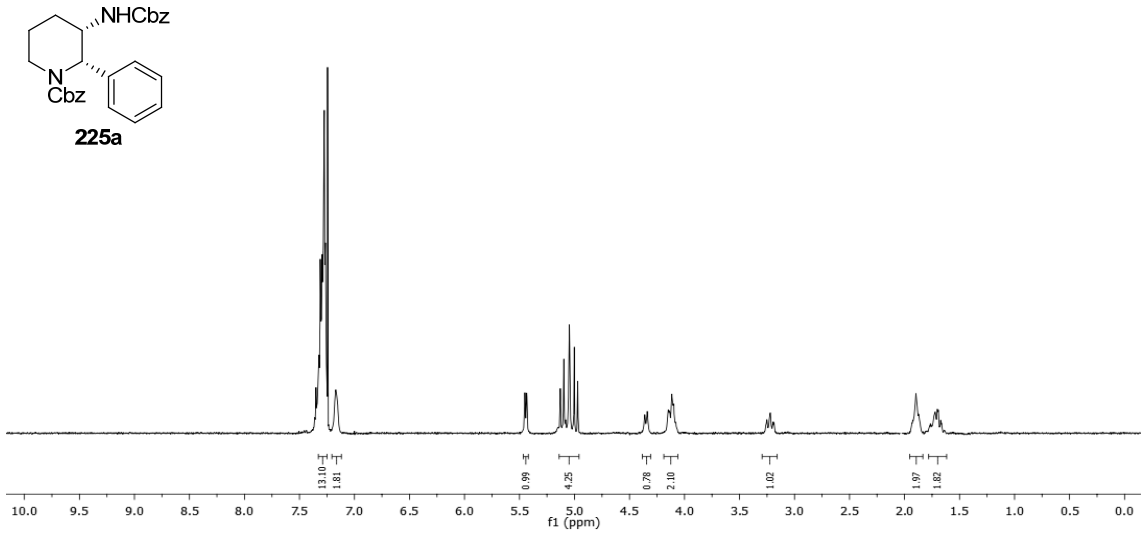


Fig AII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **225a**

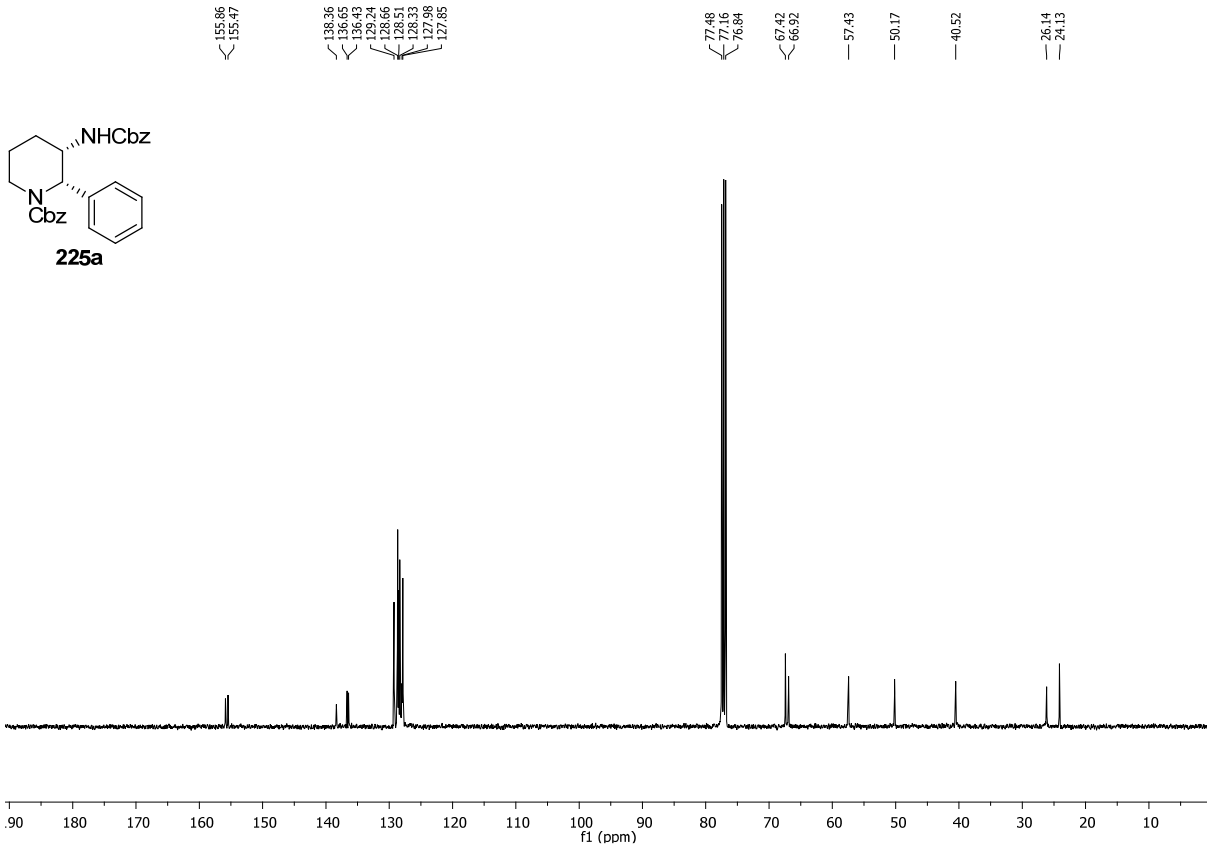


Fig AII.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **225a**

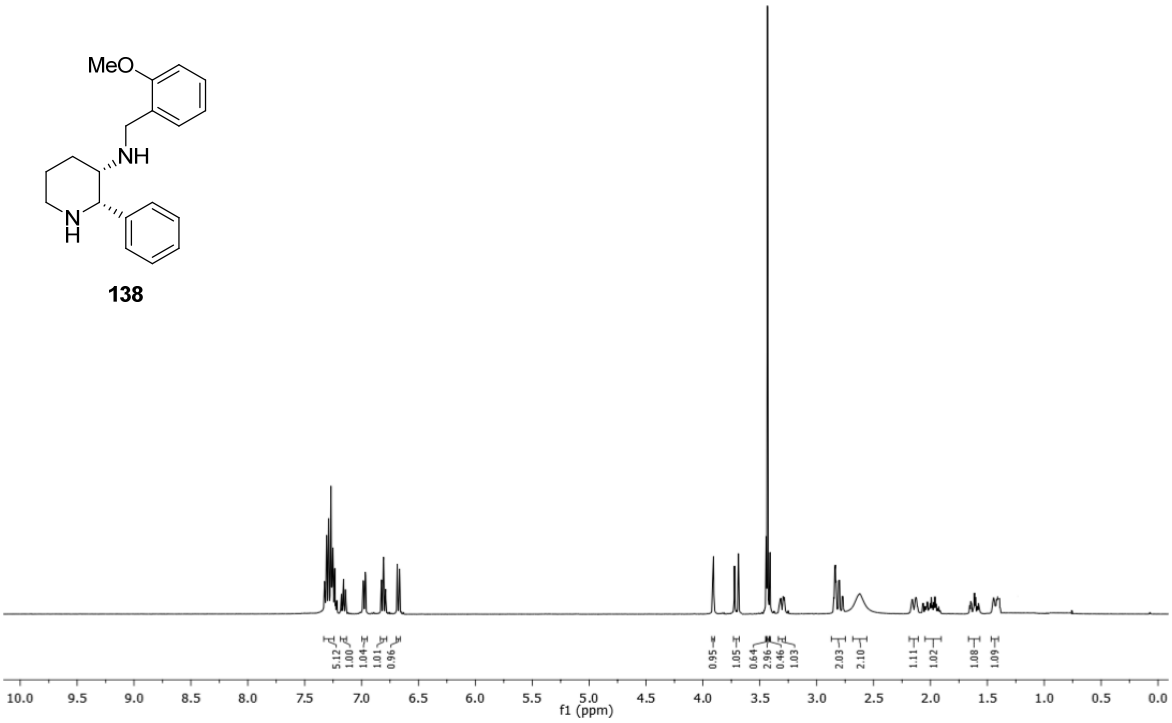


Fig AII.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **138**

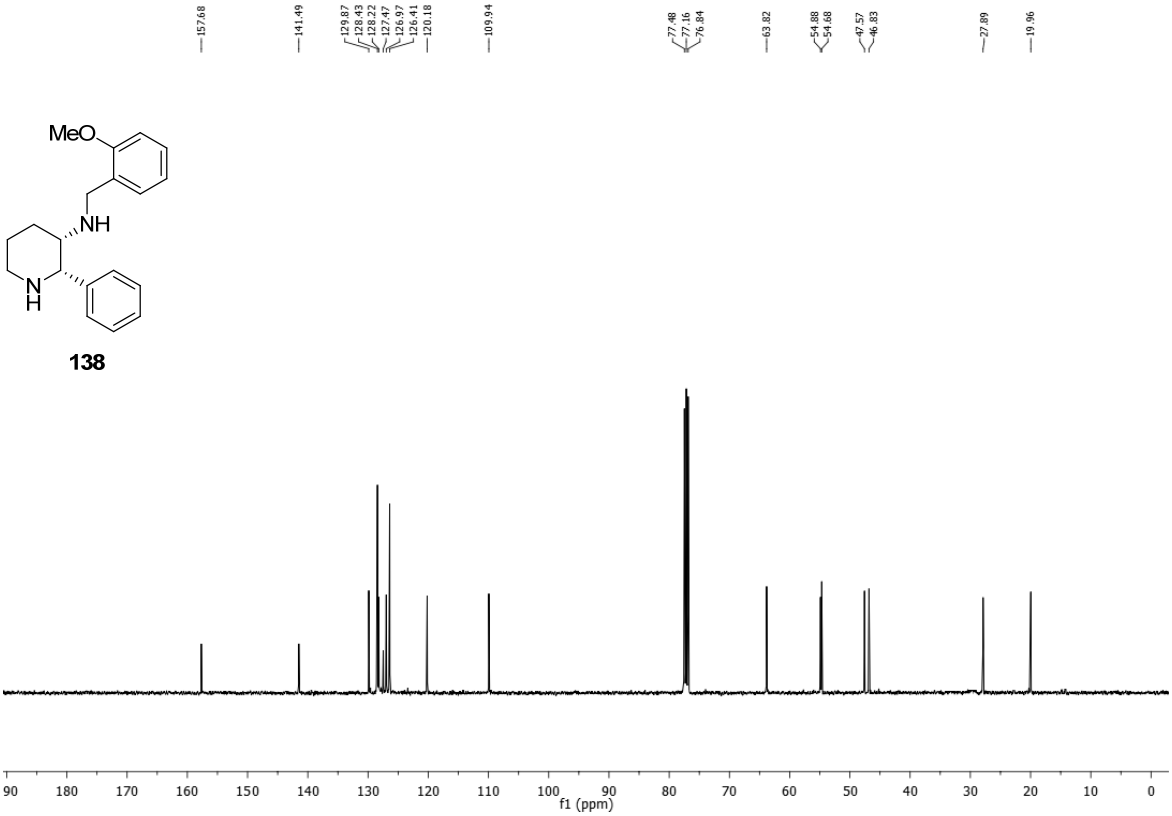


Fig AII.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **138**

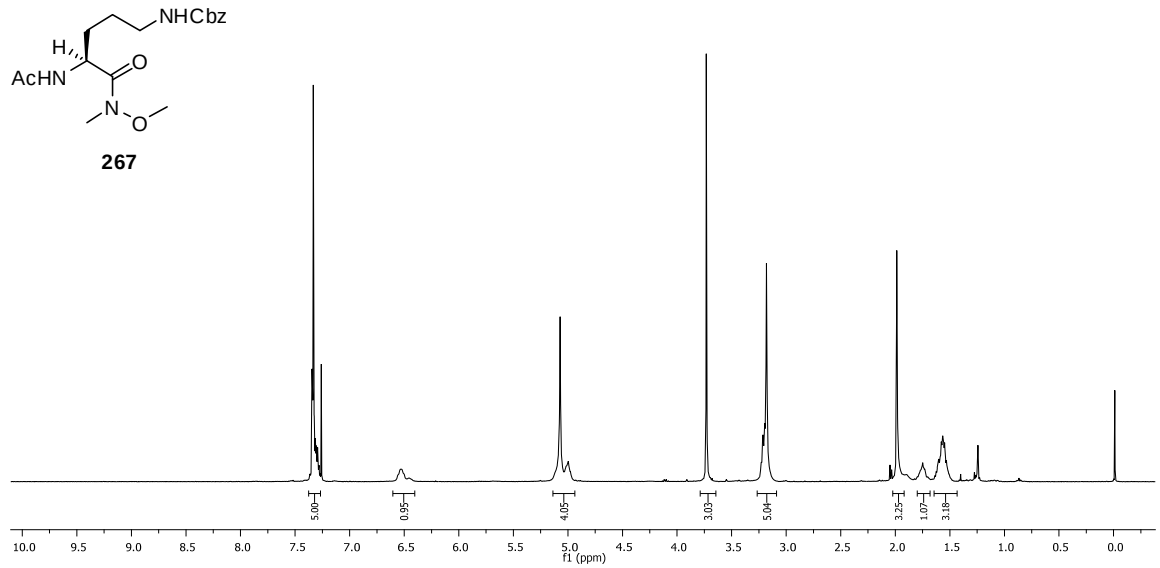


Fig AII.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **267**

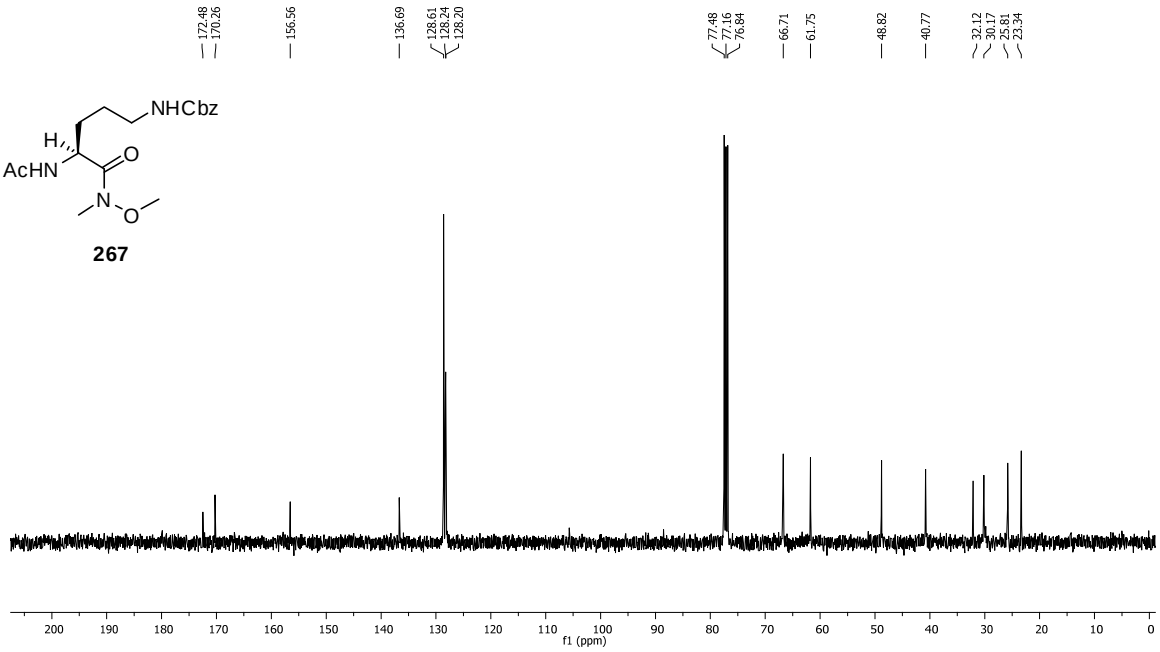


Fig AII.10: ^{13}C NMR 100 MHz, $CDCl_3$) spectrum of compound **267**

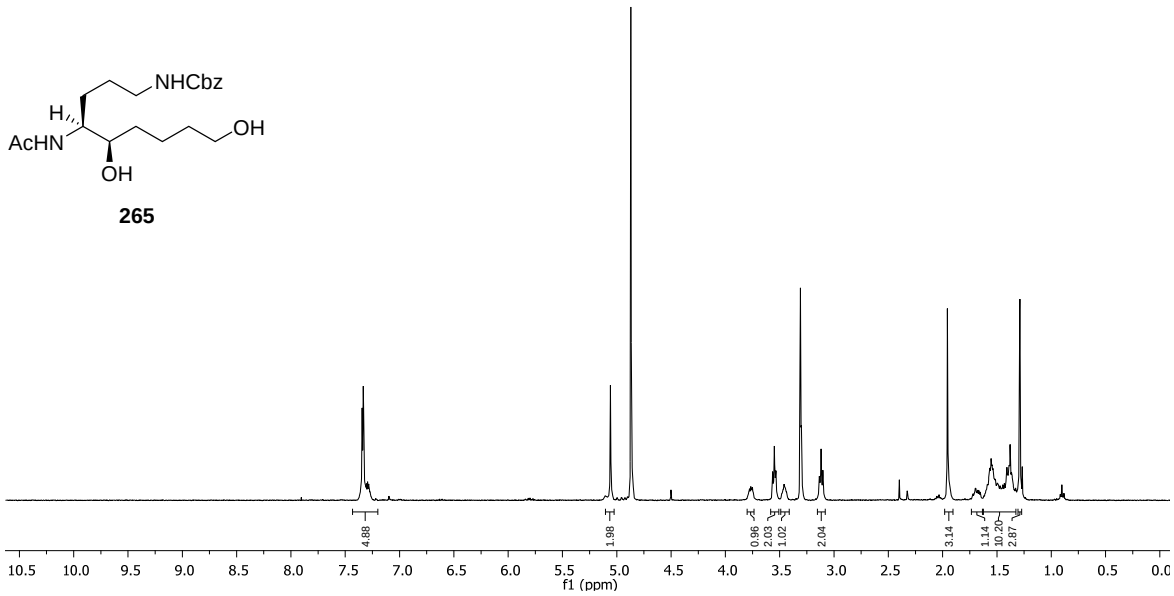


Fig AII.11: ^{1}H NMR (400 MHz, MeOH-d_4) spectrum of compound **265**

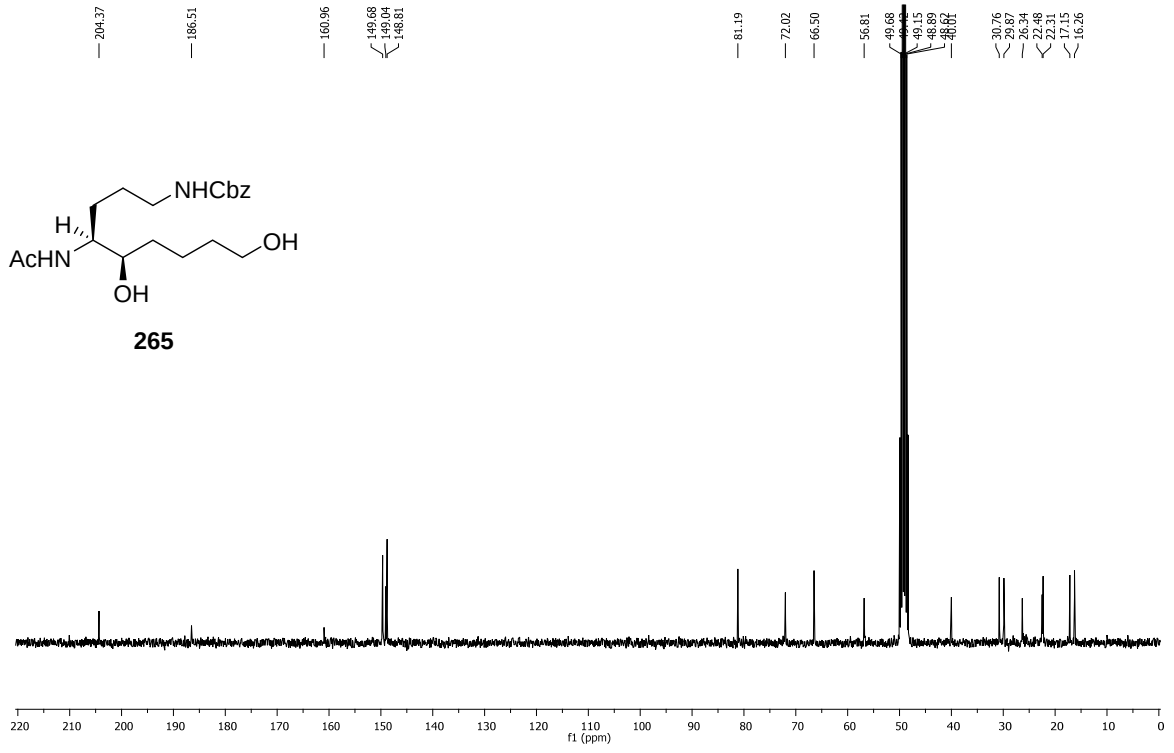


Fig AII.12: ^{13}C NMR (100 MHz, MeOH-d_4) spectrum of compound **265**

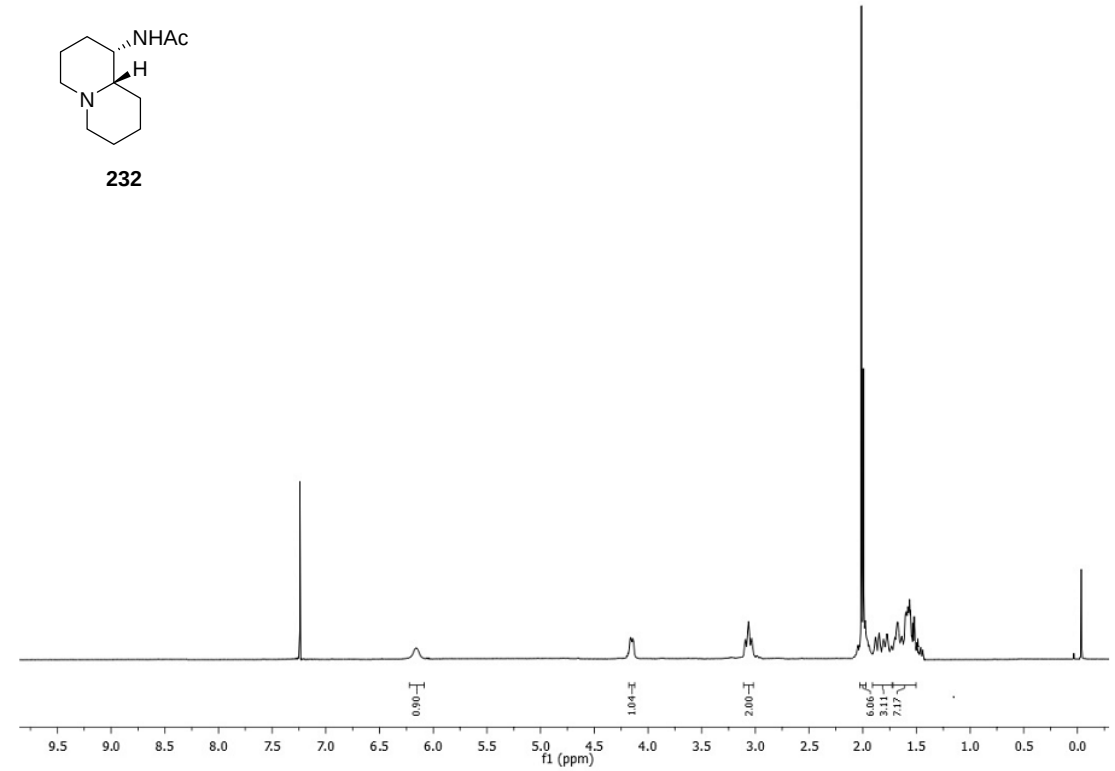


Fig AII.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **232**

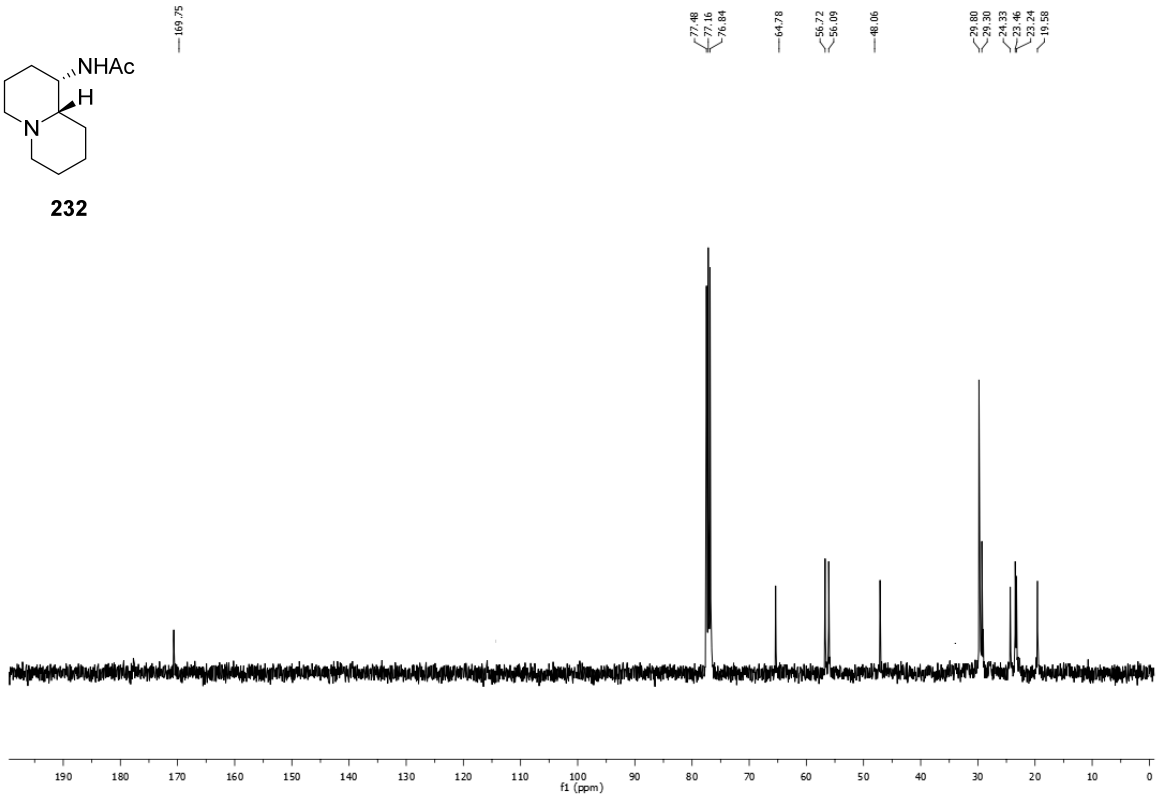


Fig AII.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **232**

2B. 8 Reference

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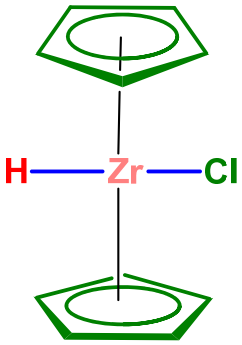
Chapter 3

Convenient *N*-decetylation and *N*-Cbz Deprotection under mild conditions



T H R E E

Convenient *N*-decetylation and *N*-Cbz Deprotection under mild conditions

3

In this chapter we present two novel and practical approaches for the deprotection of N-acetyl (N-Ac) and N-benzyloxycarbonyl (N-Cbz) groups. This chapter is further subdivided into two sections. Section A describes the use of Schwartz reagent for the efficient and facile N-deacetylation and a detailed study on N-deacetylation on various N-acetyl amines. Section B presents a novel catalytic hydrogen transfer method for the orthogonal deprotection of N-Cbz as well as for bezyl ester hydrogenolysis using $NaBH_4$ and Pd/C. For the wider applicability of the approach gram scale deprotection have been demonstrated by generating hydrogen in situ.

Section A

Orthogonal *N*-deacetylation under mild conditions using Schwartz reagent

3A. 1 Introduction

Organic compounds with amine functionality are widespread in many natural products, bioactive compounds and pharmaceuticals.[1] However, due to their remarkable nucleophilicity quite often amines are protected to carry out series of organic transformations. Nowdays protecting group free synthesis is very popular, highly desirable and demanding,[2] but in many instances protection of amines are unavoidable and thus making the reaction reliable for obtaining the target compound efficiently without any side reaction.

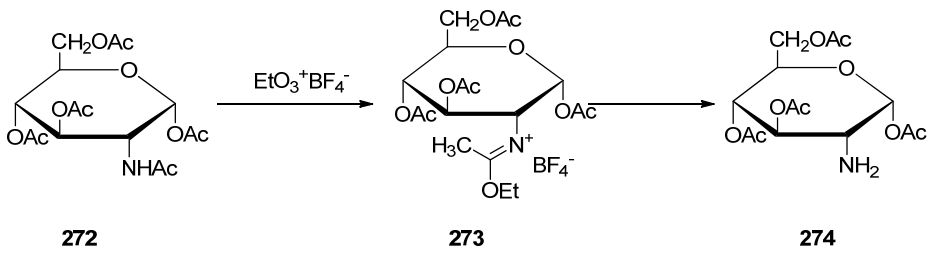
Acetyl moiety is one of the widely employed protecting group for amines in organic synthesis and also it is one of the common protecting groups used by Nature in natural product synthesis.[1] Acetylated amines (acetamides) have remarkably reduced nucleophilic

character in comparison to amines. Acetylated amines have been explored for the catalytic asymmetric hydrogenations of enamides.[3] Acetylated amines such as acetamides have been successfully utilized as directing groups in C-H activation.[4] In spite of the wide utility of acetyl protection for amines in organic synthesis, acetyl deprotection (*N*-deacetylation) is practically limited to the traditional harsh deprotecting conditions. As amide bond is robust *N*-deacetylation usually requires the use of strong base or acid at high temperature.[5] These deprotective conditions limit the scope of the use of acetylated amines along with the variety of functional groups which are sensitive to acid and base. *N*-deacetylation under harsh conditions may lead to racemization in certain cases. Nevertheless, efforts have been made in recent times in order to overcome this limitation. Some of the selected methods have been described below.

3A. 2 Selected methods for *N*-Deacetylation:

There are only few methods for N-deacetylation known in the literature. Some of these available protocols utilize harsh basic and acidic conditions. Some other methods use moisture sensitive and corrosive reagents such as oxalyl chloride, triphenyl phosphite complex under basic conditions at lower temperatures. Some of the reported methods are described in this section.

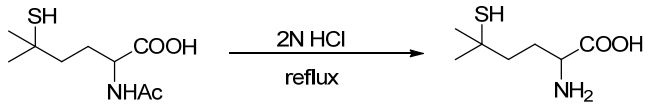
In 1967, Stephen Hanessian[6] reported the selective hydrolysis of amide bond in acetamido deoxy sugar **272** using $Et_3O^+ BF_4^-$ in dichloromethane. The reaction consists of treating the N-acetyl compound with triethyloxonium fluoroborate in DCM , followed by the hydrolysis of the inter-mediate *O*-ethyl acetamidium fluoroborate **273** with water to regenerate the amine function **274**.



272 **273** **274**

Scheme 3.1 Hanessian's approach for *N*-deacetylation

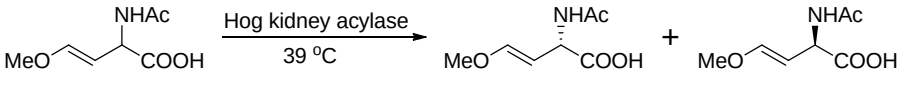
Field and co-workers[5] reported the acid hydrolysis of acetamido group using 2 N HCl under reflux condition racemic amino acid derivative. However, use of stong acidic conditions may not be suitable for enantiopure amino acids and peptides.



275 **276**

Scheme 3.2 *N*-decetylation using strong acid

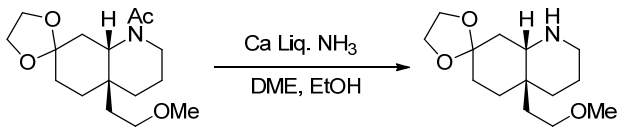
Keith ane co-wrkers[7] achieved enzymatic hydrolysis of acetamido group with hog kidney acylase. In this procedure, deprotection proceeded with the resolution, since only one enantiomer was cleaved. Similarly, DAP-deacylase enzyme has also been employed for removal of acetyl group. However, ready availability and cost of the enzyme limited the use on a regular basis on a large scale.



277 **278a** **278b**

Scheme 3.3 Enzyme catalyzed *N*-decetylation

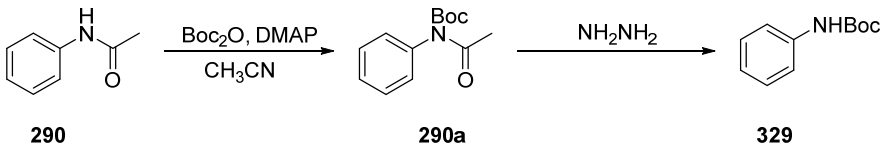
In 1982, Pearson *et al.* used metal reduction[8] protocol for the removal acetyl group in the total synthesis of limaspermine derivatives..



279 **280**

Scheme 3.4 Pearson's approach for *N*-decetylation

Ulf Ragnarsson[9] showed that amides that are difficult to be removed under conventional conditions can be removed by Boc protection followed by the deprotection of acetyl group using hydrazine. Enhancing the steric bulk and electrophilicity by Boc group facilitated the acetyl deprotection. Boc protection of amide **290** followed by treatment of resulting amide **290a** with hydrazine gave deacetylated product **329**.

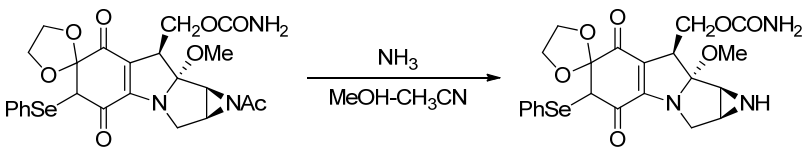


290 **290a** **329**

Scheme 3.5 N-deacetylation using Boc protection strategy

Brown and co-workers disclosed[10] a paper on relation between amidic distortion and ease of hydrolysis using base. Using high-level *ab* initio calculations they predicted that if lone pair and the carbonyl group are more orthogonal (thereby reducing the level of resonance), the rate of hydrolysis will be increased.

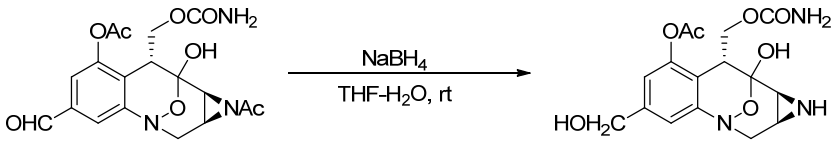
In 1993, Kasai and co-workers[11] have reported the deprotection of the acetyl group aziridine derivative **281** using NH_3 in acetonitrile.



281 **282**

Scheme 3.6 Kasai's approach for *N*-decetylation

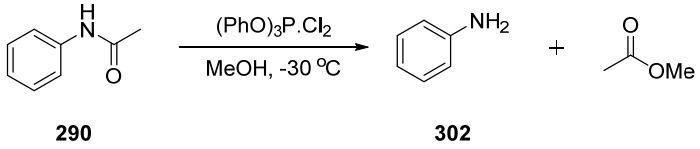
Terashima and co-workers[12] removed acetyl group of aziridine **283** using $NaBH_4$ in THF-water to afford **284** a precursor of natutral product: FR900482. However, this approach was unsuccessful for more conventional acetamides.



283 **284**

Scheme 3.7 Terashima's approach for *N*-decetylation

Recently, Prati *et al.* developed[13] a low temperature protocol for the N-deacetylation using the $(PhO)_3P^{\cdot}Cl_2$ reagent, which was prepared by the reaction of triphenyl phosphite with chlorine.

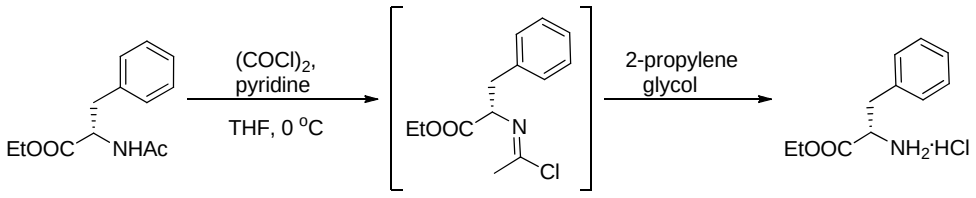


290 **302**

Scheme 3.8 Prati's approach for *N*-decetylation

However, the limitation of this methodology was the use of highly moisture sensitive and corrosive phopshite reagent.

Koenig and co-workers reported[14] a facile deprotection of secondary acetamides. Treatment of secondary acetamides **285** with oxalyl chloride led to the easy deprotection of the acetyl group via in situ formation of very sensitive imidoyl chloride **286**.

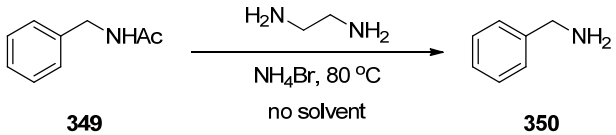


285 **286** **287**

Scheme 3.9 Koenig's approach for *N*-decetylation

The deprotection of chiral acetamides did not induce any epimerization under the deprotection conditions. Limitation for this methodology from a safety standpoint of view was the rapid evolution of the gases (CO_2 and CO) upon initial reaction of $(COCl)_2$ and the use of highly moisture sensitive and corrosive reagent.

Recently Ohshima and co-workers[15] reported microwave-assisted deacetylation of unactivated amides using ammonium-salt-accelerated trans-amidation. After extensive screening of different ammonium salts and amines, it was found that ammonium bromide and ethylene diamine worked very well in deacetylation and gave excellent yields. However, this protocol demands the sacrifice of a stoichiometric equivalent of another amine for the trans-amidation.



349 **350**

Scheme 3.10 Oshima's transamidation approach for *N*-decetylation

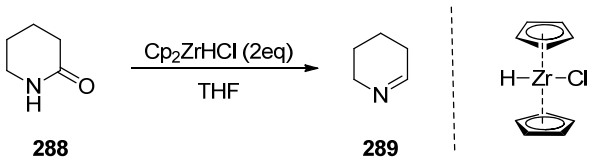
3A. 3 Present work:

3A.3.1 Objective:

As discussed in introduction, in spite of the wide utility of acetyl protection for amines in organic synthesis, acetyl deprotection (*N*-deacetylation) is practically limited to the traditional harsh deprotecting conditions. Although, some specific useful novel methods are available for the N-deacetylation, utility of most these methods is limited due to the use of strong bases or acids, reaction temperatures, racemization in certain cases, moisture sensitive and corrosive reagents. Development of mild and user friendly methods for the N-deacetylation is still stimulating and useful in synthetic organic chemistry.

3A.3.2 Background:

When we gleaned through the literature, we found that Ganem and co-workers[16] had reported the use of Schwartz reagent for the conversion of lactam **288** to imine **289** (Scheme 3.11).



288 **289**

Scheme 3.11 Conversion of lactam to imine using Schwartz reagent

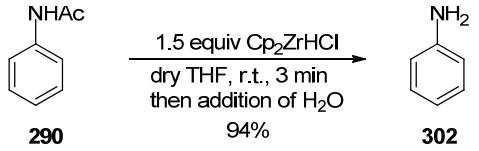
This was the first report for the conversion of amide to imine using Schwartz reagent. Later, in 2000, Gunda *et al.* elegantly used[17] the same strategy for the conversion of N, N-diethyl derived tertiary amides to different aldehydes using Schwartz reagent using acidic hydrolysis of imine.

Based on these results we envisioned that Schwartz reagent can be explored for the N-deacetylation of different acetamides. In the absence of any extensive study on straight forward N-deacetylation using Schwartz reagent we planned to explore a detailed study.

As there are not many standard protocols for *N*-deacetylation under mild conditions, it would be valuable to develop a method for *N*-deacetylation under mild conditions that would tolerate variety of functional groups. We envisioned that Schwartz reagent can be utilized for *N*-deacetylation and the protocol would particularly be very useful for laboratory scale reactions.

3A. 4 Results and Discussion:

In order to substantiate the reactivity of Schwartz reagent and to execute the strategy, we prepared *N*-acetyl aniline **290** by treating aniline with acetic anhydride in DCM. In our initial experiment, as a model reaction compound **290** was treated with Schwartz reagent (2 equiv) in anhydrous THF at room temperature. The initial formation of turbid reaction mixture changed into a clear solution in a very short time (3 min). Progress of the reaction was monitored by TLC and upon completion of the reaction it was quenched by the addition of water followed by work-up to afford the aniline **302** in excellent yield (94%).



Scheme 3.12 Model reaction of *N*-deacetylation using Schwartz reagent

The N-deacetylation was very facile and rapid (3 min). However, lowering the amount of Schwartz reagent (1-1.2 equiv) did not facilitate the complete *N*-deacetylation even after long reaction time (6 h). After, several repeat experiments we observed that 2 equiv of Schwartz reagent was essential for the complete and smooth N-deacetylation in short time. Encouraged by this initial success we planned to carry out a systematic study on this methodology by exploring different N-acetylated amines.

In order to check the substrate scope as well as to study the substituent effects on N-deacetylation, we chose amines which are sterically hindered and, also substrates containing electron withdrawing and donating groups (see table 3.1). In this regard different N-acetylated amines (**290-301**) have been prepared in good to excellent yields using known procedure[17] (See table 3.1). Aromatic substrates (**290-301**) when treated with Schwartz reagent (2 equiv) under optimized reaction condition underwent facile *N*-deacetylation in very rapid time affording corresponding amines in excellent yields (Table 3.1).

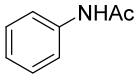
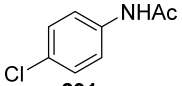
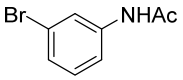
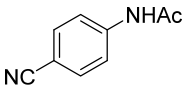
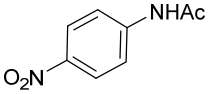
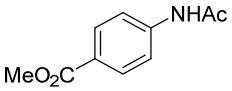
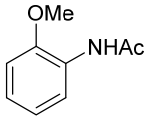
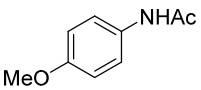
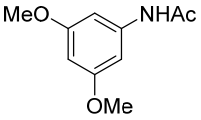
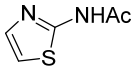
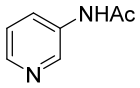
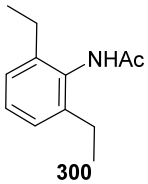
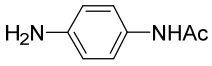
Entry	Substrate	Time (min)	Product Yield (%)
1	 **290**	3	**302** (94)
2	 **291**	3	**303** (92)
3	 **292**	3	**304** (90)
4	 **293**	4	**305** (84)
5	 **294**	4	**306** (89)
6	 **295**	4	**307** (87)
7	 **296**	4	**308** (86)
7	 **297**	2	**309** (88)
8	 **298**	3	**310** (86)
9	 **299**	3	**311** (88)
10	 **299A**	3	**311A** (89)
11	 **300**	5	**312** (87)
12	 **301**	5	**313** (90)

Table 3.1 The deprotection of various aromatic acetamides by the Schwartz reagent

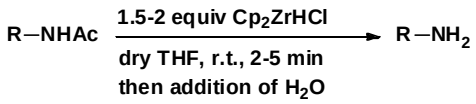
It was interesting to note that both electron donating and withdrawing moieties underwent deacetylation efficiently in rapid time (3-5 min). Electronic properties of functional groups did not have any significant impact on the reaction time and yields.

Steric factor in substrate **300** did not have any impact on the rate of deprotection and on the yield. Functional groups like cyano, nitro, ester and methoxy were stable under reaction conditions. Heteroaromatic substrate **299** underwent N-deacetylation very efficiently in a short time affording corresponding amine in excellent yield (88%).

In order to have generality of this approach N-acetylated aliphatic amines were subjected to deprotection under optimized conditions using Schwartz reagent (See table 3.2).

As expected aliphatic substrates (**314-320**) underwent facile *N*-deacetylation by affording corresponding amines in excellent yields (see Table 3.2) in very short reaction

time. We observed that rate of *N*-deacetylation of aliphatic N-acetyl amines was faster than that of aromatic N-acetyl amines. Further, tertiary amide **318**, when subjected to *N*-deacetylation afforded the corresponding secondary amine **325** in excellent yield (94%) in 3 min.



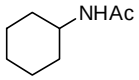
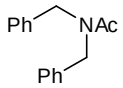
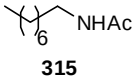
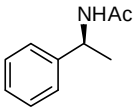
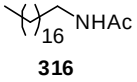
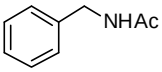
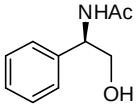
Entry	Substrate	Time (min)	Product Yield (%)	Entry	Substrate	Time (min)	Product Yield (%)
1	 **314**	2	**321** (91)	5	 **318**	3	**325**(94)
2	 **315**	2	**322** (93)	6	 **319**	2	**326** (93)
3	 **316**	2	**323** (91)				
4	 **317**	2	**324** (91)	7	 **320**	4	**327** (89)

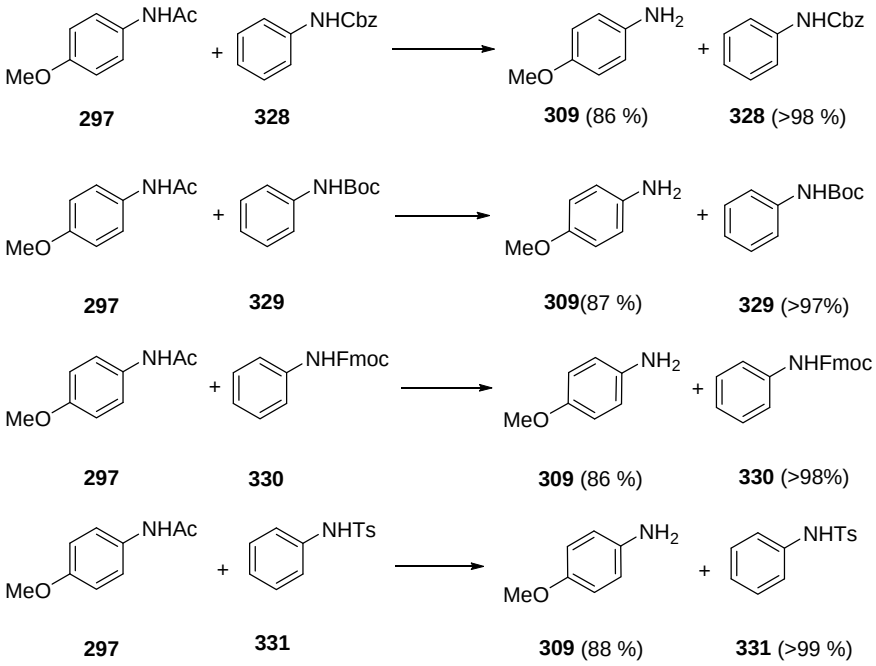
Table 3.2 The deprotection of various aliphatic acetamides by the Schwartz reagent

Further substrates with *α*-chiral centre were chosen for the experiment to investigate any possibility of epimerization during *N*-deacetylation. However, both substrates **319** and **320** underwent facile *N*-deacetylation in a short time to afford the corresponding amines **326** and **327** without any epimerization. Specific rotations for compound **326** and **327** were in close agreement with the literature value. For compound **326** specific rotation was $[\alpha]_D^{25}$ = –34.2 (*c* 1.0, $CHCl_3$) (lit.[18] $[\alpha]_D^{25}$ = – 35.1 (*c* 1.0, $CHCl_3$) and for compound **327** specific rotation $[\alpha]_D^{25}$ = -30.1 (*c* 0.76, 1 N HCl) (lit.[19] $[\alpha]_D^{25}$ = -31 (*c* 0.76, 1 N HCl).

3A.4.1 Competitive study:

In order to have a wider application of this protocol we carried out a series of competition experiments (Scheme 3.13). For the competitive experiments aniline was protected as Boc, Cbz, Fmoc and Ts using literature methods. These protected anilines were characterized by ^{1}H NMR. For the competitive experiments we selected *N*-(4-methoxyphenyl)acetamide **297** as *N*-acetyl compound.

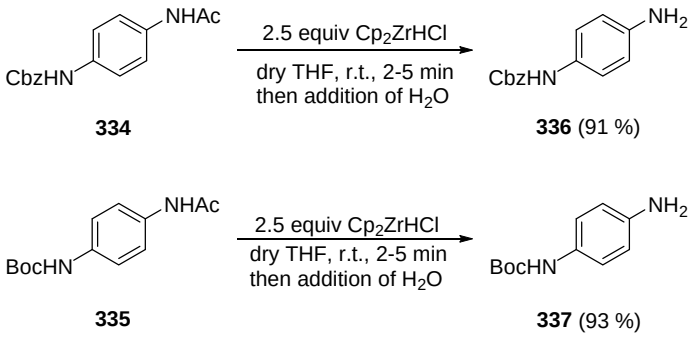
Compound **297** was treated with the competitive substrates **328-331** in an equimolar ratio under the optimized reaction conditions (Schwartz reagent 2.5 equiv, THF, r.t. 3-5 min, and then water). It was very remarkable that **297** alone underwent *N*-deacetylation chemoselectively in just 3-5 minutes affording the corresponding amine **309** in very good yields (86-88%) and the competitive substrates were recovered in almost quantitative yields (See Scheme 3.13).



Scheme 3.13 Intermolecular competitive experiments

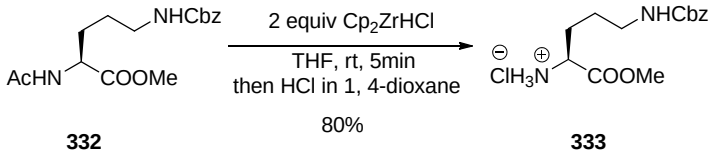
In order to substantiate any possible reactivity of the reagent on the competitive substrates, the reactions were stirred overnight. However, all the competitive substrates **328-331** were unreactive and recovered in almost quantitative yields.

These results are very important since Fmoc group is very labile and is known to undergo premature deprotection under basic conditions. We did not observe any deprotection of Fmoc group with Schwartz reagent over a long reaction time. Also, intramolecular competitive reactions were carried out using Schwartz reagent under optimized conditions. Compounds **334** and **335** containing both *N*-Ac and *N*-Boc, or *N*-Cbz moieties, when treated with the Schwartz reagent (2.5 equiv) in THF followed by the addition of water, afforded the corresponding amines **336** and **337** via chemoselective *N*-deacetylation in excellent yields (Scheme 3.14).



Scheme 3.14 Orthogonal deprotection

Further, application of this method was demonstrated on amino acid derivative: L-N^{δ}-Cbz-N^{α}-acyl ornithine methyl ester **332** (Scheme 3.15). This on treatment with Schwartz reagent (5 min) followed by the addition of HCl in 1, 4-dioxane afforded the corresponding L-N^{δ}-Cbz-ornithine methyl ester hydrochloride **333**. Observed optical rotation of the product was in close agreement with the literature value.[20] It is glad to note that reaction worked efficiently with the amino acid as well.



Scheme 3.15 Orthogonal *N*-deacetylation in amino acid

It is particularly important to note that the reagent is highly preferential to amides. This result would be synthetically very useful and can be utilized in orthogonal deprotection of *N*-acetyl moiety in the presence of different protecting groups under mild conditions which are usually labile under mild basic and acidic conditions. This protocol does not demand the use of any quenching or scavenging agents.[14] Generally *N*-deacetylation requires harsh acidic or basic conditions in which protection groups such as Boc, Fmoc, Ts would be very labile. The protocol described herein may provide an advantage to remove acetyl group at any convenient stage of the natural product synthesis.

3A. 5 Conclusions:

In summary we have described an efficient and facile method for *N*-deacetylation. The method has several distinct advantages. The deprotection requires very short reaction time (2-5 min) at room temperature affording amines in excellent yields with great chemoselectivity. Reaction conditions are very mild and many conventional protecting groups of amines were stable under the reaction condition. Furthermore, the reaction conditions enable the deprotection of chiral acetamides without any epimerization. The protocol may provide an advantage to remove acetyl group at any convenient stage of the natural product synthesis. Further study and utility of Schwartz reagent is under progress.

Section B

Orthogonal Deprotection of N-Cbz and Deprotection of Benzyl esters

3B.1 Introduction:

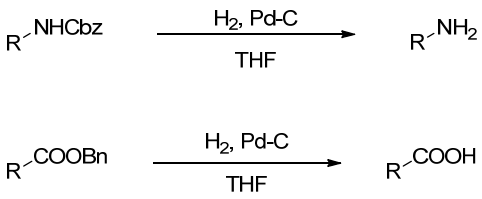
As described earlier in section-A, many organic compounds with amine functionality are widespread in many natural products, bioactive compounds and pharmaceuticals.[1] However, due to their remarkable nucleophilicity quite often amines are protected to carry out series of organic transformations. Usually, amines are protected as carbamates as their protection-deprotection strategy is generally easy and user friendly. Some of the regular and most common amine protecting groups is *tert*-butyloxycarbonyl group (Boc), benzyloxycarbonyl (Cbz), Fluorenylmethyloxycarbonyl (Fmoc). Unlike, Boc and Fmoc, Cbz group is quite stable under mild acidic as well as basic conditions. Due to this stability, Cbz group is orthogonal to many functional moieties and has been successfully exploited for the orthogonal protection/deprotection in many synthetic transformations. Cbz group is also one of the most commonly used protecting groups for amines in the total synthesis of natural products. Deprotection of Cbz group is generally carried out under hydrogenolytic conditions.

Similarly, benzyl group (Bn) has been successfully used for protecting carboxylic groups as benzyl esters. Like Cbz group, benzyl (Bn) esters can be cleaved by hydrogenolysis. Benzyl esters have also been explored in peptide chemistry and natural product synthesis. Usually, amines are protected as N-Cbz using benzyl chloroformate under alkaline conditions. Benzyl esters are prepared by the treatment of carboxylic acids with benzyl bromide under alkaline conditions.

3B.2 Selected methods for the deprotection of Cbz and Bn groups:

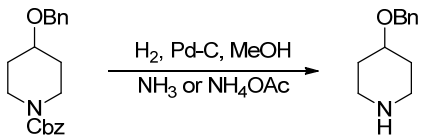
Some of the important methods for the deprotection of Cbz and benzyl ester are discussed below.

Cbz as well benzyl esters have been cleaved under catalytic hyrogenolytic conditions. Pd on charcoal under hydrogen atmosphere is commonly used for the deprotection Cbz and benzyl esters. Depending on the substrates, elevated temperature and pressure may be required sometimes.



Scheme 3.16 Deprotection of Cbz and Benzyl (Bn) ester: A general strategy

Solvents such as MeOH, EtOH, EtOAc and THF are mostly used for the catalytic hydrogenolysis. Sometimes, trace amount of either acetic acid or hydrochloric is added during the deprotection of Cbz in order to avoid the poisoning of the catalyst by the liberated free amine. To avoid the poisoning of catalyst due to the sulphur group in cysteine or methionine residue in peptide, NH_3 has been used as solvent for hydrogenolysis.[21] Ammonia has also been used for inhibiting the reduction of Benzyl ether, to achieve the selective cleavage of Cbz group (Scheme 3.18).[22]



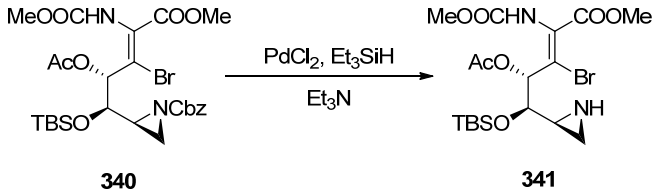
338 **339**

Scheme 3.17 Selective hydrogenolysis of Cbz group

Several hydrogen donors[23] including cyclohexene, 1, 4-dicyclohexadiene, formic acid, *cis*-decaline and ammonium formate have been used as a substitute for hydrogen for the removal of Cbz group. Royer *et al.* reported[24] convenient, rapid, and mild catalytic hydrogenolysis of the Cbz group with the use of Pd-poly (ethylenimine) PEI "ghosts" catalyst and formic acid. This catalyst finds special use in peptide chemistry.

In 2002, Joullie and co-workers[25] used H_2, Pd/C along with the ligand 2, 2′-dipyridyl in EtOAc-MeOH for Cbz deprotection in the total synthesis of Ustiloxin D. Phenolic benzyl ether survived under this reaction condition. Raney Ni (W2)[26] has also been used for the removal of Cbz group but the yields were not satisfactory and the reaction conditions needed high temperature.

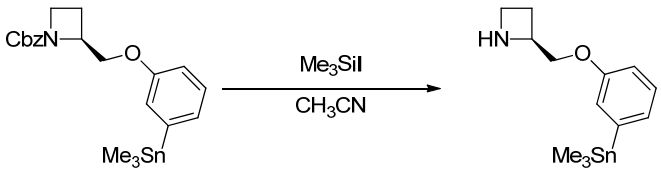
Coleman and co-worker[27] achieved deprotection of Cbz using $PdCl_2$ and triethylsilane in the total synthesis of antitumor agent azinomycin A and B.



340 341

Scheme 3.18 Et_3SiH as hydrogen donor for Cbz deprotection

In 1978, Jung and co-worker[28] reported the use of trimethylsilyl iodide (TMSI) for the deprotection of benzyl carbamates.

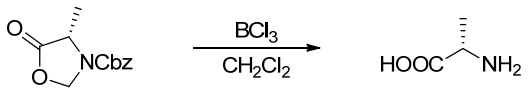


342 343

Scheme 3.19 TMSI reagent for Cbz deprotection

This method is particularly useful for the deprotection of Cbz in presence of other functional groups which are sensitive to hydrogenolysis.

In 1979, Felix et al. reported[29] the use of BBr_3 for the deprotection of Cbz and Boc groups. Likewise, BCl_3 in dichloromethane has also been used for the removal of Cbz in some cases.



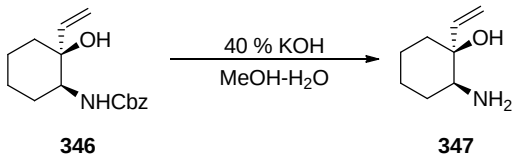
344 345

Scheme 3.20 Lewis acid catalyzed Cbz deprtection

Benzyl carbamate is readily cleaved under strongly acidic condition. For example HBr in acetic acid[30], 6 N HCl[34], HF in pyridine, trifluoromethane sulfonic acid[31] and FSO_3H have been used for the deprotection of Cbz group.

Cbz deprotection also has been carried out in very strong basic conditions. Arnaiz and co-workers[32] used 40% KOH in MeOH and H_2O for the removal of Cbz in the total synthesis of pipecolic acid derivatives.

Overman and co-workers[33] used 0.15 M $Ba(OH)_2$ in glyme/H_2O under heating condition for the deprotection of Cbz group. It was interesting note that reagents like



Scheme 3.21 Cbz deproetction in basic medium

TMSI, BBr_3, KOH/EtOH, $AlCl_3$/EtSH, MeLi/LiBr, and $MeBBr_2$ failed to remove Cbz group because of the destruction of acetylene.

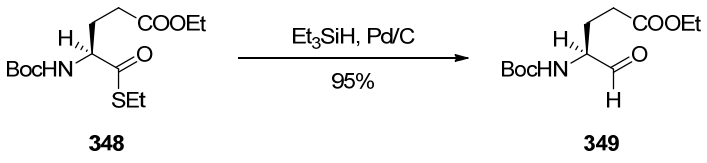
Enzymes also have been utilized for the removal of benzyl carbamates. For example Patel and co-workers[34] have developed new method for the deprotection of benzyloxycarbonyl amino acid to prepare L-amino acid and D-benzyloxycarbonyl amino acid in high yield and high enantiomeric ratio.

3B.3 Present work

Though many specific methods are available for the deprotection of Cbz group in literature, but most often N-Cbz deprotection is carried out under hydrogenolytic conditions using metal catalysts. Though widely used due its simplicity and reactivity, used of hydrogen enhances the potential danger of fire hazard.

In this regard, catalytic transfer of hydrogen (CTH) is a suitable alternative method for the reductions of many substrates as well for the deprotection of *N*-Cbz with the use of hydrogen gas.[39] For Catalytic transfer of hydrogen (CTH), molecules such as 1, 4-cyclohexadiene,[23a] hydrazine,[35] formic acid,[36] ammonium formate,[37] phosphinic acid,[38] or sodium hypophosphite[39] have been used as hydrogen donors with Pd-C as the catalyst. However, few disadvantages of some of these transfer agents are the requirement of high temperature, inapplicability for the acid or base-sensitive substrates.

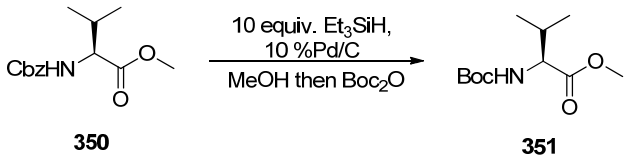
When we gleaned through the literature we found a highly efficient reduction of ethyl thiol esters **348** to aldehydes **349** using triethylsilane and catalytic amount of palladium on carbon. This method was developed by Fukuyama and co-workers[40] and has found wide applicability due to its convenience.



Scheme 3.22 Fukuyama's catalytic transfer of hydrogen (CTH) using Et_3SiH

In situ generation of molecular hydrogen by addition of triethylsilane to palladium on charcoal results in rapid and efficient reduction of multiple bonds.

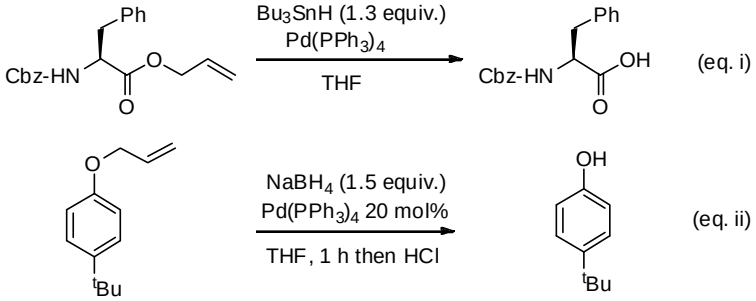
Later in 2007, Mcmurray and co-workers[41] employed the same method for the reductions of alkyne, azides, imines, and nitro groups, as well as benzyl group and allyl group deprotection.



350 **351**

Scheme 3.23 McMurray's CTH approach

Though this method is very useful for the reduction and deprotection, however, some of the limitations of this reagent are use of high equivalent of Et_3SiH (10 equiv or more), moisture sensitive, storage and handling under inert gas. Reagent is also incompatible with water, moisture, acids, strong bases, oxidizing agents, and alcohols.



Scheme 3.24 Pd catalyzed O-Deallyalation

In 1986 Guibe and co-workers reported an interesting result of O-deallylation of ester using Pd $(PPh_3)_4$ and Bu_3SnH (eq. i)[42] Similar to this approach, O-deallylation of allyl ethers was described using Pd $(PPh_3)_4$ and $NaBH_4$ system (eq. ii) by Zhu and co-workers[43]. Interestingly, under these reaction conditions carbamates (N-Cbz, N-Boc) were stable.

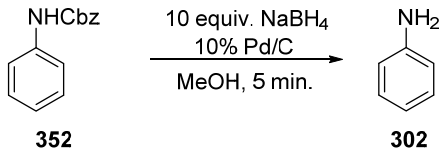
Inspired by the methods for generating hydrogen in situ and keeping in view of some of limitations of Et_3SiH, we planned to explore the combination of $NaBH_4$-Pd/C system for the deprotection of the N-Cbz group. Both $NaBH_4$ and Pd/C are less expensive and easily

available. Easy in situ generation of H_2 could be explored for the orthogonal *N*-Cbz deprotection. Hence, we decided to investigate the planned system.

3B.4 Result and discussion:

In order to execute the described strategy, we prepared *N*-Cbz aniline **352** by treating aniline with benzyl chloroformate (CbzCl) in DCM. In a model reaction to a stirred a solution of compound **352** and 10% Pd/C in methanol, $NaBH_4$ (10 equiv.) was added portion wise. We observed that addition of $NaBH_4$ in one portion to the reaction mixture was highly exothermic and the liberation of the anticipated H_2 gas was highly instantaneous.

In the initial attempt, we observed that stirring the reaction mixture for 5 min led to the facile *N*-Cbz deprotection. The completion of reaction was monitored by TLC.



Scheme 3.25 Model reaction for N-Cbz deprotection

The reaction mixture was filtered through celite and the excess solvent was removed under reduced pressure to afford crude amine **302** and which upon purification over column chromatography afforded pure **302** in 98% yield.

Encouraged by this success we planned to carry out experiments to optimize the minimum required amount of both $NaBH_4$ and Pd/C for the facile Cbz-deprotection (See Table 3.3).

Entry	% Pd/C	$NaBH_4$ (equiv)	Time (min)	Yield (%)
1	1	10	120	20
2	3	6	120	65
3	5	4	30	83
4	10	1	5	98

Table 3.3 Optimization of amount of $NaBH_4$ and Pd/C

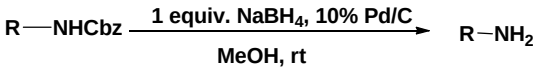
Initially, N-Cbz aniline **352** was treated with 1% of Pd/C and 10 equivalents of $NaBH_4$ in methanol. However, we observed that Cbz deprotection was very sluggish and afforded **302** in 20% yield in 120 min (entry 1, Table 3.3). Reaction was incomplete even after prolonged reaction condition. Increasing the amount of Pd/C to 3% and reducing the amount of $NaBH_4$ to 6 equiv enhanced the rate of Cbz deprotection by affording **302** in 65 % yield in 120 min (entry 2, Table 3.3). Further, use of 5% Pd/C and 4 equiv $NaBH_4$ enhanced the rate of Cbz deprotection by affording **302** in very good yield 83% in just 30 min (entry 3 Table 3.3). Keeping in view of one equivalent of $NaBH_4$ providing four hydrogens, we used 1 equiv $NaBH_4$ and increased the amount of Pd/C to 10% for the deprotection of Cbz group. Interestingly, we observed that rate of deprotection was significantly enhanced by affording **302** in 98% (pure isolated yield) in just 5 min. These results confirmed that latter two optimized reaction conditions (entry 3 and 4) are ideal for the deprotection of Cbz. For the facile and rapid laboratory scale reactions we planned to explore the optimized reaction conditions containing 1 equivalent of $NaBH_4$ and 10% Pd/C (entry 4). Encouraged by this initial success we planned to explore this approach for various Cbz protected amines.

In order to enhance the substrate scope, variety of amines were protected with benzyl choloformate (Cbz-Cl) using conventional procedure to afford N-Cbz amines (**353-361** and **336**) in very good yields. These N-Cbz protected amines were characterized by ^1H NMR and mass spectrometry prior to use them as substrates.

N-Cbz amines (**336** and **353-361**) under optimized deprotection condition (10% Pd/C, 1 equiv. of $NaBH_4$) in methanol at room temperature afforded the corresponding amines in excellent yields (93-98%) (Table 3.4).

We observed that Cbz-amines (Table 3.4) containing both electron donating and withdrawing groups underwent N-Cbz deprotection efficiently in rapid time. Electronic properties of functional groups did not have any significant impact on the reaction time and yields. Steric factor also did not have any impact on the rate of Cbz deprotection and on the yield (Table 3.4). As it was anticipated other functional groups such as methyl etser and carboxylic acid were stable under reaction conditions and did not have any impact on the rate of deprotection.

It was very interesting to note that, we did not observe any anticipated poisoning of Pd catalyst in any of the reactions. Reactions did not demand the addition of acids such as



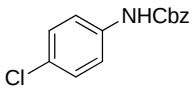
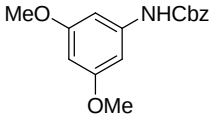
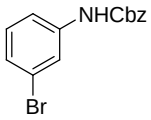
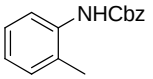
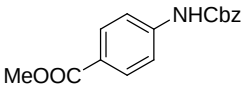
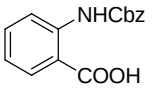
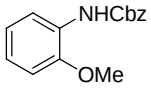
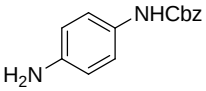
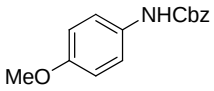
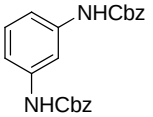
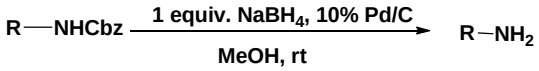
Entry	Substrate	Time (min)	Product Yield (%)	Entry	Substrate	Time (min)	Product Yield (%)
1	 **353**	7	**303** (98%)	6	 **358**	6	**310** (96%)
2	 **354**	6	**304** (96%)	7	 **359**	7	**463** (97%)
3	 **355**	9	**362** (94%)	8	 **360**	10	**364** (93%)
4	 **356**	5	**308** (98%)	9	 **336**	10	**313** (96%)
5	 **357**	8	**309** (97%)	10	 **361**	10	**365** (97%)

Table 3.4 The deprotection of N-Cbz aromatic amines

acetic acid. In order to study further, substrate **336** containing free amine group was treated under optimized reaction condition. The Cbz deprotection was very facile in yielding **313** in 96% and we did not observe any poisoning of catalyst. Under the reaction condition we did not observe any trace amount of alcohol formation due to the reduction of ester group. Further, for the general applicability N-Cbz aliphatic amines were subjected for the N-Cbz deprotection under optimized condition [$NaBH_4$ (1 equiv.) and 10% Pd/C] in methanol at room temperature.

Cbz deprotection of all the *N*-Cbz aliphatic amines underwent smoothly in rapid time (3-5 min) in excellent yields (88-98%). It was interesting to note that deprotection of N-Cbz aliphatic amines was faster than that of *N*-Cbz aromatic amines. Even the deprotection of N-Cbz secondary amine proceeded easily to afford the corresponding secondary amine **325** in excellent yield (95%) in rapid time (3 min). We did not observe any catalytic poisoning during the deprotection of *N*-Cbz aliphatic amines.

Further *N*-Cbz amine substrates with α-chiral centre were chosen for the deprotection to



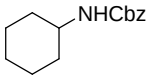
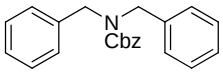
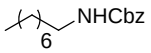
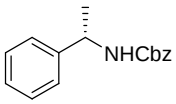
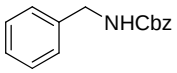
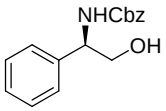
Entry	Substrate	Time (min)	Product Yield (%)	Entry	Substrate	Time (min)	Product Yield (%)
1	 **366**	4	**321** (98%)	4	 **369**	3	**325** (95)
2	 **367**	3	**322** (98%)	5	 **370**	4	**326** (94%)
3	 **368**	3	**324** (98%)	6	 **371**	5	**327** (93%)

Table 3.5 The Cbz deprotection of N-Cbz Aliphatic amines

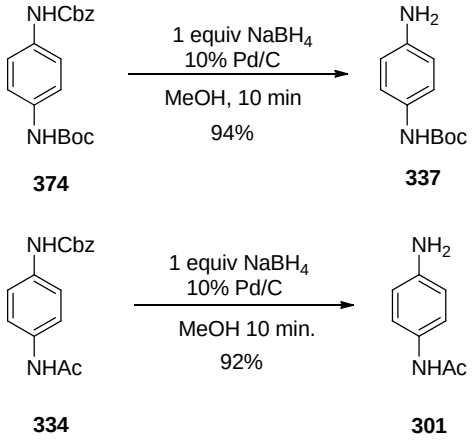
investigate any possible epimerization during *N*-Cbz deprotection. However, under optimized deprotection conditions all the *N*-Cbz protected chiral substrates underwent facile *N*-Cbz deprotection in a short time to afford the corresponding amines **326** and **327** in excellent yields. Specific rotations for the compounds **326**, **327** were in close agreement with the literature values. For compound **327** specific rotation is $[\alpha]_D^{25} = -30.4$ (*c* 0.76, 1 N HCl) (lit.[19] $[\alpha]_D^{25} = -31.0$ (*c* 0.76, 1 N HCl), and for compound **326** is $[\alpha]_D^{25} = -34.6$ (*c* 1.0, $CHCl_3$); lit. $[\alpha]^{25}{}_D = -35.1$ (*c* 1.0, $CHCl_3$). These results clearly indicated that epimerization free N-Cbz depreotection using this approach.

3B.5 Orthogonal N-Cbz deprotection and Application to Peptide

Further, as an extension of study orthogonal deprotection of N-Cbz group was carried out in presence of other protecting groups such as N-Ac and N-Boc under optimized deprotection conditions ($NaBH_4$ 1 equiv and 10% Pd/C).

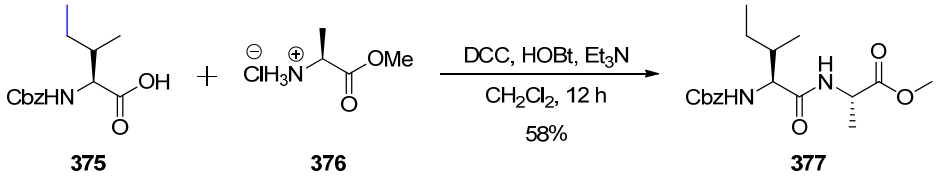
Compounds **374** and **334** containing either N-Cbz/N-Ac and N-Cbz/N-Boc moieties were treated with 1 to 2 equivalent of $NaBH_4$ and 10 % Pd/C in methanol at room temperature. As anticipated N-Cbz deprotection occurred exclusively and N-Ac as well as N-Boc moieties were intact. Corresponding N-Cbz deprotected amines **337** and **301** were isolated in excellent yield (94%, 92%, Scheme 3.26). The orthogonal deprotection

required only 1 equivalent of $NaBH_4$, additional one more equivalent of $NaBH_4$ was added to check any possibility of leaching of acetyl and Boc which are usually stable under basic condition. Compound **337** and **301** were characterized by the spectroscopic methods.



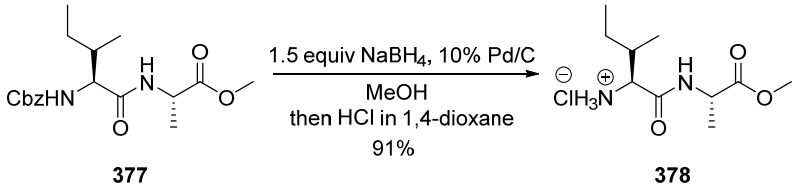
Scheme 3.26 Orthogonal deprotection of Cbz group

In order to have wider application of the present methodology we planned to explore the deprotection of N-Cbz in dipeptide. In this regard, dipeptide **377** was prepared from L-isoleucine and L-alanine. N-Cbz-L-isoleucine **375** and L-alanine methyl ester hydrochloride **376** were coupled using DCC and HOBt in CH_2Cl_2 to afford dipeptide **377**. Dipeptide **377** was characterized by spectroscopic methods (^1H, ^{13}C, Mass).



Scheme 3.27 Preparation of dipeptide

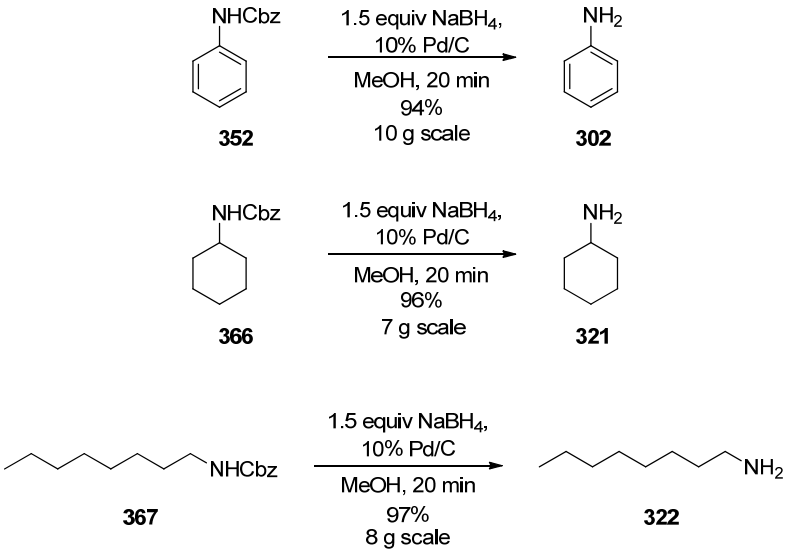
N-Cbz protected peptide **377** was then subjected to deprotection condition (1.5 equiv. $NaBH_4$ and 10% Pd/C) in methanol at room temperature. After stirring for 10 min, complete deprotection of Cbz group occurred. HCl in 1,4-dioxane was added to the dipeptide (H_2N-Ile-Ala-OMe) formed to afford stable dipeptide hydrochloride salt **378** in 91% yield.



Scheme 3.28 N-Cbz Deprotection in dipeptide

3B.6 Gram Scale Utility:

Initial studies on N-Cbz deprotection were carried out on ~500 mg scale. In order to make this approach more practical ad general for the future development, we extended this method on a gram scale. In this regard, we prepared *N*-Cbz aniline (**352**), *N*-Cbz cyclohexylamine (**366**) and *N*-Cbz octyl amine (**367**) in gram scale quantity (up to 10 g).



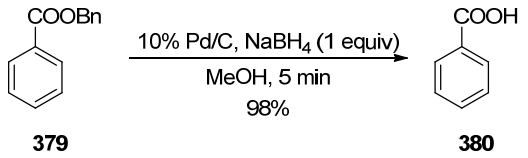
Scheme 3.29 Application to gram scale N-Cbz deprotection.

It is very interesting to note that complete *N*-Cbz deprotection of all the substrates occurred in just 20 minutes up to 10 g scale. Maximum of 1.5 equivalents of $NaBH_4$ and 10% Pd/C were required for the complete N-Cbz deprotection. Even in the large scale deprotection, we did not observe any catalytic poisoning of Pd catalyst by alkyl amines. N-Cbz deprotection was very facile and both the alkyl amines (cyclohexyl amine **321** and octyl amine **322**) were formed in excellent yields (see Scheme 3.29) without poisoning the catalyst.

3B.7 Hydrogenolysis of Benzyl ester:

After the success of N-Cbz deprotection and detailed study, we planned to extend the use of $NaBH_4$-Pd/C system for the hydrogenolysis of benzyl esters. We believed that deprotection of benzyl ester would be more facile under the reaction conditions. Benzyl ester of benzoic acid **379** was used as a model substrate to check the hydrogenolysis using the optimized reaction conditions. Benzyl benzoate **379** when treated with 1 equivalent of

$NaBH_4$ and 10% Pd/C in methanol at room temperature afforded benzoic acid **380** in 98% yield just 5 min



Scheme 3.30 Model reaction for hydrogenolysis of benzyl ester

Encouraged by this, we prepared different benzyl esters for generalizing the approach. Diffrent benzyl esters have been prepared (Scheme 3.31) and they were characterized by ^{1}H NMR. These benzyl esters (**381-384, 387-388**) were treated with 1 equivalent of $NaBH_4$ and 10% Pd/C in methanol at room temperature. Hydrogenolysis of benzyl esters occurred rapidly (5-10 min) by affording the corresponding carboxylic acids **385**, **386**, **389-392** in almost quantitative yields (Scheme 3.32).

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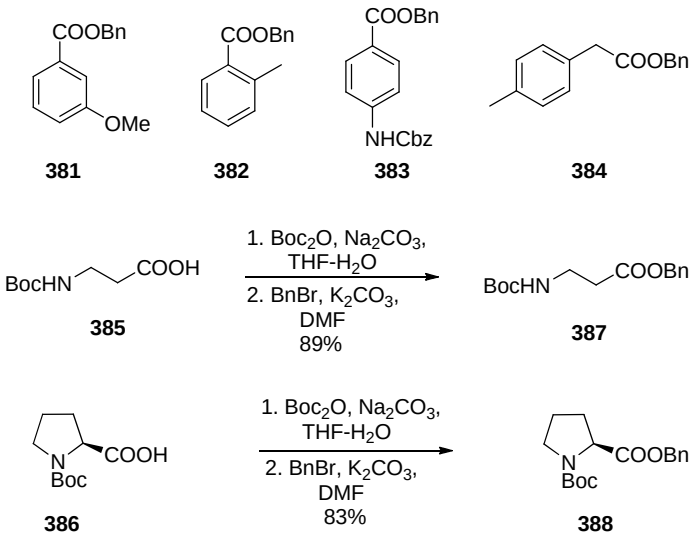
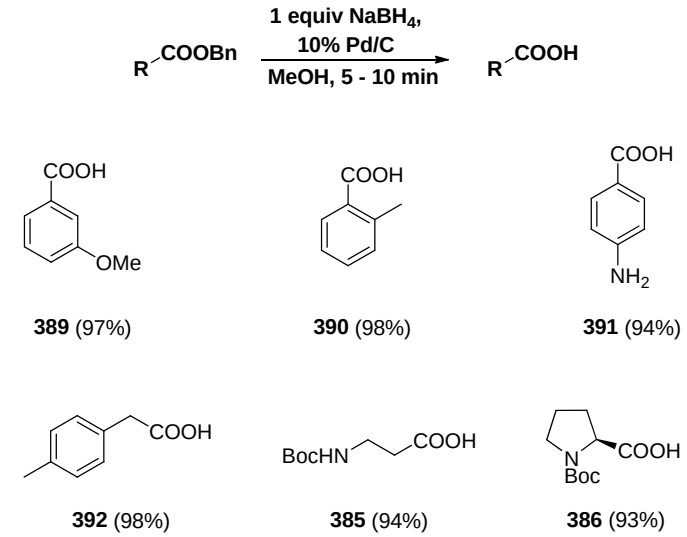


Scheme 3.31 Preparation of various benzyl esters

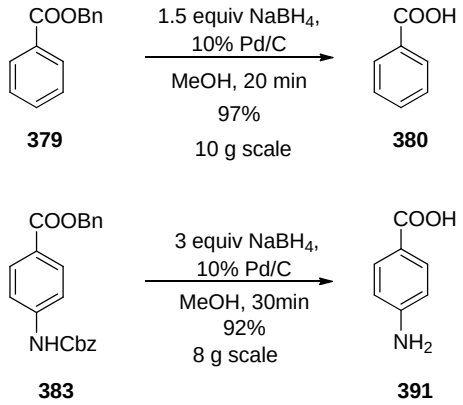
It is very important to note that the chiral substrate *N*-Boc-L-proline benzyl etser was converted into *N*-Boc-L-proline without any epimerization at chiral centre [$[\alpha]^{20}_D$ = –34.8 (*c* 0.5, MeOH); lit.[44] $[\alpha]^{20}_D$ = – 35.2 (*c* 0.5, MeOH)].



Scheme 3.32 Hydrogenolysis of various benzyl esters

3B.8 Gram Scale Application

Further application of this methodology has been demonstrated by the hydrogenolysis of benzyl esters on a gram scale.



Scheme 3.33 Gram scale hydrogenolysis of benzyl esters

Benzyl benzoate **379** (10 g) was subjected for the hydrogenolysis with 1.5 equivalent of $NaBH_4$ and 10% Pd/C in methanol. Within 20 min complete hydrogenolysis of benzyl ester occurred by affording benzoic acid **380** in 97% yield. In another demonstration, compound containing both benzyl ester and *N*-Cbz group **383** (Benzyl, *p*-N-Cbz benzoate) (8 g) was treated with $NaBH_4$ (3 equiv) and 10% Pd/C in methanol at room temperature.

Facile benzyl ester hydrogenolysis occurred in 30 minutes to afford *p*-amino benzoic acid **391** in 92% yield.

These studies concluded that $NaBH_4$ and Pd/C system is highly efficient, cost effective and practical for the deprotection of N-Cbz group and benzyl ester hydrogenolysis. In comparison to triethylsilane (Et_3SiH), $NaBH_4$ is readily available, stable to moisture, easy to handle as it is solid and more importantly less expensive (Aldrich India: Et_3SiH 100 mL ₹ 15,115.00/-, $NaBH_4$ powder, 100g ₹ 2,725.00/-). Moreover, approach is very rapid and high yielding without any epimerization.

3B.9 Conclusions

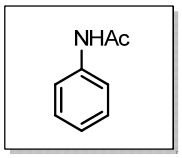
In summary we have developed an efficient catalytic hydrogen transfer method for the orthogonal deprotection of *N*-Cbz as well as for bezyl ester hydrogenolysis. The deprotection is very facile and rapid at room temperature affording amines in excellent yields with a great chemoselectivity. The reaction conditions are very mild and many of the conventional protecting groups of amines were stable under the reaction conditions. Furthermore, the reaction conditions enable the deprotection of chiral amines without any epimerization. Furthermore gram scale deprotection of Cbz and hydrogenolysis of benzyl ester have been demonstrated.

Experimental Section A:

General: Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2, argon and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High resolution mass spectrometry using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in open glass capillary and values are uncorrected.

General procedure A for Acetylation of amines:

***N*-phenylacetamide (290):**



To a stirred solution of aniline (0.5 mL, 5.3 mmol 1 equiv.) in dry DCM (10 mL) under argon was added acetic anhydride (0.66 mL, 6.4 mmol, 1.2 equiv) and the reaction was stirred at room temperature and monitored by TLC. Upon completion the reaction mixture was washed with a saturated solution of sodium carbonate and the combined organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the desired product **290** in yield (0.72 g) as a white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, 3H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 2.17 (s, 3H).

***N*-(4-chlorophenyl) acetamide (291):**

Compound **291** was prepared following the general procedure A, starting from 4-chloroaniline in 55% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 2.04 (s, 3H).

***N*-(3-bromophenyl) acetamide (292):**

Compound **291** was prepared following the general procedure A,, from 3-bromoaniline in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.13 (m, 2H), 2.18 (s, 3H)

***N*-(4-cyanophenyl)acetamide (293):**

Compound **293** was prepared following the general procedure A, from 4-cyanoaniline in 88% yield.^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.75 (s, 4H), 2.09 (s, 3H).

***N*-(4-nitrophenyl)acetamide (294):**

Compound **294** was prepared following the general procedure A, from 4-nitroaniline in 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.21 (d, *J* = 9.4 Hz, 2H), 7.82 (d, *J* = 9.3 Hz, 2H), 2.11 (s, 3H).

Methyl 4-acetamidobenzoate (295):

Compound **294** was prepared following the general procedure A, from methyl 4-aminobenzoate in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 3H), 2.19 (s, 4H).

***N*-(2-methoxyphenyl)acetamide (296):**

Compound **296** was prepared following the general procedure A, from 2-methoxyaniline in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.01 (td, *J* = 7.9, 1.4 Hz, 1H), 6.98 – 6.89 (m, *J* = 7.7, 6.7 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 3.86 (s, 3H), 2.18 (s, 3H).

***N*-(4-methoxyphenyl)acetamide (297):**

Compound **297** was prepared following the general procedure A, from 4-methoxyaniline in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.9, 6.4 Hz, 3H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 2.15 (s, 3H).

***N*-(3, 5-dimethoxyphenyl)acetamide (298):**

Compound **298** was prepared following the general procedure A, from 3, 4-dimethoxyaniline in 73% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 1.9 Hz, 1H), 6.71 (s, 2H), 6.19 (s, 1H), 3.73 (s, 6H), 2.12 (s, 3H).

***N*-(2, 6-diethylphenyl)acetamide (300):**

Compound **300** was prepared following the general procedure A, from 2, 6 diethylaniline in 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.07 (m, 3H), 6.96 (bs, 1H), 2.60 (dq, *J* = 13.8, 6.8 Hz, 4H), 1.17 (dt, *J* = 13.8, 6.8 Hz, 6H).

***N*-cyclohexylacetamide (314):**

Compound **314** was prepared following the general procedure A, from cyclohexylamine in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 1H), 3.82 – 3.68 (m, 1H), 1.99 (s, 3H), 1.96 – 1.87 (m, 2H), 1.75 – 1.67 (m, 2H), 1.66 – 1.57 (m, 1H), 1.42 – 1.29 (m, 2H), 1.21 – 1.06 (m, 3H)

***N*-octylacetamide (315):**

Compound **315** was prepared following the general procedure A, from octylamine 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (s, 1H), 3.25 – 3.16 (m, 2H), 1.95 (d, *J* = 6.9 Hz, 3H), 1.52 – 1.40 (m, 2H), 1.34 – 1.18 (m, 10H), 0.89 – 0.81 (m, 3H).

***N*-octadecylacetamide (316):**

Compound **316** was prepared following the general procedure A, from octadecan-1-amine 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.20 (dd, *J* = 12.8, 7.0 Hz, 2H), 1.96 (s, 3H), 1.51 – 1.40 (m, 2H), 1.31 – 1.16 (m, 30H), 0.84 (t, *J* = 6.9 Hz, 3H).

***N*-benzylacetamide (317):**

Compound **317** was prepared following the general procedure A, from benzylamine in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.06 (m, 5H), 5.93 (s, 1H), 4.26 (d, *J* = 5.2 Hz, 2H), 1.86 (s, 3H).

***N*-(thiazol-2-yl)acetamide (299):**

Compound **299** was prepared following the general procedure A, from 2-aminothiazole in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 3.6 Hz, 1H), 7.01 (d, *J* = 3.7 Hz, 1H), 2.35 (s, 3H).

***N*-(pyridin-3-yl) acetamide (299A):**

Compound **299A** was prepared following the general procedure A, from 3-aminopyridine in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.59 (s, 1H), 8.30 (d, *J* = 4.6 Hz, 1H), 8.20 (d, *J* = 7.4 Hz, 1H), 7.32 – 7.26 (m, 1H), 2.20 (s, 3H).

(*S*)-*N*-(1-phenylethyl)acetamide (319):

Compound **319** was prepared following the general procedure A, from (*s*)-alpha methyl benzylamine in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.23 (m, 5H), 5.95 (s, 1H), 5.16 – 5.07 (m, 1H), 1.98 (s, 3H), 1.48 (d, *J* = 6.9 Hz, 3H).

(*R*)-*N*-(2-hydroxy-1-phenylethyl) acetamide (320):

Compound **320** was prepared following the general procedure A, from (*R*)-phenylglycinol in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 6.35 (s, 1H), 5.07 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.94 – 3.85 (m, 2H), 2.07 (s, 3H), 2.02 (s, 1H).

***N*-(4-aminophenyl) acetamide (301):**

To a stirred solution of *N*-(4-nitrophenyl) acetamide **294** (1 g, 5.55 mmol) in EtOH/water (25:5 ml) was added iron powder (3.09 g, 55.5 mmol) and 2 drops of conc.HCl. The resulting mixture was refluxed for 2 h. Then 10% $NaHCO_3$ solution was added and the suspension was stirred for 10 min. After which EtOH was evaporated in vacuuo and then EtOAc was added. The aqueous layer was washed with EtOAc (2 X 20 mL) and combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuuo to afford crude product **301,** which was purified by silica gel column chromatography using EtOAc:Hexane (20:80) to give pure compound **301** (0.79 g, 95% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (bs, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 8.7 Hz, 2H), 4.77 (bs, 2H), 1.89 (s, 3H).

***N, N*-dibenzylacetamide (318):**

Compound **318** was prepared following the general procedure A, from dibenzylamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 6.97 (m, 10H), 4.52 (s, 2H), 4.36 (s, 2H), 2.14 (S, 3H).

Benzyl phenylcarbamate (328):

The compound **328** was prepared following the literature procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 9H), 7.10 – 7.04 (m, 1H), 6.72 (s, 1H), 5.21 (s, 2H).

tert-butyl phenylcarbamate (329):

The compound **329** was prepared following the literature procedure.[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.00 (t, J = 7.3 Hz, 1H), 6.48 (bs, 1H), 1.49 (s, 9H)

(9H-fluoren-9-yl) methyl phenylcarbamate (330):

To a stirred solution of aniline (0.2 g, 2.14 mmol) and pyridine (0.2 mL, 2.57 mmol) in dry DCM at 0^{o}C was added solution of Fmoc-Cl (0.61g, 2.36 mmol) in dry DCM and the resulting reaction mixture was stirred at room temperature for 1 h. After which the solution was acidified with dil.HCl. The aqueous layer was extracted with DCM (2 X 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford **330** (0.54 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.4 Hz, 2H), 7.45 – 7.27 (m, 8H), 7.08 (t, J = 7.4 Hz, 1H), 6.65 (bs, 1H), 4.55 (d, J = 6.6 Hz, 2H), 4.28 (t, J = 6.6 Hz, 1H)

4-methyl-N-phenylbenzenesulfonamide (331):

To a stirred solution of aniline (0.2 g, 2.14 mmol) and Et_3N (0.448 mL, 3.22 mmol) in dry DCM at 0 ^{o}C was added p-toluenesulfonyl chloride (TsCl) (0.49 g, 2.57 mmol) portion wise and reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was acidified by the addition of dilute HCl and the aqueous layer was extracted with DCM (2 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **331** in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.21 – 7.15 (m, 4H), 7.08 – 7.01 (m, 3H), 2.32 (s, 4H)

Benzyl (4-acetamidophenyl) carbamate (334):

The compound **334** was prepared using CbzCl and Et_3N in DCM starting from compound **301.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.66 (s, 1H), 7.50 – 7.28 (m, 9H), 5.13 (s, 2H), 2.00 (s, 3H)

tert-butyl (4-acetamidophenyl)carbamate (335):

The compound **335** was prepared using Boc_2O and Et_3N in DCM starting from compound **301.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 5H), 6.48 (bs, 1H), 2.13 (s, 3H), 1.49 (s, 9H).

(S)-methyl 2-acetamido-5-(((benzyloxy)carbonyl)amino)pentanoate (332):

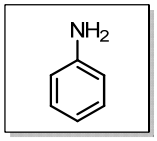
L-Ornithine hydrochloride (2.0g, 11.86mmol) and copper (II) acetate (1.184, 5.93mmol) were dissolved in 9 mL of 10% aq. sodium carbonate, and the solution was vigorously stirred for 45 minutes. To the stirred solution were added 20 mL of water and 20 mL of 1,4-dioxane, followed by slow addition of a solution of CbzCl (1.856mL, 13.047mmol) in 10 mL of 1,4-dioxane. After 6 hr, $NaBH_4$ (0.538g, 14.23mmol) was added slowely After 15 min, the copper(I) oxide precipitate formed was filtered. The clear, colorless filtrate was neutralized with dilute HCl in cold condition. L- N^{δ}-Cbz ornithine was precipitated and was filtered and washed with water. L- N^{δ}-Cbz ornithine was dissolved in 1N NaOH and to this solution acetic anhydride (1.452g, 14.23mmol) was added and raction mixture was stirred for 3 hr at rt. Ethyl acetate was added and aqueous layer was extracted with EtOAc washed with brine, dried over anhydrous sodium sulphate and evaporated in vaccuo to afford L- N^{δ}-Cbz-N^{α}-acyl ornithine which was dissolven in DMF under N_2 and K_2CO_3 (3.27g, 23.72mmol) followed MeI (1.47ml, 23.72mmol) added and resulting reaction mixture was stirred at for 2 h. After which water and EtOAc were added and organic layer was separated. Aqueous layer was extracted with EtOAc and combined organic layer washed with brine, sodium thiosulfate, dried over anhydrous $NaSO_4$ and solvent evaporated to dryness to afford crude ester **332** which was purified by silica gel column chromatography (3.25g, 85% yield).

$[\alpha]_D^{25}$ = +26 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.22 (s, 1H), 5.08 (s, 2H), 4.96 (bs, 1H), 4.60 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 12.9, 6.5 Hz, 2H), 2.02 (s, 3H), 1.94 – 1.79 (m, 1H), 1.77 – 1.68 (m, 1H), 1.61 – 1.49 (m, 2H); HRMS (ESI): Calcd. For $C_{16}H_{22}N_2O_5Na$ $(M + Na)^+$: 345.1426 found 345.1434.

General procedure B for the deacetylation of amine:

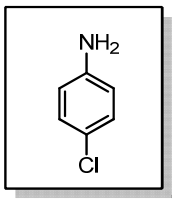
To a stirred solution of *N*-acetyl amine (0.2 g) in anhydrous THF (2 mL) was added Schwartz reagent (1.5-2 equiv) at room temperature and the reaction mixture was stirred for 2-5 min. After which, water was added to quench the reaction. Then the resulting solution was extracted with EtOAc (10 mL X 2). The combined organic layer was washed with brine solution and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford the corresponding crude amine which was purified by silica gel column chromatography to afford pure amine.

Aniline (302):[45]



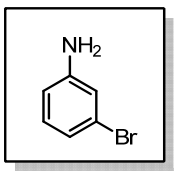
Compound **302** was obtained following the general procedure B starting from **290** as light yellow liquid (0.129 g, 94%)**.** IR (cm^{-1}) 3350, 3033, 2873, 1601, 1496; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 2H), 6.79 – 6.74 (m, 1H), 6.72 – 6.68 (m, 2H), 3.63 (bs, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 129.4, 118.7, 115.2, HRMS (ESI): Calcd. For C_6H_7N $(M + H)^+$: 94.0656 found 94.0659

4-Chloroaniline (303):[46]



Compound **303** was obtained following the general procedure B starting from **291** as a white solid (0.138 g, 92%)**.** mp = 68-70 ^oC; IR (cm^{-1}): 3472, 3364, 3156, 1614, 1492; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.7 Hz, 2H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 129.2, 123.3, 116.4, HRMS (ESI): Calcd. For C_6H_7ClN $(M+H)^+$:128.0267 found 128.0269

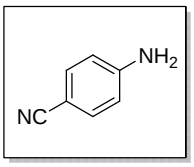
3-Bromoaniline (304):[47]



Compound **304** was obtained following the general procedure B starting from **292** as a light yellow liquid (0.144 g, 90%). IR (cm^{-1}): 3454, 3371, 3217, 2963, 1580. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, *J* = 8.0 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.59 (ddd, *J* = 7.8, 2.2, 0.9 Hz, 1H), 3.70 (bs, 2H),

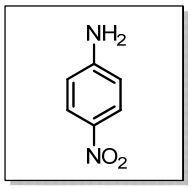
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 130.7, 123.2, 121.5, 117.9, 113.7, HRMS (ESI): Calcd. For $C_6H_7BrN\,(M+H)^+$:171.9762 found 171.9767

4-aminobenzonitrile (305):[45]



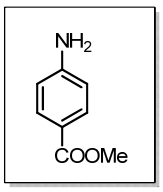
Compound **305** was obtained following the general procedure B starting from **293** as a white solid (0.123 g, 84%)**.** mp=84-85°C; IR KBr (cm^{-1}): 3466, 2220; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, *J* = 8.7 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 6.13 (bs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.5, 133.9, 121.2, 113.9, 96.0, HRMS (ESI): Calcd. For $C_7H_7N_2\,(M+H)^+$: 119.0609 found 119.0611

4-Nitroaniline (306):[45]



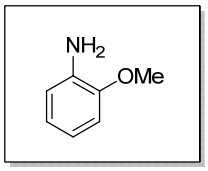
Compound **306** was obtained following the general procedure B starting from **294** as a yellow solid (0.136 g, 89%)**.** mp = 147-149 °C; IR KBr (cm^{-1}): 3470, 3373, 1583, 1285; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 9.1 Hz, 1H), 6.62 (d, *J* = 9.1 Hz, 1H), 4.38 (bs, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 129.2, 123.3, 116.4, HRMS (ESI): Calcd. For $C_6H_7N_2O_2\,(M+H)^+$: 139.0507 found 139.0512

Methyl 4-aminobenzoate (307): [45]



Compound **307** was obtained following the general procedure B starting from **295** as a light yellow solid (0.138 g, 87%). mp =109-111 °C; IR KBr (cm^{-1}): 3430, 3334, 1680, 1629; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.82 (m, 2H), 6.64–6.6 (m, 2H), 4.06 (bs, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 150.9, 131.7, 119.9, 113.9, 51.7; HRMS (ESI): Calcd. For $C_8H_{10}NO_2\,(M+H)^+$: 152.0711 found 152.0711

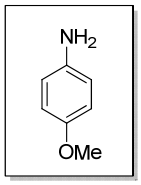
2-methoxyaniline (308):[48]



Compound **308** was obtained following the general procedure B starting from **296** as a light yellow liquid (0.128 g, 86%). IR (cm^{-1}): 3466, 3356, 2973, 2866, 1620, 1506; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.68 (m, 4H), 3.85 (s, 3H), 3.56 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

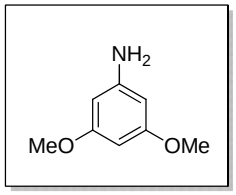
δ 147.5, 136.0, 121.2, 118.8, 115.3, 110.6, 55.6, HRMS (ESI): Calcd. For $C_7H_{10}NO$ $(M+H)^+$:124.0762 found 124.762

4-methoxyaniline (309):[46]



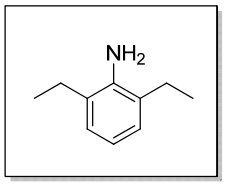
Compound **309** was obtained following the general procedure B starting from **297** as white solid (0.131g, 88%)**.** mp = 54-57 ^oC; IR (cm^{-1}): 3422, 3332; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 8.9 Hz, 1H), 6.65 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)) δ 152.9, 140.0, 116.5, 114.9, 55.9, HRMS (ESI): Calcd. For $C_7H_{10}NO$ $(M+H)^+$: 124.0762 found 124.0764

3, 5-dimethoxyaniline (310):[49]



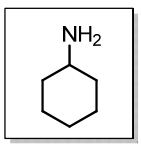
Compound **310** was obtained following the general procedure B starting from **298** as a light brown solid (0.135g, 86%). mp = 53-56 ^oC; IR (cm^{-1}): 3440, 3345, 2920, 1595**;** ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (t, *J* = 2.1 Hz, 1H), 5.87 (d, *J* = 2.1 Hz, 2H), 3.74 (2s, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 148.5, 93.9, 91.1, 55.3, HRMS (ESI): Calcd. For $C_8H_{12}NO_2$ $(M+H)^+$:154.0868 found 154.0868

2, 6-diethylaniline (312):



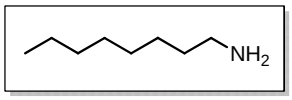
Compound **312** was obtained following the general procedure B starting from **300** as colorless oil (0.135g, 87%). IR (cm^{-1}) neat: 3389, 3022, 2967, 1620, 1448**;** ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.5 Hz, 2H), 6.73 (t, *J* = 7.5 Hz, 1H), 3.88 (bs, 2H), 2.53 (q, *J* = 7.5 Hz, 4H), 1.24 (t, *J* = 7.5 Hz, 6H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 128.1, 126.2, 118.7, 24.4, 13.2 HRMS (ESI): Calcd. For $C_5H_7N_2$ $(M+H)^+$: 150.1282 found 150.1284

Cyclohexanamine (1k):[50]



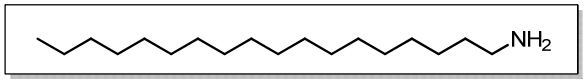
Compound **2k** was obtained following the general procedure B starting from **1k** as light yellow liquid (0.128 g, 91%). IR (cm^{-1}) neat: 3486, 2975, 2928, 2855, 1646, 1594; ^1H NMR (400 MHz $CDCl_3$) δ 2.61 (m, 1H), 1.85 – 1.77 (m, 2H), 1.75 – 1.65 (m, 2H), 1.63 – 1.55 (m, 1H), 1.39 – 1.18 (m, 4H), 1.17 – 0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.6, 37.0, 25.8, 25.3; HRMS (ESI): Calcd. For $C_6H_{14}N$ $(M+H)^+$:100.1126 found 100.1126

Octan-1-amine (321):[51]



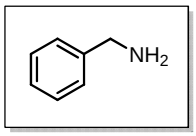
Compound **321** was obtained following the general procedure B starting from **314** as colorless liquid (0.140 g, 93%)**.** IR (cm^{-1}) neat: 3370, 3210, 1605; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (t, *J* = 7.0 Hz, 2H), 1.48 – 1.38 (m, 2H), 1.35 – 1.17 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 34.0, 32.0, 29.6, 29.4, 27.0, 22.8, 14.2, HRMS (ESI): Calcd. For $C_8H_{19}N$ $(M+H)^+$:130.1595 found 130.1599

Octadecan-1-amine (323):[52]



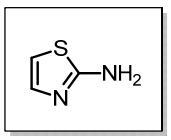
Compound **323** was obtained following the general procedure B starting from **316** as white solid (0.157g, 91%). mp = 49-51°C; IR (cm^{-1}) KBr: 3410, 3230 1635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (t, *J* = 7 Hz, 2H), 1.42 (m, 2H), 1.33 – 1.20 (m, 32H), 0.87 (t, *J* = 6.9 Hz, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.4, 34.1, 32.1, 29.9, 29.7, 29.5, 27.1, 22.8, 14.3, HRMS (ESI): Calcd. For $C_{18}H_{40}N$ $(M+H)^+$: 270.3161 found 270.3163

Benzylamine (324):[53]



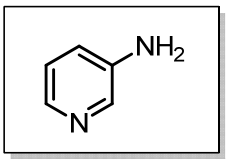
Compound **324** was obtained following the general procedure B starting from **317** as pale yellow liquid (0.13 g, 91%). IR (cm^{-1}) neat: 3361, 2953, 1642, 1576; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 4H), 7.28 – 7.22 (m, 1H), 3.87 (s, 2H), 1.50 (bs, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 128.7, 127.2, 126.9, 46.6, HRMS (ESI): Calcd. For $C_7H_{10}N$ $(M+H)^+$: 108.0813 found 108.0811

Thiazol-2-amine (311):[54]



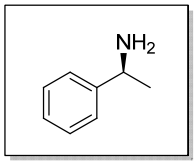
Compound **311** was obtained following the general procedure B starting from **299** as light yellow color solid (0.124g, 89%). mp = 90-92 °C; IR (cm^{-1}): 3416, 3278, 3109, 3094, 1632, 1526, 1470; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, *J* = 3.7 Hz, 1H), 6.89 (bs, 2H), 6.53 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 138.1, 106.0; HRMS (ESI): Calcd. For $C_3H_5N_2S$ $(M+H)^+$: 101.0173 found 101.0178

3-aminopyridine (311A):[48]



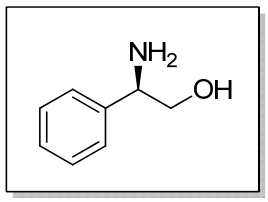
Compound **311A** was obtained following the general procedure B starting from **299A** as a light brown solid (0.123 g, 89%). mp = 63-66 ^{o}C; IR (cm^{-1}): 3360, 3145, 3045, 1627, 1565, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 4.7, 1.1 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.97 (ddd, *J* = 8.3, 2.6, 1.3 Hz, 1H), 3.57 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7, 140.0, 137.5, 123.8, 121.5, HRMS (ESI): Calcd. For $C_5H_7N_2$ $(M+H)^+$: 95.0609 found 95.0611

(*S*)-1-phenylethanamine (326):[18]



Compound **326** was obtained following the general procedure B starting from **319** as pale yellow oil (0.138 g, 93%). $[\alpha]_D^{25}$ = –34.2 (c 1.0, $CHCl_3$)(lit[14]. $[\alpha]_D^{25}$ = – 35.1 (*c* 1.0, $CHCl_3$); IR (cm^{-1}): 3363, 3027, 2966, 1598, 1492; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.30 (m, 4H), 7.26–7.21 (m, 1H), 4.12 (q, *J* = 6.6 Hz, 1H), 1.54 (bs, 2H), 1.39 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 128.6, 126.9, 125.8, 51.5, 25.8; HRMS (ESI): Calcd. For $C_8H_{12}N$ $(M+H)^+$: 122.0969 found 122.0973

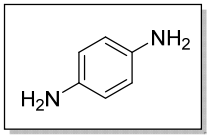
(*R*)-2-amino-2-phenylethanol (327):[19]



Compound **327** was obtained following the general procedure B starting from **320** as yellow solid.

(0.136 g, 89%). mp = 74-77 ^{o}C; $[\alpha]_D^{25}$ = -30.1 (*c* 0.76, 1N HCl) (lit.[15] $[\alpha]_D^{25}$ = -31 (*c* 0.76,1NHCl); IR (cm^{-1}): 3200, 2835, 1604, 1497, 1453; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 5H), 3.98 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.53 – 3.46 (m, 1H), 2.38 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 128.8, 127.7, 126.6, 68.0, 57.4; HRMS (ESI): Calcd. For $C_8H_{12}NO$ $(M+H)^+$: 138.0919 found 138.0920

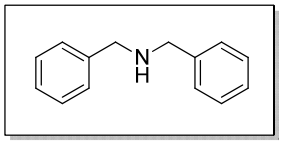
Benzene-1, 4-diamine (313):[55]



Compound **301** was obtained following the general procedure B starting from **1s** as light brown solid (0.129 g, 90%)**.** mp = 140-143^{o}C; IR (cm^{-1}): 3360, 3281, 3174; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.36 (s, 4H),

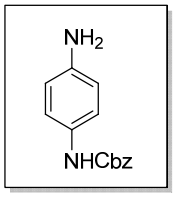
4.18 (bs, 4H), ^{13}C NMR (100 MHz, DMSO-d_6) δ 139.4, 115.9, HRMS (ESI): Calcd. For $C_6H_9N_2$ $(M+H)^+$: 109.0765 found 109.0766

Dibenzylamine (325):[56]



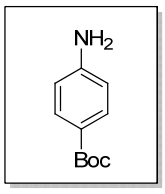
Compound **325** was obtained following the general procedure B starting from **318** as colorless liquid (0.151g, 94%). IR (cm^{-1}): 3061, 3027, 2835, 1643, 1604, 1495 ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.13 (m, 10H), 3.73 (S, 4H), 1.86 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 128.6, 128.4, 127.2, 53.2, HRMS (ESI): Calcd. For $C_{14}H_{16}N$ $(M+H)^+$: 198.1283 found 198.1289

Benzyl (4-aminophenyl)carbamate (336):[57]



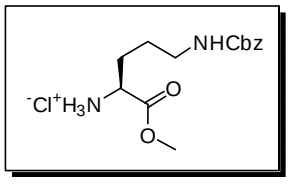
Compound **336** was obtained following the general procedure B starting from **334** as light brown solid (0.155 g, 91%)**.** mp = 90-95 ^{o}C; IR (cm^{-1}): ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 1H), 7.43 –7.28 (m, 5H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.49 (d, *J* = 8.7 Hz, 2H), 5.09 (s, 2H), 4.79 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-9) δ 154.1, 137.5, 128.9, 128.4, 128.4, 120.7, 114.49, 65.8; HRMS (ESI): Calcd. For $C_{14}H_{15}N_2O_2$ $(M+H)^+$: 243.1134 found 243.1135

Tert-butyl 4-aminobenzoate (337):[58]



Compound **337** was obtained following the general procedure B starting from **335** in (0.154g, 93%)**.** mp= 112-115 ^{o}C**;** ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (s, 1H), 7.06 (d, *J* = 7.7 Hz, 2H), 6.46 (d, *J* = 8.8 Hz, 2H), 4.73 (bs, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 144.4, 129.1, 120.6, 114.5, 78.6, 28.8; HRMS (ESI): Calcd. For $C_{11}H_{17}N_2O_2$ $(M+H)^+$: 209.1290 found 209.1292

(*S*)-5-(((benzyloxy)carbonyl)amino)-1-methoxy-1-oxopentan-2-aminium chloride (333):



To a stirred solution of *N*-acetyl amine **332** (0.2 g, 0.62mmol) in anhydrous THF (2 mL) was added Schwartz reagent (0.32 g, 1.2 mmol) at room temperature and the reaction mixture was stirred

for 2-5 min. After which, HCl in dioxane was added to quench the reaction. Excess solvent was evaporated in vaccuo and Et_2O was added to precipitate hydrochloride salt which was washed with cold hexane to afford pure **333** (0.157 g, 80%).

$[\alpha]_D^{25}$ = +13.8 (c 4.0, MeOH)(lit^{20} $[\alpha]_D^{25}$ = +14 (*c* 4, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 3H), 7.38 – 7.22 (m, 5H), 5.70 (s, 1H), 5.04 (s, 2H), 4.17 (s, 1H), 3.63 (s, 3H), 3.14 (d, *J* = 53.2 Hz, 2H), 2.06 (s, 2H), 1.72 (d, *J* = 48.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 156.9, 136.9, 128.6, 128.1, 66.7, 53.4, 53.0, 40.3, 27.6, 25.4; HRMS (ESI): Calcd. For $C_{14}H_{22}N_2O_4$ $(M)^+$: 281.1496 found 281.1503

3B.10 Experminetal Section B:

General procedure C for Cbz protection of amine:

To a solution of amine (0.5g) and $NaHCO_3$ (2 equi.) in THF (10mL) was slowly added N-carbobenzyloxy chloride (1.2 equi.). After being stirred for 2 h at 0 °C, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with dil. HCl, brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified using flash chromatography to afford Cbz protected amine.

Benzyl phenylcarbamate (352):

Compound **352** was prepared following the general procedure C, from aniline in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 7H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.02 (dd, *J* = 10.5, 4.1 Hz, 1H), 6.66 (bs, 1H), 5.15 (s, 2H).

Benzyl (4-chlorophenyl)carbamate (353):

Compound **353** was prepared following the general procedure C, from 4-chloroaniline in 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 4H), 7.37 – 7.32 (m, 3H), 7.26 (dt, *J* = 3.7, 2.4 Hz, 2H), 6.68 (s, 1H), 5.20 (s, 2H).

Benzyl (3-bromophenyl)carbamate (354):

Compound **354** was prepared following the general procedure C, from 3-bromoaniline in 86% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.41 – 7.33 (m, 5H), 7.24 (s, 1H), 7.18-7.13 (m, 2H), 6.66 (s, 1H), 5.18 (s, 2H).

Ethyl 4-(((benzyloxy)carbonyl)amino)benzoate (355):

Compound **355** was prepared following the general procedure C, from ethyl 4-aminobenzoate in 85% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.0 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.43 – 7.30 (m, 5H), 6.91 (s, 1H), 5.22 (d, *J* = 1.6 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

Benzyl (2-methoxyphenyl)carbamate (356):

Compound **356** was prepared following the general procedure C, from 2-methoxylaniline in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.46 – 7.30 (m, 6H), 7.04 – 6.93 (m, 2H), 6.88 – 6.83 (m, 1H), 5.21 (s, 2H), 3.85 (s, 3H)

Benzyl (4-methoxyphenyl)carbamate (357):

Compound **357** was prepared following the general procedure C, from 4-methoxylaniline in 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 7H), 6.86 – 6.80 (m, 2H), 6.51 (bs, 1H), 5.17 (s, 2H), 3.77 (s, 3H).

Benzyl (3,5-dimethoxyphenyl)carbamate (358);

Compound **358** was prepared following the general procedure C, from 3, 5-methoxylaniline in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.61 (d, *J* = 10.4 Hz, 3H), 6.17 (t, *J* = 2.1 Hz, 1H), 5.16 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 6H).

Benzyl o-tolylcarbamate (359):

Compound **359** was prepared following the general procedure C, from o-toluidine in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.45 – 7.32 (m, 5H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.45 (s, 1H), 5.21 (s, 2H), 2.24 (s, 3H).

2-(((benzyloxy)carbonyl)amino)benzoic acid (360):

Compound **360** was prepared following the general procedure C, 2-amino benzoic acid in 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.50 (d, *J* = 8.6 Hz, 1H), 8.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.47 – 7.32 (m, 6H), 7.08 (dd, *J* = 11.7, 4.4 Hz, 1H), 5.24 (s, 2H).

Benzyl (4-aminophenyl)carbamate (336):

To a stirred solution of 1, 4 diamono benzene (2g, 18.5 mmol) in DCM (20 mL) was added benzyl chloroformate (2.64mL, 18.5mmol) at room temperature and reaction mixture stirred for 1 h. Water and DCM were added to the reaction mixture and aqueous layer was separated, dried over anhydrous Na_2SO_4 and evaporated to dryness gave crude mono Cbz protected product which upon purification using flash chromatography afforded pure mono Cbz protected amine **336** in 82% yield.^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22 (s, 1H), 7.43 –7.28 (m, 5H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.49 (d, *J* = 8.7 Hz, 2H), 5.09 (s, 2H), 4.79 (bs, 2H).

Dibenzyl 1, 3-phenylenedicarbamate (361):

Compound **361** was prepared following the general procedure C, from 1, 3-diamino benzene 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.43 – 7.30 (m, 10H), 7.25 – 7.17 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.72 (s, 2H), 5.19 (s, 4H).

Benzyl cyclohexylcarbamate (366):

Compound **366** was prepared following the general procedure C, cyclohexyl amine in 92% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 5H), 5.08 (s, 2H), 4.63 (s, 1H), 3.50 (s, 1H), 1.93 (d, *J* = 12.4 Hz, 2H), 1.76 – 1.65 (m, 2H), 1.64 – 1.53 (m, 2H), 1.34 (dd, *J* = 24.7, 12.1 Hz, 2H), 1.23 – 1.04 (m, 2H).

Benzyl octylcarbamate (367):

Compound **367** was prepared following the general procedure C, octyl amine in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 5H), 5.07 (s, 2H), 4.73 (s, 1H), 3.16 (dd, *J* = 13.0, 6.4 Hz, 2H), 1.53 – 1.39 (m, *J* = 6.2 Hz, 2H), 1.32 – 1.17 (m, *J* = 5.4 Hz, 10H), 0.90 – 0.79 (m, *J* = 6.9, 5.6 Hz, 3H).

Benzyl benzylcarbamate (368):

Compound **368** was prepared following the general procedure C, from benzyl amine 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 10H), 5.11 (2d, *J* = 27.3 Hz, 3H), 4.39 (d, *J* = 5.9 Hz, 2H).

Benzyl dibenzylcarbamate (369):

Compound **369** was prepared following the general procedure C, from dibenzyl amine in 81% yield

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 13H), 7.16 (d, *J* = 6.0 Hz, 2H), 5.25 (s, 2H), 4.45 (d, *J* = 23.1 Hz, 4H).

(*S*)-benzyl (1-phenylethyl)carbamate (370):

Compound **370** was prepared following the general procedure C, from (*S*)-alpha methyl benzyl amine in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 10H), 5.13 – 4.92 (m, 3H), 4.83 (s, 1H), 1.46 (s, 3H).

(*R*)-benzyl (2-hydroxy-1-phenylethyl)carbamate (371):

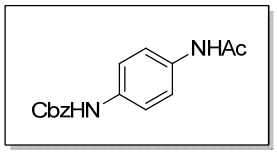
Compound **371** was prepared following the general procedure C, from (*R*)-phenyl glycinol in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 10H), 5.48 (d, *J* = 6.7 Hz, 1H), 5.09 (dd, *J* = 12.2, 6.6 Hz, 2H), 4.83 (s, 1H), 3.92 – 3.79 (m, 2H), 2.05 (s, 1H).

Benzyl tert-butyl 1, 4-phenylenedicarbamate (374):

To a stirred solution of **336** (0.2 g, 0.82 mmol) in dry DCM (5 mL) and Et_3N (0.069ml, 0.98mmol) under argon was added Boc_2O (0.114g, 0.82mmol) and the reaction was stirred at room temperature and monitored by TLC. Upon completion the reaction mixture was washed with a saturated solution of sodium carbonate followed by 5% HCl and the combined organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the desired product **374** in 91 yield (0.26g).

^{1}H NMR (400 MHz, DMSO-D6) δ 9.59 (s, 1H), 9.20 (s, 1H), 7.43 – 7.36 (m, 4H), 7.36 – 7.29 (m, 5H), 5.12 (s, 2H), 1.46 (s, 9H).

Benzyl (4-acetamidophenyl)carbamate (334):



To a stirred solution of **336** (0.2 g, 0.82 mmol) in dry DCM (5 mL) under argon was added acetic anhydride (0.093 mL, 0.9mmol) and the reaction was stirred at room temperature and monitored by TLC. Upon completion the reaction mixture was washed with a saturated solution of sodium carbonate followed by dil.HCl and the combined organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the desired product **334** in 82 yields (0.19g).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.66 (s, 1H), 7.50 – 7.28 (m, 9H), 5.13 (s, 2H), 2.00 (s, 3H)

General procedure D for esterification of carboxylic acids:

To a stirred solution of acid (0.5 g,) in dry DMF (5 mL) under argon was added Benzyl bromide (1.1 equiv) and the reaction was stirred at room temperature and monitored by TLC. Upon completion the reaction mixture was washed with a saturated solution of sodium carbonate and the combined organic layer was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to afford the desired product

Benzyl benzoate (379):

Compound **379** was prepared following the general procedure D, from benzoic acid in 92% yield

1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J = 5.7, 4.2 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.48 – 7.32 (m, 7H), 5.37 (s, 2H).

Benzyl 3-methoxybenzoate (381):

Compound **381**was prepared following the general procedure D, from 3-methoxy benzoic acid in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 1H), 7.60 (dt, *J* = 4.4, 2.2 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.42 – 7.31 (m, 4H), 7.10 (dtd, *J* = 8.3, 3.0, 1.0 Hz, 1H), 5.37 (S, 2H), 3.84 (S, 3H).

Benzyl 2-methylbenzoate (382):

Compound **382** was prepared following the general procedure D, from 2-methyl benzoic acid in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.41 – 7.29 (m, 4H), 7.25 – 7.19 (m, 2H), 5.33 (s, 2H), 2.60 (s, 3H).

Benzyl 4-(((benzyloxy)carbonyl)amino)benzoate (383)

Compound **383** was prepared following the general procedure D, 4-(((benzyloxy)carbonyl)amino)benzoic acid in 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.46 – 7.29 (m, 12H), 6.83 (s, 1H), 5.32 (s, 2H), 5.19 (S, 2H).

Benzyl 2-(p-tolyl)acetate (384):

Compound **348** was prepared following the general procedure D, from 2-(*p*-tolyl) acetic acid in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H).5.11 (s, 2H), 3.62 (s, 2H), 2.32 (s, 3H).

Benzyl 3-((tert-butoxycarbonyl)amino)propanoate (387):

Compound **387** was prepared following the general procedure D, from Boc-beta-alanine in 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.12 (s, 2H), 4.99 (s, 1H), 3.39 (dd, *J* = 11.7, 5.8 Hz, 2H), 2.56 (t, *J* = 6.0 Hz, 2H), 1.41 (s, 9H).

(*S*)-2-benzyl 1-tert-butyl pyrrolidine-1,2-dicarboxylate (388):

Compound **388** was prepared following the general procedure D, from L-Boc-Proline in 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of rotamers δ 7.37 – 7.24 (m, 5H), 5.29 – 5.01 (m, 2H), δ 4.37 (dd, *J* = 8.6, 3.3 Hz, 1H), 4.24 (dd, *J* = 8.6, 4.0 Hz, 1H), 3.62 – 3.28 (m, 1H), 2.28 – 2.09 (m, 1H), 2.03 – 1.74 (m, 3H), 1.38 (S, 9H).

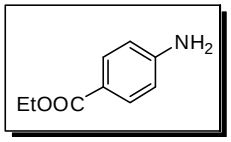
General procedure E for deprotection:

To a stirred solution of Cbz protected amine (0.2g) and 10 % Pd/C (20mg) in MeOH (2mL) was added $NaBH_4$ (1 equiv) portion wise. After completion of reaction (monitored by TLC), reaction mixture was filtered through celite and filtrate was evaporated to

dryness to afford crude amine which upon purification using flash chromatography afforded pure amine.

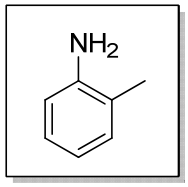
Compounds **302**, **303**, **304**, **308**, **309**, **313**, **321**, **322**, **324**, **325**, **326**, and **327** were obtained by following general procedure E from *N*-Cbz amines **353, 354**, **356**, **357**, **358**, **336**, and **366-371**. Data of these amines are in accordance with the data obtained earlier (page 137-142)

Ethyl 4-aminobenzoate (362):[59]



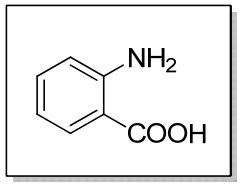
Compound **362** was obtained following the general procedure E starting from **355** as a white solid. Mp=88-89 ^{o}C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 5.0 Hz, 2H), 6.64 (d, *J* = 5.0 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.07 (bs, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 150.7, 131.7, 120.3, 114.0, 60.5, 14.6. HRMS (ESI): Calcd. For $C_9H_{11}NO_2$ $(M+Na)^+$: 188.0687 found 188.0689

***o*-Toluidine (363):**[59]



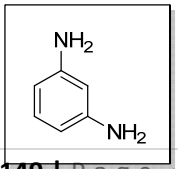
Compound **363** was obtained following the general procedure E starting from **359** as a brown liquid**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (td, *J* = 7.5, 3.3 Hz, 2H), 6.78 – 6.68 (m, 2H), 3.45 (bs, 2H), 2.20 (S, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.55, 130.53, 127.04, 122.47, 118.77, 115.06, 17.44. HRMS (ESI): Calcd. For $C_7H_{10}N$ $(M+H)^+$: 108.0813 found 108.0816

2-Aminobenzoic acid (364):[60]



Compound **364** was obtained following the general procedure E starting from **360** as a white solid. Mp= 143-145 ^{o}C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (bs, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.49 (t, *J* = 7.4 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.12, 152.04, 134.27, 131.69, 116.85, 115; HRMS (ESI): Calcd. For $C_7H_8NO_2$ $(M+H)^+$: 138.0555 found 138.0559

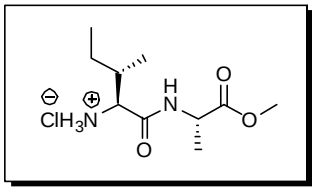
Benzene-1, 3-diamine (365):[61]



Compound **365** was obtained following the general procedure E starting from **361** as a brown solid. Mp= 63-64 ^{o}C ^{1}H NMR (400 MHz, DMSO-d_6)

δ 6.67 (dd, *J* = 10.0, 5.5 Hz, 1H), 5.84 – 5.77 (m, 3H), 4.64 (s, 4H); ^{13}NMR (100 MHz, DMSO-d_6) δ 149.62, 129.70, 103.66, 100.56; HRMS (ESI): Calcd. For $C_9H_{11}NO_2$ (M+Na) $^+$: 109.0765 found 109.07768

Dipeptide H_2N-Ile-Ala-OMe (378):



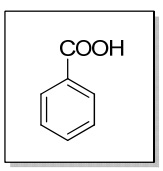
To a stirred solution of Cbz protected dipetide (0.2g) and 10 % Pd/C (20mg) in MeOH (2mL) was added $NaBH_4$ (1 equiv) portion wise. After completion of reaction (monitored by TLC), reaction mixture was filtered through celite. Reaction mixture was again cooled to 0 ^{o}C and HCl in 1, 4-dioxane (2ml) was added and stirred for 15 min. Salt was precipitated using Et_2O wahich was isolated by decantation of solvent. Resulting solid was washed with afford dipetide **378.**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.04 (m, 4H), 4.50 – 4.36 (m, 1H), 4.32 – 4.11 (m, 1H), 3.69 (s, 3H), 2.10 (s, 1H), 1.67 (s, 1H), 1.44 (d, 7.1 Hz, 3H), 1.19 (ddd, *J* = 6.9, 5.3, 1.4 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.94 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 168.4, 57.8, 52.5, 49.2, 36.8, 25, 17.3, 14.5, 11.5.; HRMS (ESI): Calcd. For $C_{10}H_{21}N_2O_3$ (M) $^+$: 217.1552 found 217.1549

General procedure F for benzyl ester hydrogenolysis:

To a stirred solution of benzyl ester (0.2g) and 10 % Pd/C (20mg) in MeOH (2mL) was added $NaBH_4$ (1 equiv) portion wise. After completion of reaction (monitored by TLC), reaction mixture was filtered through celite and filtrate was evaporated to dryness and again dissolved in EtOAc. Then reaction mixture was neutralised with $KHSO_4$. Organic layer was separated and aqueous layer was washed with EtOAc (20 ml X 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to afford crude carboxylic acid which upon purification using flash chromatography afforded pure acid.

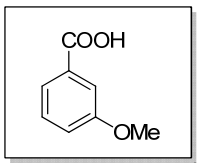
Benzoic acid (380):



Compound **380** was obtained following the general procedure F starting from **379** as a solid. Mp= 123 ^{o}C^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 8.17 – 8.12 (m, 2H), 7.66 – 7.60 (m, 1H), 7.52 – 7.46 (m, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.73, 133.98, 130.36, 129.47,

128.63; HRMS (ESI): Calcd. For $C_7H_6O_2Na$ $(M+Na)^+$: 145.0265 found 145.0267**3-**

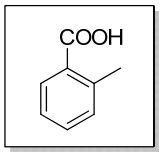
3-Methoxybenzoic acid (389):



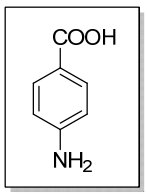
Compound **389** was obtained following the general procedure F starting from **381** as a solid. Mp=105-107 ^oC ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.71 (m, 1H), 7.63 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.39 (td, *J* = 8.0, 2.6 Hz, 1H), 7.16 (ddt, *J* = 4.5, 2.6, 1.3 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.18, 159.74, 130.69, 129.68, 122.83, 120.64, 114.51, 77.48, 77.16, 76.84, 55.61; HRMS (ESI): Calcd. For $C_8H_8O_3Na$ $(M+Na)^+$: 153.0551 found 145.0557

2-methylbenzoic acid (390):

Compound **390** was obtained following the general procedure F starting from **382** as a solid**.** Mp=104-105 ^oC, ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 1H), 7.44 (dd, *J* = 7.7, 7.1 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 2H), 2.65 (s, 3H); ^{13C} NMR (100 MHz, $CDCl_3$) δ 173.60, 141.53, 133.12, 132.08, 131.74, 128.45, 126.01, 77.48, 77.16, 76.84, 22.29; HRMS (ESI): Calcd. For $C_8H_9O_2$ $(M+H)^+$: 137.0602 found 137.0603

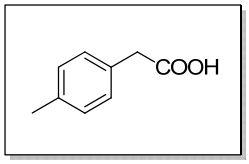


4-aminobenzoic acid (391):



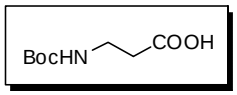
Compound **391** was obtained following the general procedure F starting from **383** as a solid**.** Mp= 187-189 ^oC**.** ^1H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 8.7 Hz, 2H), 5.86 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.09, 153.70, 131.80, 117.42, 113.13; HRMS (ESI): Calcd. For $C_7H_8NO_2$ $(M+H)^+$: 138.0555 found 137.0559

2-(p-tolyl)acetic acid (392) :



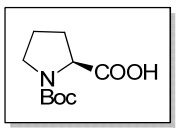
Compound **392** was obtained following the general procedure F starting from **384** as a solid**. Mp= 88-89 ^oC,** ^1H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.22 – 7.14 (m, 4H), 3.63 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.56, 137.15, 130.30, 129.47, 129.37, 40.77, 21.21; HRMS (ESI): Calcd. For $C_9H_{11}O_2$ $(M+H)^+$: 151.0759 found 151.0758

3-((tert-butoxycarbonyl)amino)propanoic acid (385):



Compound **385** was obtained following the general procedure F starting from **387** as a solid**.** Mp= 76-78 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.25 (bs, 0.22H), 5.06 (bs, 0. 56H), 3.50 (d, *J* = 18.8 Hz, 0.21H), 3.39 (d, *J* = 5.2 Hz, 1.78H), 2.57 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.66, 156.07, 79.83, 36.00, 34.60, 28.49; HRMS (ESI): Calcd. For $C_8H_{15}NO_4Na$ $(M+Na)^+$: 212.0899 found 212.0878

(*S*)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (386):



Compound **386** was obtained following the general procedure F starting from **388** as a solid. Mp=133-135 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 4.38 – 4.18 (m, 1H), 3.59 – 3.28 (m, 2H), 2.36 – 2.18 (m, 1H), 2.11 – 1.98 (m, 1H), 1.97 – 1.80 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.94, 176.19, 156.01, 154.05, 81.14, 80.46, 59.04, 46.97, 46.43, 30.92, 29.06, 28.48, 28.35, 24.39, 23.75; HRMS (ESI): Calcd. For $C_{10}H_{17}NO_4Na$ $(M+Na)^+$: 238.1055 found 238.1057

Gram scale procedure for *N*-Cbz deprotection:

To a stirred solution of Cbz protected aniline **352** (10 g, 44 mmol) and 10 % Pd/C (1 g) in MeOH (200mL) was added $NaBH_4$ (2.5g, 66mmol) portion wise. After completion of reaction (20 min) (monitored by TLC), reaction mixture was filtered through celite and filtrate was evaporated to dryness to afford crude amine which upon purification using flash chromatography afforded pure amine **302** (3.85g, 94%)

Simillarly, large scale reaction for *N*-Cbz deprotection of **366** and **367** were carried out.

Gram scale procedure for *N*-Cbz deprotection:

To a stirred solution of benzyl benzoate **379** (10g, 47.12mmol) and 10 % Pd/C (1g) in MeOH (200mL) was added $NaBH_4$ (2.64g, 70.67mmol) portion wise. After completion of reaction (20 min) (monitored by TLC), reaction mixture was filtered through celite and filtrate was evaporated to dryness and again dissolved in EtOAc. Then reaction mixture was neutralised with $KHSO_4$. Organic layer was separated and aqueous layer was washed with EtOAc (100 ml X 2). Combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to afford crude carboxylic acid which upon purification using flash chromatography afforded pure benzoic acid **380** (5.57g, 97%)**.**

3B.11 AppendixIII: ^{1}H and ^{13}C spectral data of representative compounds

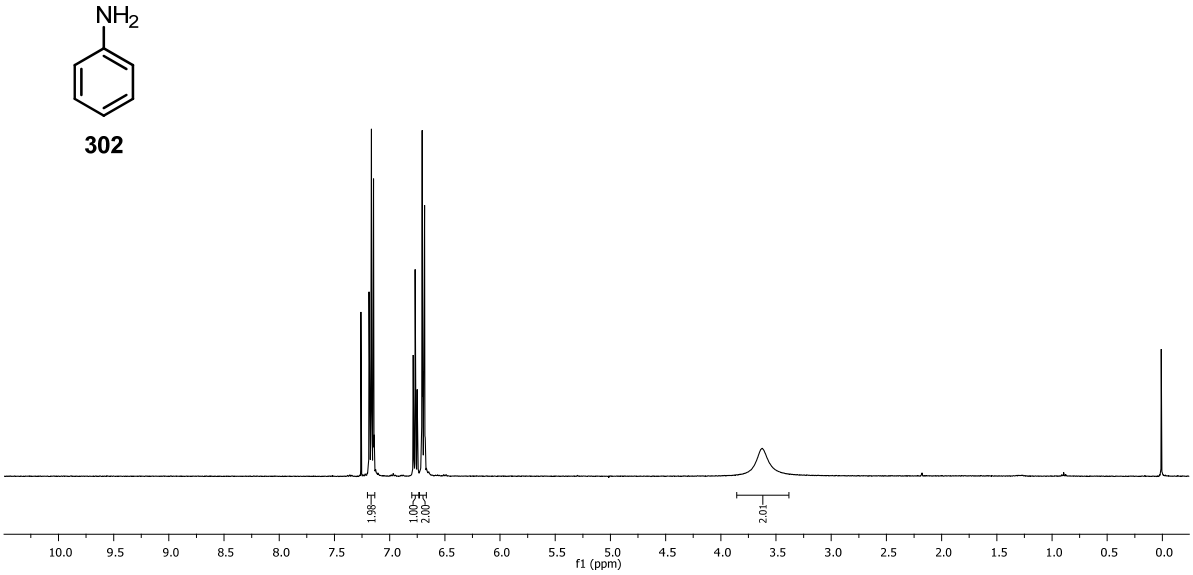


Fig AIII.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **302**

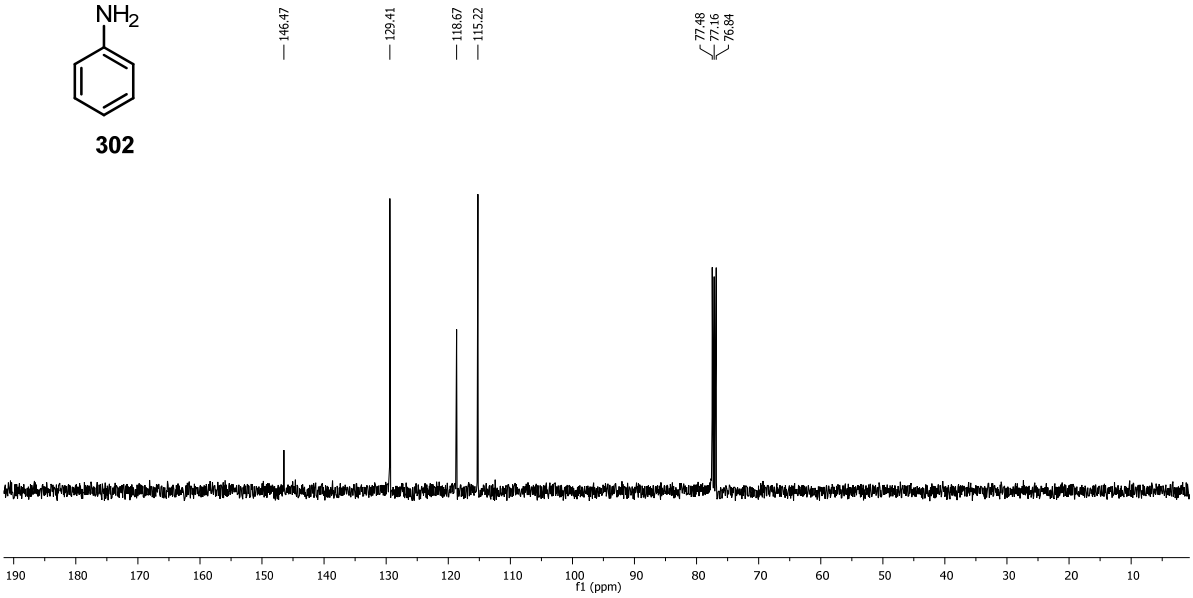


Fig AIII.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **302**

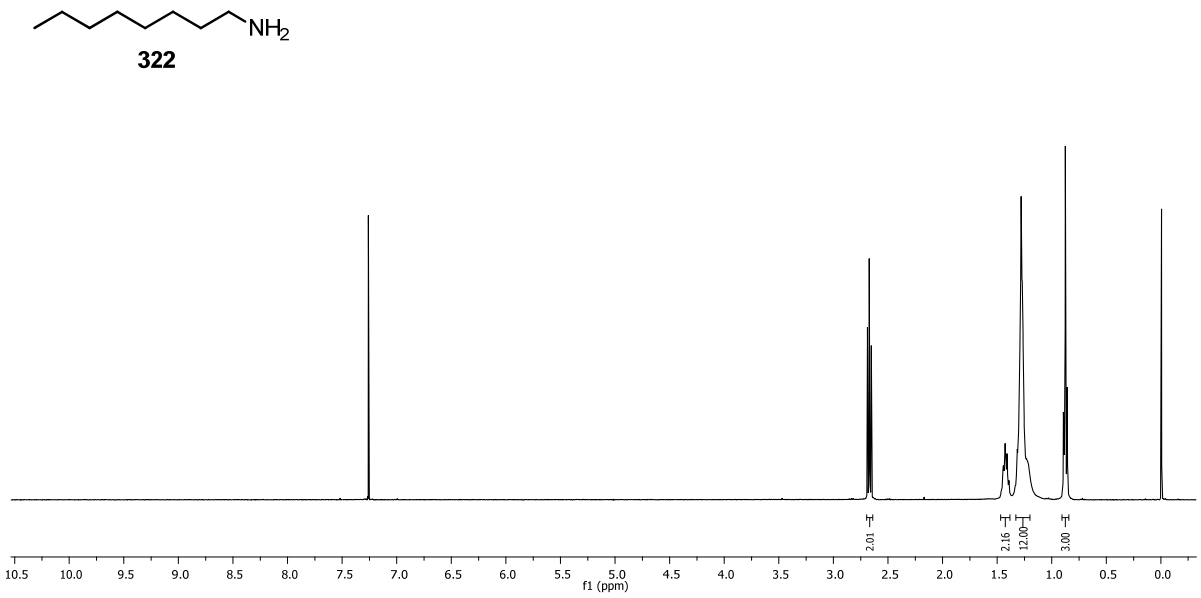


Fig AIII.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **322**

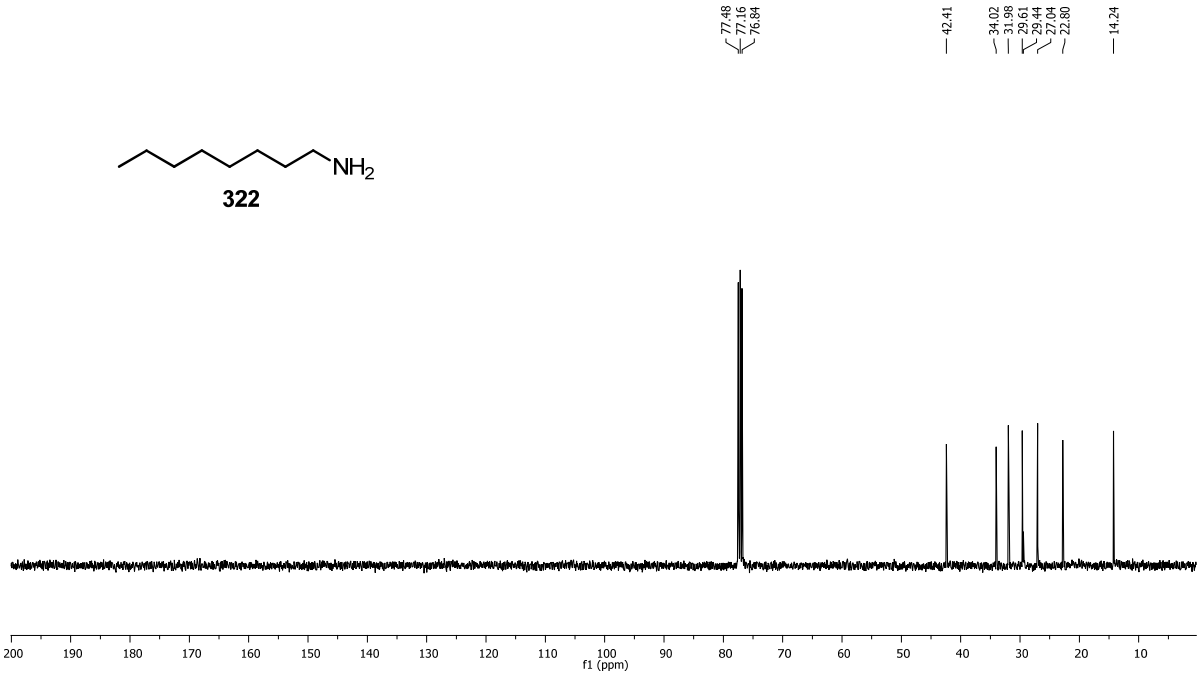


Fig AIII.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **322**

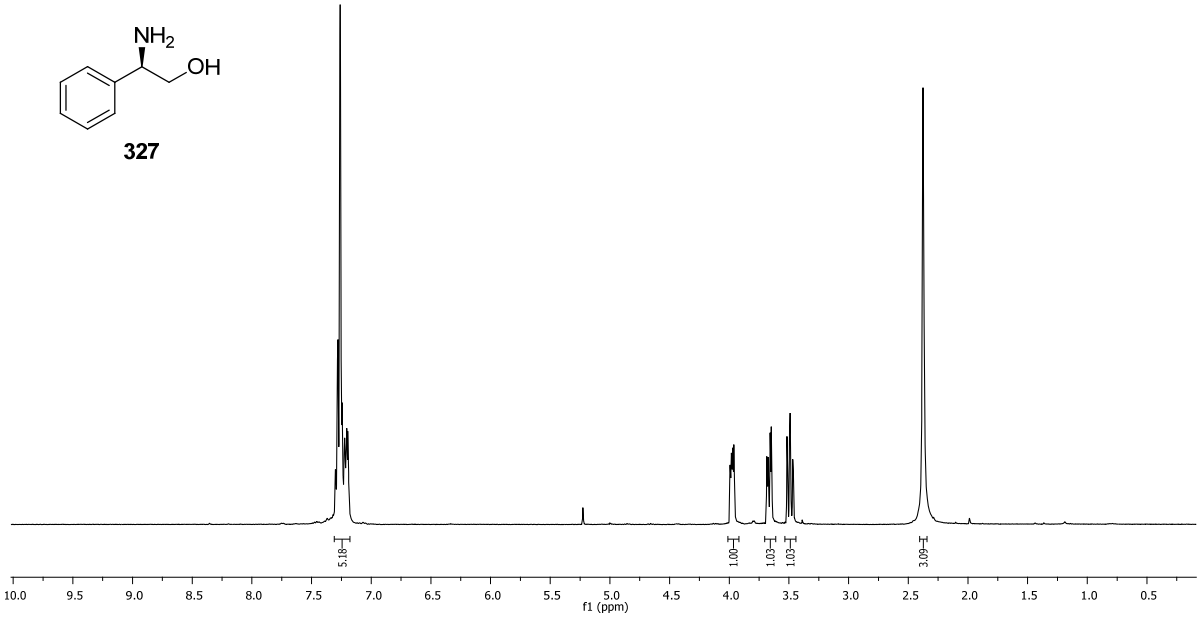


Fig AIII.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **327**

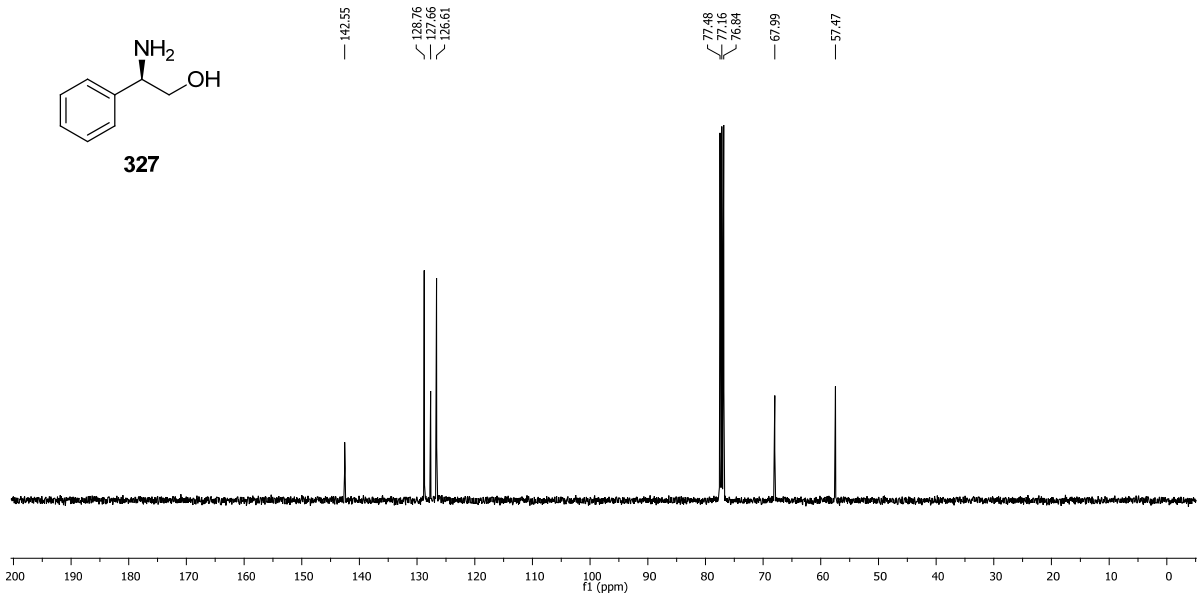


Fig AIII.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **327**

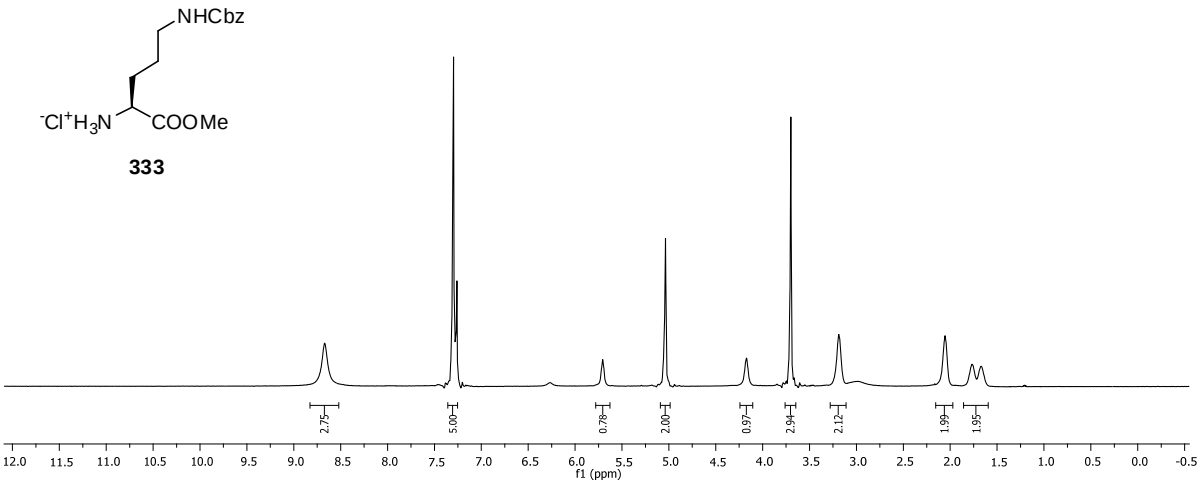


Fig AIII.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **333**

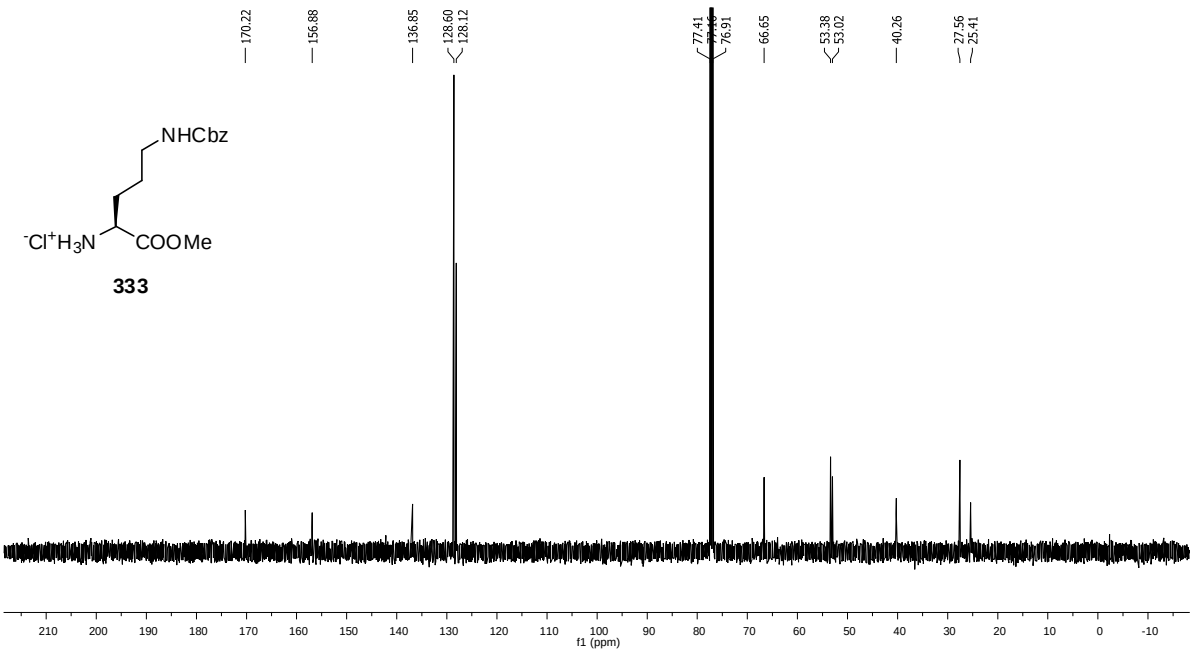


Fig AIII.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **333**

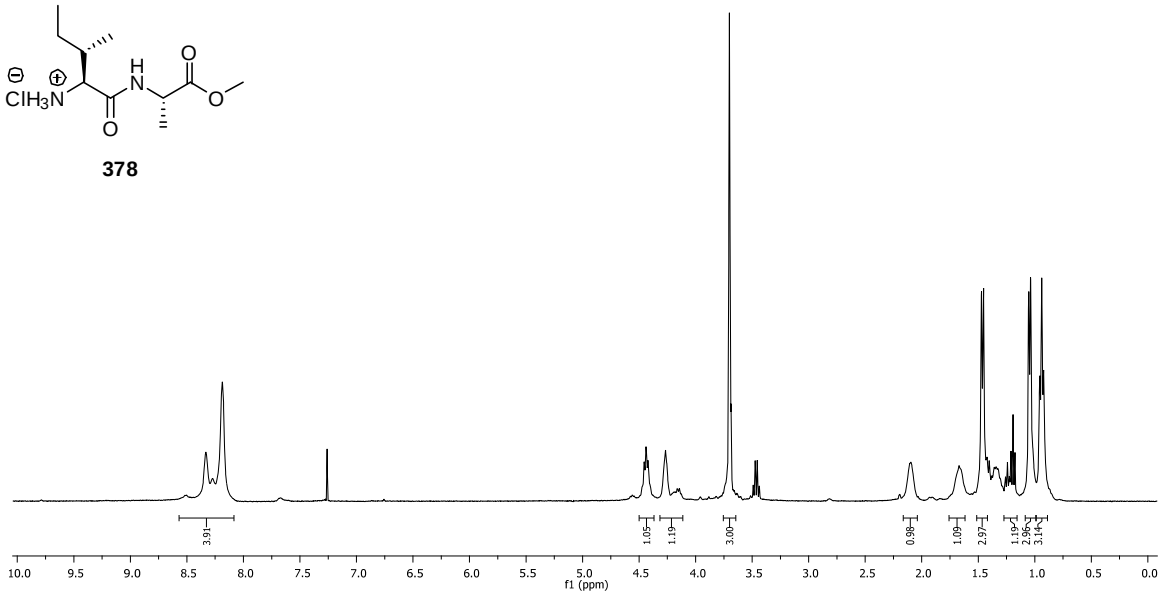


Fig AIII.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **378**

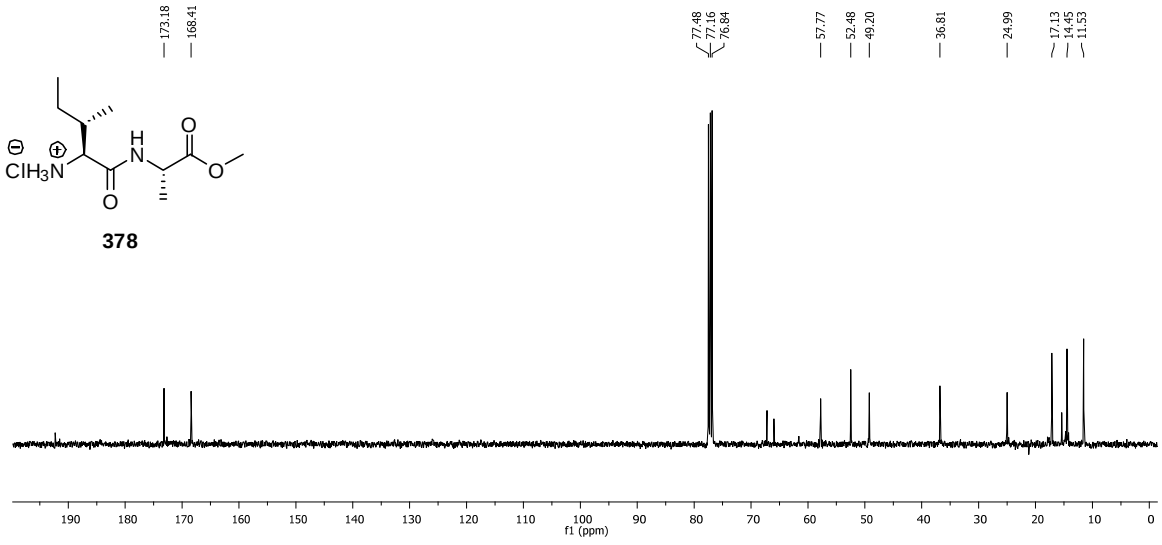


Fig AIII.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **378**

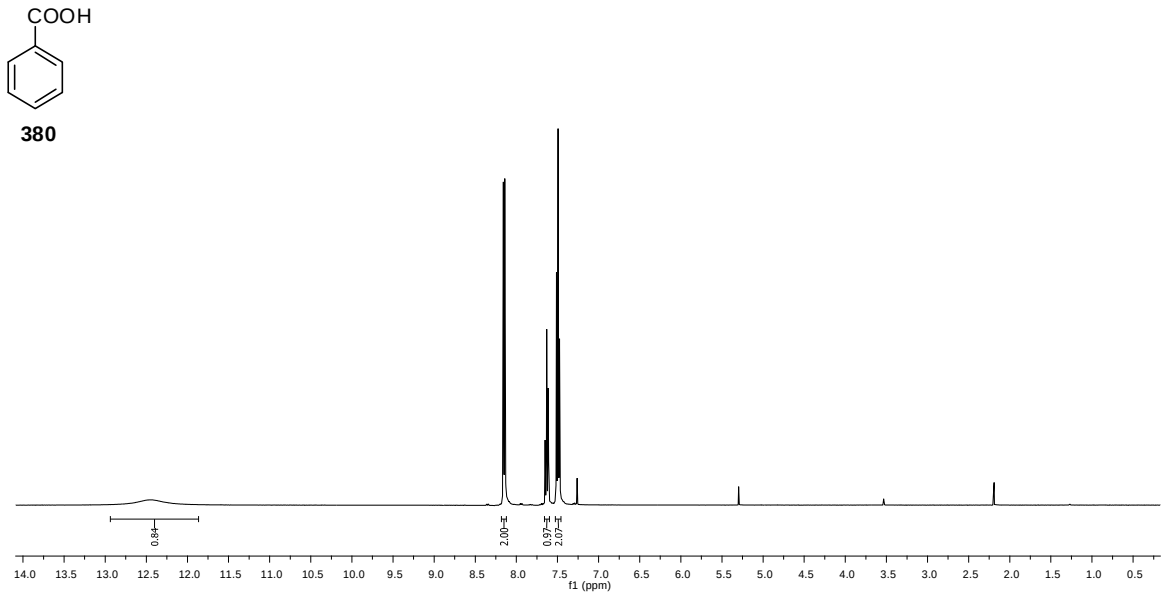


Fig AIII.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **380**

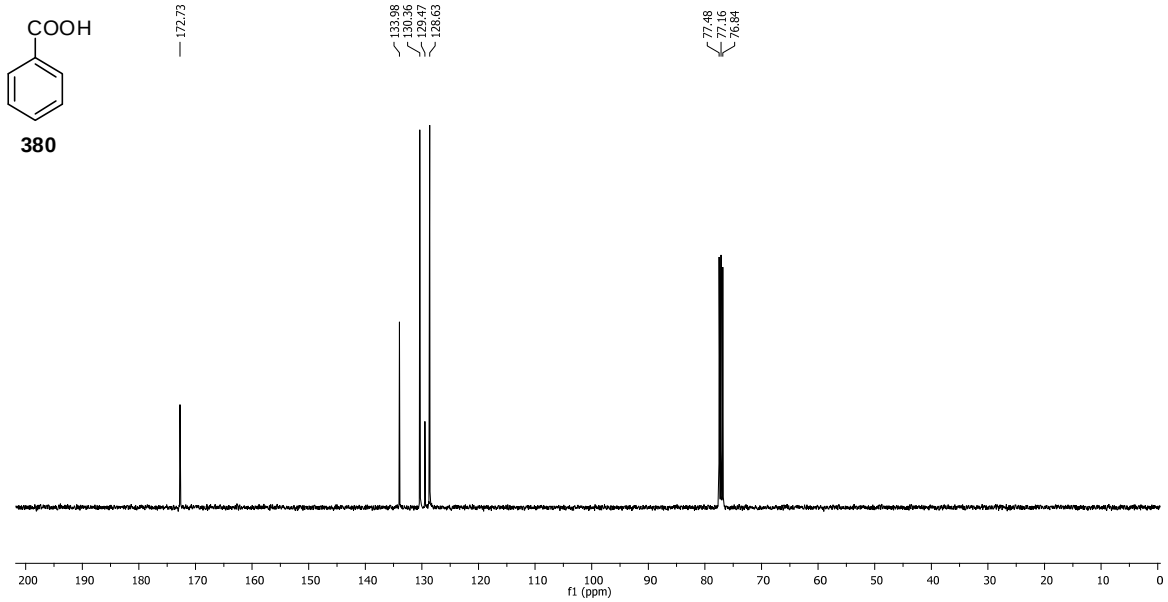


Fig AIII.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **380**

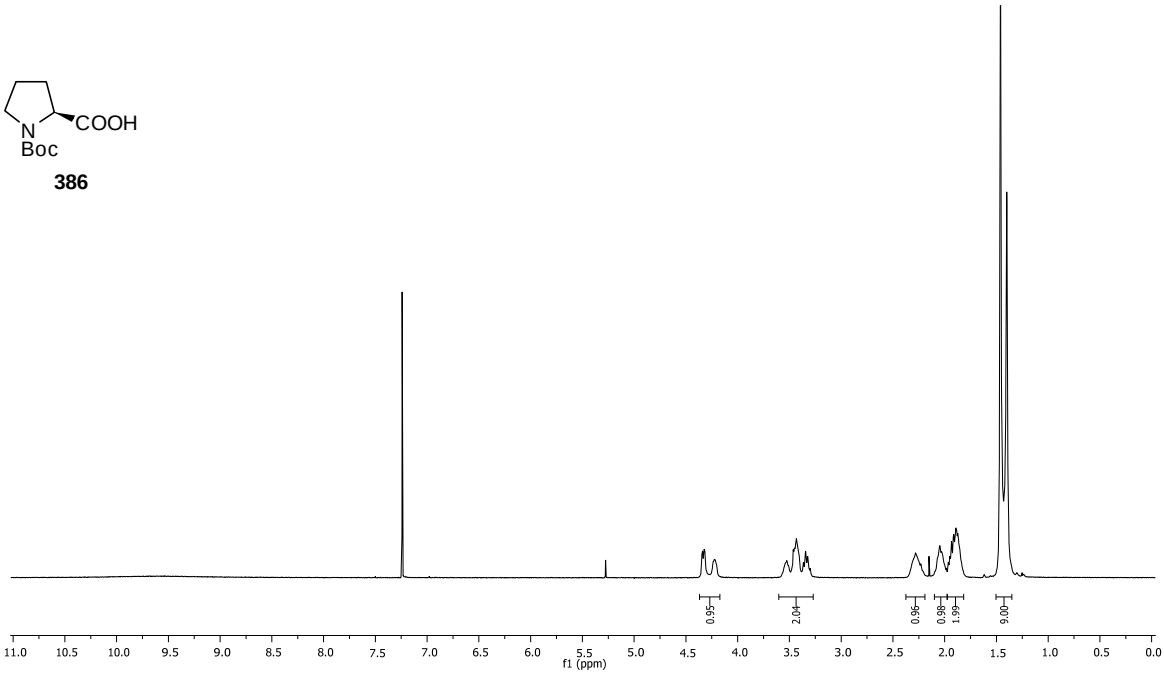


Fig AIII.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **386**

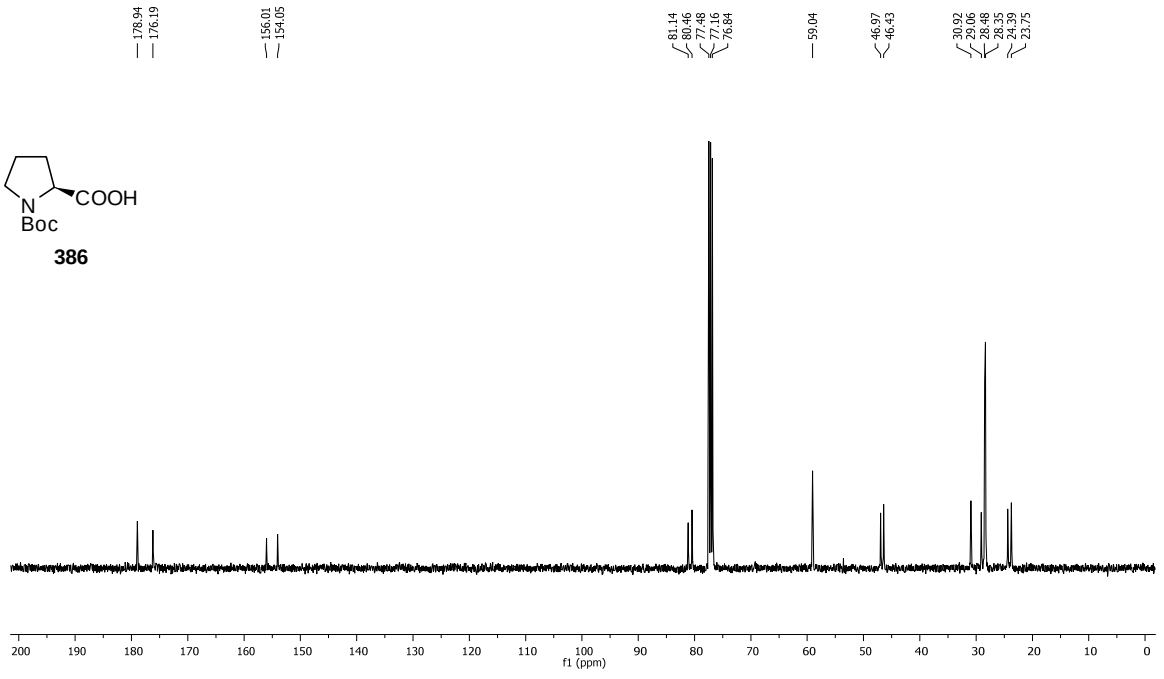


Fig AIII.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **386**

3B. 12 References

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Total synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine and formal synthesis of pumiliotoxin-251D

Prakash R. Sultane, Amar R. Mohite, Ramakrishna G. Bhat *

Department of Chemistry, Mendeleev Block, Indian Institute of Science Education and Research (IISER), Pune 411008, Maharashtra, India

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ABSTRACT

A concise and efficient synthesis of (6*R*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2** is described. The synthesis employs cross metathesis in building the key intermediate **9** and is used effectively in constructing indolizidine skeleton for the total synthesis of 1-deoxy-7, 8a-di-*epi*-castanospermine and also for the bicyclic framework of pumiliotoxin 251D **12**, **13**. The indolizidine skeleton is achieved in one pot sequence of transformations such as deprotection of Cbz group, reduction of double bond, and cyclization. The configurational and conformational structures of compound **10** are unambiguously confirmed by X-ray analysis.

Aza fused indolizidine bicyclic alkaloids are widely distributed in microorganisms, vertebrates, higher invertebrates, and plants.[1,2] These bicyclic core structures being biologically active have drawn attention of synthetic organic chemists to develop a concise and efficient strategy.[1,3] The naturally occurring polyhydroxylated indolizidine alkaloids such as (+)-castanospermine **1** and their analogues **2**, **3** have been reported to exhibit glycosidase inhibition activity,[4] and they are also known to display potential antitumor, antiviral, and immunomodulating activities (Fig. 1). Similarly, the structurally related alkaloids of pumiliotoxin **4** (Fig. 1) have been isolated and characterized from the neotropical frogs of family 'Dendrobadidae'.[5] These alkaloids are known to act as chemical defense agents against predators and have a high pharmacological activity on nerve and muscle.[6] Though several reports of racemic and enantioselective syntheses of 1-deoxy-8a-*epi*-castanospermine stereoisomers exist,[7] there are discrepancies in the reported assignments and characterization. This prompted us to synthesize 1-deoxy-7,8a-di-*epi*-castanospermine diastereomer **2**. Herein, we wish to report a short and practical synthesis as a general synthetic route to 1-deoxy-7,8a-di-*epi*-castanospermine **2** and bicyclic frameworks of pumiliotoxin 251D (**12**, **13**). Compound **9** was effectively used as a common key intermediate for the syntheses of **2**, **12,** and **13** in this approach.

(2*S*)-*N*-Cbz-pyrrolidine-2-carboxaldehyde **7** was prepared in two steps from *N*-Cbz-L-proline **5**. Compound **5** was coupled with *N*,*O*-dimethylhydroxylamine hydrochloride to give the corresponding Weinreb amide **6** in 92% yield, which on reduction with lithium aluminium hydride (LAH) led to the formation of the corresponding aldehyde **7** in 90% yield. The addition of vinyl magnesium bromide to aldehyde **7** afforded an inseparable mixture of diastereomeric alcohol **8** in 70% yield (Scheme 1).

Olefin metathesis of acyclic or cyclic olefins using alkylidene ruthenium and molybdenum catalysts[8] plays a pivotal role in the synthesis of heterocyclic framework. Thus olefin **8** was subjected to cross metathesis approach to arrive at the key intermediate **9** (Scheme 1).

The cross metathesis of **8** and methyl acrylate was performed with Grubbs' second generation catalyst (G-II) in toluene at room temperature and gave the expected *E*-isomer **9** predominantly (E/Z 20:1) in an excellent yield of 92%. Then compound **9** upon dihydroxylation[9] using OsO_4 and NMO resulted in the formation of a mixture of lactones owing to the alkaline condition of the

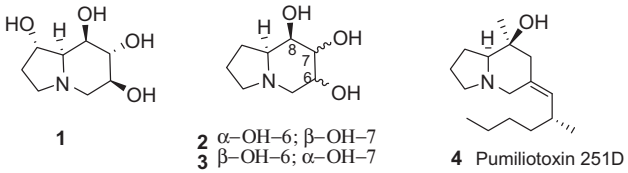

Figure 1. Polyhydroxylated indolizidine alkaloids and pumiliotoxin 251 D.

* Corresponding author. Fax: +91 20 25898022
E-mail address: rgb@iiserpune.ac.in (R.G. Bhat).

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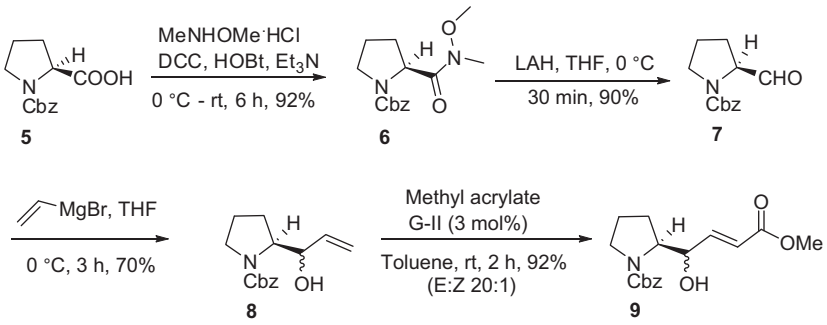
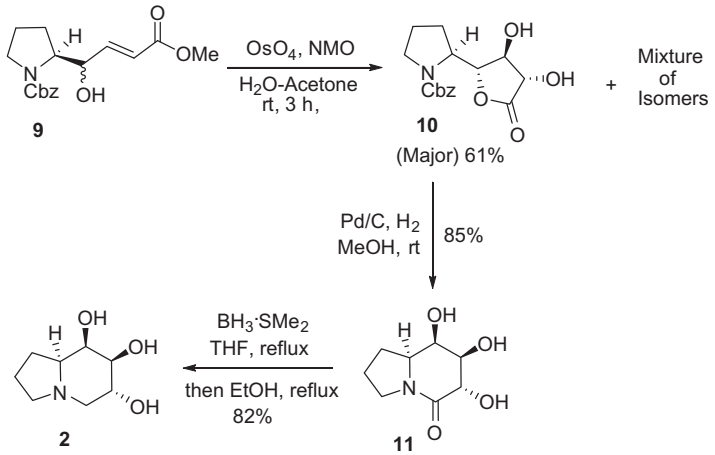


Scheme 1. Synthesis of key intermediate **9**.



Scheme 2. Synthesis of 1-deoxy-7,8a-di-*epi*-castanospermine.

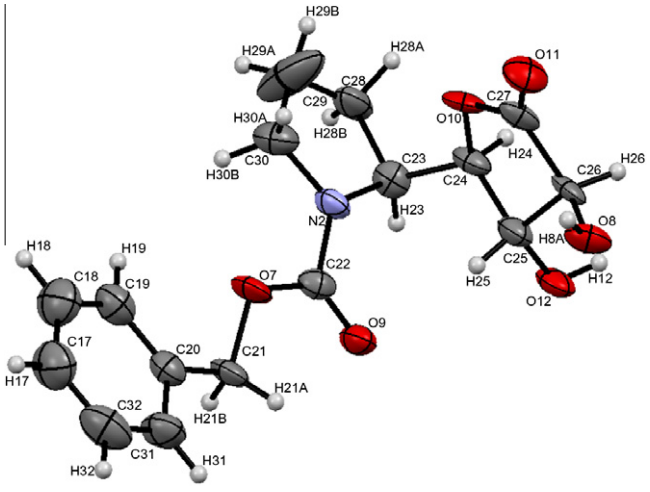


Figure 2. Molecular structure of lactone **10** by X-ray analysis (ORTEP diagram; ellipsoids are drawn at 50% probability).

reaction. The mixture was purified by column chromatography and lactone **10** was isolated in major amount (61% yield) as a white solid (Scheme 2). The molecular structure of **10** was confirmed by single-crystal X-ray analysis.[10] This gave the exclusive evidence for the stereochemistry of hydroxyl groups (Fig. 2).

Compound **10** under hydrogenolysis condition with Pd/C, H_2 deprotected the benzyloxycarbonyl (Cbz) group followed by the facile and rapid cyclization in one pot to give aza fused lactam: indolizidinone **11** in 85% yield. This on reduction with BH_3·DMS complex[7f,11] in THF gave the desired final compound 1-deoxy-7,8a-di-*epi*-castanospermine **2** in 82% yield (Scheme 2).

It is important to note that in contrast to the usual practice,[11] we successfully reduced the amide bond without protecting any of the hydroxyl groups thus minimizing the extra two steps in the route. After completion of reaction it was refluxed with EtOH to avoid the formation of amine-borane complex. Thus, the synthesis of (6*R*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2** was accomplished in a total of 7 steps with an overall yield of 23%. ^{1}H and ^{13}C NMR data for compound **2** do not match with the spectral data reported by Chan et al.[7a] However, the data of its enantiomer reported by Martin et al.[7c] and Pandey et al.[7d] were in close agreement with the spectral data of **2**. Specific rotation of compound **2** was in close agreement with that of its enantiomer (for **2**, obs: $[\alpha]_D^{25}$ −30 *c* 0.5, MeOH; its enantiomer $[\alpha]_D^{27}$ +26.1 *c* 0.45, MeOH).[7d] Our assignment is further supported by the X-ray crystal structure of compound **10**.

Earlier Gallagher[12d] and Nubbemyer[12i,j] have reported the synthesis of pumiliotoxin 251D **4** using indolizidine bicyclic frameworks (**12–14**) as key intermediates (Fig 3).

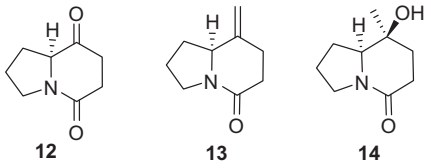
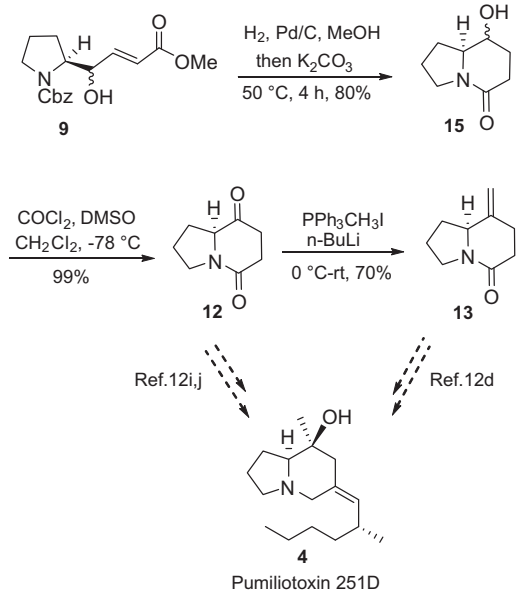


Figure 3. Key intermediates of pumiliotoxin 251D



Scheme 3. Formal synthesis of pumiliotoxin 251D.

Encouraged by this we planned to utilize effectively olefin **9** for the synthesis of the compounds **12** and **13** (Scheme 3). Compound **9** on treatment with Pd/C, H_2 in MeOH, followed by the addition of K_2CO_3 gave the corresponding alcohol **15** in 80% yield. It is striking to note that the sequence of transformations viz. deprotection of benzyloxycarbonyl (Cbz) group, reduction of double bond, and facile cyclization takes place in one pot. Subsequently, alcohol **15** upon Swern oxidation, gave indolizidinedione **12** in almost quantitative yield of 99%. Thus compound **12** was obtained in an overall yield of 42% in 6 steps. Spectral data for compound **12** were in close agreement with the reported values (obs: $[\alpha]_D^{20}$ −243, *c* 1.56, $CHCl_3$ lit.[12i,j] $[\alpha]_D^{20}$ −245, *c* 1.56, $CHCl_3$).

Finally when compound **12** was subjected to Wittig olefination afforded bicyclic lactam **13** in 70% yield. Spectral data for compound **13** were in close agreement with the reported values (Obs: $[\alpha]_D^{20}$ −99.6, *c* 1.2, $CHCl_3$; lit.[12d] $[\alpha]_D^{20}$ −98.3 *c* 1.2, $CHCl_3$). While both the compounds **12** and **13** have been explored earlier as key intermediates for the synthesis of pumiliotoxin 251D,[12d,i,j] it is evident that **13** is a more viable and an efficient precursor of pumiliotoxin 251D than **12**, as the conversion of **12** to the corresponding tertiary alcohol **14** was diastereoselectively poor (1:1.9).[12i,j] But the conversion of bicyclic lactam **13** to the corresponding tertiary alcohol **14** was highly diastereoselective (10:1).[12d] Also in comparison with the reported procedures,[12] synthesis routes to **12** and **13** described in this Letter are shorter and better yielding.

In summary, we have developed a concise and convenient total synthesis of (*6R*,*7S*,*8R*, *8aS*)-6,7,8-trihydroxyindolizidine (1-deoxy-7,8a-di-*epi*-castanospermine) **2**. This procedure requires a total of 7 steps starting from *N*-Cbz-L-Proline **5** and proceeded in overall 23% yield. X-ray analysis of **10** established its unambiguous structural determination, which in turn confirmed the configurational structure of **2**. In addition, the formal synthesis of pumiliotoxin 251D was accomplished in a total of 6 or 7 steps starting from **5** in an overall 30% yield. Olefin **9** resulting from cross metathesis was used as a common key intermediate for both the syntheses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.061.

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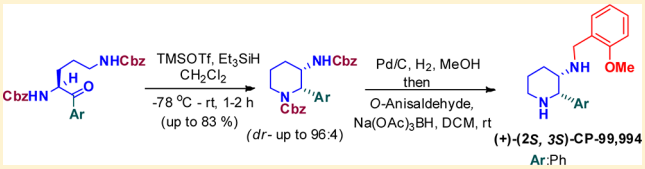
Stereoselective Approach to *cis*-2,3-Disubstituted Piperidines via Reduction of *N*-Acyliminium Ion Intermediate: Enantioselective Synthesis of (+)-(2*S*,3*S*)-CP-99,994

Prakash R. Sultane and Ramakrishna G. Bhat*

Mendeleev Block, Department of Chemistry, Indian Institute of Science Education and Research (IISER), Pune, Maharashtra, 411008, India

Supporting Information

ABSTRACT: A very simple and efficient stereoselective approach to *cis*-2,3-disubstituted piperidines via the reduction of *N*-acyliminium ion intermediates is described. Application of this methodology is exemplified by the enantioselective total synthesis of (+)-(2*S*,3*S*)-CP-99,994.



Functionalized piperidines are widely distributed in various bioactive alkaloids.[1] Piperidine motifs are also very important pharmacophores for many molecules in clinical and preclinical trials.[2] In particular, 2-aryl-3-amino piperidines are present in many bioactive molecules and drugs. Some of the compounds derived from this general structure are well-known as substance P (SP) receptor antagonists. For example, molecules such as (+)-(2*S*,3*S*)-CP-99,994 (**1**)[3] and (+)-(2*S*,3*S*)-CP-122,721 (**2**)[4] are known to be nonpeptide antagonists of neurokinin-1 (NK-1) substance P receptor (Figure 1). Likewise **3** and **4** have also shown the ability to antagonize the action of substance P.[5]

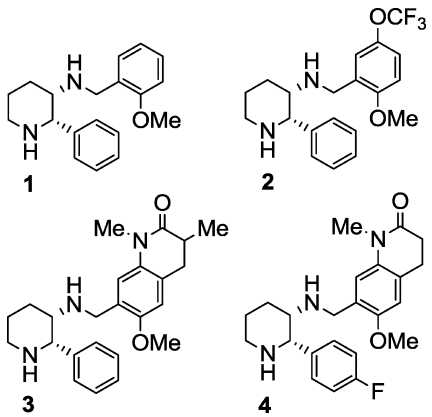
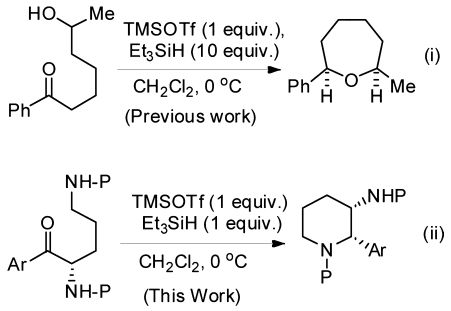


Figure 1. Antagonists of neurokinin-1 (NK-1) substance P receptor.

Interestingly, a *cis* relationship between the two substituents on the piperidine and importantly 2*S*,3*S* configurations are necessary for high affinity binding to human NK-1 receptor.[6] Evidently, significant effort has been made for the asymmetric synthesis of these piperidine derivatives because of their bioactivity.[7−9] However, there are only few approaches[7f,10] for the construction of 2-aryl-3-amino piperidines with diverse aryl groups at C-2, while controlling the stereochemistry of C-2 and C-3 positions. Hence the development of new enantioselective synthetic approaches to functionalized piperidines is still stimulating and useful. With this initiative, and also in connection with our program devoted to the synthesis of functionalized piperidines,[11] herein we describe a highly practical and short approach for the enantioselective synthesis of *cis*-2,3-disubsituted piperidines and concise and efficient asymmetric synthesis of (2*S*,3*S*)-(+)-CP-99,994 (**1**) relying on diastereoselective reduction of diamino ketones.

Earlier, diastereopure oxygenated heterocycles have been prepared by the reductive condensation of hydroxy ketones catalyzed by trimethylsilyl triflate in high yields (Scheme 1, eq i).[12] In spite of the application of this stereoselective and high yielding approach to oxa-heterocycles,[13] to the best of our knowledge this method has not been explored to date for the asymmetric synthesis of substituted piperidines.

Scheme 1. Synthesis of *cis*-2,3-Piperidines via Reductive Cyclization



Hence we planned to synthesize the functionalized piperidines relying on diastereoselective reductive cyclization

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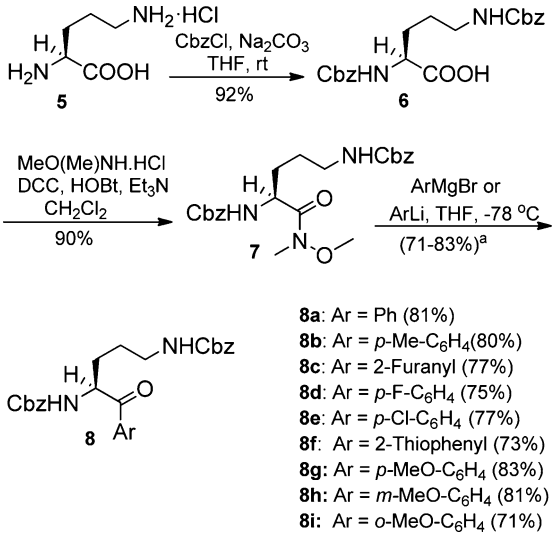
of the corresponding enantiopure diamino ketones (Scheme 1, eq ii).

In order to execute the strategy, it was essential to synthesize suitable enantiopure diamino ketone so as to facilitate the intramolecular cyclization. We envisioned that required diamino ketone can be constructed from easily accessible and less expensive enantiomerically pure L-ornithine **5** (Scheme 2).

Scheme 2. Synthesis of Diamino Ketones 8



[a]Isolated yield of purified compound.

Compound **5** upon treatment with benzyl chloroformate in alkaline condition afforded the corresponding $N(\alpha),N(\delta)$-bis-Cbz-ornithine **6** in excellent yield.[14] This was converted efficiently to *N*-methoxy-*N*-methylamide (Weinreb's amide) **7** in a short time following the common coupling condition.[15] Compound **7** when subjected to treatment with either aryl magnesium bromides (Grignard reagents)[16] or aryl lithium[17] in tetrahydrofuran (THF) at −78 °C afforded the corresponding diaminoarylketones (**8a**−**8i**) in very good yields (up to 83%) (Scheme 2).

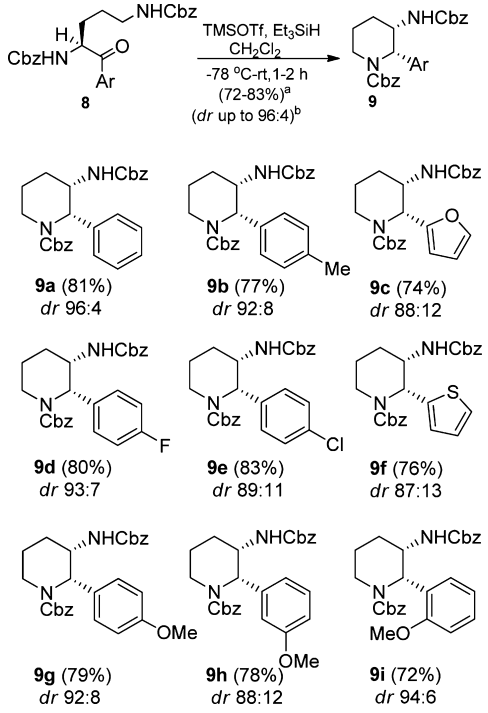
We surmised that 2,3-disubstituted piperidines can be built by intramolecular cyclization of diaminoarylketones via *N*-acyliminium ion intermediate, which could be further reduced by silyl hydrides. In order to explore the new possibility, we subsequently treated the diaminoarylketone **8a** with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at −78 °C to afford the piperidine derivative **9a** in very good yield (81%) (Scheme 3).

We observed that optimization of the reaction condition to −78 °C gave the highest yield with excellent diastereoselectivity (96:4). It is gratifying to note that reductive cyclization was highly 2,3-*cis*-diastereoselctive.

Diastereomeric ratio was determined by ^{1}H NMR. The *cis* relationship of the substituents at C-2 and C-3 in compound **9a** was unambiguously deduced from the J_{2-3} coupling constant (J = 6.4 Hz), NOE and NOESY studies (Figure 2).[18] The structure of **9a** was unequivocally established by single-crystal X-ray analysis (Figure 2).[19]

Encouraged by this initial success, we planned to synthesize various 2,3-*cis*-piperidines to demonstrate the synthetic utility of this approach. Strength of the approach lies in the fact that diverse organolithium or Grignard reagents can be effectively

Scheme 3. Stereoselective Synthesis of *cis*-2,3-Disubstituted Piperidines with Diverse Functionality at C-2



[a]Isolated yield of purified compound. [b]dr is determined by ^{1}H NMR.

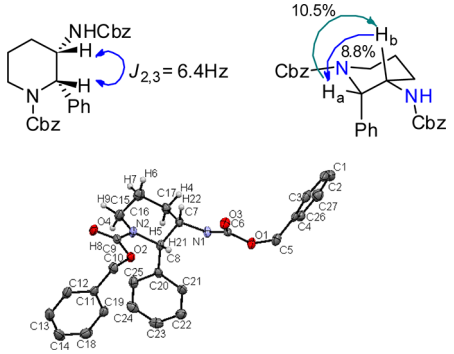


Figure 2. NOE and X-ray single crystal structure of compound **9a** (ORTEP diagram, ellipsoid drawn at 50% probability; aromatic hydrogens and hydrogens at C5, C10, N1, are omitted for clarity).

utilized to prepare various diaminoketone derivatives. Diaminoketones (**8b**−**8i**) upon treatment with trimethylsilyl triflate (TMSOTf) (1 equiv) and triethylsilane (Et_3SiH) (1 equiv) in CH_2Cl_2 at −78 °C afforded the corresponding piperidine derivatives (**9b**−**9i**) in very good yields (up to 83%) and diastereoselectivity (up to 96:4). The stereochemistry of the piperidine derivatives (**9b**−**9i**) was assigned by the analogy.

The high diastereoselectivity observed in the reduction of *N*-acyliminium ion intermediate has been rationalized on the basis of stereoselective addition of hydride ion. High diastereoselectivity leading to *cis*-2,3-disubstituted piperidines could be explained by the plausible mechanistic pathway as shown in Scheme 4. Carbonyl group of the enantiopure diaminoketone gets activated by TMSOTf, which in turn facilitates the intramolecular cyclization by the nucleophilic attack of secondary amine via a planar *N*-acyliminum ion intermediate (I) with a restricted rotation. Subsequently, silane hydride

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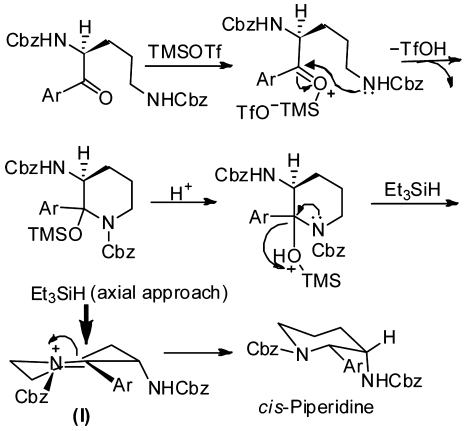
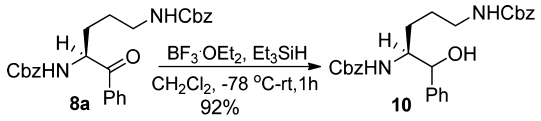
Scheme 4. Plausible Mechanism for the Stereoselective Synthesis of Piperidines via *N*-Acyliminium Ion



(Et_3SiH) approaches from the least sterically hindered face (axial approach) to afford (2*S*,3*S*)-*cis*-piperidines.[20]

It is interesting to note that diaminoarylketone (**8a**), when subjected to reaction with $BF_3{\cdot}Et_2O$ and Et_3SiH,[21] afforded the corresponding amino alcohol **10** even after prolonged reaction condition (Scheme 5). Attempts to synthesize the expected

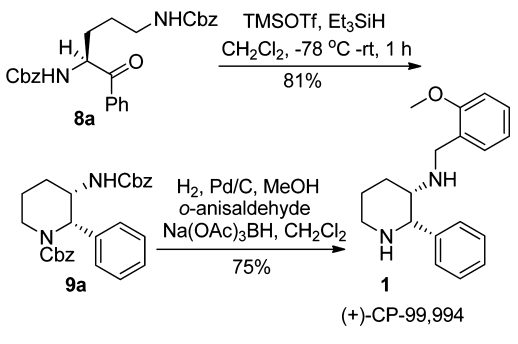
Scheme 5. Reaction of 8a with $BF_3{\cdot}OEt_2$ and Et_3SiH



product **9a** by increasing the amount of $BF_3{\cdot}Et_2O$ along with varying the reaction temperature (−78, 0 °C, and rt) exclusively led to the formation of compound **10**. We also changed the mode of addition by adding Et_3SiH followed by $BF_3{\cdot}Et_2O$, but diaminoarylketone resulted in the formation of amino alcohol **10**.

After successfully synthesizing different 2*S*,3*S*-*cis*-piperidines, we envisioned to apply this methodology for the enantioselective synthesis of (+)-CP-99,994 (**1**). Compound **9a** was treated with Pd/C, H_2 in methanolic solution for 6 h, and the resulting reaction mixture was filtered and treated with *o*-anisaldehyde followed by the addition of $Na(OAc)_3BH$ to furnish the enantiomerically pure (+)-CP-99,994 (**1**) in good yield (75%) (Scheme 6). ^1H, ^{13}C NMR, IR spectroscopic data were in accordance with the reported values.[7e] Final comparison of optical data with reported value[7d] and single X-ray crystal data of **9a** confirmed the configurational

Scheme 6. Enantioselective Synthesis of (+)-CP-99,994



assignment of compound **1**. Enantioselective synthesis of **1** has been achieved in an overall yield of 40% in five steps from L-ornithine **5**.

In conclusion, we have described a highly efficient and useful approach for constructing *cis*-2-aryl 3-amino piperidines with an option of introducing diverse aryl groups at C-2 position. This also gives an easy access to condense different aldehydes at C-3 amine functionality without compromising the stereochemistry. The method described herein opens a wide and easy access to synthesize piperidine derivatives and in particular synthesis of various congeners of (+)-CP-99,994 to test the biological activity against NK1-receptor. The application of this method is further exemplified by the short and concise enantioselective synthesis of (+)-CP-99,994.

EXPERIMENTAL PROCEDURE

General Methods. Unless otherwise noted, all reactions have been carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard, *J* values are given in Hz. ^{13}C NMR are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-*d* and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by High resolution mass spectrometry using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as thin films on sodium chloride or KBr discs and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in an open glass capillary, and values are uncorrected.

Weinreb Amide (7). To a cooled and stirred reaction mixture of (*S*)-*N*,*N*-dibenzyloxycarbonylornithine[14] (20 g, 50 mmol), Et_3N(17.4 mL, 125 mmol), HOBt (6.75 g, 50 mmol) followed by DCC (12.37 g, 40.11 mmol) in CH_2Cl_2 (70 mL) were added at 0 °C, and the reaction mixture was stirred for 30 min while maintaining 0 °C and then allowed to stir at room temperature for 6 h. The precipitate that formed was removed by filtration, and the filter cake (residue) was washed with EtOAc. The filtrate was diluted with additional EtOAc and washed with saturated aqueous $NaHCO_3$, water, 5% HCl, and brine solution. The solution was dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated in vacuo to give Weinreb amide, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish pure Weinreb amide **7** as a white solid (20.34 g, 92% yield): R_f = 0.3 petroleum ether:EtOAc (50:50); $[\alpha_D^{25}]$ −4 (*c* 1, $CHCl_3$); mp = 69−71 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.23 (m, 10H), 6.01 (bs, 1H), 5.38 (bs, 1H), 5.21−4.92 (m, 4H), 4.70 (s, 1H), 3.69 (s, 3H), 3.13 (m, 5H), 1.82−1.46 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 156.3, 156.1, 136.6, 136.2, 128.3, 127.96, 127.92, 127.8, 66.6, 66.3, 61.4, 50.5, 40.4, 31.8, 29.6, 25.6; HRMS (ESI) Calcd. for $C_{23}H_{29}N_3O_6Na$ $(M + Na)^+$ 466.1954 found 466.1954.

General Procedure A for the Preparation of Ketones (8) from Weinreb Amide (7). To a solution of Weinreb amide **7** (0.221 g, 0.5 mmol) in 2 mL of dry THF at −78 °C was added freshly prepared arylmagnesium bromide (2 mmol, 4 equiv), and the solution was allowed to warm to 0 °C. After the completion of the reaction (monitored by TLC), 1 N HCl (5 mL) was added. The resultant mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with saturated brine solution (2 × 20 mL), filtered and concentrated to give crude ketone, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish desired ketone (**8a**−**8i**).

(*S*)-*N*,*N*′-Dibenzyl (5-oxo-5-phenylpentane-1,4-diyl)-dicarbamate (8a). The title compound **8a** was synthesized according

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to the general procedure A for ketones from Weinreb amide **7** and phenylmagnesium bromide. Product was isolated as a white solid (0.185 g, 81% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +24 (*c* 1, $CHCl_3$); mp = 101−103 °C; IR (cm^{-1}) 3320, 1676, 1545; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40−7.25 (m, 10H), 5.81 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 5.16−4.99 (m, 4H), 4.77 (s, 1H), 3.24−3.10 (m, 2H), 1.98−1.88 (m, 1H), 1.75−1.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6, 156.5, 156.2, 136.6, 136.3, 135.0, 134.1, 129.1, 128.8, 128.7, 128.6, 128.3, 128.2, 127.8, 127.1, 67.2, 66.8, 65.5, 55.2, 40.7, 31.0, 25.6, HRMS (ESI) Calcd. for $C_{27}H_{28}N_2O_5Na$ $(M + Na)^+$ 483.1896, found 483.1896

(*S*)-*N*,*N*′-Dibenzyl 5-oxo-5-(*p*-tolyl)pentane-1,4-diyldicarbamate (8b). The title compound **8b** was synthesized according to the general procedure A for ketone from Weinreb amide **7** and *p*-methylphenylmagnesium bromide. Product was isolated as white solid (0.19 g, 80% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +49 (*c* 1, $CHCl_3$); mp = 83−85 °C, IR (cm^{-1}) 3326, 1704, 1689, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 2H), 7.40−7.18 (m, 12H), 5.83 (d, *J* = 7.6 Hz, 1H), 5.38−5.30 (m, 1H), 5.09 and 5.04 (2s, 4H), 4.79 (s, 1H), 3.17−3.11 (m, 2H), 2.4(s, 3H), 1.96−1.87 (m, 1H), 1.74−1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 156.5, 156.2, 145.2, 136.6, 136.4, 131.7, 129.8, 128.9, 128.7, 128.65, 128.62, 128.3, 128.2, 67.1, 66.8, 55.1, 40.8, 31.2, 25.5, 21.9; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_5$ $(M + H)^+$ 475.2233, found 475.2237.

(*S*)-*N*,*N*′-Dibenzyl (5-(furan-2-yl)-5-oxopentane-1,4-diyl)-dicarbamate (8c). To a stirred solution of furan (0.81 g, 12 mmol) in dry THF at −78 °C was added *n*-BuLi (5.3 mL, 8.57 mmol, 1.6 M solution in hexane), and the reaction mixture was stirred for 30 min maintaining the temperature. The resulting reaction mixture was transferred to solution of Weinreb amide (**7**) (0.76 g, 1.71 mmol) in THF at −78 °C via cannula, after which the reaction mixture was allowed to warm to room temperature. After complete consumption of Weinreb amide **7**, the reaction mixture was quenched with 1 N HCl. The resultant mixture was then extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine solution (saturated NaCl) (1 × 40 mL), filtered and concentrated to give the corresponding crude ketone, which was purified over silica gel using column chromatography (EtOAc:petroleum ether, 3:7) to furnish desired furanyl ketone **8c** as a dark gray solid (0.17 g, 77% yield): R_f = 0.5 petroleum ether:EtOAc (50:50); mp = 94−96 °C; IR (cm^{-1}) 3330, 1706, 1692, 1546.; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.40−7.20 (m, 11H), 6.50 (s, 1H), 5.89 (d, *J* = 7.8 Hz, 1H), 5.05 (m, 6H), 3.27−2.92 (m, 2H), 1.89 (s, 1H), 1.60 (dq, *J* = 24.0, 7.5, 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 156.5, 156.1, 150.6, 147.4, 136.6, 136.2, 128.5, 128.1, 128.02, 119.3, 112.7, 66.9, 66.5, 55.5, 40.5, 30.3, 25.7; HRMS(ESI) Calcd. for $C_{25}H_{26}N_2O_6Na$ $(M + Na)^+$ 473.1689, found 473.1684.

(*S*)-*N*,*N*′-Dibenzyl 5-(4-fluorophenyl)-5-oxopentane-1,4-diyl-dicarbamate (8d). The title compound **8d** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-fluorophenylmagnesium bromide. Product was isolated as a white solid (0.178 g, 75%): R_f = 0.5 petroleum ether:EtOAc (50:50); $[\alpha_D^{25}]$.+28.1 (*c* 1, $CHCl_3$); mp = 95−96 °C; IR (cm^{-1}) 3370, 1706, 1677, 1516 ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.32 (m, 10H), 7.14 (t, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 5.1 (s, 2H), 5.0 (s, 2H), 4.76 (bs, 1H), 3.17 (bs, 2H), 1.93 (m, 1H), 1.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 167.5, 164.9, 156.5, 156.2, 136.5, 136.3, 131.5, 131.4, 130.7, 128.6, 128.5, 128.2, 128.1, 116.3, 116.1, 67.1, 66.7, 55.0, 40.6, 30.7, 25.6; HRMS (ESI) Calcd. for $C_{27}H_{27}N_2O_5FNa$ $(M + Na)^+$ 501.1802, found 501.1797.

(*S*)-*N*,*N*′-Dibenzyl (5-(4-chlorophenyl)-5-oxopentane-1,4-diyl)dicarbamate (8e). The title compound **8e** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-chlorophenylmagnesium bromide. Product was isolated as a white solid (0.19 g, 77% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +22.8 (*c* 1, $CHCl_3$); mp = 99−101 °C; IR (cm^{-1}) 3335, 1677, 1656, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.32 (m, 10H), 5.73 (d, *J* = 8.2 Hz, 1H), 5.31 (s, 1H), 5.10 (s, 2H), 5.05 (s, 2H), 4.76 (bs, 1H), 3.17 (bm, 2H), 1.92 (m, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 156.5, 156.2, 140.7, 136.6, 136.3, 132.6, 130.2, 129.5, 128.70, 128.7, 128.4, 128.2, 67.2, 66.8, 55.1, 40.7, 34.1, 30.9, 25.7; HRMS (ESI) Calcd. for $C_{27}H_{28}N_2ClO_5$ $(M + H)^+$ 495.1686, found 495.1684.

(*S*)-*N*,*N*′-Dibenzyl 5-oxo-5-(thiophene-2-yl)pentane-1,4-diyl-dicarbamate (8f). The title compound **8f** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and 2-thiophenemagnesium bromide. Product was isolated as a white solid (0.17 g, 73% yield): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +26 (*c* 1, $CHCl_3$); mp = 98−99 °C; IR (cm^{-1}) 1685, 1667, 1515; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.71 (d, *J* = 4.6 Hz, 1H), 7.41−7.28 (m, 10H), 7.20−7.12 (m, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 5.28−5.13 (m, 1H), 5.10 and 5.07 (2s, 4H), 4.85 (m, 1H), 3.20 (bm, 3H), 2.05−1.92 (m, 1H), 1.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 156.5, 156.1, 141.3, 136.6, 136.3, 135.4, 133.4, 128.7, 128.6, 128.3, 128.2, 67.2, 66.8, 56.1, 40.7, 31.6, 25.8; HRMS (ESI) Calcd. for $C_{25}H_{26}N_2O_5SNa$ $(M + Na)^+$ 489.1460, found 489.1463.

(*S*)-*N*,*N*′-Dibenzyl 5-(4-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8g). The title compound **8g** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *p*-methoxyphenylmagnesium bromide. Product was isolated as a colorless oil (0.2 g, 83%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +28.4 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3320, 1706, 1646, 1531; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.41−7.27 (m, 10H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.83 (d, *J* = 7.8 Hz, 1H), 5.31 (bm, 1H), 5.1 and 5.0 (2s, 4H), 4.79 (bs, 1H), 3.86 (s, 3H), 3.16 (bm, 2H), 2.02−1.84 (m, 1H), 1.69−1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 164.4, 156.5, 156.2, 136.4, 131.1, 128.7, 128.6, 128.3, 128.2, 127.0, 114.3, 67.1, 66.7, 55.7, 54.7, 40.8, 31.4, 22.5; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.1993.

(*S*)-*N*,*N*′-Dibenzyl 5-(3-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8h). The title compound **8h** was synthesized according to the general procedure A for ketones from Weinreb amide **7** and *meta*-methoxyphenylmagnesium bromide. Product was isolated as colorless oil (0.198 g, 81%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +22.8 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3340, 1692, 1666, 1517; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.4 Hz, 1H), 7.45 (s, 1H), 7.41−7.26 (m, 11H), 7.13 (dd, *J* = 8.1, 2.5 Hz, 1H), 5.82 (d, *J* = 7.8 Hz, 1H), 5.41−5.27 (m, 1H), 5.1 and 5.07 (2s, 4H), 4.81 (s, 1H), 3.83 (s, 3H), 3.16 (m, 2H), 1.94 (m, 1H), 1.66−1.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 160.1, 156.5, 156.2, 136.6, 136.3, 135.6, 130.1, 128.7, 128.6, 128.3, 128.2, 121.3, 120.7, 112.9, 67.1, 66.8, 55.61, 55.3, 40.7, 31.1, 25.6.HRMS (ESI) Calcd. for $C_{28}H_{3O}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.1992.

(*S*)-*N*,*N*′-Dibenzyl 5-(2-methoxyphenyl)-5-oxopentane-1,4-diyldicarbamate (8i). The title compound **8i** was synthesized according to the general procedure for ketones from Weinreb amide **7**and *ortho*-methoxyphenylmagnesium bromide. Product was isolated as white solid (0.173 g, 71%): R_f = 0.5 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ +10 (*c* 1, $CHCl_3$); mp = 97−99 °C; IR (cm^{-1}) 1706, 1680, 1560; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.3 Hz, 1H), 7.54−7.45 (m, 1H), 7.37−7.26 (m, 10H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 5.44 (m, 1H), 5.07 (2s, 4H), 4.80 (s, 1H), 3.89 (s, 3H), 3.14 (s, 2H), 1.90 (m, 1H), 1.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 158.8, 156.4, 134.9, 131.4, 128.7, 128.2, 124.9, 121.2, 111.9, 67.0, 66.7, 59.5, 55.9, 40.9, 30.3, 29.8, 25.8; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_6Na$ $(M + Na)^+$ 513.2002, found 513.2003.

General Procedure B for Cyclization. To a stirred solution of ketone (**8a**−**8i**) (0.5 mmol) in CH_2Cl_2 (1 mL) at −78 °C were added successively Et_3SiH (0.6 mmol) and TMSOTf (0.6 mmol), and the reaction mixture was stirred for 30 min maintaining the temperature, after which the reaction mixture was allowed to warm to room temperature. After complete consumption of starting material (monitored by TLC), the reaction mixture was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give cyclized product (2,3-disubstituted piperidine), which was purified over silica gel using

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column chromatography (EtOAc:petroleum ether, 2:8) to furnish 2,3-disubstituted piperidine derivative (**9a**–**9i**).

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-phenylpiperidine-1-carboxylate (9a). Synthesized according to the general procedure B. Product was isolated as white solid (0.18 g, 81% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −2 (*c* 1, $CHCl_3$); mp = 127−129 °C; IR (cm^{-1}) 3390, 1691.1518; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 13H), 7.17 (bm, 2H), 5.44 (d, *J* = 6.4 Hz, 1H), 5.21−4.90 (m, 4H), 4.35 (d, *J* = 9.1 Hz, 1H), 4.21−4.04 (m, 2H), 3.22 (m, 1H), 1.93−1.85 (m, 2H), 1.81−1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 155.5, 138.4, 136.6, 136.4, 129.2, 128.7, 128.1, 128.3, 128.0, 127.8, 67.4, 66.9, 57.4, 50.2, 40.5, 26.1, 24.1; HRMS (ESI) Calcd. for $C_{27}H_{29}N_2O_4$ $(M + H)^+$ 445.2127, found 445.2128.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(*p*-tolyl)-piperidine-1-carboxylate (9b). Synthesized according to the general procedure B. Product was isolated as colorless oil (0.176 g, 77% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −4.1 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3329, 1695, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 8H), 7.19 (m, 4H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.41 (d, *J* = 6.3 Hz, 1H), 5.20−4.93 (m, 4H), 4.38 (d, *J* = 9.1 Hz, 1H), 4.12 (m, 2H), 3.20 (t, *J* = 12.9 Hz, 1H), 2.32 (s, 3H), 1.89 (d, 2H), 1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.5, 137.6, 136.7, 136.5, 135.2, 129.4, 129.2, 128.6, 128.5, 128.3, 128.0, 127.9, 77.5, 77.2, 76.8, 67.4, 66.9, 57.2, 50.2, 40.4, 26.2, 24.2, 21.1; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_4$ $(M + Na)^+$ 459.2284, found 459.2285.

(2*R*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(furan-2-yl)-piperidine-1-carboxylate (9c). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.160 g, 74% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −19.6 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3326, 1694, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 10H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.16 (bs, 1H), 5.45 (bs, 1H), 5.26 (d, *J* = 7.7 Hz, 1H), 5.21−5.01 (m, 4H), 4.39 (s, 1H), 4.09 (d, *J* = 6.6 Hz, 1H), 2.92 (t, *J* = 12 Hz, 1H), 1.84−1.75 (m, 2H), 1.67−1.59 (m, 2H), 1.56−1.47 (m, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.0, 142.2, 136.3, 128.7, 128.6, 128.4, 110.5, 107.7, 67.5, 67.1, 54.6, 47.0, 40.2, 24.6, 19.7; HRMS (ESI) Calcd. For $C_{25}H_{26}N_2O_5Na$ $(M + Na)^+$ 457.1739, found 457.1742.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-fluorophenyl)piperidine-1-carboxylate (9d). Synthesized according to the general procedure B. Product was isolated as a white solid (0.184 g, 80% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −2.1 (*c* 1, $CHCl_3$); mp = 139−141 °C; IR (cm^{-1}) 3322, 1692, 1656, 1529; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.23 (m, 13H), 6.95 (t, *J* = 8.6 Hz, 2H), 5.46 (d, *J* = 6.4 Hz, 1H), 5.21−4.94 (m, 4H), 4.32 (d, *J* = 8.6 Hz, 1H), 4.13 (d, *J* = 11.9 Hz, 2H), 3.20 (t, *J* = 14.7 Hz, 1H), 1.98−1.87 (m, 2H), 1.86−1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 136.6, 136.4, 130.8, 130.8, 128.7, 128.5, 128.4, 128.1, 127.9, 115.7, 115.4, 67.5, 67.0, 56.8, 50.1, 40.4, 26.0, 24.0; HRMS (ESI) Calcd. for $C_{27}H_{28}FN_2O_4$ $(M + H)^+$ 463.2033, found 463.2037.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-chlorophenyl)piperidine-1-carboxylate (9e). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.198 g, 83% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −4.6 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3341, 1694, 1646, 1530; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 7.20 (d, *J* = 2.7 Hz, 3H), 7.17 (s, 2H), 5.43 (d, *J* = 6.5 Hz, 1H), 5.16−4.87 (m, 4H), 4.33 (d, *J* = 8.8 Hz, 1H), 4.15−4.04 (m, 2H), 3.22−3.14 (m, 1H), 1.91−1.83 (m, 2H),1.78−1.68 (m, 1H), 1.67−157 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.4, 137.0, 136.5, 136.3, 133.8, 130.4, 128.7, 128.8, 128.5, 128.4, 128.4, 128.1, 127.9, 127.8, 67.5, 67.5, 67.0, 56.8, 50.1, 40.6, 25.9, 23.98; HRMS (ESI) Calcd. for $C_{27}H_{28}ClN_2O_4$ $(M + H)^+$ 479.1738, found 479.1746.

(2*R*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(thiophen-2-yl)piperidine-1-carboxylate (9f). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.17 g, 76% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −16.7 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3390, 1694, 1518; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 10H), 6.98−6.92 (m, 1H), 5.63 (s, 1H), 5.26 (d, *J* = 8.4 Hz, 1H), 5.18−5.03 (m, 4H), 4.37 (d, *J* = 8.0 Hz, 1H), 4.18−3.99 (m, 2H), 3.08−2.92 (m, 2H), 1.94−1.77 (m, 2H), 1.68−1.56 (m, 1H), 1.52−1.47(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 155.6, 141.5, 136.5, 136.3, 128.7, 128.6, 128.4, 128.2, 127.9, 127.2, 125.09, 124.9, 67.7, 67.1, 56.2, 48.9, 39.7, 24.0, 19.7.HRMS (ESI) Calcd. for $C_{25}H_{26}N_2O_4SNa(M + Na)^+$ 473.1511, found 473.1511.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(4-methoxyphenyl)piperidine-1-carboxylate (9g). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.187 g, 79% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −24.1 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3329, 1695, 1516; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.24 (m, 10H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.44 (s, 1H), 5.30 (m, 1H), 5.20−5.05 (m, 4H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.20−4.09 (m, 1H), 3.80 (s, 3H), 2.89 (t, *J* = 11.3 Hz, 1H), 1.73 −1.58 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 156.9, 155.8, 136.6, 136.4, 129.0, 128.7, 128.3, 128.4, 128.1, 127.8, 127.6, 114.3, 67.0, 58.2, 55.4, 48.0, 39.9, 23.7, 19.8; HRMS (ESI) Calcd. for $C_{28}H_{31}N_2O_5$ $(M + H)^+$ 475.2233, found 475.2237.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(3-methoxyphenyl)piperidine-1-carboxylate (9h). Synthesized according to the general procedure B. Product was isolated as colorless viscous oil (0.184 g, 78% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −10 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3331, 1692, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 9H), 7.20 (s, 2H), 6.86 (m, 3H), 5.42 (d, *J* = 5.8 Hz, 1H), 5.18−4.95 (m, 4H), 4.44 (d, *J* = 8.8 Hz, 1H), 4.18−4.05 (m, 2H), 3.69 (s, 3H), 3.28−3.17 (m, 1H), 1.98−1.83 (m, 2H), 1.83−1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 155.8, 155.5, 139.8, 136.6, 136.4, 129.6, 128.7, 128.6, 128.5, 128.3, 128.2, 128, 127.9, 121.3, 115.4, 113.1, 67.4, 66.9, 57.4, 55.2, 50.1, 40.5, 26.8, 24.1; HRMS (ESI) Calcd. for $C_{28}H_{30}N_2O_5Na$ $(M + Na)^+$ 497.2052, found 497.2051.

(2*S*,3*S*)-Benzyl 3-(benzyloxycarbonylamino)-2-(2-methoxyphenyl)piperidine-1-carboxylate (9i). Synthesized according to the general procedure B. Product was isolated in 72% yield as colorless viscous oil (0.17g, 72% yield): R_f = 0.6 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ + 2.6 (*c* 1, $CHCl_3$), IR (cm^{-1}) 3428, 1695, 1413; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.33 (m, 5H), 7.25−7.21 (m, 4H), 7.16−7.08 (m, 3H), 6.91−6.85 (m, 2H), 5.43 (d, *J* = 2.5 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 5.11−5.06 (m, 4H), 4.5 (bs, 1H), 4.28−4.21 (m, 1H), 3.8(s, 3H), 3.35−3.28 (m, 1H), 1.80−1.71 (m, 2H), 1.64−1.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 156.7, 145.2, 136.6, 131.1, 130.4, 128.6, 128.4, 128.2, 127.9, 127.5, 126.9, 120.4, 110.9, 67.3, 66.8, 56.6, 55.4, 41.5, 41.3, 24.0, 19.2; HRMS(ESI) Calcd. for $C_{28}H_{30}N_2O_5Na$ $(M + Na)^+$ 497.2052, found 497.2045.

Synthesis of 1,2-Amino Alcohol (10). $BF_3{\cdot}OEt_2$ (0.192 mL, 1.53 mmol) was added to a solution of Et_3SiH (0.6 g, 5.1 mmol) in CH_2Cl_2 (2 mL) at room temperature. The solution was stirred for 5 min and then transferred via cannula to a stirred solution of ketone **8a** (0.2 g, 0.51 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, whereupon the cooling-bath was removed and stirring was continued at room temperature for an additional 1 h. The reaction mixture was recooled to −78 °C and poured into a mixture of saturated aqueous $NaHCO_3$. The organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford a white solid **10** (0.184 g, 92% yield): R_f = 0.4 petroleum ether:EtOAc (50:50), $[\alpha_D^{25}]$ −27.8 (*c* 1, $CHCl_3$); mp =116−117 °C; IR (cm^{-1}) 3290, 1686, 1545; ^1H NMR (400 MHz, DMSO-d_6) δ 7.43−7.07 (m, 16H), 7.04 (d, *J* = 9.2 Hz, 1H), 5.35 (d, *J* = 4.9 Hz, 1H), 5.06−4.76 (m, 4H), 4.45 (t, *J* = 5.5 Hz, 1H), 3.52 (m, 1H), 2.90 (m, 2H), 1.63−1.11 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 155.8, 143.7, 137.4, 137.3, 128.4, 128.3, 127.75, 127.7, 127.6, 127.3, 126.7, 126.5, 74.7, 65.1, 64.8, 56.8, 40.5, 26.5, 26.3 HRMS (ESI) Calcd. for $C_{27}H_{30}N_2O_5Na$ $(M + Na)^+$ 485.2052, found 485.2055.

Asymmetric Synthesis of (+)-CP-99,994. A mixture of **9a** (0.4 g, 0.87 mmol), and Pd/C (10%, 0.1 g), in MeOH (5 mL) was stirred under an atmosphere of H_2 at rt for 6 h. The crude mixture was filtered through a pad of Celite, and the filtrate was concentrated under vacuum to give crude diamine. To a solution of the crude diamine in CH_2Cl_2 (5 mL) and 2-methoxybenzaldehyde (0.118 g, 0.87 mmol)

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was added $NaBH(OAc)_3$ (0.276 g, 1.30 mmol), and the resulting mixture was stirred under an argon atmosphere for 20 h at room temperature. Saturated aqueous Na_2CO_3 solution (10 mL) was added, and the organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a mixture of $CHCl_3$/MeOH (80:20) as eluent to give **1** (0.21 g, 75%) as a pale yellow oil: R_f = 0.6 DCM:MeOH (20:80), $[\alpha_D^{25}]$ +66.7 (*c* 1, $CHCl_3$); IR (cm^{-1}) 3328, 2923, 1465; Lit.[7d] $[\alpha]_D^{25}$ +67.2 (1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 7.16 (td, *J* = 7.9, 1.7 Hz, 1H), 6.98 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.81 (td, *J* = 7.3, 0.8 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 3.91 (d, *J* = 2.2 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.43(s, 3H), 3.34−3.27 (m, 1H), 2.87−2.82 (m, 2H), 2.6(bs, 2H), 2.14 (d, *J* = 12.5 Hz, 1H), 2.06−1.92 (m, 1H), 1.65−1.57 (m, 1H), 1.43 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 141.5, 129.9, 128.4, 128.2, 127.5, 127.0, 126.4, 120.2, 109.9, 63.8, 54.9, 54.7, 47.6, 46.8, 27.9, 20.0; HRMS (ESI) Calcd. for $C_{19}H_{25}N_2O$ $(M + H)^+$:297.1967, found 297.1969. HPLC Chiralpak IC, *n*-Hexane/2-propanol 10:90, 290 nm; Retention Time t_{major} = 8.04 min, t_{minor} = 10.11 min; *ee* = 97% (please see the Supporting Information).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR, ^{13}C NMR spectra for the compounds **1**, **7**, **8a**−**8i**, **9a**−**9i**, and **10**. NOE, NOESY, COSY, single crystal X-ray (CIF) and HPLC data of compound **9a**. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rgb@iiserpune.ac.in

Notes

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Chemoselective N-deacetylation under mild conditions†

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Prakash R. Sultane, Trimbak B. Mete and Ramakrishna G. Bhat*

A mild and efficient chemoselective N-deacetylation using the Schwartz reagent at room temperature in rapid time is described. The mild and neutral conditions enable orthogonal N-deacetylation in the presence of some of the common protecting groups (*viz*. Boc, Fmoc, Cbz, Ts). The deprotection conditions did not induce any epimerization at the chiral amino centre.

Organic compounds with amine functionality are widespread in many natural products, bioactive compounds and pharmaceuticals.[1] However, due to their remarkable nucleophilicity quite often amines are protected to carry out a series of organic transformations. Though protecting group free synthesis is highly desirable and demanding,[2] in many instances the protection of amines is unavoidable, thus making the reaction reliable for obtaining the target compound efficiently without any side reactions.

The acetyl moiety is one of the widely employed protecting group for amines in organic synthesis and also it is one of the most common protecting groups used by nature in natural product synthesis.[1,3] Acetylated amines (acetamides) have a remarkably reduced nucleophilic character in comparison to amines. Acetylated amines have been explored for the catalytic asymmetric hydrogenations of enamides.[4] Acetylated amines such as acetamides have been successfully utilized as directing groups in C–H activation.[5] In spite of the wide utility of acetyl protection for amines in organic synthesis, acetyl deprotection (N-deacetylation) is practically limited to the traditional harsh deprotecting conditions. As the amide bond is robust, N-deacetylation usually requires the use of a strong base or acid at a high temperature.[3] These deprotective conditions limit the scope of acetylated amines along with the variety of functional groups which are sensitive to acid and base. N-deacetylation under harsh conditions may lead to racemization in certain cases. Nevertheless, efforts have been made in recent times to overcome this limitation. Some of the available protocols utilize moisture sensitive and corrosive reagents such as oxalyl chloride,[6] and a triphenyl phosphite complex[7] under basic conditions at lower temperatures. Recently an elegant method has been described by employing transamidation using an ammonium salt.[8] However, this protocol demands the sacrifice of a stoichiometric equivalent of another amine for the transamidation. While searching through the literature, we learnt that the Schwartz reagent has been elegantly and effectively employed for the conversion of carboxamides to imines, and also for the conversion of amides to aldehydes.[9] However to the best of our knowledge, the Schwartz reagent has not been exploited for a straight forward N-deacetylation protocol. Also there are not many standard protocols for N-deacetylation under mild conditions. Based on this consideration it would be valuable to develop a method for N-deacetylation under mild conditions that can tolerate a variety of functional groups. We envisioned that the Schwartz reagent can be utilized for N-deacetylation and the protocol would particularly be very useful for laboratory scale reactions.

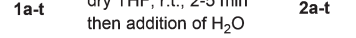
Herein, we wish to report a convenient selective N-deacetylation protocol using the Schwartz reagent at room temperature in a very short time (2–5 min). Moreover, we demonstrate the selective (orthogonal) deprotection by carrying out competition experiments. The methodology proved to be very efficient for aromatic, heteroaromatic and aliphatic amides and also no epimerization was observed during the N-deacetylation of chiral acetamides.

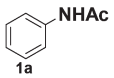
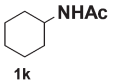
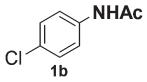
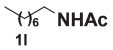
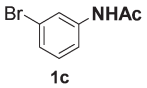
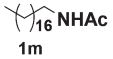
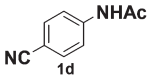
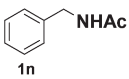
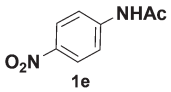
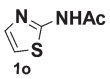
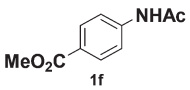
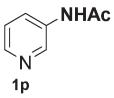
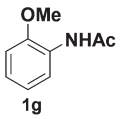
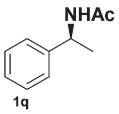
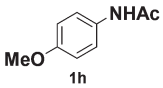
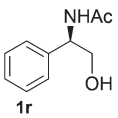
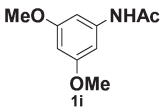
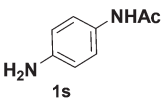
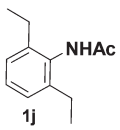
In order to demonstrate the utility of the Schwartz reagent we began our study with the synthesis of various *N*-acetamides (**1a–1t**) starting from the corresponding amines with varying electronic and steric properties (Table 1). In our initial experiment, compound **1a** was treated with the Schwartz reagent in anhydrous THF at room temperature. The turbid reaction mixture changed into a clear solution in a very short time (3 min). The completion of the reaction was monitored by TLC and the reaction was quenched by the addition of water and

Mendeleev Block, Department of Chemistry, Indian Institute of Science Education & Research (IISER), Pune, 411008 Maharashtra, India. E-mail: rgb@iiserpune.ac.in; Fax: +91-(20)-25899790; Tel: +91-20-25908092

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data and copies of ^{1}H-NMR for compounds **1a–1t**, **3**, **4**, **5**, **6**, **7**, **8**, **11**. ^{1}H and ^{13}C-NMR spectra for the compounds **2a–2t**, **9**, **10**, **12**. See DOI: 10.1039/c3ob41971a

Table 1 The deprotection of various acetamides by the Schwartz reagent[a]

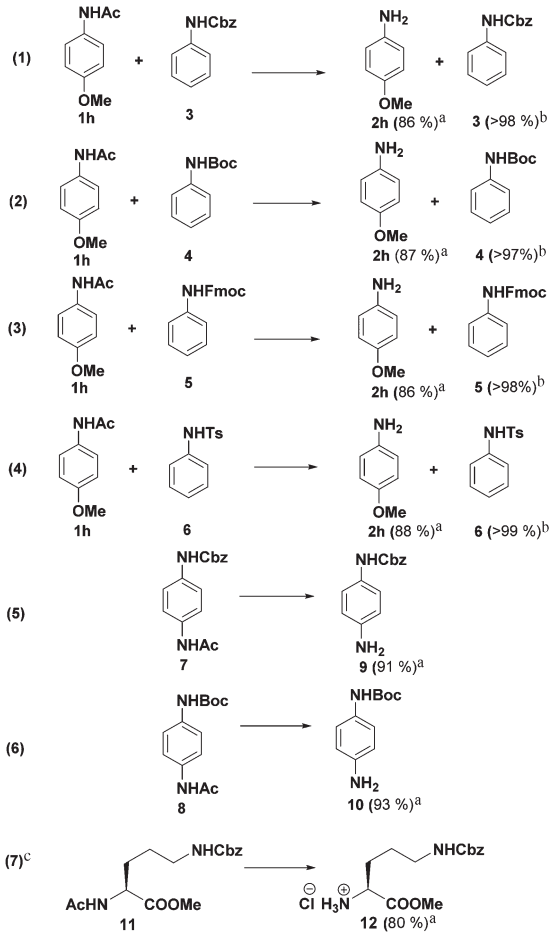


Entry	Substrate	Time (min)	Product yield[b] (%)	Entry	Substrate	Time (min)	Product yield[b] (%)
1	 1a	3	**2a** (94)	11	 1k	2	**2k** (91)
2	 1b	3	**2b** (92)	12	 1l	2	**2l** (93)
3	 1c	3	**2c** (90)	13	 1m	2	**2m** (91)
4	 1d	4	**2d** (84)	14	 1n	2	**2n** (91)
5	 1e	4	**2e** (89)	15	 1o	3	**2o** (88)
6	 1f	4	**2f** (87)	16	 1p	3	**2p** (89)
7	 1g	4	**2g** (86)	17	 1q	2	**2q** (93)
8	 1h	2	**2h** (88)	18	 1r	4	**2r** (89)
9	 1i	3	**2i** (86)	19	 1s	5	**2s** (90)
10	 1j	5	**2j** (87)	20	 1t	3	**2t** (94)

[a] A maximum of 1.5–2 equiv. of the Schwartz reagent is required for the complete conversion. [b] The yield of the isolated products.

worked up to afford the corresponding **2a** in an excellent yield (94%, Table 1).

Encouraged by the initial result a variety of substrates were examined for the N-deacetylation. Substrates with both electron withdrawing and donating functional moieties (**1b–1i**) underwent N-deacetylation in a very rapid time affording the corresponding amines (**2b–2i**) in excellent yields (Table 1). The electronic properties of the functional groups did not have any significant impact on the reaction time and yield. The steric factor in substrate **1j** did not have any impact on the rate of deprotection. The N-deacetylation of aliphatic and heteroaromatic substrates was very efficient in a short time affording the corresponding amines (**2k–2p**) in excellent yields. The N-deacetylation was highly chemoselective. Substrates with an α-chiral centre were chosen for the study to investigate the possibility of epimerization during the N-deacetylation. Chiral substrates (**1q** and **1r**) underwent facile N-deacetylation in a short time to afford the corresponding amines (**2q** and **2r**) without any



Scheme 1 Chemoselective N-deacetylation in a series of competition experiments. The substrates were treated in an equimolar ratio (1 : 1). The reactions were carried out using the Schwartz reagent (2.5 equiv.) at room temperature in dry THF for 5 min and then the reaction was quenched with H_2O. The same reaction mixtures were stirred overnight to study the reactivity profile of other protecting groups under the reaction conditions. [a]The values in brackets show the yields of the isolated products. [b]The yield of the recovered substrates. [c]The reaction was quenched with HCl in 1,4-dioxane to make a stable salt.

epimerization.[10] We observed that even the tertiary acetamide (**1t**) was equally susceptible to the deacetylation conditions to afford the free amine (**2t**) in an excellent yield (Table 1).

In order to have a wider application of this protocol we carried out a series of competition experiments (Scheme 1).

Initially, for the competition experiments substrates (**3–6**) containing commonly used protecting groups such as Cbz, Boc, Fmoc, Ts were considered (Scheme 1).

Compound **1h** was treated with the competitive substrates (**3–6**) in an equimolar ratio under the optimized reaction conditions (Schwartz reagent 2.5 equiv., THF, room temperature, 3–5 min, then water). It is very remarkable that **1h** alone underwent N-deacetylation chemoselectively in just 3–5 minutes affording the corresponding amine **2h** in an excellent yield and the competitive substrates were recovered in almost quantitative amounts (Scheme 1). In order to substantiate any possible reactivity of the reagent on the competitive substrates, the reactions were stirred overnight. However, all of the competitive substrates (carbamates **3–6**) were unreactive and were recovered in almost quantitative yields.

Also, when compounds (**7** and **8**) containing both *N*-Ac and *N*-Boc, or *N*-Cbz moieties were treated with the reagent in THF followed by the addition of water, the corresponding amines (**9** and **10**) were afforded *via* chemoselective N-deacetylation in excellent yields (Scheme 1). Furthermore, the application of this method was demonstrated on an amino acid derivative: L-N^{δ}-Cbz-N^{α}-acyl ornithine methyl ester **11**. On treatment with the Schwartz reagent (5 min) followed by the addition of HCl in 1,4-dioxane compound **11** afforded the corresponding L-N^{δ}-Cbz-ornithine methyl ester hydrochloride **12**.[10] It is particularly important to note that the reagent is highly preferential to amides. This result would be synthetically very useful and can be utilized in the orthogonal deprotection of the *N*-acetyl moiety in the presence of various other protecting groups under mild conditions. The protocol does not demand the use of any quenching or scavenging agents.[6,11] Also, generally N-deacetylation requires harsh acidic or basic conditions in which protection groups such as Boc, Fmoc, Ts would be highly labile.

Conclusions

In summary we have described an efficient and facile method for N-deacetylation. The method has several distinct advantages. The deprotection requires a very short reaction time (2–5 min) at room temperature affording amines in excellent yields with a great chemoselectivity. The reaction conditions are very mild and many of the conventional protecting groups of amines were stable under the reaction conditions. Furthermore, the reaction conditions enable the deprotection of chiral acetamides without any epimerization. The protocol may provide an advantage to remove the acetyl group at any convenient stage of the natural product synthesis. Further study of the Schwartz reagent and its utility is under progress.

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Notes and references

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10 The observed optical rotation of the products were in agreement with the literature values (please see ESI†).

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