Diastereoselective Aldehyde-Amine-Alkyne Coupling Reaction: Synthesis of Biologically Active Molecules

A thesis

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of the degree of

Doctor of Philosophy

By

Sharad Chandrakant Deshmukh

ID: 20103071

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2016

Dedicated

to…

My Parents

And

My Beloved Family

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "***Diastereoselective Aldehyde-Amine-Alkyne Coupling Reaction: Synthesis of Biologically Active Molecules"*** submitted by **Mr. Sharad Chandrakant Deshmukh** 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: 19th May 2016

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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.

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List of Symbols and Abbreviations

A^3	Aldehyde-Amine-Alkyne
AA^3	Asymmetric Aldehyde-Amine-Alkyne
MCRs	Multicomponent Reactions
ee	Enantiomeric excess
Boc	*tert*-Butoxycarbonyl
IC_{50}	Half maximal inhibitory concentration
HPLC	High Performance Liquid Chromatography
MALDI	Matrix Assisted Laser Desorption Ionization
Boc	*tert*-Butoxycarbonyl
DIBAL-H	Diisobutylaluminium hydride
RCM	Ring-closing metathesis
MOM	Methoxymethyl ether
THF	Tetrahydrofuran
DIAD	Diisopropyl azodicarboxylate
PPh_3	Triphenylphosphine
Et_2O	Diethyl ether
Na_2SO_4	Sodium sulphate
SAR	Structural activity relationship
AHBA	α-hydroxy-β-amino acid
Bn	Benzyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TBDMS-Cl	*tert*-butyldimethylsilyl chloride
TBAF	Tetrabutylammonium fluoride
EDC	*N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide
HOBt	1-hydroxybenzotriazole monohydrate
AcOH	Acetic acid
GABA	γ-Aminobutyric acid
Cbz	Carboxybenzyl
Et_3N	Triethylamine
Ac_2O	Acetic anhydride
MsCl	Methanesulfonyl chloride
TFA	Trifluoroacetic acid

DMP	Dess–Martin periodinane
LAH	Lithium aluminium hydride
PTSA	p-toluenesulfonic acid
n-BuLi	n-Butyllithium
NaOEt	Sodium ethoxide
K_2CO_3	Potassium carbonate
NaOH	Sodium hydroxide
Ph	phenyl
Me	methyl
t-BuOH	*tert*-Butyl alcohol
HCl	Hydrochloric acid
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon-13 nuclear magnetic resonance spectroscopy
HR-MS	High resolution mass spectrometry
IR	Infrared spectroscopy
XRD	X-ray diffraction
ORTEP	Oak ridge thermal ellipsoid plot
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
Brine	Saturated aqueous sodium chloride
t_R	Response time
H_2S	Hydrogen Sulfide
h	Hour
min	Minute
A	Absorbance
mg	Milligram(s)
mmol	Millimole(s)
µM	Micromolar
µL	Microlitre
mL	Millilitre
mol	Mole(s)
M.p.	Melting point
α	Alpha

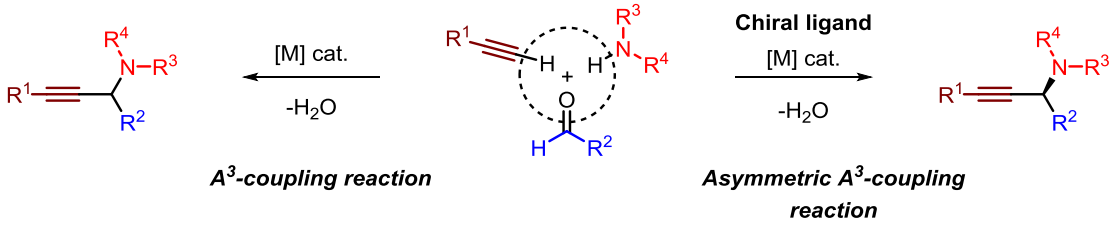
β	Beta
γ	Gamma
δ	Delta
br	Broad singlet
m	Multiplet
s	Singlet
d	Doublet
dd	Doublet of doublet
t	Triplet
ϕ	Quantum yield
^{o}C	Degree Celsius
rt	Room temperature
δ	Chemical shift
calcd.	Calculated
cm^{-1}	Reciprocal centimetres
Hz	Hertz
MHz	Mega Hertz
IR	Infrared spectroscopy
J	Coupling constant
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Methylene chloride
CCl_4	Carbon tetrachloride
DMF	*N*,*N* –Dimethylformamide
DMSO	Dimethyl sulfoxide
D_2O	Deuterated water
Na_2SO_4	Sodium sulphate
EtOAc	Ethyl acetate
CH_3CN	Acetonitrile

Synopsis

The thesis entitled "***Diastereoselective Aldehyde-Amine-Alkyne Coupling Reaction: Synthesis of Biologically Active Molecules***" includes four chapters.

Chapter 1: Introduction: Aldehyde-Amine-Alkyne [A^3] Coupling Reaction

The first chapter presents a brief overview of the importance, synthetic methods, and application of propargylamines. Propargylamines are important intermediates for the synthesis of natural products, amino acids derivatives, and drug molecules. Recently, the three-component coupling reaction of an aldehyde, an alkyne, and an amine, commonly called A^3-coupling, have been used for the synthesis of propargylamine in the presence of a transition-metal catalyst (Scheme 1). Since the discovery of A^3-coupling reactions, various transition metal catalysts *e g.* Cu(I), Ag(I), Cu(II), Fe(III), In(III), Zn(II), Ni(II), Hg(I), Co(II), Au(II), Ir(II), Zr(II), Pd(II), etc. have been utilized for the C-H activation of the terminal alkyne. Also, an enantioselective aldehyde-amine-alkyne **(**AA^3)-coupling reactions have been discovered for the synthesis of chiral propargylamines. To date, a number of chiral ligands with metal catalyst have been used in enantioselective A^3-coupling reactions for improvement in the catalyst loadings, wide substrate scope, and high enantioselectivity.



Scheme 1: A^3-coupling reactions for the synthesis of achiral and chiral propargylamines.

Applications of A^3-coupling reactions have been demonstrated for the synthesis of natural products ((*S*)-coniine, naamine family alkaloids, etc.), biologically active compounds (artemisinin derivatives, γ-butyrolactones, etc.) and amino acids derivatives (β,γ–alkynyl α-amino acid derivatives, etc.). Also, A^3-coupling reactions have been used for the synthesis of a range of nitrogen-containing heterocycles such as imidazole derivatives, polycyclic pyrroles, oxazoles, quinolones, benzazepine derivatives, etc.

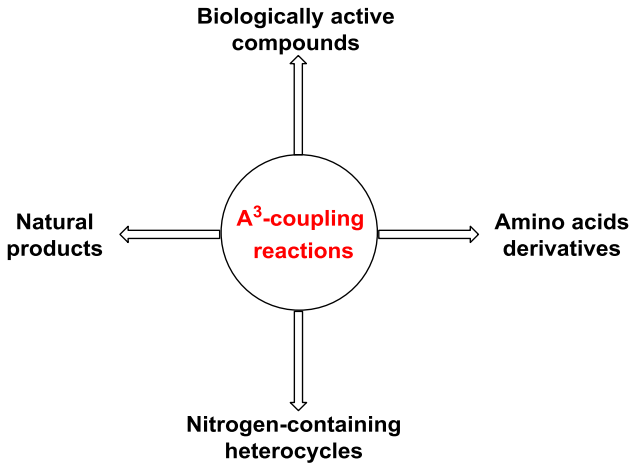


Figure 1: Various synthetic applications of A^3-coupling reactions.

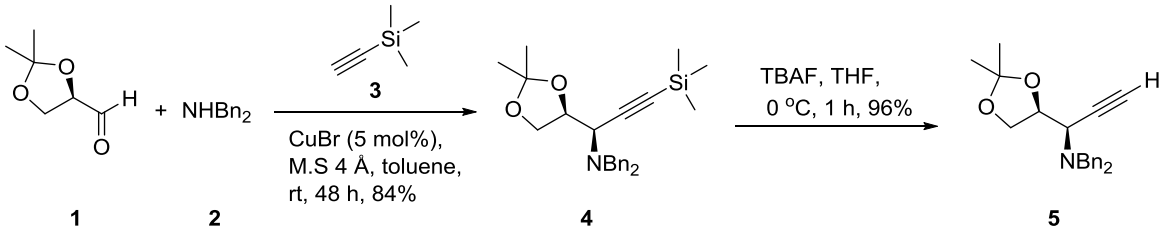
Chapter 2: Diastereoselective Construction of *syn*-α-Aminoalchohols: Synthesis of (+)-β-Conhydrine and its Analogues

The chiral α-amino alcohol moiety is present in many biologically active alkaloids. Nojirimycin, (+)-α-conhydrine, bulgecin C, swainsonine, (-)-erycibelline, etc. are the examples of natural products with α-amino alcohols scaffold present in their structures. These naturally occurring alkaloids have various biological activity, and some are showing glycosidase inhibitory properties. Therefore, synthesis of chiral α-amino-alcohols has become prime targets for synthetic chemists worldwide.

In this chapter, we have demonstrated the new route for the synthesis of chiral α-amino-alcohols using Cu(I) catalyzed using diastereoselective three-component coupling reaction of an aldehyde, an amine, and an alkyne. Application of our methodology addresses the synthesis of (+)-β-conhydrine along with its analogues having two different diversity features i) ring size variation and ii) variation of a side arm.

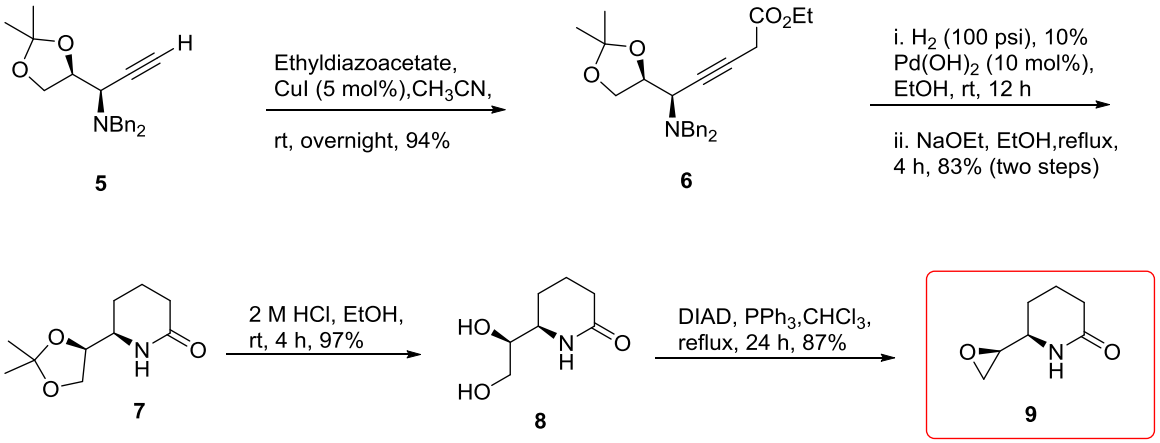
The methodology in the diastereoselective construction of the α-amino alcohol was evaluated by the reaction of (*R*)-glyceraldehyde acetonide **1** and di-benzylamine **2** with of various terminal alkynes in the presence of CuBr as a catalyst in toluene as solvent. We observed (2*S*,3*R*)-α-amino alcohol derivative was formed as a single diastereomer whenever a terminal alkyne with an aliphatic side-chain was introduced. However, with an alkenyl or an aryl group on the terminal alkyne, slight loss of diastreoselectivity was obtained. Crystal structure analysis and theoretical calculations were also supportive to the formation of *syn*-α-amino alcohols as major products. The TMS-protected propargylamine **4** was used for the synthesis of (+)-β-conhydrine and its piperidine as well as pyrrolidine

analogues. The trimethylsilyl group of **4** was deprotected under TBAF conditions which gave the terminal alkyne **5** in 96% yield (Scheme 2). The intermediate **5** has been used for the construction of piperidine as well as pyrrolidine rings.



Scheme 2: Synthesis of key intermediate **5**.

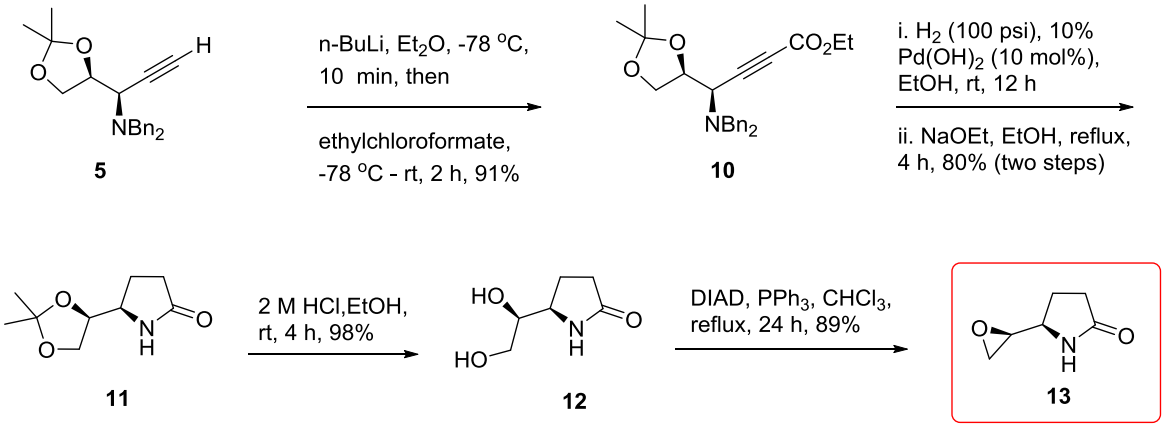
For the construction of piperidine ring, the terminal alkyne **5** was treated with ethyldiazoacetate in a presence of CuI (5 mol%) catalyst to give compound **6** (Scheme 3). When the alkyne **6** was treated with 10% $Pd(OH)_2/C$ (10 mol%) under hydrogen atmosphere (100 psi), complete hydrogenolysis of benzyl groups along with the complete reduction of the alkyne moiety occurred. Further treatment with NaOEt resulted in deprotection of ester followed by cyclization to provide the δ-lactam **7** with 83% yield over two steps. In the next step, the deprotection of ketal moiety of **7** was carried out by ethanolic HCl to give the diol **8** in 94% yield. Under the Mitsunobu conditions, the diol **8** was then converted to the epoxy compound **9** with 87% yield.



Scheme 3: Synthesis of epoxy intermediate **9.**

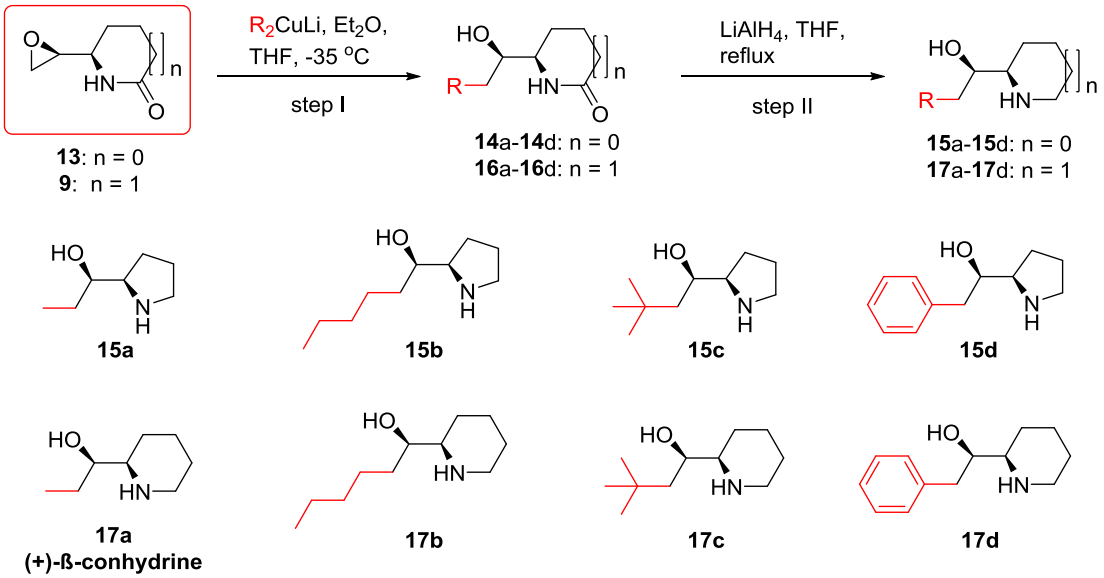
For the construction of pyrrolidine ring, the terminal alkyne **5** was treated with ethylchloroformate and *n*-BuLi to give the ester **10** (Scheme 4). The ester **10** was reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere to facilitate complete hydrogenolysis and alkyne reduction. Subsequent treatment with NaOEt provided the γ-lactam **11** in 80% yield over two steps. Further ketal group of **11** was deprotected by

ethanolic HCl to afford the diol **12** in 98% yield. The diol **12** was then converted to the epoxy-γ-lactam intermediate **13** in 89% yield by reacting with DIAD in the presence of PPh_3 (Mitsunobu conditions).



Scheme 4: Synthesis of epoxy intermediate **13**.

This key intermediate epoxy-γ and epoxy-δ-lactam intermediates **9** and **13** were considered for the synthesis of (+)-β-conhydrine and its analogues (Scheme 5). Unexpected formation of halohydrins were observed in the presence of Grignard reagents. For better nucleophilicity of R^-, we decided to use the Gilman reagent. The treatment of epoxide **9** and **13** with Gilman reagents (R = Me, Bu, *t*Bu and Ph) provided the desired lactam **14a-14d** and **16a-16d** as the single regioisomers. Finally, the γ-lactam was reduced by $LiAlH_4$ in THF under refluxing conditions to provide (+)-β-conhydrine **17a** and its analogues (**15a-15d, 17b-17d**). The present work features a synthesis of (+)-β-conhydrine over eight steps in 26% yield and its seven analogues in 21-28% yields.



Scheme 5: Synthesis of (+)-β-conhydrine and its analoges.

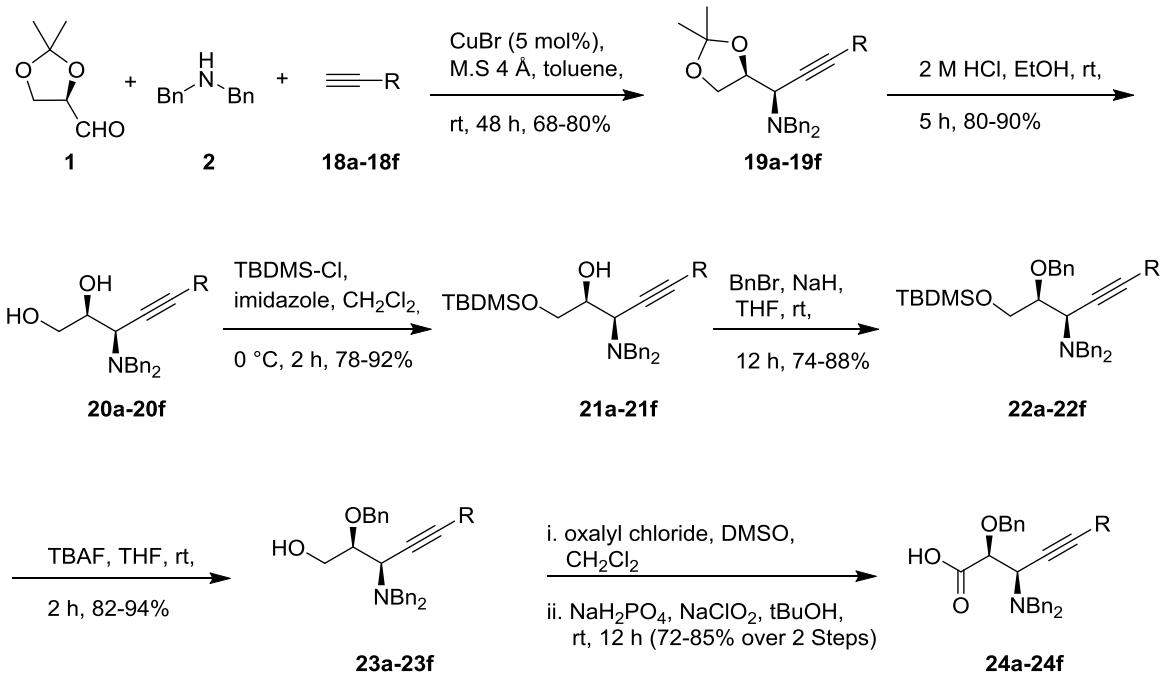
Chapter 3: Synthesis of (2*S*,3*R*)-α-Hydroxy-β-Amino Acids and Enantiomers of Vigabatrin

This chapter has been divided into two sections.

Section-A: (2*S*,3*R*)-α-Hydroxy-β-Amino Acids (AHBAs): Synthesis of Valinoctin A, (2*S*,3*R*)-3-Amino-2-Hydroxydecanoic Acid and A Fluorescence Labelled AHBA

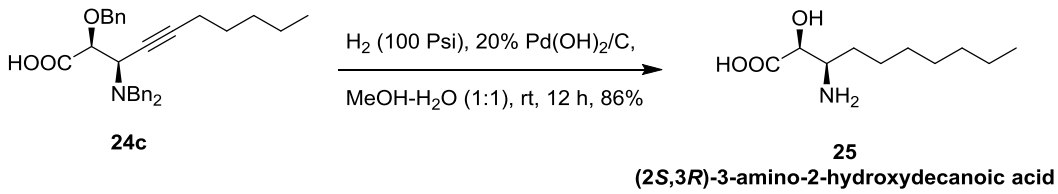
The α-hydroxy-β-amino acids (AHBAs), especially the (2*S*,3*R*)-AHBAs, are present in several naturally occurring and biologically active peptides. Bestatin, amastatin, valinoctin A, microginin, scytonemin A etc. are examples of biologically active compounds having (2*S*,3*R*)-α-hydroxy-β-amino acids as key structural components. Due to this, synthesis of (2*S*,3*R*)-α-hydroxy-β-amino acids has received considerable attention. Based on our report on the diastereoselective construction of (2*S*,3*R*)-α-amino alcohols, we proposed the methodology for the synthesis of (2*S*,3*R*)-α-hydroxy-β-amino acid ((2*S*,3*R*)-AHBA) analogues via the Cu(I)-catalyzed (*R*)-glyceraldehyde acetonide-dibenzylamine-terminal alkyne coupling reaction.

Three-component reactions were carried out using (*R*)-glyceraldehyde acetonide **1**, dibenzylamine **2**, and a series of terminal alkynes **18a-18f** (a = $-C_3H_7$, b = $-C_4H_9$, c = $-C_5H_{11}$, d = $-C_6H_{13}$, e = −Ph, f = −1-pyrenyl). We observed good-to-excellent diastereoselectivity with the terminal alkyne either an aliphatic (propyl, butyl, pentyl, and hexyl) or an aromatic (phenyl and 1-pyrenyl) side-chain (Scheme 6). The acetonide deprotection each three-component coupling products **19a-19f** using methanolic HCl afforded the diol **20a-20f** with 80-90% yields. Protection of a primary alcohol moiety of the diols **20a-20f** was carried out by treating with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in CH_2Cl_2 at room temperature to obtain corresponding silylethers **21a-21f** in 78-92% yields. Subsequent protection of the secondary hydroxyl group of **21a-21f** was achieved by reacting with sodium hydride and benzyl bromide in THF at room temperature to obtain **22a-22f** in 74-88% yields. Desilylation of protected diols **22a-22f** with tetrabutylammonium fluoride (TBAF) furnished the primary alcohols **23a-23f** in 82-94% yields. In the next step, Swern oxidation conditions were applied during the conversion of **23a**−**23f** to the corresponding aldehydes. The crude aldehydes were oxidized further using Pinnick reaction conditions ($NaClO_2$, NaH_2PO_4, 2-metyl-2-butene in *tert*-BuOH) to furnish alkynyl side-chain containing (2*S*,3*R*)-AHBA derivatives **24a**−**24f** in 72−85% yields.



Scheme 6: Synthesis of (2*S*,3*R*)-α-hydroxy-β-amino acids.

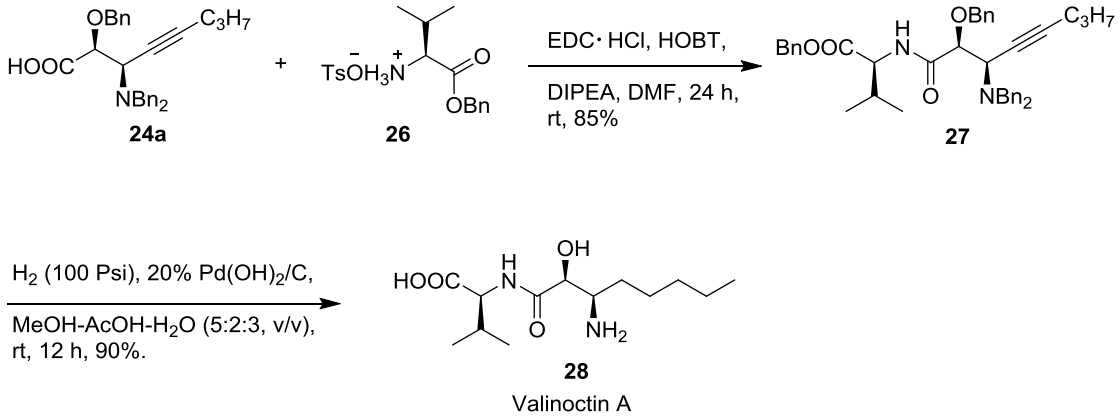
The applications of the methodology in the synthesis of nonproteinogenic amino acid (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA), and natural product valinoctins A were also demonstrated. When carboxylic acid **24c** was subjected to 100 Psi H_2 (in a Parr low-pressure hydrogenation apparatus), 20% $Pd(OH)_2/C$ (10 mol%) in MeOH at room temperature, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond occurred to form (2*S*,3*R*)-AHDA **25** (Scheme 7). Purification of **25** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) to achieve 86% yield.



Scheme 7: Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid.

Further, the reaction of carboxylic acid **24a** and L-valine benzyl ester 4-toluenesulfonate **26** under *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole monohydrate (HOBt) coupling conditions in DMF afforded to dipeptide **27** with 84% yield (Scheme 8). The dipeptide **27** was then treated with H_2 (100 Psi), 20% $Pd(OH)_2/C$ (10 mol%) in MeOH-AcOH-H_2O

(5:2:3, v/v (mL)) at room temperature to give valinoctin A **28** in 90% yield. Cell permeability of fluorescent-labeled amino acid **24f** was also demonstrated by live-cell imaging studies.



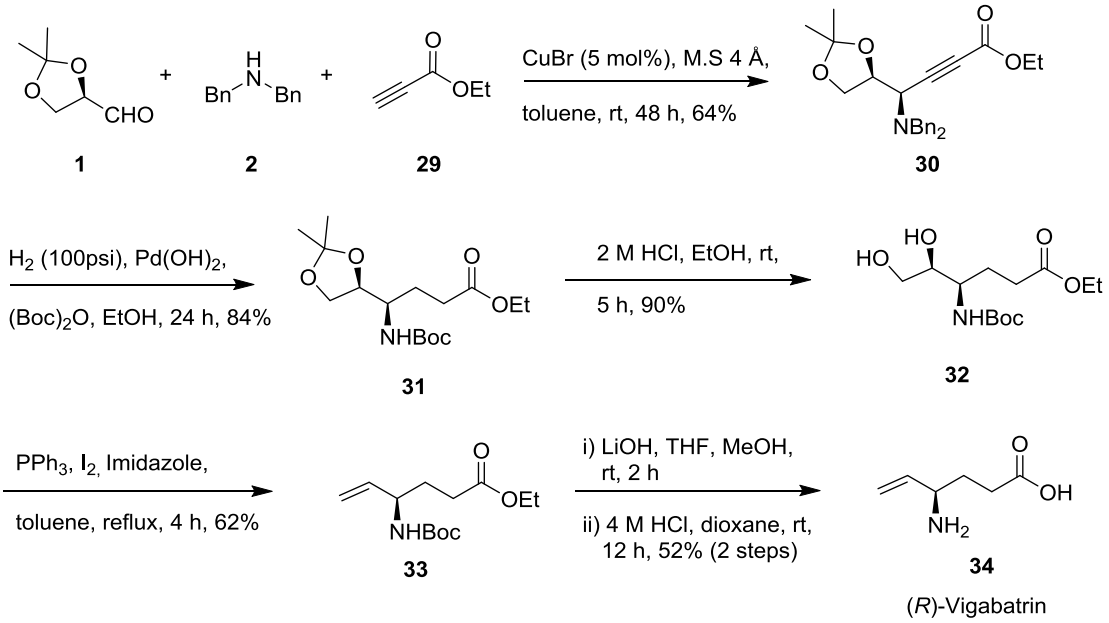
Scheme 8: Synthesis of valinoctin A.

Chapter 3: Section-B: An Enantiodivergent Synthesis of Both (*R*)- and (*S*)-Vigabatrin

Vigabatrin (γ-vinyl GABA) is a significant anticonvulsant drug marketed in the racemic form as Sabril in Europe. Vigabatrin is a highly selective irreversible inhibitor of GABA-aminotransferase (GABA-T) which degrades GABA to succinic semialdehyde. There are only a few approaches known for vigabatrin synthesis from non-natural starting materials and mostly involved natural amino acids as starting materials. As a part of the ongoing research work on the synthesis of chiral α-amino alcohol via A^3-coupling reaction established in our laboratory, we proposed a methodology for the synthesis of both enantiomers of vigabatrin.

For the synthesis of (*R*)-vigabatrin, (*R*)-glyceraldehyde acetonide **1,** dibenzylamine **2** were reacted with the ethyl propionate **29** under CuBr (5 mol%) catalytic conditions in toluene at room temperature, to give propargylamine derivative **30**. The compound **30** was formed as single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 76% yield (Scheme 9). No formation of the *anti*-diastereomer was observed under the applied reaction conditions. The ester **30** was then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere to allow complete hydrogenolysis of benzyl groups and the reduction of C≡C bond. Subsequent *N*-Boc protection of the free amine provided compound **31** in 64% yield over two steps. Further ketal group of **31** was deprotected by ethanolic HCl to afford the diol **13** in 84% yield. The diol **13** was then converted to the alkene **33** in one pot with 62%

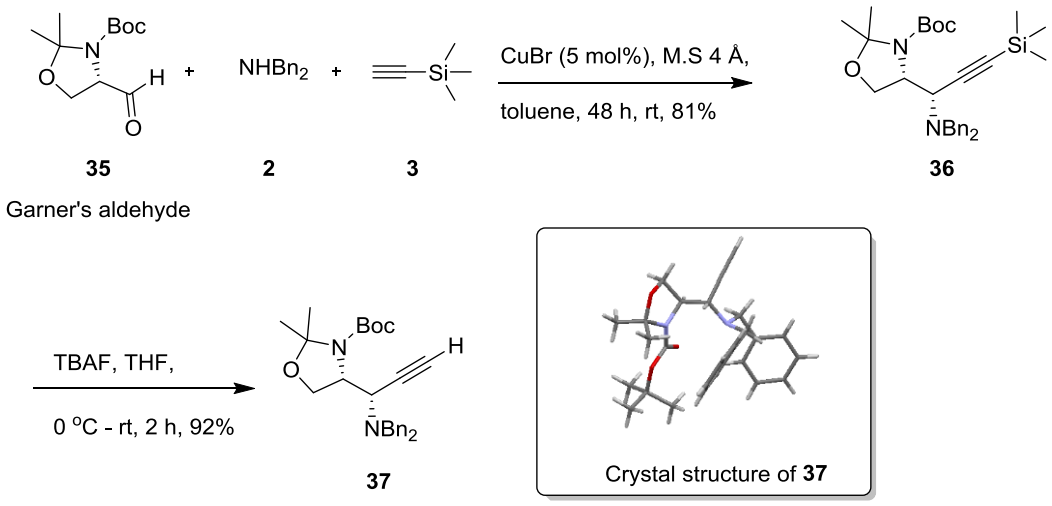
yield by reacting with PPh_3, I_2, and imidazole. Finally, ester hydrolysis of **14** with LiOH followed by *N*-Boc deprotection using hydrochloric acid gave (*R*)-vigabatrin **5**. Purification of **5** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) to achieve 52% yield over two steps. Similarly, the (*S*)-vigabatrin was synthesized from (*S*)-glyceraldehyde acetonide in six steps with 18% overall yield.



Scheme 9: Synthesis of (*R*)-vigabatrin.

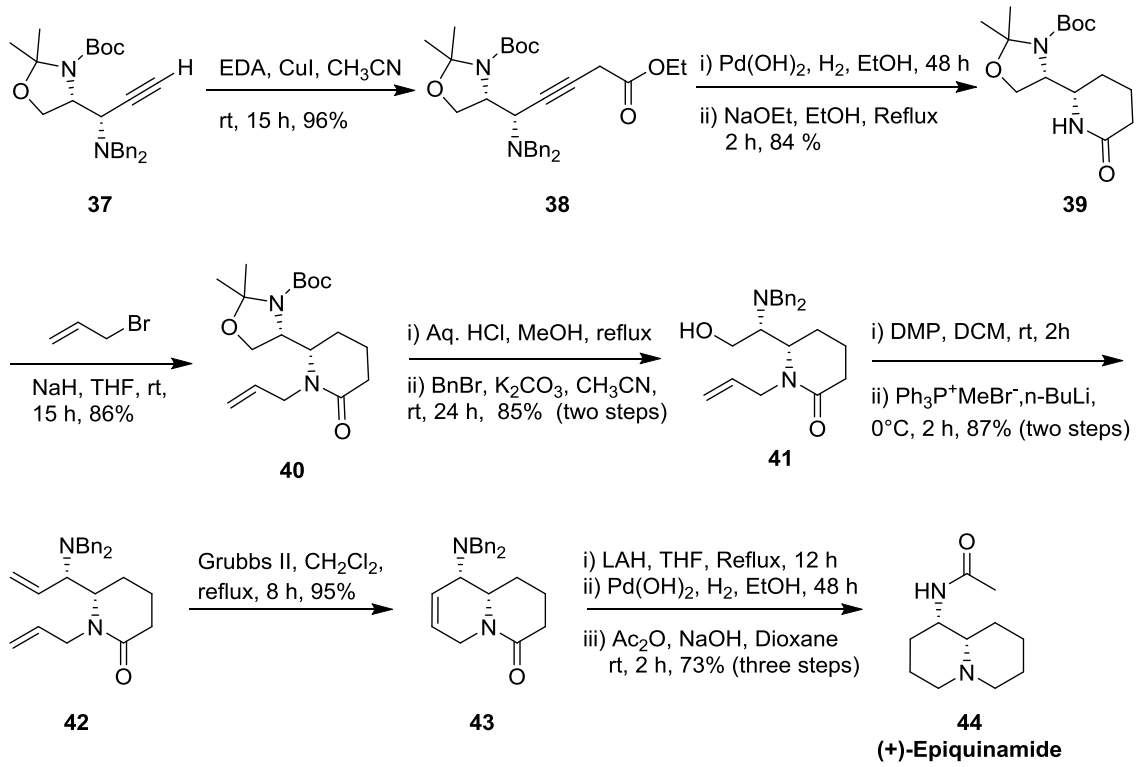
Chapter 4: Diastereoselective Construction of *syn*-1,2-Diamine: Stereoselective Synthesis of (+)-Epiquinamide and its Indolizidine Analogue

In this chapter, we have developed a suitable and effective novel synthetic procedure for the stereoselective synthesis (+)-epiquinamide and its indolizidine analogue. As a further application of ongoing research work on diastereoselective aldehyde-amine-alkyne (A^3) coupling reaction, we have planned synthesis of (+)-epiquinamide and its analogue from Garner's aldehyde **35**, dibenzyl amine **2**, and TMS acetylene **3**. The coupling of **35**, **2**, and **3** under CuBr (5 mol%) catalytic conditions in toluene at room temperature gave substituted propargyl **36** as a single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 81% yield. Silyl deprotection of **36** in the presence of TBAF in THF afforded alkyne **37** with 92% yield (Scheme 10). The stereochemistry of α-β-diamine was confirmed by X-ray crystal structure of alkyne **37.**



Scheme 10: Synthesis of key intermediate **37**.

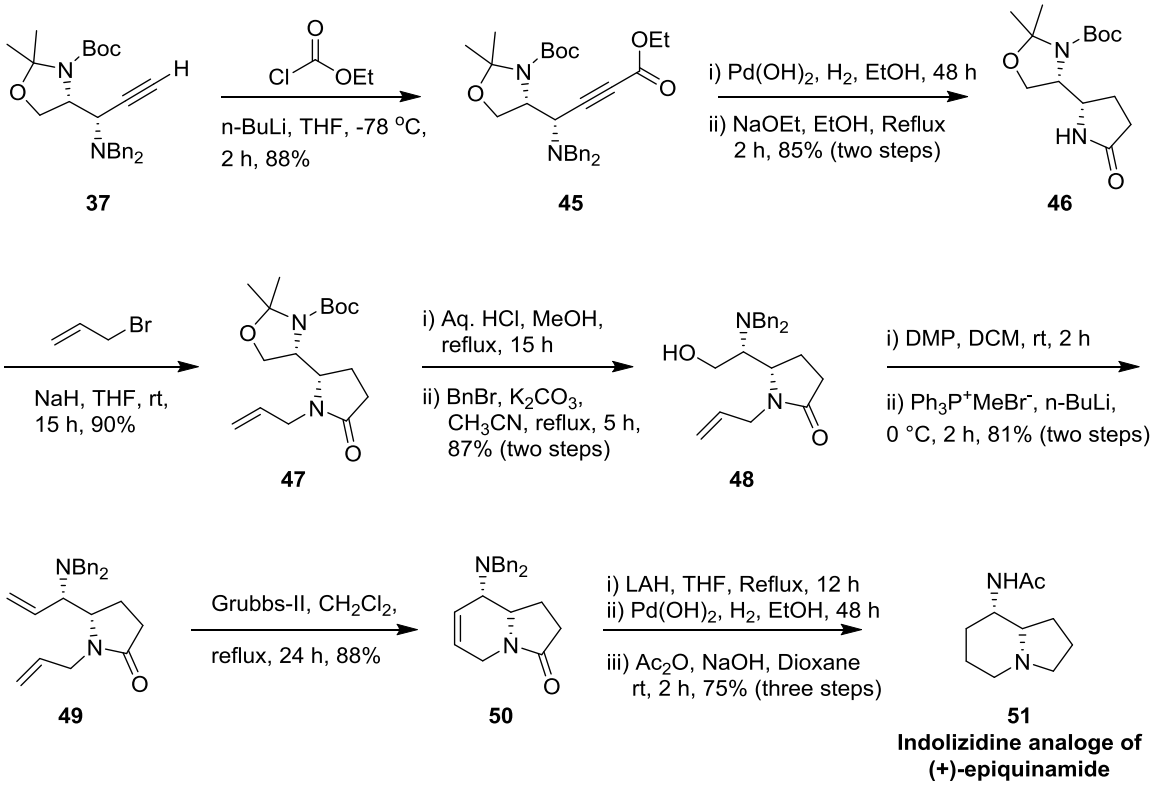
Key intermediate **37** was further used for the construction of indolizidine and quinolizidine scaffolds. Treatment of terminal alkyne **37** with ethyl diazoacetate in the presence of CuI (5 mol%) catalyst furnished ester **38** in 96% yield (Scheme 11). The reaction of ester **38** with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C occurred. Subsequent treatment of the ester formed with NaOEt gave the six-member lactam **39** in 84% yield over two steps. The lactam **39** was treated with allyl bromide in the presence of NaH in THF to give allyl protected lactam **40** in 86% yield. Further, deprotection of acetonide and Boc groups was achieved under aqueous HCl methanol reflux conditions. The reaction of the free amine with benzyl bromide in the presence of K_2CO_3 resulted *N*-dibenzyl protected alcohol **41** in 85% yield over 2 steps. The alcohol **41** was converted into aldehyde using DMP mediated mild oxidising condition. The reaction of an aldehyde with $Ph_3P^+CH_3Br^-$ salt and *n*-BuLi in THF provided **42** in 87% yield (2 steps). The reaction of **42** with Grubb's second generation catalyst in CH_2Cl_2 provided quinolizidine product **43** in 95% yield. The reduction of lactam **43** was done in the presence of LAH to give protected amine. Subsequently, the reduction of the double bond and debenzylation with hydrogen atmosphere under 10% $Pd(OH)_2/C$ (10 mol%) catalytic condition, and *N*-acetylation using Ac_2O in dioxane afforded **(+)**-epiquinamide **44** in 73% yield over 3 steps. Therefore, starting from Garner's aldehyde **35,** the synthesis of (+)-epiquinamide **44** was completed in 14 steps (i.e. 9 purification steps) with overall 27 % yield.



Scheme 11: Synthesis of (+)-epiquinamide.

After achieving the natural product (+)-epiquinamide in hand, we aimed the synthesis of its indolizidine analogues from the key intermediate **37**. Reaction of terminal alkyne **37** with ethyl chloroformate in the presence of *n*-BuLi gave ester **45** with 88% yield (Scheme 12). The ester **45** when reacted with 10% $Pd(OH)_2/C$ (10 mol%) under hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond were achieved. Subsequent treatment with NaOEt provided the γ-lactam **46** in 85% yield over two steps. The lactam **46** was reacted with allyl bromide in the presence of NaH in THF to give allyl protected lactam **47** in 90% yield. Further, deprotection of acetonide and Boc groups of lactam **47** was achieved under aqueous HCl methanol reflux conditions. The reaction of a free amine with benzyl bromide in the presence of K_2CO_3 resulted *N*-dibenzyl protected alcohol **48** in 87% yield over 2 steps. The alcohol **48** was converted into aldehyde using DMP mediated mild oxidising condition. The aldehyde was reacted with $Ph_3P^+CH_3Br^-$ salt and n-BuLi in THF to give bis-olefin **49** in 81% yield. The reaction of **49** with Grubb's second generation catalyst in CH_2Cl_2 provided indolizidine product **50** in 88% yield. The reduction of lactam **50** was done in the presence of LAH to give protected amine. Subsequently, the reduction of the double bond and debenzylation with hydrogen atmosphere under 10% $Pd(OH)_2/C$ (10 mol%) catalytic condition, and *N*-

acetylation using Ac_2O in dioxane afforded indolizidine analogue of epiquinamide **51** in 75% yield over 3 steps. Therefore, starting from Garner's aldehyde **35**, the synthesis indolizidine analogue of (+)-epiquinamide **51** was completed in 14 steps (i.e. 9 purification steps) with overall 23% yield.



Scheme 12: Synthesis of indolizidine analogues of (+)-epiquinamide.

Note : The compound numbers in synopsis are different from thesis.

List of Publications

1. **Deshmukh, S. C**.; Roy, A.; Talukdar, P. "Diastreoselective Construction of *syn*-α-Oxyamines *via* Three-Component α-Oxyaldehyde-Dibenzylamine-Alkynes Coupling Reaction: Application in the Synthesis of (+)-β-Conhydrine and its Analogues" *Org. Biomol. Chem.* **2012**, *10*, 7536**.**

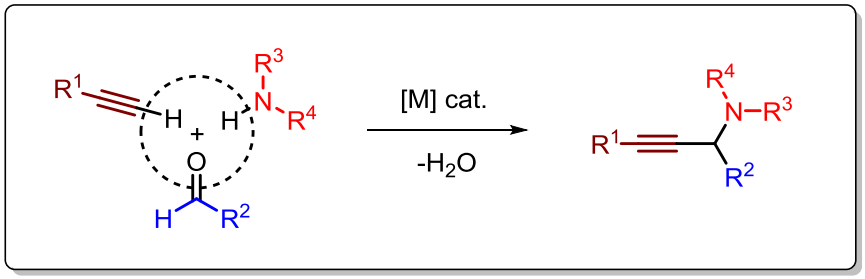
2. **Deshmukh, S. C**.; Talukdar, P. "Stereoselective Synthesis of (2*S*,3*R*)−α-Hydroxy-β-Amino Acids (AHBAs): Valinoctin A, (2*S*,3*R*)−3-Amino-2-Hydroxydecanoic Acid, and Fluorescent-Labeled (2S,3R)−AHBA" *J. Org. Chem.* **2014**, *79*, 11215.

3. **Deshmukh, S. C**.; Talukdar, P. "Stereoselective Synthesis of (+)-Epiquinamide and its Novel Indolizidine Analogue" *Submitted.*

4. **Deshmukh, S. C**.; Talukdar, P. "Enantiodivergent Synthesis of (*R*)-and (*S*)-Vigabatrin *via* Three-Component α-Oxyaldehyde-Dibenzylamine-Alkynes Coupling Reaction" *Manuscript Under Preparation.*

Chapter 1

Introduction: Aldehyde-Amine-Alkyne [A^3] Coupling Reaction



1.1 Importance of Propargylamines

The propargylamines are one of the most common structural sub-units that can be found in therapeutic drugs *e.g.* selegiline (**1**),[1] ladostigyl (**2**),[2] rasagiline,[3] pargyline,[4] etc. and complex natural products which shows interesting biological activities *e.g.* dynemicin A (**3**),[5] uncialamycin,[6] etc. Selegiline (**1**) is a selective irreversible monoamine oxidase inhibitor and used to reduce symptoms of early-stage Parkinson's disease.[1] Ladostigyl (2), is a dual cholinesterase and monoamine oxidase inhibitor and used for Alzheimer's disease.[2] Dynemicin A (**3**), isolated from the bacteria *Micromonospora chernisa*, displays antibiotic as well as cytotoxic activities.[5] DPC 961 (**4**) is an HIV reverse transcriptase inhibitor and was synthesized by Magnus and coworkers in 2003, along with several active derivatives (Figure 1.1).[7]

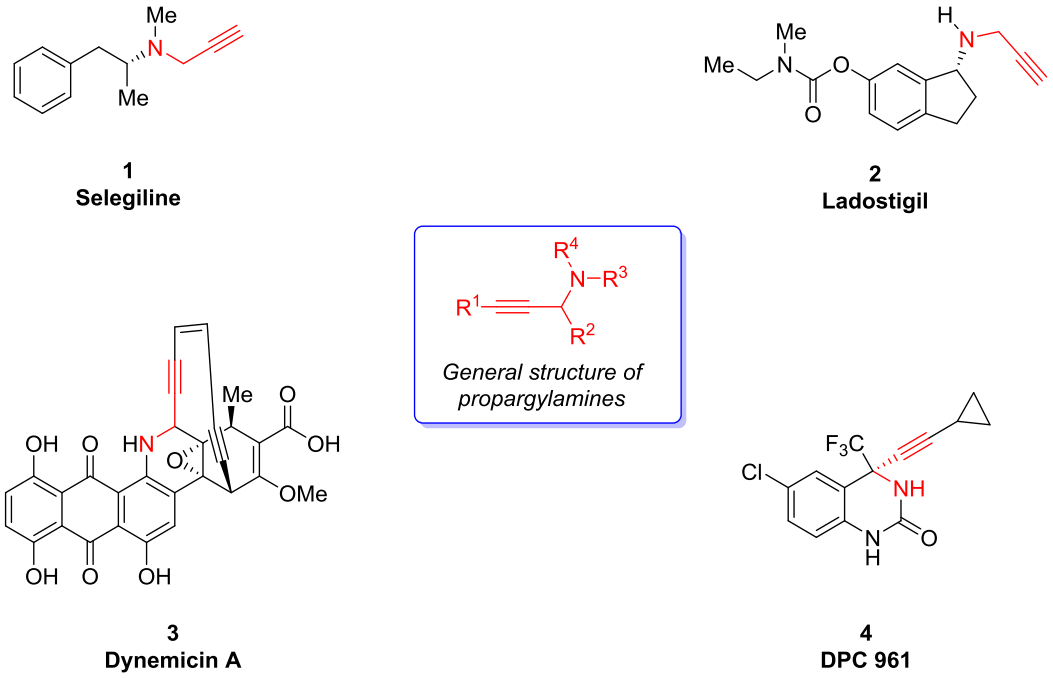


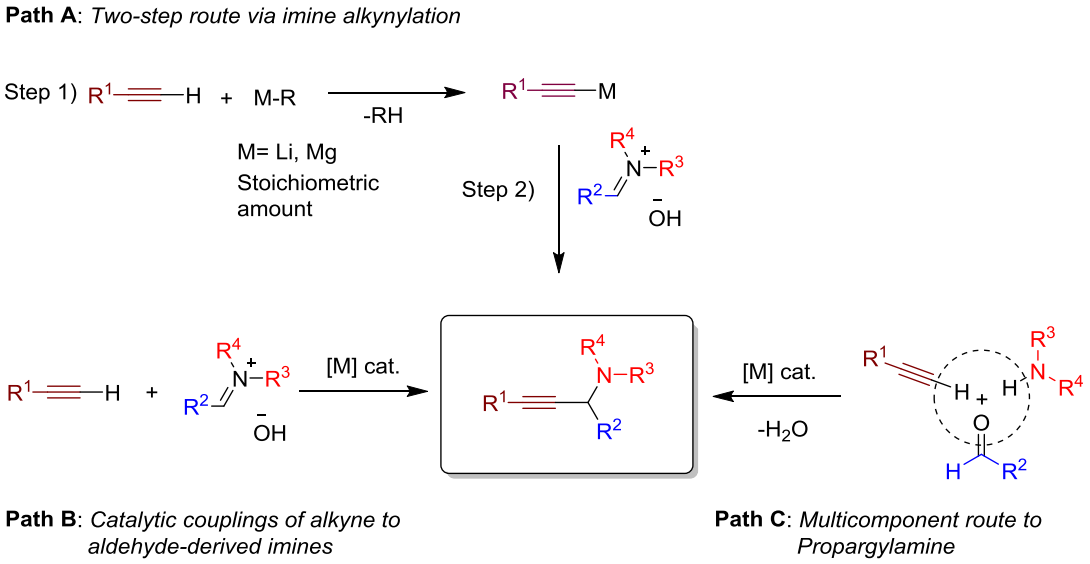
Figure 1.1: Biologically active compounds containing propargylamine.

Propargylamines have been used as precursors to prepare a variety of heterocycles *e.g.* oxazoles,[8] pyrroles,[9] imidazoles,[10] cyclopropylpyrrolidines[11] etc. They are also key intermediates for the preparation of numerous naturally occurring nitrogen containing compounds,[12] pharmaceuticals,[13] plant protectives (herbicides and fungicides).[14]

Propargylamines are essential intermediates due to the rich chemistry correlated with the alkynyl group.[15] Due to the importance of both chiral and achiral propargylamine, numerous synthetic routes have been developed to access propargylamines from a wide range of starting materials.[16]

1.2 Synthetic routes to Propargylamines

Traditionally, propargylamines are prepared in two steps *via* the addition of a metal acetylide to the C=N bonds of imines. As acetylinic proton has a lower acidity (p*Ka* ~ 25), strong bases such as lithium and magnesium reagents are usually employed in the reactions with imines leading to propargylamines (Scheme 1.1 path a).[16c,17] The stoichiometric quantities of organometallic reagent and the use of moisture sensitive lithium and Grignard reagents requires strict control of the reaction conditions, and an inert atmosphere is main disadvantages of this method preparation of propargylamines. Consequently, a milder and more atom efficient route to propargylamines has been developed, in which catalytic quantities of transition metals are used. The acidity of the C–H bond increases due to a π-complexes formation of metals with terminal alkynes. This increased acidity allows weakly basic amines to deprotonate the C–H bond and generate the desired organometallic alkynyl nucleophile (Scheme 1.1 path b).[18]



Scheme 1.1: Approaches for the synthesis of propargylamines.

Further, *in situ* formation of the imine or iminium ion from an aldehyde and an amine intensively give rise to the facile transition-metal catalyzed three-component coupling of an aldehyde, an alkyne, and an amine usually referred as A^3-coupling (Scheme 1.1 path c).[19]

1.3 Mechanism of Aldehyde-Amine-Alkyne Coupling Reaction

The tentative mechanism of aldehyde-amine-alkyne (A^3) coupling reaction has been proposed (Figure 1.2).[16e] The *in-situ* formation of a metal-acetylide species *via* C-H activation of the alkyne is a key step in the mechanism of A^3- coupling reaction. Formation of this metal-acetylide complex is poorly understood. Due to low acidity of the acetylinic proton, deprotonation is not possible with starting amine or the final propargylamine which are presented in the reaction medium. Therefore, it may proceed through a π-metal alkyne complex that increases the acidity of the C–H bond. The metal acetylide is then reacted with the imine or iminium ion (formed by *in-situ* reaction of the aldehyde and amine) to provide the propargylamine with the renewal of metal catalyst.

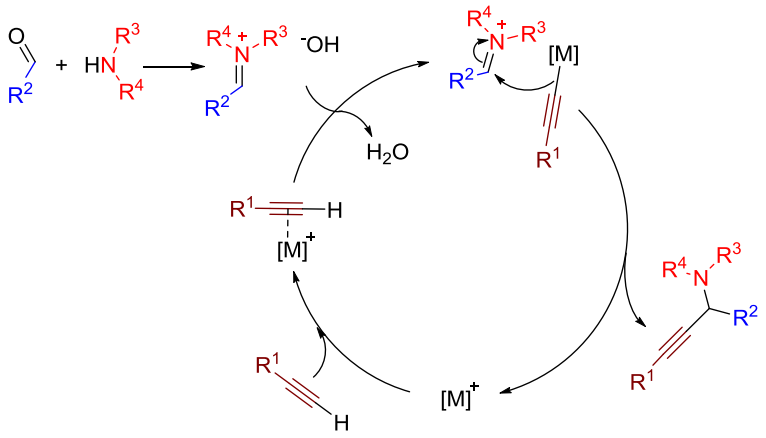
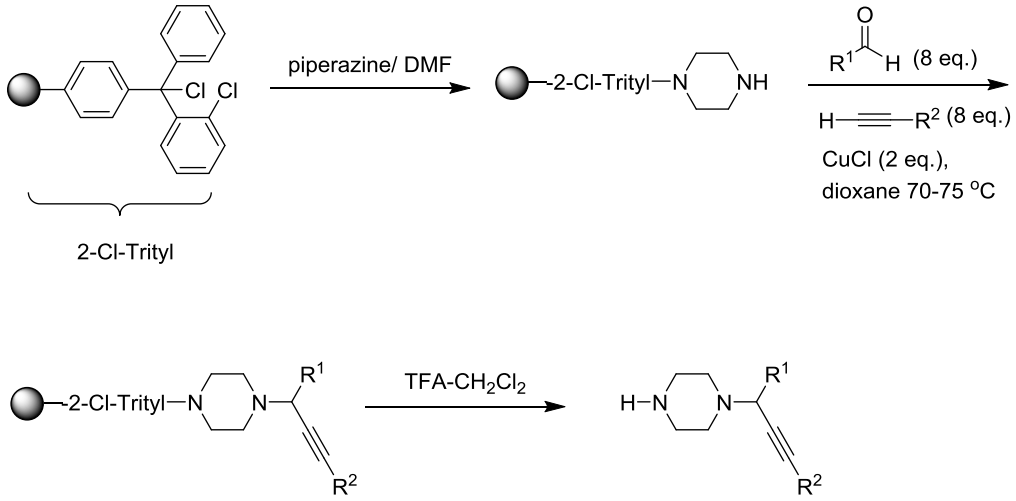


Figure 1.2: Mechanism of the A^3-coupling reaction.

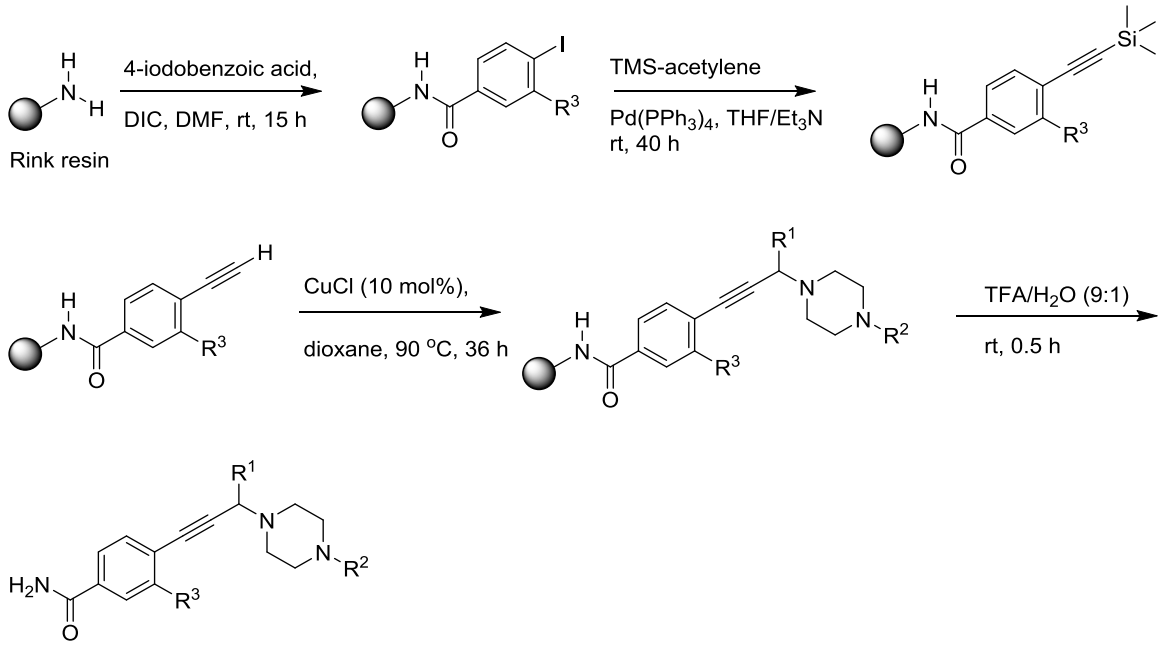
1.4 Development of Aldehyde-Amine-Alkyne Coupling Reaction

Dax and co-workers in 1998, reported the first work on the A^3-coupling reaction.[20] The solid-phase synthesis of propargylamines was described by a three-component Mannich-type condensation of an alkyne, aldehyde, and secondary amine, catalyzed by two equivalents of CuCl (Scheme 1.2). The amine or the aldehyde could be attached to the polymer resin, and the A^3 coupled products were prepared in good yields. However, this reaction does not meet the ideal requirements for an A^3-coupling reaction due to the use of stoichiometric amounts of copper chloride.



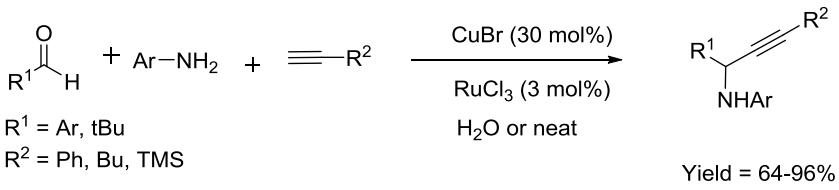
Scheme 1.2: Synthesis of propargylamines by Dax and co-workers.

Later in the same year, Rivero and Dyatkin reported a similar solid-phase coupling reaction of aryl alkyne, various substituted aldehyde, and secondary amines with CuCl (10 mol%) as a catalyst to provide propargylamines (Scheme 1.2).[21] This reaction procedure was the first reported example of an A^3-coupling reaction. In this reaction, any of the three substrates could be bound to the resin and the propargylamine products were obtained in high yields after cleavage from the polymer support.



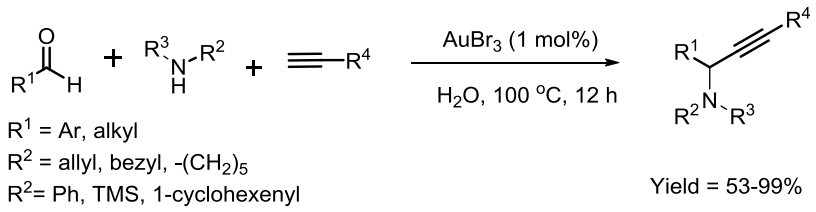
Scheme 1.3: Synthesis of propargylamine by Rivero and Dyatkin.

In 2002, Li and co-workers reported an A^3-coupling reaction for the synthesis of *N*-aryl propargylamines using a bimetallic Ru-Cu catalyst system in water, and under solvent-free conditions (Scheme 1.4).[22] The authors found that the addition of phenylacetylene to an *in-situ* generated imine (formed by the condensation of aldehydes with anilines) was catalyzed by copper complexes albeit in low conversion. Several copper complexes such as CuCl, $CuCl_2$, CuBr, CuI and CuO all shown moderate catalytic activity. However, when $RuCl_3$ (3 mol%) was added as the co-catalyst yield of the A^3-coupled product was increased from 30% to 90%. But when $RuCl_3$ has used alone as the catalyst no desired product was obtained. The reaction was applicable to a broad range of aromatic, aliphatic imines. This reaction was also used for imines that were easily hydrolyzed in water. The yield of product decreased when aliphatic aldehydes were used, because of unwanted trimerization of the aldehydes. This method was restricted for the use of anilines and aromatic or aliphatic aldehyde without α-hydrogen.



Scheme 1.4: Cu-Ru catalyzed the A^3-coupling reaction.

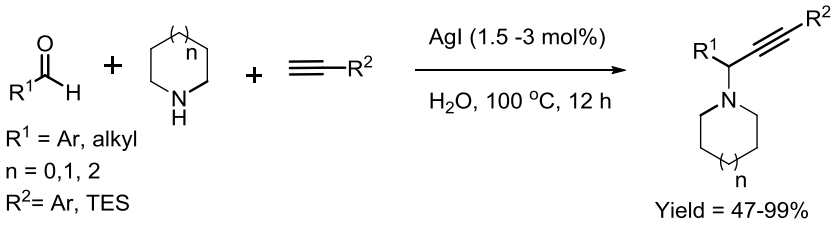
The same authors subsequently, reported A^3-coupling reaction for the synthesis of tertiary propargylamines using aldehydes, secondary amines, and alkynes in the presence of a gold catalyst (Scheme 1.5).[23] The gold salts such as AuCl, AuI, $AuBr_3$, and $AuCl_3$ were tested, and all showed superb catalytic activities. Au(III) salts acted slightly better than Au(I) salts in A^3-coupling reaction. Propargylamines are obtained with a low loading (1 mol%) of either Au(I) or Au(III). The desired product was not observed in the absence of either Au(I) or Au(III). The excellent conversion was observed in the water, whereas low conversion and more byproducts were observed with the use of organic solvents such as THF, toluene, and DMF. Under the optimal conditions (1 mol% of $AuBr_3$), various substrates including alkynes (both aromatic and aliphatic) and aldehydes (both aromatic and aliphatic) gave the propargylamines with 53 to 99% yields. Low yields were observed with aliphatic aldehydes than aromatic aldehydes. The authors attributed this due to the competitive trimerization of aliphatic aldehydes. This procedure was restricted to the use of secondary dialkylamines.



Scheme 1.5: $AuCl_3$ catalyzed A^3- coupling reaction.

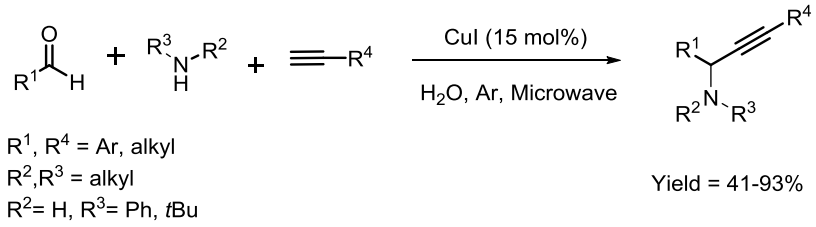
For the better yields with aliphatic aldehydes, Ag(I) salt was used as a catalyst in the A^3-coupling reactions by Li and co-workers (Scheme 1.5).[24] They noticed a change in the reactivity of aliphatic and aromatic aldehydes compared to the previously reported Au(III)-catalyzed procedure. Propargylamines were obtained with of AgI (1.5- 3 mol%) in

water as well as organic solvents such as toluene and DMF. This methodology was limited to the use of cyclic secondary amines.



Scheme 1.6: AgI catalyzed A^3- coupling reaction.

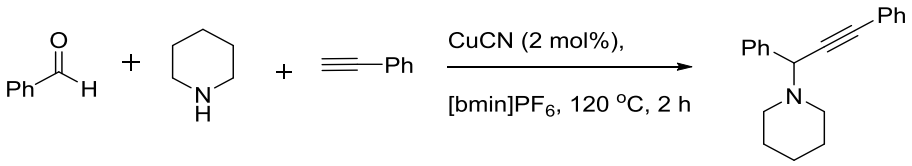
Later, the microwave-assisted solvent-free A^3-coupling procedure has been developed to overcome substrate scope limitations of the protocols reported by Li and co-worker. In 2004, Tu and co-workers described a microwave-assisted CuI-catalyzed A^3-coupling reactions for synthesis propargylamines.[25] The microwave-assisted A^3 coupling reactions were carried out water in the presence of 15 mol % CuI catalyst. With several substrates in optimal condition gave the desired propargylamines in good to excellent yields (Scheme 1.7). Afterward, CuBr-catalyzed a microwave-assisted solvent-free A^3-coupling procedure described by Varma and co-workers for the use of secondary amines.[26]



Scheme 1.7: Microwave-assisted CuI-catalyzed A^3-coupling reactions.

As an expensive metal catalyst (silver, gold etc.) is frequently lost at the end of the reaction, recycling of the metal catalyst is an important challenge in the A^3-coupling reactions. Park and Alper in 2005, described Cu(I) catalyzed methodology in an ionic liquid for the recyclability of the catalyst.[27] In these reactions, 2 mol% of copper compounds (CuI, CuBr, CuCl, CuCN, $Cu(OAc)_2$ and Cu powder) in $[bmim]PF_6$ were used to give propargylamines in 60–98% conversion (Scheme 1.8). After completion of the reaction, the extraction of the reaction mixture with diethyl ether gave the desired product.

The recovered ionic liquid layer was recycled for five to ten times and slightly drop in activity was observed.

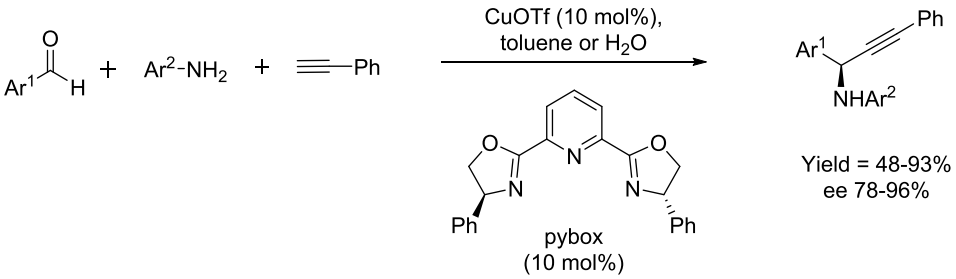


Scheme 1.8: Cu catalyzed A^3-coupling reactions in the ionic liquid.

Later, various research groups have reported A^3-coupling reactions with different metal catalysts such as Fe(III),[28] In(III),[29] Zn(II),[30] Ni(II),[31] Hg(I),[32] Co(II),[33] Ir(II),[34] Bi(III),[35] Mn(II),[36] Sn(II)[37] etc. Also, catalysts composed of metal nanoparticles on different supports[38] and N-heterocyclic carbene-metal complexes as a catalyst[34,39] have been used in A^3-coupling reactions. Now, research is focused on improvement of the A^3-coupling reaction for the wide substrate scope, low loading of catalyst and decrease in reaction time. Therefore, A^3 coupling with new and more efficient catalysts for the synthesis of propargylamine is still a subject of interest in synthetic organic chemistry.

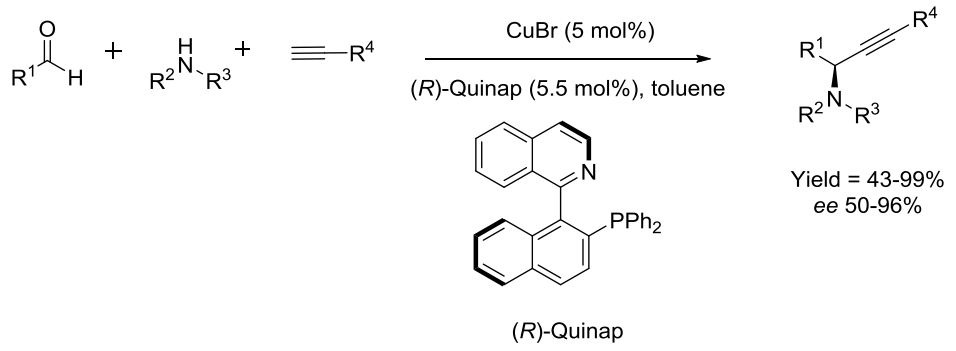
1.5 Development of Asymmetric Aldehyde-Amine-Alkyne (AA^3) Coupling Reaction

As chiral propargylamines are useful intermediates for the preparation of various nitrogen-containing natural products, enantioselective A^3-coupling reactions have gained considerable attention in organic synthesis. Li and co-worker in 2002, reported first enantioselective an aldehyde-amine-alkyne (A^3) coupling reaction (Scheme 1.9).[40] A variety of chiral ligands with either CuBr and CuOTf (10 mol%) as the catalyst, in both toluene and water were examined for the A^3-coupling reaction of phenylacetylene, benzaldehyde, and aniline. The combination of tridentate bis(oxazolinyl)pyridine (pybox) ligand (10 mol%) with CuOTf (10 mol%), the highest enantiomeric excess was obtained. The various aromatic imine (prepared from aromatic aldehydes and anilines) with phenyl acetylene under optimal conditions gave the corresponding propargylamines with the 48 to 93% yield and 78 to 96% enantioselectivity. Slightly higher yields and enantioselectivities were observed in toluene as a solvent than in water.



Scheme 1.9: AA^3-coupling reactions catalyzed by CuOTf/pybox

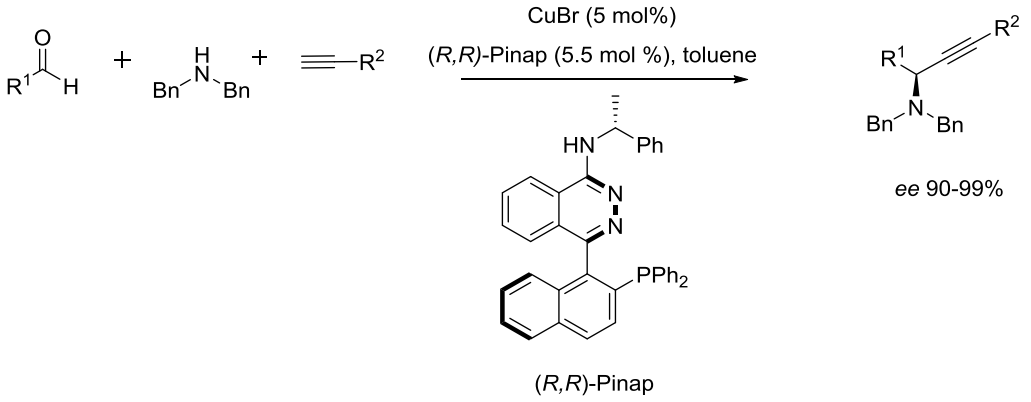
Subsequently, Knochel and co-workers reported A^3-coupling of aldehyde, secondary amine, and alkyne for the synthesis of chiral propargylamines (Scheme 1.10).[41] Various chiral ligands, *e.g.* diphosphanes, aminophosphanes, and diamines, with copper(I) bromide were studied in AA^3-coupling reaction. High enantioselectivities and yield were observed with (*R*)-Quinap in combination with CuBr. The optimized condition of (*R*)-Quinap (5.5 mol%) and CuBr (5 mol%), secondary amines, aromatic and aliphatic aldehydes and alkynes in toluene as a solvent gave chiral tertiary propargylamines in yields (43-99%) and enantioselectivities (50-98%). The high enantiomeric excesses were observed with trimethylsilylacetylene than other alkynes. The limitations of this method are long reaction time and expensive catalyst and difficult synthesis of (*R*)-Quinap in enantiopure form.



Scheme 1.10 AA^3-coupling reactions catalyzed by CuBr/Quinap.

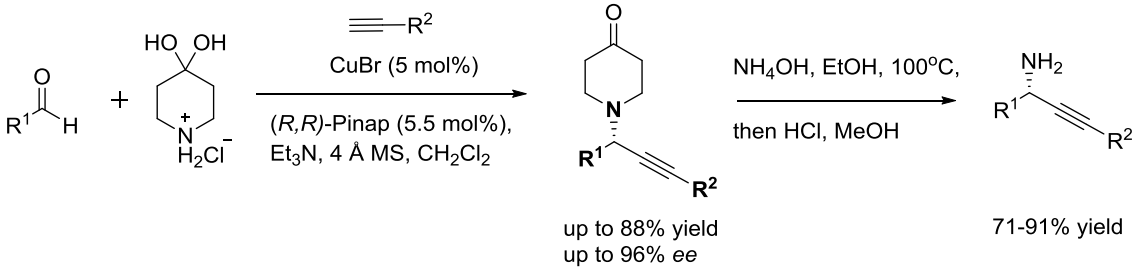
Carreira and co-workers in 2004, reported a novel P,N ligands for AA^3-coupling reactions (Scheme 1.11).[42] The P,N ligands (Pinap) were synthesized from 1,4-dichlorophthalazine and 2-naphthol. AA^3-coupling reactions with several substrates using

CuBr/(*R*,*R*)-Pinap catalyst gave enantioenriched propargylamines with high enantioselectivities (90-99%). The author was observed higher enantioselectivity compared to the corresponding reactions with quinap as a chiral ligand (used in Knochel work).



Scheme 1.11: AA^3-coupling reactions catalyzed by CuBr/(*R*,*R*)-Pinap.

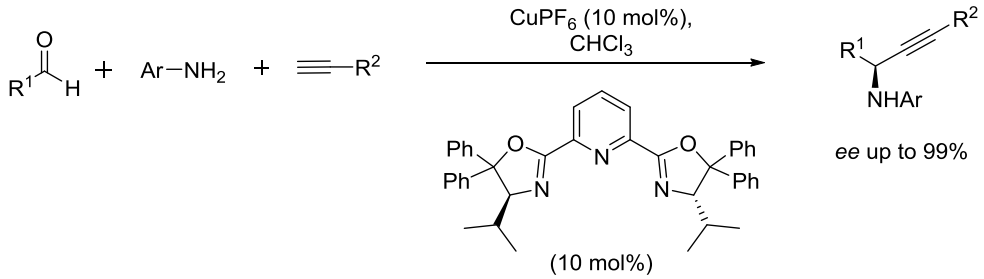
The same author in 2006, reported CuBr/(*R*,*R*) Pinap-catalyzed reactions of aldehydes, alkynes, and 4-piperidone hydrochloride hydrate (amine component) (Scheme 1.12).[43] Three-component coupling in under optimal condition gave the corresponding propargylamines with yields up to 88% and enantioselectivities up to 96%. The deprotection of piperidone group using either NH_4OH/EtOH or a polymer-supported scavenger amine provided primary propargylamines as their hydrochloric acid salts.



Scheme 1.12: AA^3-coupling reactions catalyzed by CuBr/Pinap.

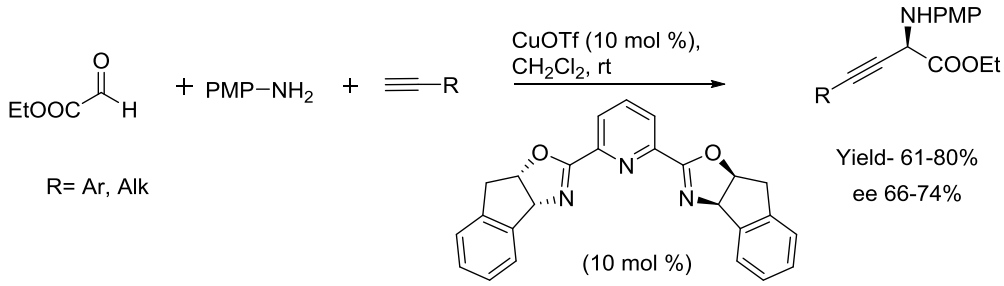
In 2006, Bisai and Singh reported modified Li's method using *i*-Pr-pybox-diPh ligand and $CuPF_6$ as the catalyst (Scheme 1.13).[44] The three-component coupling reaction was examined using 10 mol% of pybox and *i*-Pr-pybox-diPh ligand, which noticeably

shown that diphenyl groups have a drastic effect on enhancing the enantioselectivities. The AA^3-coupling reactions of different aldehydes, alkyne (aromatic and aliphatic), and aromatic amines in the optimized condition of *i*-Pr-pybox-diPh ligand and $CuPF_6$ gave a variety of propargylamines in good to excellent yields (up to 99%) and enantioselectivities (up to 99%). The author has proposed a transition-state model for the stereochemical result of the AA^3-coupling reactions.



Scheme 1.13: AA^3-coupling reactions using *i*-Pr-pybox-diPh ligand.

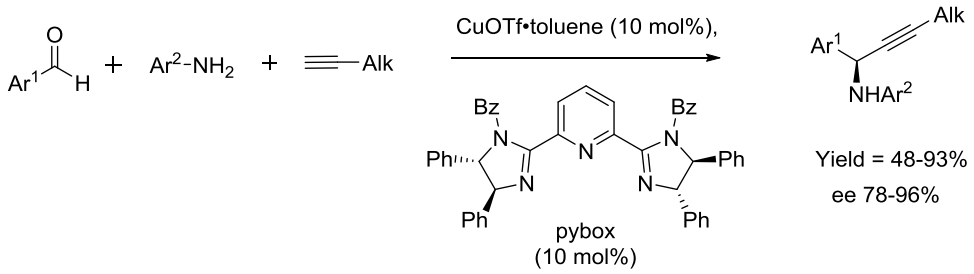
Later, Chan and co-workers reported enantioselective three-component coupling reaction for the synthesis of chiral aliphatic and aromatic β,γ–alkynyl α-amino acid derivatives (Scheme 1.14).[45] Author modified Li's protocol, instead of an aromatic aldehyde, ethyl glyoxylate has been used to give chiral propargylamines. Under the optimized conditions of CuOTf/pybox (10 mol%), reactions of ethyl glyoxylate, PMB-NH_2 and various alkynes (aromatic and aliphatic) provided β,γ–alkynyl α-amino acid derivatives with yields 61 to 80% and enantioselectivity 64 to 74%.



Scheme 1.14: AA^3-coupling reactions using *i*-Pr-pybox-diPh ligand.

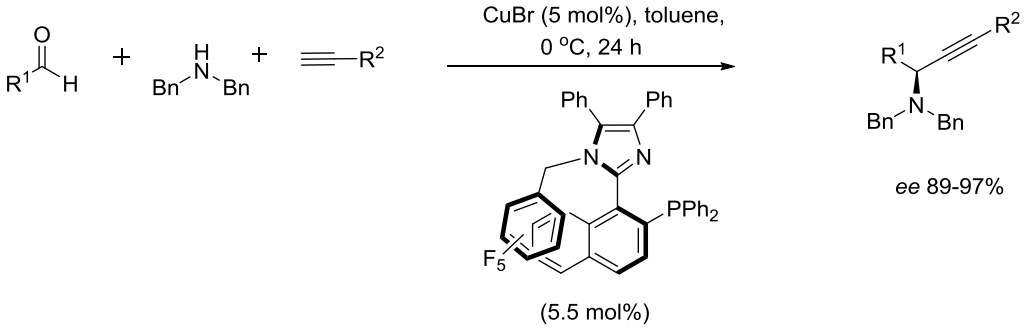
In 2010, Nakamura and co-workers studied the AA^3-coupling reactions with Cu(I) catalysts and chiral bis(imidazoline)s ligands (Scheme 1.15).[46] The high yields and

enantioselectivities were observed with $(CuOTf)_2$.toluene, *N* -benzoyl 1,3-bis(imidazolin-2-ly)pyridine. The three-component reaction of various aldehydes, amines, and aliphatic alkynes under the optimal condition provided chiral propargylamines in good yields and with high enantioselectivity (up to 98%)**.** The author obtained better yields and enantioselectivity compared to the previous report of Li and co-worker.



Scheme 1.15 AA^3-coupling reactions using *i*-Pr-pybox-diPh ligand.

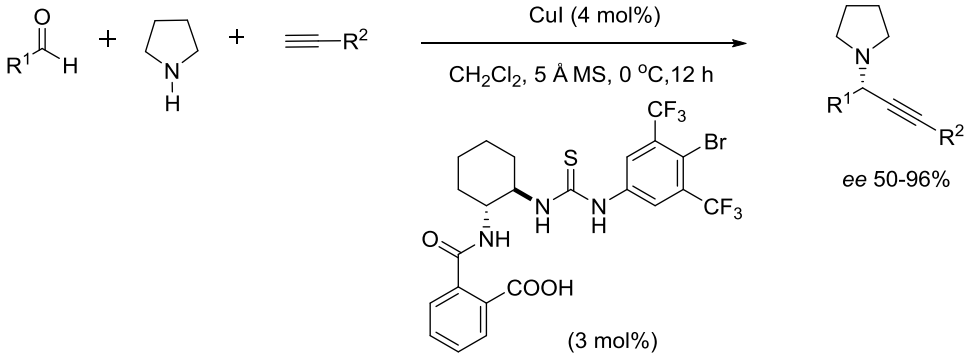
Aponick and co-worker in 2013, prepared a chiral imidazole based biaryl P, N-ligand and used in the enantioselective A^3-coupling reaction (Scheme 1.16).[47] With optimal conditions, AA^3-coupling reactions variety of aromatic and aliphatic aldehydes gave high yields and high enantioselectivities.



Scheme 1.16: AA^3-coupling reactions using imidazole based biaryl P, N-ligand.

In 2015, Zhao and Seidel have developed new organocatalyst containing both a carboxylic acid and a thiourea subunit for the synthesis of chiral propargylamines (Scheme 1.17).[48] Using optimal condition of CuI and organocatalyst (3 mol%), AA^3-coupling reactions of aldehyde, cyclic amines, and alkynes gave chiral propargylamines in good yields and high enantioselectivities. Pyrrolidine-based propargylamines further converted

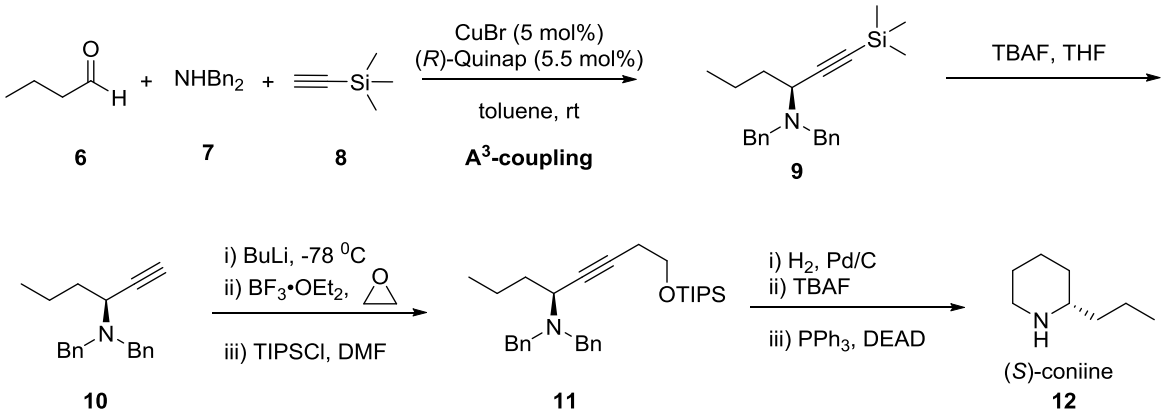
to allenes without loss of enantiopurity. To date, this is the lowest catalyst loadings report for the asymmetric A^3 coupling reactions with secondary amines.



Scheme 1.17: AA^3-coupling reactions using thiourea based organocatalyst.

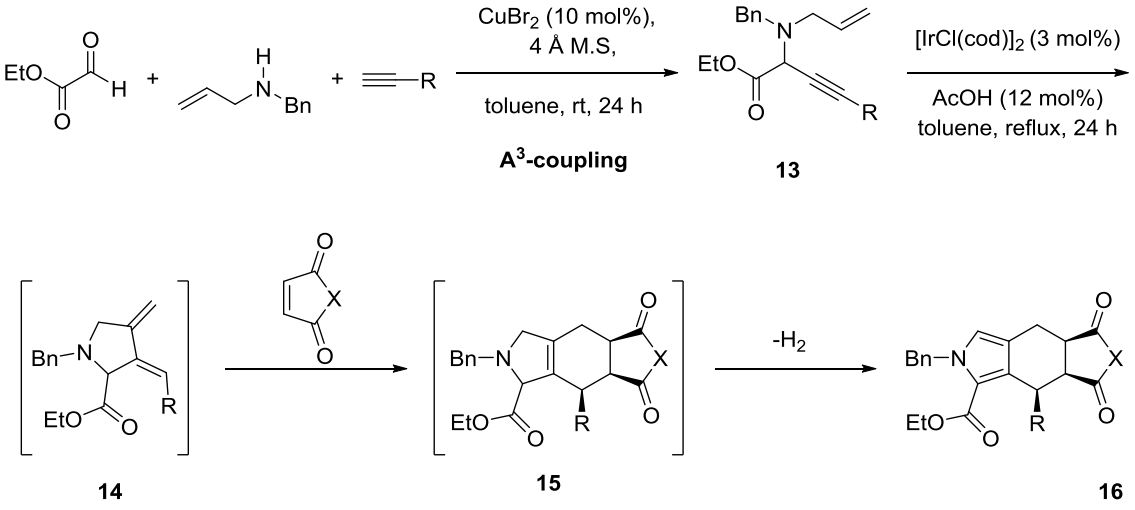
1.6 Applications of Aldehyde-Amine-Alkyne Coupling Reaction

In 2004, Knochel and co-workers reported CuBr/(*R*)-Quinap catalyzed the A^3-coupling reaction for the synthesis of enantiomerically enriched propargylamines and applied for the synthesis of alkaloid (*S*)-(+)-coniine (Scheme 1.18).[12c] Coniine is a poisonous alkaloid found in poison hemlock which induces curare type paralysis. A coupling of propionaldehyde, dibenzylamine, TMS-acetylene in the presence of CuBr/(*R*)-Quinap provided propargylamine **9**. The deprotection of TMS using TBAF provided alkyne **10**. Treatment of the terminal alkyne using *n*-BuLi followed by alkylation with ethylene oxide furnished alcohol which further treated with TIPSCl (tri*i*sopropyl silylchloride) to provide the TIPS protected alcohol **11.** Finally, debenzylation, reduction of triple bond, desilylation followed by an intramolecular Mitsunobu reaction resulted in the formation of (*S*)-(+)-coniine **12** with an overall yield of 41% and with 90% *ee*.



Scheme 1.18: Synthesis of (*S*)-(+)-coniine.

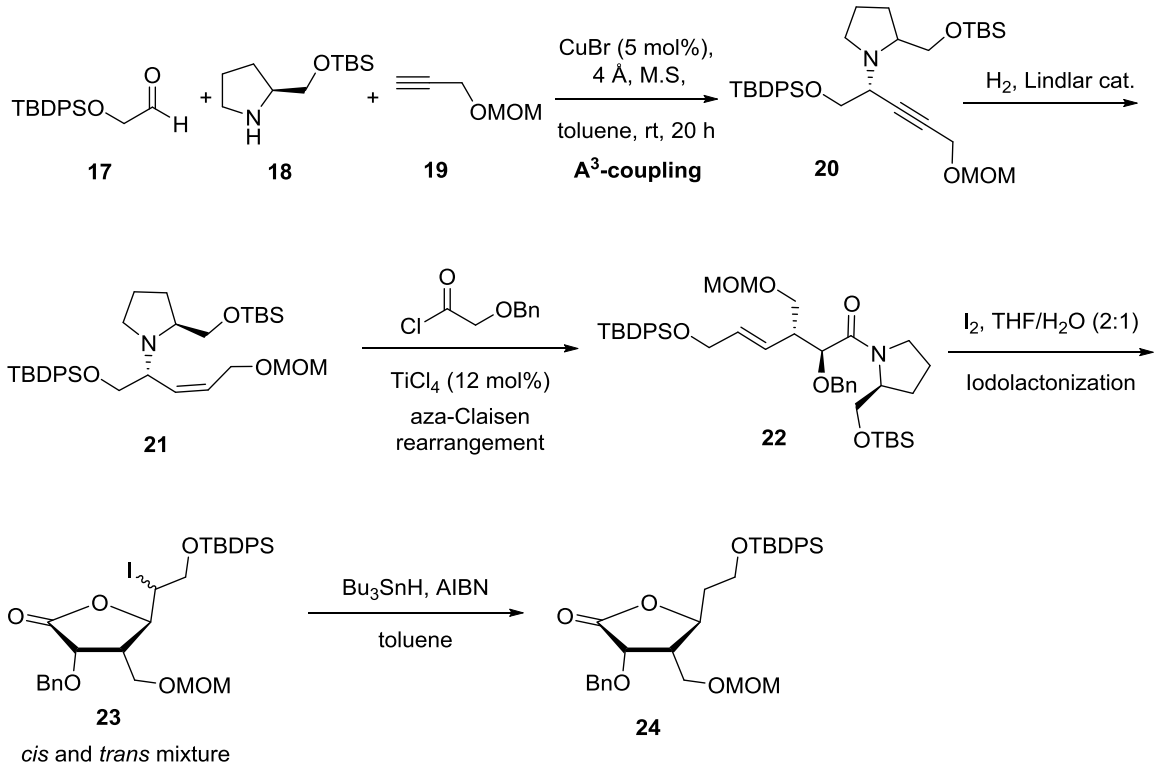
Yamamoto and co-workers in 2005, developed a one-pot strategy towards polycyclic pyrrole-2-carboxylates (Scheme 1.19).[49] Pyrrole-2-carboxylate is a common structural subunit which is found in biologically active natural products. The A^3 coupling reaction of ethyl glyoxalate, benzyl allylamine, and an alkyne in the presence of $CuBr_2$ provided glycinate-tethered 1,6-enynes **13**. Further, the Ir-catalyzed cycloisomerization/Diels–Alder reaction/dehydrogenative aromatization sequence were provided desired the polycyclic pyrroles **16**.



Scheme 1.19: Synthesis of polycyclic pyrroles.

In the same year, Xu and Rozners reported the synthesis of *trans*-3,4-dialkyl-γ-lactones using a Cu(I)-catalyzed A^3-coupling reaction (Scheme 1.20).[50] Chiral *trans*-3,4-

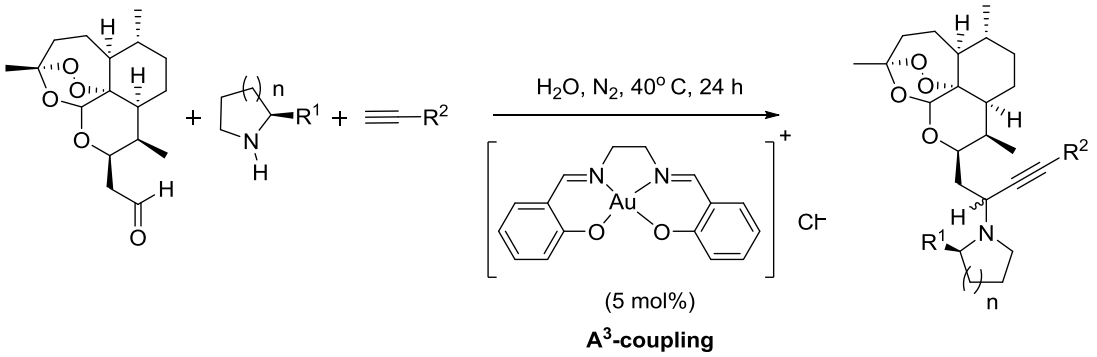
dialkyl-γ-lactones are present in natural products and intermediates of biologically active compound. A CuBr catalyzed the A^3-coupling reaction of aldehyde **17**, chiral amine **18**, and alkyne **19** provided chiral propargylamine derivative **20**. The reduction of compound **20** using Lindlar catalyst provided compound **21**. The compound **21** was treated with $TiCl_4$, DIPEA to give unsaturated amide **22**. Further, iodolactonization of **22** in a THF/water mixture provided inseparable mixture undesired *cis*/desired *trans* **23.** Finally, removal of iodine on treatment with tributyltin hydride, AIBN gave γ-butyrolactone **24**. The synthesis of the target γ-butyrolactone **24** was completed in five steps and with 32% overall yield.



Scheme 1.20: Synthesis of *trans*-3,4-dialkyl-γ-butyrolactones.

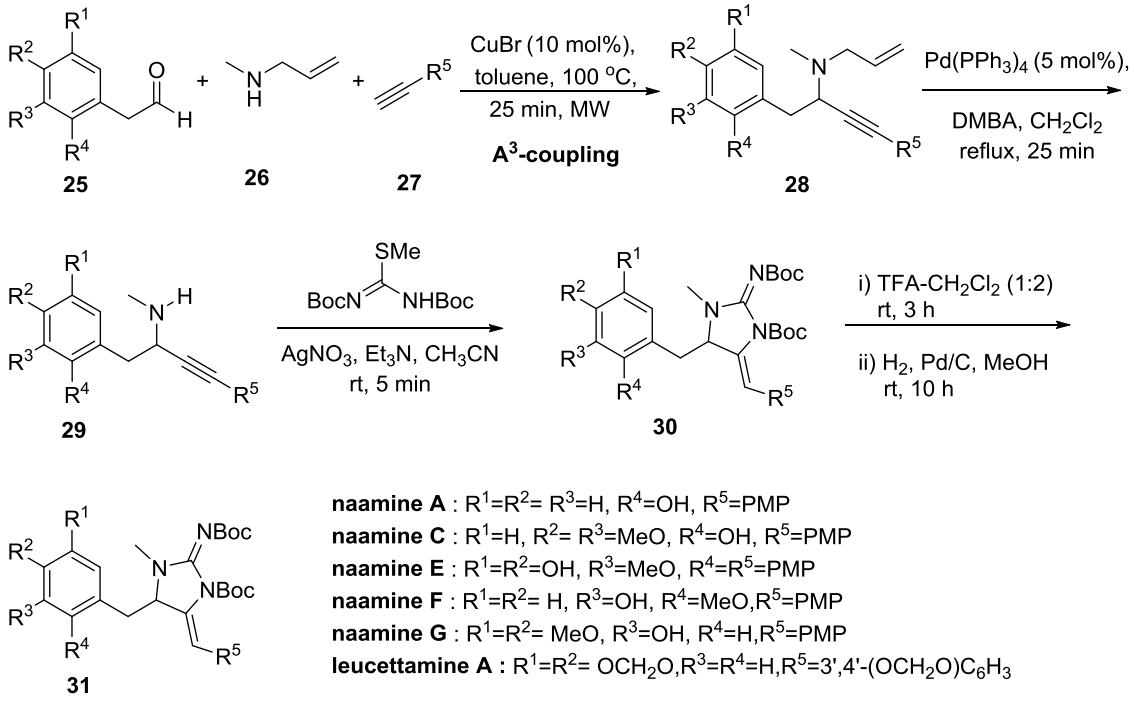
Wong, Che and co-workers in 2006, synthesized propargylamines using Au(III) salen complex-catalyst in the three-component coupling reaction (Scheme 1.21).[51] High diastereoselectivities were observed in the A^3 coupling of various aldehydes, alkynes and chiral prolinol derivatives as the amine component. The methodology further applied for the synthesis of propargylamine-modified artemisinin derivatives. Artemisinin was

isolated from an ancient Chinese herb *Artemisia annua* and it displays antimalarial activity. The three-component reaction of artemisinin aldehyde, chiral prolinol derivatives (amine component), and alkynes provided ranges of propargylamines in good yields and high diastereoselectivity. Propargylamine-modified artemisinin derivatives shown cytotoxicity against a human hepatocellular carcinoma cell line (HepG2) with an IC_{50} value up to 1.1 mM.



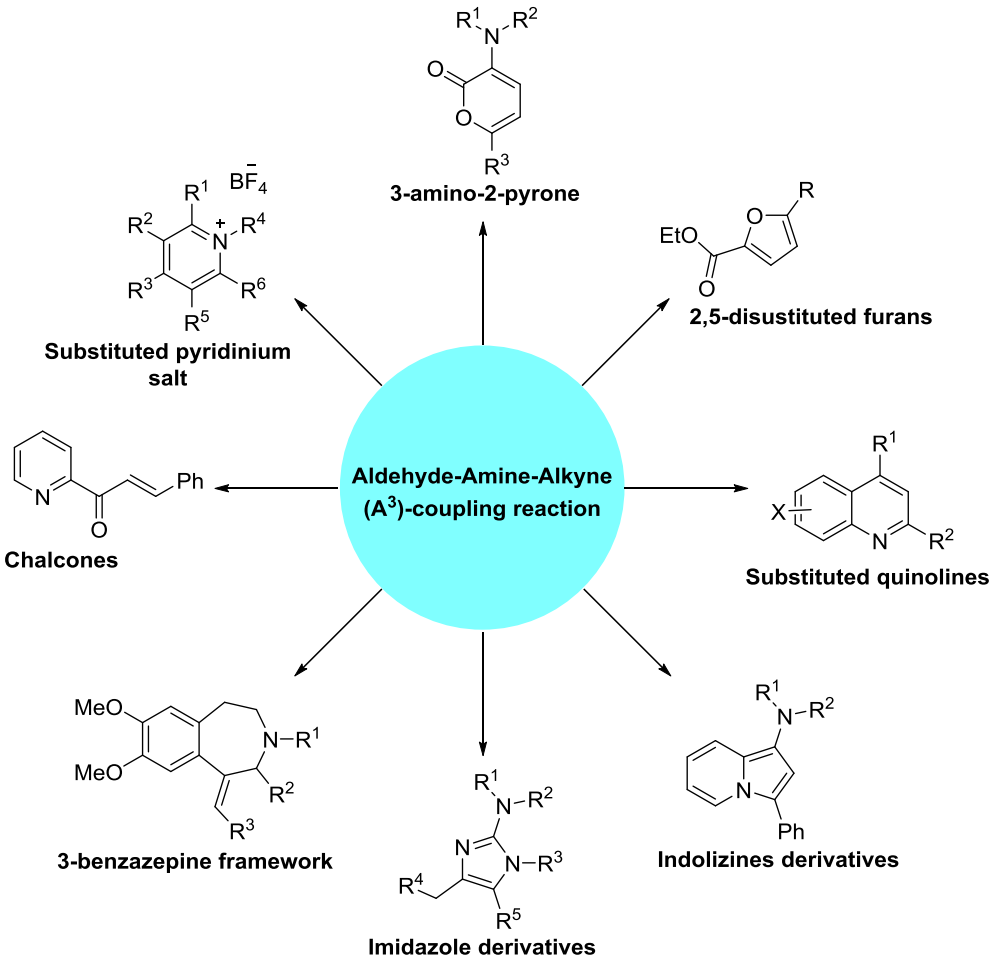
Scheme 1.21: Synthesis of artemisinin derivatives using A^3-coupling.

Recently, the synthesis of naamine family alkaloids has been demonstrated by Van der Eycken and co-workers (Scheme 1.22).[52] A copper (I)-catalyzed microwave assisted A^3-coupling reaction of a various aldehyde, alkyne, and *N*-methyl-allylamine gave the tertiary *N*-methylallylpropargylamines **28**. Further, deallylation in the presence of $Pd(PPh_3)_4$, 1,3-dimethylbarbituric acid (DMBA), followed by silver(I)-promoted cycloguanylation provided compound **30**. Finally, Boc deprotection and debenzylation furnished the naamines A, C, E–G and leucettamine A with excellent yields.



Scheme 1.22: Synthesis of alkaloids of the naamine family.

The aldehyde-amine-alkyne (A^3) coupling reactions not only used for the synthesis of natural products and biologically active compounds, also the synthesis of a range of heterocycles such as imidazole derivatives,[52] 3-benzazepine framework,[53] indolizines derivatives,[54] substituted quinolones,[55] chalcones,[56] substituted pyridinium salt,[57] 3-amino-2-pyrone,[58] 2,5-disustituted furans,[58] etc. (Scheme 1.23).



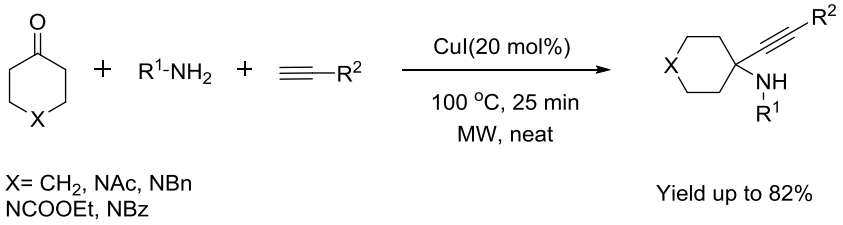
Scheme 1.23: Synthesis of various heterocycles using A^3-coupling reactions.

1.7 Modifications of Aldehyde-Amine-Alkyne Coupling Reaction

In situ formation of an imine or iminium ion from the corresponding aldehyde and amine is one of the crucial steps in the aldehyde-amine-alkyne (A^3)-coupling reaction. As formation of such species can also possible from other precursors, A^3 -coupling was found quite flexible for component replacements. Further, the A^3 -coupling reaction was modified by i) replacements of the aldehyde component,[59] ii) replacements of the amine component,[60] iii) replacements of the alkyne component,[61] iv) intramolecular version of the A^3 -coupling,[62] v) decarboxylative modifications of the A^3 -coupling.[63]

1.7.1 Replacements of the aldehyde component

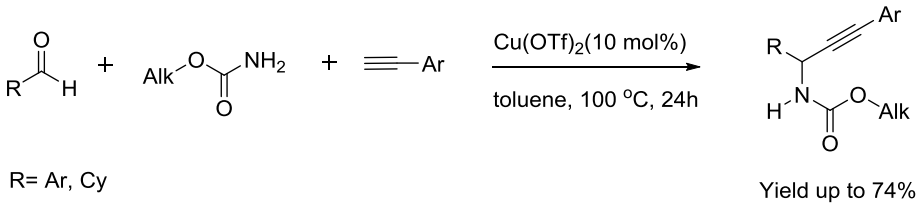
The application of ketones instead of aldehydes was described by Van der Eycken and co-workers.[59c] A microwave-assisted coupling of a ketone, an alkyne and a primary amine (KA2-coupling) in the presence of Cu(I)-catalyst gave access to quaternary carbon-containing secondary propargyl amines (up to 82% isolated yield). The good yields were observed when 6-membered (hetero)cyclic ketones were used (Scheme 1.24).



Scheme 1.24: Microwave-assisted coupling of a ketone, an alkyne, and a primary amine.

1.7.2 Replacements of the amine component

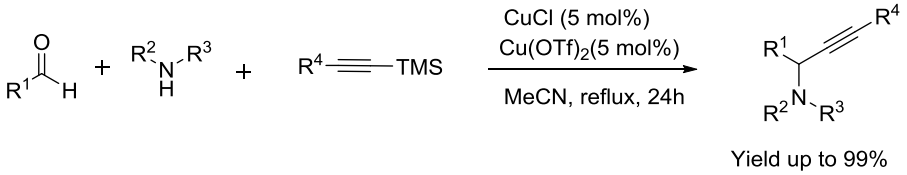
A Cu(II)-triflate-catalyzed coupling of an aldehyde, a carbamate (amine replacement) and an alkyne, was developed by Li and co-workers for the synthesis of propargylcarbamate.[60a] The methodology was restricted to the use of aromatic aldehydes and alkynes. (Scheme 1.25).



Scheme 1.25: $Cu(OTf)_2$-catalyzed coupling of an aldehyde, a carbamate, and an alkyne.

1.7.3 Replacements of the alkyne component

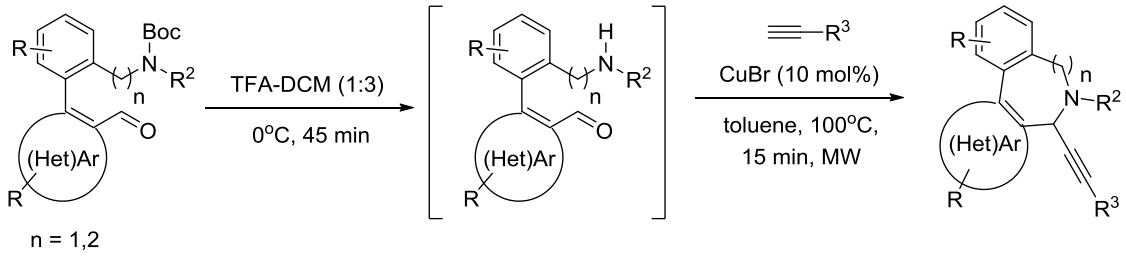
Sakai and co-workers in 2008, replaced the terminal alkyne with an alkynylsilane.[61] The Cu(I)/Cu(II) catalyzed three-component coupling of an aldehyde, an alkyne, and an alkynylsilane were provided the desired propargylamines in up to 99% yield (Scheme 1.26).



Scheme 1.26: CuCl/$Cu(OTf)_2$ catalyzed coupling of an aldehyde, an amine, and an alkynylsilane.

1.7.4 Intramolecular version of the A^3-coupling

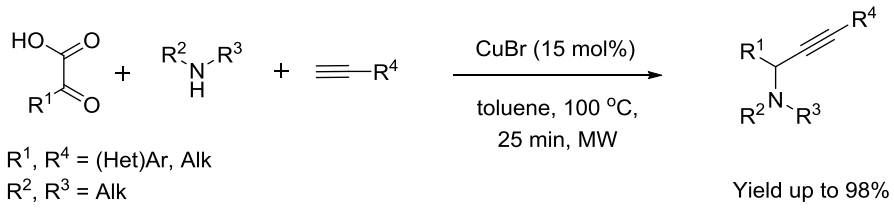
Van der Eycken and co-workers described an intramolecular A^3-coupling reaction for the construction of medium-sized rings.[62] A one-pot deprotection A^3-coupling sequence gave diversity-oriented access towards dibenzoazocines and dibenzoazepines (Scheme 1.27).



Scheme 1.27: One-pot deprotection/A^3-coupling.

1.7.5 Decarboxylative modifications of the A^3-coupling

Van der Eycken and co-workers was reported a decarboxylative modification of the A^3-coupling.[63b] The reaction was applicable for various aliphatic and (hetero)-aromatic 2-oxoacetic acids, secondary and primary aliphatic amines as well as for aromatic and aliphatic alkynes (Scheme 1.28).



Scheme 1.28: CuBr-catalyzed coupling of a 2-oxoaceticacid, an amine, and an alkyne.

1.8 Research outlook

Even though great numbers of aldehyde-amine-alkyne (A^3) coupling reactions are reported for the synthesis of propargylamines, there is wide scope to develop a new A^3 coupling reactions for the synthesis of chiral propargylamines with high diastereoselectivity. For this perspective, we were interested in designing and development of new diastereoselective aldehyde-amine-alkyne (A^3) coupling reactions for the synthesis of chiral *syn*-α-amino alcohols and *syn*-α,β-diamines derivatives. With this primary objective in mind, we were also interested to employ chiral *syn*-α-amino alcohols and *syn*-α, β-diamines derivatives in the synthesis of natural products and its analogues as well as unnatural amino acids.

In this thesis, in Chapter 2, we have demonstrated methodology for the diastereoselective formation of *syn*-α-amino alcohol derivatives using A^3-coupling reactions of (*R*)-glyceraldehyde acetonide, dibenzylamine with terminal alkynes and its application in the synthesis of (+)-β-conhydrine and its piperidine as well as pyrrolidine analogs. In Chapter 3, we have established A^3-coupling reactions of (*R*)-glyceraldehyde acetonide, dibenzylamine with terminal alkynes for the stereoselective synthesis of an alkynyl side-chain containing (2*S*,3*R*)-α-hydroxy-β-amino acid. The utility of the methodology was demonstrated by the stereoselective synthesis of valinoctin A and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid ((2*S*,3*R*)-AHDA). The photophysical properties and cell permeability of a pyrenelabeled (2*S*,3*R*)-AHBA were determined. Synthesis of both enantiomers of vigabatrin was achieved by using diastereoselective A^3-coupling reactions. Further, we have established diastereoselective routes to synthesis of *syn*-α,β-diamine derivative and its utility for the stereoselective synthesis of the quinolizidine alkaloid (+)-epiquinamide and its novel indolizidine analogue in Chapter 4.

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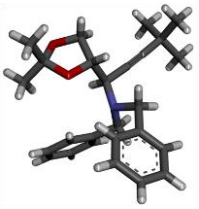
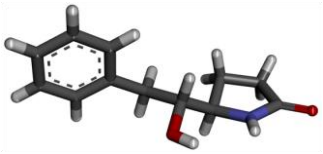
Chapter 2

Diastreoselective Construction of *syn*-α-Amino alcohols: Synthesis of (+)-β-Conhydrine and its Analogues



Crystal structure of **44c**



Crystal structure of **52d**

Crystal structure of **55b**

2.1 Introduction

Hydroxylated chiral pyrrolidine and piperidine scaffolds are very frequently encountered in many biologically active natural products.[1] These scaffolds have inspired the synthesis of focused compound libraries for the drug discovery research.[2] Also, special attention is paid to pyrrolidine and piperidine having chiral α-amino alcohols structural unit, since they are present in many biologically active alkaloids.[3] The chiral α-amino alcohol moiety is present around piperidine natural product *e.g.* nojirimycin (**1**) and (+)-α-conhydrine (**2**) (Figure 2.1), etc. Detoxin A (**3**), 1,4-dideoxy-1,4-imino hexitol (**4**), (Figure 2.1), bulgecin C, casuarine, australine, etc. are examples of pyrrolidine natural products with chiral α-amino alcohol moiety present in their structures.

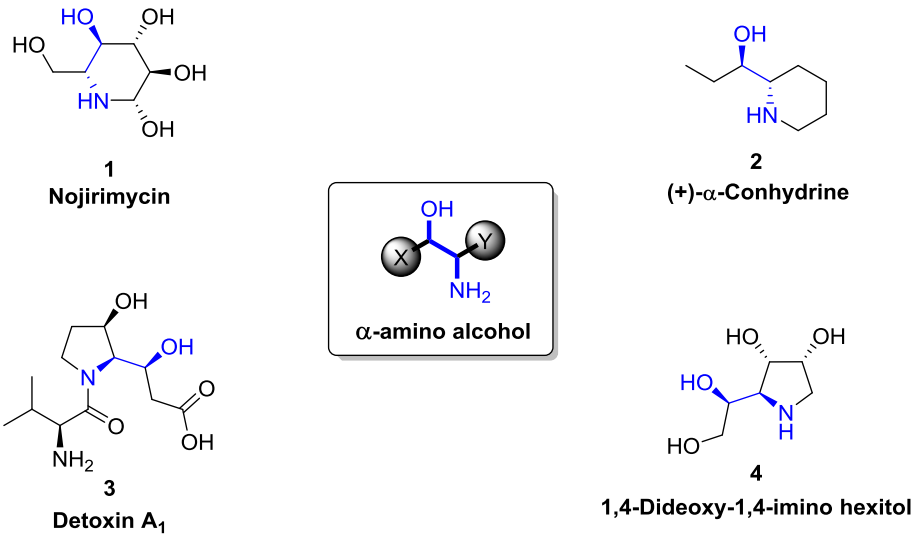


Figure 2.1: Structures of natural products having chiral α-amino alcohol moiety.

Interestingly, many indolizidine alkaloids also consist α-amino alcohol as an important chiral scaffold. Example of these natural products are (-)-swainsonine (**5**), (-)-castanospermine (**6**) (Figure 2.2), etc. (-)-Erycibelline is a nortropane alkaloid in which α-amino alcohol scaffold is also present. These naturally occurring alkaloids have glycosidase inhibitory properties which have been the subject of an intense research during the last two decades for antiviral, anticancer, antidiabetic drug discovery.[4] Therefore, these therapeutically relevant pyrrolidine and piperidine alkaloids have become prime targets for synthetic chemists worldwide.

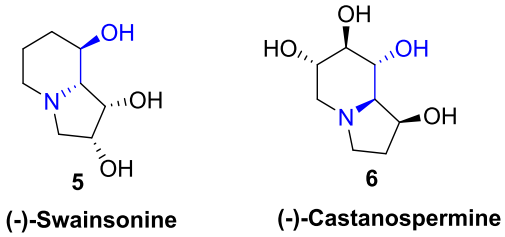


Figure 2.2: Structures of indolizidine alkaloids having α-amino alcohol scaffold.

Among those, conhydrine, which was isolated by Wertheim in 1856 from seeds and leaves of the poisonous plant *Conium maculatum L*, exhibits potent antiviral and antitumor activities.[5] This alkaloid co-occurs in the plant with alkyl piperidines (*e.g.* coniine, *N*-methylconiine and γ-coniceine), piperidine alcohols (*e.g.* pseudoconhydrine and *N*-methylpseudoconhydrine), and piperidine ketone (*e.g.* conhydrinone). Conhydrine can occur in four different diastereomeric forms due to the presence of two chiral centres in the molecule (Figure 2.3**)**.

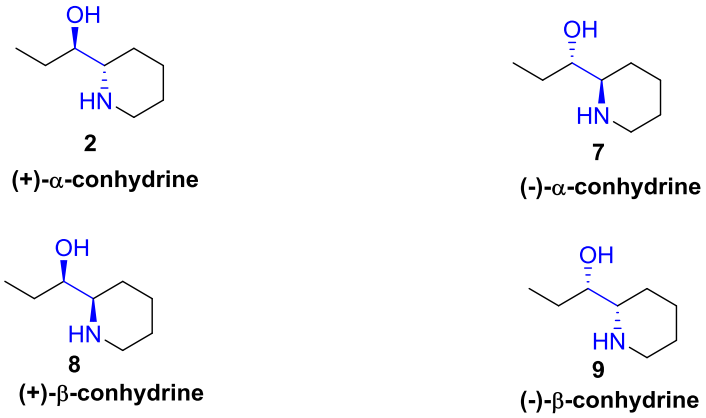


Figure 2.3: Possible diastereomeric forms of conhydrine.

2.2 Reported Synthesis of Conhydrine and Its Isomers

Since its structural elucidation in 1933,[6] a number of total syntheses, both in racemic and optically active forms have been established. The synthesis of α- and β-conhydrine have been reported using chiral,[7] and achiral starting materials.[8] use of chiral auxiliaries,[9] or catalytic asymmetric synthesis (Organo and Metal Catalysis).[10] However, these enantioselective syntheses of α- and β-conhydrine are relatively long, with moderate

overall yields. Also, there are only a few reports in the literature which are focused on the preparation of conhydrine and its analogues. Apart from the synthesis of enantiomer and diastereoisomers of (+)-α-conhydrine (**2**), two independent structural diversity of the natural product have been addressed through the variation (i) of ring size and (ii) side arm functionality (Figure 2.4**)**.

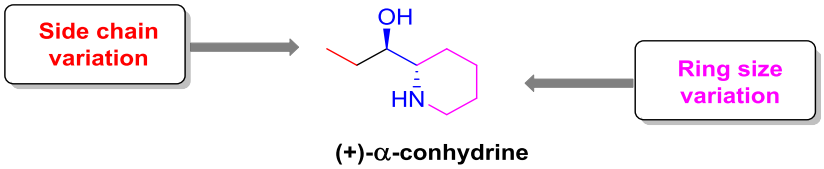
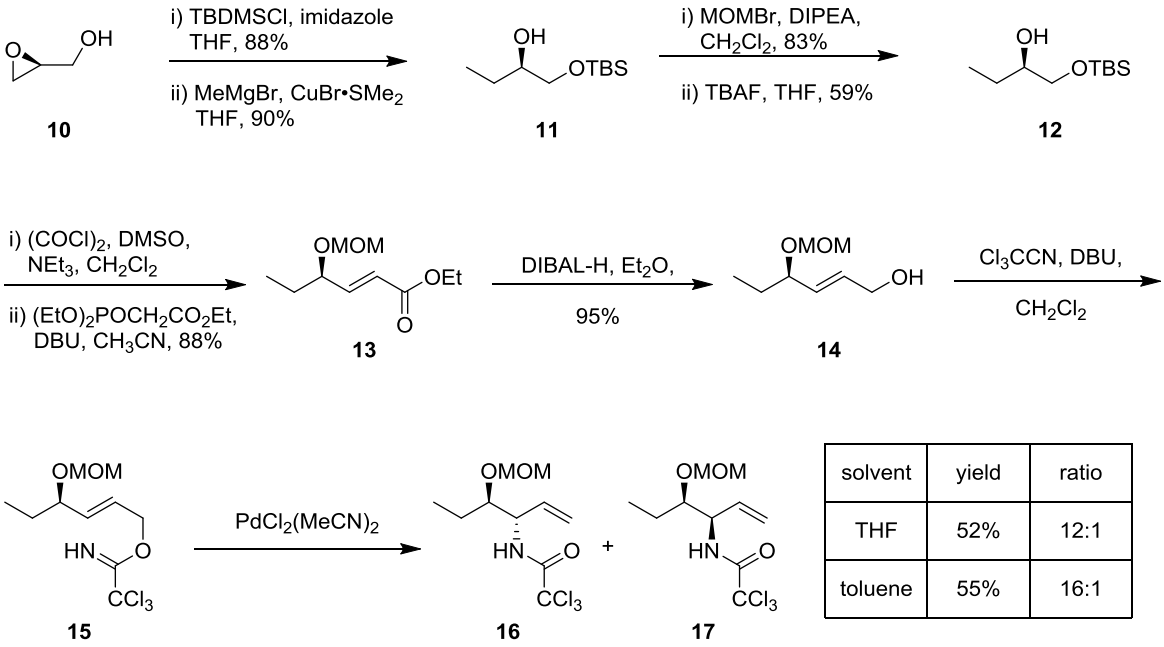


Figure 2.4: Structural diversity approaches for the generation of conhydrine analogues.

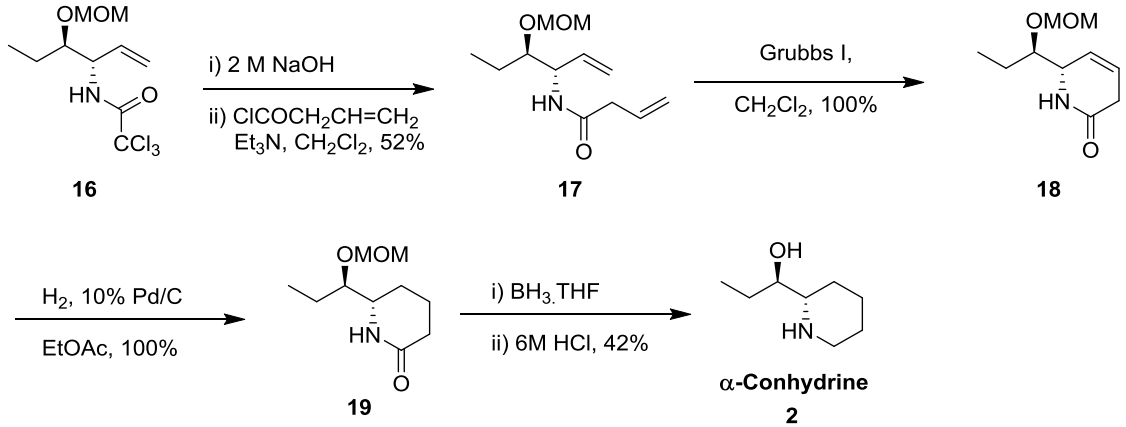
2. 2. 1 Synthesis of conhydrine and analogue by Sutherland *et al.*

In 2007, Sutherland and co-workers used Overman reaction approach[7d] to construct (+)-α-conhydrine (**2**) (Scheme 2.2), and the first ring-contracted pyrrolidine analogue (Scheme 2.3). The silyl protection of (*S*)-glycidol **10** followed by the regioselective ring opening of the epoxide using a copper-catalyzed Grignard reaction resulted in the formation of compound **11**. The formation of the MOM-ether and then desilylation using TBAF in THF provided alcohol **12**. Swern oxidation followed by Wittig reaction furnished ester **13.** The allylic alcohol **14** was obtained by reduction of the ester using DIBAL-H. The reaction of alcohol **14** with Cl_3CCN and DBU gave allylic trichloroacetimidate **15**. The aza-Claisen rearrangement of **15** in the presence of $PdCl_2(MeCN)_2$ afforded **16** and **17** with excellent diastreoselectivity.



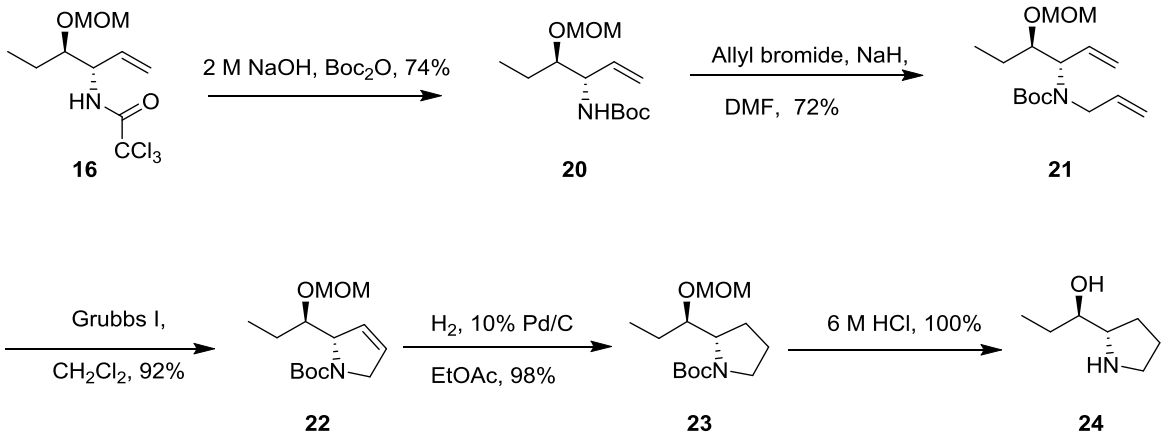
Scheme 2.1 Synthesis of α-amino alcohol intermediate **16**.

The intermediate **16** further utilised for synthesis (+)-α-conhydrine and its novel pyrrolidine analogues. Hydrolysis of **16** followed by acylation with 3-butenoyl chloride provided diene **17.** Ring-closing metathesis of **17** using Grubbs I catalyst gave piperidines skeleton **18**. Reduction of the alkene using Pd on carbon gave compound **19**. Reduction of the lactam with borane-THF, and MOM deprotection under acidic conditions furnished the (+)–α-conhydrine **2** (over 13-steps in 4% overall yield)**.**



Scheme 2.2: Synthesis of α-conhydrine by Sutherland and co-workers.

Amide hydrolysis of **16** with subsequent protection of amine with the Boc group gave **20** in good yield. Then allylation of **20** followed by ring closing metathesis afforded pyrrolidine ring **22** in quantitative yield. Further hydrogenation, Boc deprotection, and MOM deprotection gave pyrrolidine analogue of α-conhydrine **24**.

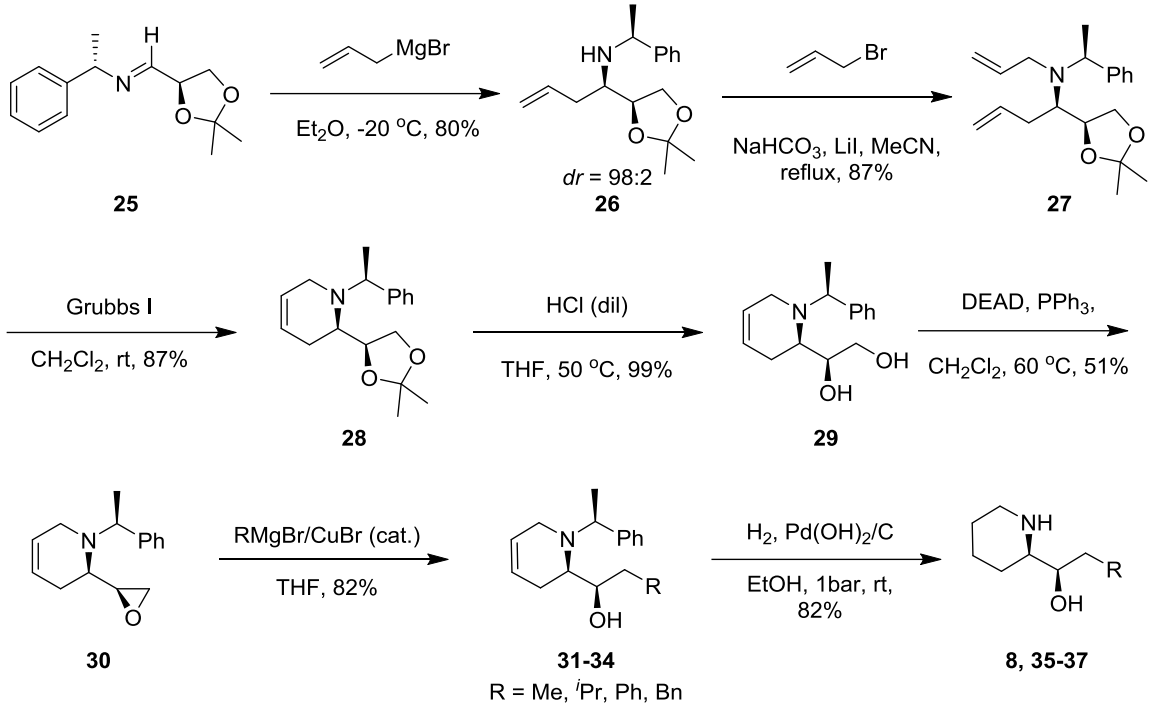


Scheme 2.3: Synthesis of pyrrolidine analogue of α-conhydrine by Sutherland and co-workers.

2. 2. 2 Synthesis of conhydrine and analogue by Gálvez *et al.*

Gálvez and co-workers in 2011,[7c] have reported a methodology for the synthesis of (+)-β-conhydrine **8** and also also its analogues having varied side arms (Scheme 2.4). The imine **25**, synthesized from D-glyceraldehyde and (*S*)-phenylethylamine, was subjected to diastereoselective addition of allymagnesium bromide in diethyl ether at -20 °C ensuing the homoallyl amine **26**. With the various Lewis acid, the different diastereomeric ratio of *syn* and *trans* isomers was observed in the Grignard reaction. But, the formation of required *syn* isomer was observed in the absence of Lewis acid in 80% yield. The piperidine skeleton **28** was prepared by allylation of a *syn* isomer **27** followed by Grubbs I generation catalyzed ring-closing metathesis. Then acetonide deprotection **27** in acidic condition and epoxidation under Mitsunobu reaction conditions gave epoxide **30**. The opening of epoxide **30** using MeMgBr in the presence of catalytic copper(I) bromide from the less hindered side was resulted in compound **31.** Finally, the compound **31** was subjected to hydrogenation using $Pd(OH)_2/C$ to give (+)-β -conhydrine **8** (over 7-steps in

21% overall yield). Similarly, epoxide ring opening with different Grignard reagent followed by hydrogenation gave (+)-β-conhydrine analogues (**35**-**37**).

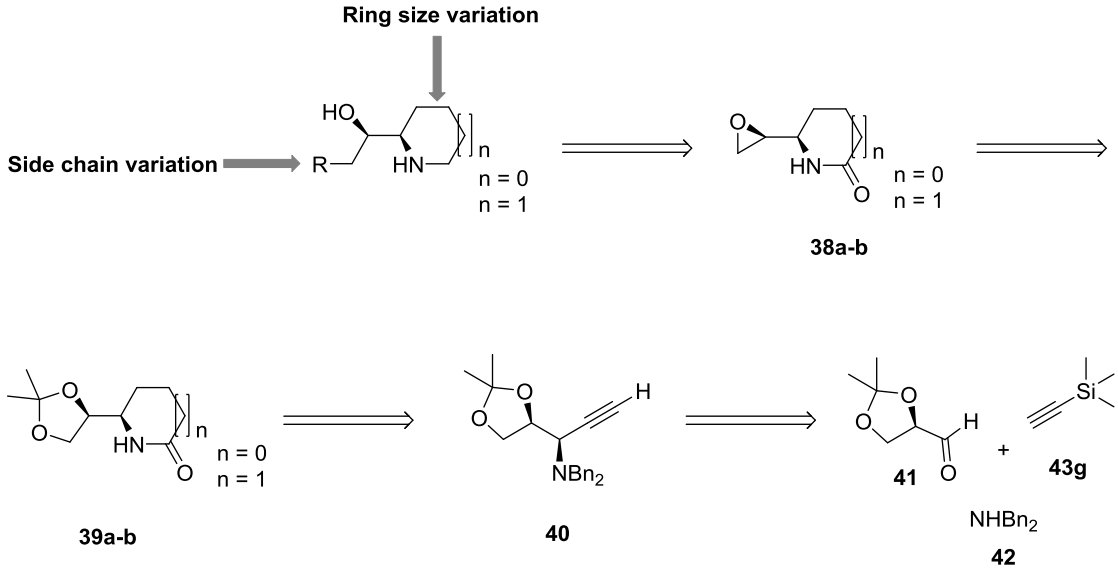


Scheme 2.4: Synthesis (+)-β-conhydrine and its analogues by Gálvez and co-workers.

2.3 Present Work and Synthetic Planning

Even though the various strategies used in the synthesis of conhydrine, any synthetic approach towards the convenient generation of the natural product and its analogues with both ring size and side chain variation through a common strategy remains unabated. As part of our research program aimed at developing enantioselective syntheses of pyrrolidine and piperidine alkaloids, we introduced the three-component aldehyde-amine-terminal alkyne coupling reaction as a key strategy for the construction of piperidine and pyrrolidine scaffolds present in conhydrine and its analogues. Our strategic plan involved the use of an acetonide protected D-glyceraldehyde **41** as the chiral precursor which can result in the hydroxypiperidine stereochemical feature of (+)-β-conhydrine. As shown in the retrosynthetic analysis (Scheme 2.5), we visualised that (+)-β-conhydrine and its analogues could be fabricated from the epoxide **38a-b** via nucleophilic addition followed by reduction of lactam. We expected that epoxide would be a key intermediate for the

preparation of side chain analogues through the addition of various nucleophiles. The epoxide **38a-b** could be obtained from **39a-b** using actonoide deprotection and epoxiation through Mitsunobu reaction of diol. The lactam **39a-b** could be obtained from alkyne **40** via esterification, reduction of triple bond, debenzylation and cyclization in basic condition. The alkyne **40** could be obtained from Cu(I)-catalysed (A^3) coupling reaction of an acetonide protected D-glyceraldehyde **41**, dibenzyl amine **42**, TMS-acetylene **43g**, followed by desilylation of propargyl amine derivative.



Scheme 2.5: Retrosynthetic analysis of conhydrine and its analogues.

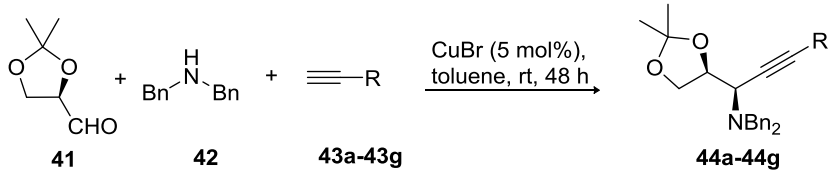
2.4 Result and Discussion

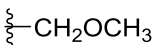
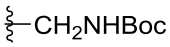
We decided to rely on the principle of diastereoselective construction of the α-amino alcohol followed by the formation of either a piperidine or a pyrrolidine ring. In this regard, we realized the importance of the metal catalyzed α-oxyaldehyde-amine-alkyne (three-component) coupling reaction reported by Huang *et. al.*[11] for the diastereoselective construction of *syn*-α-amino alcohol which can be applied in the synthesis of (+)-β-conhydrine. Starting from the optically pure acetonide protected glyceraldehyde, piperidine and phenylacetylene an AuI catalyzed (5 mol %) three-component reaction in water at room temperature was successful in constructing the corresponding *syn*-α-amino alcohol product in 65% yield and with *syn*/*anti* ratio up to 82:18. We realized that simple

alteration of the alkyne and the amine components would be necessary for further construction of piperidine and pyrrolidine rings. On the other hand, the acetonide protected 1,2-diol moiety would also be helpful for accessing analogues of conhydrine having varied side arm functionality. We realized that the three- component coupling (A^3-coupling) reaction would also be significant providing a shorter synthetic route. However, a further improvement of diastereoselectivity during the three-component coupling (A^3-coupling) reaction described by Huang *et. al* was necessary to establish the novelty of our strategy. Therefore, we decided to introduce a disubstituted amine with bulkier substituents which can also be removed easily whenever necessary. A terminal alkyne, substituted with a protecting group, orthogonal to that of amine was thought to be idle for chain elongation for further construction of either piperidine or pyrrolidine ring. Our judgement led to the selection of the dibenzylamine **42** anticipating the role of benzyl group for driving the diastereoselectivity. Additionally, the hydrogenolysis condition for removing this protecting group is also suitable for the complete reduction of the alkyne C≡C bond. We also decided to replace AuI with CuBr due to the established importance of the Cu(I) salt in the three-component aldehyde-amine-alkyne coupling reaction.[12] Also, the ready availability, low toxicity, insensitivity to air, cheaper price led us to explore the methodology with a Cu(I) halide.

The methodology in diastreoselective construction of the α-amino alcohol was evaluated by the reaction of aldehyde **41** and di-benzylamine **42** with **42** with of various terminal alkynes in the presence of CuBr as a catalyst in toluene as solvent. Substitution pattern of terminal alkynes were varied from **43a** to **43g** (Table 1). The A^3-coupling of **41**, **42** and phenyl acetylene **43a** (R = -Ph) resulted in the formation of the major *syn*-diastereomer **44a** in 68% yield and with *syn/anti* = 78:22. The coupling with cyclohexenyl acetylene **43b**, the *syn*-α-amino alcohol **44b** with 65% yield in diastereoselectivity, *syn/anti* = 91:9 was observed. Diastereomeric ratio was determined based on ^{1}H NMR and reversed phase HPLC analyses. By varying alkyne **43c-43f** (R = -tBu, -CH_2OCH_3,-CH_2OTBDPS, -CH_2NHBoc, and -TMS) with aliphatic side chain an excellent *syn* to *anti* ratio of > 99% **44c-44f** was observed with 73%, 88% ,70%, 76%, and 84%, respectively.

Table 1: Diastreoselective construction of the α-amino alcohols via aldehyde-amine-alkyne (A^3) coupling reaction.



entry	alkyne	R	product	% yield	*syn / anti*
1	**43a**		**44a**	68	78:22
2	**43b**		**44b**	65	91:09
3	**43c**		**44c**	73	>99%
4	**43d**		**44d**	88	>99%
5	**43e**		**44e**	70	>99%
6	**43f**		**44f**	76	>99%
7	**43g**		**44g**	84	>99%

The *syn*-stereochemistry of the A^3-coupling product was confirmed by the crystal structure of the α-amino alcohol **44c** (Figure 2.5A). The relative stereochemistry of the acetonide protected secondary hydroxyl group and the dibenzyl protected amino group in **44c** matched the stereochemistry present in the unnatural (+)-β-conhydrine. Excellent diastereoselectivity observed in each of these multi-component reactions was further rationalized by the geometry optimization study of the intermediate iminium cation **45** (Figure 2.5B). Interestingly, the computational gas-phase modeling at 0 K by the DFT-B3LYP/6-311G(d,p) method using Gaussian 03 confirmed the presence of a sterically crowded *si*-face (Figure 2.5C and 2.5D) allowing attack of the alkynide anion preferentially from the more accessible *re*-face. Due to π-stacking interactions between the phenyl groups of the iminium cation **45** and phenyl acetylene **43a** allow the addition of the

alkyne ylide from the *si*-face although steric crowding governs the formation of the *syn*-product **44a**. As a result, the anti-addition product was also formed as the minor isomer reducing the diastereoselectivity during the aldehyde-amine-alkyne coupling reaction.

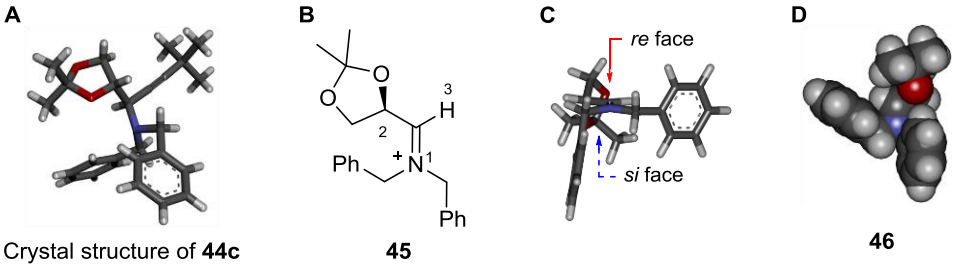
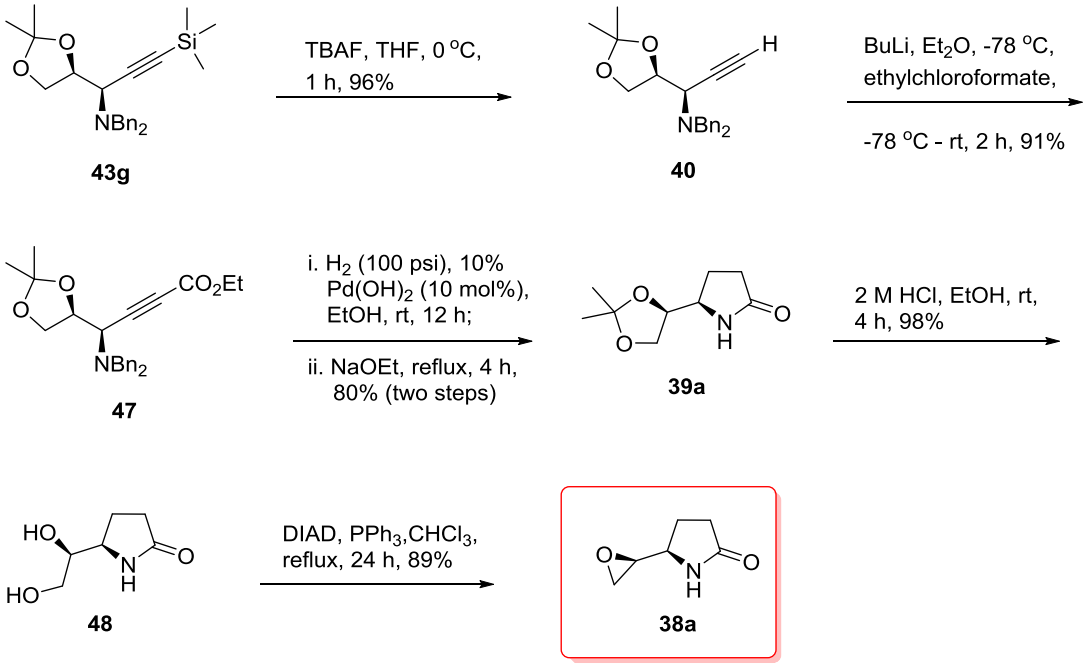


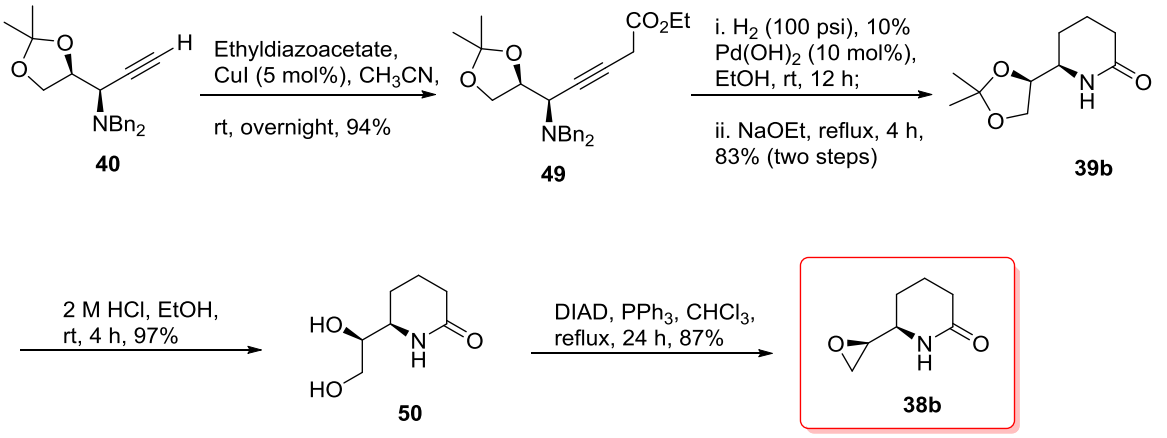
Figure 2.5 X-ray crystal structure of **44c** (A); representation of the iminium cation **45** (B); side view of DFT-B3LYP/6-311G(d,p) geometry optimized structure of **45** (C) and the space filling model of optimized structure of **46** from the more hindered *si* face (D).

The TMS-protected aminoalkyne **44g** was used for next steps to construct the pyrrolidine and piperidine scaffolds. The trimethylsilyl group of **44g** was deprotected under TBAF conditions which gave the terminal alkyne **40** in 96% yield (Scheme 2.6). Using ethylchloroformate and the terminal alkyne **40** in the presence of n-BuLi gave the ester moiety of **47** with 91% yield. The ester **47** then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond followed by cyclization using NaOEt to provide the γ-lactam **39a** in 80% yield over two steps. Further ketal group of **39a** was deprotected by ethanolic HCl to afford the diol **48** in 98% yield. The diol **48** was then converted to the epoxy-γ-lactam intermediate **38a** in 89% yield by reacting with DIAD in the presence of PPh_3 (Mitsunobu reaction conditions).



Scheme 2.6: Synthesis of the epoxy-γ-lactam **38a**.

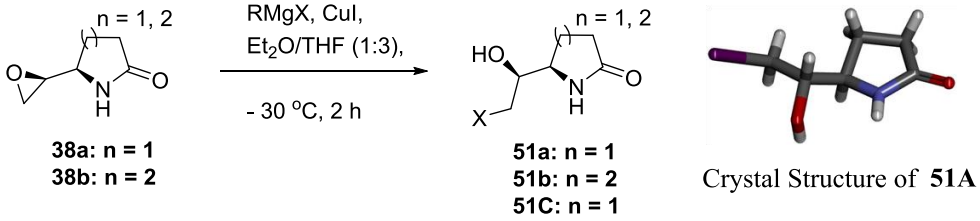
The TMS-protected aminoalkyne **44g** was used for next steps to construct the pyrrolidine and piperidine scaffolds. The trimethylsilyl group of **44g** was deprotected under TBAF conditions which gave the terminal alkyne **40** in 96% yield (Scheme 2.6). Using ethylchloroformate and the terminal alkyne **40** in presence of n-BuLi gave the ester moiety of **47** with 91% yield. The ester **47** then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of of C≡C bond followed by cyclization using NaOEt to provide the γ-lactam **39a** in 80% yield over two steps. Further ketal group of **39a** was deprotected by ethanolic HCl to afford the diol **48** in 98% yield. The diol **48** was then converted to the epoxy-γ-lactam intermediate **38a** in 89% yield by reacting with DIAD in presence of PPh_3 (Mitsunobu reaction conditions).



Scheme 2.7: Synthesis of the epoxy-δ-lactam **38b**.

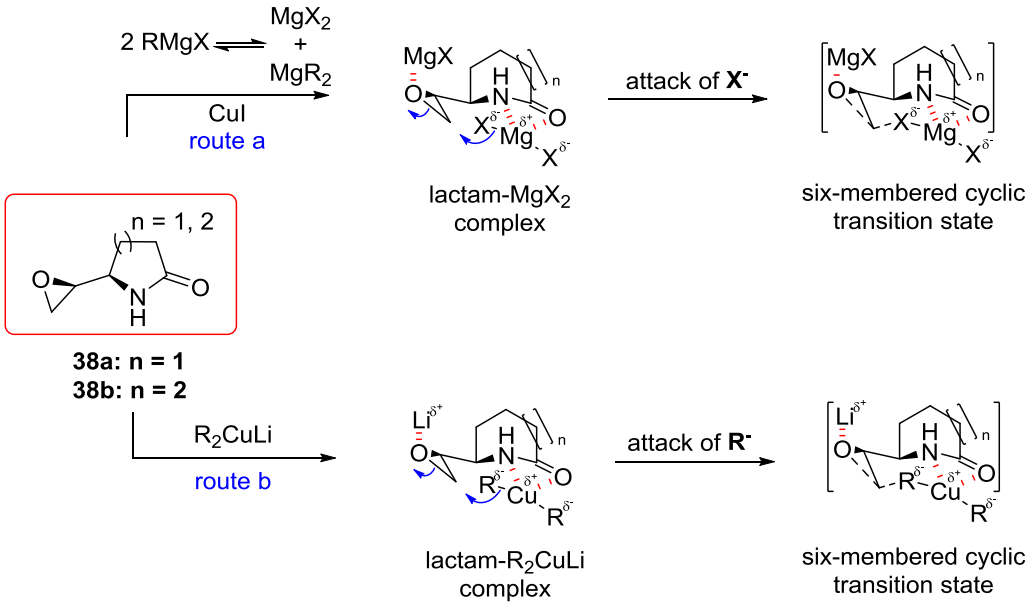
As methodology described by Fray *et. al.*,[14] we treated the epoxide **38a** with methylmagnesium iodide in presence of 20 mol% CuI which result in unexpected iodohydrin **51a** in 53% yield (Table 2). The change of the Grignard reagent to methylmagnesium bromide also gave the corresponding bromo derivative **51b** in 53% yield. Also, epoxide opening product **51c** by iodide was also formed in 56% yield during the reaction of **38b** with methylmagnesium iodide. The structure of the unexpected halohydrine **51a** was confirmed by X-ray crystallography (Table 2). Unexpected formation of halohydrins **51a-51c** indicate that the halide (X^- = I^- and Br^-) is acting as the better nucleophile Br^-) is acting as the better nucleophile compared to the alkyl anion (R^-) from the Grignard reagent.

Table 2: Formation of halohydrins 51a-51c from epoxylactams in presence of Grignard conditions. X-ray crystal structure of 51a.



entry	epoxide	R	X	product	% yield
1	**38a**	⌇—Me	I	**51a**	53
2	**38b**	⌇—Me	I	**51b**	53
3	**38a**	⌇—Me	Br	**51c**	56

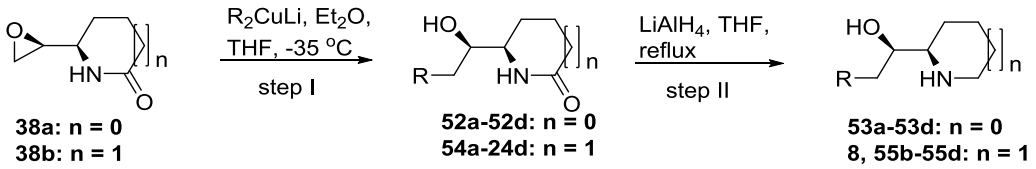
As Schlenk equilibrium of Grignard reagent results into the formation of MgX_2 and X^- , MgX_2 chelate with the lactam and favors attack of X^- to the terminal epoxy-carbon via the 6-membered cyclic transition state (Scheme 2.8, route a).[15] We believed that the lactam-Mg^{2+} complexation-motif if exists, can be turned into advantage by altering the nucleophile. Therefore, for better nucleophilicity of R^-, we decided to use the Gilman reagent（organocopper based ylides), due to which regioselective intramolecular attack of R^- and a lactam-Cu^+ complexation result into formation of hydroxy-γ-lactam (Scheme 2.8, route b).[16]



Scheme 2.8: Proposed regioselective pathways for intramolecular epoxide ring-opening by X^- (route a) and R^- (route b).

The treatment of Me_2CuLi with the epoxide **38a** in Et_2O-THF provided the desired hydroxy-γ-lactam **52a** as the single regioisomer in 77% yield (Table 3, entry 1, step I). Finally, the γ-lactam **52a** was reduced by $LiAlH_4$ in THF under refluxing conditions to provide **53a** as the pyrrolidine analogue of (+)-β-conhydrine in 81% yield (Table 3, entry 1, step II). The epoxy group of **38a** was also opened with other Gilman reagents (R = Bu, t-Bu and Ph) to obtain hydroxy-γ-lactams **52b-52d** with 76%, 72% and 68% yields, respectively. The hydroxy-γ-lactams **52b-52d** were then converted to corresponding pyrrolidine analogues **53b-53d** with 86%, 84%, and 72% yields, respectively (Table 3, entries 2-4). The epoxy-δ-lactam intermediate **38b** when treated with Me_2CuLi to furnish the single regioisomeric hydroxy-δ-lactam **54a** with 73% yield which on after LAH reduction of **54a** provided (+)-β-conhydrine **8** with 78% yield (in 8-steps with 26% overall yield).

Table 3: Synthesis of β-(+)-conhydrine 8 and its analogues 53a-53d, 55b-55d.



entry	epoxide	R	Step I		Step II	
			product	% yield	product	% yield
1	**38a**	—Me	**52a**	77	**53a**	81
2	**38a**	—Bu	**52b**	76	**53b**	86
3	**38a**	—^{t}Bu	**52c**	72	**53c**	84
4	**38a**	—Ph	**52d**	68	**53d**	72
5	**38b**	—Me	**54a**	73	**8**	78
6	**38b**	—Bu	**54b**	73	**55b**	73
7	**38b**	—^{t}Bu	**54c**	75	**55c**	77
8	**38b**	—Ph	**54d**	77	**55d**	78

The structure of the $LiAlH_4$ reduction product was confirmed by comparing the recorded NMR (^{1}H- and ^{13}C) spectral and specific rotation data (observed: + 7.1 in EtOH, reported + 7.9 in EtOH) with the data available in the literature.[9d] We also synthesized (+)-β-conhydrine analogues **55b**, **55c** and **55c** (R = Bu, t-Bu and Ph) following the epoxide opening followed by lactam reduction strategy (Table 3, entries 6-8) in **21-28**% yields.

The desired stereochemistry present in (+)-β-conhydrine was confirmed by the crystal structure of the hydroxy-γ-lactam **52d** (Figure 2.6A) and that of hydroxy-δ-lactam **55b** (Figure 2.6B).

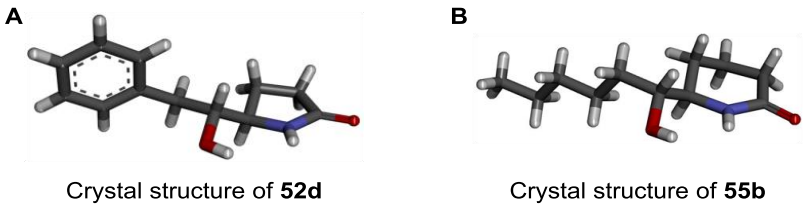


Figure 2.6 X-ray crystal structures of hydroxy-γ-lactam **52d** (**A**) and hydroxy-δ-lactam **55b** (**B**).

2.5 Conclusion

A Cu(I) catalyzed three-component coupling reaction strategy was efficiently employed for the diastereoselective construction of *syn*-α-amino alcohols which was confirmed by single-crystal X-ray diffraction study and theoretical calculation. The methodology was further applied in the synthesis of (+)-β-conhydrine and its analogues having varied ring size and side arm functionality. Ring size variation was addressed by the construction of piperidine and pyrrolidine rings. On the other hand, side arm variation was implemented by regioselective opening of epoxides by Gilman's reagents. A lactam-Cu(I) complexation motif was proposed indicating an intramolecular attack of the R^- on terminal epoxide carbon via six-membered transition state. Single-crystal X-ray diffraction studies allowed the conformation of stereochemistry of epoxide opened products which were finally converted to (+)-β-conhydrine and its analogues. Present work reports the synthesis of (+)-β-conhydrine over eight-steps in 26% overall yield along with its seven analogs over same number of steps in 21-28% yields. Although, the present work covered the synthesis of piperidine, pyrrolidine analogues, the methodology is also amenable for further variation in the ring size and with broader prospect of employing wide ranges of side arm functionality. Synthesized (+)-β-conhydrine analogues deserve to be evaluated for their biological activity and elaborated to other structurally diverse analogues for structure activity relation (SAR) studies.

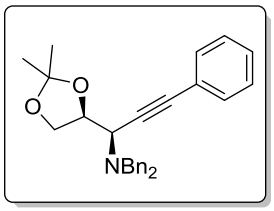
2.6 Experimental Section

General Methods: The acetonide protected D-glyceraldehyde was prepared from D-mannitol according to the published methods.[17] Other substrates and reagents were purchased from common commercial sources and used without additional purification. THF and diethyl ether was pre-dried over Na wire. Then the solvent was refluxed over Na (1% w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue colour of the benzophenone ketyl radical anion persists. All reactions were conducted under the nitrogen atmosphere. Solvents: petroleum ether and ethyl acetate (EtOAc) were distilled prior to thin layer and column chromatography. Reactions were controlled using TLC on silica. Column chromatography was performed on silica gel (100–200 mesh).

General copper(I) catalyzed aldehyde-amine-alkyne reaction procedure.

Method A: To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **41** (1.0 mmol) in dry toluene (2.0 mL) were added dibenzylamine **42** (1.0 mmol), 4 Å molecular sieves (500 mg), CuBr (0.05 mmol), and alkyne **43a-43g** (1.0 mmol). The reaction mixture was stirred at room temperature for 48 h. After completion, the reaction mixture was filtered through celite bed and washed with Et_2O (2 × 10 mL). The combined filtrate was concentrated under reduced pressure to obtain liquid which was further purified by column chromatography over silica gel (*Eluent:* 0-5% EtOAc in petroleum ether) to furnish corresponding multi-component reaction product **44a-44g**.

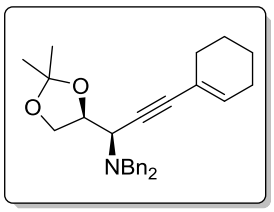
Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylprop-2-yn-1-amine 44a ($C_{28}H_{29}NO_2$).



Following the Method A, reaction of **41** (300 mg, 2.30 mmol) with **42** (456 g, 2.31 mmol) and alkyne **43a** (0.250 g, 2.44 mmol) in dry toluene (5 mL) in the presence of CuBr (18 mg, 0.13 mmol), 4 Å molecular sieves (1.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **44a** (644 mg, 68%) as colorless oil. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067 ; $[\alpha]_D^{25}$ = - 70.30 (*c* = 0.5, $CHCl_3$); ^1H NMR (400

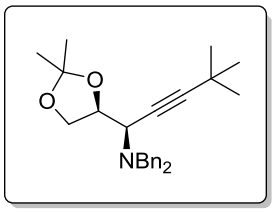
MHz, $CDCl_3$) δ (ppm): 7.49 – 7.45 (m, 6H), 7.35 – 7.32 (m, 3H), 7.30 (t, *J* = 7.3 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 2H), 4.36 (q, *J* = 6.4 Hz, 1H), 4.06 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.97 – 3.90 (m, 3H), 3.80 (d, *J* = 7.4 Hz, 1H), 3.55 (d, *J* = 13.9 Hz, 2H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 132.0 (2C), 129.1 (4C), 128.5 (2C),128.3 ,128.4 (4C), 127.1 (2C), 123.0, 109.8, 86.9, 84.4, 76.5, 67.5, 56.2, 55.6 (2C), 26.7, 25.7; HRMS (ESI) Calcd. for $C_{28}H_{30}NO_2$ $[M + H]^+$ 412.2277, found 412.2281.

Synthesis of (*R*)-*N*,*N*-dibenzyl-3-(cyclohex-1-en-1-yl)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-amine 44b ($C_{28}H_{33}NO_2$).



Following the Method A, reaction of **41** (245 mg, 1.88 mmol) with **42** (374 mg, 1.90 mmol) and alkyne **43b** (200 mg, 1.88 mmol) in dry toluene (5 mL) in the presence of CuBr (14 mg, 0.10 mmol), 4 Å molecular sieves (1.12 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **44b** (508 mg, 65%) as colorless oil. IR (KBr) ν (cm^{-1}): 2925,1605, 1494, 1456, 1372, 1257, 1209, 1134, 1070, 1029, 1002; $[\alpha]_D^{25}$ = - 158.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.23 (t, *J* = 7.3 Hz, 2H), 6.18 - 6.15 (m, 1H), 4.30 (q, *J* = 6.4 Hz, 1H), 4.03 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.91-3.85 (m, 3H), 3.70 (d, *J* = 7.4 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 2H), 2.21 - 2.17 (m, 2H), 2.16 – 2.12 (m, 2H) 1.72-1.60 (m, 4H), 1.35 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.7(2C), 135.0, 129.0 (4C), 128.3 (4C), 127.0 (2C), 120.4, 109.7, 88.7, 81.2, 76.5, 67.5, 56.1, 55.5 (2C), 29.8, 29.7, 26.7, 25.7, 22.4, 21.6 ; HRMS (ESI) Calcd. for $C_{28}H_{34}NO_2$ 416.2590 $[M + H]^+$, found 416.2583.

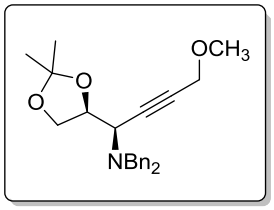
Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4,4-dimethylpent-2-yn-1-amine 44c ($C_{26}H_{33}NO_2$).



Following the Method **A**, reaction of **41**(174 mg, 1.34 mmol) with **42** (213 mg, 1.12 mmol) and alkyne **43c** (100 mg, 1.12 mmol) in dry toluene (5.0 mL) in the presence of CuBr (9 mg, 0.06 mmol), 4Å molecular sieves (2.00 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1 % EtOAc in petroleum

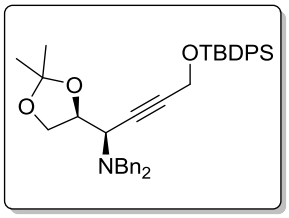
ether) to furnish **44c** (348 mg, 73%) as colorless solid. Mp.76–78 ^{o}C, IR (KBr) ν (cm^{-1}): 2958, 2873, 1609, 1585, 1456, 1285, 1121, 1078; $[\alpha]_D^{25}$ = - 133.67 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 7.2 Hz, 4H), 7.28 (t, *J* = 7.3 Hz, 4H), 7.20 (t, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 6.5 Hz, 1H), 3.98 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.82 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 2H), 3.56 (d, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 14.0 Hz, 2H), 1.32 (s, 3H), 1.26 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.2 (4C), 127.0 (2C), 109.5, 96.0, 76.5, 72.6, 67.6, 55.8, 55.4 (2C), 31.5 (3C), 27.7, 26.7, 25.9; HRMS (ESI) Calcd. for $C_{26}H_{34}NO_2$ 392.2590 $[M + H]^+$, found 392.2589.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-methoxybut-2-yn-1-amine 44d ($C_{24}H_{29}NO_3$).



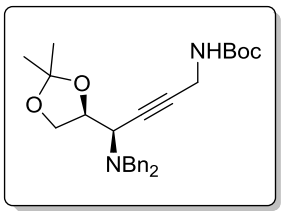
Following the Method **A**, reaction of **41** (204 mg, 1.57 mmol) with **42** (272 mg, 1.43 mmol) and alkyne **43d** (100 mg, 1.43 mmol) in dry toluene (8.0 mL) in the presence of CuBr (12 mg, 0.08 mmol), 4 Å molecular sieves (2.00 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **44d** (480 g, 88%) as light yellow oil. IR (neat) ν (cm^{-1}): 2928, 1508, 1495, 1371, 1252, 1210, 1187, 1146, 1098, 1028; $[\alpha]_D^{25}$ = - 135.20 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.2 Hz, 4H), 7.29 (t, *J* = 7.2 Hz, 4H), 7.21 (t, *J* = 7.2 Hz, 2H), 4.29 (q, *J* = 6.3 Hz, 1H), 4.20 (d, *J* = 1.8 Hz, 2H), 4.00 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.89 - 3.85 (m, 3H), 3.62 (d, *J* = 7.2 Hz, 1H), 3.46 (d, *J* = 14.0 Hz, 2H), 3.60 (s, 3H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4 (2C), 129.0 (4C), 128.3 (4C), 127.1 (2C), 109.8, 82.3, 81.4, 76.3, 67.4, 60.1, 57.6, 55.5 (2C), 55.4, 26.6, 25.5; HRMS (ESI) Calcd. for $C_{24}H_{30}NO_3$ $[M + H]^+$ 380.2226, found 380.2224.

Synthesis of (*R*)-*N*,*N*-dibenzyl-4-((tert-butyldiphenylsilyl)oxy)-1-((*S*)-2,2-dimethyl-,3-dioxolan-4-yl)but-2-yn-1-amine 44e ($C_{39}H_{45}NO_3Si$).



Following the Method A, reaction of **41** (500 mg, 3.84 mmol) with **42** (760 g, 3.84 mmol) and alkyne **43e** (1.13 g, 3.84 mmol) in dry toluene (8.0 mL) in the presence of CuBr (27 mg, 0.19 mmol), 4 Å molecular sieves (2.00 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **44e** (1.62 g, 70%) as colorless oil. IR (Neat) ν (cm^{-1}): 2983, 2889, 2361, 1508, 1492, 1455, 1370, 1209, 1029, 1088, 967, 838; $[\alpha]_D^{25}$ = - 64.60 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (dd, *J* = 7.8, 1.5 Hz, 4H), 7.46 - 7.38 (m, 10H), 7.30 (t, *J* = 7.1 Hz, 4H), 7.23 (t, *J* = 7.3 Hz, 2H), 4.34 (d, *J* = 1.8 Hz, 2H), 4.21 (q, *J* = 6.2 Hz, 1H), 3.92 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.82 (d, *J* = 13.9 Hz, 2H), 3.77 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.54 (dt, *J* = 7.8, 1.8 Hz, 1H), 3.40 (d, *J* = 14.0 Hz, 2H), 1.34 (s, 3H), 1.26 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.6 (2C), 135.8 (4C), 133.4 (2C), 130.0 (2C), 129.0 (4C), 128.3 (4C), 127.9 (4C), 127.0 (2C), 109.7, 85.0, 80.0, 76.2, 67.4, 55.5, 55.4 (2C), 52.9, 26.8 (3C), 26.6, 25.7, 19.4; HRMS (ESI) Calcd. For $C_{39}H_{46}NO_3Si$ 604.3247 $[M + H]^+$, found 604.3245.

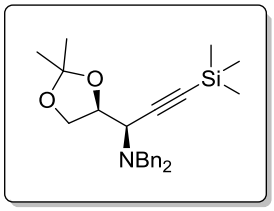
Synthesis of *tert*-butyl ((*R*)-4-(dibenzylamino)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-yn-1-yl)carbamate 44f ($C_{28}H_{36}N_2O_4$).



Following the Method A, reaction of **41** (456 mg, 3.50 mmol) with **42** (691 mg, 3.50 mmol) and alkyne **43f** (0.60 g, 3.50 mmol) in dry toluene (8.0 mL) in the presence of CuBr (25 mg, 0.19 mmol), 4 Å molecular sieves (1.75 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 5% EtOAc in petroleum ether) to furnish **44f** (1.20 g, 76%) as colorless oil. IR (Neat) ν (cm^{-1}): 3566, 2980, 1699, 1495, 1455, 1367, 1245, 1160, 1069; $[\alpha]_D^{25}$ = - 104.0 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (br d, *J* = 5.0 Hz, 4H), 7.29 (d, *J* = 7.4 Hz, 4H), 7.21 (d, *J* = 7.1 Hz, 2H), 4.70 (br s, 1H), 4.22 – 4.27 (m, 1H), 4.00 – 3.97 (m, 3H), 3.83 (dd, *J* = 8.2, 6.0 Hz, 3H), 3.56 (d, *J* = 4.8 Hz, 1H), 3.43 (d, *J* = 13.3 Hz, 2H), 1.46 (s, 9H),

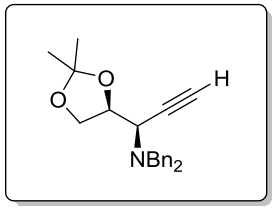
1.31 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.4, 139.4 (2C), 129.0 (4C), 128.3 (4C), 127.1 (2C), 109.7, 82.8, 80.1, 78.0, 76.3, 67.3, 55.5 (2C), 55.4, 30.8, 28.5(3C), 26.6, 25.5; HRMS (ESI) Calcd. for $C_{28}H_{37}N_2O_4$ 465.2753 $[M + H]^+$, found 465.2757.

(*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-doxolan-4-yl)-3-(trimethylsilyl)prop-2-yn-1-amine 44g ($C_{25}H_{33}NO_2Si$).



Following the Method A, reaction of **41** (5.00 g, 38.4 mmol) with **42** (6.91 g, 34.9 mmol) and alkyne **43g** (3.46 g, 34.9 mmol) in dry toluene (75 mL) in the presence of CuBr (275 mg, 1.92 mmol), 4 Å molecular sieves (190.10 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **44g** (11.95 g, 84%) as colorless oil. IR (KBr) ν (cm^{-1}): 2986, 2161, 1647, 1495, 1370, 1250, 1074, 1001; $[\alpha]_D^{20}$ = -113.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.2 Hz, 4H), 7.30 (t, *J* = 7.4 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 4.01 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.88 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.83 (d, *J* = 14.2 Hz, 2H), 3.61 (d, *J* = 7.4 Hz, 1H), 3.43 (d, *J* = 14.2 Hz, 2H), 1.22 (s, 3H), 1.34 (m, 3H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 129.1 (4C), 128.3 (4C), 127.1 (2C), 109.7, 100.7, 91.7, 76.2, 67.5, 56.5 (2C), 55.5, 26.7, 25.8, 0.4 (3C); HRMS (ESI) Calcd. for $C_{25}H_{34}NO_2Si$ 408.2359 $[M + H]^+$, found 408.2355.

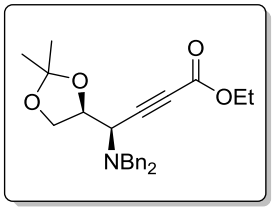
Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-yn-1-amine 40 ($C_{22}H_{25}NO_2$).



To a solution of TMS-alkyne **44g** (7 g, 17.2 mmol) in dry THF (40 mL) placed at 0 ˚C, TBAF (2.25 g, 8.6 mmol, 1 M in THF) was added drop wise and the mixture was stirred at this temperature for 1 h. The reaction mixture was diluted by adding H_2O (50 mL) followed by the extraction of the product in Et_2O (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to afford **40** (5.37 g, 93%) as colorless oil. IR (KBr) ν (cm^{-1}): 3289, 3027, 2986, 2805, 1715,

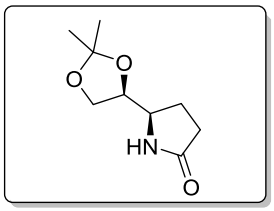
1602, 1370, 1257, 1150, 1074, 1027; $[\alpha]_D^{25}$ = - 99.1 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.6 Hz, 4H), 7.23 (t , *J* = 7.3 Hz, 2H), 4.29 (q, *J* = 6.2 Hz, 1H), 4.01 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.91 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.89 (d, *J* = 14.2 Hz, 2H), 3.57 (d, *J* = 7.3 Hz, 1H), 3.46 (d, *J* = 13.7 Hz, 2H), 2.37 (s, 1H), 1.33 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4 (2C), 129.0 (4C), 128.4 (4C), 127.2 (2C), 109.8, 78.7, 76.4, 74.5, 67.2, 55.5 (2C), 55.1, 26.6, 25.5; HRMS (ESI) Calcd. for $C_{22}H_{26}NO_2$ 336.1966 $[M + H]^+$, found 336.1965.

Synthesis of (*R*)-ethyl 4-(dibenzylamino)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-ynoate 47 ($C_{25}H_{29}NO_4$).



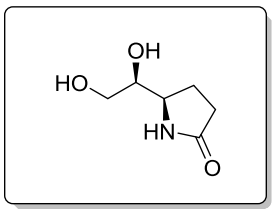
To a solution of **40** (4.00 g, 11.90 mmol) in dry Et_2O (40 mL) cooled at -78 ^oC was added dropwise n-BuLi (8.2 mL, 13.10 mmol, 1.6 M in hexane). The reaction mixture was stirred at the same temperature for 30 min followed by addition of ethyl chloroformate (2.58 g, 23.80 mmol). The reaction mixture was allowed to come to room temperature and stirred for 2 h. The reaction mixture was quenched with water (20 mL) and the product was extracted with Et_2O (2 × 30 mL), dried over Na_2SO_4. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **47** (4.12 g, 85%) as colorless oil. IR (KBr) ν (cm^{-1}): 2986, 2220, 1713, 1495, 1454, 1370, 1243, 1148, 1074; $[\alpha]_D^{25}$ = -123.9 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.3 Hz, 4H), 7.28-7.20 (t, *J* = 7.3 Hz, 2H), 4.32 (q, *J* = 6.5 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.03 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.93 (d, *J* = 14.3 Hz, 2H), 3.90 (dd, *J* = 8.5, 5.9 Hz, 1H), 3.70 (d, *J* = 7.1 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.26 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.5, 138.8 (2C), 129.0 (4C), 128.4 (4C), 127.3 (2C), 110.1, 83.1,78.7, 75.8, 67.1, 62.3, 55.7 (2C), 55.2, 26.5, 25.4, 14.2 ; HRMS (ESI) Calcd. for $C_{25}H_{30}NO_4$ 408.2175 $[M + H]^+$, found 408.2184.

Synthesis of (*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pyrrolidin-2-one 39a ($C_9H_{15}NO_3$).



To a solution of **47** (10.00 g, 24.54 mmol) in EtOH (100 mL) was added 10% $Pd(OH)_2/C$ (2.45 g, 2.45 mmol) and the reaction mixture was stirred at room temperature under 100 psi pressure of hydrogen for 24 h. The reaction mixture was filtered through celite and the celite bed was washed with EtOH (2 × 20 mL). To the combined solution was added NaOEt (1.67 g, 24.54 mmol) and refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent:* 60% EtOAc in petroleum ether) to furnish the pure **39a** (3.73 g, 82% over 2 steps) as colourless oil. IR (KBr) ν (cm^{-1}): 3261, 2987, 2894, 1631, 1456, 1381, 1328, 1292, 1217, 1074; $[\alpha]_D^{25}$ = - 47.2 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.14 (br s, 1H), 4.04 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.96 (dd, *J* = 7.2, 5.4 Hz, 1H), 3.66 (dd, *J* = 8.5, 5.4 Hz, 1H), 3.61 (q, *J* = 6.8 Hz, 1H), 2.36 - 2.31 (m, 2H), 2.20 – 2.11 (m, 1H), 1.73 – 1.66 (m, 1H), 1.33 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.0, 110.1, 79.3, 66.2, 67.1, 29.8, 26.8, 25.3, 23.1; HRMS (ESI) Calcd. for $C_9H_{15}NO_3Na$ 208.0949 $[M + Na]^+$, found 208.0949.

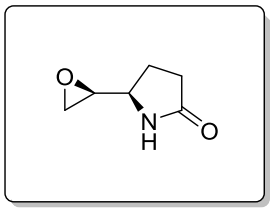
Synthesis of (*R*)-5-((*S*)-1,2-dihydroxyethyl)pyrrolidin-2-one 48 ($C_6H_{11}NO_3$).



To a solution of **39a** (2.12 g, 11.5 mmol) in EtOH (20 mL) was added 2 M HCl (6 mL) and the mixture was stirred at room temperature for 2 h. After completion of the reaction, the solution was neutralized with solid K_2CO_3 and reaction mixture was concentrated under reduced pressure. The crude product was subjected to by column chromatography over silica gel (*Eluent*: 20% MeOH in $CHCl_3$) to furnish the pure **48** (1.58 g, 95%) as white solid. Mp. 94–96 ^oC; IR (KBr) ν (cm^{-1}): 3229, 2927, 1651, 1416, 1393, 1269, 1106, 1085, 1039, 1008; $[\alpha]_D^{25}$ = - 11.6 (*c* = 0.5, MeOH); ^1H NMR (400 MHz, DMSO-D_6) δ (ppm): 7.40 (br s, 1H), 4.76 (d, *J* = 4.6 Hz, 1H), 4.53 (t, *J* = 5.0 Hz, 1H), 3.56 - 3.52 (m, 1H), 3.35 - 3.32 (m, 2H), 3.31 - 3.25 (m, 1H), 2.16 - 1.96 (m, 3H),

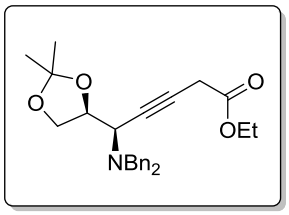
1.84 - 1.75 (m, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ (ppm): 177.2, 74.2, 62.9, 55.3, 30.1, 23.3; HRMS (ESI) Calcd. for $C_6H_{11}NO_3Na$ 168.0637 $[M + Na]^+$, found 168.0634.

Synthesis of (*R*)-5-((*S*)-oxiran-2-yl)pyrrolidin-2-one 38a ($C_6H_9NO_2$).



To a solution of **48** (1.20 g, 8.27 mmol) in anhydrous $CHCl_3$ (80 mL) were added PPh_3 (3.26 g, 12.41 mmol) and DIAD (2.51 g, 12.41 mmol). The reaction mixture was reflux for 36 h and then allowed to come to room temperature. The reaction mixture was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish the pure **38a** (884 mg, 84%) as colorless oil. IR (KBr) ν (cm^{-1}): 2948, 1682, 1462, 1437, 1279, 1255, 1108, 877; $[\alpha]_D^{25}$ = - 55.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.60 (br s, 1H), 3.46 (q, *J* = 6.3 Hz, 1H), 2.96 (ddd, *J* = 6.2, 3.7, 2.5 Hz, 1H), 2.82 (t, *J* = 4.6 Hz, 1H), 2.63 (dd, *J* = 4.6, 2.7 Hz, 1H), 2.48 - 2.25 (m, 3H), 2.10 - 1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.6, 56.0, 54.7, 44.9, 29.7, 23.8; HRMS (MALDI): Calcd. for $C_6H_{11}KNO_3$ 184.0371 $[M + H_2O + K]^+$, found 184.0469.

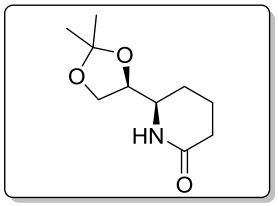
Synthesis of (*R*)-ethyl 5-(dibenzylamino)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-ynoate 49 ($C_{26}H_{31}NO_4$).



To a solution of **40** (4 g, 11.9 mmol) in CH_3CN (40 mL) were added ethyldiazoacetate (1.62 g, 14.2 mmol) and CuI (112 mg, 0.59 mmol, 5 mol%). The reaction mixture was stirred for 12 h at room temperature. Then crude reaction mixture was concentrated in vacuo and subsequently filtered through a short the pad of silica by eluting with Et_2O. The filtrate was further concentrated *in vacuo*. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% EtOAc in petroleum ether) to furnish **49** (4.72 g, 94%) as pale yellow oil. IR (KBr) ν (cm^{-1}): 2984, 17.44, 1560, 1495, 1370, 1258, 1072, 1028; $[\alpha]_D^{25}$ = -70.50 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.3 Hz, 4H), 7.28 (t , *J* = 7.6 Hz, 4H), 7.20 (t, *J* = 8.0 Hz, 2H), 4.28 - 4.19 (m, 3H), 4.00 (dd, *J* = 8.2,6.4 Hz, 1H), 3.89 - 3.84 (m, 3H), 3.58 (dt, *J* = 7.3, 2.3 Hz, 1H), 3.47 (d, *J* = 13.7 Hz, 2H), 3.35 (d, *J* = 2.3 Hz, 2H), 1.34 - 1.21 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (100

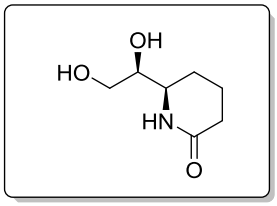
MHz, $CDCl_3$) δ (ppm): 168.4, 139.6 (2C), 128.9 (4C), 128.3 (4C), 127.0 (2C), 109.8, 78.4, 78.3, 76.4, 67.4, 61.7, 55.5 (3C), 26.6, 26.3, 25.6, 14.3; HRMS (ESI) Calcd. for $C_{26}H_{31}NO_4Na$, 444.2151 $[M + Na]^+$, found 444.2150.

Synthesis of (*R*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)piperidin-2-one 39b ($C_{10}H_{17}NO_3$).



To a solution of **49** (6.30 g, 14.9 mmol) in ethanol (60 mL) placed in a par apparatus was added 10% $Pd(OH)_2/C$ (2.09 g, 1.49 mmol) and subsequently stirred under 100 psi H_2 pressure at room temperature for 24 h. The reaction mixture was filtered through the small celite pad. To the resulting filtrate was added NaOEt (1.01 g, 14.9 mmol) and refluxed for 2 h. The reaction mixture was dried under reduced pressure and re-dissolved in EtOAc (30 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to afford **39b** (2.36 g, 81% over 2 steps) as yellow oil. IR (KBr) ν (cm^{-1}): 3322, 2994, 2858, 1659, 1463, 1378, 1292, 1221, 1160, 1085, 1031; $[\alpha]_D^{25}$ = - 14.4 (*c* = 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.20 (br s, 1H), 4.04 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.85 - 3.89 (m, 1H), 3.66 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.32 – 3.29 (td, *J* = 9.2, 4.6 Hz, 1H), 2.45 - 2.38 (m, 1H), 2.30 - 2.27 (m, 1H), 1.94 - 1.91 (m, 1H), 1.76 - 1.68 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.33 - 1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.7, 109.9, 79.2, 66.3, 56.3, 31.4, 26.9, 25.4, 24.9, 19.8; HRMS (ESI) Calcd. for $C_{10}H_{17}NO_3Na$ 222.1106 $[M + Na]^+$, found 222.1106.

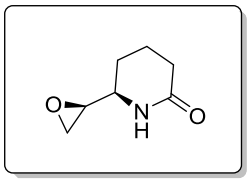
Synthesis of (*R*)-6-((*S*)-1,2-dihydroxyethyl)piperidin-2-one 50 ($C_7H_{13}NO_3$).



To a solution of **39b** (2.10 g, 199.08 mmol) in EtOH (20 mL) was added 2 M HCl (5 mL) and the mixture was stirred for 2 h at room temperature. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 20% MeOH in $CHCl_3$) to afford **50** (1.58 g, 94%) as colorless oil. IR (KBr) ν (cm^{-1}): 3291,

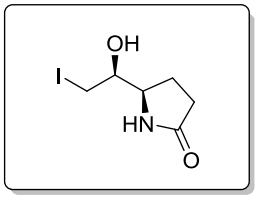
3205, 2911, 1646, 1473, 1404, 1309, 1167, 1028, 955; $[\alpha]_D^{25}$ = + 4.40 (*c* = 0.4, MeOH); ^{1}H NMR (500 MHz, DMSO-D_6) δ (ppm): 6.62 (br s, 1H), 4.88 (d, *J* = 5.3 Hz, 1H), 4.56 (t, *J* = 5.5 Hz, 1H), 3.44 - 3.40 (m, 1H), 3.36 - 3.31 (m, 1H), 3.24 - 3.19 (m, 2H), 2.09 - 2.00 (m, 2H), 1.72 (t, *J* = 5.4 Hz, 1H), 1.55 - 1.44 (m, 1H), 1.35 - 1.28 (m, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ (ppm): 171.1, 74.4, 63.4, 55.0, 31.7, 25.1, 20.2; HRMS (ESI) Calcd. for $C_7H_{13}NO_3Na$ 182.0793 $[M + Na]^+$, found 182.0797.

Synthesis of (*R*)-6-((*S*)-oxiran-2-yl)piperidin-2-one 38b ($C_7H_{11}NO_2$).



To a solution of **50** (830 mg, 5.22 mmol) in anhydrous $CHCl_3$ (20 mL) were added PPh_3 (1.51 g, 5.74 mmol) and DIAD diisopropylazodicarxylate (1.16 g, 5.74 mmol). The reaction mixture was refluxed for 24 h. The reaction mixture was allowed to come to the room temperature and solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to afford **38b** (604 mg, 82%) as colorless oil. IR (KBr) ν (cm^{-1}): 2950, 1645, 1473, 1395, 1302, 1175, 919; $[\alpha]_D^{25}$ = - 30.80 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.50 (br s, 1H), 3.08 - 3.03 (m, 1H), 2.94 - 2.91 (m, 1H), 2.82 (t, *J* = 4.6 Hz, 1H), 2.62 (dd, *J* = 4.6, 2.3 Hz, 1H), 2.43 - 2.27 (m, 2H), 1.98 - 1.88 (m, 2H), 1.76 - 1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.1, 55.8, 55.1, 45.2, 31.4, 25.1, 19.5; HRMS (ESI) Calcd. for $C_7H_{11}NO_2Na$ 164.0687 $[M + Na]^+$, found 164.0685.

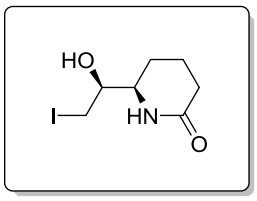
Synthesis of (*R*)-5-((*S*)-1-hydroxy-2-iodoethyl)pyrrolidin-2-one 51a ($C_6H_{10}INO_2$).



To the solution of the epoxide **38a** (252 mg, 1.97 mmol) in THF (8 mL) was added to CuI (74 mg, 0.39 mmol) and methylmagnesium iodide (655 mg in 8 mL in Et_2O, 3.94 mmol) at -30 °C during 15 min. The reaction mixture was allowed to warm to 0 °C, stirred for 2.5 h. After completion, the reaction mixture was quenched by addition of NH_4Cl (20 mL). Compound was extracted in CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The dried mass was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish the pure **51a** (268 mg, 53%) as white solid. Mp. 124–126 °C; IR (KBr) ν (cm^{-1}): 3862, 3300, 3161, 1660, 1411, 1188, 1041;

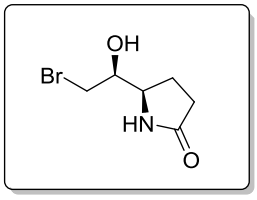
$[\alpha]_D^{25}$ = - 19.25 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-D_6) δ (ppm): 7.6 (br s, 1H), 5.41 (d, *J* = 5.5 Hz, 1H), 3.61 (dt, *J* = 8.2, 4.5 Hz, 1H), 3.36 (dt, *J* = 11.4, 5.1 Hz, 1H), 3.30 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.17 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.15 - 1.97 (m, 3H), 1.80 - 1.72 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 177.0, 73.6, 57.5, 30.3, 23.6, 12.0 ; HRMS (ESI) Calcd. for $C_6H_{10}INO_2Na$ 277.9653 $[M + Na]^+$, found 277.9653.

Synthesis of (*R*)-6-((*S*)-1-hydroxy-2-iodoethyl)piperidin-2-one 51b ($C_7H_{12}INO_2$).



To the solution of the epoxide **38b** (100 mg, 0.71 mmol) in THF (8 mL) was added to CuI (27 mg, 0.14 mmol) and methylmagnesium iodide (236 mg in 8 mL in Et_2O, 1.42 mmol) at -30 ºC during 15 min. The reaction mixture was allowed to warm to 0 ºC, stirred for 2.5 h. After completion, the reaction mixture was quenched by addition of NH_4Cl (20 mL). Compound was extracted in CH_2Cl_2 (2 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The dried mass was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish the pure **51b** (107 mg, 56%) as white solid. Mp. 117–119 ºC; IR (KBr) ν (cm^{-1}): 3402, 3198, 2945, 1636, 1541, 1339, 1263, 1168, 1036; $[\alpha]_D^{25}$ = + 9.25 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.93 (br s, 1H), 3.48 – 3.26 (m, 3H), 3.25 – 3.14 (m, 2H), 2.48 – 2.38 (m, 1H), 2.33 – 2.18 (m, 1H), 2.00 – 1.88 (m, 2H), 1.36 – 1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.1, 73.2, 57.6, 31.1, 24.8, 19.7, 11.1; HRMS (ESI) Calcd. for $C_7H_{12}INO_2Na$ 291.9810 $[M + Na]^+$, found 291.9811.

Synthesis of (*R*)-5-((*S*)-2-bromo-1-hydroxyethyl)pyrrolidin-2-one 51c ($C_6H_{10}BrNO_2$).



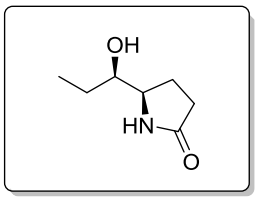
To the solution of the epoxide **38a** (50mg, 0.394 mmol) in THF (6 mL) was added to CuI (15 mg, 0.08 mmol) and methylmagnesium bromide [3.0 M in Et_2O] (0.26 mL, 0.79 mmol) at -30 ºC during 15 min. The reaction mixture allowed to warm to 0 ºC, stirred for 2.5 h. After completion, the reaction mixture was quenched by addition of NH_4Cl (10 mL). Compound was extracted in CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The dried mass was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish the pure **51c** (43 mg, 53%) as white solid. Mp. 135 – 136

^{o}C; IR (KBr) ν (cm^{-1}): 3315, 3212, 2924, 1666, 1459, 1382, 1286, 1181, 1060, 950; $[\alpha]_D^{25}$ = - 16.4 (*c* = 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 3.85- 3.80 (m, 1H), 3.65 – 3.60 (m, 1H), 3.47 (dd, *J* = 14.6, 8.9, 1H), 3.38 (dd, *J* = 10.7, 6.7, 1H), 2.41 – 2.32 (m, 1H), 2.29 – 2.18 (m, 2H), 1.93 – 1.88 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 180.2, 73.8, 57.2, 33.9, 29.9, 23.3; HRMS (ESI) Calcd. for $C_6H_{11}BrNO_2$ 207.9973 $[M + H]^+$, found 207.9973.

General procedure for opening of epoxide Gilman reagent.

Method B: To a suspension of CuI (5.00 mmol) in dry Et_2O (20 mL) placed at -35 ^{o}C, was added dropwise BuLi (10.00 mmol, 1.6 M in hexane). To the suspension was added dropwise the solution of either of the epoxides **38a** and **38b** (1.00 mmol) in dry THF (4.5 mL) and the mixture was stirred for an additional 2 h at same temperature. The reaction mixture was carefully quenched at -35 ^{o}C with saturated NH_4Cl (15 mL). The reaction mixture was allowed to room temperature with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated *in vacuo*. The dried mass was subjected to column chromatography over silica gel to furnish the pure lactam **52a**-**52d**, **54a**-**54d**.

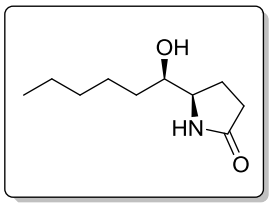
Synthesis of (*R*)-5-((*R*)-1-hydroxypropyl)pyrrolidin-2-one 52a ($C_7H_{13}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding MeLi (1.6 M) in pentane (11 mL, 17.30 mmol) to a suspension of CuI (1.64 g, 8.66 mmol) in dry Et_2O (40 mL) at -35 ^{o}C. Opening of the epoxide was carried out by adding a solution of **38a** (220 mg, 1.73 mmol) in dry THF (6 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **52a** (191 mg, 77%) as colorless oil. IR (KBr) ν (cm^{-1}): 3266, 2930, 1670, 1459, 1417, 1270, 1122, 1078, 1042; $[\alpha]_D^{25}$ = - 30.0 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO) δ (ppm): 7.44 (br s, 1H), 4.59 (d, *J* = 5.6 Hz, 1H), 3.34 (dt, *J* = 7.4, 5.1 Hz, 1H), 3.08 (dt, *J* = 9.0, 5.3 Hz, 1H), 2.04 – 1.89 (m, 3H), 1.70 – 1.62 (m, 1H), 1.35 – 1.28 (m, 1H), 1.25 – 1.16 (m, 1H), 0.82

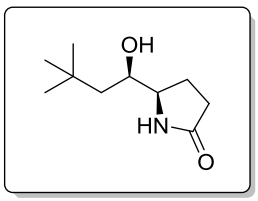
(t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 179.3, 76.6, 59.6, 30.7, 26.3, 23.8, 10.0; HRMS (ESI) Calcd. For $C_7H_{13}NO_2Na$ 166.0844 $[M + H]^+$, found 166.0844.

Synthesis of (*R*)-5-((*R*)-1-hydroxyhexyl)pyrrolidin-2-one 52b ($C_{10}H_{19}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding BuLi (1.6 M) in hexane (15.0 mL, 23.6 mmol) to a suspension of CuI (2.24 g,11.8 mmol) in dry Et_2O (40 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38a** (300 mg, 2.36 mmol) in dry THF (5 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **52b** (332 mg, 76%) as white solid. Mp. 60–62 ^oC; IR (KBr) ν (cm^{-1}): 3417, 3221, 2931, 1685, 1457, 1363, 1270, 1133, 1072, 1057; $[\alpha]_D^{25}$ = - 9.75 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.54 (br s, 1H), 3.52 (q, *J* = 7.1 Hz, 1H), 3.42 – 3.33 (m, 1H), 2.70 – 2.58 (m, 1H), 2.39 – 2.28 (m, 2H), 2.21 – 2.09 (m, 1H), 1.82 – 1.74 (m, 1H), 1.56 – 1.41 (m, 2H), 1.41 – 1.20 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 179.1, 75.3, 59.9, 33.4, 31.9, 30.7, 25.2, 23.9, 22.7, 14.1; HRMS (ESI) Calcd. for $C_{10}H_{20}NO_2$ 186.1415 $[M + H]^+$, found 186.1415.

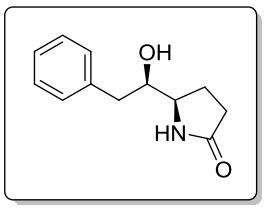
Synthesis of (*R*)-5-((*R*)-1-hydroxy-3,3-dimethylbutyl)pyrrolidin-2-one 52c ($C_{10}H_{19}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding ^{t}BuLi (1.6 M) in pentane (14.8 mL, 23.6 mmol) to a suspension of CuI (2.24 g,11.8 mmol) in dry Et_2O (40 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38a** (300 mg, 2.36 mmol) in dry THF (8 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **52c** (315 mg, 72%) as white solid. Mp. 100–102 ^oC; IR (KBr) ν (cm^{-1}): 3364, 3274, 2950, 1683, 1633, 1363, 1283, 1094, 1070, 102; $[\alpha]_D^{25}$ = - 0.80 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (br s, 1H), 3.47 – 3.44 (m, 2H), 3.41 – 3.17 (m, 1H), 2.36 – 2.31 (m,

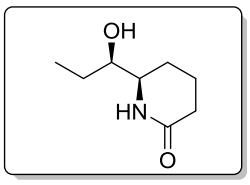
2H), 2.16 – 2.07 (m, 1H), 1.72 – 1.66 (m, 1H), 1.34 – 1.23 (m, 2H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 179.3, 73.1, 60.8, 46.9, 30.7, 30.2, 30.1 (3C), 23.9; HRMS (ESI) Calcd. $C_{10}H_{20}NO_2$ 186.1415 $[M + H]^+$, found 186.1415.

Synthesis of (*R*)-5-((*R*)-1-hydroxy-2-phenylethyl)pyrrolidin-2-one 52d ($C_{12}H_{15}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding PhLi (1.6 M) in pentane (14.8 mL, 23.6 mmol) to a suspension of CuI (2.24 g,11.8 mmol) in dry Et_2O (40 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38a** (300 mg, 2.36 mmol) in dry THF (8 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **52d** (329 mg, 68%) as white solid. Mp. 138–140 ^oC; IR (KBr) ν (cm^{-1}): 3377, 3258, 2917, 2852, 1631, 1636, 1494, 1311, 1266, 1101, 1067. $[\alpha]_D^{20}$ = - 30.30 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.31 (m, 2H), 7.28 – 7.26 (m, 1H), 7.24 - 7.21 (m, 2H), 6.54 (br s, 1H), 3.64 – 3.59 (m, 2H), 2.88 – 2.84 (m, 1H), 2.62 (dd, *J* = 13.8, 8.2 Hz, 1H), 2.55 (br d, *J* = 4.1 Hz, 1H), 2.41 – 2.36 (m, 2H), 2.27 – 2.20 (m, 1H), 1.92 – 1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 178.9, 137.5, 129.5 (2C), 128.8 (2C), 126.8, 76.1, 58.8, 40.1, 30.5, 23.9; HRMS (ESI) Calcd. for $C_{12}H_{15}NO_2Na$ 228.1000 $[M + Na]^+$, found 228.1009.

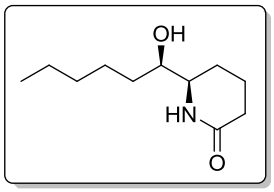
Synthesis of (*R*)-6-((*R*)-1-hydroxypropyl)piperidin-2-one 54a ($C_8H_{15}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding MeLi (1.6 M) in pentane (11 mL, 17.7 mmol) to a suspension of CuI (1.68 g, 8.85 mmol) in dry Et_2O (40 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38b** (250 mg, 1.77 mmol) in dry THF (7 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **54a** (203 mg, 73%) as colorless oil. IR (KBr) ν (cm^{-1}): 3384, 2958, 1645, 1487, 1416, 1323, 1166, 1090; $[\alpha]_D^{25}$ = + 3.8 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-D_6) δ (ppm): 6.76 (s, 1H), 4.88 (d, *J* = 5.5 Hz, 1H),

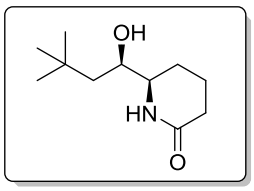
3.18 - 3.09 (m, 2H), 2.16 - 2.03 (m, 2H), 1.82 - 1.76 (m, 2H), 1.59 - 1.45 (m, 2H), 1.28 - 1.20 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-D_6) δ (ppm): 170.9, 74.9, 57.4, 31.7,25.5, 24.6, 20.1,10.4; HRMS (ESI) Calcd. for $[C_8H_{15}NO_2Na]^+$ 180.1000 $[M + Na]^+$, found 180.1004.

Synthesis of (*R*)-6-((*R*)-1-hydroxyhexyl)piperidin-2-one 54b ($C_{11}H_{21}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding BuLi (1.6 M) in hexane (9 mL, 14.2 mmol) to a suspension of CuI (1.36 g, 7.10 mmol) in dry Et_2O (30 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38b** (200 mg, 1.42 mmol) in dry THF (6 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **54b** (206 mg, 73%) as colorless solid. Mp. 70–72 ^oC; IR (KBr) ν (cm^{-1}): 3422, 2950, 1660, 1479, 1348, 1272, 1154, 1077, 1030; $[\alpha]_D^{25}$ = + 11.5 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.84 (br s, 1H), 3.62 – 3.58 (m, 1H), 3.32 (br s, 1H), 3.22 - 3.18 (m, 1H), 2.45 - 2.37 (m, 1H), 2.24 (ddd, *J* = 17.7, 12.0, 6.0 Hz, 1H), 1.93 - 1.87 (m, 2H), 1.77 (br s, 1H), 1.72 - 1.62 (m, 1H), 1.34 - 1.20 (m, 7H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7, 74.9, 57.7, 33.5, 31.9, 31.2, 25.1, 24.7, 22.6, 20.0, 14.1; ; HRMS (ESI) Calcd. for $C_{11}H_{21}NO_2$ $[M + Na]^+$ 222.1470, found 222.1475.

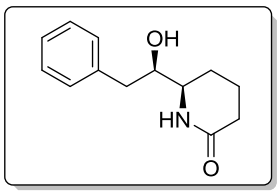
Synthesis of (*R*)-6-((*R*)-1-hydroxy-3,3-dimethylbutyl)piperidin-2-one 54c ($C_{11}H_{21}NO_2$).



Following the Method B, the Gilman reagent was prepared by adding tert-BuLi (1.6 M) in pentane (4.5 mL, 7.10 mmol) to a suspension of CuI (0.68 g, 3.55 mmol) in dry Et_2O (20 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38b** (100 mg, 0.71 mmol) in dry THF (5 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **54c** (106 mg, 75%) as white solid. Mp. 101–103 ^oC; IR (KBr) ν (cm^{-1}): 3270, 2950, 1669, 1623, 1363,

1374, 1230, 1166, 1072, 1021; $[\alpha]_D^{20}$ = + 26.50 (*c* = 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.81 (br s, 1H), 3.47 – 3.34 (m, 2H), 3.15 – 3.09 (m, 1H), 2.36 – 2.31 (m, 1H), 2.25 – 2.17 (m, 1H), 1.95 – 1.89 (m, 2H), 1.70 – 1.61 (m, 1H), 1.42 – 1.37 (m, 1H), 1.32 – 1.21 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 72.7, 58.2, 47.5, 31.3, 30.3, 30.2 (3C), 25.4, 20.0; HRMS (ESI) Calcd. for $C_{11}H_{21}NO_2$ 222.1470 $[M + Na]^+$, found 222.1470.

Synthesis of (*R*)-6-((*R*)-1-hydroxy-2-phenylethyl)piperidin-2-one 54d ($C_{13}H_{17}NO_2$).



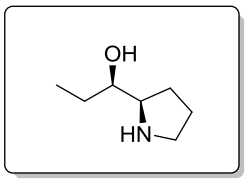
Following the Method B, the Gilman reagent was prepared by adding PhLi (1.6 M) in dibutyl ether (4.4 mL, 7.10 mmol) to a suspension of CuI (0.68 g, 3.55 mmol) in dry Et_2O (20 mL) at -35 ^oC. Opening of the epoxide was carried out by adding a solution of **38b** (100 mg, 0.71 mmol) in dry THF (5 mL) to the freshly prepared Gilman reagent and stirring for 2 h at the same temperature. The crude product was subjected to column chromatography over silica gel (*Eluent*: 4% MeOH in $CHCl_3$) to furnish **54d** (120 mg, 77%) as white solid. Mp. 105–106 ^oC; IR (KBr) ν (cm^{-1}): 3518, 2964, 2873, 1654, 1600, 1501, 1579, 1448, 1285, 1123, 1073; $[\alpha]_D^{25}$ = + 7.20 (*c* = 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (t, *J* = 7.3 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.22 - 7.18 (m, 2H), 6.62 (br s, 1H), 3.60 – 3.53 (m, 1H), 3.33 – 3.27 (m, 1H), 2.94 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.55 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.48 (d, *J* = 4.6 Hz, 1H), 2.43 – 2.35 (m, 1H), 2.24 (ddd, *J* = 17.8, 11.9, 6.2 Hz, 1H), 2.02 -1.92 (m, 2H), 1.76 – 1.64 (m, 1H), 1.44 – 1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.2, 137.1, 129.6 (2C), 129.0 (2C), 127.0, 75.8, 57.4, 40.0, 31.3, 25.2, 20.0; HRMS (ESI) Calcd. for $C_{13}H_{17}NO_2Na$ 242.1157 $[M + Na]^+$, found 242.1152.

General procedure for reduction of lactam by $LiAlH_4$.

Method C: To a suspension of $LiAlH_4$ (3.00 mmol) in dry THF (10 mL) placed at 0 ^oC was added a solution of either of the lactams **52a-52d**, **54a-24d** (1.00 mmol) in THF (5 mL) and the resulting mixture was stirred at reflux for 8 h. After cooling to 0 ^oC, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (8 mL). The crude product was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were

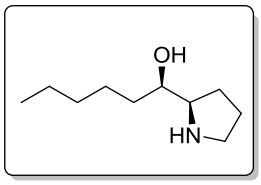
dried over Na_2SO_4 and concentrated under vacuum. The dried mass was subjected to column chromatography over silica gel to furnish the pure lactam **53a-53d**, **8a, 55b-55d**.

Synthesis of (*R*)-1-((*R*)-pyrrolidin-2-yl)propan-1-ol 53a ($C_7H_{15}NO$).



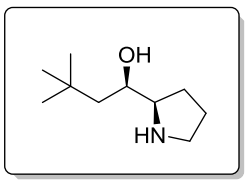
Following the Method C, reaction of **52a** (160 mg, 1.12 mmol) with $LiAlH_4$ (127 mg, 3.36 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **53a** (117 mg, 81%) as yellow oil. IR (KBr) ν (cm^{-1}): 3447, 2962, 2923, 1460, 1370, 1267, 1052, 1027; $[\alpha]_D^{25}$ = + 4.0 (*c* = 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.35 (br s, 1H), 3.83 (br s, 1H), 3.62 – 3.55 (m, 1H), 3.39 – 3.35 (m, 2H), 2.14 – 1.93 (m, 3H), 1.75 – 1.63 (m, 1H), 1.62- 1.49 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 72.6, 65.3, 45.0, 27.6, 27.5, 24.4, 9.8; HRMS (ESI) Calcd. for $C_7H_{15}NO$ 130.1232 $[M + H]^+$, found 130.1230.

Synthesis of (*R*)-1-((*R*)-pyrrolidin-2-yl)hexan-1-ol 24b ($C_{10}H_{21}NO$).



Following the Method C, reaction of **52b** (150 mg, 0.810 mmol) with $LiAlH_4$ (92 mg, 2.43 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **53b** (119 mg, 86%) as yellow oil. IR (KBr) ν (cm^{-1}): 3586, 3372, 2933, 1470, 1381, 1139, 1071, 1021. $[\alpha]_D^{25}$ = + 4.1 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.86 (td, *J* = 9.2, 3.6 Hz, 1H), 3.54 (q, *J* = 9.2 Hz, 1H), 3.26 (t, *J* = 7.8 Hz, 2H), 2.12 – 1.91 (m, 3H), 1.73 – 1.63 (m, 4H), 1.53- 1.35 (m, 4H), 1.39 – 1.23 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 71.4, 65.7, 45.0, 34.5, 31.8, 27.7, 25.0, 24.4, 22.7, 14.2; HRMS (ESI) Calcd. for $C_{10}H_{21}NO$ 172.1701 $[M + H]^+$, found 172.1706.

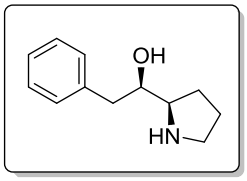
Synthesis of (*R*)-3,3-dimethyl-1-((*R*)-pyrrolidin-2-yl)butan-1-ol 53c ($C_{10}H_{21}NO$).



Following the Method C, reaction of **52c** (150 mg, 0.81 mmol) with $LiAlH_4$ (92 mg, 2.43 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$)

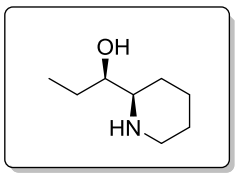
provided **53c** (116 mg, 84%) as pale yellow oil. IR (KBr) ν (cm^{-1}): 3301, 2951, 2858, 1478, 1370, 1181, 1081, 1021; $[\alpha]_D^{25}$ = + 5.4 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.95 (t, *J* = 9.0 Hz, 1H), 3.59 - 3.50 (m, 1H), 3.40 - 3.36 (m, 2H), 2.10 – 1.98 (m, 3H), 1.71 – 1.62 (m, 1H), 1.51 (dd, *J* = 14.4, 9.2 Hz, 1H), 1.31 - 1.20 (m, 1H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 69.5, 66.2, 48.0, 45.2, 30.5, 30.2 (3C), 28.0, 24.4; HRMS (ESI) Calcd. for $C_{10}H_{21}NO$ 172.1701 $[M + H]^+$, found 172.1703.

Synthesis of (*R*)-2-phenyl-1-((*R*)-pyrrolidin-2-yl)ethanol 53d ($C_{12}H_{17}NO$).



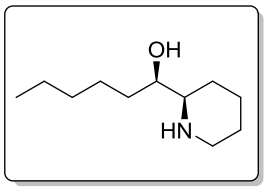
Following the Method C, reaction of **52d** (120 mg, 0.58 mmol) with $LiAlH_4$ (102 mg, 1.74 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **53d** (81 mg, 72%) as colorless oil. IR (KBr) ν (cm^{-1}): 3410, 3238, 2921, 1605, 1498, 1370, 1280, 1132, 1042; $[\alpha]_D^{25}$ = + 3.3 (*c* = 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.23 – 7.15 (m, 5H), 3.87 (td, *J* = 8.2, 3.6 Hz, 1H), 3.35 (q, *J* = 9.2 Hz, 1H), 3.09- 3.04 (m, 2H), 2.74 (dd, *J* = 13.7, 3.2 Hz, 1H), 2.68 – 2.62 (m, 1H), 1.89- 1.82 (m, 2H), 1.81 – 1.73 (m, 1H), 1.59 – 1.50 (m, 1H), 1.27 – 1.23 (m, 1H): ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.1, 129.7 (2C), 128.4 (2C), 126.4, 72.8, 64.1, 45.4, 41.1, 28.0, 25.0; HRMS (ESI) Calcd. for $C_{12}H_{18}NO$ 192.1388 $[M + H]^+$, found 192.1384.

Synthesis of Synthesis of (+)-β-conhydrine (8a).



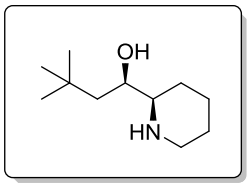
Following the Method C, reaction of **54a** (150 mg, 0.95 mmol) with $LiAlH_4$ (108 mg, 2.86 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided (+)-β-conhydrine **8** (107 mg, 78%) as colorless oil. IR (KBr) ν (cm^{-1}): 3447, 3326, 2965, 2855, 1467, 1392, 1128, 1030; $[\alpha]_D^{25}$ = + 7.1 (*c* = 0.6, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.24 - 3.20 (m, 1H), 3.11 - 3.07 (m, 2H), 2.57 (t, *J* = 10.3 Hz, 1H), 2.36 (t, *J* = 7.5 Hz, 1H), 1.78 – 1.76 (m, 1H), 1.65 – 1.52 (m, 3H), 1.39 – 1.29 (m, 3H), 1.78 – 1.09 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 72.6, 62.9, 45.4, 26.5, 25.4, 22.6, 22.3, 9.8; HRMS (ESI) Calcd. for $C_8H_{18}NO$ 144.1388 $[M + H]^+$, found 144.1380.

Synthesis of (*R*)-1-((*R*)-piperidin-2-yl)hexan-1-ol 55b ($C_{11}H_{23}NO$).



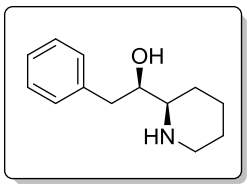
Following the Method C, reaction of **54b** (180 mg, 0.90 mmol) with $LiAlH_4$ (102 mg, 2.71 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **55b** (122 mg, 73%) as colorless oil. IR (KBr) ν (cm^{-1}): 3404, 2932, 2856, 1458, 1331, 1306, 1130, 1115, 1054; $[\alpha]_D^{25}$ = + 12.9 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.28 (td, *J* = 7.8, 1.8 Hz, 1H), 3.10 - 3.05 (m, 1H), 2.81 - 2.56 (br s, 1H), 2.57 (dt, *J* = 11.7, 2.7 Hz, 1H), 2.34 (ddd, *J* = 10.6, 7.7, 2.7 Hz, 1H), 1.81 - 1.73 (m, 1H), 1.67 - 1.56 (m, 2H), 1.50 - 1.43 (m, 2H), 1.34 - 1.26 (m, 8H), 1.17 – 1.08 (m, 1H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 74.0, 61.4, 46.4, 33.7, 32.0, 29.1, 26.2, 25.5, 24.4, 22.7, 14.2; HRMS (ESI) Calcd. For $C_{11}H_{23}NO$ 186.1858 $[M + H]^+$, found 186.1858.

Synthesis of (*R*)-3,3-dimethyl-1-((*R*)-piperidin-2-yl) butan-1-ol 55c ($C_{11}H_{23}NO$).



Following the Method C, reaction of **54c** (50 mg, 0.25 mmol) with $LiAlH_4$ (57 mg, 1.50 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **55c** (36 mg, 77%) as colorless oil. IR (KBr) ν (cm^{-1}): 3439, 3161, 2954, 1480, 1448, 1363, 1223, 1117, 1052; $[\alpha]_D^{25}$ = + 14.8 (*c* = 0.75, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 3.43 (td, *J* = 7.7, 2.5 Hz, 1H), 3.14 - 3.07 (m, 2H), 2.57 (dt, *J* = 11.5, 3.0 Hz, 1H), 2.26 (ddd, *J* = 10.6, 7.9, 2.7 Hz, 1H), 1.81 - 1.42 (m, 4H), 1.41 - 1.19 (m, 4H), 1.19 - 1.08 (m, 1H), 0.97 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 72.0, 62.8, 48.4, 47.0, 31.0 (3C), 30.9, 29.7, 26.4, 25.0; HRMS (ESI) Calcd. for $C_{11}H_{24}NO$ 186.1858 $[M + H]^+$, found 186.1853.

Synthesis of (*R*)-2-phenyl-1-((*R*)-piperidin-2-yl)ethanol 55d ($C_{13}H_{19}NO$).



Following the Method C, reaction of **24d** (120 mg, 0.55 mmol) with $LiAlH_4$ (104 mg, 2.74 mmol) followed by purification by column chromatography over silica gel (*Eluent:* 30% MeOH in $CHCl_3$) provided **55d** (88 mg, 78%) as oil. IR (KBr) ν (cm^{-1}): 3415, 3290,

2933, 2851, 1599, 1495, 1424, 1306, 1298, 1120, 1042; $[\alpha]_D^{25}$ = + 16.4 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29 – 7.26 (m, 2H), 7.22 – 7.17 (m, 3H), 3.58 – 3.47 (m, 2H), 3.07 – 3.01 (m, 1H), 2.86 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.60 – 2.42 (m, 3H), 1.78 – 1.69 (m, 2H), 1.55- 1.53 (m, 1H), 1.38 – 1.18 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 139.4, 130.3 (2C), 129.1 (2C), 127.0, 75.5, 61.4, 46.8, 40.8, 29.2, 26.3, 24.7; HRMS (ESI) Calcd. for $C_{13}H_{20}NO$ 206.1545 $[M + H]^+$, found 206.1541.

2.7 Theoretical Calculation

The molecular geometries of **45** were fully optimized at a level of density functional theory employing the hybrid functional B3LYP [18] with Pople's basis set 6-311G(d,p) where polarization functions were added to all the atoms and diffuse functions to the heavy atoms. All the calculations were performed with the development version of Gaussian 03.[19]

Table 4: Atomic coordinates calculated for 45 from DFT B3LYP/6-311G(d,p) geometry optimization.

Atom #	Atom Type	x	y	z
1	C	2.198	-1.977	-1.666
2	C	0.766	-1.685	-1.171
3	C	0.546	-0.209	-0.991
4	O	0.750	-2.203	0.154
5	C	2.126	-2.577	0.537
6	O	2.935	-1.968	-0.460
7	C	2.228	-4.097	0.521
8	C	2.455	-1.961	1.880
9	N	-0.530	0.462	-1.188
10	C	0.585	2.531	-0.207
11	C	1.603	3.127	-0.960

12	C	2.711	3.685	-0.328
13	C	2.809	3.651	1.062
14	C	1.797	3.065	1.820
15	C	0.688	2.508	1.190
16	C	-0.618	1.943	-0.883
17	C	-2.857	-0.205	-0.589
18	C	-2.648	-1.019	0.530
19	C	-3.628	-1.114	1.513
20	C	-4.822	-0.405	1.385
21	C	-5.036	0.403	0.272
22	C	-4.054	0.506	-0.712
23	C	-1.815	-0.120	-1.684
24	H	2.230	-2.947	-2.172
25	H	2.611	-1.216	-2.330
26	H	0.005	-2.176	-1.776
27	H	1.387	0.342	-0.577
28	H	1.525	-4.527	1.235
29	H	2.001	-4.504	-0.466
30	H	3.240	-4.399	0.798
31	H	1.788	-2.355	2.648
32	H	3.483	-2.203	2.154
33	H	2.351	-0.876	1.837
34	H	1.522	3.172	-2.042
35	H	3.490	4.154	-0.917
36	H	3.668	4.092	1.554
37	H	1.865	3.054	2.902
38	H	-0.106	2.066	1.783
39	H	-0.809	2.420	-1.848
40	H	-1.515	2.051	-0.272

41	H	-1.726	-1.582	0.639
42	H	-3.463	-1.749	2.376
43	H	-5.585	-0.486	2.150
44	H	-5.964	0.951	0.165
45	H	-4.229	1.131	-1.582
46	H	-1.603	-1.096	-2.113
47	H	-2.155	0.530	-2.491

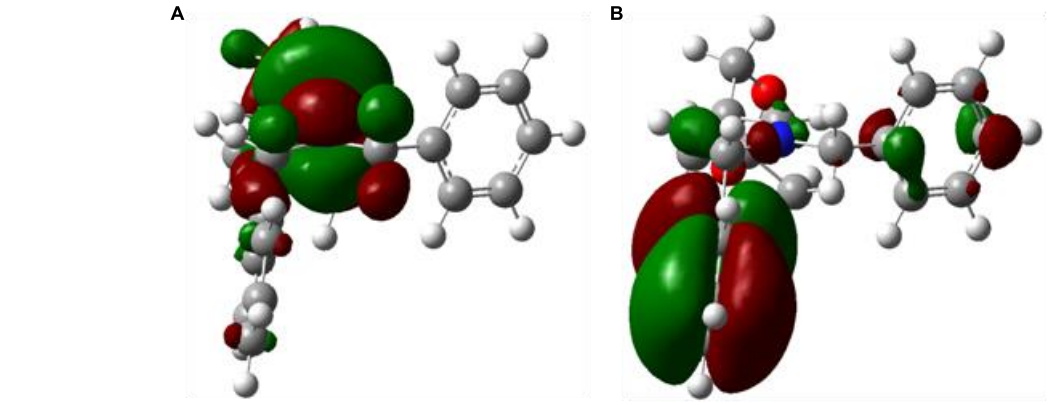


Figure 2.7:. View of the frontier molecular orbitals (MOs), HOMO (**A**) and LUMO (**B**) of the iminium cation **46** generated from DFT B3LYP/6-311G(d,p) geometry optimization.

2.8 Crystal Structures

Single-crystal X-ray diffraction analysis. Single crystals of **44c**, **51a**, **52d** and **55b** suitable for X-ray diffraction study were grown as mentioned below. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336033).

Crystal structure of compound 44c (CCDC 861123): Compound **44c** was crystallized from ethyl acetate / chloroform (1:1) at 25 ^{o}C. A colorless rectangular shaped crystal with approximate dimensions 0.09 x 0.07 x 0.08 mm gave an Monoclinic with space group $P4_3$;

a = 13.877 (5) *b* = 13.877 (5) *c* = 12.453 (5) Å, α = 90º β = 90º γ = 90º; *V* = 2398.09 ; *T* = 296 (2) K; *Z* = 4; ρ_{calc} = 1.084 Mgm^{-3}; $2\theta_{max}$ = 56.74º; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0368 (for 2459 reflection *I>2σ(I)*), *wR* = 0.1046 which was refined against ǀ*F2*ǀ and S = 0.855 for 268 parameters and 4900 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S20] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.067 mm^{-1}; Minimum/maximum residual electron density 0.171 / -0.157 eÅ^{-3}.

Crystal structure of compound 51a (CCDC 856727): Compound **51a** was crystallized from chloroform at 25 ºC. A colorless needle shaped crystal with approximate dimensions 0.09 x 0.08 x 0.07 mm gave an monoclinic with space group C2; *a* = 24.717 (2) *b* = 4.8349 (4) *c* = 15.6744 (13) Å, α = 90º β = 113.833º γ = 90º; *V* = 1713.4 (2); *T* = 296 (2) K; *Z* = 2; ρ_{calc} = 2.009 Mgm^{-3}; $2\theta_{max}$ = 56.74º; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0300 (for 2729 reflection *I>2σ(I)*), *wR* = 0.0716 which was refined against ǀ*F2*ǀ and S = 0.904 for 188 parameters and 3078 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S20] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 3.688 mm^{-1}; Minimum/maximum residual electron density 0.659 / -0.853 eÅ^{-3}.

Crystal structure of compound 52d (CCDC 859884): Compound **52d** was crystallized from ethyl acetate and chloroform (1:1) at 25 ºC. A colorless rectangular shaped crystal with approximate dimensions 0.14 x 0.13 x 0.12 mm gave an Triclinic with space group

$P2_12_12_1$; a = 5.4457 (9) b = 8.3138 (13) c = 23.660 (4) Å, α = 90° β = 90° γ = 90°; V = 1071.2 (3); T = 296 (2) K; Z = 4; ρ_{calc} = 1.273 Mgm^{-3}; $2\theta_{max}$ = 57.04°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0396 (for 2361 reflection $I>2\sigma(I)$), wR = 0.1059 which was refined against $|F2|$ and S = 1.064 for 138 parameters and 2731 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S20] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.087 mm^{-1}; Minimum/maximum residual electron density 0.168 / -0.221 $eÅ^{-3}$.

Crystal structure of compound 55b (CCDC 865442): Compound **55b** was crystallized from chloroform at 25 °C. A colorless needle shaped crystal with approximate dimensions 0.8 x 0.7 x 0.7 mm gave an Monoclinic with space group $P2_1$; a = 5.1574 (8) b = 7.2509 (11) c = 15.552 (3) Å, α = 90° β = 94.590 (3) ° γ = 90°; V = 579.714 (3); T = 296 (2) K; Z = 2; ρ_{calc} = 1.142 Mgm^{-3}; $2\theta_{max}$ = 56.82°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0361 (for 2329 reflection $I>2\sigma(I)$), wR = 0.0892 which was refined against $|F2|$ and S = 1.082 for 130 parameters and 2657 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S20] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.077 mm^{-1}; Minimum/maximum residual electron density 0.112 / -0.097 $eÅ^{-3}$.

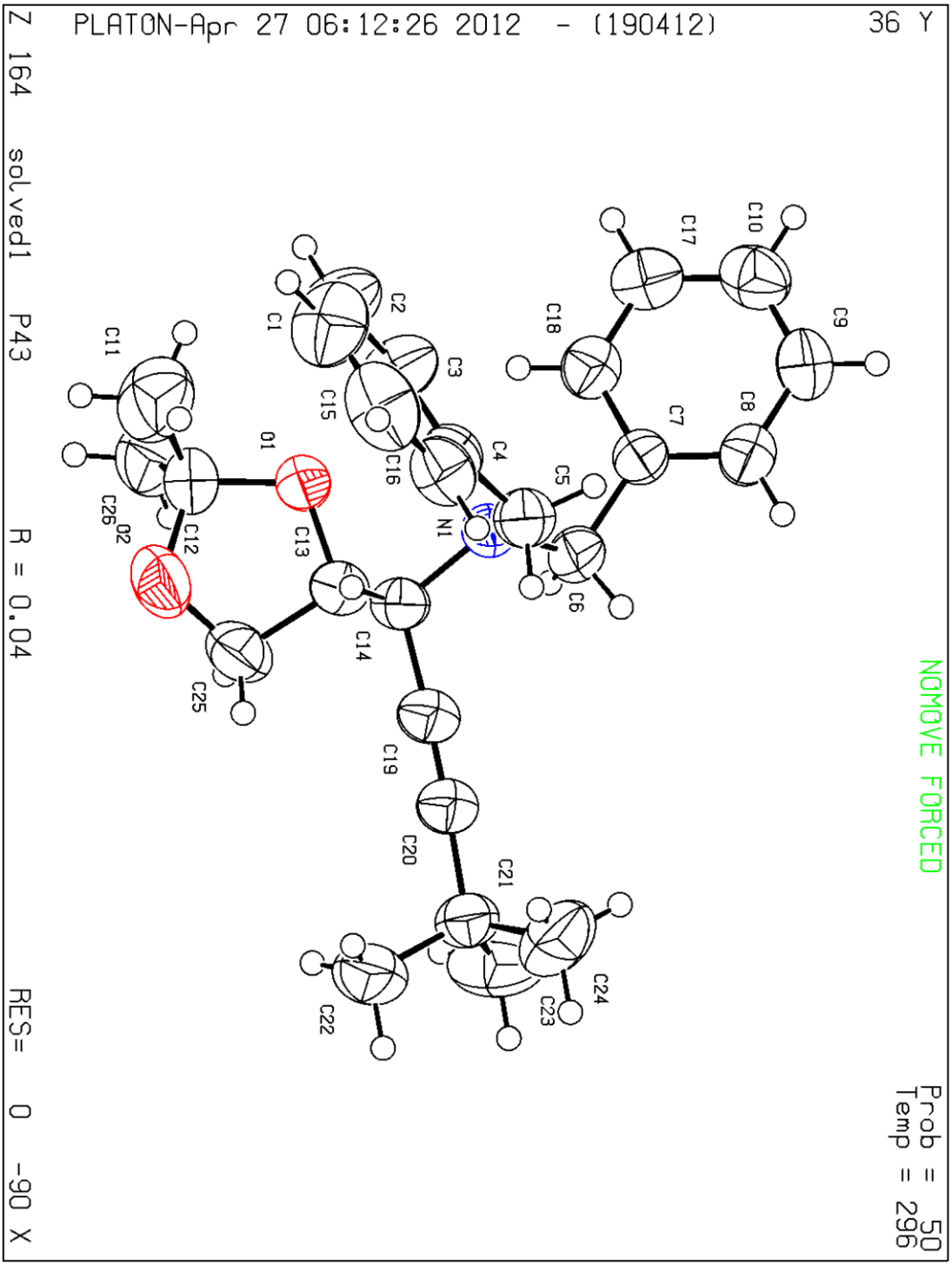


Figure 2.8 ORTEP diagram of **44c.**

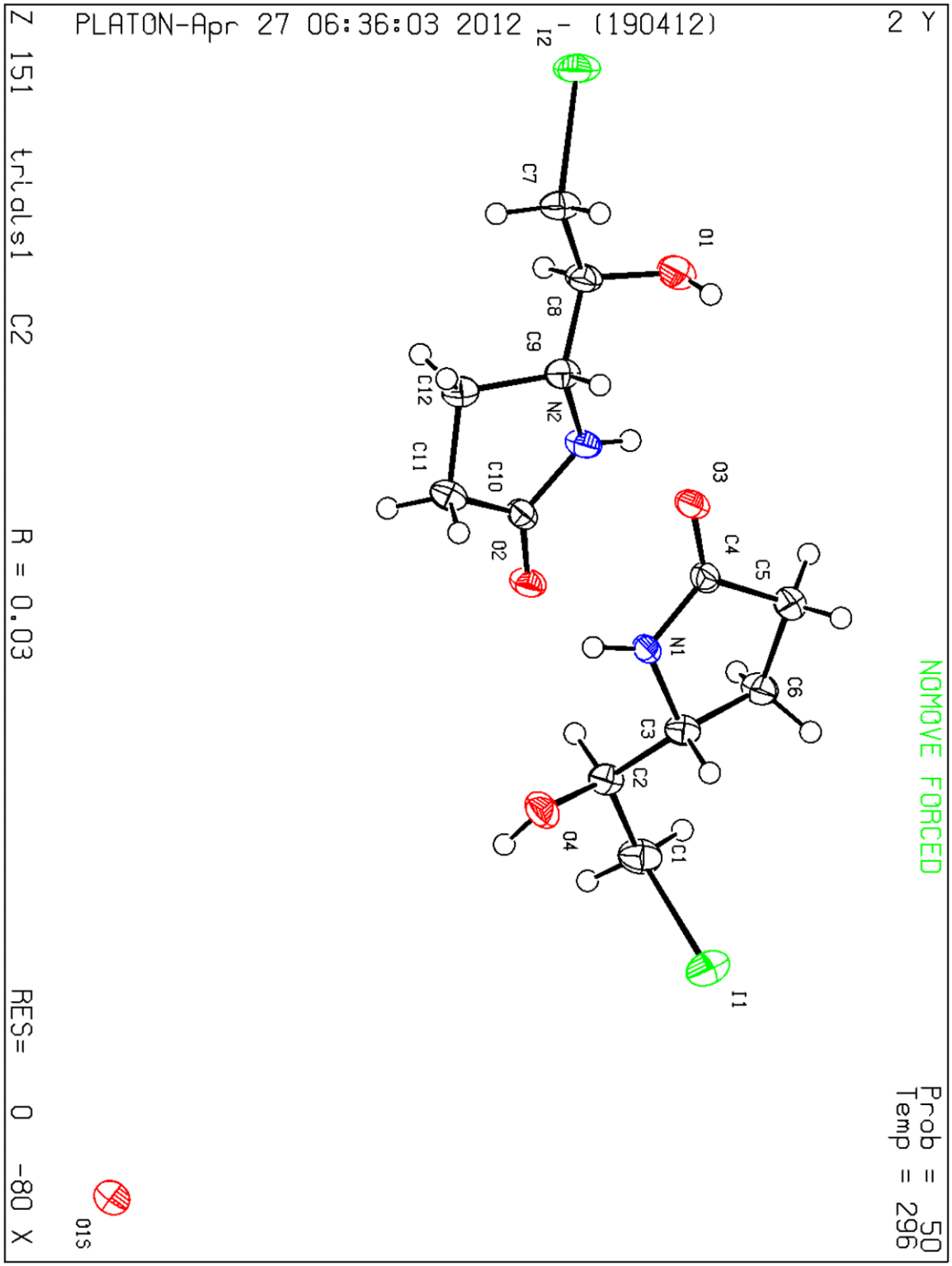


Figure 2.9 ORTEP diagram of **51a.**

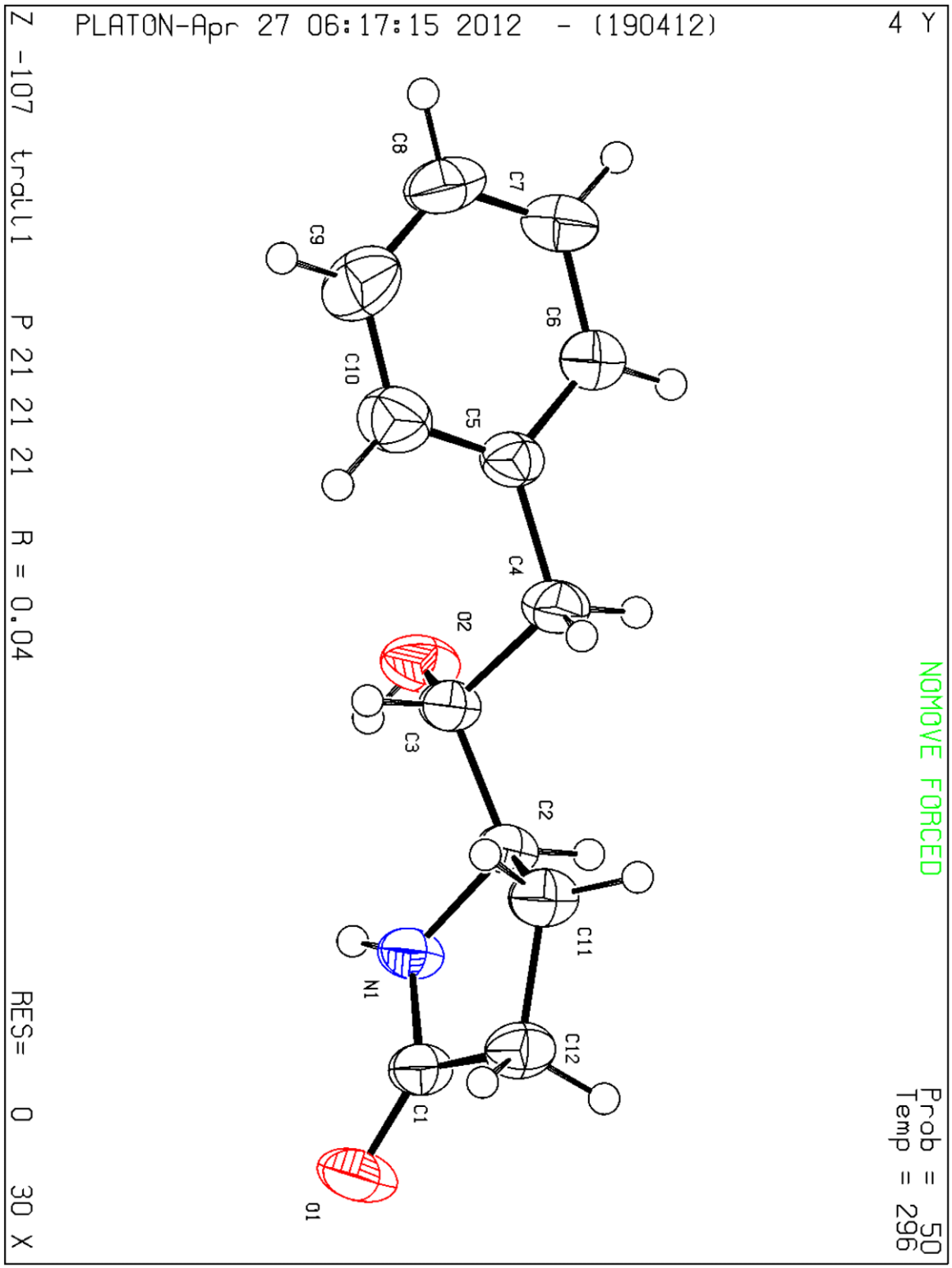


Figure 2.10 ORTEP diagram of **52d.**

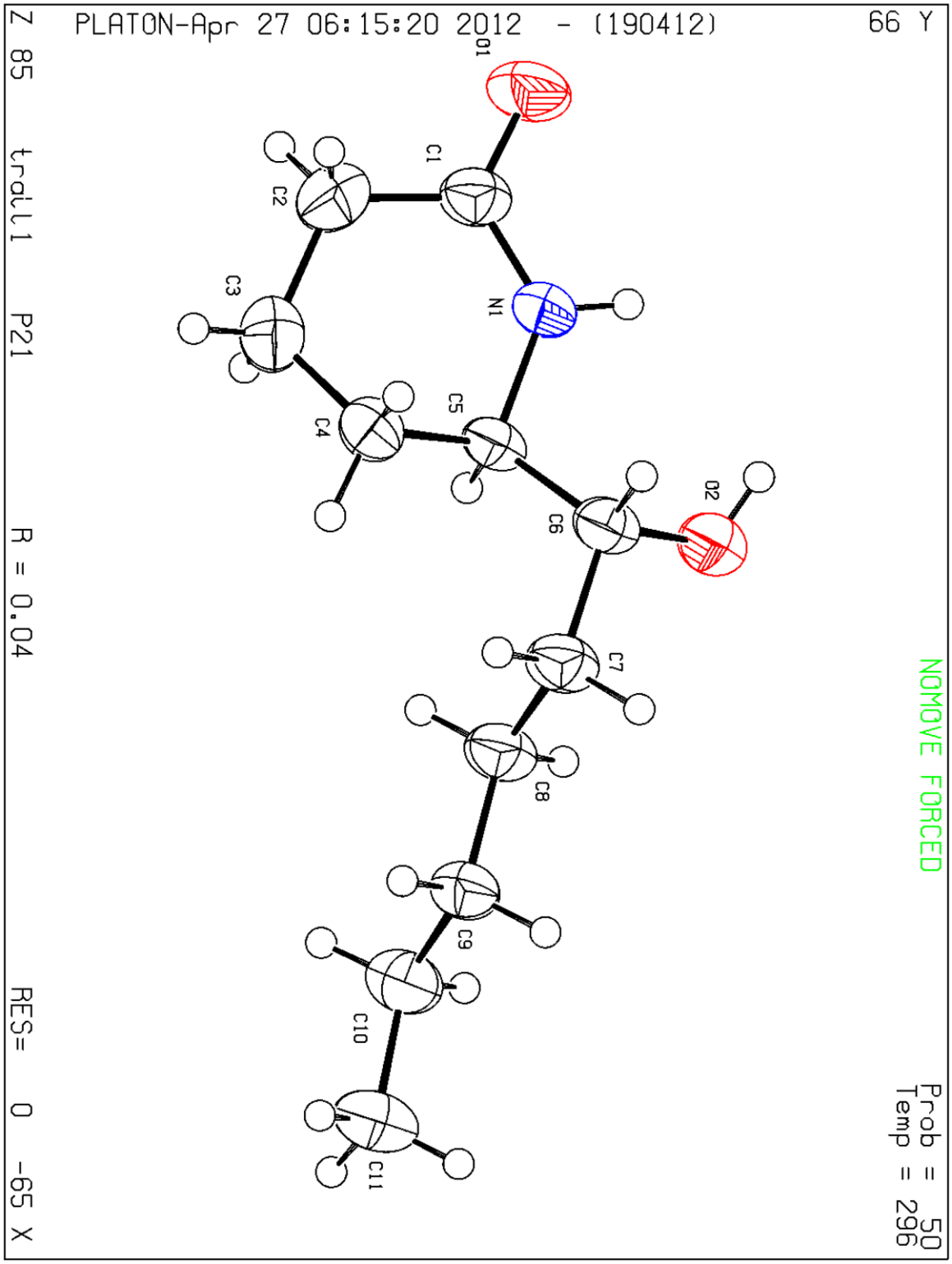


Figure 2.11 ORTEP diagram of **55b.**

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

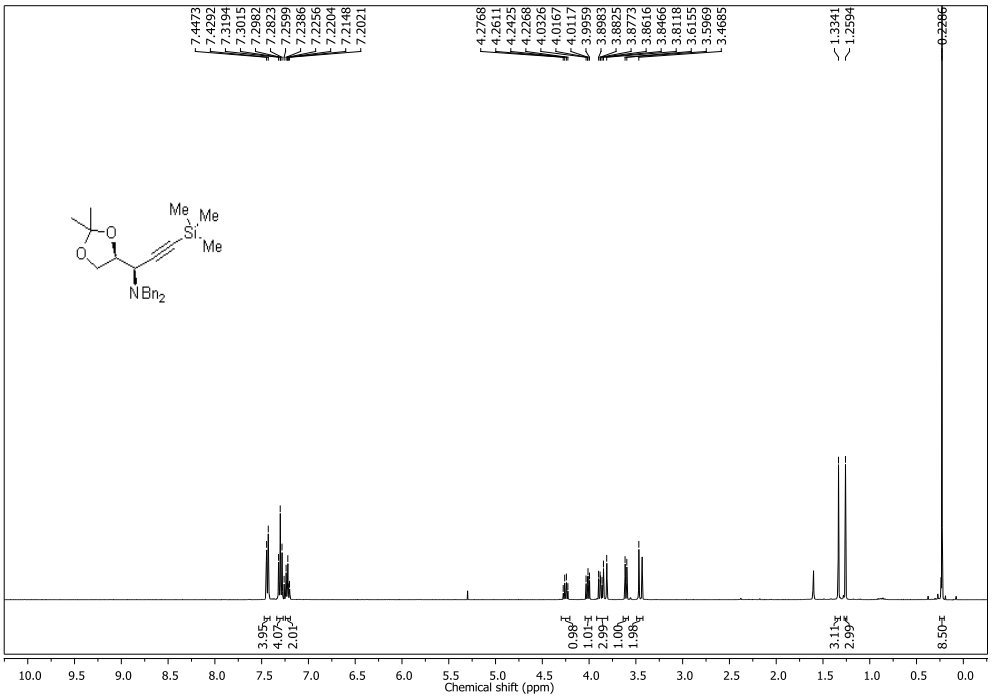


Figure 2.12: ^{1}H NMR spectra of **44g** in $CDCl_3$.

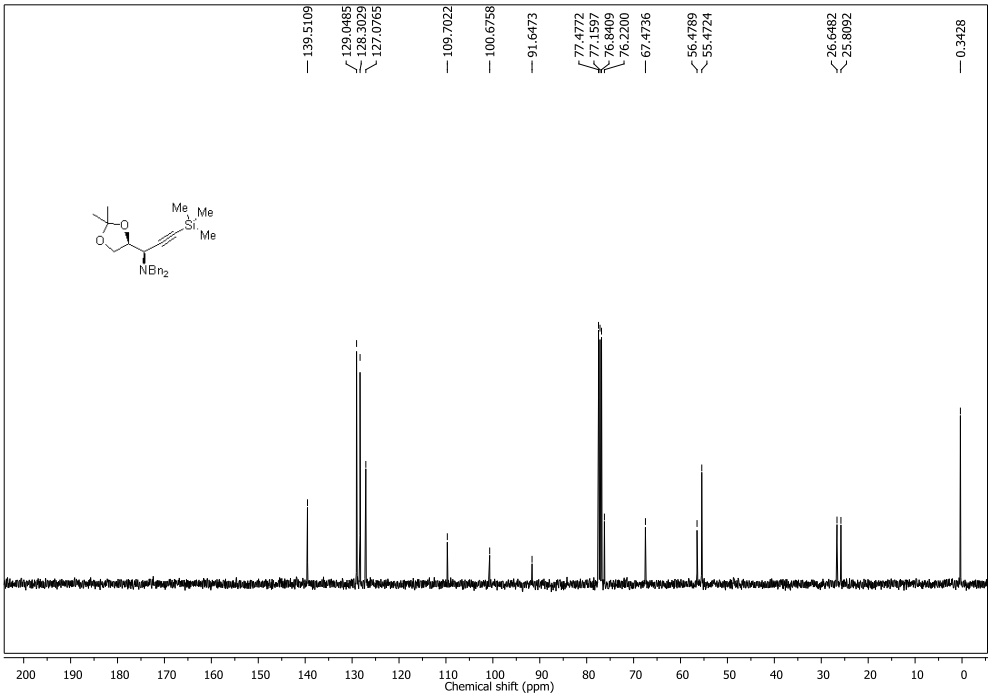


Figure 2.13: ^{13}C NMR spectra of **44g** in $CDCl_3$.

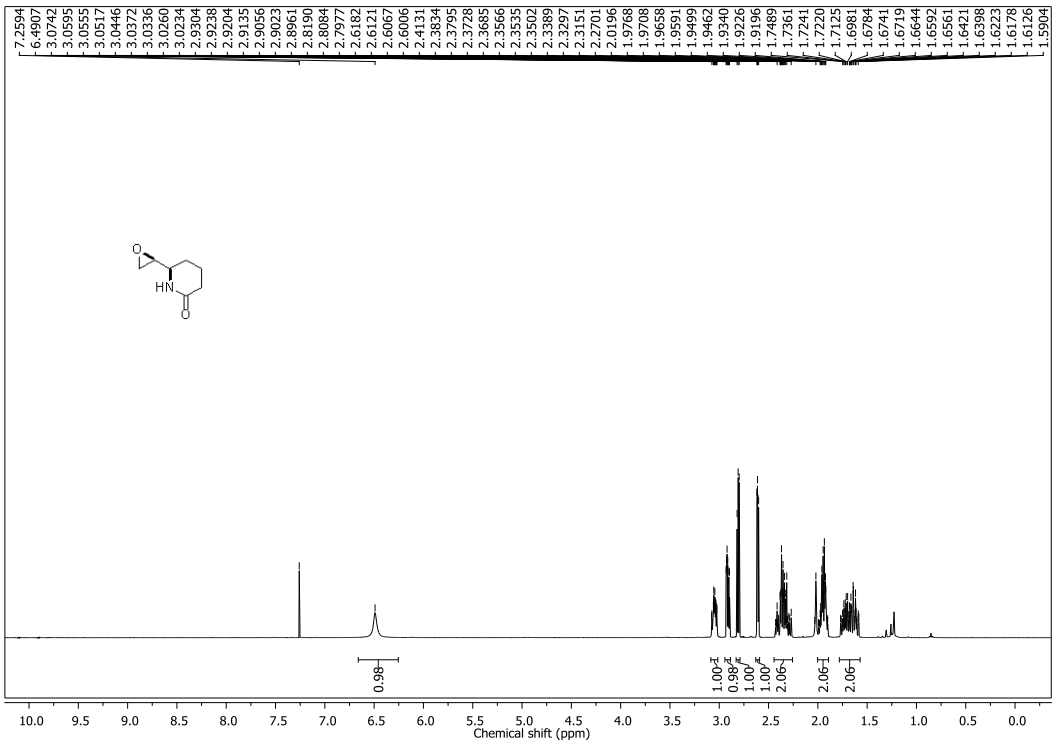


Figure 2.14: ^{1}H NMR spectra of **38b** in $CDCl_3$.

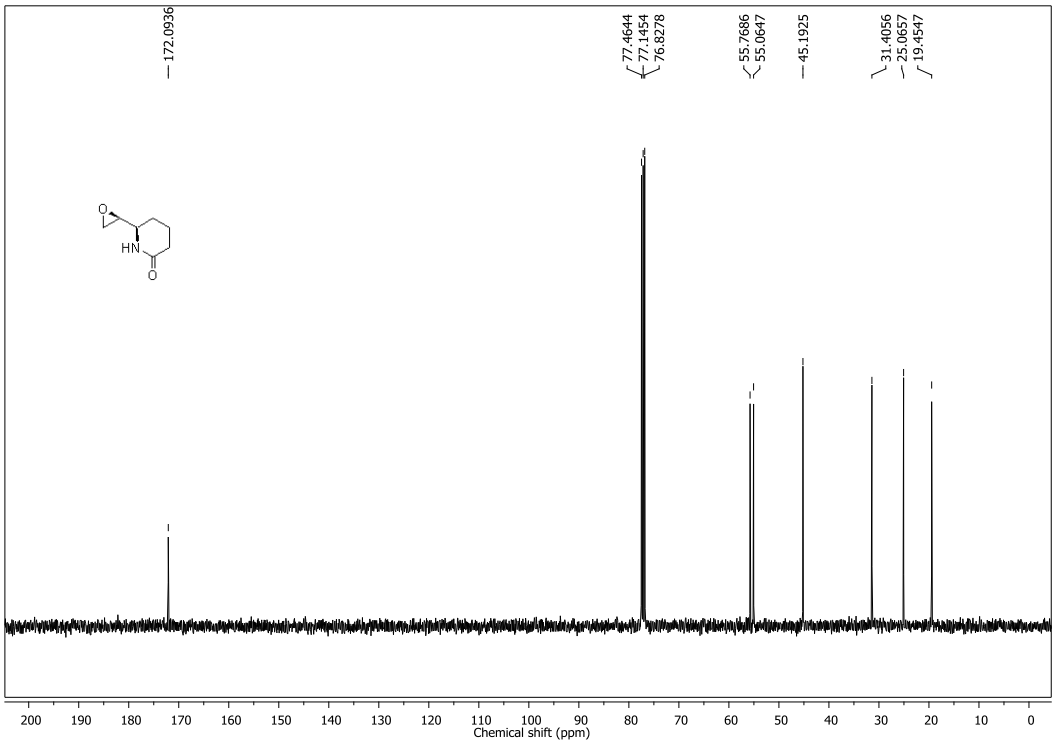


Figure 2.15: ^{13}C NMR spectra of **38b** in $CDCl_3$.

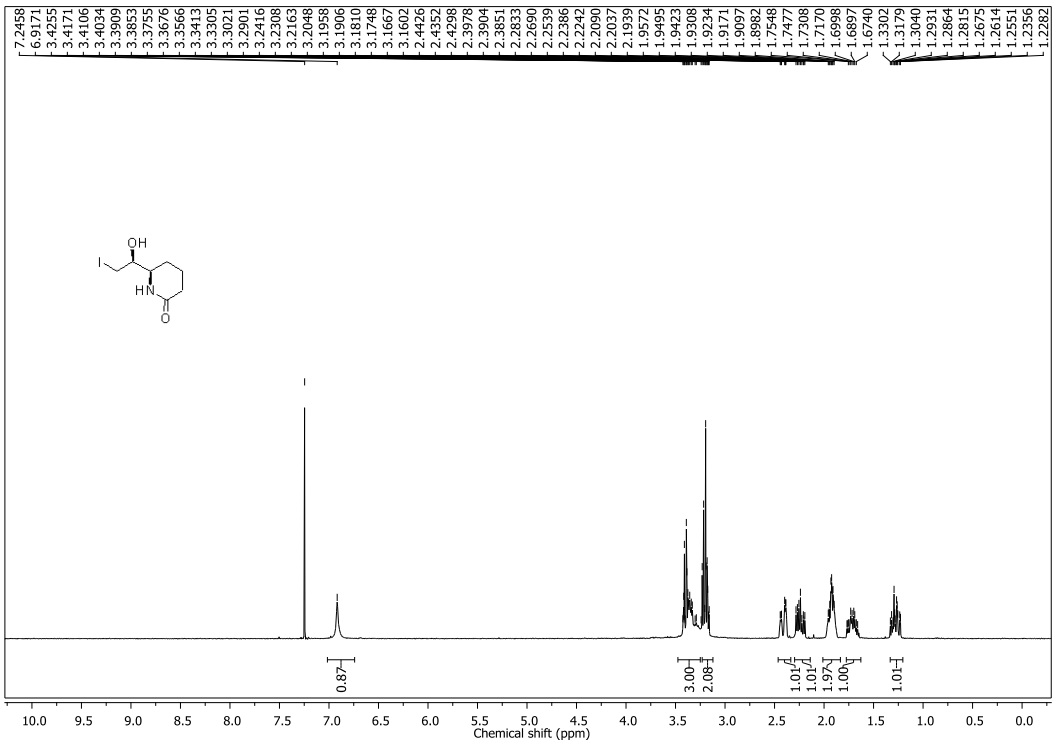


Figure 2.16: ^{1}H NMR spectra of **51b** in $CDCl_3$.

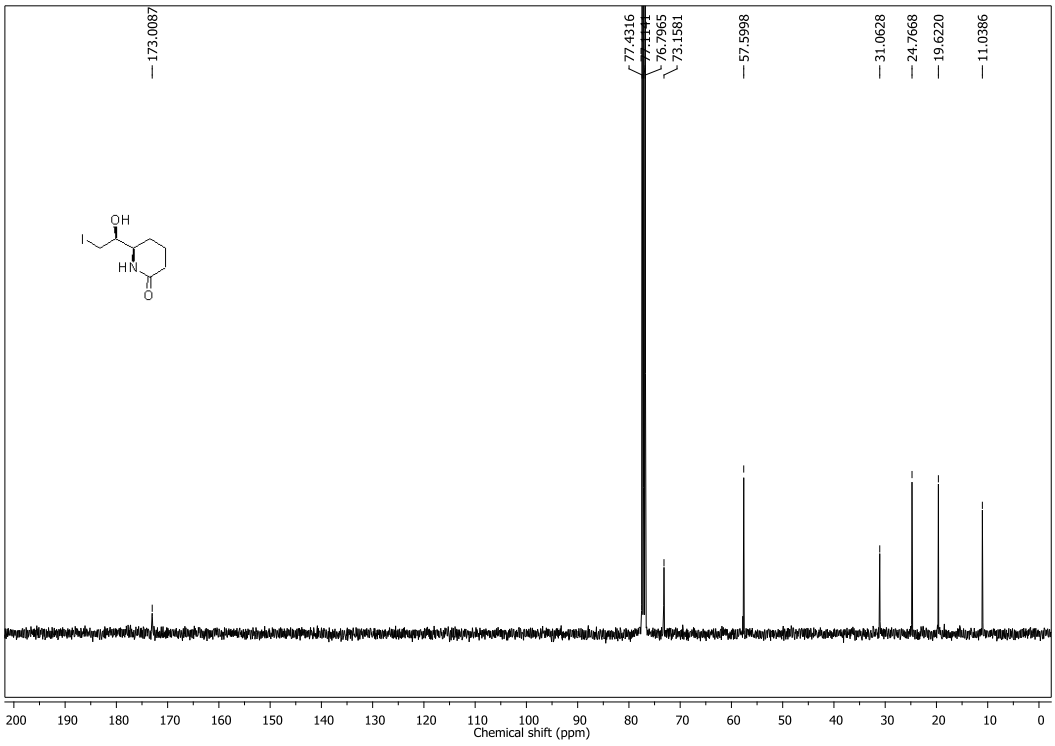


Figure 2.17: ^{13}C NMR spectra of **51b** in $CDCl_3$.

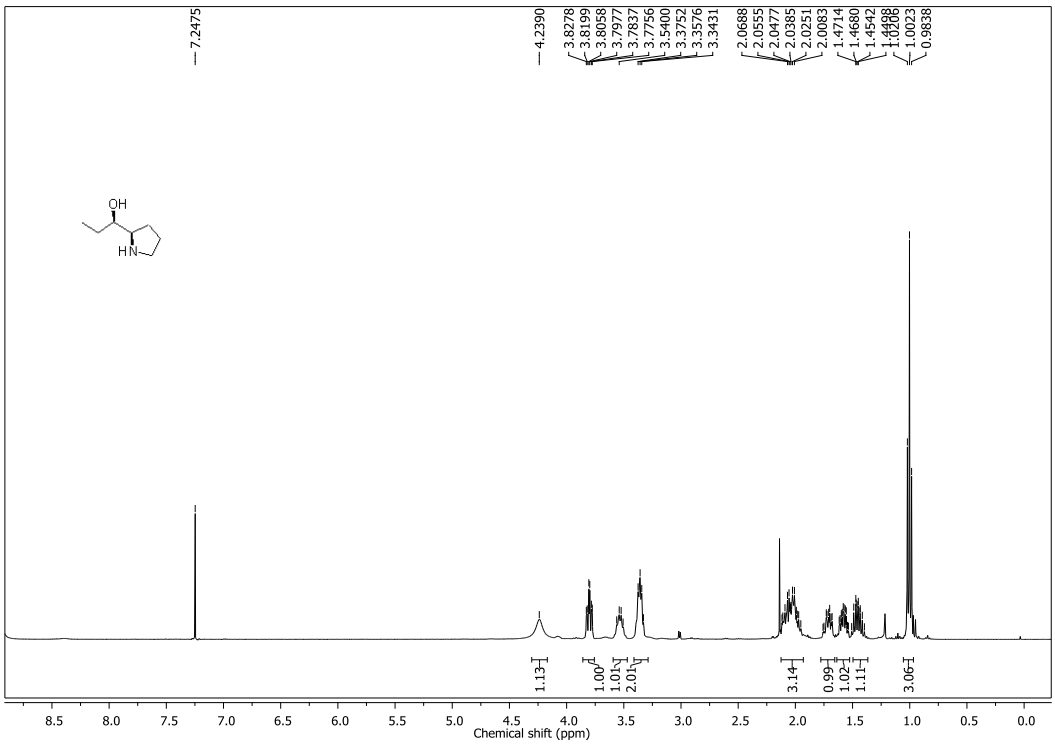


Figure 2.18: ^{1}H NMR spectra of **53a** in $CDCl_3$.

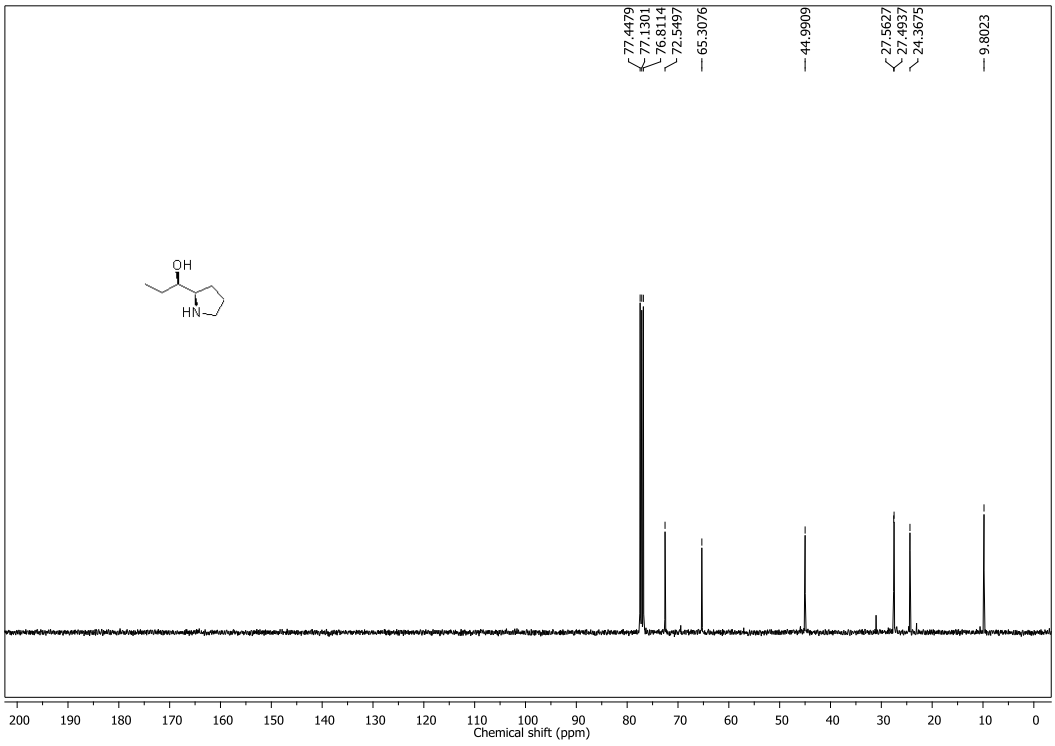


Figure 2.19: ^{13}C NMR spectra of **53a** in $CDCl_3$.

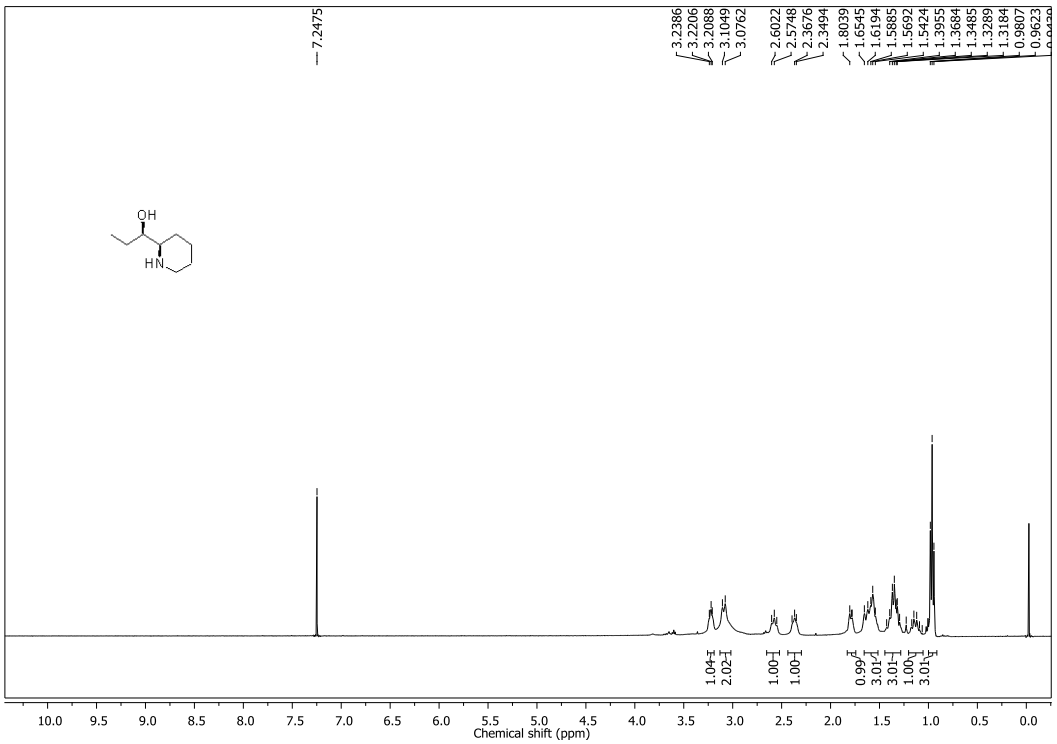


Figure 2.20: ^{1}H NMR spectra of **8a** in $CDCl_3$.

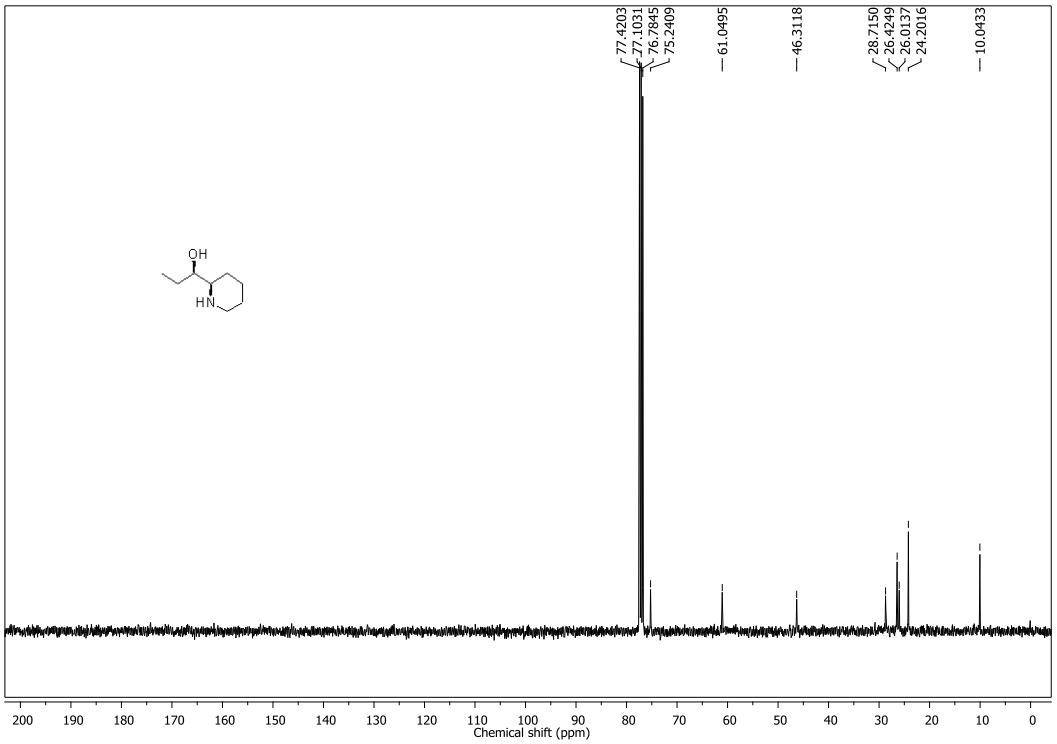


Figure 2.21: ^{13}C NMR spectra of **8a** in $CDCl_3$.

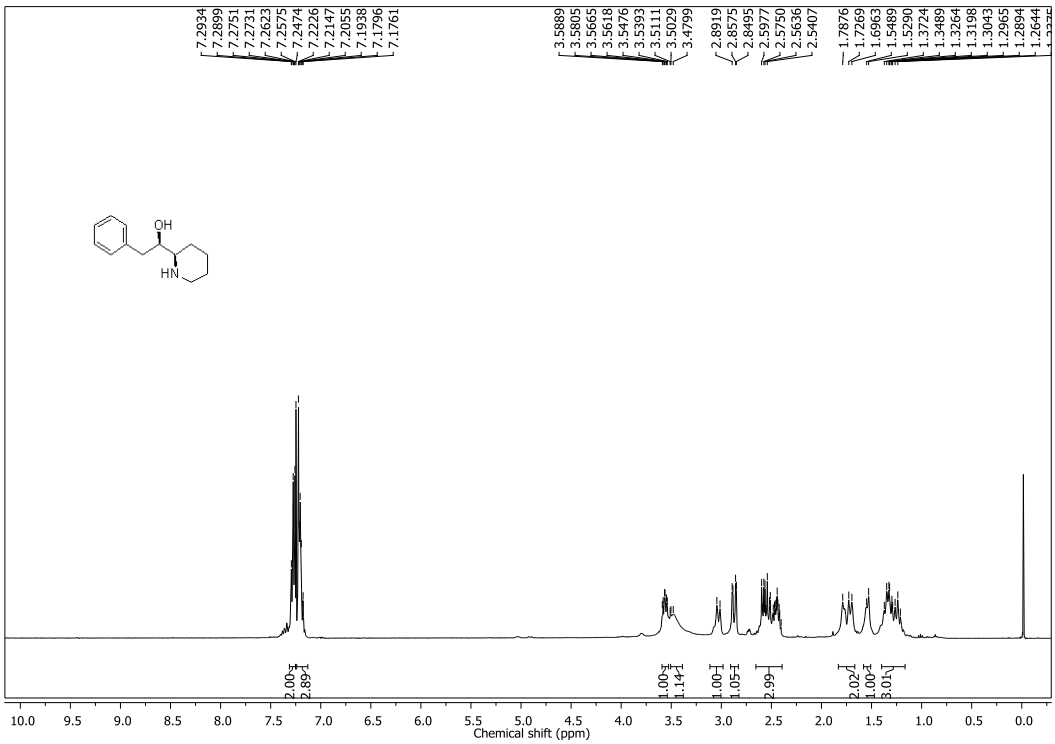


Figure 2.22: ^{1}H NMR spectra of **78** in $CDCl_3$.

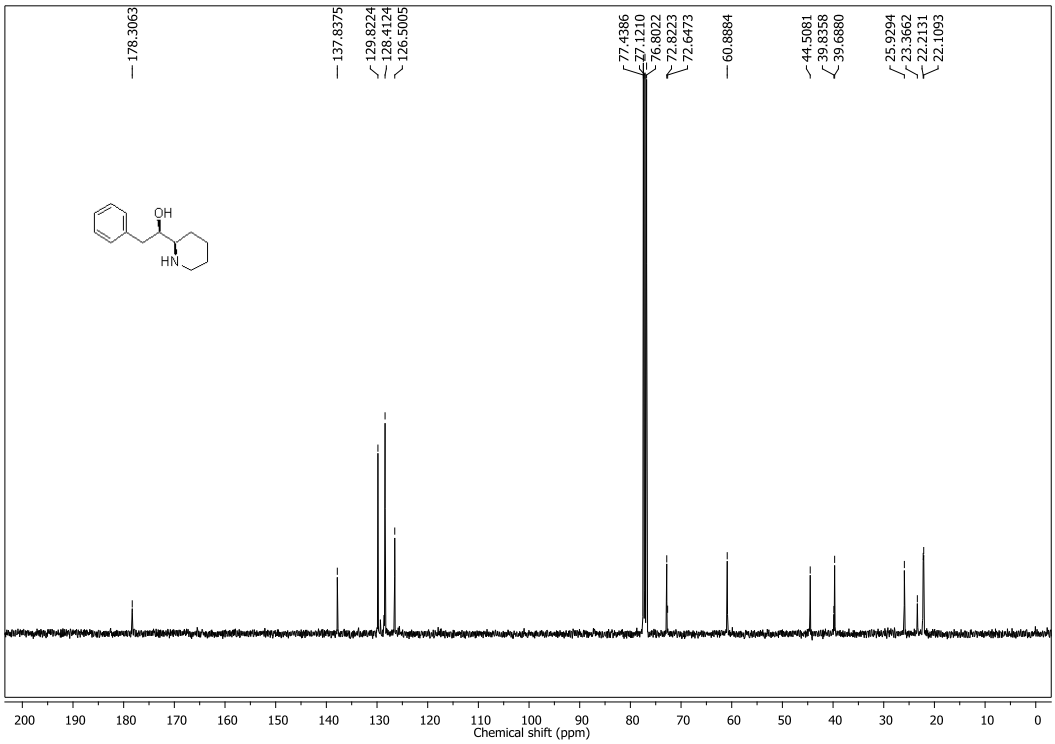


Figure 2.23: ^{13}C NMR spectra of **78** in $CDCl_3$.

2.10 References

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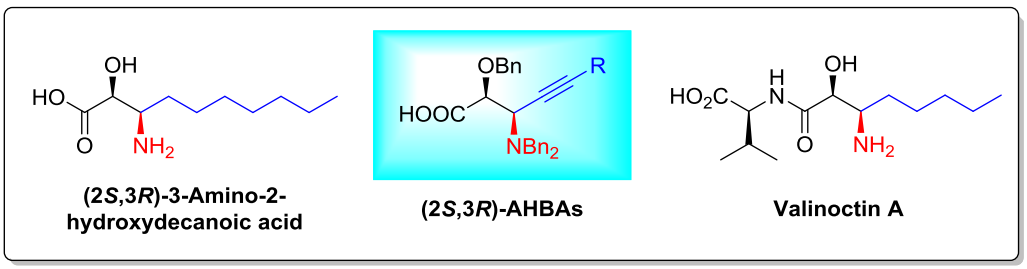
Chapter 3

Section A

(2*S*,3*R*)-α-Hydroxy-β-Amino Acids (AHBAs): Synthesis of Valinoctin A, (2*S*,3*R*)-3-Amino-2-Hydroxydecanoic Acid and A Fluorescence Labelled AHBA



(2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid

(2*S*,3*R*)-AHBAs

Valinoctin A

3A.1 Introduction

There has been increasing interest in synthetic routes to synthesis nonproteinogenic amino acids due to their extensive applications in medicinal chemistry and drug discovery.[1] Enantiomerically enriched α-hydroxy-β-amino acids are of considerable importance as being constituents of numerous biologically active natural products and naturally occurring peptides which show a wide range of biological activities.[2] In addition, enantiomerically enriched α-hydroxy-β-amino acids (AHBA) have been utilized as substrates for the synthesis of a wide variety of peptide isosteres, peptido mimetics and β-lactams.[3] Bestatin (**1**),[4] amastatin (**2**),[5] valinoctin A (**3**),[6] microginin (**4**),[7] paclitaxel,[8] scytonemin A,[9] KRI-1314,[10] dideoxykanamycin A,[11] etc. are examples of biologically active compounds having AHBAs as key structural components.

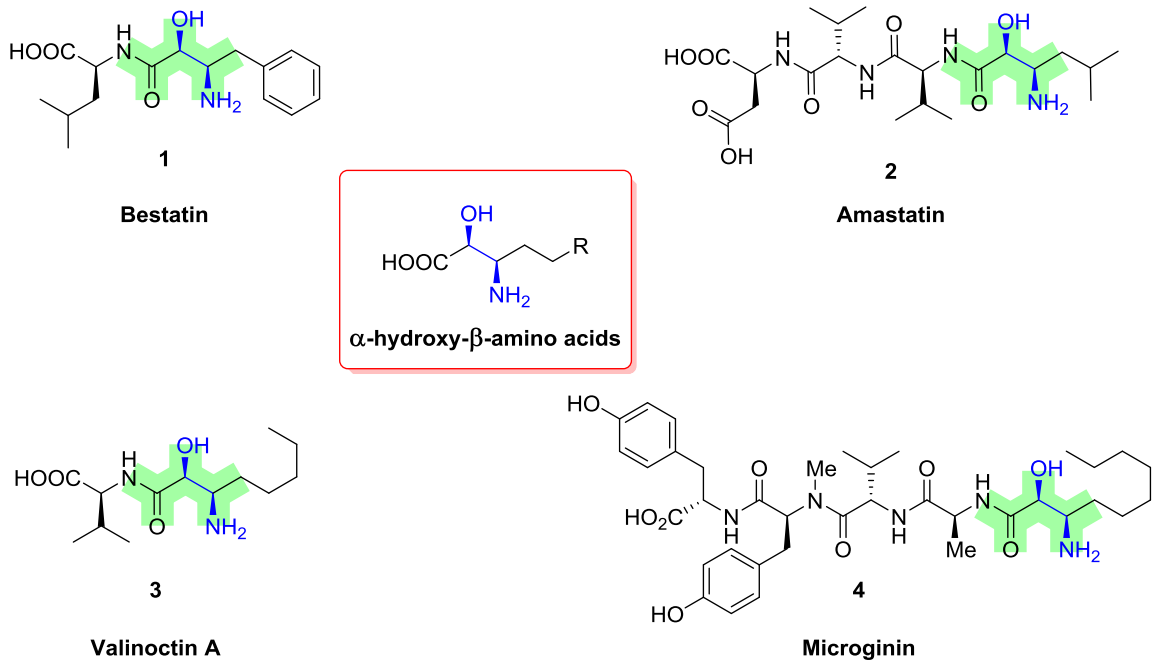


Figure 3A.1: Structures of biologically active compounds containing a α-hydroxy-β-amino acids moiety.

In these molecules, the *syn* stereochemistry of the amino alcohol fragment is also preserved. The (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid component is common in bestatin (**1**), phebestin[12] and probestin.[13] Structural activity relationship (SAR) studies

on these and other related molecules suggest that the *syn*-amino alcohol fragment and the 2*S*-configuration of the AHBA are crucial for their potent aminopeptidase inhibitory activity.[14] Bestatin (Ubenimex) (**1**), has been used for immunotherapy of acute leukaemia, cancer chemotherapy and adjuvant therapy.[15] Amastatin (**2**) is a reversible metalloprotease inhibitor and also a competitive inhibitor of leucine aminopeptidase (LAP) and aminopeptidase A (APA).[5] This natural tripeptide consists of (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid as the key *N*-terminal residue. Valinoctins A (**3**) is a novel farnesyl protein transferase inhibitor, isolated from the fermentation broth of *Streptomyces* strain MJ858-NF.[6] In this di-peptide natural product, the *N*-terminal residue (2*S*,3*R*)-3-amino-2-hydroxyoctanoic acid is a key AHBA with *syn*-α-amino alcohol fragment. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid, a homologous AHBA is present in the linear pentapeptide natural product microginin (**4**) which possesses inhibitory activities against angiotensin-converting enzyme (ACE).[16] Scytonemin A, a potent calcium antagonistic has (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid as the AHBA component.[9] As a result, synthesis of (2*S*,3*R*)-α-Hydroxy-β-Amino Acids has received considerable attention.

3A.2 Methods for Synthesis of α-Hydroxy-β-Amino Acids

In recent year, several stereoselective methods for the synthesis of α-hydroxy-β-amino acids have been developed. For example, carbohydrate based precursors with two defined chiral centers were occasionally used to delineate the stereochemistry around the α-amino alcohol component. Although, these chiron approaches are efficient to access AHBAs in enantiopure form, they are synthetically less demanding due to the presence of predefined stereocenters.[17] Various diastereoselective methodologies, on the other hand, were applied extensively as the more flexible and challenging chiron route to chiral AHBAs. In each of these strategies, a tailored chiral precursor was used for the diastereospecific construction of the second chirality. The reported examples following such approaches are (i) diastereospecific reaction on either carbohydrate or α-amino acid based precursors,[18] (ii) nucleophilic opening of chiral epoxides,[19] (iii) electrophilic hydroxylation of chiral enolates,[20] (iv) nucleophilic addition to chiral α-amino aldehydes and imines,[21] (v) stereoselective reduction of ketones,[22] and (vi) multicomponent reactions.[23] Asymmetric synthetic strategies for AHBAs were also reported based on (i)

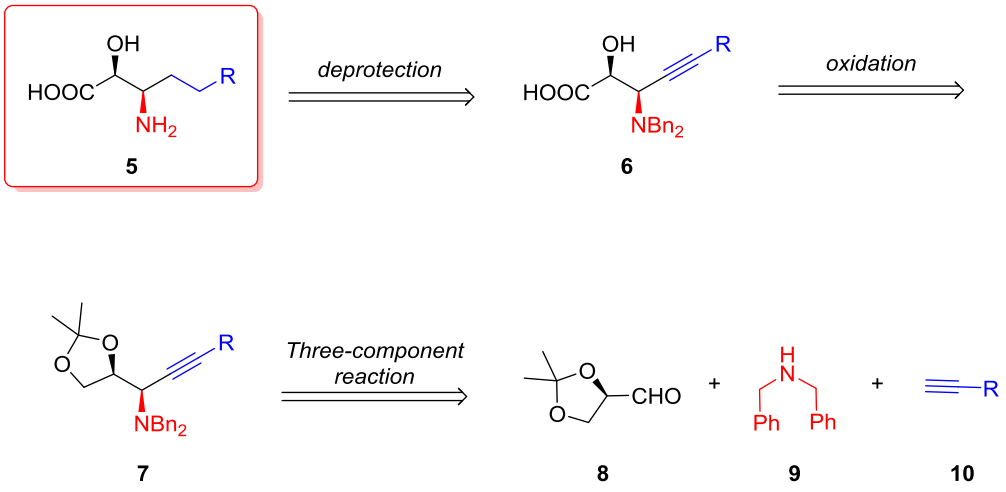
chemoenzymatic,[24] (ii) dynamic kinetic resolution,[25] and (iii) chiral catalysis.[26] However, most of these approaches have limitations due to the formation of either diastereomer or enantiomer as an undesired product. Although, AHBAs can be accessed through numerous strategies, control of the relative and absolute stereochemistry of the asymmetric carbons during the synthesis is of significant challenge.

3A.3 Present work and Synthetic Planning

A simple and suitable solution to the aforementioned critical limitations was proposed based on our recent report on the diastereoselective construction of (2*S*,3*R*)-α-amino alcohols.[27] The Cu(I)-catalyzed reaction of (*R*)-glyceraldehyde acetonide, dibenzylamine, and terminal alkyne was reported for the formation of a (2*S*,3*R*)-α-amino alcohol. A plausible mechanism for the reaction was proposed via the formation of an iminium cationic intermediate, followed by the addition of the alkynide anion, generated in the reaction. In this three component methodology, the (2*S*,3*R*)-α-amino alcohol derivative was formed as a single diastereomer whenever a terminal alkyne with an aliphatic side-chain was introduced. To explain these observations, geometry optimization of the iminium cation was carried out, and the result indicates large steric hindrance on its *si*-face. Therefore, the addition of the alkynide anion from the more accessible *re*-face led to the formation of the (2*S*,3*R*)-diastereomer. The (2*S*,3*R*)-stereochemistry around the α-amino alcohol moiety was confirmed by single-crystal X-ray diffraction studies. The three-component coupling reaction was also amenable to incorporating either an alkenyl or an aryl group on the terminal alkyne, although, with slight loss of diastereoselectivity. Formation of the minor (2*S*,3*S*)-diastereomer was rationalized based on the π-stacking interaction between a phenyl group of the iminium cation and an alkenyl/aryl group of the approaching anion. This noncovalent interaction led to the addition of the alkynide anion from the sterically crowded *si*-face. The presence of (i) the (2*S*,3*R*)-stereochemistry around the α-amino alcohol moiety, and (ii) an aliphatic side-chain, in various naturally occurring AHBAs (**1**−**4**), encouraged us to apply the three component reactions as a diastereoselective route to this class of amino acids. Such a strategy was planned also to access alkynyl side-chain containing (2*S*,3*R*)-AHBA analogues. Synthesis of this new class of molecules can be indispensable for building SAR and understanding their binding

to the target proteins. Fluorescent-labeled (2*S*,3*R*)-AHBAs are already known for the determination of their absolute configuration.[28] Peptides and proteins derived from these types of compounds are also the powerful tools for investigating receptor−ligand binding,[29] protein structures,[30] and enzyme activity in vitro as well as in vivo. Therefore, synthesis of a fluorescent-labeled (2*S*,3*R*)-AHBA was also envisaged. Peptides and proteins derived from these types of compounds are also powerful tools in the investigation of receptor-ligand-binding, protein structures, and enzyme activity.

To address all these aims, a general retrosynthetic analysis was planned (Scheme 3A.1). Synthesis of the representative (2*S*,3*R*)-AHBA **5** was proposed from the corresponding alkynyl side-chain containing (2*S*,3*R*)-AHBA **6**. Benzyl (Bn) protective groups on **6** were selected to ensure a single-step protocol for the reduction of the C-C bond and removal of all benzyl protective groups. Synthesis of AHBA **6** was planned from ketal **7**. Diastereoselective synthesis of the ketal **7** was proposed based on our reported reaction involving (*R*)-glyceraldehyde acetonide **8**, dibenzylamine **9**, and terminal alkyne **10**. A manipulation of the R-group, comprising aliphatic (R = $-C_3H_7$, $-C_4H_9$, $-C_5H_{11}$, and $-C_6H_{13}$), and aromatic (R = −Ph, −1- pyrenyl) functionalities, was proposed to synthesize various alkynyl side-chain containing (2*S*,3*R*)-AHBA analogues. The pyrene moiety was selected as the tethered group, due to its intrinsic fluorescence. To demonstrate the usefulness of the proposed methodology, synthesis of valinoctin A (**3**) was planned from 1-pentynyl side-chain containing (2*S*,3*R*)-AHBA. Similarly, synthesis of (2*S*,3*R*)-AHDA considered from 1-heptynyl side-chain containing (2*S*,3*R*)-AHBA.

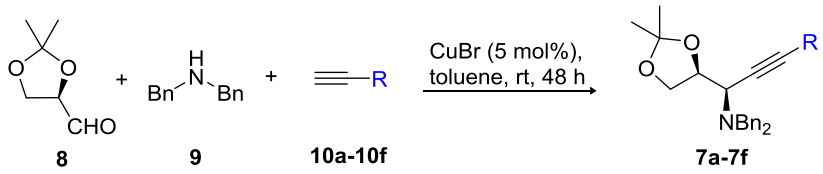


Scheme 3A.1: Retrosynthetic analysis of (2*S*,3*R*)-AHBA library generation.

3A.4 Results and Disscusion

The reported CuBr (5 mol%) catalytic conditions in toluene at room temperature was used for incorporating varied R-groups with the desired *syn*-α-amino alcohol stereochemistry. Aldehyde **8** and dibenzylamine **9** when reacted with the terminal alkyne **10a** (R = $–C_3H_7$) under CuBr (5 mol%) catalytic conditions in toluene at room temperature, substituted alkyne **7a** was formed as single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 76% yield (Table 3A.1, entry 1). No formation of *anti*-diastereomer was detected under the applied reaction conditions. The introduction of other terminal alkynes (**10b**-**10d**) with the aliphatic arm at one end also provided *syn*-diastereomeric coupling products (**7b**-**7d**) with 73-80% yields (Table 3A.1, entries 2-4). The reaction of phenylacetylene **10e** with **8** and **9** under the comparable reaction conditions provided formation of **7e** (yield = 65%) as major diastereomer with *syn*/*anti* = 78:22 (Table 3A.1, entry 5, step 1) and this result were consistent with our earlier report of the reaction. Similarly, when the three-component protocol was applied to 1-pyrenylacetylene **10f**, the reaction resulted in the formation of the major *syn*-diastereomer **7f** with *syn*/*anti* = 90:10 and 72% isolated yield (Table 3A.1, entry 6).

Table 3A.1: Diastereoselective construction of the α-amino alcohols via A^3-coupling.

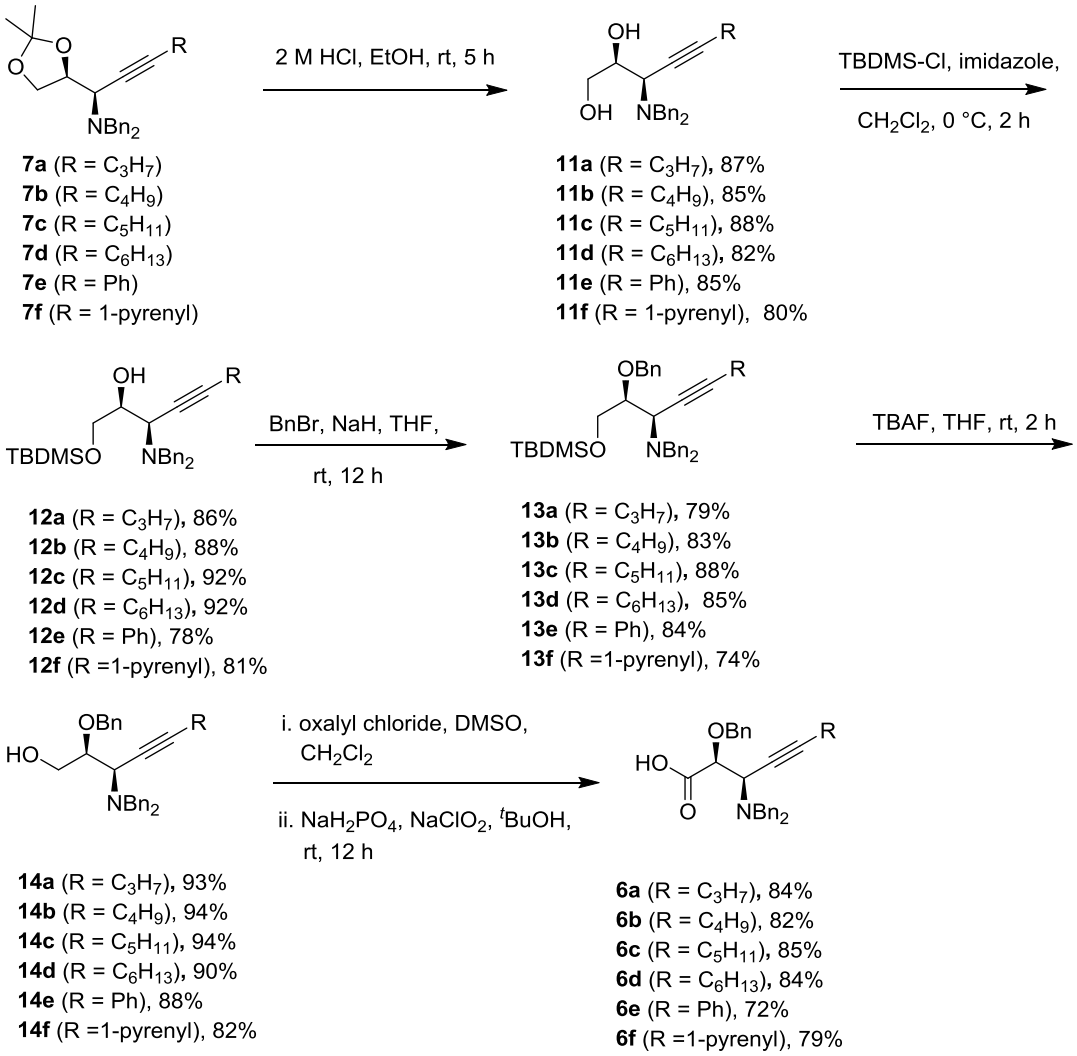


8 9 10a-10f 7a-7f

entry	alkyne	R	product	% yield	*syn / anti*
1	**10a**	C_3H_7	**7a**	76	>99%
2	**10b**	C_4H_9	**7b**	73	>99%
3	**10c**	C_5H_{11}	**7c**	80	>99%
4	**10d**	C_6H_{13}	**7d**	78	>99%
5	**10e**	Ph	**7e**	68	78:22
6	**10f**	1-pyrenyl	**7f**	72	90:10

Subsequently, ketal group of each three-component coupling products **7a-7f** was deprotected by methanolic HCl to afford the diol **11a-11f** with 80-90% yields. (Scheme 3A.2). Selective oxidation of primary alcohols of **11b** to corresponding carboxylic acid using (TEMPO-mediated oxidations) TEMPO, $NaClO_2$, and NaOCl in NaH_2PO_4 provided a low yield of 10%. Therefore, a protection-deprotection strategy was explored in the synthesis of (2*S*,3*R*)-AHBAs. Selective protection of a primary alcohol moiety of the diols **11a-11f** was carried out by treating with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole in DCM at room temperature to obtain corresponding silyl ethers **12a-12f** in 78-92% yields. Subsequent protection of the secondary hydroxyl group of **12a-12f** was achieved by reacting with benzyl bromide and sodium hydride in THF at room temperature to obtain **13a-13f** in 74-88% yields. Desilylation of protected diols **13a-13f** with tetrabutylammonium fluoride (TBAF) furnished the primary alcohols **14a-14f** in 82-94% yields. In the next step, Swern oxidation conditions were applied during the

conversion of **14a**−**14f** to the corresponding aldehydes. The extremely mild oxidation protocol is well-known in the literature for the oxidation of the primary hydroxyl group, avoiding epimerization on the chiral α-carbon. Crude aldehydes were then used directly in the next step, without column chromatographic purification. The crude aldehydes were oxidized further using Pinnick reaction conditions ($NaClO_2$, NaH_2PO_4, 2-metyl-2-butene in *tert*-BuOH) to furnish alkynyl side-chain containing (2*S*,3*R*)-AHBA derivatives **6a**−**6f** in 72−85% yields. In the two-step oxidation protocol, alcohols bearing R = alkyl groups (**14**a−**14**d) provided slightly better yields compared to those with R = aryl groups (**14**e−**14**f). Apart from NMR spectroscopic characterization of all synthesized compounds, pyrene-containing (2*S*,3*R*)-AHBA **7f** was also analyzed by high-performance liquid chromatography (HPLC) for purity.



7a (R = C_3H_7)
7b (R = C_4H_9)
7c (R = C_5H_{11})
7d (R = C_6H_{13})
7e (R = Ph)
7f (R = 1-pyrenyl)

11a (R = C_3H_7), 87%
11b (R = C_4H_9), 85%
11c (R = C_5H_{11}), 88%
11d (R = C_6H_{13}), 82%
11e (R = Ph), 85%
11f (R = 1-pyrenyl), 80%

12a (R = C_3H_7), 86%
12b (R = C_4H_9), 88%
12c (R = C_5H_{11}), 92%
12d (R = C_6H_{13}), 92%
12e (R = Ph), 78%
12f (R =1-pyrenyl), 81%

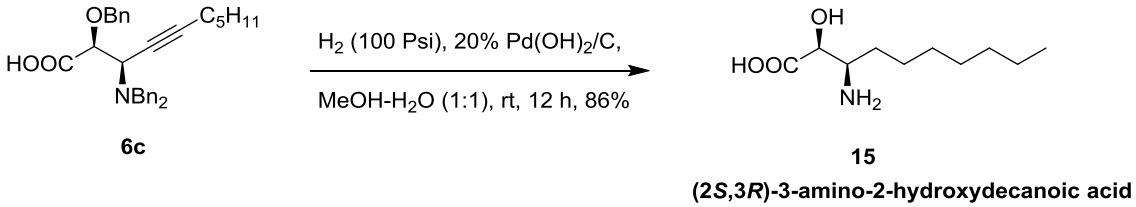
13a (R = C_3H_7), 79%
13b (R = C_4H_9), 83%
13c (R = C_5H_{11}), 88%
13d (R = C_6H_{13}), 85%
13e (R = Ph), 84%
13f (R =1-pyrenyl), 74%

14a (R = C_3H_7), 93%
14b (R = C_4H_9), 94%
14c (R = C_5H_{11}), 94%
14d (R = C_6H_{13}), 90%
14e (R = Ph), 88%
14f (R =1-pyrenyl), 82%

6a (R = C_3H_7), 84%
6b (R = C_4H_9), 82%
6c (R = C_5H_{11}), 85%
6d (R = C_6H_{13}), 84%
6e (R = Ph), 72%
6f (R =1-pyrenyl), 79%

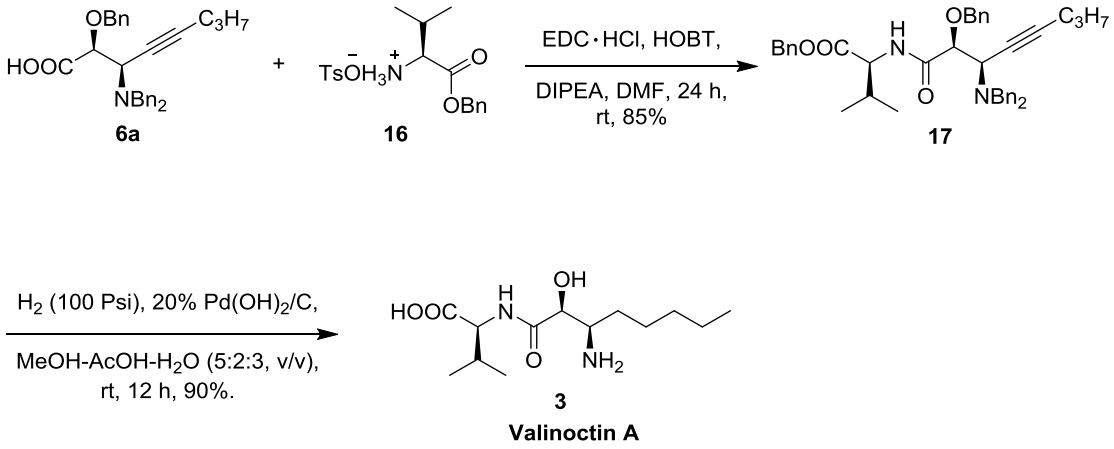
Scheme 3A.2: Synthesis of alkynyl side chain containing protected (2*S*,3*R*)-AHBAs **6a-6f.**

In the next stage, applications of the methodology in the synthesis of nonproteinogenic amino acid (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid and natural product Valinoctins A were demonstrated. When carboxylic acid **6c** was subjected to 100 Psi H_2 (in a Parr low-pressure hydrogenation apparatus), 20% $Pd(OH)_2/C$ (10 mol%) in MeOH at room temperature, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond occurred to form (2*S*,3*R*)-AHDA **15** (Scheme 3A.3). Purification of **15** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) to achieve 86% yield. The structure of the product confirmed by comparing the recorded ^{1}H-NMR, melting point, specific rotation and matched with the data available in the literature.[31]



Scheme 3A.3: Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid.

Further, the reaction of carboxylic acid **6a** and L-valine benzyl ester 4-toluenesulfonate **16** under by *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole monohydrate (HOBt) coupling conditions in DMF afforded to dipeptide **17** with 84% yield (Scheme 3A.4). The dipeptide **17** was then treated with H_2 (100 Psi), 20% $Pd(OH)_2/C$ (10 mol%) in MeOH-AcOH-H_2O (5:2:3, v/v (mL)) at room temperature to give valinoctin A **3** in 90% yield. ^{1}H-NMR, melting point and specific rotation analysis of **3** were adequate to match with previously reported data.[32]



Scheme 3A.4: Synthesis of valinoctin A.

3A.5 Photophysical properties and live cell imaging

UV-visible absorption and fluorescence properties of fluorescently labeled (2*S*,3*R*)-AHBA **6f** also investigated in chloroform (Figure 3A.2). Compound **6f** (2.0 μM) displayed absorption bands at λ = 331 (ε_{331} = 22,000 M^{-1} cm^{-1}), 347 (ε_{347} = 48,000 M^{-1} cm^{-1}) and 366 nm (ε_{366} = 68,400 M^{-1} cm^{-1}). Upon excitation at λ = 366 nm, **6f** displayed fluorescence bands at λ = 385, 406 and 428 nm. The fluorescence quantum yield of

compound **6f** in chloroform is 0.23, using the reference quinine sulfate (Φf = 0.55, in 0.1 M H_2SO_4).

We further investigated the permeability of amino acid **6f** in DLD1 cancer cells by fluorescence microscopy techniques. When these cells were incubated with compound **6f** (20 µM) in 1 : 1000 DMSO/OptiMEM media for 30 min at 37 °C, strong fluorescence was observed within incubated cells (Figure 3A.2).

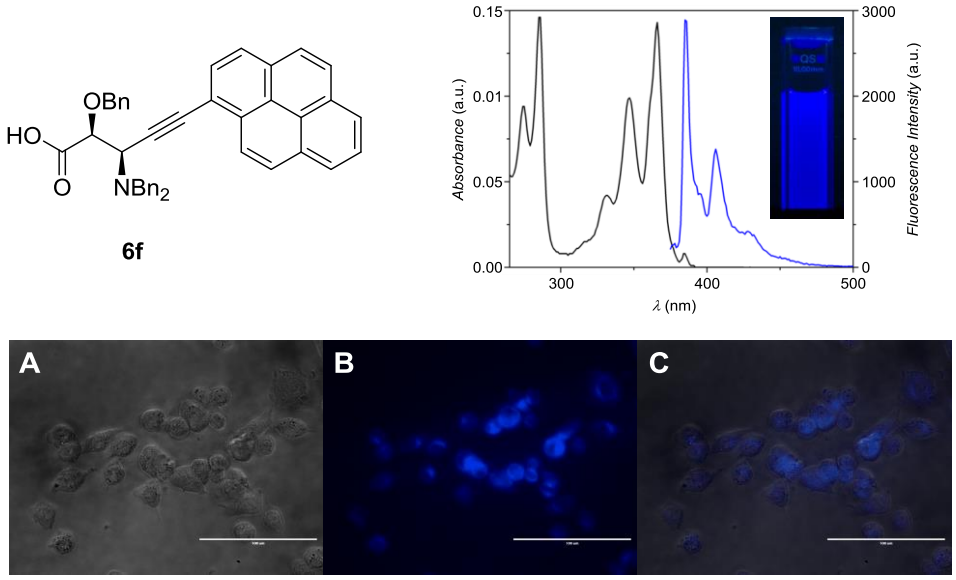


Figure 3A.2 UV-visible (black) and fluorescence (blue) spectra of pyrene substituted (2*S*,3*R*)-AHBA **6f** (2.0 µM) in chloroform. Cuvette image of **6f** (50 µM) in chloroform taken under hand held UV lamp, λ_{ex} = 365 nm (*inset*). Transmission (A) fluorescence (B) and overlay (C) images of DLD1 cancer cells upon incubation of fluorescently labeled (2*S*,3*R*)-AHBA **7f**.

3A.6 Conclusion

In conclusion, a new stereoselective methodology was developed for the synthesis of (2*S*,3*R*)-α-hydroxy-β-amino acid ((2*S*,3*R*)-AHBA) analogues via the Cu(I)-catalyzed (*R*)- glyceraldehyde acetonide-dibenzylamine-terminal alkyne coupling reaction. Tuneability of the terminal alkyne with either an aliphatic (propyl, butyl, pentyl, and hexyl) or an aromatic (phenyl and 1-pyrenyl) side-chain and good-to-excellent diastereoselectivity rendered the three-component reactions as an efficient strategy for the synthesis of alkynyl side-chain containing (2*S*,3*R*)-AHBA derivatives. The generality of the approach was demonstrated by the stereoselective synthesis of valinoctin A, a naturally

occurring farnesyl protein transferase inhibitor. Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA), the N-terminal residue of the natural linear pentapeptide microginin, was also achieved based on the methodology. Considering the broad applications of fluorescent- labeled amino acids, the UV−visible and fluorescence spectra of the pyrene-containing compound AHBA were determined. Cell permeability of the compound was also demonstrated by live-cell imaging studies.

3A.7 Experimental Section

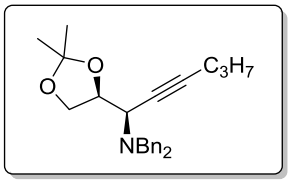
General Considerations: All reactions were carried out under a nitrogen atmosphere. All the chemicals were purchased from commercial sources and used as received unless stated otherwise. Solvents such as petroleum ether, ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), and methanol (MeOH) were distilled prior to thin-layer and column chromatography. Column chromatographies were performed on silica gel (100−200 mesh). TLCs were carried out on silica gel 60-F-254 precoated plates. 1H NMR spectra were recorded at 400 or 500 MHz using tetramethylsilane as an internal standard (δ: 0.0 ppm) and 13C NMR spectra at 100 or 125 MHz using CDCl3 as an internal standard (δ: 77.16 ppm). The 1H NMR spectra were reported as follows: δ (position of the proton, multiplicity, coupling constant J in Hz, number of protons), and the 13 NMR spectra were reported as follows: δ (position of carbon). The following abbreviations were used to describe peak patterns wherever appropriate: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded either on an electron spray ionization time-of-flight (ESITOF)or on a Matrix-assisted laser desorption/ionization (MALDI Scheme TOF-TOF) mass spectrometer. Melting points were determined with a micro melting point apparatus. HPLC analyses were performed on an apparatus equipped with either an analytical reversed-phase column or an analytical reversed-phase chiral column. Photophysical properties were determined on a UV−visible spectrophotometer and a steadystate spectrophotometer. Live cell imaging studies were carried out using a fluorescence microscope.

General copper(I) catalyzed aldehyde-amine-alkyne reaction procedure.

***Method A*:** To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **8** (1.0 mmol) in dry toluene (2.0 mL) were added dibenzylamine **9** (1.0 mmol), alkyne **10a-10f** (1.0 mmol), CuBr (0.05 mmol), 4 Å molecular sieves (500 mg) and the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was filtered through celite bed and washed with Et_2O (2 × 10 mL). The combined filtrate was concentrated under reduced pressure to obtain liquid which was further purified by

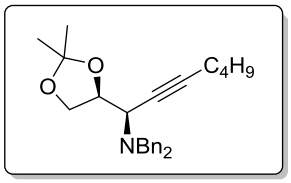
column chromatography over silica gel (*Eluent:* 2-5% EtOAc in petroleum ether) to furnish corresponding multi-component reaction product **7a-7f**.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-yn-1-amine 7a ($C_{25}H_{31}NO_2$).



Following the *Method A*, reaction of **8** (2.50 g, 19.20 mmol) with **9** (3.80 g, 19.20 mmol) and alkyne **10a** (1.30 g, 19.20 mmol) in dry toluene (40 mL) in the presence of CuBr (138 mg, 0.96 mmol), 4 Å molecular sieves (10.00 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **8a** (5.50 g, 76%) as colorless oil. IR (KBr) ν (cm^{-1}): 2966, 2876, 1497, 1453, 1372, 1214, 1148, 1069; $[\alpha]_D^{25}$ = - 118.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 5.7 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 4H), 7.22 (t, *J* = 6.6 Hz, 2H), 4.26 (q, *J* = 6.6 Hz, 1H), 4.00 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.87–3.83 (m, 3H), 3.56 (d, *J* = 5.6 Hz, 1H), 3.46 (d, *J* = 13.4 Hz, 2H), 2.25 (t, *J* = 6.1 Hz, 2H), 1.56–1.16 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.7 (2C), 128.9 (4C), 128.2 (4C), 126.9 (2C), 109.7, 87.0, 76.5, 74.6, 67.5, 55.6, 55.4 (2C), 26.6, 25.6, 22.5, 20.8,13.6; HRMS (ESI) Calcd. for $C_{25}H_{32}NO_2$ 378.2433 $[M + H]^+$, found 378.2434.

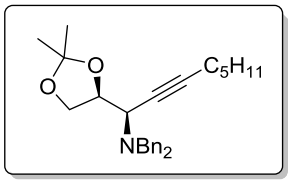
Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-2-yn-1-amine 7b ($C_{26}H_{33}NO_2$).



Following the *Method A*, reaction of **8** (2.00 g, 15.40 mmol) with **9** (3.05 g, 15.40 mmol) and alkyne **10b** (1.27 g, 15.40 mmol) in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol), 4 Å molecular sieves (7.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **7b** (4.40 g, 73 %) as colorless oil. IR (KBr) ν (cm^{-1}): 2932, 2871, 1496, 1454, 1373, 1250, 1214, 1148, 1069; $[\alpha]_D^{25}$ = - 63.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.4 Hz, 4H), 7.29 (t, *J* = 7.2 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 3.99 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.87–3.82 (m,

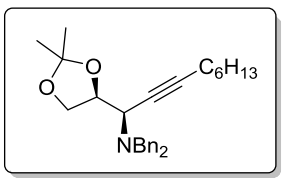
3H), 3.55 (dt, *J* = 7.2, 2.1 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 2H), 2.27 (td, *J* = 6.8, 2.0 Hz, 2H), 1.57–1.50 (m, 4H), 1.33 (s, 3H), 1.26 (s, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 128.9 (4C), 128.2 (4C), 126.9 (2C), 109.6, 87.0, 76.5, 74.5, 67.5, 55.7, 55.4 (2C), 31.2, 26.6, 25.7, 22.0, 18.5,13.7; HRMS (ESI) Calcd. for $C_{26}H_{34}NO_2$ 392.2589 $[M + H]^+$, found 392.2589.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)oct-2-yn-1-amine 7c ($C_{27}H_{35}NO_2$).



Following the *Method A*, reaction of **8** (2.00 g, 15.40 mmol) with **9** (3.05 g, 15.40 mmol) and alkyne **10c** (1.48 g, 15.40 mmol) in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol), 4 Å molecular sieves (7.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **7c** (4.98 g, 80 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 2929, 2858, 1499, 1455, 1367, 1214, 1100, 1031; $[\alpha]_D^{25}$ = - 88.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 2H) , 4.25 (q, *J* = 6.4 Hz, 1H), 4.01 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.89 – 3.82 (m, 3H), 3.56 (dt, *J* = 7.6, 2.2 Hz, 1H), 3.46 (d, *J* = 13.9 Hz, 2H), 2.27(td, *J* = 7.0, 2.1 Hz, 2H), 1.61 – 1.51 (m, 2H) 1.48– 1.36 (m, 4H), 1.34 (s, 3H), 1.27 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.3 (4C), 127.0 (2C), 109.7, 88.7, 76.6, 74.6, 67.6, 55.7, 55.5 (2C), 31.2, 28.8, 26.7, 25.7, 22.4, 18.8, 14.2; HRMS (ESI) Calcd. for $C_{27}H_{36}NO_2$ 406.2746 $[M + H]^+$, found 406.2746.

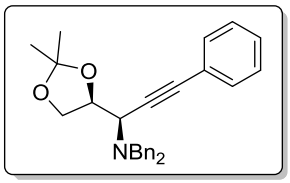
Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)non-2-yn-1-amine 7d ($C_{28}H_{37}NO_2$).



Following the *Method A*, reaction of **8** (2.00 g, 15.40 mmol) with **9** (3.05 g, 15.40 mmol) and alkyne **10d** (1.70 g, 15.40 mmol) in dry toluene (30 mL) in the presence of CuBr (110 mg, 0.77 mmol), 4 Å molecular sieves (7.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **7d** (5.04 g, 78 %) as colorless oil. IR (KBr) ν (cm^{-1}):

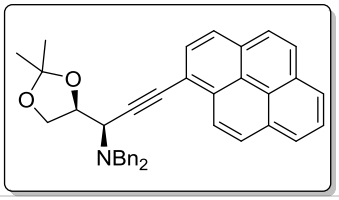
2933,1517, 1457, 1374, 1215, 1215, 1150, 1073; $[\alpha]_D^{25}$ = - 74.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 7.3 Hz, 4H), 7.29 (dd, *J* = 10.2, 4.6 Hz, 4H), 7.21 (t, *J* = 7.3 Hz, 2H), 4.25 (q, *J* = 6.4 Hz, 1H), 4.00 (dd, *J* = 8.3, 6.4 Hz, 1H), 3.87–3.82 (m, 3H), 3.55 (dt, *J* = 7.5, 2.1 Hz, 1H), 3.45 (d, *J* = 13.9 Hz, 2H), 2.26 (td, *J* = 6.9, 2.1 Hz, 2H), 1.61–1.50 (m, 4H), 1.49-1.41 (m, 2H), 1.37–1.33 (m, 2H), 1.32 (s, 3H) , 1.26 (s, 3H), 0.92 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.8 (2C), 129.0 (4C), 128.3 (4C), 127.0 (2C), 109.7, 87.1, 76.6, 74.5, 67.5, 55.6, 55.4 (2C), 31.4, 29.1, 28.6, 26.6, 25.7, 22.7, 18.8, 14.2; HRMS (ESI) Calcd. for $C_{28}H_{38}NO_2$ 420.2903 $[M + H]^+$, found 420.2911.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-phenylprop-2-yn-1-amine 7e ($C_{28}H_{29}NO_2$).



Following the *Method A*, reaction of **8** (3.00 g, 23.0 mmol) with **9** (4.56 g, 23.10 mmol) and alkyne **10e** (2.50 g, 24.40 mmol) in dry toluene (50 mL) in the presence of CuBr (180 mg, 1.3 mmol), 4 Å molecular sieves (15.0 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **7e** (6.44 g, 68%) as colorless oil. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25}$ = - 70.30 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 – 7.45 (m, 6H), 7.35 – 7.32 (m, 3H), 7.30 (t, *J* = 7.3 Hz, 4H), 7.22 (t, *J* = 7.3 Hz, 2H), 4.36 (q, *J* = 6.4 Hz, 1H), 4.06 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.97 – 3.90 (m, 3H), 3.80 (d, *J* = 7.4 Hz, 1H), 3.55 (d, *J* = 13.9 Hz, 2H), 1.34 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 132.0 (2C), 129.1 (4C), 128.5 (2C), 128.3, 128.4 (4C), 127.1 (2C), 123.0, 109.8, 86.9, 84.4, 76.5, 67.5, 56.2, 55.6 (2C), 26.7, 25.7; HRMS (ESI) Calcd. for $C_{28}H_{30}NO_2$ $[M + H]^+$ 412.2277, found 412.2281.

Synthesis of (*R*)-*N*,*N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(pyren-1-yl)prop-2-yn-1-amine 7f ($C_{38}H_{33}NO_2$).



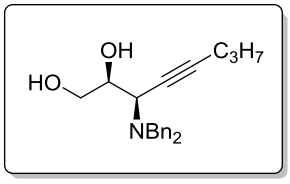
Following the *Method A*, reaction of **8** (2.00 g, 15.4 mmol) with **9** (3.05 g, 15.4 mmol) and alkyne **10f** (3.51 g, 15.4 mmol) in dry toluene (30 mL) in the presence of CuBr (110

mg, 0.77 mmol), 4 Å molecular sieves (7.50 g) was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 5% EtOAc in petroleum ether) to furnish **7f** (5.92 g, 72 %) as pale yellow oil. IR (KBr) ν (cm^{-1}): 3021, 2364, 1647, 1427, 1368, 1214; $[\alpha]_D^{25}$ = - 149.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.60 (d, *J* = 9.1 Hz, 1H), 8.27 – 8.19 (m, 3H), 8.17(t, *J* = 7.3 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.09–8.03(m, 2H), 7.56 (d, *J* = 7.3 Hz, 4H), 7.36 (t, *J* = 7.4 Hz, 4H), 7.29 – 7.25 (m, 2H), 4.56 (q, *J* = 6.3 Hz, 1H), 4.22 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.17 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.11– 4.06 (m, 3H), 3.76 (d, *J* = 13.9 Hz, 2H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.5 (2C), 132.1, 131.4 (2C), 131.1, 130.2 (2C), 129.1 (4C), 128.6 (2C), 128.3 (4C), 127.4, 127.2 (2C), 126.4, 125.8 (2C), 125.5, 124.6, 124.4, 117.5, 109.9, 90.2, 85.9, 76.6, 67.7, 56.7, 55.9 (2C), 26.7, 25.7; HRMS (ESI) Calcd. for $C_{38}H_{34}NO_2$ 536.2590 $[M + H]^+$, found 536.2586.

General procedure for deprotection of acetonides.

***Method B*:** To a solution of **7a-7f** (1 mmol) in MeOH (2.0 mL) was added 2 M HCl (0.5 mL) and the mixture was stirred for 5 h at room temperature. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and reaction mixture was concentrated. The reaction mixture was diluted by adding H_2O (20 mL) followed by the extraction of the product in Ethyl acetate (2 × 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product **11a-11f** was purified by column chromatography over silica gel.

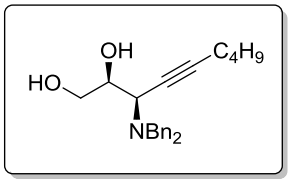
Synthesis of (2*S*,3*R*)-3-(dibenzylamino)oct-4-yne-1,2-diol 11a ($C_{22}H_{27}NO_2$).



Following the *Method B*, reaction of **7a** (5.00 g, 13.3 mmol) with 2 M HCl (6.5 mL) was carried out in methanol (30 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 10% EtOAc in petroleum ether) to furnish **11a** (3.90 g, 87 %) as colorless oil. IR (KBr) ν (cm^{-1}): 3445, 3062, 2962, 2930, 1495, 1454, 1375, 1335, 1287, 1249, 1100, 1071, 1036; $[\alpha]_D^{25}$ = - 113.8 (*c* = 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.25 (m, 9H), 7.24 – 7.23 (m, 1H), 3.86 (d, *J* = 13.4 Hz, 2H), 3.84 – 3.79 (m, 1H), 3.67 – 3.63 (m, 1H), 3.55 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.51

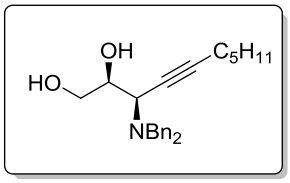
(dt, *J* = 9.9, 2.1 Hz, 1H), 3.44 (d, *J* = 13.4 Hz, 2H), 2.28 (td, *J* = 7.0, 2.1 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.2, 129.3, 128.7, 127.6, 70.5, 63.4, 55.3, 22.5, 20.9, 13.7; HRMS (ESI) Calcd. for $C_{22}H_{28}NO_2$ 338.2120 $[M + H]^+$, found 338.2117.

Synthesis of (2*S*,3*R*)-3-(dibenzylamino)non-4-yne-1,2-diol 11b ($C_{23}H_{29}NO_2$).



Following the *Method B*, reaction of **7b** (4.00 g, 10.2 mmol) with 2 M HCl (5.0 ml) was carried out in methanol (20 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 10% EtOAc in petroleum ether) to furnish **11b** (3.16 g, 88%) as colorless oil. IR (KBr) ν (cm^{-1}): 3438, 3061, 2956, 2930, 1496, 1454, 1371, 1335, 1290, 1248, 1100, 1070; $[\alpha]_D^{25}$ = - 99.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.23 (m, 10H), 3.85 (d, *J* = 13.4 Hz, 2H), 3.83 – 3.77 (m, 1H), 3.67 – 3.62 (m, 1H), 3.55 (d, *J* = 11.6 Hz, 1H), 3.50 (dt, *J* = 9.9, 2.1 Hz, 1H), 3.43 (d, *J* = 13.3 Hz, 2H), 2.30 (td, *J* = 7.0, 2.1 Hz, 2H), 1.59 – 1.43 (m, 4H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (2C), 129.3 (4C), 128.7 (4C), 126.7 (2C), 88.7, 73.4, 70.5, 63.4, 55.2, 53.9 (2C), 31.1, 22.1, 18.6, 13.8; HRMS (ESI) Calcd. for $C_{23}H_{30}NO_2$ 352.2277 $[M + H]^+$, found 352.2277.

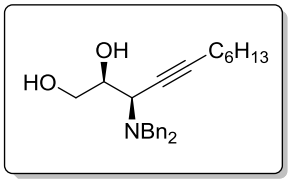
Synthesis of (2*S*,3*R*)-3-(dibenzylamino)dec-4-yne-1,2-diol 11c ($C_{24}H_{31}NO_2$).



Following the *Method B*, reaction of **7c** (4.5 g, 11.1 mmol) with 2 M HCl (6.0 ml) was carried out in methanol (25 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 12% EtOAc in petroleum ether) to furnish **11c** (3.65 g, 90%) as colorless oil.; IR (KBr) ν (cm^{-1}): 3438, 3061, 2956, 2930, 1496, 1454, 1371, 1335, 1290, 1248, 1100, 1070; $[\alpha]_D^{25}$ = - 59.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.23 (m, 10H), 3.89 – 3.79 (m, 3H), 3.67 – 3.62 (m, 1H), 3.55 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.51 (dt, *J* = 9.9, 2.1 Hz, 1H), 3.44 (d, *J* = 13.3 Hz, 2H), 2.29 (td, *J* = 7.1, 2.2 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.46 – 1.34 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.4 (2C), 129.2 (4C), 128.6 (4C), 127.5 (2C), 88.7,

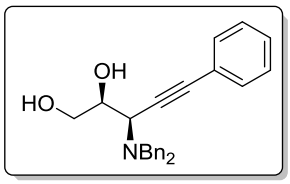
73.3, 70.4, 63.3, 55.2, 53.9 (2C), 31.2, 28.7, 22.3, 18.8, 14.2; HRMS (ESI) Calcd. for $C_{24}H_{32}NO_2$ 366.2433 $[M + H]^+$, found 366.2429.

Synthesis of (2*S*,3*R*)-3-(dibenzylamino)undec-4-yne-1,2-diol 11d ($C_{25}H_{33}NO_2$).



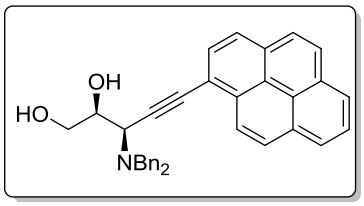
Following the *Method B*, reaction of **7d** (4.5 g, 9.54 mmol) with 2 M HCl (5.0 mL) was carried out in methanol (20 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 10% EtOAc in petroleum ether) to furnish **11d** (3.15g, 87%) as colorless oil. IR (KBr) ν (cm^{-1}): 3438, 3061, 2956, 2930, 1496, 1454, 1371, 1335, 1290, 1248, 1100, 1070; $[\alpha]_D^{25}$ = - 115.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 – 7.26 (m, 9H), 7.25- 7.23 (m, 1H), 3.98 – 3.76 (m, 3H), 3.65 (dt, *J* = 9.9, 3.4 Hz, 1H), 3.59 – 3.53 (m, 1H), 3.51 (dt, *J* = 9.8, 2.0 Hz, 1H), 3.44 (d, *J* = 13.3 Hz, 2H), 2.29 (td, *J* = 6.9, 2.1 Hz, 2H), 1.68 – 1.53 (m, 2H), 1.51 – 1.42 (m, 2H), 1.39 – 1.29 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.5 (2C), 129.2 (4C), 128.7 (4C), 127.5 (2C), 88.7, 73.4, 70.5, 63.3, 55.2, 53.9 (2C), 31.4, 29.0, 28.7, 22.7, 18.8, 14.2; HRMS (ESI) Calcd. for $C_{25}H_{34}NO_2$ 380.2589 $[M + H]^+$, found 380.2584.

Synthesis of (2*S*,3*R*)-3-(dibenzylamino)-5-phenylpent-4-yne-1,2-diol 11e ($C_{25}H_{25}NO_2$).



Following the *Method B*, reaction of **7e** (3.5 g, 8.51 mmol) with 2 M HCl (4.25 mL) was carried out in methanol (18 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 14% EtOAc in petroleum ether) to furnish **11e** (2.70 g, 85%) as pale yellow oil. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25}$ = - 70.30 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.53 – 7.48 (m, 2H), 7.41 – 7.36 (m, 6H), 7.33 – 7.31 (m, 5H), 7.26 (t, *J* = 7.2 Hz, 2H), 3.98 (d, *J* = 13.4 Hz, 2H), 3.84 – 3.74 (m, 3H), 3.62 – 3.54 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 139.9, 132.8 (2C), 130.3 (4C), 129.5 (8C), 128.4(2C), 124.1, 88.9, 84.5, 72.7, 64.4, 56.5 (2C), 55.8; HRMS (ESI) Calcd. for $C_{25}H_{26}NO_2$ $[M + H]^+$ 372.1964, found 372.196.

Synthesis of (2*S*,3*R*)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-yne-1,2-diol 11f ($C_{35}H_{29}NO_2$).

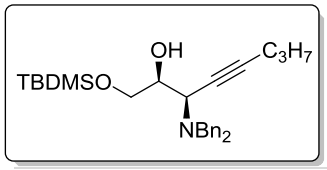


Following the *Method B*, reaction of **7f** (3.0 g, 5.60 mmol) with 2 M HCl (3.00 mL) was carried out in methanol (12 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 18% EtOAc in petroleum ether) to furnish **11f** (2.22 g, 85%) as a yellow oil. IR (KBr) ν (cm^{-1}): 3743, 3023, 2967, 2364, 1647, 1547, 1532, 1516, 1453, 1427, 1368, 1222; $[\alpha]_D^{25}$ = - 96.6 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 9.1 Hz, 1H), 8.25 – 8.19 (m, 3H), 8.18 – 8.09 (m, 3H), 8.06 – 8.02 (m, 2H), 7.42 – 7.35 (m, 8H), 7.33 – 7.27 (m, 2H), 4.11 (d, *J* = 13.3 Hz, 2H), 4.07 – 4.01 (m, 2H), 3.96 (dt, *J* = 9.9, 3.1 Hz, 1H), 3.81 (dd, *J* = 11.8, 3.4 Hz, 1H), 3.74 (d, *J* = 13.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.2 (2C), 132.1, 131.5 (2C), 131.1, 130.2 (2C), 129.3 (4C), 128.8 (2C), 128.7, 127.7 (4C), 127.3, 126.4, 125.8 (2C), 125.3, 124.6 (2C), 124.4, 117.1, 88.3, 87.2, 70.5, 63.3, 55.6, 54.7 (2C); HRMS (ESI) Calcd. for $C_{35}H_{30}NO_2$ 496.2276 $[M + H]^+$, found 496.2279.

General procedure of Selective protection of primary hydroxyl group.

***Method C*:** To a cold (0 °C) solution of the diol **11a-11f** (1.0 mmol) and imidazole (1.2 mmol) in dry CH_2Cl_2 (4.0 mL) was added dropwise a solution of TBDMSCl (1.1 mmol) in CH_2Cl_2 (6 mL). Reaction mixture was stirred for 30 min at 0 °C and 2 h at room temperature. The reaction mixture was quenched by adding sat. $NaHCO_3$ (5 mL) and aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), combined organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residues **12a-12f** over a silica gel column using ethyl acetate/petroleum ether.

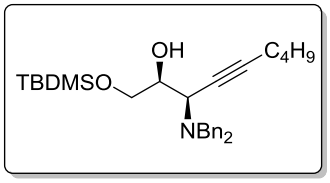
Synthesis of (2*S*,3*R*)-1-((tert-butyldimethylsilyl)oxy)-3-(dibenzylamino)oct-4-yn-2-ol 12a ($C_{28}H_{41}NO_2Si$).



Following the *Method C*, reaction of **11a** (3.00 g, 8.90 mmol) with imidazole (727 mg, 10.68 mmol) and TBDMSCl (1.14 g,

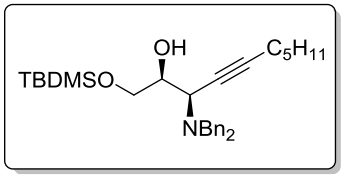
9.79 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **12a** (3.45 g, 86 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3449, 3062, 3029, 2957, 2930, 2857, 1495, 1458, 1404, 1367, 1291, 1211, 1252, 1125, 1030; $[\alpha]_D^{25}$ = - 105.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.31 – 7.27 (m, 8H), 7.24 – 7.21 (m, 2H), 3.88 – 3.83 (m, 3H), 3.67 – 3.62 (m, 2H), 3.57 – 3.52 (m, 1H), 3.41 (d, *J* = 13.3 Hz, 2H), 2.28 (td, *J* = 6.9, 1.9 Hz, 2H), 1.63 – 1.54 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.76 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.6 (2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 71.2, 61.1, 55.0, 53.3 (2C), 26.0 (3C), 22.6, 20.9, 18.4, 13.7, -5.3, -5.4; HRMS (ESI) Calcd. for $C_{28}H_{42}NO_2Si$ 452.2985 $[M + H]^+$, found 452.2985.

Synthesis of (2*S*,3*R*)-1-((tert-butyldimethylsilyl)oxy)-3-(dibenzylamino)non-4-yn-2-ol 12b ($C_{29}H_{43}NO_2Si$).



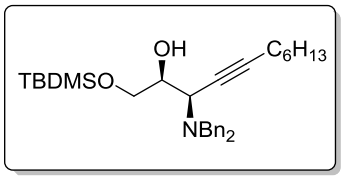
Following the *Method C*, reaction of **11b** (2.50 g, 7.12 mmol) with imidazole (581 mg, 8.54 mmol) and TBDMSCl (911 mg, 7.83 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **12b** (2.92 g, 88 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3449, 3062, 3029, 2957, 2930, 2857, 1495, 1458, 1404, 1367, 1291, 1211, 1252, 1125, 1030; $[\alpha]_D^{25}$ = - 74.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29 – 7.25 (m, 8H), 7.23 – 7.20 (m, 2H), 3.88 – 3.78 (m, 4H), 3.66 – 3.58 (m, 2H), 3.53 (dt, *J* = 9.5, 1.7 Hz, 1H), 3.39 (d, *J* = 13.3 Hz, 2H), 2.29 (td, *J* = 6.8, 2.0 Hz, 2H), 1.58 – 1.45 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 2H), 0.75 (s, 9H), -0.05 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7 (2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 88.9, 74.0, 71.2, 64.2, 55.0 (2C), 53.4, 31.2, 26.0 (3C), 22.1, 18.6, 18.4, 13.7, -5.3, -5.4; HRMS (ESI) Calcd. for $C_{29}H_{44}NO_2Si$ 466.3141 $[M + H]^+$, found 466.3146.

Synthesis of (2*S*,3*R*)-1-((tert-butyldimethylsilyl)oxy)-3-(dibenzylamino)dec-4-yn-2-ol 12c ($C_{30}H_{45}NO_2Si$).



Following the *Method C*, reaction of **11c** (3.00 g, 8.21 mmol) with imidazole (671 mg, 9.86 mmol) and TBDMSCl (1.05 g, 9.03 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **12c** (3.62 g, 92 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3029, 2929, 2857, 1532, 1497, 1459, 1367, 1292, 1251, 1125, 1070; $[\alpha]_D^{25}$ = - 75.0 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 8H), 7.26 – 7.21 (m, 2H), 3.89 – 3.77 (m, 4H), 3.67 – 3.61 (m, 2H), 3.55 (dt, *J* = 9.6, 2.0 Hz, 1H), 3.40 (d, *J* = 13.3 Hz, 2H), 2.29 (td, *J* = 7.0, 2.0 Hz, 2H), 1.60 – 1.54 (m, 2H), 1.49 – 1.33 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.76 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.7(2C), 129.3 (4C), 128.6 (4C), 127.4 (2C), 87.9, 74.1, 71.4, 64.2, 55.1 (2C), 53.4, 31.2, 29.8, 28.8, 26.0 (3C), 22.3, 19.0, 18.4, 14.2, -5.3, -5.4; HRMS (ESI) Calcd. for $C_{30}H_{46}NO_2Si$ 480.3298 $[M + H]^+$, found 480.3293.

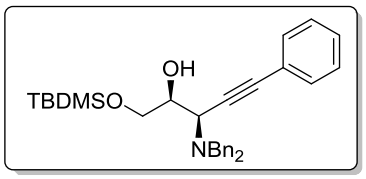
Synthesis of (2*S*,3*R*)-1-((tert-butyldimethylsilyl)oxy)-3-(dibenzylamino)undec-4-yn-2-ol 12d ($C_{31}H_{47}NO_2Si$).



Following the *Method C*, reaction of **11d** (3.10 g, 8.18 mmol) with imidazole (668 mg, 9.82 mmol) and TBDMSCl (1.05 g, 9.00 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **12d** (3.71 g, 92 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3021, 2931, 2858, 1516, 1490,1461, 1368, 1290, 1215, 1120; $[\alpha]_D^{25}$ = - 94.25 (*c* = 1.0, $CHCl_3$); δ 7.32 – 7.27 (m, 8H), 7.26 – 7.22 (m, 2H), 3.88 – 3.79 (m, 4H), 3.67 – 3.61 (m, 2H), 3.54 (dt, *J* = 9.6, 1.9 Hz, 1H), 3.40 (d, *J* = 13.3 Hz, 2H), 2.29 (td, *J* = 6.9, 2.0 Hz, 2H), 1.62 – 1.43 (m, 6H), 1.39 – 1.29 (m, 4H), 0.93(t, *J* = 7.3 Hz, 3H), 0.76 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.6 (2C), 129.2 (4C), 128.6 (4C), 127.4 (2C), 87.9, 74.0, 71.2, 64.1, 55.03 (2C),

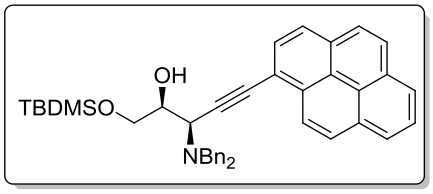
53.3, 31.4, 29.0, 28.7, 26.0 (3C), 22.7, 18.8, 18.3, 14.2, -5.3, -5.5; HRMS (ESI) Calcd. for $C_{31}H_{48}NO_2Si$ 494.3454 $[M + H]^+$, found 494.3454.

Synthesis of (2*S*,3*R*)-1-((tert-butyldimethylsilyl)oxy)-3-(dibenzylamino)-5-phenylpent-4-yn-2-ol 12e ($C_{31}H_{39}NO_2Si$).



Following the *Method C*, reaction of **11e** (2.10 g, 5.66 mmol) with imidazole (462 mg, 6.79 mmol) and TBDMSCl (724 mg, 6.23 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **12e** (2.17 g, 78 %) as a white solid. M.p 79-81 ºC. IR (KBr) ν (cm^{-1}): 2987, 2808, 1592, 1495, 1370, 1256, 1210, 1149, 1067; $[\alpha]_D^{25}$ = - 70.30 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.50 – 7.47 (m, 2H), 7.41 – 7.35 (m, 7H), 7.35 – 7.29 (m, 4H), 7.27 – 7.20 (m, 2H), 3.96 (d, *J* = 13.3 Hz, 2H), 3.88 (dd, *J* = 15.1, 5.9 Hz, 2H), 3.81 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.53 (d, *J* = 13.3 Hz, 2H), 0.77 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 139.9 (2C), 132.8 (2C), 130.3 (5C), 129.6 (4C),129.5 (2C), 128.4 (2C) , 124.1, 88.7, 84.8, 72.5, 65.0, 56.4 (2C), 54.9, 26.4(3C), 19.1, -5.2, -5.3; HRMS (ESI) Calcd. for $C_{31}H_{40}NO_2Si$ $[M + H]^+$ 486.2828, found 486.2824.

Synthesis of (2*S*,3*R*)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-yne-1,2-diol 12f ($C_{41}H_{43}NO_2Si$).



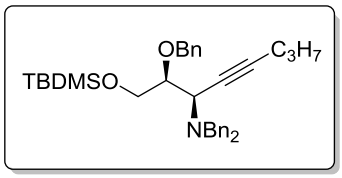
Following the *Method C*, reaction of **11f** (1.60 g, 3.23 mmol) with Imidazole (264 mg, 3.88 mmol) and TBDMSCl (413 mg, 3.55 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 5% EtOAc in petroleum ether) to furnish **12f** (1.59 g, 81 %) as a yellow thick oil. IR (KBr) ν (cm^{-1}): 3449, 3062, 3030, 2956, 2930, 2857, 1496, 1498, 1404, 1367, 1291, 1252, 1125, 1030; $[\alpha]_D^{25}$ = -101.20 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J* = 9.1 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.23 – 8.12 (m, 4H), 8.12 – 8.06 (m, 2H), 8.04 (t, *J* = 6.0 Hz,

1H), 7.42 (d, *J* = 7.2 Hz, 4H), 7.35 (t, *J* = 7.5 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 2H), 4.13 – 4.07 (m, 3H), 4.04 (dd, *J* = 12.3, 3.0 Hz, 1H), 3.97 – 3.89 (m, 2H), 3.86 (s, 1H), 3.71 (d, *J* = 13.3 Hz, 2H), 0.79 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 138.4 (2C), 132.1, 131.4, 131.3, 131.1, 130.1 (2C), 129.4 (4C), 128.8 (4C), 128.6, 128.3, 127.6 (2C), 127.3, 126.4, 125.8 (2C), 125.4, 124.6, 124.4, 117.5, 89.7, 86.7, 71.2, 64.1, 55.5 (2C), 54.3, 26.1 (3C), 18.4, -5.2, -5.4; HRMS (ESI) Calcd. for $C_{41}H_{44}NO_2Si$ 610.3141 $[M + H]^+$, found 610.3142.

General procedure of protection of secondary hydroxyl groups.

***Method D*:** To the suspension of NaH (60% in mineral oil, 1.5 mmol) in dry THF (5.0 mL) was added alcohol **12a-12f** (1.0 mmol) at 0 °C under inert atmosphere. After stirring the reaction for 10 min at 0°C, benzyl bromide (1.5 mol) was added and reaction mixture stirred for 12 h. The reaction mixture was quenched with methanol and extracted with ethyl acetate (2 × 10 mL). Solvent was removed under vaccuo, crude compound was purified by silica gel column chromatography using petether:ethyl acetate to give benzyl ether **13a-13e**.

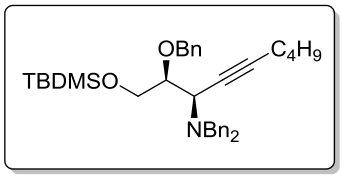
Synthesis of (2*S*,3*R*)-*N*,*N*-dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)oct-4-yn-3-amine 13a ($C_{35}H_{47}NO_2Si$).



Following the *Method D*, reaction of **12a** (2.50 g, 5.54 mmol) with NaH (60% in mineral oil, 334 mg, 8.31 mmol) and benzyl bromide (1.42 g, 8.31 mmol) in dry THF (30 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **13a** (2.37 g, 79 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3062, 3028, 2957, 2930, 2859, 1647, 1546, 1532, 1498, 1458, 1366, 1252, 1211, 1137, 1101, 1031; $[\alpha]_D^{25}$ = - 59.75 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.36 (t, *J* = 6.3 Hz, 6H), 7.30 (t, *J* = 6.3 Hz, 2H), 7.26 – 7.24 (m, 5H), 7.18 (t, *J* = 7.2 Hz, 2H), 4.71 (d, *J* = 2.2 Hz, 2H), 3.96 (d, *J* = 13.8 Hz, 2H), 3.82 – 3.80 (m, 2H), 3.67 – 3.58 (m, 2H), 3.40 (d, *J* = 13.8 Hz, 2H), 2.26 (td, *J* = 6.9, 1.6 Hz, 2H), 1.59 – 1.56 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.81 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.1 (4C), 128.3

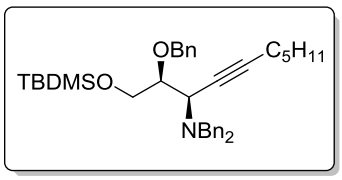
(4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 86.8, 82.0, 75.4, 73.2, 65.6, 55.9 (2C), 53.6, 26.0 (3C), 22.7, 21.0, 18.4, 13.8, -5.3 (3C); HRMS (ESI) Calcd. for $C_{35}H_{48}NO_2Si$ 542.3454 $[M + H]^+$, found 542.3467.

Synthesis of (2*S*,3*R*)-*N*,*N*-dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)non-4-yn-3-amine 13b ($C_{36}H_{49}NO_2Si$).



Following the *Method D*, reaction of **12b** (2.20 g, 4.73 mmol) with NaH (60% in mineral oil, 284 mg, 7.09 mmol) and benzyl bromide (1.21 g, 7.09 mmol) in dry THF (25 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **13b** (2.18 g, 83 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3023, 2930, 2858, 1498, 1459, 1366, 1293, 1251, 1215, 1125, 1057; $[\alpha]_D^{25}$ = - 40.40 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.35 (m, 6H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 5H), 7.22 – 7.17 (m, 2H), 4.73 (d, *J* = 2.8 Hz, 2H), 3.98 (d, *J* = 13.8 Hz, 2H), 3.84 (d, *J* = 4.3 Hz, 2H), 3.68 – 3.59 (m, 2H), 3.41 (d, *J* = 13.8 Hz, 2H), 2.31 (td, *J* = 6.8, 1.7 Hz, 2H), 1.60 – 1.46 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.1 (4C), 128.3 (4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 86.9, 82.0, 75.2, 73.2, 65.6, 55.8 (2C), 53.6, 31.3, 26.0 (3C), 22.2, 18.6, 18.4, 13.8, -5.3 (2C); HRMS (ESI) Calcd. for $C_{36}H_{50}NO_2Si$ 556.3611 $[M + H]^+$, found 556.3607.

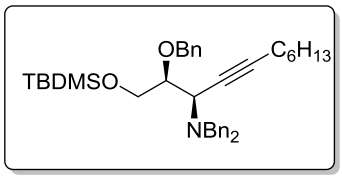
Synthesis of (2*S*,3*R*)-*N*,*N*-dibenzyl-2-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)dec-4-yn-3-amine 13c ($C_{37}H_{51}NO_2Si$).



Following the *Method D*, reaction of **12c** (3.0 g, 6.26 mmol) with NaH (60% in mineral oil, 376 mg, 9.39 mmol) and benzyl bromide (1.61 g, 9.39 mmol) in dry THF (35 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **13c** (3.14 g, 88 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3020, 2932, 2857, 1517, 1460, 1366, 1251, 1215, 1101,1035; $[\alpha]_D^{25}$ = - 41.25 (*c* = 0.8, $CHCl_3$); ^1H NMR (400 MHz,

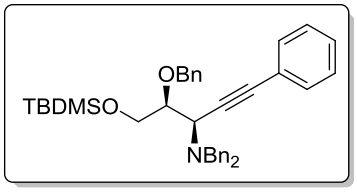
$CDCl_3$) δ (ppm): δ 7.40 – 7.33 (m, 6H), 7.30 (m, 2H), 7.28 – 7.22 (m, 5H), 7.19 (dd, *J* = 8.3, 6.1 Hz, 2H), 4.72 (s, 2H), 3.96 (d, *J* = 13.8 Hz, 2H), 3.82 (d, *J* = 3.9 Hz, 2H), 3.68 – 3.59 (m, 2H), 3.42-3.39 (m, 4H), 2.28 (td, *J* = 6.9, 1.5 Hz, 2H), 1.61 – 1.56 (m, 2H), 1.49 – 1.30 (m, 4H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.84 (s, 9H), -0.01 (s, 6H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0(2C), 139.5, 129.0 (4C), 128.5 (4C), 128.3, 128.2, 127.9, 127.8, 127.2, 126.9 (2C), 86.9, 82.0, 75.3, 73.2, 65.6, 58.2, 55.9 (2C), 53.6, 31.2, 28.9, 26.0 (3C), 22.4, 18.9, 18.4, 14.2, -5.3 (2C); HRMS (ESI) Calcd. for $C_{37}H_{52}NO_2Si$ 570.3767 [M + H]$^+$, found 570.3767.

Synthesis of (2*S*,3*R*)-*N*,*N*-dibenzyl-2-(benzyloxy)-1-((terbutyldimethylsilyl)oxy)undec-4-yn-3-amine 13d ($C_{38}H_{53}NO_2Si$).



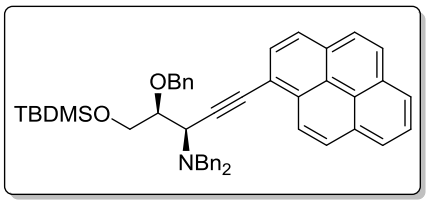
Following the *Method D*, reaction of **12d** (3.2 g, 6.49 mmol) with NaH (60% in mineral oil, 390 mg, 9.74 mmol) and benzyl bromide (1.67 g, 9.74 mmol) in dry THF (35 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **13d** (3.22 g, 85 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3029, 2928, 2857, 1496, 1458, 1361, 1252, 1211, 1100, 1032; $[\alpha]_D^{25}$ = - 54.80 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.36 (t, *J* = 6.3 Hz, 6H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 5H), 7.18 (d, *J* = 7.1 Hz, 2H), 4.72 (d, *J* = 1.8 Hz, 2H), 3.97 (d, *J* = 13.8 Hz, 2H), 3.83 – 3.77 (m, 2H), 3.64 – 3.59 (m, 2H), 3.39 (d, *J* = 13.8 Hz, 2H), 2.28 (td, *J* = 6.8, 1.7 Hz, 2H), 1.60 – 1.56 (m, 2H), 1.50 – 1.42 (m, 2H), 1.28 – 1.34 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.81 (s, 9H), -0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 140.0 (2C), 139.5, 129.0 (4C), 128.3 (4C), 128.2 (2C), 127.6 (2C), 127.2, 126.9 (2C), 87.0, 82.0, 75.3, 73.2, 65.6, 55.9 (2C), 53.6, 31.5, 29.2, 28.8 26.0 (3C), 22.8, 19.0, 18.4, 14.3, -5.3 (2C); HRMS (ESI) Calcd. for $C_{38}H_{54}NO_2Si$ 584.3924 [M + H]$^+$, found 584.3924.

Synthesis of (3*R*,4*S*)-*N*,*N*-dibenzyl-4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-1-phenylpent-1-yn-3-amine 13e (C38H45NO2Si).



Following the *Method D*, reaction of **12e** (1.75 g, 3.61 mmol) with NaH (60% in mineral oil, 216 mg, 5.41 mmol) and benzyl bromide (925 mg, 5.41 mmol) in dry THF (20 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 1% EtOAc in petroleum ether) to furnish **13e** (1.74 g, 84 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3028, 2854, 1600, 1492, 1455, 1358, 1254, 1144, 1099, 1068, 1028; $[\alpha]_D^{25}$ = - 69.00 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 7.50 – 7.46 (m, 2H), 7.42 – 7.33 (m, 9H), 7.33 – 7.23 (m, 7H), 7.23 – 7.19 (m, 2H), 4.72 (s, 2H), 4.04 (d, *J* = 13.7 Hz, 2H), 3.96 (dd, *J* = 10.5, 6.1 Hz, 2H), 3.88 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.50 (d, *J* = 13.6 Hz, 2H), 0.82 (s, 9H), -0.02 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 140.8 (2C), 140.3, 132.8 (3C), 130.1 (4C), 129.5 (4C), 129.3 (4C), 129.2 (2C), 128.7 (2C), 128.4, 128.1 (2C), 124.5, 88.0, 86.1, 82.5, 73.8, 65.5, 57.0 (2C), 54.8, 26.4 (3C), 19.1, -5.2 (2C); HRMS (ESI) Calcd. for C38H46NO2Si $[M + H]^+$ 576.3298, found 576.3298.

Synthesis of (3*R*,4*S*)-*N*,*N*-dibenzyl-4-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-1-(pyren-1-yl)pent-1-yn-3-amine 13f ($C_{48}H_{49}NO_2Si$).



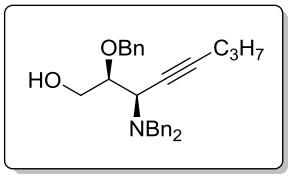
Following the *Method D*, reaction of **12f** (1.75 g, 2.05 mmol) with NaH (60% in mineral oil, 123 mg, 3.08 mmol) and benzyl bromide (526 mg, 3.08 mmol) in dry THF (10 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 2% EtOAc in petroleum ether) to furnish **13f** (1.06 g, 74 %) as a yellow oil. IR (KBr) ν (cm^{-1}): 3417, 3221, 2931, 1685, 1457, 1363, 1270, 1133, 1072, 1057; $[\alpha]_D^{25}$ = - 69.00 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 7.31 – 7.21 (m, 8H), 7.26 – 7.21 (m, 2H), 3.88 – 3.83 (m, 3H), 3.80 (s, 3H), 3.66 (t, *J* = 3.7 Hz, 1H), 3.63 (t, *J* = 4.2 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.41 (d, *J* = 13.3 Hz, 2H), 2.28 (td, *J* = 6.9, 1.9 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.76 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ (ppm): 138.6 (2C), 129.4 (4C), 128.6 (4C), 127.4 (2C), 71.2, 61.1, 55.0, 53.3 (2C), 26.02, 22.60, 20.9, 18.4, 13.8, -5.2, -5.4; HRMS (ESI) Calcd. for $C_{48}H_{50}NO_2Si$ 700.3611 $[M + H]^+$, found 700.3597.

General procedure for TBDMS deprotection.

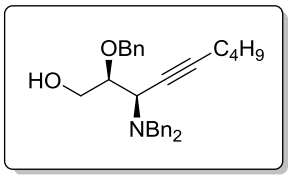
***Method E*:** To a solution of **13a-13f** (1.0 mmol) in dry THF (4.0 mL) placed at 0˚C, TBAF (1.0 mmol, 1 M in THF) was added drop wise and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted by adding H_2O (5.0 mL) followed by the extraction of the product in Et_2O (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product **14a-14f** was purified by column chromatography over silica gel.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)oct-4-yn-1-ol 14a ($C_{29}H_{33}NO_2$).



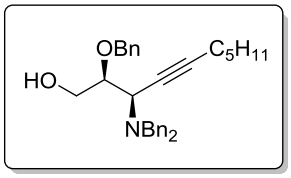
Following the *Method E*, reaction of **13a** (1.75 g, 3.23 mmol) with TBAF (844 mg, 3.23 mmol, 1 M in THF) in dry THF (30 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 8% EtOAc in petroleum ether) to furnish **14a** (1.28 g, 93 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3450, 3062, 3029, 2931, 2873, 1547, 1497, 1454, 1365, 1209, 1098, 1074, 1033; $[\alpha]_D^{25}$ = - 26.40 (*c* =1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, *J* = 7.2 Hz, 4H), 7.36–7.27 (m, 9H), 7.26 – 7.21 (m, 2H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.07 (d, *J* = 13.6 Hz, 2H), 3.83 – 3.76 (m, 1H), 3.69 (dt, *J* = 4.4, 2.2 Hz, 1H), 3.68 – 3.57 (m, 2H), 3.42 (d, *J* = 13.6 Hz, 2H), 2.31 (td, *J* = 7.1, 2.2 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3 (2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.2 (2C), 87.6, 80.6, 74.3, 73.1, 63.3, 56.2 (2C), 54.6, 22.6, 20.9, 13.7; HRMS (ESI) Calcd. for $C_{29}H_{34}NO_2$ 428.2589 $[M + H]^+$, found 428.2588.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)non-4-yn-1-ol 14b ($C_{30}H_{35}NO_2$).



Following the *Method E*, reaction of **13b** (1.60 g, 2.88 mmol) with TBAF (2.88 mL, 2.88 mmol, 1 M in THF) in dry THF (25 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 8% EtOAc in petroleum ether) to furnish **14a** (1.19 g, 94 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3465, 3062, 3029, 2929, 2866, 1495, 1453, 1359, 1247, 1208, 1096, 1072, 1032; $[\alpha]_D^{25}$ = - 58.20 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (d, *J* = 7.1 Hz, 4H), 7.36 – 7.26 (m, 9H), 7.25 –7.21 (m, 2H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.07 (d, *J* = 13.6 Hz, 2H), 3.80 (d, *J* = 10.3 Hz, 1H), 3.69 (dt, *J* = 4.3, 2.1 Hz, 1H), 3.64–3.57 (m, 2H), 3.42 (d, *J* = 13.6 Hz, 2H), 2.33 (td, *J* = 6.9, 2.1 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.56–1.47 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.3(2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.2 (2C), 87.7, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.2, 22.2, 18.6, 13.8; HRMS (ESI) Calcd. for $C_{30}H_{36}NO_2$ 442.2746 $[M + H]^+$, found 442.2747.

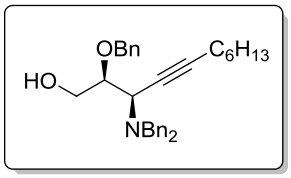
Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)dec-4-yn-1-ol 14c ($C_{31}H_{37}NO_2$).



Following the *Method E*, reaction of **13c** (2.50 g, 4.39 mmol) with TBAF (4.39 ml, 4.39 mmol, 1 M in THF) in dry THF (40 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 8% EtOAc in petroleum ether) to furnish **14c** (1.88 g, 94 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3465, 3062, 3021, 2928, 2860, 1516, 1461, 1368, 1247, 1214, 1100, 1072, 1030; $[\alpha]_D^{25}$ = - 12.80 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 4H), 7.34–7.28 (m, 9H), 7.25–7.21 (m, 2H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.6Hz, 1H), 4.08 (d, *J* = 13.6 Hz, 2H), 3.80 (dd, *J* = 10.4, 3.0 Hz, 1H), 3.70–3.3.68 (dd, *J* = 5.2, 1.9 Hz, 1H), 3.64–3.57 (m, 2H), 3.42 (d, *J* = 13.6 Hz, 2H), 2.89 (s, 1H), 2.36 – 2.29 (m, 2H), 1.64–1.58 (m, 2H), 1.51 – 1.34 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4 (2C), 138.6, 129.1 (4C), 128.5 (4C), 128.4 (2C), 127.8 (2C), 127.7, 127.3 (2C), 87.8, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.3,

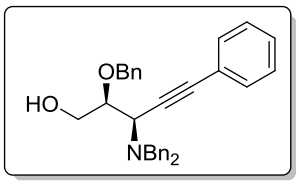
28.8, 22.4, 18.9, 14.2; HRMS (ESI) Calcd. for $C_{31}H_{38}NO_2$ 456.2903 $[M + H]^+$, found 456.2903.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)undec-4-yn-1-ol 14d ($C_{32}H_{39}NO_2$).



Following the *Method E*, reaction of **13d** (2.50 g, 4.29 mmol) with TBAF (4.29 ml, 4.29 mmol, 1 M in THF) in dry THF (40 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 8% EtOAc in petroleum ether) to furnish **14d** (1.80 g, 90 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3468, 3060, 3027, 2921, 2860, 1510, 1441, 1358, 1246, 1213, 1101, 1073, 1028 $[\alpha]_D^{25}$ = - 78.20 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, *J* = 7.2 Hz, 4H), 7.36 – 7.26 (m, 9H), 7.26 – 7.21 (m, 2H), 4.82 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.07 (d, *J* = 13.6 Hz, 2H), 3.79 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.68 (dt, *J* = 4.3, 2.1 Hz, 1H), 3.64 – 3.55 (m, 2H), 3.41 (d, *J* = 13.7 Hz, 2H), 2.87 (s, 1H), 2.32 (td, *J* = 7.0, 2.1 Hz, 2H), 1.63 – 1.57 (m, 2H), 1.51–1.45 (m, 2H), 1.38 – 1.28 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.4, 138.6 (2C), 129.1 (4C), 128.5 (4C), 127.8 (2C), 127.7 (2C), 127.3, 87.8, 80.6, 74.2, 73.2, 63.3, 56.2 (2C), 54.7, 31.5, 29.1, 28.8, 22.8, 18.9, 14.3; HRMS (ESI) Calcd. for $C_{32}H_{40}NO_2$ 470.3059 $[M + H]^+$, found 470.3054.

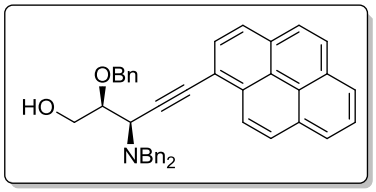
Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)-5-phenylpent-4-yn-1-ol 14e ($C_{32}H_{31}NO_2$).



Following the *Method E*, reaction of **13e** (1.40 g, 2.43 mmol) with TBAF (2.43 ml, 2.43 mmol, 1 M in THF) in dry THF (25 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 10% EtOAc in petroleum ether) to furnish **14e** (1.19 g, 88 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3431, 3035, 2935, 2820, 2465, 1813, 1589, 1512, 1469, 1367, 1230, 1117, 1038; $[\alpha]_D^{25}$ = - 93.25 (*c* = 0.8, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ (ppm): 7.51-7.48 (m, 2H), 7.42- 7.39 (m, 6H), 7.35 – 7.31 (m, 3H), 7.30 – 7.22 (m, 7H), 7.21 – 7.16 (m, 2H), 4.73 (s, 2H), 4.04 (d, *J* = 13.7 Hz, 2H), 3.90 (d, *J* = 6.3 Hz, 1H), 3.86 – 3.78 (m, 2H), 3.77 – 3.72 (m, 1H),

3.50 (d, *J* = 13.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 140.6 (2C), 140.1, 132.8 (3C), 130.1 (4C), 129.5 (4C), 129.3 (2C), 129.2 (2C), 128.8, 128.2 (2C), 128.1 (2C), 124.3, 88.2, 85.6, 82.5, 74.2, 64.0, 57.1(2C), 55.7; HRMS (ESI) Calcd. for $C_{32}H_{32}NO_2$ 462.2433 $[M + H]^+$, found 462.2431.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-yn-1-ol 14f ($C_{42}H_{35}NO_2$).



Following the *Method E*, reaction of **13f** (1.10 g, 1.57 mmol) with TBAF (1.57 mL, 1.57 mmol, 1 M in THF) in dry THF (15 mL) at 0 °C was carried out. The crude product was subjected to column chromatography over silica gel (*Eluent*: 12% EtOAc in petroleum ether) to furnish **14f** (755 mg, 82 %) as a yellow oil. IR (KBr) ν (cm^{-1}): 3451, 3025, 2967, 2938, 1648, 1547, 1516, 1453, 1427, 1368, 1219, 1100, 1070, 1030; $[\alpha]_D^{25}$ = - 93.25 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.65 (d, *J* = 9.1 Hz, 1H), 8.25 – 8.21 (m, 2H), 8.19 – 8.11 (m, 4H), 8.09 – 8.03 (m, 2H), 7.50 (d, *J* = 7.3 Hz, 4H), 7.39 (dt, *J* = 14.8, 7.0 Hz, 6H), 7.30 (ddd, *J* = 7.1, 5.1, 2.6 Hz, 5H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 13.5 Hz, 2H), 4.20 (d, *J* = 5.1 Hz, 1H), 4.01 (dd, *J* = 11.7, 4.7 Hz, 1H), 3.91 (q, *J* = 4.8 Hz, 1H), 3.79 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.72 (d, *J* = 13.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 139.2 (2C), 138.5, 132.3, 131.4, 131.2, 130.1 (2C), 129.3 (4C), 128.7 (4C), 128.6 (2C), 128.4, 127.8 (2C), 127.5 (2C), 127.4, 126.8(2C), 126.6 (2C), 125.6 (2C), 124.6, 117.6, 90.1, 86.5, 80.9, 73.4, 63.3, 56.8 (2C), 55.4; HRMS (ESI) Calcd. for $C_{42}H_{36}NO_2$ 586.2746 $[M + H]^+$, found 586.2751.

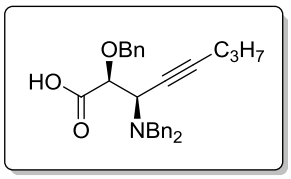
General procedure for oxidation of primary alcohol to acid.

Method F: A solution of oxalyl chloride (2.00 mmol) in dry CH_2Cl_2 (5 mL) was cooled at -78˚C, DMSO (4.40 mmol) was added dropwise and the mixture was stirred for 15 min. To this mixture was added a solution of alcohol **14a-14e** (1.34 mmol) in CH_2Cl_2 and stirred at -78˚C for 30 min. Subsequently, Et_3N (6.80 mmol) was added and reaction mixture was stirred at 0˚C for additional 30 min. Then reaction mixture was diluted by adding CH_2Cl_2 and H_2O (10 mL) followed by the extraction of the product in CH_2Cl_2 (2 ×

10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give corresponding aldehyde product. The crude product was used for next rection.

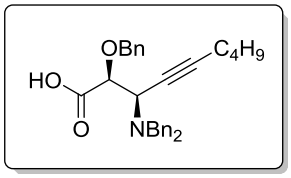
To a solution of aldehyde (2.00 mmol) and 2-methyl-2-butene (20.0 mmol) in 25 mL tBuOH-H_2O (3 :1) placed at 0 ^oC, were added added NaH_2PO_4 (2.00 mmol) and $NaClO_2$ (2.00 mmol) and the rection mixture was stirred at rt for 10 h. The mixture was concentrated, diluted with H_2O, acidified with 1 N HCl until pH = 2-3 was reached and extracted with ethyl acetate. The combined organic layer was wased with brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product **6a-6e** was purified by column chromatography over silica gel using EtOAc in petroleum ether as eluent.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)oct-4-ynoic acid 6a ($C_{29}H_{31}NO_3$).



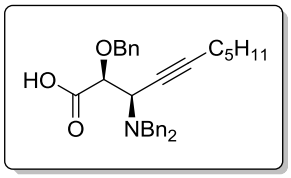
Following the *Method F*, the Swern oxidation of alcohol **14a** (1.0 g, 2.34 mmol) was carried out to obtain corresponding aldehyde (994 mg, 2.34 mmol) as a crude product which was further oxidized using NaH_2PO_4 (281 mg, 2.34 mmol), 2-methyl -2-butene (3.28 g, 46.8 mmol) and $NaClO_2$ (212 mg, 2.34 mmol) in 25 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 20 % EtOAc in petroleum ether) to furnish **6a** (867 mg, 84 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3743, 3061, 3027, 2963, 1726, 1612, 1497, 1455, 1373, 1213, 1143, 1101, 1028; $[\alpha]_D^{25}$ = - 132.00 (*c* = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.36 – 7.27 (m, 13H), 4.91 (d, *J* = 11.8 Hz, 1H), 4.69 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 13.1 Hz, 2H), 3.95 (d, *J* = 3.6 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.48 (d, *J* = 13.3 Hz, 2H), 2.33 (td, *J* = 7.0, 2.2 Hz, 2H), 1.68–1.60 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 137.3, 135.8 (2C), 129.8 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.6, 79.2, 74.0, 71.3, 56.5 (2C), 53.1, 22.3, 21.0, 13.7; HRMS (ESI) Calcd. for $C_{29}H_{32}NO_3$ 442.2382 $[M + H]^+$, found 442.2382.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)non-4-ynoic acid 6b ($C_{30}H_{33}NO_3$).



Following the *Method F*, the Swern oxidation of alcohol **14a** (1.0 g, 2.34 mmol) was carried out to obtain corresponding aldehyde (925 mg, 2.10 mmol) as a crude product which was further oxidized using NaH_2PO_4 (252 mg, 2.10 mmol), 2-methyl -2-butene (2.94 g, 42.0 mmol),and $NaClO_2$ (190 mg, 2.10 mmol) in 12.5 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 20 % EtOAc in petroleum ether) to furnish **6b** (784 mg, 82 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3743, 3027, 2930, 2866, 1734, 1647, 1547, 1498, 1455, 1370, 1213, 1143, 1101, 1028; $[\alpha]_D^{25}$ = - 75.80 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.36-7.33 (m, 2H), 7.33 – 7.29 (m, 10H), 7.28 – 7.26 (m, 1H), 4.92 (d, *J* = 11.8 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 13.3 Hz, 2H), 3.96 (d, *J* = 3.6 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.47 (d, *J* = 13.2 Hz, 2H), 2.35 (td, *J* = 7.0, 2.1 Hz, 2H), 1.64–1.56 (m, 2H), 1.55 – 1.45 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 137.3, 135.5 (2C), 129.9 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.9, 79.3, 73.9, 71.1, 56.5 (2C), 53.4, 30.9, 22.2, 18.6, 13.7; HRMS (ESI) Calcd. for $C_{30}H_{34}NO_3$ 456.2539 $[M + H]^+$, found 456.2540.

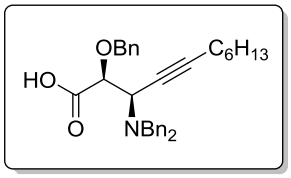
Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)dec-4-ynoic acid 6c ($C_{31}H_{35}NO_3$).



Following the *Method F*, the Swern oxidation of alcohol **14c** (600 mg, 1.32 mmol) was carried out to obtain corresponding aldehyde (598 mg, 1.32 mmol) as crude product which was further oxidized using NaH_2PO_4 (158 mg, 1.32 mmol), 2-methyl -2-butene (1.85 g, 26.4 mmol),and $NaClO_2$(119 mg, 1.32 mmol).in 15 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 20 % EtOAc in petroleum ether) to furnish **6c** (526 mg, 85 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3744, 3023, 2931, 2863, 1740, 1648, 1516, 1454, 1368, 1214, 1101, 1033; $[\alpha]_D^{25}$ = - 74.00 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 – 7.35

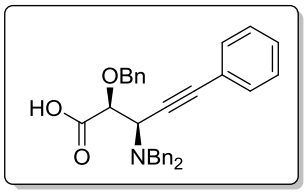
(m, 2H), 7.34 – 7.31 (m, 2H), 7.31- 7.27 (m, 10H), 7.26-7.24 (m, 1H), 4.90 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 1H), 4.36 (d, *J* = 13.1 Hz, 2H), 3.96 (d, *J* = 3.7 Hz, 1H), 3.92 – 3.88 (m, 1H), 3.46 (d, *J* = 13.3 Hz, 2H), 2.33 (td, *J* = 7.0, 2.1 Hz, 2H), 1.62- 1.57 (m, 2H), 1.47 – 1.43 (m, 2H), 1.40 – 1.32 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.9, 137.3, 135.8(2C), 129.8 (4C), 128.9 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.8, 79.2, 74.0, 71.1, 56.5 (2C), 53.1, 31.3, 28.5, 22.3, 18.9, 14.2; HRMS (ESI) Calcd. for $C_{31}H_{36}NO_3$ 470.2695 $[M + H]^+$, found 470.2695.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)undec-4-ynoic acid 6d ($C_{32}H_{37}NO_3$).



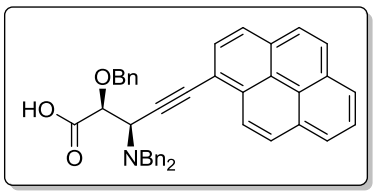
Following the *Method F*, the Swern oxidation of alcohol **14d** (1.20 g, 2.56 mmol) was carried out to obtain corresponding aldehyde (1.18 g, 2.56 mmol) as crude product which was further oxidized using (307 mg, 2.56 mmol), 2-methyl -2-butene (3.59 g, 51.2 mmol) and $NaClO_2$(232 mg, 2.56 mmol). in 30 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 20 % EtOAc in petroleum ether) to furnish **6d** (1.04 g, 84 %) as a colorless oil. IR (KBr) ν (cm^{-1}): 3744, 3061, 3021, 2931, 1740, 1612, 1516, 1455, 1369, 1214, 1143, 1100, 1028; $[\alpha]_D^{25}$ = - 114.50 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 – 7.37 (m, 2H), 7.36 – 7.26 (m, 13H), 4.92 (d, *J* = 11.8 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.38 (d, *J* = 13.0 Hz, 2H), 3.96 (d, *J* = 3.6 Hz, 1H), 3.92 – 3.88 (m, 1H), 3.48 (d, *J* = 13.2 Hz, 2H), 2.34 (td, *J* = 7.0, 2.1 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.52 – 1.44 (m, 2H), 1.37 – 1.30 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 137.2, 135.6 (2C), 129.9 (4C), 129.0 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.0, 89.9, 79.2, 74.1, 71.0, 56.5 (2C), 53.1, 31.5, 28.8 (2C), 22.8, 20.0, 14.2; HRMS (ESI) Calcd. for $C_{32}H_{38}NO_3$ 484.2852 $[M + H]^+$, found 484.2850.

Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)-5-phenylpent-4-ynoic acid 6e ($C_{32}H_{29}NO_3$).



Following the *Method F*, the Swern oxidation of alcohol **14f** (1.00 g, 2.00mmol) was carried out to obtain corresponding aldehyde (998 mg, 2.20 mmol) as a crude product which was further oxidized using NaH_2PO_4 (264mg, 2.20 mmol), 2-methyl -2-butene (3.14 g, 44.0 mmol),and $NaClO_2$(199 mg, 2.20 mmol) in 25 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 25 % EtOAc in petroleum ether) to furnish **6e** (753mg, 72 %) as a white solid. Mp 130-132 °C IR (KBr) ν (cm^{-1}): 3744, 3565, 3022, 2964, 1740, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = - 143.20 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 7.51-7.48 (m, 2H), 7.39 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.39-7.35 (m, 7H), 7.27 – 7.21 (m, 7H), 7.20 – 7.15 (m, 2H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 11.9 Hz, 1H), 4.20 (d, *J* = 5.2 Hz, 1H), 4.14 (s, 1H), 4.10 (d, *J* = 5.1 Hz, 2H), 3.42 (d, *J* = 13.6 Hz, 2H);^{13}C NMR (100 MHz, CD_3OD) δ (ppm): 173.4, 140.3, 139.0 (2C), 132.9 (2C), 130.3 (4C), 129.5 (2C), 129.3 (4C), 129.2 (2C), 129.0 (2C), 128.7 (2C), 128.1 (2C), 124.3, 88.7, 84.2, 82.4, 74.2, 57.4 (2C), 55.7; HRMS (ESI) Calcd. for $C_{32}H_{30}NO_3$ 476.2226 $[M + H]^+$, found 476.2230.

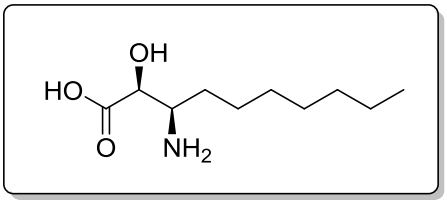
Synthesis of (2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)-5-(pyren-1-yl)pent-4-ynoic acid 6f ($C_{42}H_{33}NO_3$).



Following the *Method F*, the Swern oxidation of alcohol **14f** (275 mg, 0.47 mmol) was carried out to obtain corresponding aldehyde aldehyde (273 mg, 0.47 mmol) as crude product which was further oxidized using NaH_2PO_4 (57 mg, 0.47 mmol), 2-methyl -2-butene (660 mg, 9.4 mmol),and NaClO2(42 mg ,0.47 mmol) in 6 mL tBuOH-H_2O (3.5 :1). The crude product was purified by column chromatography over silica gel (*Eluent*: 30 % EtOAc in petroleum ether) to furnish **6f** (184 mg, 79 %) as a yellow solid. Mp 214-216 °C IR (KBr) ν (cm^{-1}): 3744, 3565, 3022, 2964, 1740, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = - 143.20 (*c* = 0.5,

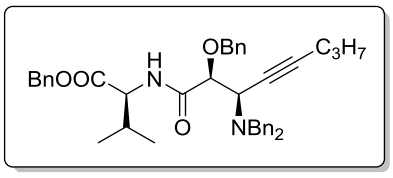
$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 9.1 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 2H), 8.19 – 8.12 (m, 3H), 8.10 – 8.03 (m, 3H), 7.43 (dd, *J* = 12.1, 4.8 Hz, 6H), 7.37 (t, *J* = 7.2 Hz, 4H), 7.31 (dd, *J* = 8.3, 5.8 Hz, 2H), 7.21 (dd, *J* = 6.4, 3.6 Hz, 3H), 5.02 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 13.1 Hz, 2H), 4.39 (d, *J* = 3.8 Hz, 1H), 4.28 (d, *J* = 3.8 Hz, 1H), 3.73 (d, *J* = 13.3 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 137.0, 136.3(2C), 132.5, 131.8, 131.3, 131.0, 131.1, 130.2 (2C), 129.9 (4C), 129.0 (4C), 128.9, (2C), 128.7 (2C), 128.6, 128.3(2C), 128.2, 128.0, 127.3, 126.5, 126.0 (2C), 125.4, 124.6, 124.4, 87.8, 86.6, 79.6, 74.2, 56.9 (2C), 54.0; HRMS (ESI) Calcd. for $C_{42}H_{34}NO_3$ 600.2539 $[M + H]^+$, found 600.2538.

Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid 15 ($C_{10}H_{21}NO_3$).



To a solution of **6c** (40 mg, 0.085 mmol) in methanol: water(1:1) (10 mL) placed in a parr apparatus was added 20% $Pd(OH)_2/C$ (3mg, 0.0085mmol) and subsequently stirred under 100 psi H_2 pressure at room temperature for 12 h. The reaction mixture was filtered through a celite pad. The solvent was evaporated under reduced pressure which was further purified by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) (*Eluent:* 5% aqueous NH_4OH) to furnish **15** as a white solid (86%, 14.8 mg). Mp: 218-220 ºC.; $[\alpha]_D^{25}$ = + 5.7 (*c* = 0.6, 1M HCl); ^{1}H NMR (400 MHz, D_2O) δ (ppm): 4.12 (dd, *J* = 28.8, 2.1 Hz, 1H), 3.48 (dt, *J* = 11.9, 6.4 Hz, 1H), 1.60-1.79 (m, 2H), 1.48 – 1.16 (m, 12H), 0.85 (t, *J* = 6.0 Hz, 3H). HRMS (ESI) Calcd. for $C_{10}H_{22}NO_3$ 204.1599 $[M + H]^+$, found 204.1604.

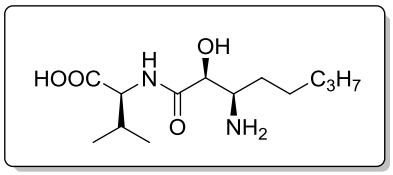
Synthesis of Benzyl ((2*S*,3*R*)-2-(benzyloxy)-3-(dibenzylamino)oct-4-ynoyl)-L-valinate 16 ($C_{41}H_{46}N_2O_4$).



To a solution of **6a** (100 mg, 0.23 mmol) and L-valine benzyl ester (56 mg, 0.27 mmol) in DMF (2 mL) were added EDCl·HCl (52 mg, 0.27 mmol), HOBt (36 mg, 0.27 mmol) and DIPEA (74 mg, 0.58 mmol). The mixture was stirred at room temperature for 24 h. After removal of the solvent in vacuo, the residue was dissolved in EtOAc (5.0 mL), washed with 5% citric acid, 5% sodium

bicarbonate, and saturated NaCl, dried over Na_2SO_4, and concentrated in vacuo. The crude product was subjected to column chromatography over silica gel (*Eluent*: 6% EtOAc in petroleum ether) to furnish **16** (123 mg, 85%) as colorless oil; IR (KBr) ν (cm^{-1}): 3565, 3022, 2964, 1740, 1680, 1532, 1516, 1454, 1427, 1368, 1215, 1100; $[\alpha]_D^{25}$ = - 86.0 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 9.1 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 2H), 8.19 – 8.12 (m, 3H), 8.10 – 8.03 (m, 3H), 7.43 (dd, *J* = 12.1, 4.8 Hz, 6H), 7.37 (t, *J* = 7.2 Hz, 4H), 7.31 (dd, *J* = 8.3, 5.8 Hz, 2H), 7.21 (dd, *J* = 6.4, 3.6 Hz, 3H), 5.02 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 13.1 Hz, 2H), 4.39 (d, *J* = 3.8 Hz, 1H), 4.28 (d, *J* = 3.8 Hz, 1H), 3.73 (d, *J* = 13.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.8, 170.3, 139.5(2C), 137.2, 135.5, 129.0 (4C), 128.7 (2C), 128.5 (4C), 128.3(2C), 128.2 (4C), 128.1 (2C), 127.0 (2C), 87.6, 83.9, 74.4, 74.0, 57.0, 56.3 (2C), 54.8, 31.3, 22.5, 21.0, 19.1, 17.9 (2C), 13.8; HRMS (ESI) Calcd. for $C_{41}H_{47}N_2O_4$ 631.3536 $[M + H]^+$, found 631.3529.

Synthesis of ((2*S*,3*R*)-3-amino-2-hydroxyoctanoyl)-L-valine ($C_{13}H_{26}N_2O_4$) 3.



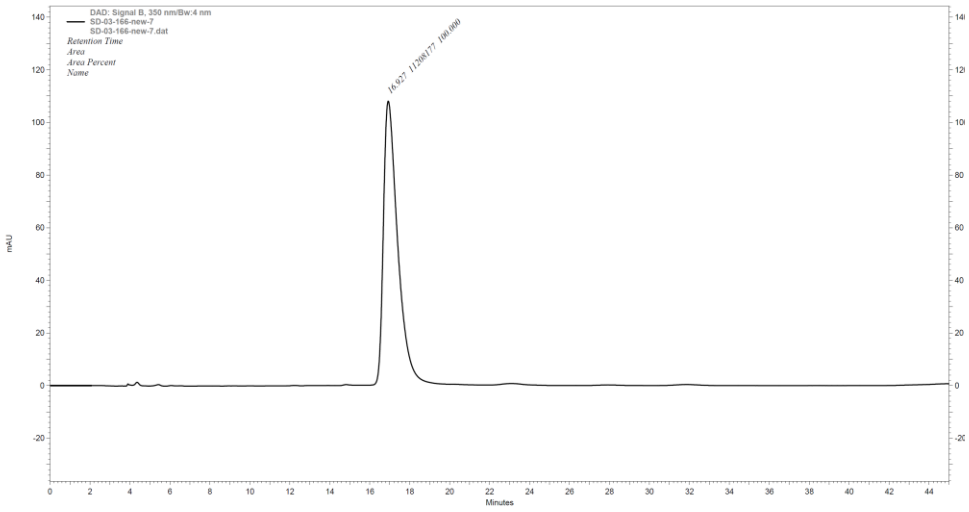
To a solution of **16** (80 mg, 0.127 mmol) in MeOH-AcOH-H_2O (5:2:3, v/v (mL)), placed in a parr apparatus was added 20% $Pd(OH)_2/C$ (4 mg, 0.0127 mmol) and subsequently stirred under 100 psi H_2 pressure at room temperature for 12 h. The reaction mixture was filtered through celite pad and which was further purified by Sephadex LH-20 to furnish **3** (31 mg, 90%) as white solid; Mp 214-216 °C; IR (KBr) ν (cm^{-1}): 3344, 3265, 2964, 1670, 1532, 1516, 1454, 142, 1215, 1100;$[\alpha]_D^{25}$ = - 23.5 (*c* = 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm): 4.25 (d, *J* = 3.3 Hz, 1H), 4.22 (d, *J* = 4.4 Hz, 1H), 3.45 – 3.39 (m, 1H), 2.31 – 2.14 (m, 1H), 1.87 – 1.78 (m, 1H), 1.65 – 1.43 (m, 3H), 1.39 – 1.35 (m, 3H), 1.01 – 0.96 (m, 6H), 0.94 (t, *J* = 6.8 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 177.9, 173.0, 70.8, 61.4, 55.4, 32.7, 32.0, 30.5, 26.1, 23.4, 20.2, 18.4, 14.3. HRMS (ESI) Calcd. for $C_{13}H_{27}N_2O_4$ 275.1971 $[M + H]^+$, found 275.1972.

3A.8 Cell culture and fluorescence imaging

The 0.4 million Human colorectal cancer cells (DLD1) were seeded in a 6 well plate in RPMI-1640 medium supplemented with 10% fetal bovine serum. Cells were grown at 37ºC in CO_2 incubator for 24 h. For compound treatment, RPMI was replaced with 1 ml of reduced serum medium OptiMEM (Gibco) and cells were incubated with compound 14e (20 µM) concentration in 1:1000 (DMSO:OptiMEM) medium for 30min at 37ºC. After washing with DPBS (Dulbecco`s Phosphate Buffered Saline) three times to remove the remaining compound, the fluorescence images were acquired with a fluorescent microscope (EVOS cell imaging system) with 40 X objective. Excitation and emission did in DAPI region.

3A.9 HPLC analysis of 7f.

Column: CHIRALPAK IC (0.46 cm × 25 cm); **Flow rate:** 1.0 mL/min; **Method:** Isocratic, mobile phase: 5 % Isopropanol and 95 % n-heptane; **Wavelength:** 350 nm.



DAD: Signal B, 350 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
16.927	11208177	100.00	226190	100.00

Figure 3A.3: HPLC analysis of 7f.

3A.10 Appendix II: ^{1}H and ^{13}C spectral data of representative compounds

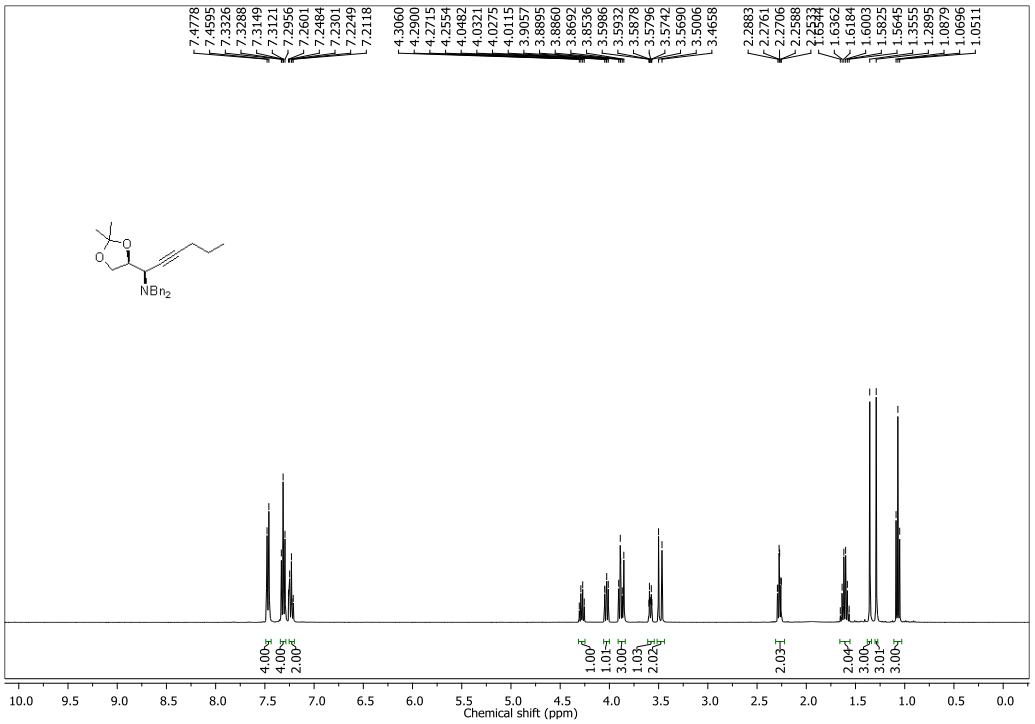


Figure 3A.4: ^{1}H NMR spectra of **7a** in $CDCl_3$.

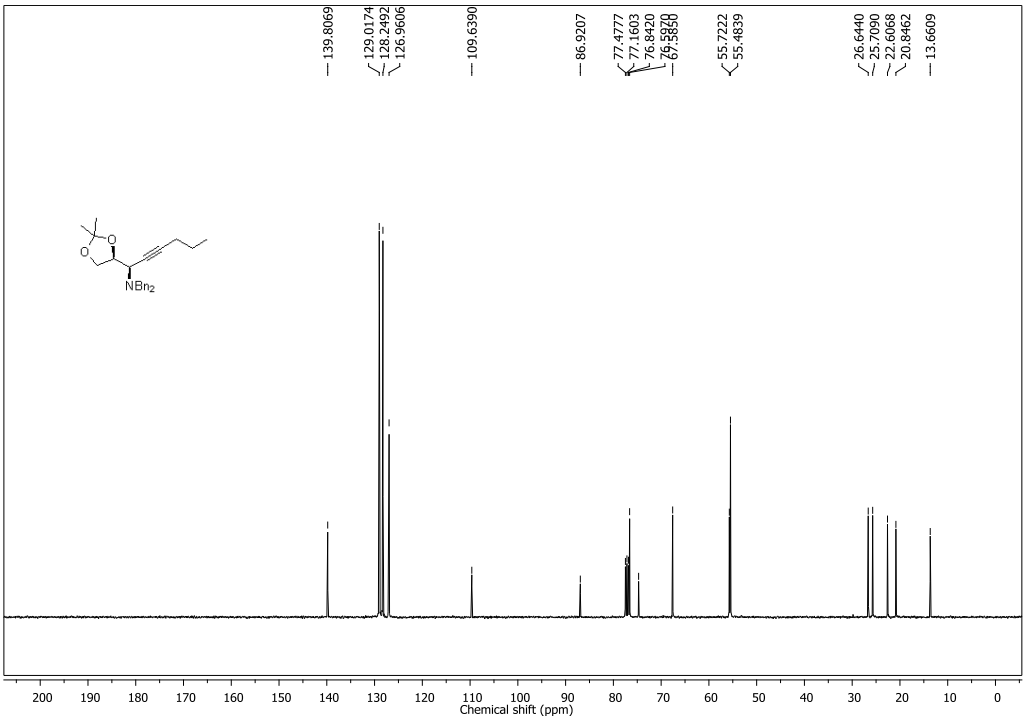


Figure 3A.5: ^{13}C NMR spectra of **7a** in $CDCl_3$.

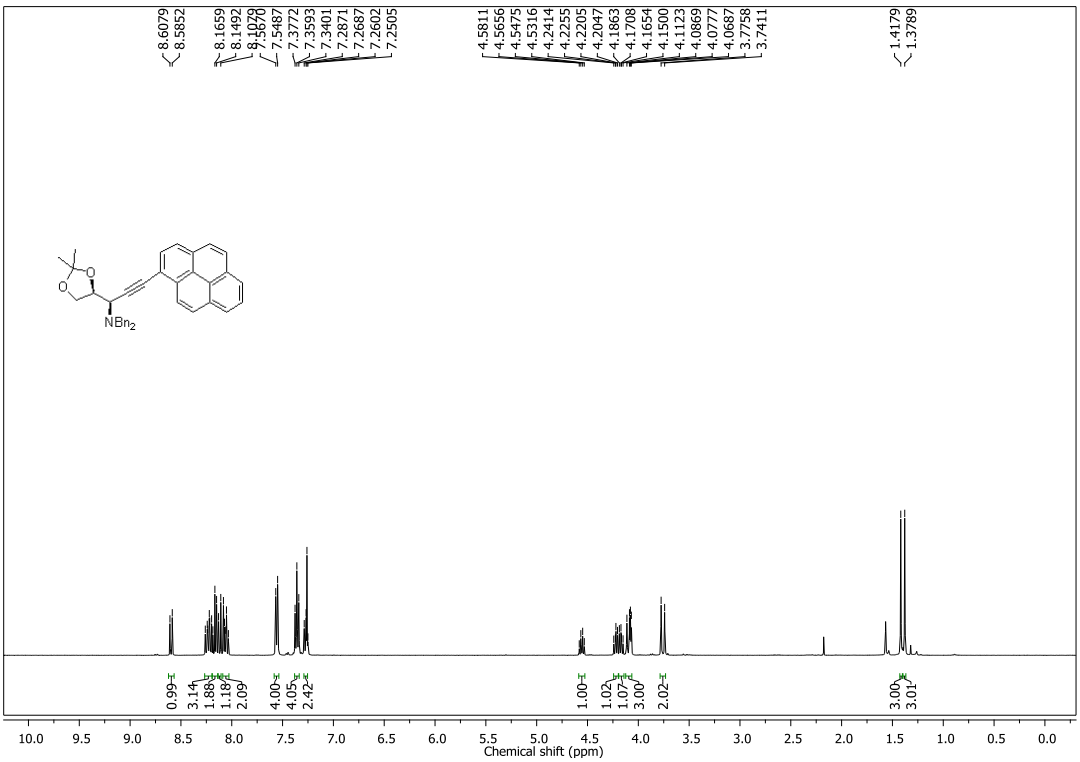


Figure 3A.6: ^{1}H NMR spectra of **7f** in $CDCl_3$.

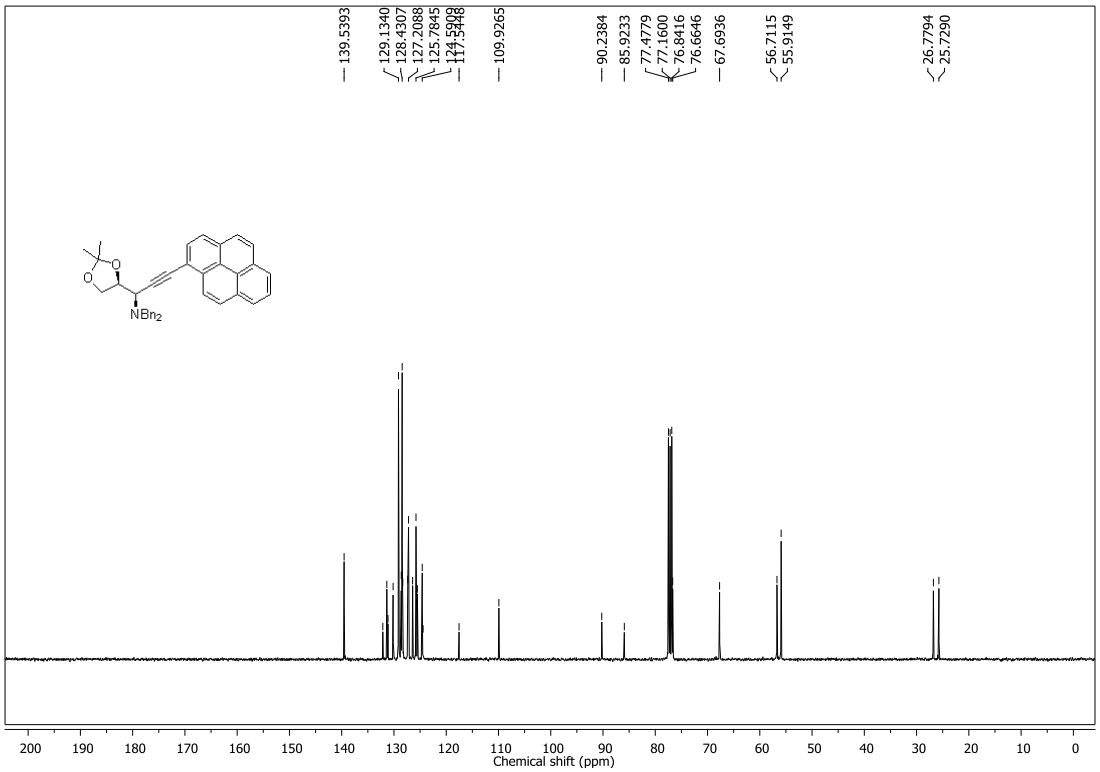


Figure 3A.7: ^{13}C NMR spectra of **7f** in $CDCl_3$.

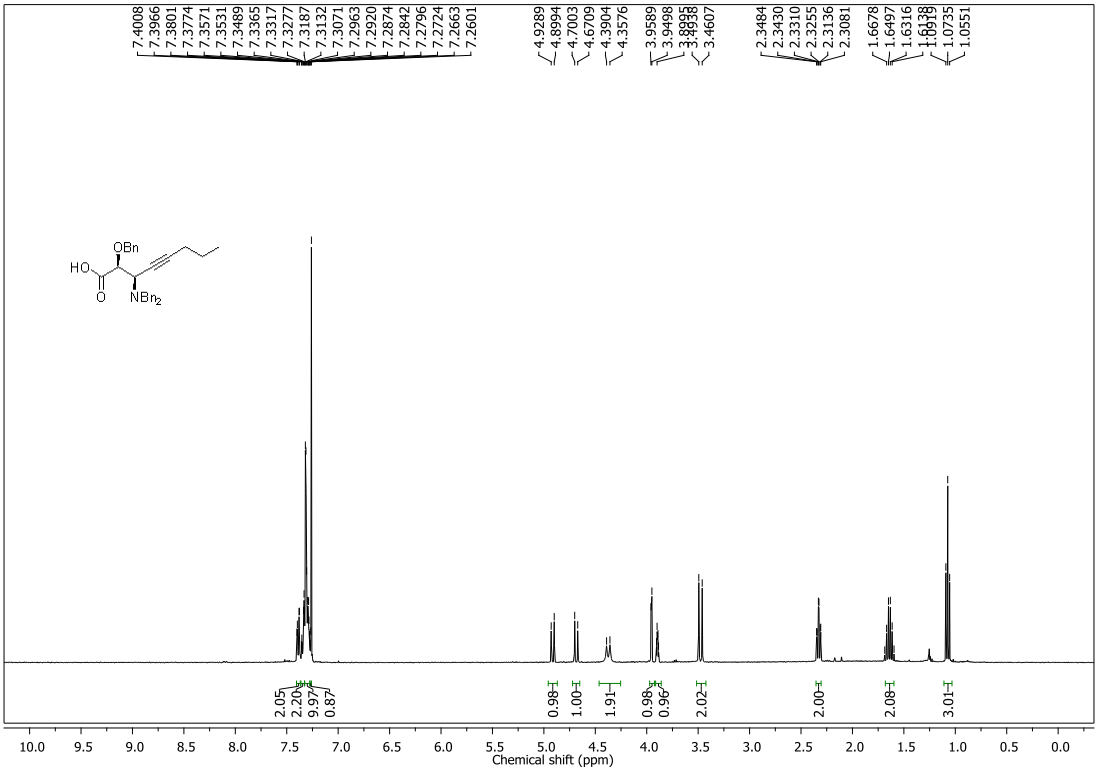


Figure 3A.8: ^{1}H NMR spectra of **6a** in $CDCl_3$.

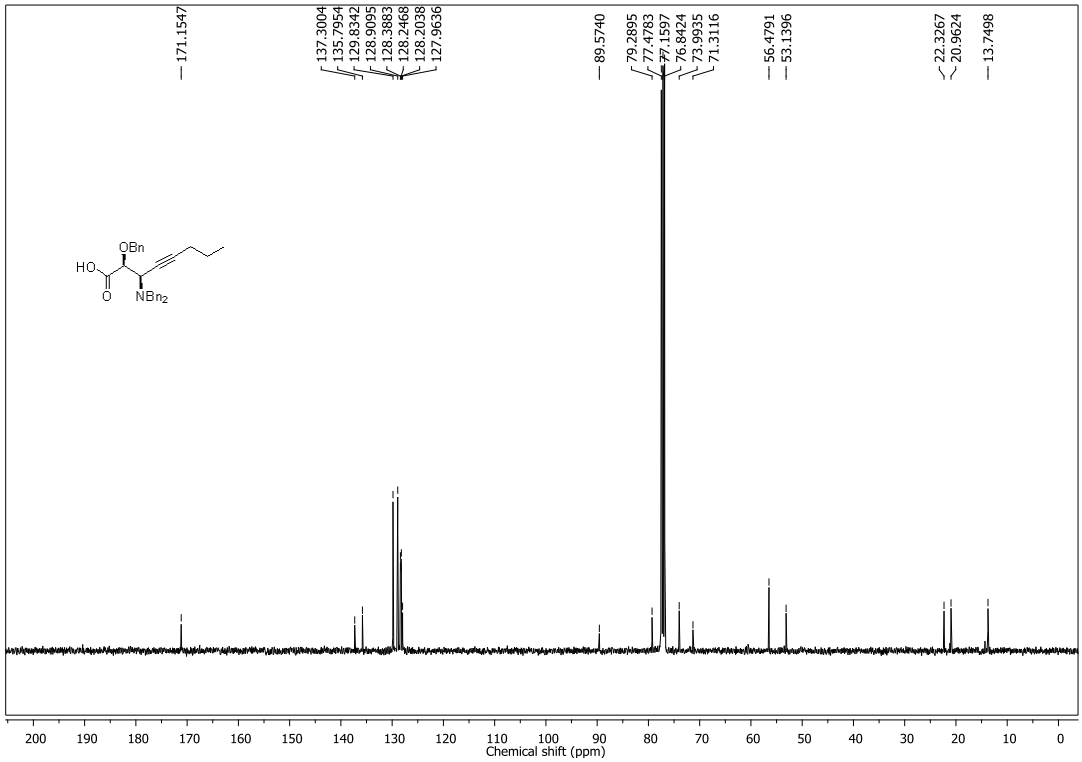


Figure 3A.9: ^{13}C NMR spectra of **6a** in $CDCl_3$.

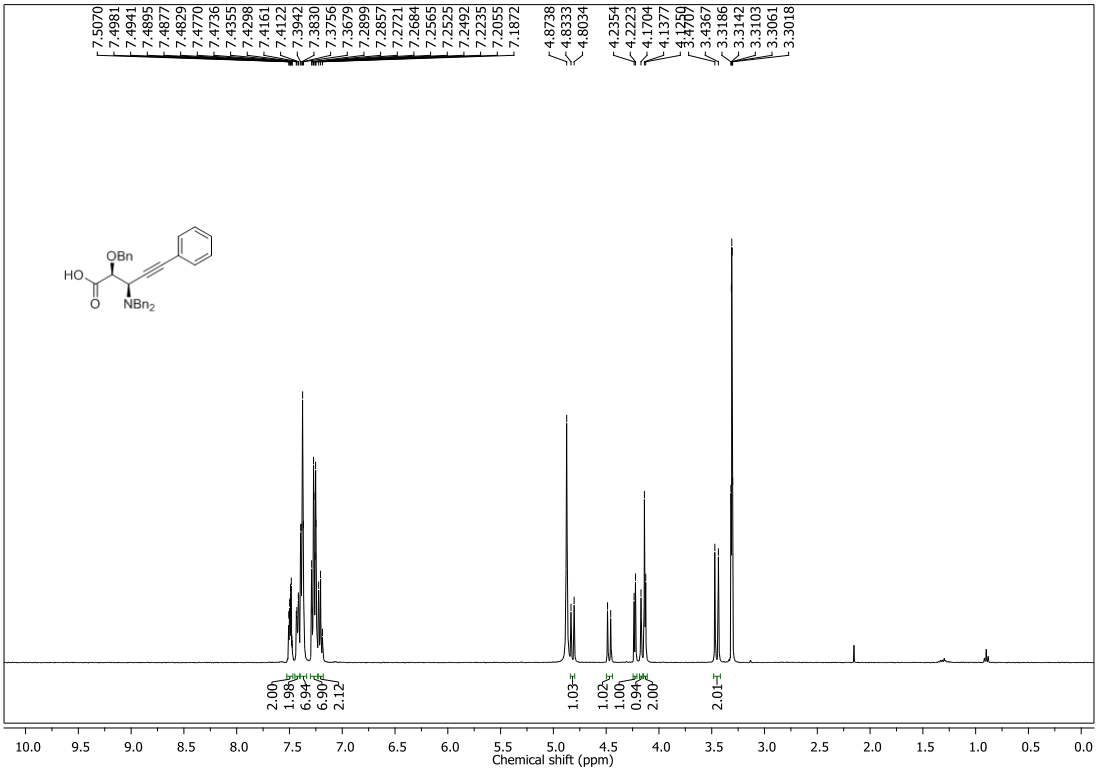


Figure 3A.10: ^{1}H NMR spectra of **6e** in $CDCl_3$.

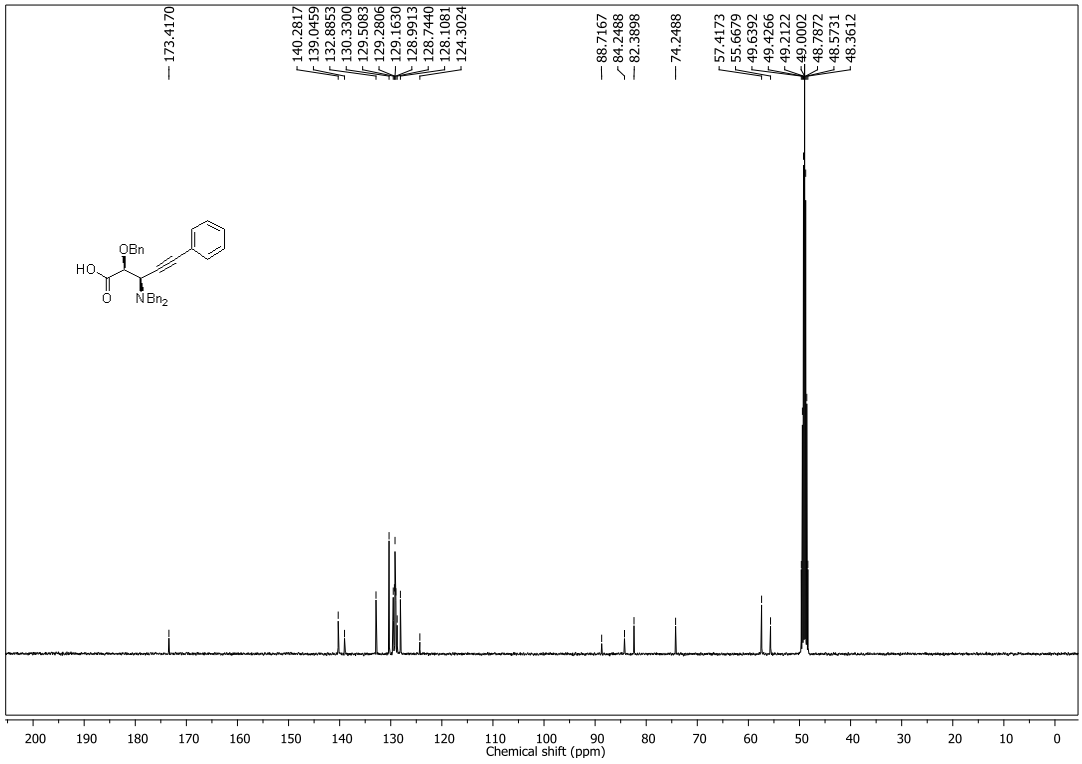


Figure 3A.11: ^{13}C NMR spectra of **6e** in $CDCl_3$.

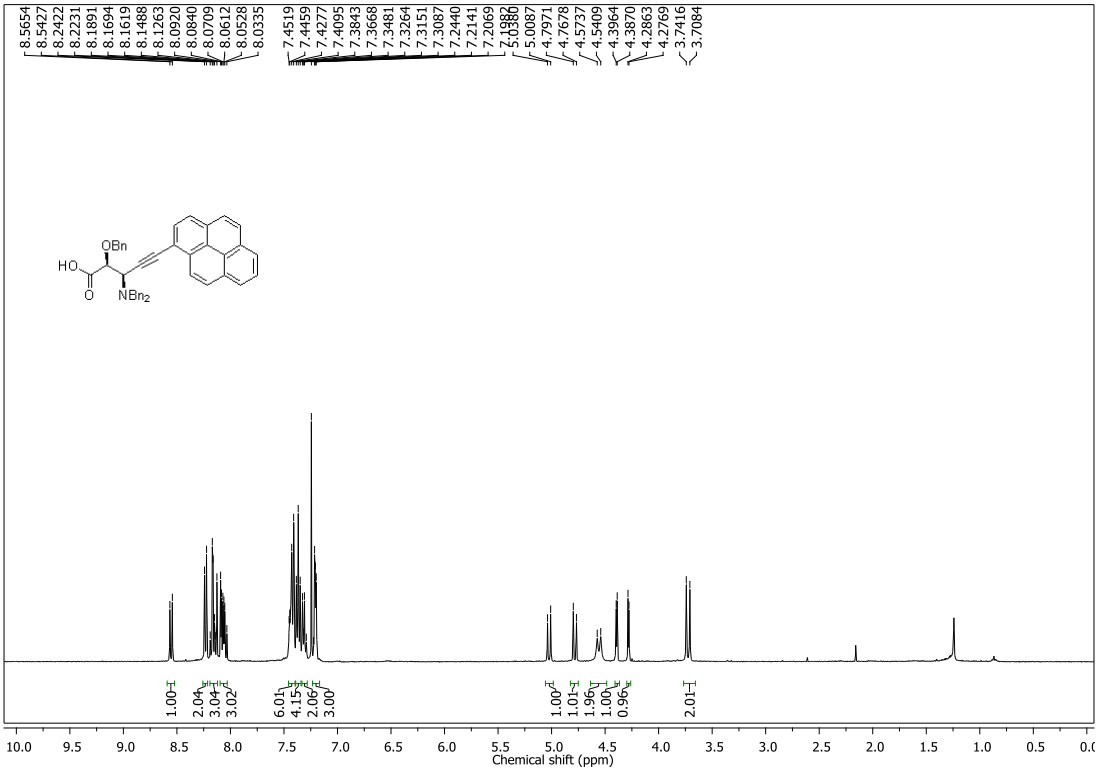


Figure 3A.12: ^{1}H NMR spectra of **6f** in $CDCl_3$.

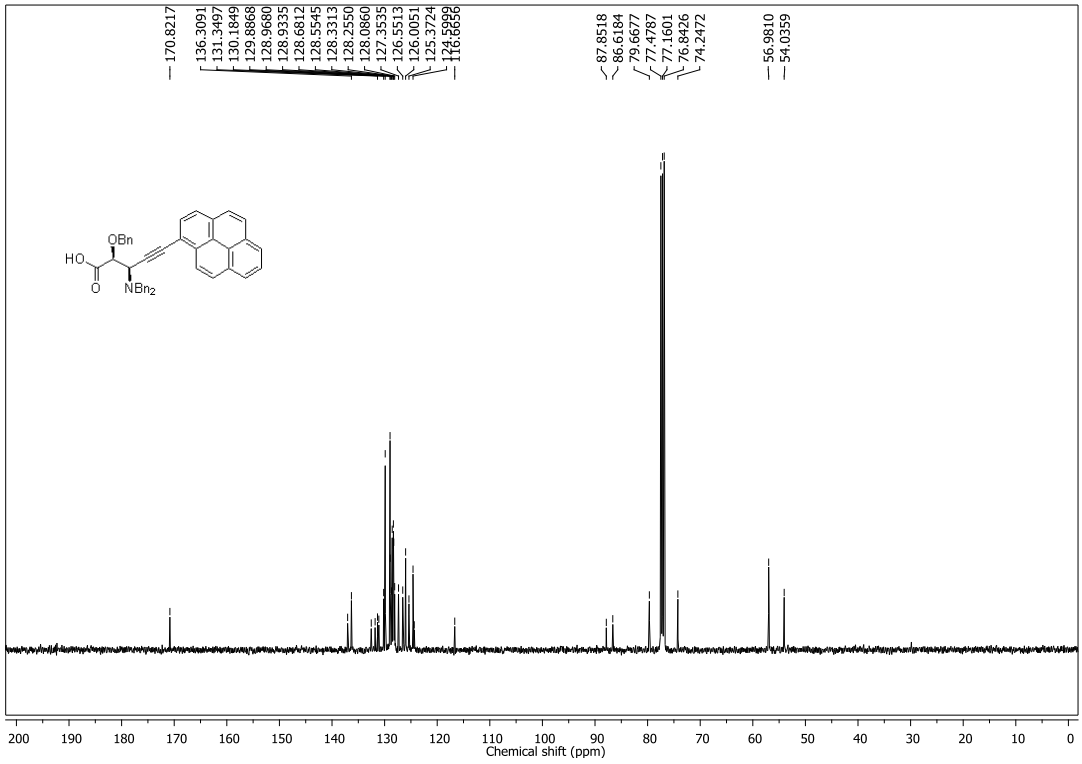


Figure 3A.13: ^{13}C NMR spectra of **6f** in $CDCl_3$.

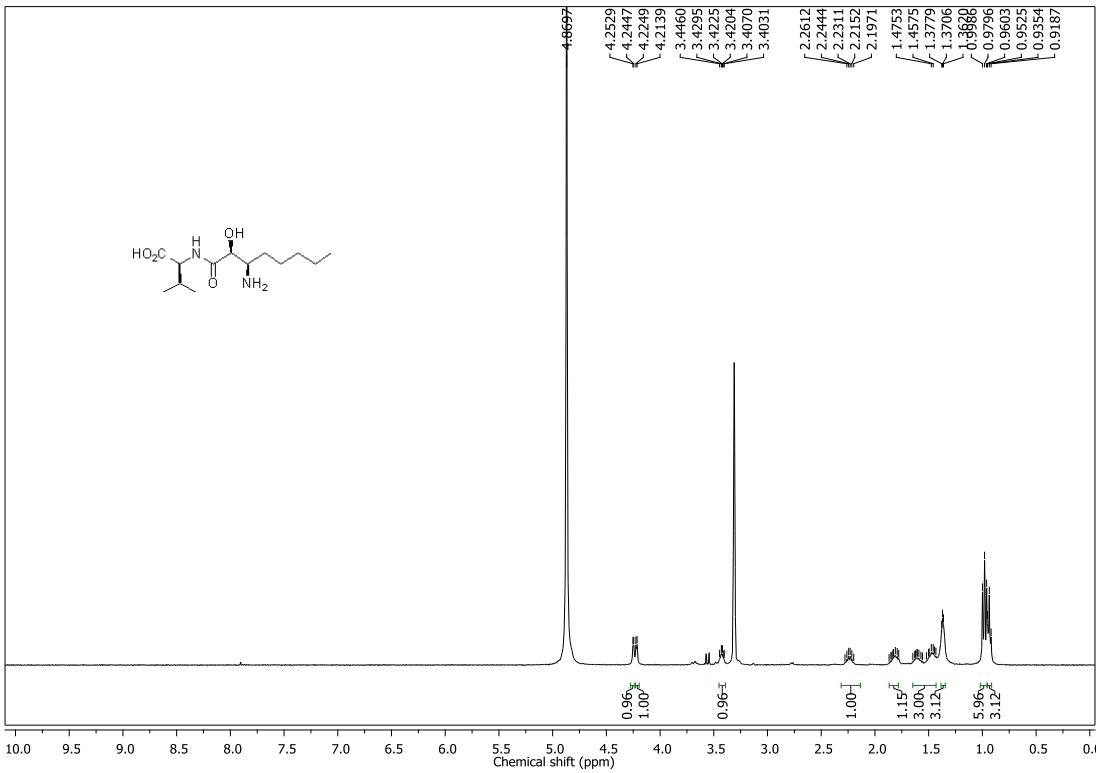


Figure 3A.14: ^{1}H NMR spectra of **3** in CD_3OD.

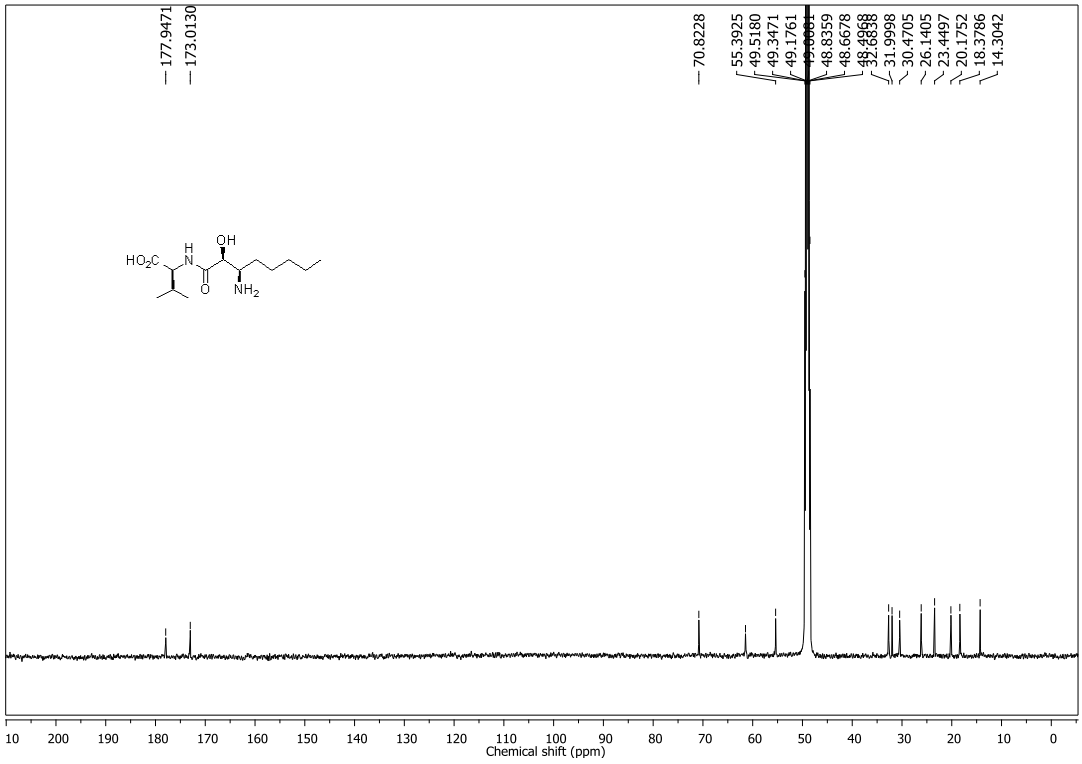


Figure 3A.15. ^{13}C NMR spectrum of **3** in CD_3OD.

3A.11 References

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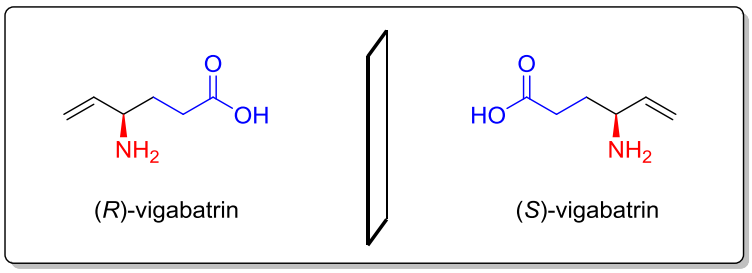
Chapter 3

Section B

An Enantiodivergent Synthesis of Both (*R*)- and (*S*)-Vigabatrin



3B.1 Introduction

Stereoselective synthesis of the γ-aminobutyric acid (GABA) derivative is a vital and remarkable subject in organic synthesis as GABA (**1**) is a significant inhibitory neurotransmitter in the mammalian central nervous system.[1] Deficiency of GABA has been associated with several significant neurological disorders such as Parkinson's disease,[2] Alzheimers disease,[3] epilepsy,[4] Huntington's chorea[5] and other psychiatric disorders, such as anxiety and peripheral neuropathic pain,[6] etc. Also, it has been noticed that an increase in GABA blocks the effects of drug addiction to nicotine and cocaine.[7] However, administration of GABA orally or intravenously is not an effective therapy due to low lipophilicity and poor ability to cross the blood-brain barrier (BBB).[8] Due to this, more lipophilic GABA derivatives which mimic or interfere with GABA have been investigated. For example, (*S*)-vigabatrin (**2**), (*R*)-baclofen (**3**), (*S*)-pregabalin (**4**), etc. are the GABA derivatives which are used as drugs (Figure 3B.1).

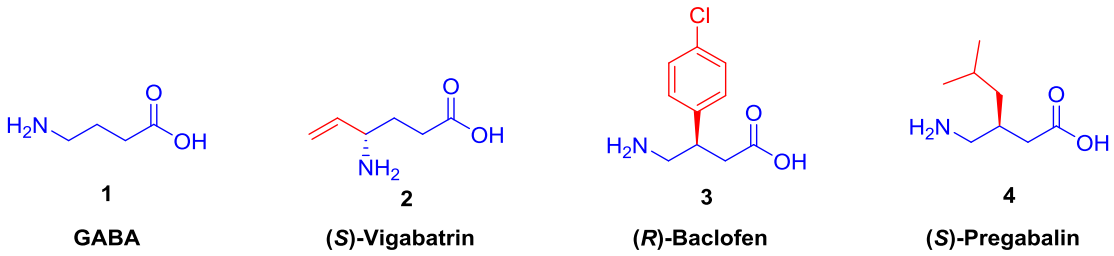


Figure 3B.1: Structures of drugs containing γ - amino acid backbone.

Vigabatrin (γ-vinyl GABA) (**2**) is a significant anticonvulsant drug marketed in the racemic form as Sabril in Europe. Vigabatrin is a highly selective irreversible inhibitor of GABA-aminotransferase (GABA-T) which degrades GABA to succinic semialdehyde.[9] Baclofen (3-(4-chlorophenyl)-4-aminobutyric acid) (**3**) is a selective agonist at the $GABA_B$ receptor and is used as a muscle relaxant and antispastic agent.[10] (*S*)-Pregabalin ((*S*)-3-aminomethyl-5-methylhexanoic acid) (**4**) and gabapentin (Neurontin) were established by Pfizer for the treatment of fibromyalgia-related pain and migraine pain, respectively.[11]

As vigabatrin has a chiral center at the γ-carbon atom, (*R*)-vigabatrin and (*S*)-vigabatrin, are two enantiomers possible (Figure 3B.2). It has been observed that the (*S*)-enantiomer of vigabatrin is pharmacologically active.

Figure 3B.2: Structures of (*R*)-vigabatrin and (*S*)-vigabatrin.

Vigabatrin is an example of an unsaturated amino acid due to C=C double bond present in its structure. Such unsaturated amino acids have confirmed to be useful in providing a handle for chemical transformations to epoxides, alcohols, halides, amines, aldehydes, carboxylic acids, etc. Also, Verdine and coworkers have demonstrated that the C=C bonds can be used in chemical stapling which reinforces α-helix formation (Figure 3B.3).[12] The strategy has shown significant potential in the development of a new class of peptide-based drugs.[13] So, nonproteinogenic amino acids with unsaturated side chains have gained much attention in the field of synthetic chemistry, medicinal chemistry, peptidomimetic research, and design of foldamers.

Figure 3B.3: Chemical stapling method to stabilize the α-helix motif.

3B.2 Reported Synthesis of Vigabatrin

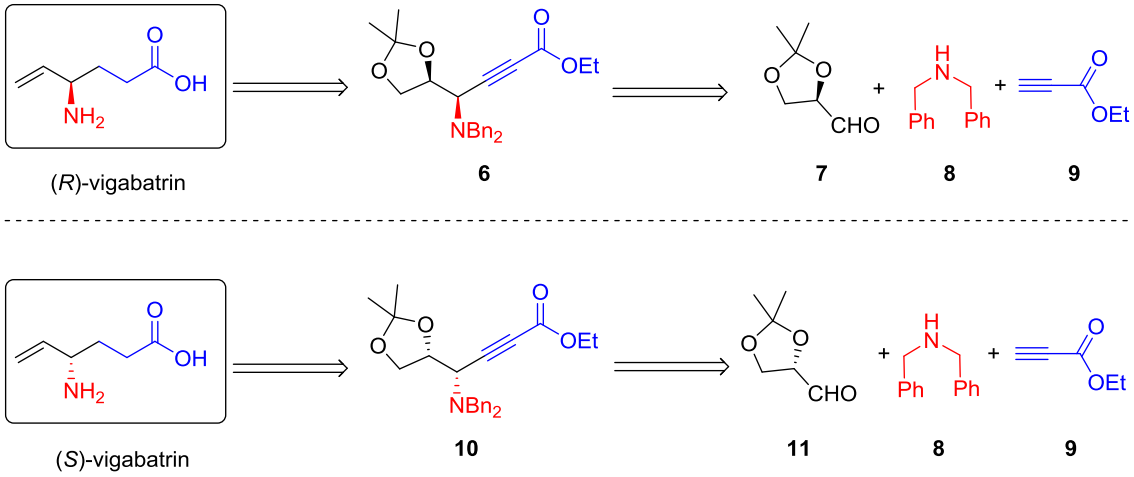
Until now, several methods have been reported for the synthesis of enantiomerically pure **2** and its enantiomer. Most of these methods involved natural amino acids as starting materials, *e.g*. L-glutamic acid or L-methionine.[14]

Also, few approaches are known for vigabatrin synthesis from non-natural starting materials. Such as, starting from vinyl oxirane, Helmchen and co-worker reported the synthesis of (*S*)-vigabatrin via Iridium-catalyzed aminations of allylic carbonates.[15] Overman and co-worker described COP-Cl catalyzes the rearrangement of (*E*)-allylic trichloroacetimidates to prepare (*S*)-vigabatrin.[16] Oliver Reiser and co-workers reported the synthesis of (*S*)-vigabatrin from inexpensive pyrrole in seven steps.[17] Stacey E. Brenner-Moyer and co-workers reported the synthesis of (*S*)-vigabatrin via oregano cascade reactions involving dienamine catalysis.[18] Yannick Vallée and co-workers used alkylation of nitrones strategy for the synthesis of (*S*)-vigabatrin and (*R*)-vigabatrin.[19] Sudalai and co-workers achieved a synthesis of (*S*)-vigabatrin using a Cobalt-catalyzed hydrolytic kinetic resolution of racemic epoxide.[20] The synthesis of key intermediate for (*R*)- and (*S*)-vigabatrin from D-glucose or D-galactose as the chiral starting materials was demonstrated by Aidhen and co-workers.[21] Even though the various strategies are used in the synthesis of vigabatrin, convenient method for both (*R*)- and (*S*)-vigabatrin is still challenge for the organic chemist.

3B.3 Present work and Synthetic Planning

As an ongoing research work on chiral α-amino alcohol using the multi-component reaction of aldehydes, amines, and alkynes in our laboratory,[22] we became interested in the synthesis of both enantiomers of vigabatrin due to its potential bioactivity. A retrosynthetic analysis was planned to target (*R*)- and (*S*)-vigabatrin (Scheme 3B.1). Synthesis of (*R*)-vigabatrin **5** was proposed from *syn*-α-amino alcohol derivative **6** via deprotection, reduction, and hydrolysis. Alkyne **6** could be obtained from (*R*)-glyceraldehyde acetonide **7**, dibenzylamine **8** and terminal alkyne **9** via the aldehyde-amine-alkyne three-component coupling. Similarly, (*S*)-vigabatrin **2** was planned from (*S*)-

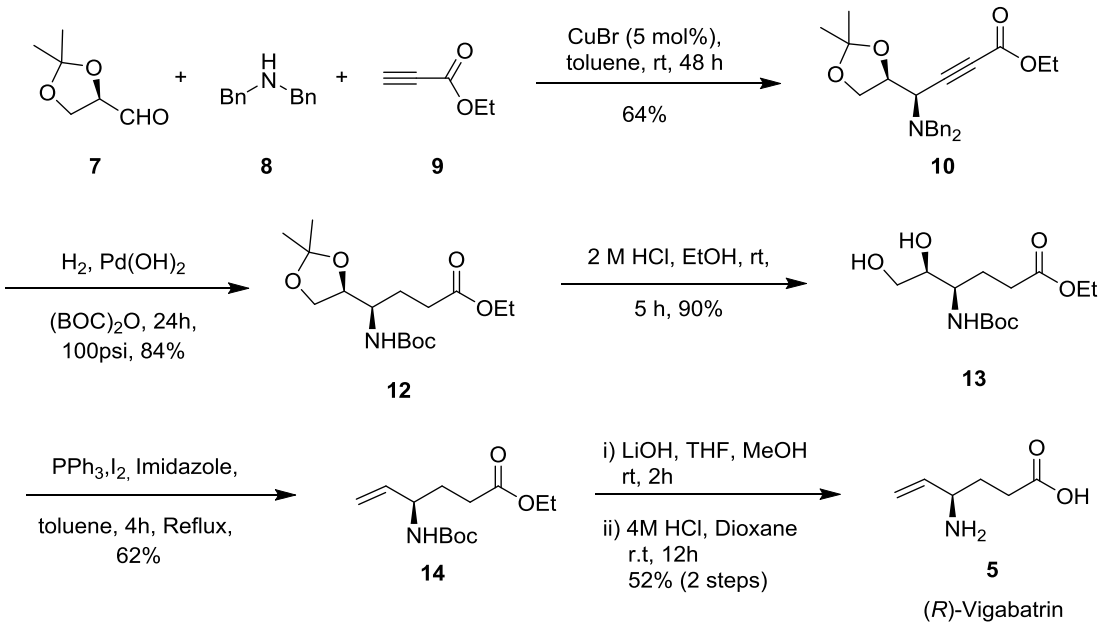
glyceraldehyde acetonide **11**, dibenzylamine **8** and terminal alkyne **9** via the aldehyde-amine-alkyne three-component coupling reaction.



Scheme 3B.1: Retrosynthetic analysis of (*R*)- and (*S*)-vigabatrin.

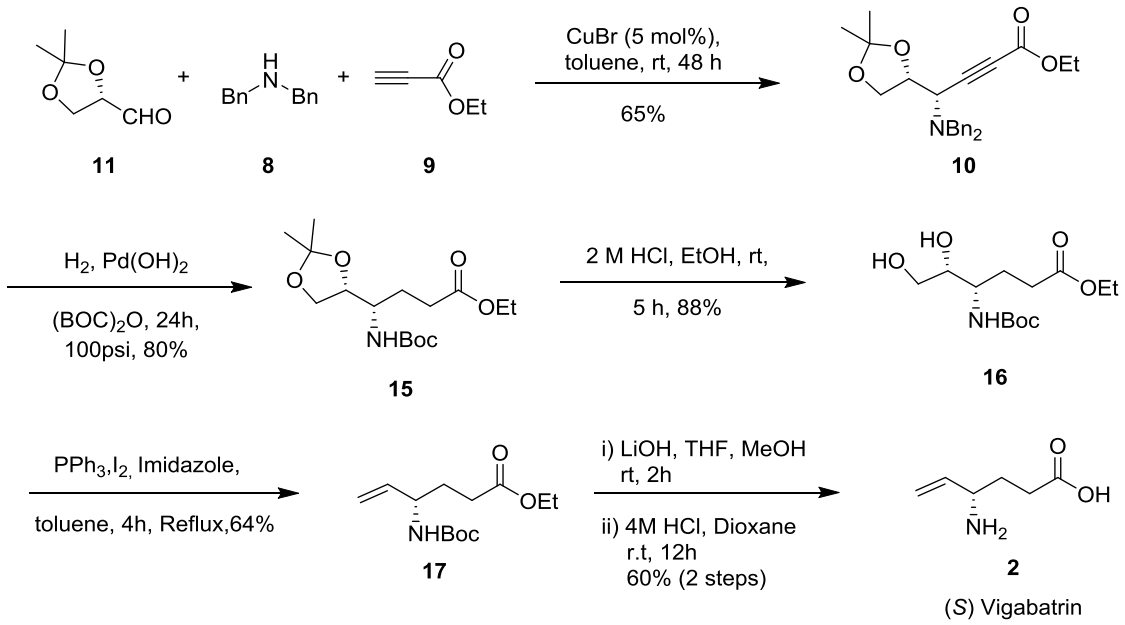
3B.4 Results and Discussion

In order to prepare (*R*)-vigabatrin, (*R*)-glyceraldehyde acetonide **7,** dibenzylamine **8** were reacted with the ethyl propionate **9** under CuBr (5 mol%) catalytic conditions in toluene at room temperature, to give propargylamine derivative **6.** The compound **6** was formed as single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 76% yield (Scheme 3B.2). The formation of *anti*-diastereomer was not detected under the applied reaction conditions. The ester **6** was then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond followed by concomitant *N*-Boc protection provided compound **12** in 64% yield over two steps. Further ketal group of **12** was deprotected by ethanolic HCl to afford the diol **13** in 84% yield. The diol **13** was then converted to the alkene **14** in one pot with 62% yield by reacting with PPh_3, I_2, and imidazole. Finally, ester hydrolysis of **14** with LiOH followed by *N*-Boc deprotection using hydrochloric acid gave (*R*)-vigabatrin **5**. Purification of **5** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) to achieve 52% yield over two steps. The structure of the product confirmed by comparing the recorded ^{1}H-NMR, melting point, specific rotation and matched with the data available in the literature.[14e]



Scheme 3B.2: Synthesis of (*R*)-vigabatrin

For the synthesis of (*S*)-vigabatrin, L-glyceraldehyde acetonide was prepared from L-ascorbic acid according to the known literature method. The (*S*)-glyceraldehyde acetonide **11,** dibenzylamine **8,** ethyl propionate **9** were reacted under CuBr (5 mol%) catalytic conditions in toluene at room temperature, substituted propargylamine derivative **10** was formed as single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 65% yield (Scheme 3B.3). No formation of *anti*-diastereomer was detected under the applied reaction conditions. The ester **10** was then treated with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond followed by simultaneous *N*-Boc protection to give a compound **15** in 80% yield over two steps. The ketal group of **15** was deprotected by ethanolic HCl to give the diol **16** in 88% yield. The diol **16** was then converted to the alkene **17** in one pot with 64% yield by reacting with PPh_3, I_2, and imidazole. Finally, ester hydrolysis of **17** with LiOH followed by *N*-Boc deprotection using hydrochloric acid gave (*S*)-vigabatrin **2**. Purification of **2** was carried out by ion-exchange chromatography (Dowex 50w × 8, 200-400 mesh) to achieve 60% yield over two steps. The structure of the product confirmed by comparing the recorded ^{1}H-NMR, melting point, specific rotation and matched with the data available in the literature.[19]



Scheme 3B.3: Synthesis of (*S*)-vigabatrin

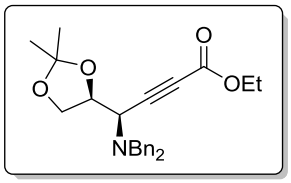
3B.5 Conclusion

In conclusion, we have developed a new enantio-divergent route for the synthesis of (*R*)- and (*S*)-vigabatrin. A Cu(I) catalyzed α-oxyaldehyde-dibenzylamine-alkyne coupling reaction facilitated the diastereoselective construction of *syn*-α-amino alcohols. The synthesis of (*R*)-vigabatrin was achieved in six steps with 16% overall yield starting from (*R*)-glyceraldehyde acetonide. Similarly, the (*S*)-vigabatrin was synthesized from (*S*)-glyceraldehyde acetonide in six steps with 18% overall yield. In addition, our synthetic scheme has provided opportunities to access unsaturated amino acids derivatives which can be used in chemical stapling.

3B.6 Experimental Section

General Methods: The acetonide-protected D-glyceraldehyde was prepared from D-mannitol according to the published methods.[23] The L-glyceraldehyde acetonide was prepared from L-ascorbic acid according to the known literature method.[24] Other substrates and reagents were purchased from common commercial sources and used without additional purification. Toluene was pre-dried over Na wire. Then the solvent was refluxed over Na (1% w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue colour of the benzophenone ketyl radical anion persists. All reactions were conducted under the nitrogen 60 atmosphere. Solvents: petroleum ether and ethyl acetate (EtOAc) were distilled prior to thin layer and column chromatography. Reactions were controlled using TLC on silica. Column chromatography was performed on silica gel (100–200 mesh).

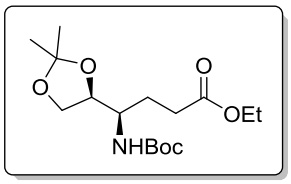
Synthesis of ethyl (*R*)-4-(dibenzylamino)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) but-2-ynoate 6 ($C_{25}H_{29}NO_4$).



To a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **7** (2.0g, 15.4 mmol) in dry toluene (40 mL) were added dibenzylamine **8** (3.04 g, 15.4 mmol), ethyl propionate **9** (1.52 g, 15.4 mmol), CuBr (110 mg, 0.77 mmol), 4 Å molecular sieves and the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was filtered through celite bed and washed with Et_2O (3 × 20 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **6** (4.00 g, 64%) as a colorless oil. IR (KBr) ν (cm^{-1}): 2986, 2220, 1713, 1495, 1454, 1370, 1243, 1148, 1074 ; $[\alpha]_D^{25}$ = -123.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.3 Hz, 4H), 7.31 (t, *J* = 7.3 Hz, 4H), 7.28-7.20 (t, *J* = 7.3 Hz, 2H), 4.32 (q, *J* = 6.5 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.03 (dd, *J* = 8.5, 6.6 Hz, 1H), 3.93 (d, *J* = 14.3 Hz, 2H), 3.90 (dd, *J* = 8.5, 5.9 Hz, 1H), 3.70 (d, *J* = 7.1 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.5, 138.8 (2C), 129.0 (4C),

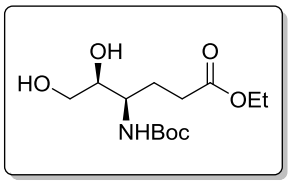
128.4 (4C), 127.3 (2C), 110.1, 83.1,78.7, 75.8, 67.1, 62.3, 55.7 (2C), 55.2, 26.5, 25.4, 14.2; HRMS (ESI) Calcd. for $C_{25}H_{30}NO_4$ 408.2175 $[M + H]^+$, found 408.2184.

Synthesis of ethyl (*R*)-4-((tert-butoxycarbonyl)amino)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butanoate 12 ($C_{16}H_{29}NO_6$).



To a solution of **6** (3.50 g, 8.60 mmol) in EtOH (100 mL) was added 10% $Pd(OH)_2/C$ (86 mg, 0.860 mmol) and Boc anhydride (3.75 g, 8.60 mmol). The reaction mixture was stirred at room temperature under 100 psi pressure of hydrogen for 24 h. The reaction mixture was filtered through celite and the celite bed was washed with EtOH (3 × 20 mL). To the combined solution was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent:* 15% EtOAc in petroleum ether) to furnish the pure **12** (2.30 g, 84% over 2 steps) as a colorless oil. IR (KBr) ν (cm^{-1}): 3560, 3062, 2982, 1700, 1368, 1245, 1160, 1069, 1030; $[\alpha]_D^{25}$ = - 31.3 (*c* = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.65 (d, *J* = 9.8 Hz, 1H), 4.17 – 4.08 (m, 3H), 3.99 (dd, *J* = 8.1, 6.7 Hz, 1H), 3.66 (dd, *J* = 8.1, 7.4 Hz, 2H), 2.39 – 2.26 (m, 2H), 1.73 – 1.61 (m, 2H), 1.44 (s, 9H), 1.42 (s, 3H), 1.33 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.4, 156.3, 109.3, 79.6, 77.5, 66.5, 60.6, 50.2, 31.1, 28.8, 28.5 (3C), 26.4, 25.1, 14.4; HRMS (ESI) Calcd. for $C_{16}H_{30}NO_6$ 332.2073 $[M + H]^+$, found 332.2075.

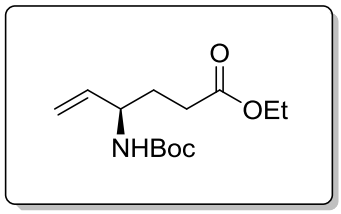
Synthesis of ethyl (4*R*,5*S*)-4-((tert-butoxycarbonyl)amino)-5,6-dihydroxyhexanoate 13 ($C_{13}H_{25}NO_6$).



To a solution of **12** (1.80 g, 5.43 mmol) in EtOH (20 mL) was added 2 M HCl (5 mL) and the mixture was stirred for 2 h at room temperature. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAC in petroleum ether) to afford **13** (1.42 g, 90%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3550, 3220, 3062, 2928, 1698, 1390, 1269, 1106, 1085, 1039, 1010; $[\alpha]_D^{25}$ = - 15.0 (*c* = 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.81 (dd, *J* = 19.4, 8.5 Hz, 1H),

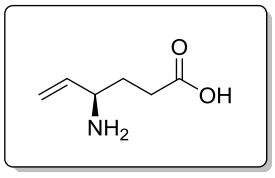
4.12 (dd, *J* = 14.0, 7.0 Hz, 2H), 3.75 – 3.64 (m, 2H), 3.60 – 3.54 (m, 1H), 3.47 (dd, *J* = 10.9, 7.0 Hz, 1H), 2.45 – 2.30 (m, 2H), 1.97 – 1.84 (m, 1H), 1.59 (dd, *J* = 18.0, 8.7 Hz, 1H), 1.44 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 157.2, 80.1, 73.1, 63.6, 60.8, 50.9, 33.8, 31.3, 28.3 (3C), 14.2; HRMS (ESI) Calcd. for $C_{13}H_{25}NaNO6$ 314.1580 $[M + Na]^+$, found 314.1579.

Synthesis of ethyl (*R*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate 14 ($C_{13}H_{23}NO_4$).



To a solution of diol **13** (1.20 g, 4.12 mmol) in dry toluene (50 mL) was added imidazole (1.12 g, 16.50 mmol) and Ph_3P (4.33g, 16.50 mmol). The resulting reaction mixture was refluxed and I_2 (1.04 g, 4.12 mmol) was added in portions. The mixture was refluxed for 3 h, then it was allowed to cool to room temprature and was treated with I_2 (1.04 g, 4.12 mmol) and NaOH (1.4 M, 25 mL). After the disappearance of the red solid, H_2O was added to the mixture. The organic phase was washed with an aqueous solution of sodium thiosulfate, dried (MgSO4), and concentrated in vacuo. The crude product was purified by column chromatography to furnish **14** (0.657 g, 62%) as a colorless oil. IR (KBr) ν (cm^{-1}): 3370, 2985, 1700, 1680, 1449, 1390, 1285, 1120, 1040; $[\alpha]_D^{25}$ = - 8.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 5.81 – 5.65 (m, 1H), 5.19 – 5.08 (m, 2H), 4.54 (s, 1H), 4.13 (dd, *J* = 14.2, 7.1 Hz, 3H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.88 (td, *J* = 13.5, 7.1 Hz, 1H), 1.78 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.43 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.5, 155.5, 138.2, 115.1, 79.5, 60.7, 52.5, 30.9, 30.0, 28.5 (3C), 14.3; HRMS (ESI) Calcd. for $C_{13}H_{23}NNO_4$ 280.1525 $[M + Na]^+$, found 280.1521.

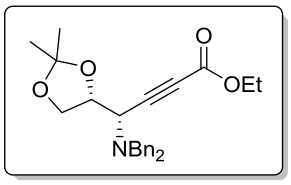
Synthesis of (*R*)-4-aminohex-5-enoic acid 5 ($C_6H_{11}NO_2$).



To a solution of **14** (50.0 mg, 0.194 mmol) in THF/MeOH (4 mL, 5:1) was added an aqueous solution of 2 M LiOH (292 μL, 0.583 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was concentrated to remove organic solvents and diluted with Et_2O (10 mL). The aqueous layer was acidified with 1N HCl at 0 °C and extracted with methylene chloride (2 x 10

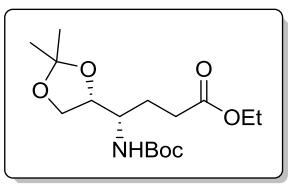
mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the corresponding acid product. The crude product was dissolved in anhydrous 1,4-dioxane (2 mL) was added 4 M HCl in dioxane (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The acid mixture was then concentrated under vacuum and the resulting material was passed through a column of Dowex 50W ion exchange resin (H^+ form) (*Eluent*: 2 N NH_4OH) to furnish **5** (13mg, 52%) as white solid. M.P. 162-164ºC IR (KBr) ν (cm^{-1}): 3438, 2956, 1645, 1575, 1380, 1110, 1002; $[\alpha]_D^{25}$ = - 11.8 (*c* = 0.5 H_2O) (Lit. $[\alpha]_D^{25}$ = - 12.0 (*c* = 0.5 H_2O); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 5.79 (td, *J* = 17.9, 8.5 Hz, 1H), 5.36 (dd, *J* = 10.9, 7.1 Hz, 2H), 3.72 (dt, *J* = 17.1, 8.4 Hz, 1H), 2.18 (t, *J* = 7.0 Hz, 1H), 1.99 – 1.79 (m, 1H), 1.70 – 1.52 (m, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 182.6, 133.0, 120.7, 53.5, 33.0, 31.7; HRMS (ESI) Calcd. for $C_6H_{12}NO_2$ 130.0868 $[M + H]^+$, found 130.0870.

Synthesis of ethyl (*S*)-4-(dibenzylamino)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl) but-2-ynoate 10 ($C_{25}H_{29}NO_4$).



To a solution of (*S*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **11** (800 mg, 3.08 mmol) in dry toluene (20 mL) were added dibenzylamine **8** 608 mg, 3.08 mmol), ethyl propionate **9** (302 mg, 3.08 mmol), CuBr (22 mg, 0.15 mmol), 4 Å molecular sieves and the reaction mixture was stirred at room temperature for 48 h. After completion of the reaction, the reaction mixture was filtered through celite bed and washed with Et_2O (3 × 10 mL). The crude product was subjected to column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to furnish **10** (815 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ = +124.0 (*c* = 1.0, $CHCl_3$). All other spectral data is same as that of (**6**).

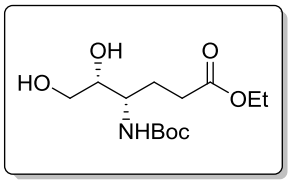
Synthesis of ethyl (*S*)-4-((tert-butoxycarbonyl)amino)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butanoate 15 ($C_{16}H_{29}NO_6$).



To a solution of **10** (750 mg, 1.84 mmol) in EtOH (10 mL) was added 10% $Pd(OH)_2/C$ and Boc anhydride (804 mg, 3.68 mmol). The reaction mixture was stirred at room temperature under 100 psi pressure of hydrogen for 24 h. The reaction mixture was

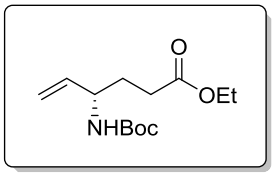
filtered through celite and the celite bed was washed with EtOH (2 × 10 mL). To the combined solution was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent:* 15% EtOAc in petroleum ether) to furnish the pure **15** (488 g, 80% over 2 steps) as a colourless oil. $[\alpha]_D^{25}$ = +30.2 (*c* = 0.6, $CHCl_3$). All other spectral data is same as that of (**12**).

Synthesis of ethyl (4*S*,5*R*)-4-((tert-butoxycarbonyl)amino)-5,6-dihydroxyhexanoate 16 ($C_{13}H_{25}NO_6$).



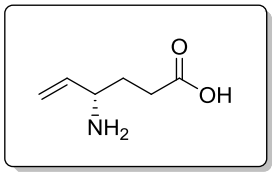
To a solution of **15** (450 mg, 1.36 mmol) in EtOH (5 mL) was added 2 M HCl (2 mL) and the mixture was stirred for 2 h at room temperature. After the completion of the reaction, the solution was neutralized with solid K_2CO_3 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAC in petroleum ether) to afford **16** (348 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ = + 15.72 (*c* = 1.0, $CHCl_3$). All other spectral data is same as that of (**13**).

Synthesis of ethyl (*S*)-4-((tert-butoxycarbonyl)amino)hex-5-enoate 17 ($C_{13}H_{23}NO_4$).



To a solution of diol **16** (300 mg, 1.03 mmol) in dry toluene (50 mL) was added imidazole (280 mg, 4.13 mmol) and Ph_3P (1.08 g, 4.13 mmol). The resulting reaction mixture was refluxed and I_2 (260 mg, 1.03 mmol) was added in portions. The mixture was refluxed for 3 h, then it was allowed to cool to room temprature and was treated with I_2 (260 mg, 1.03 mmol) and NaOH (1.4 M, 8 mL). After the disappearance of the red solid, H_2O was added to the mixture. The organic phase was washed with an aqueous solution of sodium thiosulfate, dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by column chromatography to furnish **17 (**170 mg, 64%) as a colorless oil. $[\alpha]_D^{25}$ = + 9.1 (*c* = 1.0, $CHCl_3$). All other spectral data is same as that of (**14**).

Synthesis of (*S*)-4-aminohex-5-enoic acid 2 ($C_6H_{11}NO_2$).



To a solution of **17** (50.0 mg, 0.194 mmol) in THF/MeOH (4 mL, 5:1) was added an aqueous solution of 2 M LiOH (292 μL, 0.583 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The mixture was concentrated to remove organic solvents and diluted with Et_2O (10 mL). The aqueous layer was acidified with 1N HCl at 0 °C and extracted with methylene chloride (2 x 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give the corresponding acid product. The crude product was dissolved in anhydrous 1,4-dioxane (2 mL) and to this solution was added 4M HCl in dioxane (2 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The acid mixture was then concentrated under vacuum and the resulting material was passed through a column of Dowex 50W ion exchange resin (H^+ form) (*Eluent*: 2N NH_4OH) to furnish **2** (15 mg, 60%) as a white solid. $[\alpha]_D^{25}$ = + 11.2 (*c* = 0.5 H_2O) (Lit. $[\alpha]_D^{25}$ = + 12.4 (*c* = 0.515 H_2O); All other spectral data is same as that of (**5**).

3B.7 Appendix III: ^{1}H and ^{13}C spectral data of representative compounds

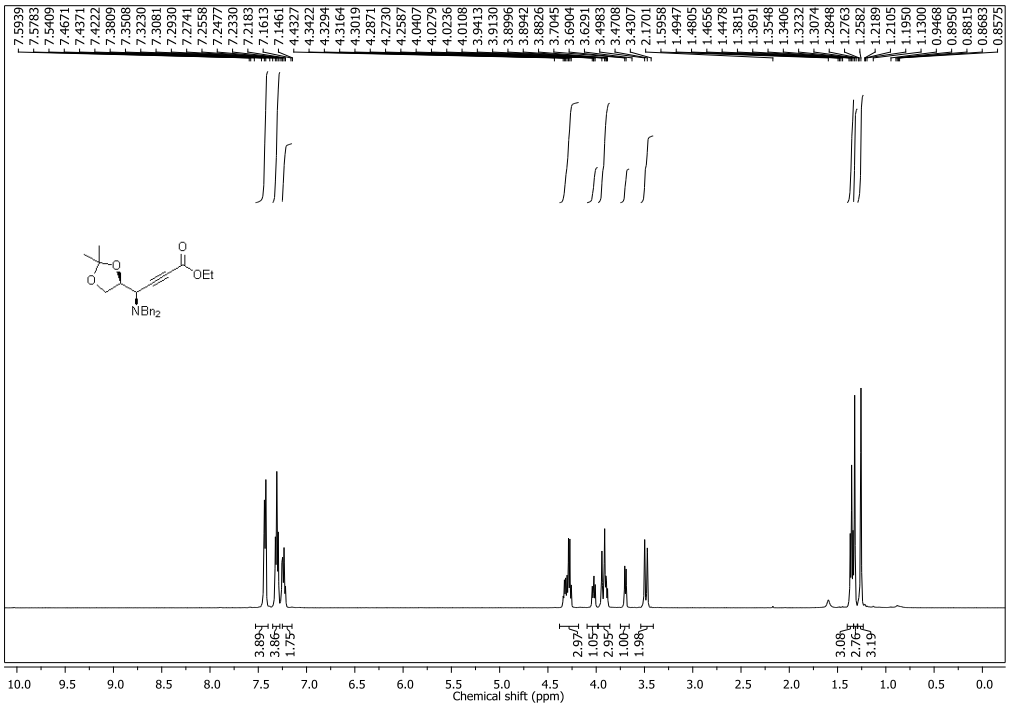


Figure 3B.4: ^{1}H NMR spectra of **10** in $CDCl_3$.

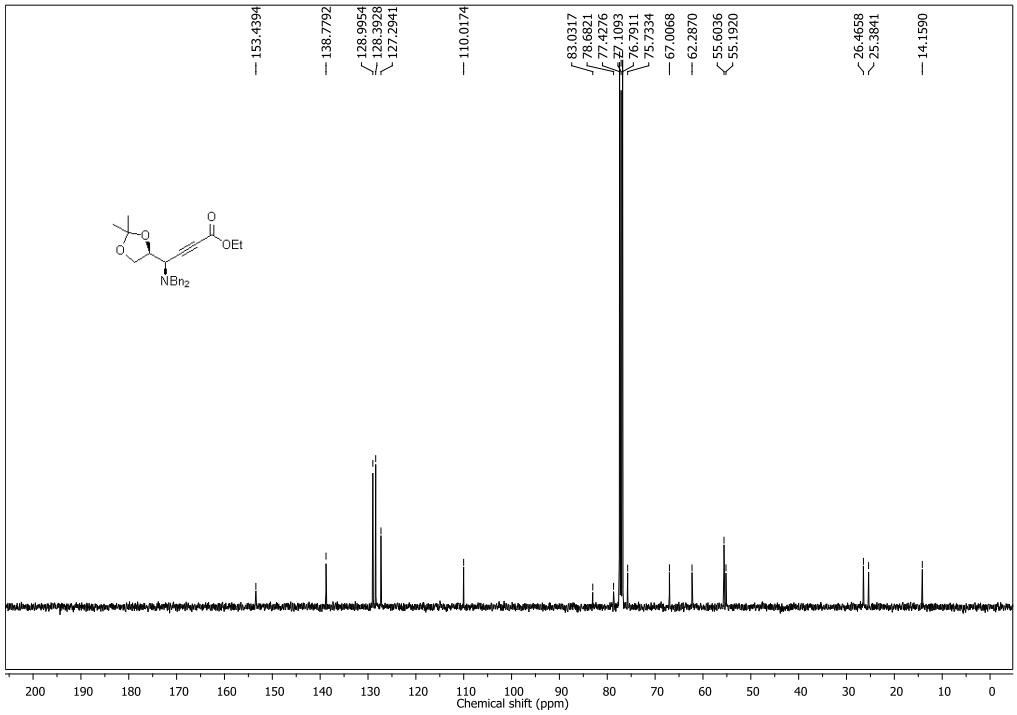


Figure 3B.5: ^{13}C NMR spectra of **10** in $CDCl_3$.

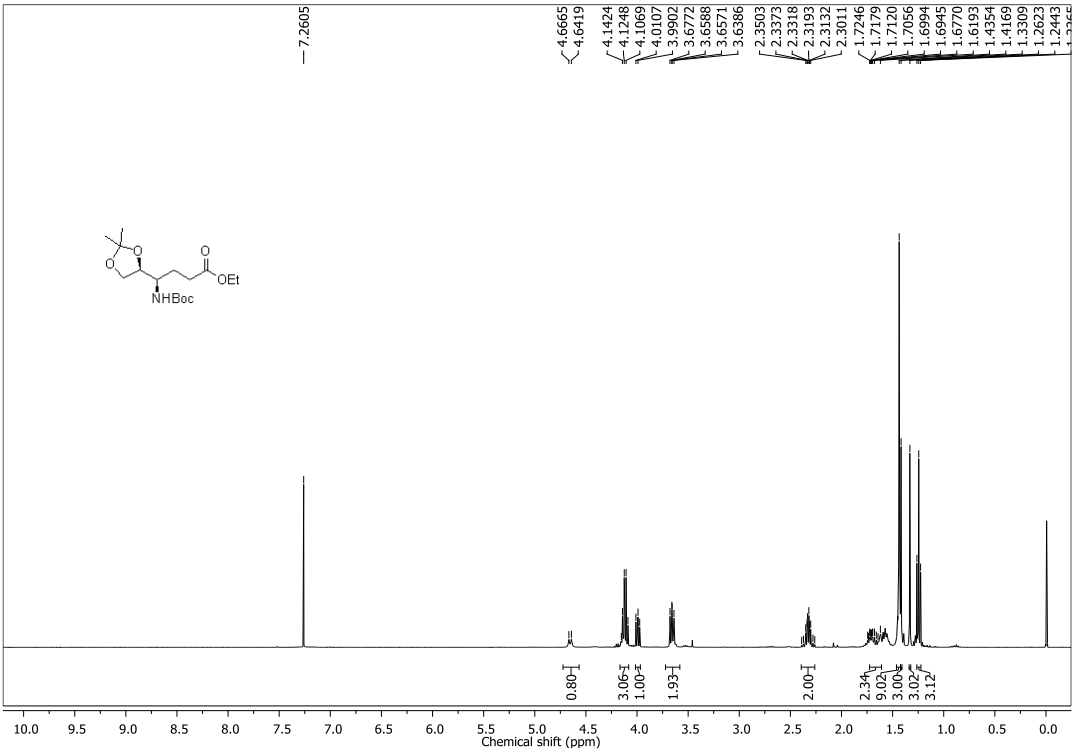


Figure 3B.6: ^{1}H NMR spectra of **12** in $CDCl_3$.

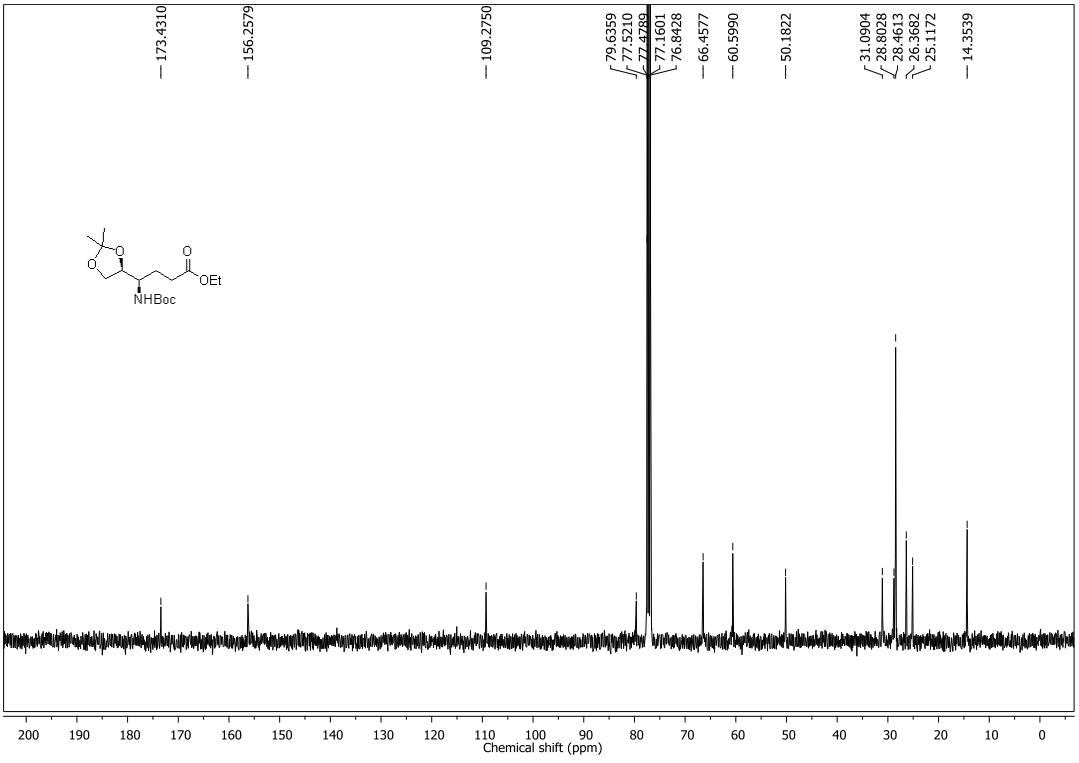


Figure 3B.7: ^{13}C NMR spectra of **12** in $CDCl_3$.

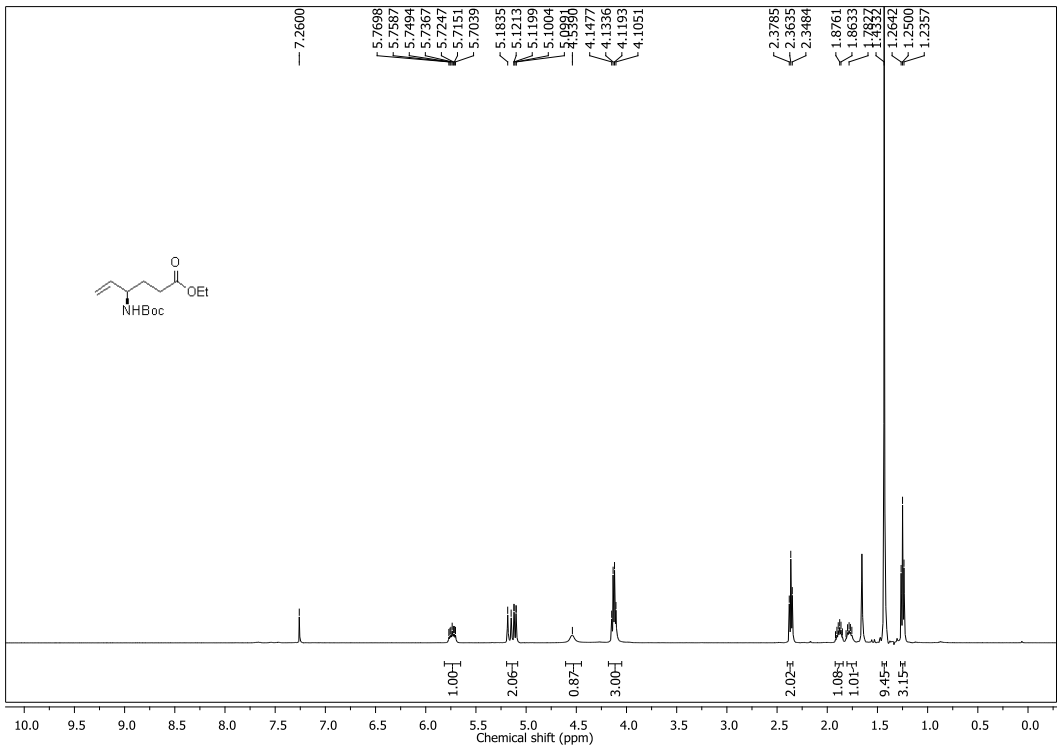


Figure 3B.8: ^{1}H NMR spectra of **14** in $CDCl_3$.

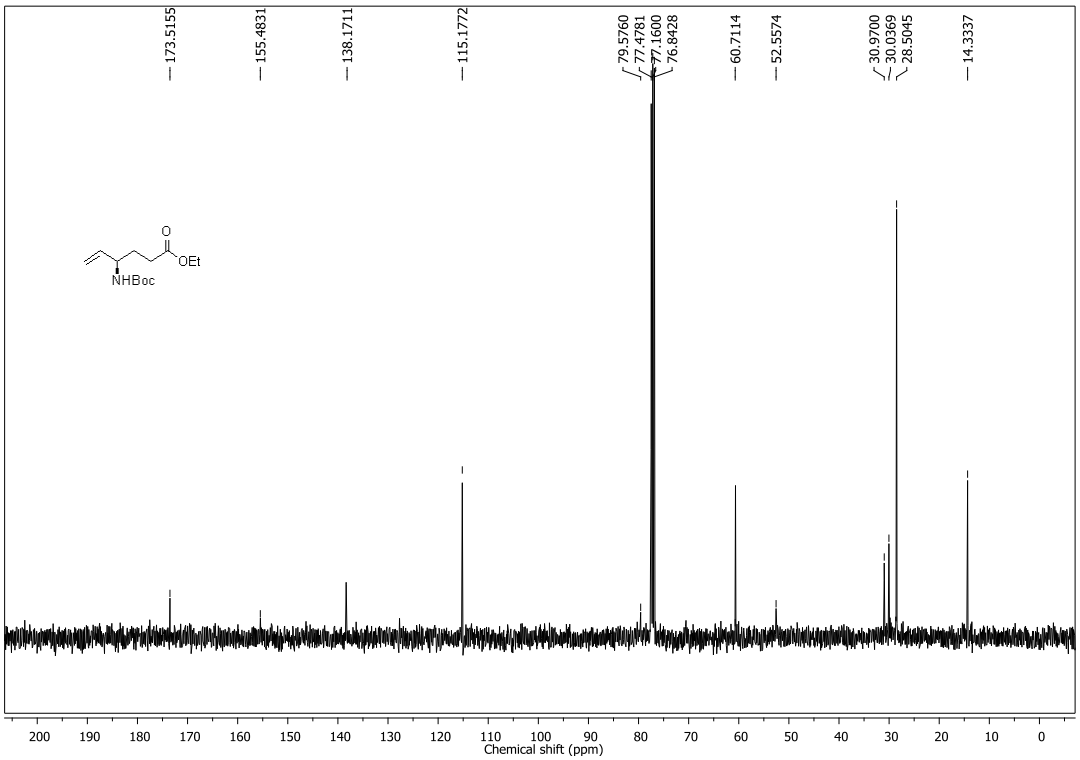


Figure 3B.9: ^{13}C NMR spectra of **14** in $CDCl_3$.

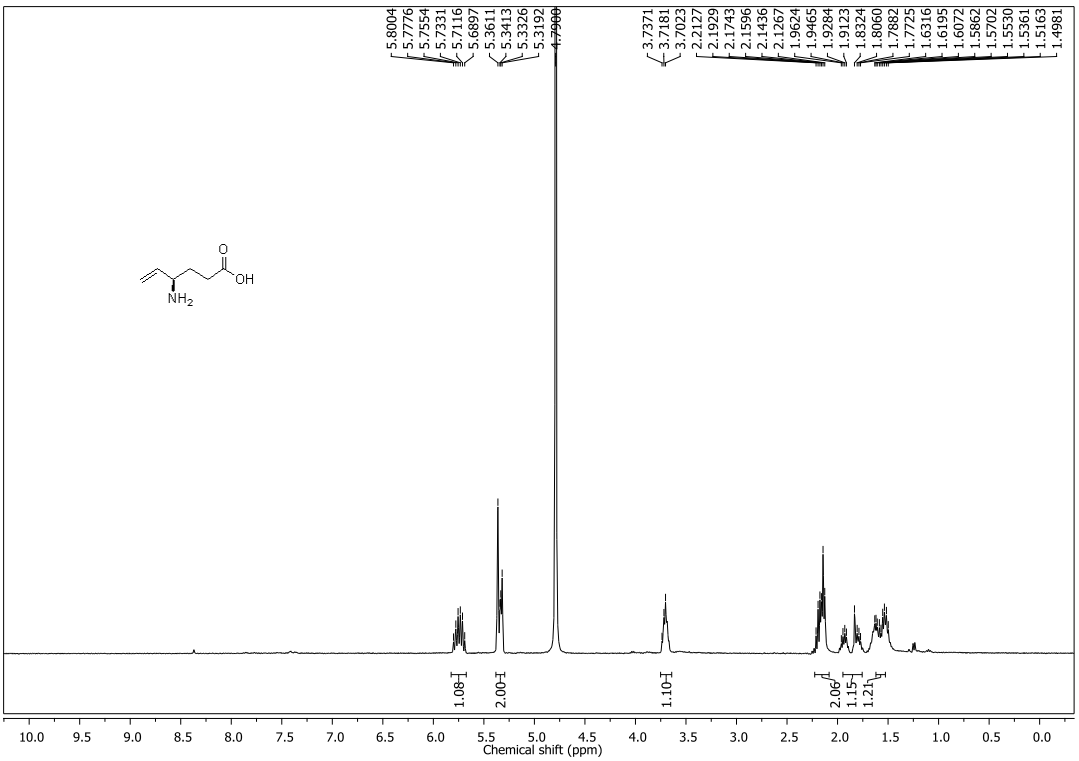


Figure 3B.10: ^{1}H NMR spectra of **5** in D_2O.

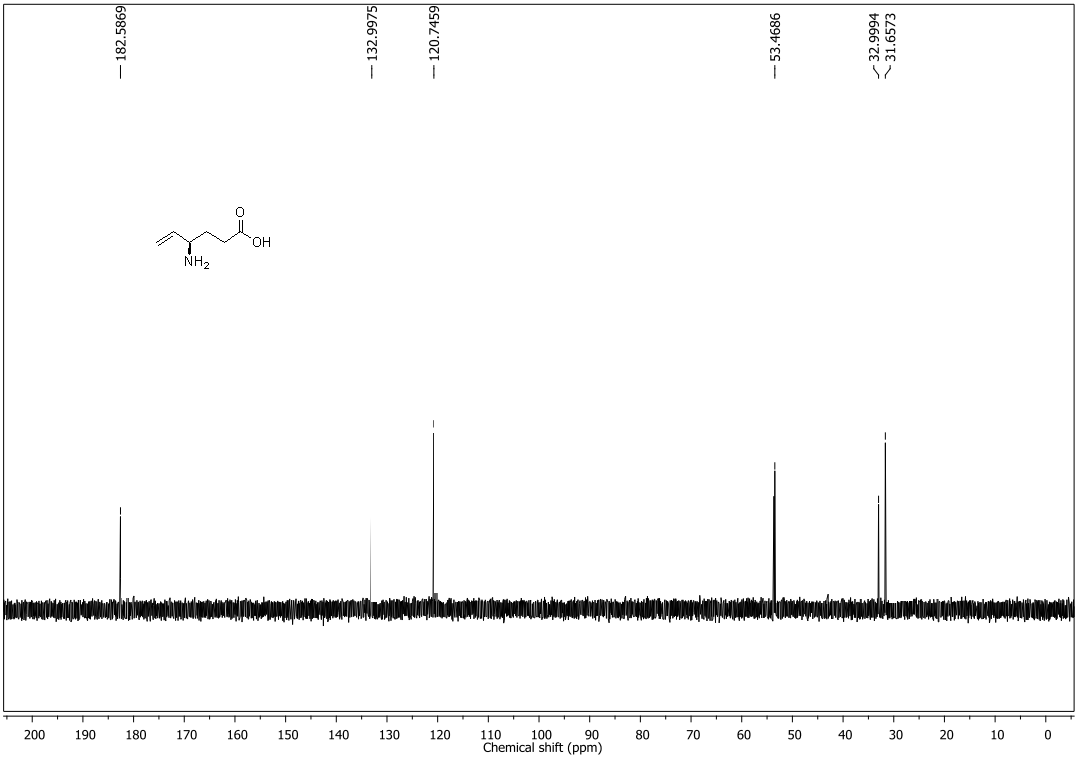


Figure 3B.11: ^{13}C-NMR spectrum of **5** in D_2O.

3B.8 References

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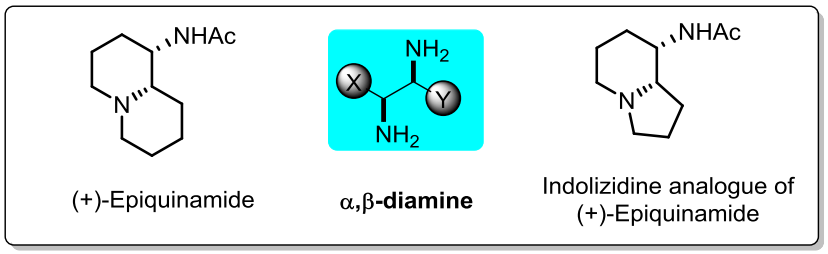
Chapter 4

Diastreoselective Construction of *syn* α,β-Diamine: Stereoselective Synthesis of (+)-Epiquinamide and its Indolizidine Analogue



4.1 Introduction

Chiral α,β-diamine moieties are present in many natural products and biologically active compounds.[1] Agelastatin A (**1**),[2] saxitoxin,[3] balanol,[4] pactamycin,[5] etc. are the examples being the natural products in which the chiral α,β-diamine moiety is present. This chiral moiety is also found in a number of drug molecules *e.g.* tamiflu (oseltamivir) (**2**),[6] biotin (**3**),[7] penicillin, eloxatin, etc. The chiral α,β-diamines also exists in transition-metal-based catalysts and organocatalysts *e.g.* Grubb's metathesis catalyst (**4**), Jacobsen epoxidation catalyst, Noyori hydrogenation catalyst, organocatalysts, etc. Consequently, the synthesis of chiral α,β-diamines have gained considerable attention in the past few years.[8]

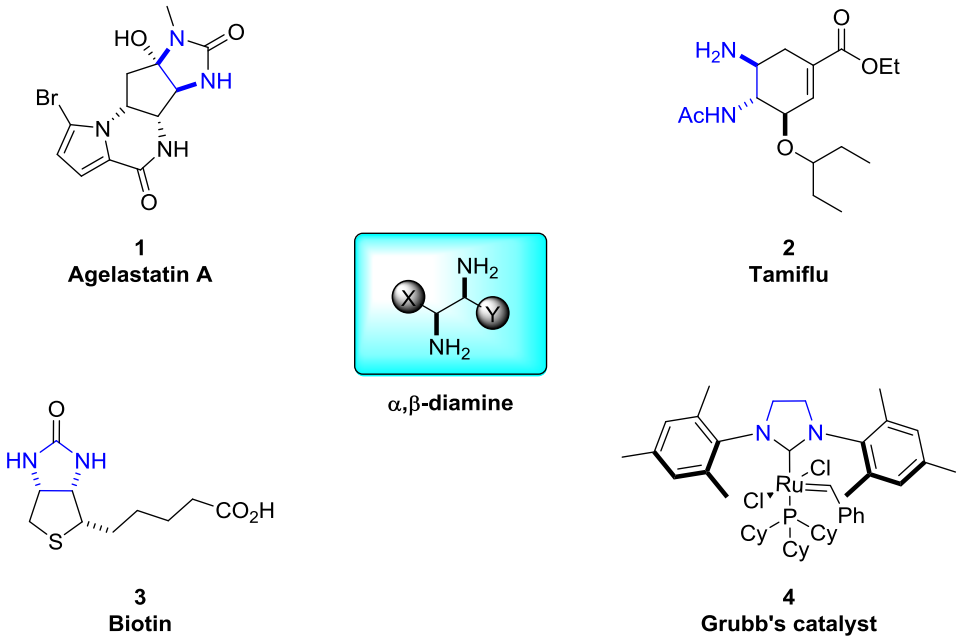


Figure 4.1: Important compounds containing α,β-diamine.

Alkaloids isolated from amphibian skin have been attracted much attention due to their interesting biological activities.[9] Amphibian skin includes a variety of alkaloids such as pyrrolidines, piperidines, indolizidines, quinolizidines decahydroquinolines, pyrrolizidines, tricyclic gephyrotoxins, pyrrolizidine oximes, pseudophrynamines, coccinellines, cyclopentaquinolizidines, etc. In 2002, Daly and co-workers isolated quinolizidine alkaloids epiquinamide (**5**) containing chiral α,β-diamines along with

epibatidine (**6**) from the poison frog *Epipedobates tricolor* (Figure 4.2).[10] Epiquinamide is a novel structural class of potent nicotinic agonists, and selective β2 nicotinic receptors.[11] Epiquinamide has the potential to be a lead molecule for the development of new therapeutics agent. But, insufficient natural availability (240 μg from 183 frogs) of this alkaloid is the major limitation in biological studies.

5
(+)-Epiquinamide

6
Epibatidine

Figure 4.2: Structure of (+)-epiquinamide and epibatidine.

As a consequence of interesting biological activities**,** pharmacologists, and synthetic chemist have given much attention towards quinolizidine alkaloid (+)-epiquinamide and its stereoisomers. The relative stereochemistry of the natural product (**5**) has been confirmed in earlier reports. Even though the various strategies are used in the synthesis of epiquinamide and its stereoisomers but any synthetic approach with fewer synthetic steps and the convenient generation analogues are still challenging.

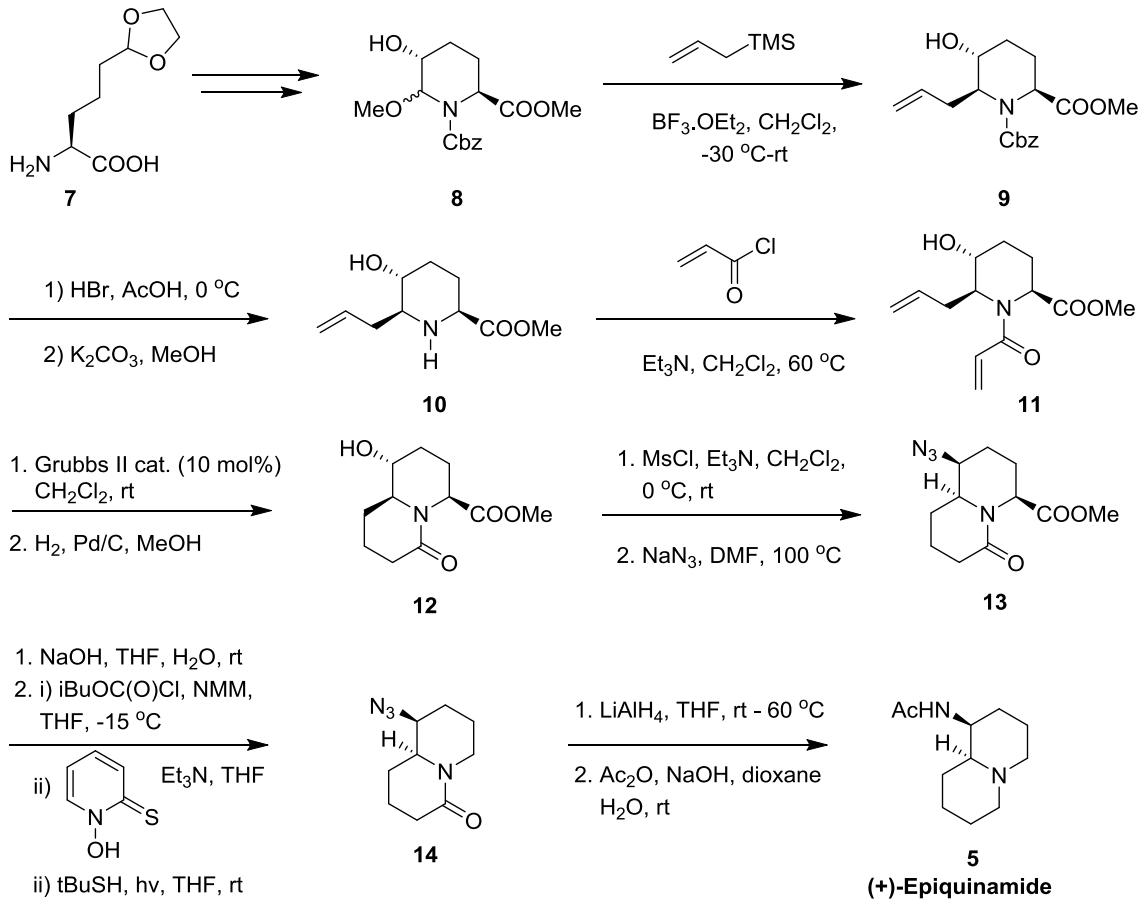
4.2 Reported Total Synthesis of (+)-Epiquinamide

Till date, various approaches have been reported for the synthesis of epiquinamide and its isomers.[12] The different strategies towards the total synthesis of natural (+)-epiquinamide are outlined below.

4. 2. 1 Synthetic Approach of (+)-Epiquinamide by Blaauw *et al.*

The first total synthesis of (+)-epiquinamide was reported by Blaauw and coworkers in 2005,[13] starting from L-allysine ethylene acetal **7** (Scheme 4.3). A diastereoselective *N*-acyliminium ion allylation and a ring-closing metathesis reaction were the main key steps involved in their approach. Cbz protected pipecolic ester **8** was prepared from L-allysine ethylene acetal **7 (**94% yield over 4-steps**)** in 96:4 diastereomeric ratio. The reaction of ester **8** with $BF_3{\cdot}OEt_2$ in the presence of allyl trimethyl silane

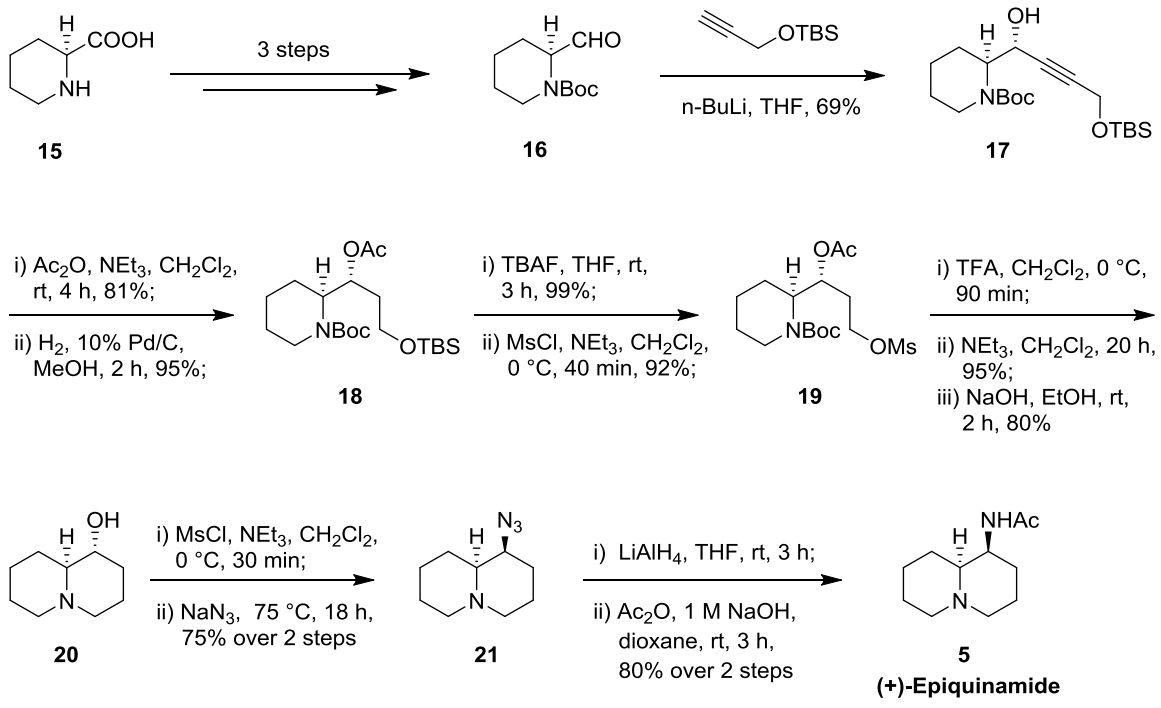
afforded the (*2S,5R,6S*)-configured product **9** as a single diastereomer via *N*-acyliminium ion intermediate. Deprotection of the Cbz moiety under acidic conditions followed by the introduction of an acryloyl group using one equivalent of acryloyl chloride provided the bis-olefinic product **10**. The reaction of **10** with a catalytic amount of Grubb's second generation ruthenium catalyst and followed by hydrogenation of double bond afforded the bicyclic lactam **11**. The mesylation of the alcohol **11** using MsCl and Et_3N followed by treatment with sodium azide provided azide derivative **12**. Ester hydrolysis of **12** followed by coupling with 2-mercaptopyridine-N-oxide resulted in activated ester which was then irradiated in the presence of 2-methylpropane-2-thiol, to afford **14** in 49% yield. LAH-mediated reduction of both the azide as well as the lactam followed by *N*-acetylation using Ac_2O gave the desired (+)-epiquinamide **5** (15-steps with the overall yield of 15.5%).



Scheme 4.3: Blaauw's approach for the synthesis of (+)-epiquinamide.

4. 2. 2 Synthetic Approach of (+)-Epiquinamide by Barker *et al.*

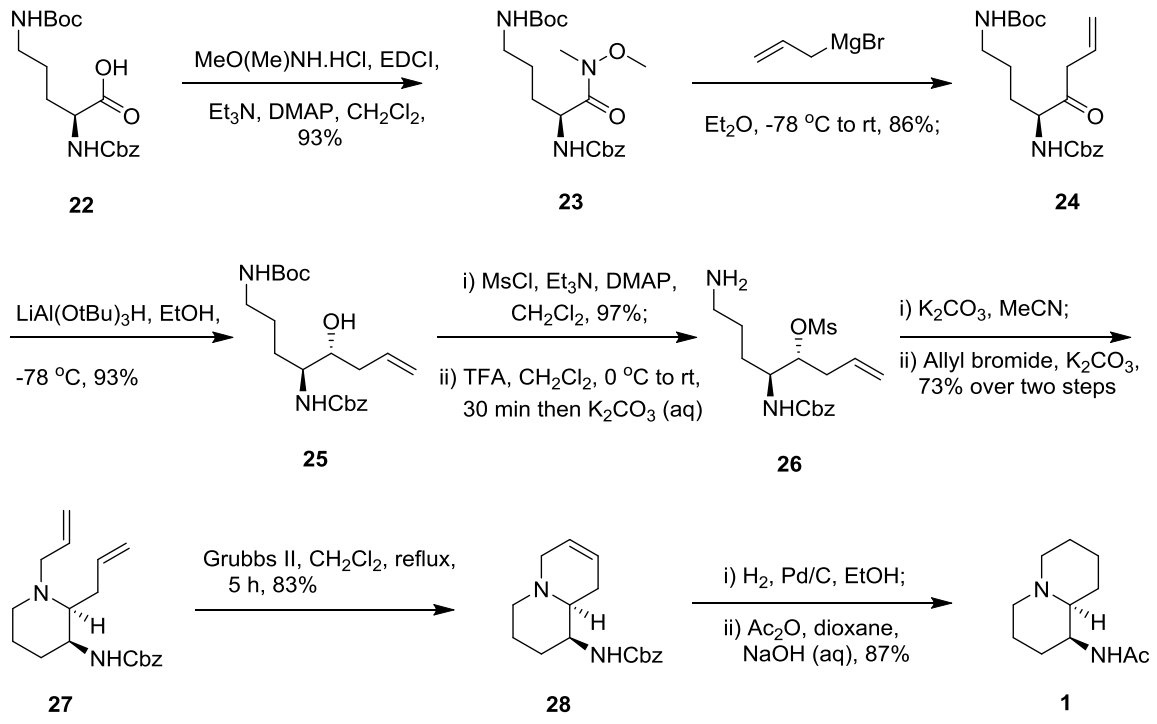
In 2006, Barker and coworkers reported the synthesis of (+)-epiquinamide **5** starting from commercially available (-)-pipecolinic acid **15** (Scheme 4.4).[14] The (-)-pipecolinic acid **15** was converted to aldehyde **16** in 3 steps. The addition of alkyne anion of TBDMS-protected propargyl alcohol to aldehyde **16** provided alkynol **17** with 69% yield. The acetylation of alcohol **17** was achieved using acetyl chloride and the alkyne reduced to give the silyl ether **18** in 77% yield over two steps. Silyl deprotection using TBAF and mesylatation of alcohol resulted to compound **19**. The Boc deprotection with TFA followed by neutralization with NEt_3 gave bicyclic skeleton and hydrolysis of acetyl ester with NaOH furnished compound **20** in 80% yield. The alcohol **20** was converted azide **21** via the mesylation. Reduction of azide **21** was achieved in 92% yield using $LiAlH_4$ to give amine, which was further acetylation resulted into (+)-epiquinamide **5.** The synthesis of (+)-epiquinamide **5** was completed starting from (-)-pipecolinic acid **15** in 12-steps with overall 13% yield.



Scheme 4.4: Barker's approach for the synthesis of (+)-epiquinamide.

4. 2. 3 Synthetic Approach of (+)-Epiquinamide by Gerwick *et al.*

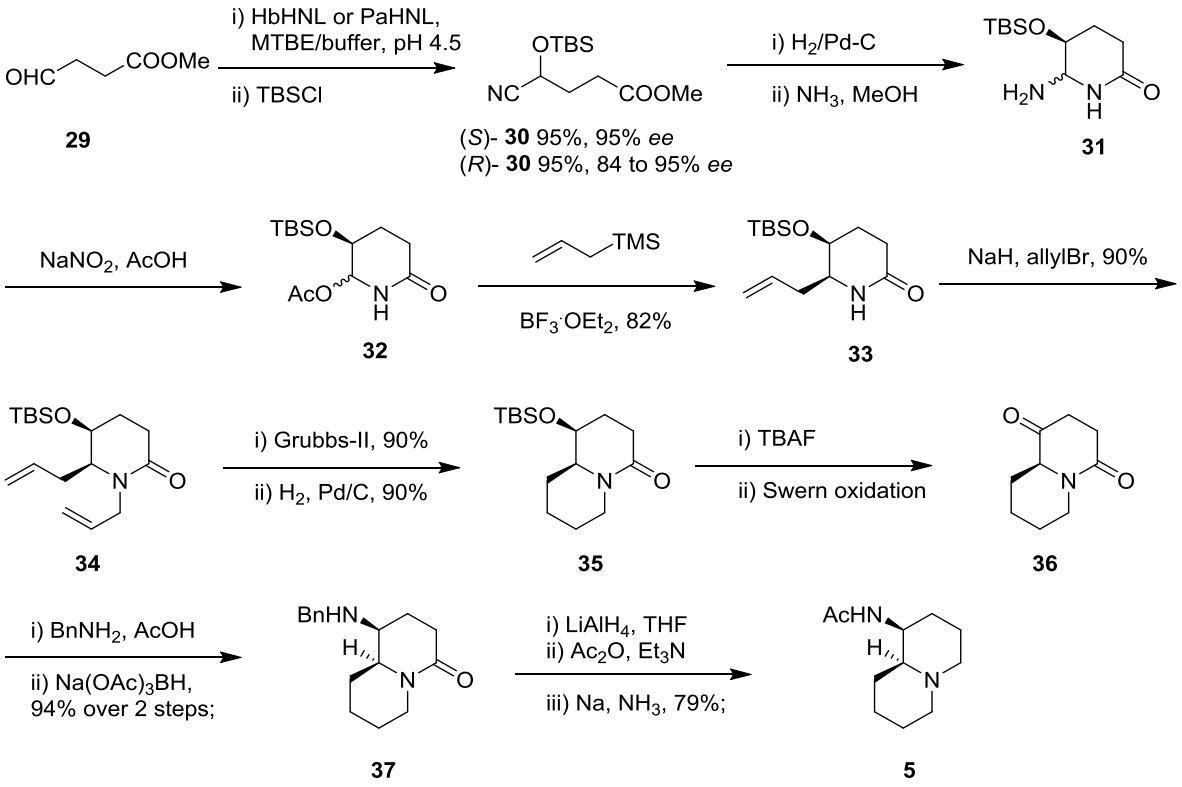
In 2006, Gerwick and coworkers reported a short and practical synthesis of (+)-epiquinamide and its enantiomer starting from ornithine derivative **22** (Scheme 4.5).[15] The ornithine derivative **22** was converted to the Weinreb amide **23** using a common coupling condition. The reaction of **23** with an allyl Grignard reagent resulted in ketone **24**. The chelation-controlled hydride reduction of **24** gave alcohol **25**. Further mesylation of alcohol and removal of the Boc group in TFA/CH_2Cl_2 gave the free amine **26**. The intramolecular S_N^2 cyclization made by K_2CO_3 followed by *N*-alkylation in acetonitrile yielded the diallyl piperidine **27**. The ring closing metathesis of **27** using the Grubb's second-generation catalyst provided quinolizidine skeleton **28**. Finally, one pot deprotection, alkene reduction, and followed by acetylation gave (+)-epiquinamide **5** (9-steps with 38% overall yield). The synthesis of the other enantiomer (-)-epiquinamide was performed in the same manner starting with commercially available *N*-Boc-*N*-Cbz- D-ornithine.



Scheme 4.5: Gerwick's approach for the synthesis of (+)-epiquinamide.

4. 2. 4 Synthetic Approach of (+)-Epiquinamide by Rutjes *et al.*

In 2008, Rutjes and co-workers reported the synthesis of (+)-epiquinamide from the readily prepared succinic semialdehyde **29**.[16] The aldehyde **29** was converted into both enantiomeric forms of the corresponding cyanohydrins **30** using crude cell lysates from the rubber tree and almond-containing hydroxynitrile lyases. The (*S*)-selective HNL from Heveca brasiliensis (HbHNL) and an (*R*)- selective HNL from Prunus amygdalus (PaHNL) provided reductive amination of **30** gave the corresponding *N*,*N*-acetal **31** as a 2:1 mixture of cis/trans-isomers. The compound **31** was treated with $NaNO_2$ in neat acetic acid to provide N,O-acetal **32**. The compound **32** was treated with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ to give compound **33** (4.2:1 mixture of cis/trans-isomers). Cis isomer **33** was treated with NaH and allyl bromide to furnish compound **34**, which was transformed into the bicyclic lactam **35** via RCM followed by hydrogenation. TBS deprotection of **35** using TBAF, followed by swern oxidation provided bicyclic ketone **36**. The compound **37** was prepared by reductive amination of **36** with benzyl amine. Finally, reduction, acetylation, and debenzylation of **37** gave the (+)- epiquinamide **5** in 70% *ee*.

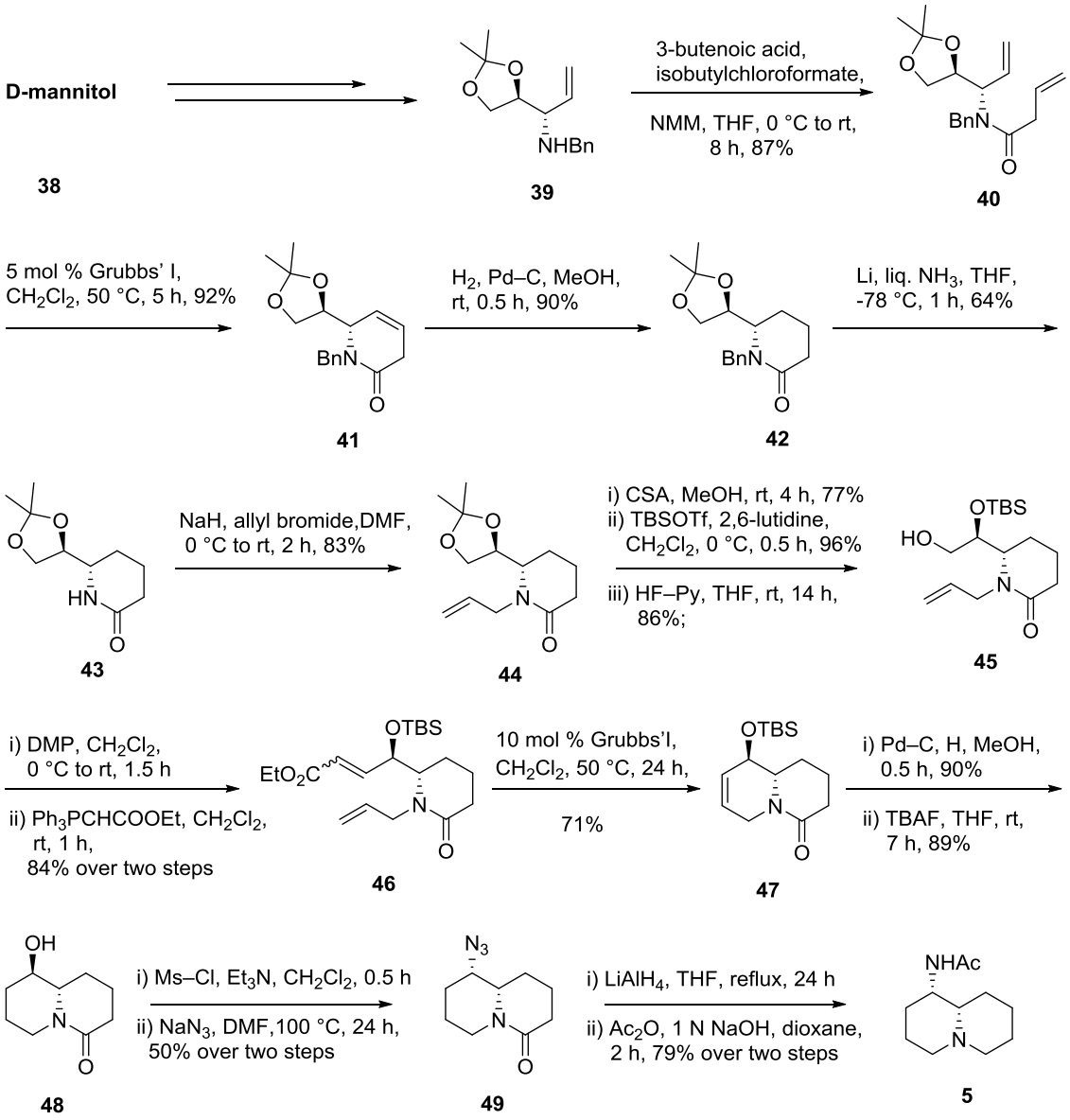


Scheme 4.6: Rutjes approach for the synthesis of (+)-epiquinamide.

4. 2. 5 Synthetic Approach of (+)-Epiquinamide by Ghosh *et al.*

In 2009, Ghosh *et al.* reported the synthesis of (+)-epiquinamide from D-mannitol **38** (Scheme 4.7).[17] D- mannitol was converted to bis-olefinic compound **40** via *N*-Acylation of intermediate **39** with 3-butenoic acid using isobutyl chloroformate. The ring-closing metathesis of bis-olefinic compound **40** using Grubb's 1st generation catalyst in CH_2Cl_2 at 50 °C for 6 h provided the six-membered lactam **41**. Hydrogenation of lactam **41** under Pd–C as a catalyst in methanol resulted in compound **42**. The debenzylation of **42** under Li/ liq. NH_3 followed by *N*-Allylation of **43** with NaH and allyl-bromide in DMF afforded compound **44**. The acetonide deprotection of **44** followed by routine protecting-group operations afforded primary alcohol **45.** The oxidation of alcohol **45** using Dess–Martin periodinane (DMP) reagent followed by Wittig olefination with stable ylide Ph_3P=CHCOOEt provided bis-olefinic compound **46**. The ring-closing metathesis of **46** using 10 mol % of Grubb's 1st generation catalyst in CH_2Cl_2 gave compound **47** in 71% yield. The double bond reduction followed by TBS deprotection of secondary alcohol

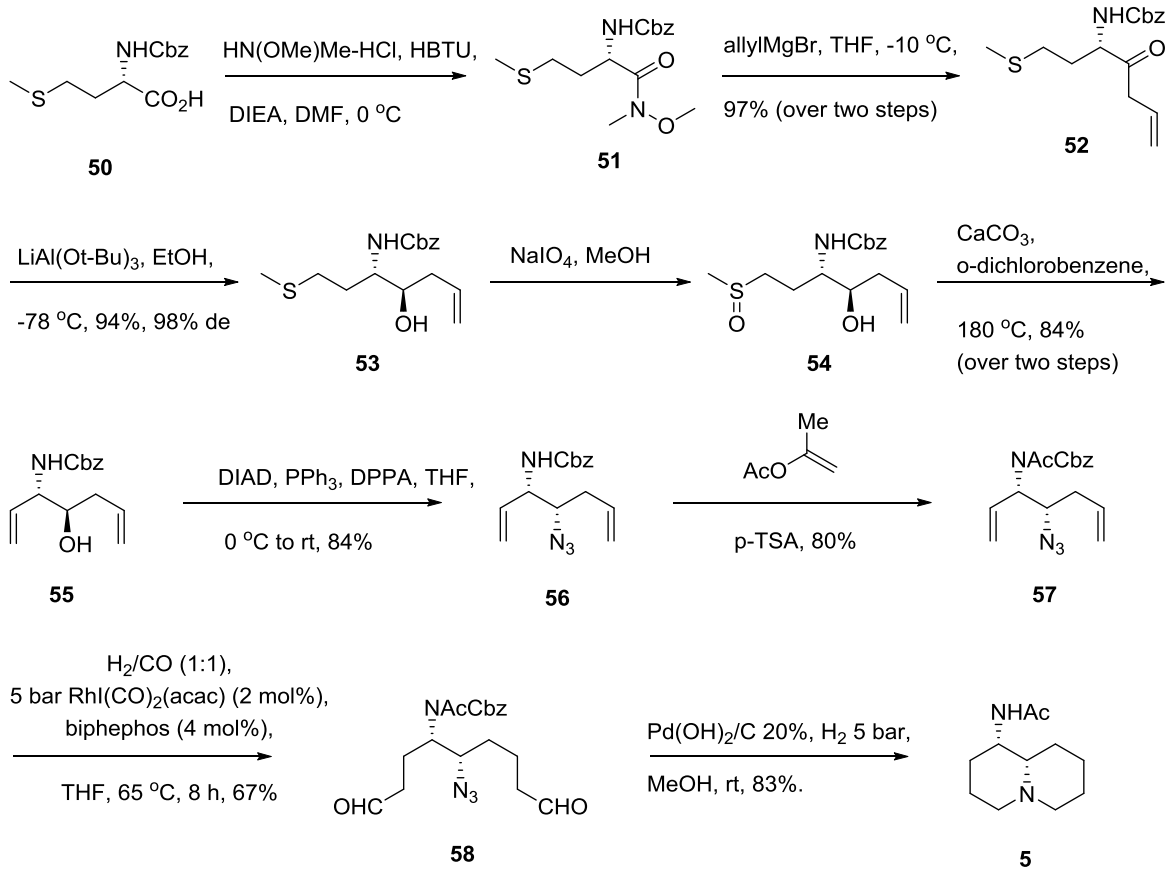
afforded alcohol **48**. The alcohol **48** on mesylation followed by S_N2 displacement with NaN_3 afforded azide **49**. The LAH reduction of azide **49** followed by *N*-acetylation provided epiquinamide **(+)-5.**



Scheme 4.7: Ghosh's approach for the synthesis of (+)-epiquinamide**.**

4. 2. 6 Synthetic Approach of (+)-Epiquinamide by Breit *et al.*

In 2010, Breit *et al*. synthesized (+)-epiquinamide from Cbz-L-methionine based on a double hydroformylation of a bis-homoallylic azide followed by a tandem catalytic hydrogenation/reductive bisamination (Scheme 4.8).[18] The Weinreb amide **51** was prepared from Cbz-L-methionine **50** using standard coupling conditions. Further treatment of weinrab amide **51** with allylmagnesium chloride gave the corresponding homoallylic ketone **52.** The desired *anti* amino alcohol **53** was synthesised from the reduction of ketone **52** with a lithium tris-*tert*-butoxy aluminum hydride. The oxidation of sulphide **53** using sodium *meta*-periodate gave compound **54** quantitatively with a ~1:1 mixture of sulfoxide diastereomers. The bis homoallylic alcohol **55** was prepared from thermal treatment of sulfoxide **54** in the presence of calcium carbonate. The azido group with desired stereochemistry was introduced using mitsunobu reaction with alcohol **55**. The protected *N*-Cbz, *N*-acylated product **57** was prepared under mild acidic conditions using *p*TSA in isopropenylacetate as a solvent, which further converted into an aldehyde **58** in 67% yield. The reduction of azido group into a free amine and two reductive aminations in the presence of Pearlman's catalyst gave the bicyclic quinolizidine ring, and finally, Cbz deprotection afforded **5** in 83% yield. The (+)-epiquinamide **5** was synthesised in nine steps with 29% overall yield.

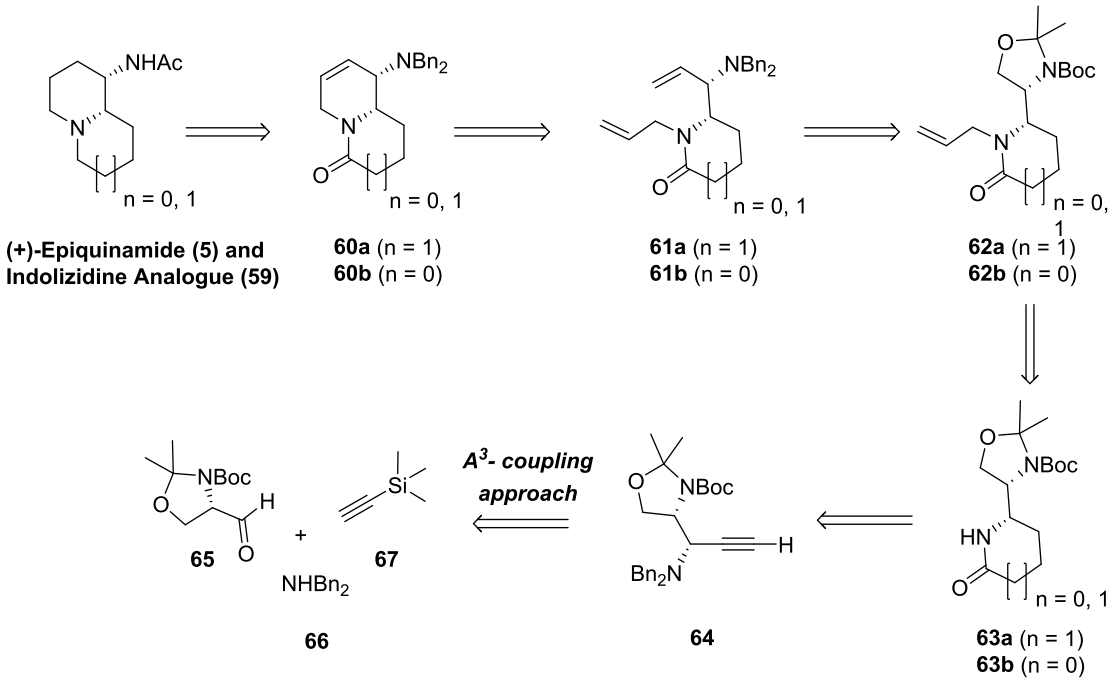


Scheme 4.8: Breit's approach for the synthesis of (+)-epiquinamide.

4.3 Present Work and Synthetic Planning.

Although, there are various synthetic methods available for the preparation of (+)-epiquinamide **1** as described above, all of these methods are planned to synthesize only epiquinamide with specific stereochemistry. It is still a challenge to develop a method that is practical for the synthesis of epiquinamide and its analouges. We have planned a suitable and efficient synthetic procedure for the stereoselective synthesis of (+)-epiquinamide and its novel indolizidine analogues. As an ongoing research work on diastereoselective aldehyde- amine- alkyne (A^3) coupling reaction,[19] we have planned construction of *syn* α-β-diamine which is present in (+)-epiquinamide from Garner's aldehyde, dibenzyl amine, TMS-acetylene. We planned strategy towards the construction of quinolizidine and indolizidine scaffolds present in (+)-epiquinamide and its analogue from common terminal alkyne intermediate.

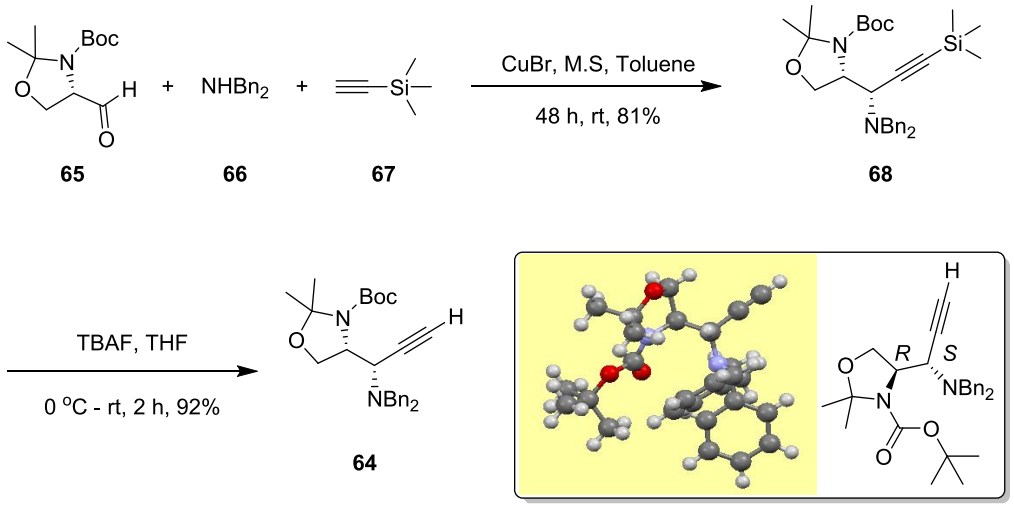
As shown in the retrosynthetic analysis (Scheme 4.7), we visualised that (+)-epiquinamide **5** and indolizidine analogue **59** could be fabricated from the quinolizidine intermediate **60a** and indolizidine intermediate **60b** respectively via reduction of lactum, reduction of double bond, debenzylation, and acetylation of amine. We expected that bicyclic unsaturated compounds **60a** and **60b** would be a key intermediate for the preparation of hydroxylated analogues as well as some more analogues through the formation of epoxide. The bicyclic framework **60a-b** could be obtained using Grubb's ring closing metathesis of bis-olefin **61a-b**. The bis-olefin **61a-b** can be prepared from **62a-b** via acetonide deprotection, oxidation of primary alcohol and Wittig olefination. The **62a-b** could be obtained from lactum **63a-b** via allyalation in basic condition. Lactum **63a** could be obtained from terminal alkyne **64** via alkylation with ethyl diazoacetate, the reduction of triple bond, debenzylation, and cyclization in basic condition. Similarly, lactum **63b** could be obtained from a terminal alkyne **64** via alkylation with ethyl chloroformate, reduction of triple bond, debenzylation and cyclization in basic condition. The alkyne **64** could be obtained from Cu-catalyzed (A^3) coupling reaction of Garner's aldehyde **65**, dibenzyl amine **66**, TMS-acetylene **67**, followed by desilylation of the multicomponent product.



Scheme 4.9: Retrosynthetic analysis.

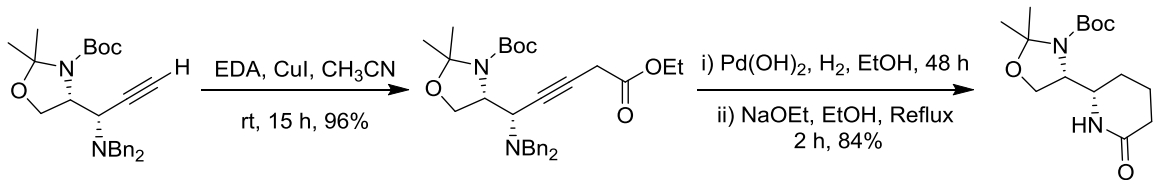
4.4 Results and Discussion

We started synthesis with the preparation of Garner's aldehyde **65** from commercially available L-serine methyl ester hydrochloride salt according to the published procedures.[20] Garner's aldehyde **65** and dibenzylamine **66** when reacted with the TMS-acetylene **67** under CuBr (5 mol%) catalytic conditions in toluene at room temperature, substituted propargyl amine **68** was formed as single *syn*-diastereomer (*syn* to *anti* ratio of > 99%) with 81% yield. The *anti*-diastereomer was not noticed under the applied reaction conditions. The silyl deprotection of **68** in the presence of TBAF in THF afforded terminal alkyne **64** with 92% yield**.** The stereochemistry of α-β-diamine was confirmed by X-ray crystal structure of alkyne **64** (Scheme 4.10).



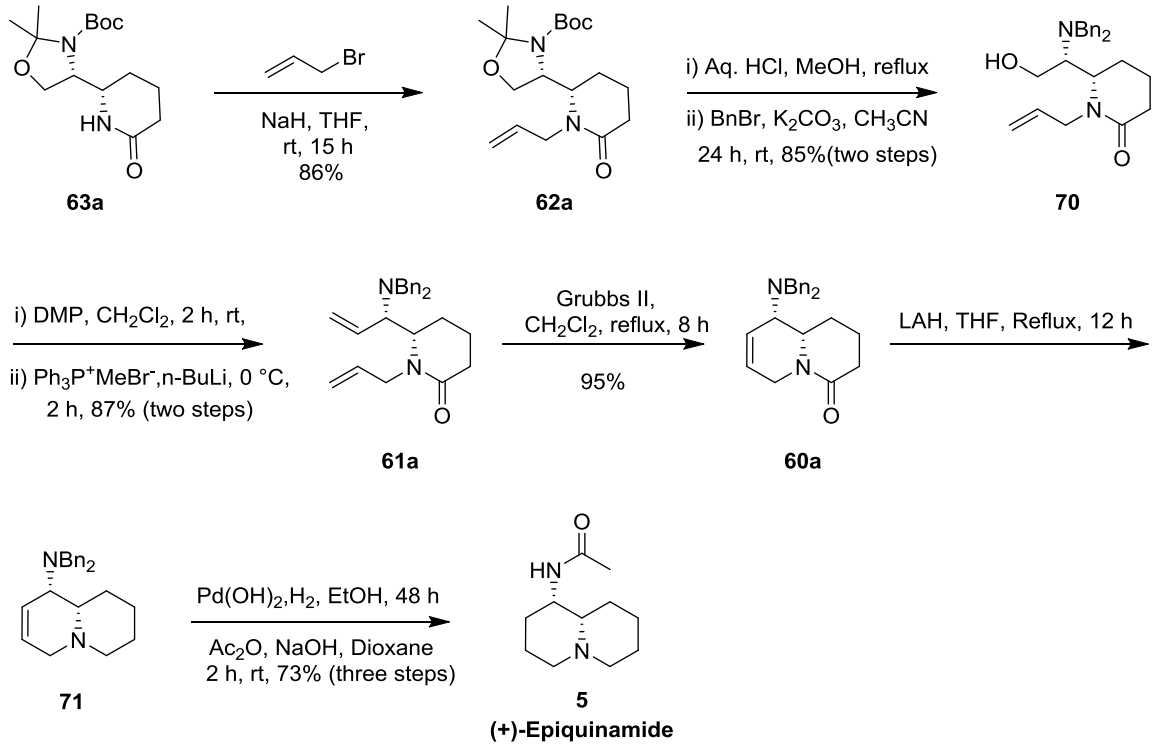
Scheme 4.10: Synthesis and crystal structure of key intermediate **64**.

Key intermediate **64** further used for the construction of five and six-member lactam **63a-b.** Treatment of terminal alkyne **64** with ethyl diazoacetate under 5 mol% CuI resulted in ester **69** with allene isomer in 94:06 ratios (determined from the ^{1}H-NMR data) was formed in 96% yield. The reaction of ester **69** with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond followed by cyclization using NaOEt to afford the six-member lactam **63a** in 84% yield over two steps (Scheme 4.11).



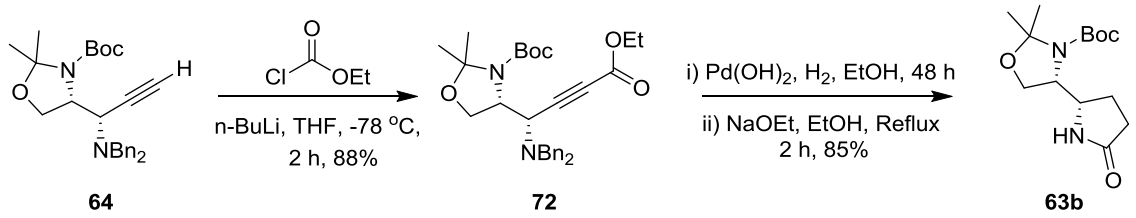
Scheme 4.11: Synthesis of six-member lactam **63a.**

The lactam **63a** was treated with allyl bromide in the presence of NaH in THF to give allyl protected lactam **62a** in 86% yield. Further, acetonide and Boc deprotection was achieved in one pot by using concentrated aqueous HCl in methanol reflux condition. The reaction of a free amine with benzyl bromide in the presence of K_2CO_3 resulted *N*-dibenzyl protected alcohol **70** in 87% yield over 2 steps. The alcohol **70** was converted into aldehyde using DMP mediated mild oxidising condition. The reaction of an aldehyde with Ph_3PCH_3Br salt and *n*-BuLi in THF provided **61a** in 87% yield (2steps). The reaction of **61a** with Grubb's second generation catalyst in dichloromethane provided quinolizidine skeleton **60a** in 95% yield. The reduction of lactam **60a** was done in the presence of LAH to give protected amine **71**. Finally, the reduction of the double bond and debenzylation with 10% $Pd(OH)_2/C$ (10 mol%) under hydrogen atmosphere followed by *N*-acetylation using Ac_2O in dioxane afforded epiquinamide **(+)-1** in 73% yield after 3 steps (Scheme 4.12). The synthesis of (+)-epiquinamide **1** was completed in 14 steps (9 purification steps) with overall 27 % yield starting from Garner's aldehyde **65.** The ^{1}H, ^{13}C NMR and specific rotation data of the compound **5** are in close agreement with the literature value.[13]



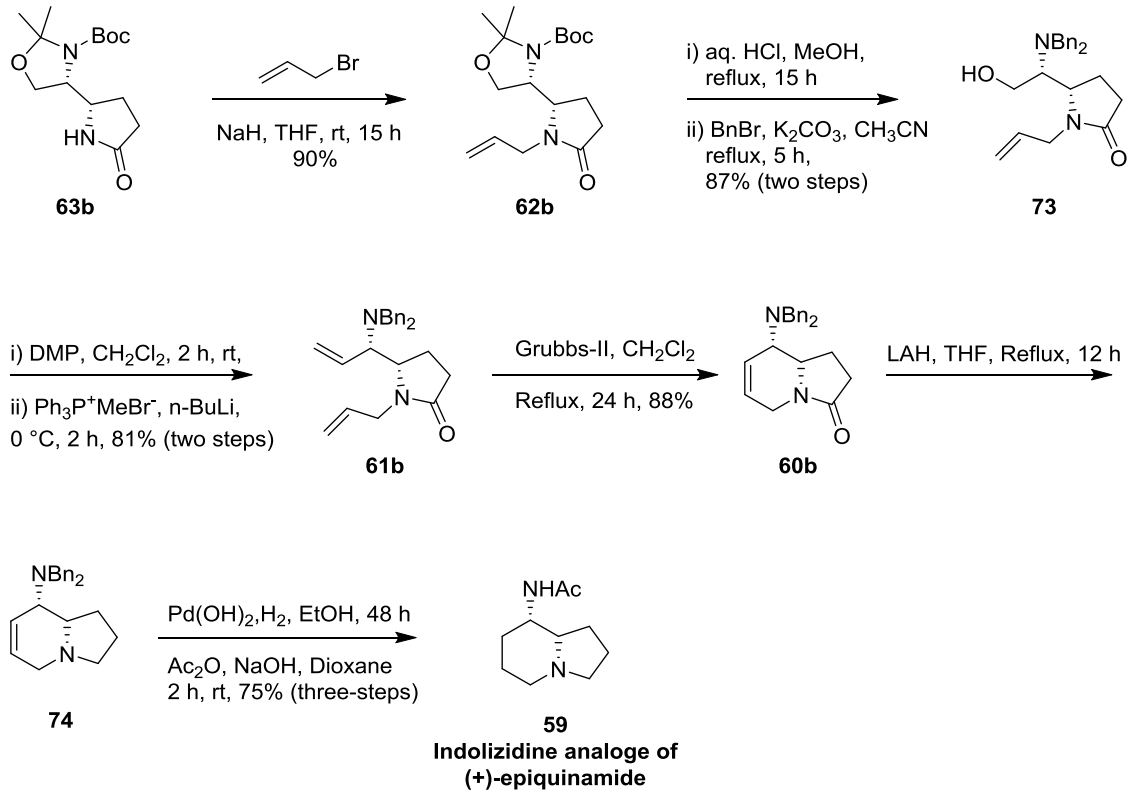
Scheme 4.12: Synthesis of (+)-epiquinamide **5**.

After getting natural (+)-epiquinamide in hand, we moved to the synthesis of its indolizidine analogues from key intermediate **64**. Treatment of ethyl chloroformate and the terminal alkyne **64** in the presence of *n*-BuLi gave the ester moiety of **72** with 88% yield. The ester **72** then reacted with 10% $Pd(OH)_2/C$ (10 mol%) under 100 psi hydrogen atmosphere, complete hydrogenolysis of benzyl groups and the reduction of C≡C bond followed by cyclization using NaOEt provided the γ-lactam **63b** in 85% yield over two steps (Scheme 4.13).



Scheme 4.13: Synthesis of five-member lactam **63b.**

The lactam **63b** was reacted with allyl bromide in the presence of NaH in THF to give allyl protected lactam **62b** in 90% yield. The acetonide and Boc deprotection using concentrated aqueous HCl in methanol reflux condition gave free amine which treated with benzyl bromide in the presence of K_2CO_3 resulted *N*-dibenzyl protected alcohol **73** in 87% yield over 2 steps. The alcohol **73** was converted into aldehyde using DMP mediated mild oxidising condition. The aldehyde was reacted with Ph_3PCH_3Br salt and *n*-BuLi in THF to give bis-olefin **61b** in 81% yield. The reaction of **61b** with Grubb's second generation catalyst in dichloromethane provided indolizidine skeleton **60b** in 88% yield. The reduction of lactam **60b** was done in the presence of LAH to give protected amine **74**. Finally, the reduction of the double bond and debenzylation with 10% $Pd(OH)_2/C$ (10 mol%) under hydrogen atmosphere followed by *N*-acetylation using Ac_2O in dioxane afforded indolizidine analogue of epiquinamide **59** in 75% yield after 3 steps (Scheme 4.14). The synthesis of **59** was completed in 14 steps (9 purification steps) with overall 23 % yield starting from Garner's aldehyde **65.**



Scheme 4.14: Synthesis of indolizidine analogues (+)-epiquinamide **59**.

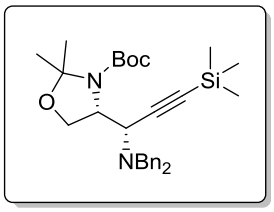
4.5 Conclusions

In conclusion, the total synthesis of (+)-epiquinamide was achieved in total 9 purifications steps with an overall yield of 27% from Garner's aldehyde. Using same strategy, we have synthesised novel indolizidine analogue of (+)-epiquinamide in similar steps and 23% overall yield. The strategy involved Cu catalysed A^3 coupling reaction of Garner's aldehyde, dibenzyl amine, TMS-acetylene to get the desired *syn* stereochemistry of diamine presence in (+)-epiquinamide. The *syn* stereochemistry of α-β-diamine was confirmed by X-ray crystal structure of alkyne **64.** This key intermediate used for the construction of both five as well as six-member lactam. Grubb's ring closing metathesis approach used for the preparation of indolizidine and quinolizidine skeletons.

4.6 Experimental Section

General Methods: The acetonide-protected Garner's aldehyde was prepared from L-serine methyl ester hydrochloride according to the published methods. Other substrates and reagents were purchased from common commercial sources and used without additional purification. THF and Diethyl ether was pre-dried over Na wire. Then the solvent was refluxed over Na (1% w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue colour of the benzophenone ketyl radical anion persists. All reactions were conducted under the nitrogen 60 atmosphere. Solvents: petroleum ether and ethyl acetate (EtOAc) were distilled prior to thin layer and column chromatography. Reactions were controlled using TLC on silica. Column chromatography was performed on silica gel (100–200 mesh).

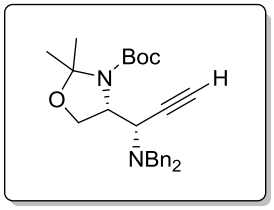
Synthesis of tert-butyl (*R*)-4-((*S*)-1-(dibenzylamino)-3-(trimethylsilyl)prop-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 68 ($C_{30}H_{42}N_2O_3Si$).



To a solution of *tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate **65** (3.50 g, 15.28 mmol) in dry toluene (75 mL) were added dibenzylamine **66** (3.00 g, 15.28 mmol), 4 Å molecular sieves, CuBr (110 mg, 0.05 mmol), and TMS-acetylene **67** (1.50 g, 15.28 mmol). The reaction mixture was stirred at room temperature for 48 h. After completion, the reaction mixture was filtered through celite bed and washed with Et_2O (2 × 30 mL). The combined filtrate was concentrated under reduced pressure to obtain liquid which was further purified by column chromatography over silica gel (*Eluent:* 2% EtOAc in petroleum ether) to furnish corresponding multi-component reaction product **68** (6.28 g, 81%) as colorless oil. IR (KBr) ν (cm^{-1}): 2971, 2160, 1695, 1488, 1454, 1371, 1248, 1167, 1095, 1001; $[\alpha]_D^{25}$ = + 80.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, J = 7.3 Hz, 4H), 7.26 (t, J = *J* = 7.4 Hz, 4H), 7.19 (t, J = 7.2 Hz, 2H), 4.35 (dd, J = 9.4, 5.3 Hz, 1H), 4.13 (d, J = 9.2 Hz, 1H), 3.95 (d, J = 13.2 Hz, 2H), 3.87 (dd, J = 9.1, 5.5 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.32 (d, J = 13.2 Hz, 2H), 1.59 (s, 9H), 1.43 (s, 3H), 0.96 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.2, 139.7 (2C), 129.6 (4C), 128.1 (4C), 126.9 (2C), 101.7, 94.3, 92.3, 79.9, 66.3, 57.8, 57.4, 55.1 (2C), 28.7 (3C),

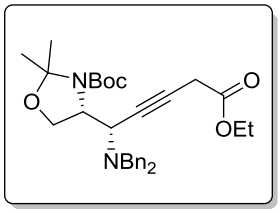
27.4, 24.9, 0.38 (3C); HRMS (ESI) Calcd. for $C_{30}H_{43}N_2O_3Si$ 507.3043 $[M + H]^+$, found 507.3045.

Synthesis of tert-butyl (*R*)-4-((*S*)-1-(dibenzylamino)prop-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 64 ($C_{27}H_{34}N_2O_3$).



To a solution of **68** (5.80 g, 11.46 mmol) in dry THF (60 mL) placed at 0˚C, TBAF (3.00 g, 11.46 mmol, 1 M in THF) was added drop wise and the mixture was stirred at this temperature for 1 h. The reaction mixture was diluted by adding H_2O (50 mL) followed by the extraction of the product in EtOAc (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 3% EtOAc in petroleum ether) to afford **64** (4.58 g, 92%) as a white solid. Mp. 108–110 ºC; IR (KBr) ν (cm^{-1}): 3295, 2976, 1695, 1488, 1453, 1372, 1247, 1167, 1097, 1053; $[\alpha]_D^{25}$ = + 52.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.4 Hz, 4H), 7.25 (t, *J* = 7.2 Hz, 4H), 7.18 (t, *J* = 7.1 Hz, 2H), 4.37 (dd, *J* = 9.4, 5.3 Hz, 1H), 4.12 (d, *J* = 9.3 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 2H), 3.89 – 3.85 (m, 1H), 3.60 (d, *J* = 8.3 Hz, 1H), 3.32 (d, *J* = 13.2 Hz, 2H), 2.43 (d, *J* = 1.8 Hz, 1H), 1.57 (s, 9H), 1.42 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.3, 139.5 (2C), 129.6 (4C), 128.1 (4C), 126.9 (2C), 94.4, 80.0, 79.5, 75.4, 66.2, 57.3, 56.9, 55.1 (2C), 28.7 (3C), 27.4, 24.9; HRMS (ESI) Calcd. for $C_{27}H_{35}N_2O_3$ 435.2647 $[M + H]^+$, found 435.2651.

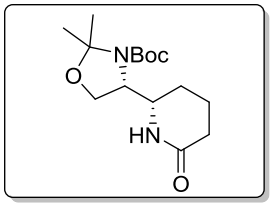
Synthesis of tert-butyl (*R*)-4-((*S*)-1-(dibenzylamino)-5-ethoxy-5-oxopent-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 69 ($C_{31}H_{40}N_2O_5$).



To a solution of **64** (4.40 g, 5.06 mmol) in CH_3CN (40 mL) were added ethyldiazoacetate (960 mg, 5.06 mmol) and CuI (48 mg, 0.25 mmol, 5 mol%). The reaction mixture was stirred for 12 h at room temperature. Then crude reaction mixture was concentrated in vacuo and subsequently filtered through a short the pad of silica by eluting with Et_2O. The filtrate was further concentrated *in vacuo*. The crude product was subjected to column chromatography over silica gel (*Eluent*: 5% EtOAc in petroleum ether) to furnish **69** (5.0

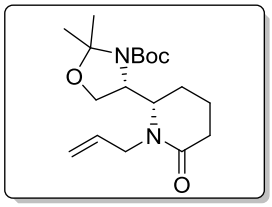
g, 96%) as pale yellow oil. IR (KBr) ν (cm^{-1}): 2978, 1692, 1563, 1454, 1373, 1251, 1141, 1098, 1065; $[\alpha]_D^{25}$ = -39.2 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 7.3 Hz, 4H), 7.28 (t , *J* = 7.6 Hz, 4H), 7.20 (t, *J* = 8.0 Hz, 2H), 4.28 - 4.19 (m, 3H), 4.00 (dd, *J* = 8.2,6.4 Hz, 1H), 3.89 - 3.84 (m, 3H), 3.58 (dt, *J* = 7.3, 2.3 Hz, 1H), 3.47 (d, *J* = 13.7 Hz, 2H), 3.35 (d, *J* = 2.3 Hz, 2H), 1.34 - 1.21 (m, 6H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 168.4, 139.6 (2C), 128.9 (4C), 128.3 (4C), 127.0 (2C), 109.8, 78.4, 78.3, 76.4, 67.4, 61.7, 55.5 (3C), 26.6, 26.3, 25.6, 14.3; HRMS (ESI) Calcd. for $C_{31}H_{41}N_2O_5$, 521.3015 $[M + H]^+$, found 521.3020.

Synthesis of tert-butyl (*R*)-2,2-dimethyl-4-((*S*)-6-oxopiperidin-2-yl) oxazolidine-3-carboxylate 63a ($C_{15}H_{26}N_2O_4$).



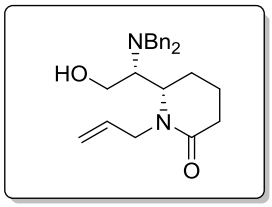
To a solution of **69** (5.00 g, 9.60 mmol) in ethanol (50 mL) placed in a par apparatus was added 10% $Pd(OH)_2/C$ (480 mg, 0.48 mmol) and subsequently stirred under 100 psi H_2 pressure at room temperature for 24 h. The reaction mixture was filtered through the small celite pad. To the resulting filtrate was added NaOEt (654 mg, 9.60 mmol) and refluxed for 2 h. The reaction mixture was dried under reduced pressure and re-dissolved in EtOAc (40 mL). The organic layer was washed with H_2O (2 × 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to afford **63a** (2.40 g, 84% over 2 steps) as a white solid. Mp. 174–176 ^oC; IR (KBr) ν (cm^{-1}): 3210, 2973, 1663, 1478, 1374, 1306, 1252, 1171, 1083, 1035; $[\alpha]_D^{25}$ = - 41.6 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.06 (br s, 1H), 4.04 – 3.84 (m, 3H), 3.68 (ddd, *J* = 31.1, 16.2, 6.9 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.35 – 2.24 (m, 1H), 2.00 – 1.87 (m, 2H), 1.80 – 1.64 (m, 2H), 1.52 (s, 3H), 1.50 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.6, 153.2, 94.7, 81.0, 64.4, 60.4, 55.2, 31.5, 28.5(3C), 27.0, 24.6(2C), 19.8; HRMS (ESI) Calcd. for $C_{15}H_{26}N_2O_4$ 299.1971 $[M + H]^+$, found 299.1972.

Synthesis of tert-butyl (*R*)-4-((*S*)-1-allyl-6-oxopiperidin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 62a ($C_{18}H_{30}N_2O_4$).



To a solution of **63a** (2.20 g, 7.38 mmol) in dry THF (30 mL), NaH (354 mg, 14.76 mmol) was added at 0 ºC. The solution was allowed to warm to room temperature and stirred for 30 min after which NaI (220 mg, 1.47 mmol) and allyl bromide (1.07 g, 8.85 mmol) were added at 0 ºC and stirred for 2h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was washed with brine (2 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 3% MeOH in chloroform) to afford **62a** (2.21 g, 86%) as a colourless thick oil. IR (KBr) ν (cm^{-1}): 2975, 1693, 1641, 1459, 1368, 1255, 1167, 1083; $[\alpha]_D^{25}$ = -23.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 5.87 – 5.72 (m, 1H), 5.22 – 5.04 (m, 2H), 4.41 – 3.94 (m, 3H), 3.85 (ddd, *J* = 11.5, 9.8, 4.3 Hz, 3H), 2.53 – 2.26 (m, 2H), 1.97 – 1.82 (m, 2H), 1.62 (s, 3H), 1.48 (S, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 152.5, 134.2, 116.9, 95.0, 80.8, 64.1, 58.1, 48.4, 32.9, 28.6(3C), 23.9, 18.8; HRMS (ESI) Calcd. for $C_{18}H_{31}N_2O_4$ 339.2284 $[M + H]^+$, found 339.2284.

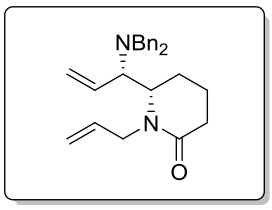
Synthesis of (*S*)-6-((*R*)-1-(dibenzylamino)-2-hydroxyethyl)piperidin-2-one 70 ($C_{21}H_{26}N_2O_2$).



To a a stirred solution of **62a** (2.00 g, 10.1 mmol) in MeOH (20 mL), concentrated aq HCl (1.0 mL) was added and the reaction mixture was reflux for 15h. Then crude reaction mixture was concentrated in vacuo and residue was partitioned between $CHCl_3$ (40 mL) and 1 M aq NaOH (40 mL). The layers were separated and the organic layer was washed with 1 M aq NaOH (2 × 30 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 30 mL). Then combined organic layers were dried and concentrated in vacuo. The residue was dissolved in dry acetonitile (30 mL) and BnBr (2.53 g, 14.8 mmol), K_2CO_3 (3.27 g, 23.6 mmol) were added. The reaction mixture was heated at reflux for 5h and then concentrated in vacuo. The residue was partitioned

between EtOAc (40 mL) and H_2O (40 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **70** (1.90 g, 85% over 2 steps) as a colourless oil. IR (KBr) ν (cm^{-1}): 3370, 2946, 1612, 1481, 1415, 1324, 1266, 1178, 1063, 1029; $[\alpha]_D^{25}$ = + 12.8 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.35 – 7.31 (m, 8H), 7.25 (d, *J* = 5.8 Hz, 2H), 5.70 (ddd, *J* = 22.5, 11.0, 5.9 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.87 (d, *J* = 17.2 Hz, 1H), 4.42 (dd, *J* = 15.2, 4.8 Hz, 1H), 3.90 – 3.80 (m, 1H), 3.77 – 3.69 (m, 2H), 3.58 (dd, *J* = 15.2, 6.8 Hz, 1H), 3.16 (td, *J* = 7.7, 3.8 Hz, 1H), 2.43 – 2.30 (m, 2H), 2.08 – 1.99 (m, 1H), 1.82 (dd, *J* = 11.8, 6.2 Hz, 2H), 1.71 – 1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0, 139.3, 133.6, 128.8 (4C), 128.7 (4C), 127.5, 117.2, 60.0, 58.5, 55.5, 54.9, 49.5, 30.9, 25.5, 17.9; HRMS (ESI) Calcd. for $C_{21}H_{27}N_2O_2$ 379.2385 $[M + H]^+$, found 379.2387.

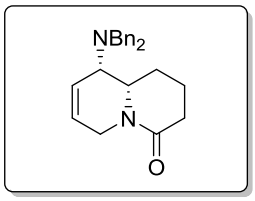
Synthesis of (*S*)-1-allyl-6-((*S*)-1-(dibenzylamino)allyl)piperidin-2-one 61a ($C_{25}H_{30}N_2O$).



A solution of **70** (1.80 g, 4.76 mmol) in dry CH_2Cl_2 (40 mL) was treated with Dess-Martin periodinane (2.42 g, 5.71 mmol) at room temperature. After 2 h, aqueous solution of 10% $Na_2S_2O_3$ (30 mL) was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution, water, and dried over Na_2SO_4. The solvent was evaporated, and the residue was dried to afford crude aldehyde as a yellow liquid. The crude aldehyde was used for next reaction without purification. To a suspention of methyl triphenylphosphonium bromide (3.40 g, 9.52 mmol) in THF (40 mL) at 0 ºC was added dropwise *n*-BuLi (4.76 mL, 2 M solution in cyclohexane, 9.52 mmol) resulting in a yellow solution. After two hours, a solution of aldehyde in THF (20 mL) was added and the reaction mixture was stirred for 15 hours. Then reaction mixture was quenched by aqueous NH_4Cl solution (20 mL) and then extracted with ethyl acetate (2 × 50 mL). The combined organic extract was washed with H_2O (40 mL), brine solution (40 mL) and then dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **61a**

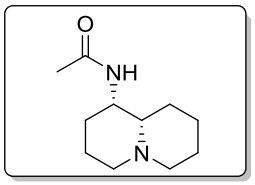
(1.55 g, 87% over 2 steps) as yellow oil. IR (KBr) ν (cm^{-1}): 2952, 2850, 1652, 1542, 1465, 1372, 1270, 1110, 1020; $[\alpha]_D^{25}$ = + 12.3 (*c* = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, *J* = 7.1 Hz, 4H), 7.34 (t, *J* = 7.6 Hz, 4H), 7.26 – 7.22 (m, 2H), 5.78 – 5.63 (m, 2H), 5.42 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.13 – 5.01 (m, 3H), 4.88 (ddd, *J* = 17.4, 2.9, 1.7 Hz, 1H), 3.98 (d, *J* = 14.3 Hz, 2H), 3.69 – 3.60 (m, 2H), 3.37 – 3.26 (m, 3H), 2.29 – 2.19 (m, 1H), 1.86 – 1.70 (m, 3H), 1.68 – 1.60 (m, 1H), 1.55 (dd, *J* = 8.3, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.0, 139.0 (2C), 133.8, 132.1, 128.7 (4C), 128.3 (4C), 127.2 (2C), 120.8, 116.8, 64.7, 54.5, 54.2 (2C), 50.1, 29.7, 25.5, 16.0; HRMS (ESI) Calcd. for $C_{25}H_{31}N_2O$ 375.2436 $[M + H]^+$, found 375.2439.

Synthesis of (9*S*,9a*S*)-9-(dibenzylamino)-1,2,3,6,9,9a-hexahydro-4H-quinolizin-4-one 60a ($C_{23}H_{26}N_2O$).



Grubbs II catalyst (136 mg, 0.16 mmol) was added to a stirred solution of **61a** (1.20 g, 3.20 mmol) in anhydrous, degassed CH_2Cl_2 (40 mL) at room tempreature. The resultant mixture was reflux for 48 h and then concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **60a** (1.04 g, 95%) as a colourless oil. IR (KBr) ν (cm^{-1}): 3031, 2944, 2839, 1633, 1493, 1334, 1250, 1159, 1120, 1071, 1029; $[\alpha]_D^{25}$ = + 31.2 (*c* = 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (d, *J* = 7.5 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.23 (t, *J* = 7.3 Hz, 2H), 6.11– 6.03 (m, 2H), 4.59 (d, *J* = 19.8 Hz, 1H), 3.84 (d, *J* = 13.9 Hz, 2H), 3.57 (d, *J* = 20.0 Hz, 1H), 3.51 – 3.43 (m, 1H), 3.38 (d, *J* = 13.9 Hz, 2H), 3.16 – 3.09 (m, 1H), 2.57 – 2.39 (m, 2H), 2.33 – 2.23 (m, 1H), 2.00 – 1.96 (m, 1H), 1.68 – 1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.0, 139.9 (2C), 128.8 (4C), 128.5 (4C), 128.0, 127.1 (2C), 121.6, 57.5, 55.9(2C), 54.2, 42.9, 33.4, 29.8, 25.7, 19.8; HRMS (ESI) Calcd. for $C_{23}H_{27}N_2O$ 347.2123 $[M + H]^+$, found 347.2128.

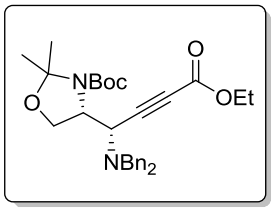
Synthesis of N-((1*S*,9a*S*)-octahydro-2H-quinolizin-1-yl)acetamide 5 ($C_{11}H_{20}N_2O$).



To a suspension of $LiAlH_4$ (132 mg, 3.48 mmol) in dry THF (20 mL) placed at 0°C was added a solution of **60a** (400 mg, 1.16 mmol)

in THF (10 mL) and the resulting mixture was stirred at reflux for 8 h. After cooling to 0 ^{o}C, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The crude product was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was dissolved in ethanol (20 mL) added 10% $Pd(OH)_2/C$ (120 mg, 0.12 mmol) and subsequently stirred under H_2 atmosphere at room temperature for 48h. The reaction mixture was filtered through the small celite pad and filtrate was concentrated under vacuum. The residue was dissolved in dioxane (12 mL) and treated with 1M aqueous NaOH (11.6 mL, 11.60 mmol) and acetic anhydride (548 µL, 5.80 mmol). After stirring for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and $CHCl_3$ (20 mL). The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 20 mL). The crude product was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to afford (+)-epiquinamide **5** (165 mg, 73% over 3 steps) as a white solid. Mp. 130–132 ^{o}C; IR (KBr) ν (cm^{-1}): 3322, 2932, 2858, 1657, 1453, 1378, 1292, 1142, 1082; $[\alpha]_D^{25}$ = + 27.2 (*c* = 0.22, $CHCl_3$) [Lit. $[\alpha]_D^{25}$ = + 28.0 (*c* = 0.23, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.20 (br s, 1H), 4.04 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.85 - 3.89 (m, 1H), 3.66 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.32 – 3.29 (td, *J* = 9.2, 4.6 Hz, 1H), 2.45 - 2.38 (m, 1H), 2.30 - 2.27 (m, 1H), 1.94 - 1.91 (m, 1H), 1.76 - 1.68 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.33 - 1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.1, 64.9, 56.8, 56.6, 47.8, 29.6, 28.7, 25.1, 23.7, 23.5, 20.2; HRMS (ESI) Calcd. for $C_{11}H_{21}N_2O$ 197.2654 $[M + H]^+$, found 197.1657.

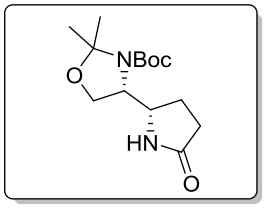
Synthesis of tert-butyl (*R*)-4-((*S*)-1-(dibenzylamino)-4-ethoxy-4-oxobut-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate 72 ($C_{30}H_{38}N_2O_5$).



To a solution of **64** (5.00 g, 11.50 mmol) in dry Et_2O (50 mL) cooled at -78 ^{o}C was added dropwise *n*-BuLi (6.9 mL, 13.80 mmol, 2.0 M in cyclohexane). The reaction mixture was stirred at the same temperature for 30 min followed by addition of ethyl chloroformate (2.50 g, 23.00 mmol). The reaction mixture was allowed to come to room temperature and stirred for 2 h. The reaction mixture was quenched with water (30 mL) and the product was extracted with EtOAc (2 × 40 mL), dried over Na_2SO_4. The crude

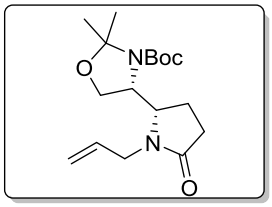
product was subjected to column chromatography over silica gel (*Eluent*: 5% EtOAc in petroleum ether) to furnish **72** (5.13 g, 88%) as a colorless oil. IR (KBr) ν (cm^{-1}): 2980, 2933, 2228, 1750, 1713, 1454, 1370, 1337, 1243, 1161, 1098, 1015; $[\alpha]_D^{25}$ = + 81.0 (*c* = 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 7.3 Hz, 4H), 7.28 – 7.24 (m, 4H), 7.19 (t, *J* = 7.2 Hz, 2H), 4.42 (dd, *J* = 9.2, 5.3 Hz, 1H), 4.28 (t, *J* = 7.1 Hz, 2H), 4.03 (dd, *J* = 18.1, 11.4 Hz, 3H), 3.88 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.34 (d, *J* = 13.2 Hz, 2H), 1.57 (s, 9H), 1.42 (s, 3H), 1.36 (d, *J* = 7.1 Hz, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 153.6, 153.2, 139.0 (2C), 129.6 (4C), 128.2 (4C), 127.2 (2C), 94.5, 84.0, 80.2, 79.8, 66.1, 62.3 (2C), 57.0, 55.2 (2C), 28.7 (3C), 27.3, 24.8, 14.2; HRMS (ESI) Calcd. for $C_{30}H_{39}N_2O_5$ 507.2829 $[M + H]^+$, found 507.2832.

Synthesis of tert-butyl (*R*)-2,2-dimethyl-4-((*S*)-5-oxopyrrolidin-2-yl)oxazolidine-3-carboxylate 63b ($C_{14}H_{24}N_2O_4$).



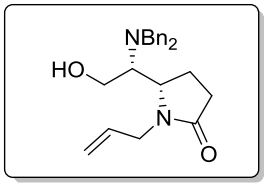
To a solution of **72** (4.00 g, 7.90 mmol) in EtOH (80 mL) was added 10% $Pd(OH)_2/C$ (790 mg, 0.79 mmol) and the reaction mixture was stirred at room temperature under 100 psi pressure of hydrogen for 24 h. The reaction mixture was filtered through celite and the celite bed was washed with EtOH (2 × 40 mL). To the combined solution was added NaOEt (537 mg, 7.90 mmol) and refluxed for 2 hours. The reaction mixture was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography over silica gel (*Eluent:* 4% MeOH in Chloroform) to furnish the pure **63b** (1.90 g, 85% over 2 steps) as a white solid. Mp. 140–142 ^oC; IR (KBr) ν (cm^{-1}):3195, 2978, 1689, 1459, 1370, 1257, 1169, 1089; $[\alpha]_D^{25}$ = - 13.3 (*c* = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.10 – 3.77 (m, 4H), 2.40 – 2.26 (m, 2H), 2.21– 1.95 (m, 2H), 1.60 (s, 3H), 1.52 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 153.4, 94.2, 78.8, 64.5, 59.4, 54.2, 31.8, 28.4 (3C), 24.6, 25.2, 22.2; HRMS (ESI) Calcd. for $C_{14}H_{25}N_2O_4$ 280.1814 $[M + H]^+$, found 280.1815.

Synthesis of tert-butyl (*R*)-4-((*S*)-1-allyl-5-oxopyrrolidin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 63b ($C_{17}H_{28}N_2O_4$).



To a solution of **63b** (1.80 g, 6.33 mmol) in dry THF (25 mL), NaH (30 mg, 12.6 mmol) was added at 0 ºC. The solution was allowed to warm to room temperature and stirred for 30 min after which NaI (188 mg, 1.26 mmol) and allyl bromide (919 mg, 7.60 mmol) were added at 0 ºC and stirred for 2h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 40 mL). The organic layer was washed with brine (2 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (*Eluent*: 3% MeOH in chloroform) to afford **62b** (1.90 g, 90%) as a colourless thick oil. IR (KBr) ν (cm^{-1}): 2978, 2934, 1684, 1362, 1253, 1166, 1080; $[\alpha]_D^{25}$ = - 37.2 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.84 – 5.67 (m, 1H), 5.29 – 5.12 (m, 2H), 4.34 – 4.13 (m, 2H), 4.10 – 3.98 (m, 1H), 3.92 (dd, *J* = 16.6, 9.7 Hz, 1H), 3.86 – 3.59 (m, 2H), 2.56 – 2.31 (m, 2H), 2.15 – 1.97 (m, 2H), 1.66 (s, 3H), 1.50 (d, *J* = 7.6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.4, 153.2, 132.8, 117.2, 96.4, 79.8, 64.6, 58.4, 48.4, 32.9, 28.4(3C), 24.9(2C), 18.9; HRMS (ESI) Calcd. for $C_{17}H_{29}N_2O_4$ 325.2127 $[M + H]^+$, found 325.2130.

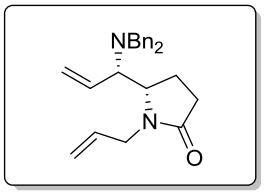
Synthesis of (*S*)-5-((*R*)-1-(dibenzylamino)-2-hydroxyethyl)pyrrolidin-2-one 73 ($C_{20}H_{24}N_2O_2$).



To a a stirred solution of **62b** (1.50 g, 4.63 mmol) in MeOH (15 mL), concentrated aq HCl (0.75 mL) was added and the reaction mixture was reflux for 15h. Then crude reaction mixture was concentrated in vacuo and residue was partitioned between $CHCl_3$ (30 mL) and 1M aqueous NaOH (30 mL). The layers were separated and the organic layer was washed with 1 M aq NaOH (2 ×20 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 20 mL). Then combined organic layers were dried and concentrated *in vacuo*. The residue was dissolved in dry acetonitile (20 mL) and BnBr (1.93 g, 11.57 mmol), K_2CO_3 (2.56 g, 18.52 mmol) were added. The reaction mixture was

heated at reflux for 5h and then concentrated in vacuo. The residue was partitioned between EtOAc (40 mL) and H_2O (40 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried and concentrated in vacuo. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **73** (1.90 g, 87% over 2 steps) as a colourless oil. IR (KBr) ν (cm^{-1}): 3322, 2994, 2858, 1659, 1463, 1378, 1292, 1221, 1160, 1085, 1031; $[\alpha]_D^{25}$ = - 7.80 (*c* = 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.20 (br s, 1H), 4.04 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.85 - 3.89 (m, 1H), 3.66 (dd, *J* = 8.6, 5.5 Hz, 1H), 3.32 – 3.29 (td, *J* = 9.2, 4.6 Hz, 1H), 2.45 - 2.38 (m, 1H), 2.30 - 2.27 (m, 1H), 1.94 - 1.91 (m, 1H), 1.76 - 1.68 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.33 - 1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.7, 109.9, 79.2, 66.3, 56.3, 31.4, 26.9, 25.4, 24.9, 19.8; HRMS (ESI) Calcd. for $C_{20}H_{24}N_2O_2$ 365.2229 $[M + H]^+$, found 365.2230.

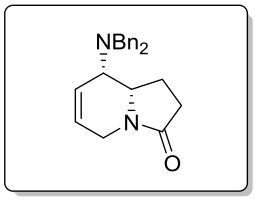
Synthesis of (*S*)-1-allyl-5-((*S*)-1-(dibenzylamino)allyl)pyrrolidin-2-one 60b ($C_{24}H_{28}N_2O$).



A solution of **75** (1.00 g, 2.75 mmol) in dry CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (1.40 g, 3.29 mmol) at room temperature. After 2 h, aqueous solution of 10% $Na_2S_2O_3$ (15 mL) was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution, water, and dried over Na_2SO_4. The solvent was evaporated, and the residue was dried to afford crude aldehyde as a yellow liquid. The crude aldehyde was used for next reaction without purification. To a suspention of methyl triphenylphosphonium bromide (1.96 g, 5.50 mmol) in THF (20 mL) at 0 ºC was added dropwise *n*-BuLi (2.75 mL, 2 M solution in cyclohexane, 5.50 mmol) resulting in a yellow solution. After two hours, a solution of aldehyde in THF (10 ml) was added and the reaction mixture was stirred for 15 hours. Then reaction mixture was quenched by aqueous NH_4Cl solution (10 mL) and then extracted with ethyl acetate (2 × 30 mL). The combined organic extract was washed with H_2O (20 mL), brine solution (20 mL) and then dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **61b** (802 mg, 81% over 2 steps) as yellow oil. IR (KBr) ν (cm^{-1}): 2959, 2862, 1654, 1542,

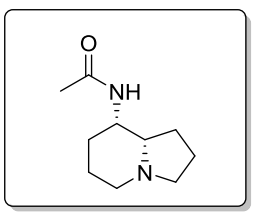
1470, 1380, 1278, 1132, 1010; $[\alpha]_D^{25}$ = - 20.2 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 – 7.29 (m, 8H), 7.26 – 7.21 (m, 2H), 5.84 (ddd, *J* = 17.2, 10.4, 9.1 Hz, 1H), 5.58 (dddd, *J* = 17.4, 10.2, 7.3, 4.7 Hz, 1H), 5.25 – 5.16 (m, 1H), 5.05 – 4.99 (m, 1H), 4.82 (ddd, *J* = 17.0, 3.0, 1.4 Hz, 1H), 4.28 (ddt, *J* = 15.5, 4.5, 1.7 Hz, 1H), 3.92 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.85 (d, *J* = 14.0 Hz, 2H), 3.57 – 3.43 (m, 3H), 3.34 (dd, *J* = 9.0, 4.5 Hz, 1H), 2.36 – 2.18 (m, 2H), 2.05 – 1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 175.2, 139.5 (2C), 132.7, 131.9, 128.6 (4C), 128.5, 127.2 (4C), 121.4 (2C), 117.6, 63.8, 59.1, 55.2 (2C), 43.8, 30.3, 21.6; HRMS (ESI) Calcd. for $C_{24}H_{29}N_2O$ 361.2280 $[M + H]^+$, found 361.2282.

Synthesis of (8*S*,8a*S*)-8-(dibenzylamino)-1,5,8,8a-tetrahydroindolizin-3(2H)-one 60b ($C_{22}H_{24}N_2O$).



Grubbs II catalyst (52 mg, 0.061 mmol) was added to a stirred solution of **61b** (220 mg, 0.61 mmol) in anhydrous, degassed CH_2Cl_2 (20 mL) at room tempreature. The resultant mixture was reflux for 48 h and then concentrated in vacuo. The crude product was purified by column chromatography over silica gel (*Eluent*: 30% EtOAc in petroleum ether) to afford **60b** (178 mg, 88%) as a colourless oil. IR (KBr) ν (cm^{-1}): 3021, 2990, 2852, 1642, 1472, 1374, 1252, 1160, 1120, 1075, 1029; $[\alpha]_D^{25}$ = + 14.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.28 (m, 8H), 7.26 – 7.20 (m, 2H), 6.17 – 6.02 (m, 2H), 4.24 (dd, *J* = 19.0, 2.2 Hz, 1H), 3.74 (d, *J* = 14.1 Hz, 2H), 3.69 – 3.53 (m, 2H), 3.42 (d, *J* = 14.1 Hz, 2H), 3.26 (dd, *J* = 4.9, 1.7 Hz, 1H), 2.91 – 2.76 (m, 1H), 2.40 (ddd, *J* = 26.0, 13.9, 6.7 Hz, 2H), 2.01 – 1.92 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 174.9, 139.9, 128.8, 127.6, 127.3, 122.7, 57.7, 56.2, 53.0, 41.0, 30.6, 19.1; HRMS (ESI) Calcd. for $C_{22}H_{25}N_2O$ 333.1967 $[M + H]^+$, found 333.1970.

Synthesis of N-((8*S*,8a*S*)-octahydroindolizin-8-yl)acetamide 59 ($C_{10}H_{18}N_2O$).



To a suspension of $LiAlH_4$ (51 mg, 1.33 mmol) in dry THF (5 mL) placed at 0 °C was added a solution of **60b** (150 mg, 0.45 mmol) in THF (5 mL) and the resulting mixture was stirred at reflux for 8 h. After cooling to 0 °C, the reaction mixture was quenched by the

addition of saturated aqueous NH_4Cl (5 mL). The crude product was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was dissolved in ethanol (10 mL) added 10% $Pd(OH)_2/C$ (45 mg, 0.045 mmol) and subsequently stirred under H_2 atmosphere at room temperature for 48h. The reaction mixture was filtered through the small celite pad and filtrate was concentrated under vacuum. The residue was dissolved in dioxane (5 mL) and treated with 1M aqueous NaOH (4.5 mL, 4.5 mmol) and acetic anhydride (206 µL, 2.25 mmol). After stirring for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) and $CHCl_3$ (10 mL). The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 10 mL). The crude product was purified by column chromatography over silica gel (*Eluent*: 60% EtOAc in petroleum ether) to afford **59** (59 mg, 68% over 3 steps) as a pale yellow oil. IR (KBr) ν (cm^{-1}): 2932, 2858, 1258, 1085, 1050; $[\alpha]_D^{25}$ = + 7.4 (*c* = 0.28, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 (s, 1H), 4.44 – 4.37 (m, 1H), 3.30 (dd, *J* = 14.7, 6.1 Hz, 2H), 2.43 (s, 1H), 2.32 – 2.20 (m, 2H), 2.03 (s, 3H), 2.00 (d, *J* = 4.4 Hz, 1H), 1.97 – 1.90 (m, 2H), 1.89 – 1.80 (m, 3H), 1.67 (d, *J* = 5.8 Hz, 1H), 1.54 – 1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.8, 67.2, 53.8, 52.8, 44.5, 29.1, 25.0, 23.3, 22.8, 20.1; HRMS (ESI) Calcd. for $C_{10}H_{19}N_2O$ 183.1497 $[M + H]^+$, found 183.1501.

4.7 Crystal Structure

Crystal structure of compound 64 ($C_{27}H_{34}N_2O_3$): Compound **64** was crystallized from ethyl acetate and chloroform (1:1) at 25 °C. A colorless rectangular shaped crystal with approximate dimensions 0.12 x 0.11 x 0.10 mm gave a Triclinic with space group $P2_12_12_1$; *a* = 9.6160 (4) *b* = 14.5436 (5) *c* = 18.6618 (7) Å, α = 90° β = 90° γ = 90°; *V* = 2609.88 (17); *T* = 296 (2) K; *Z* = 4; ρ_{calc} = 1.106 Mgm^{-3}; $2\theta_{max}$ = 68.465°; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0461 (for 4171 reflection $I>2\sigma(I)$), *wR* = 0.1435 which was refined against $|F2|$ and S = 1.145 for 294 parameters and 4790 unique reflections. The structure was obtained by direct methods

using SHELXS-97. All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.568 mm^{-1}; Minimum/maximum residual electron density 0.168 / -0.221 $eÅ^{-3}$.

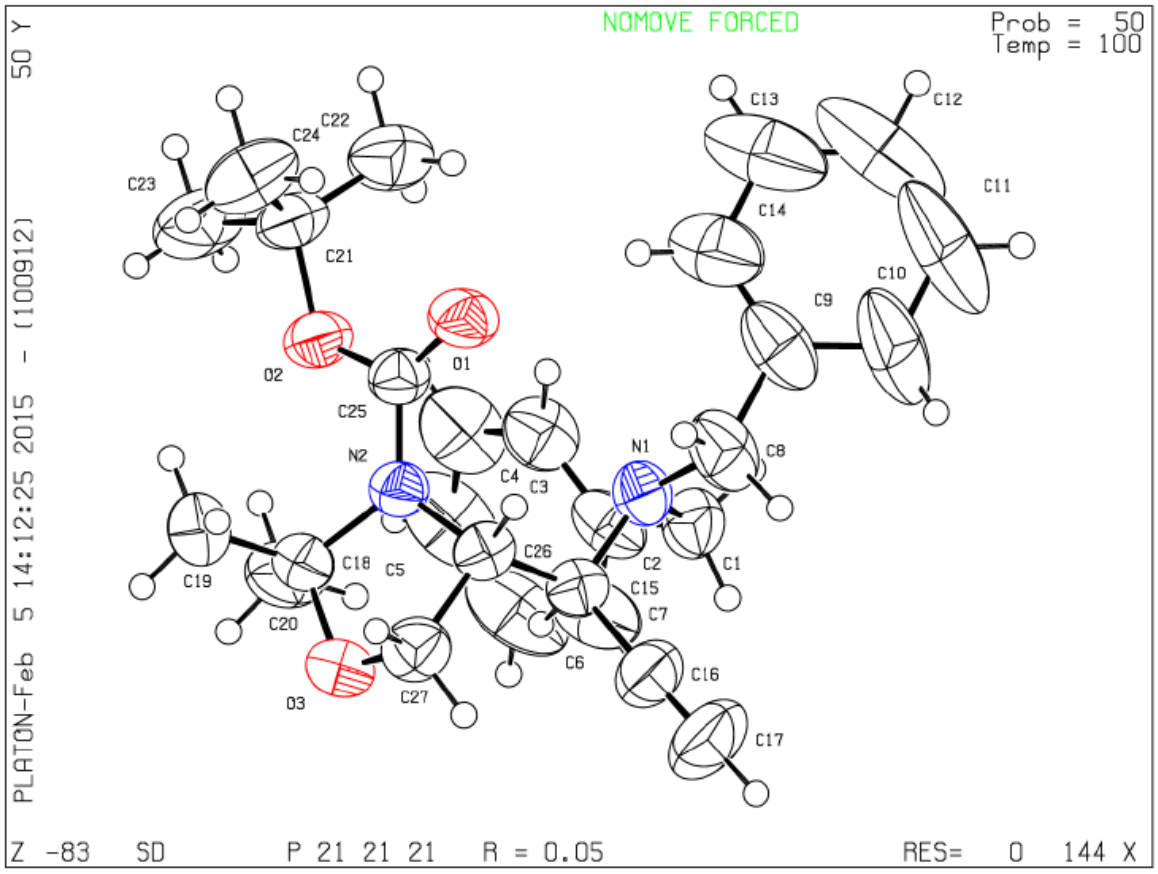


Figure 4.3: ORTEP diagram of **64**.

4.8 Appendix IV: ^{1}H and ^{13}C spectral data of representative compounds

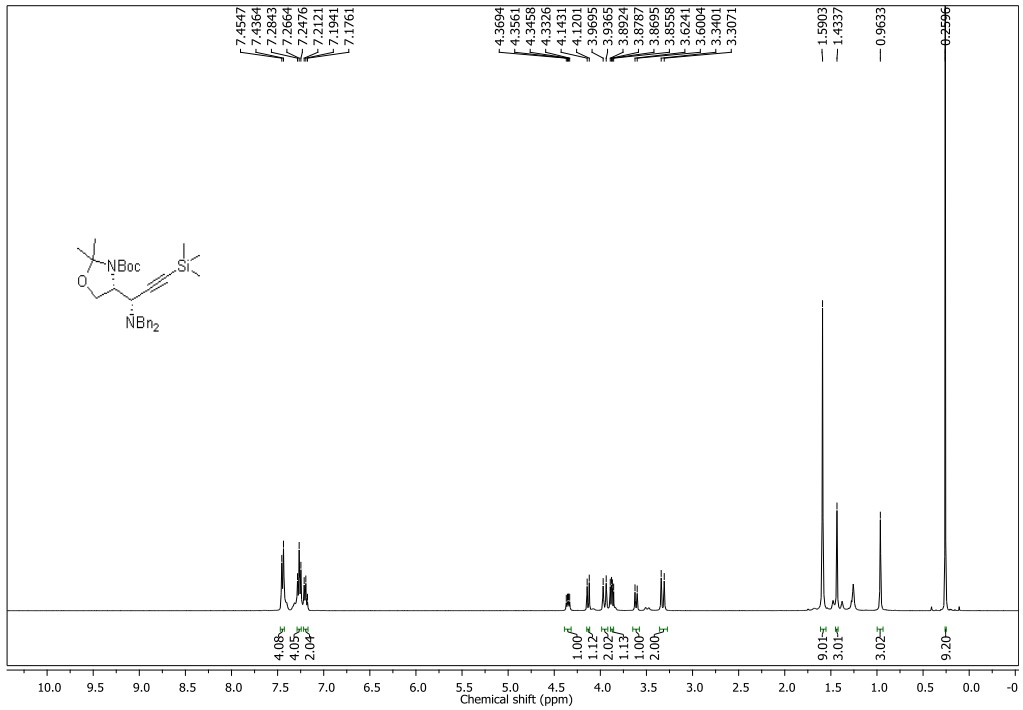


Figure 4.4: ^{1}H NMR spectra of **71** in $CDCl_3$.

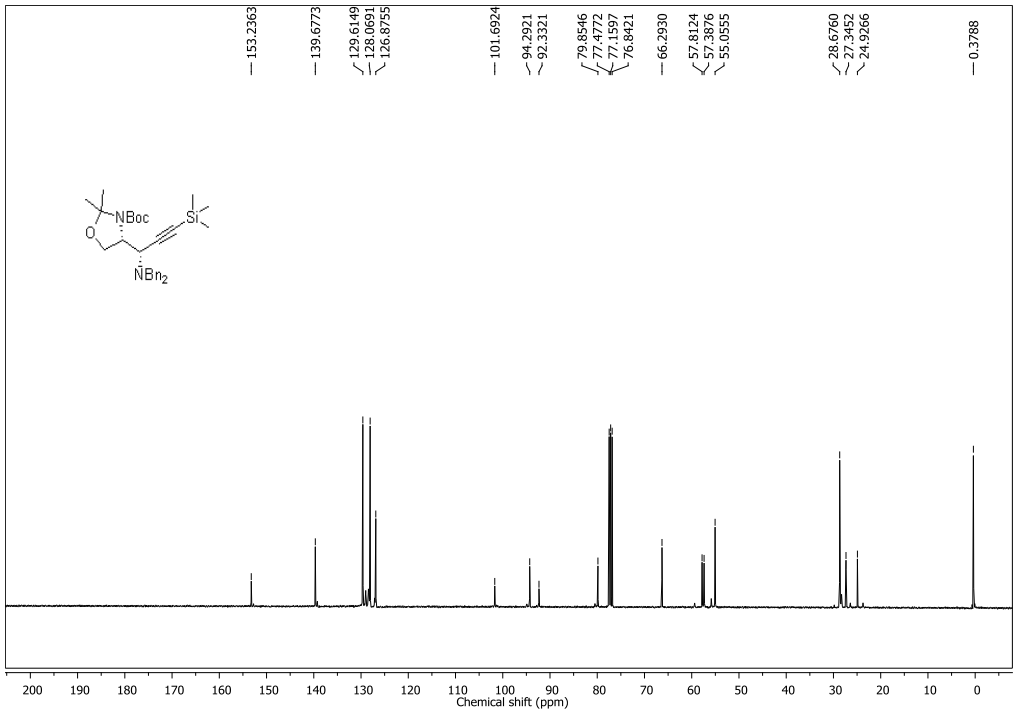


Figure 4.5: ^{13}C NMR spectra of **71** in $CDCl_3$.

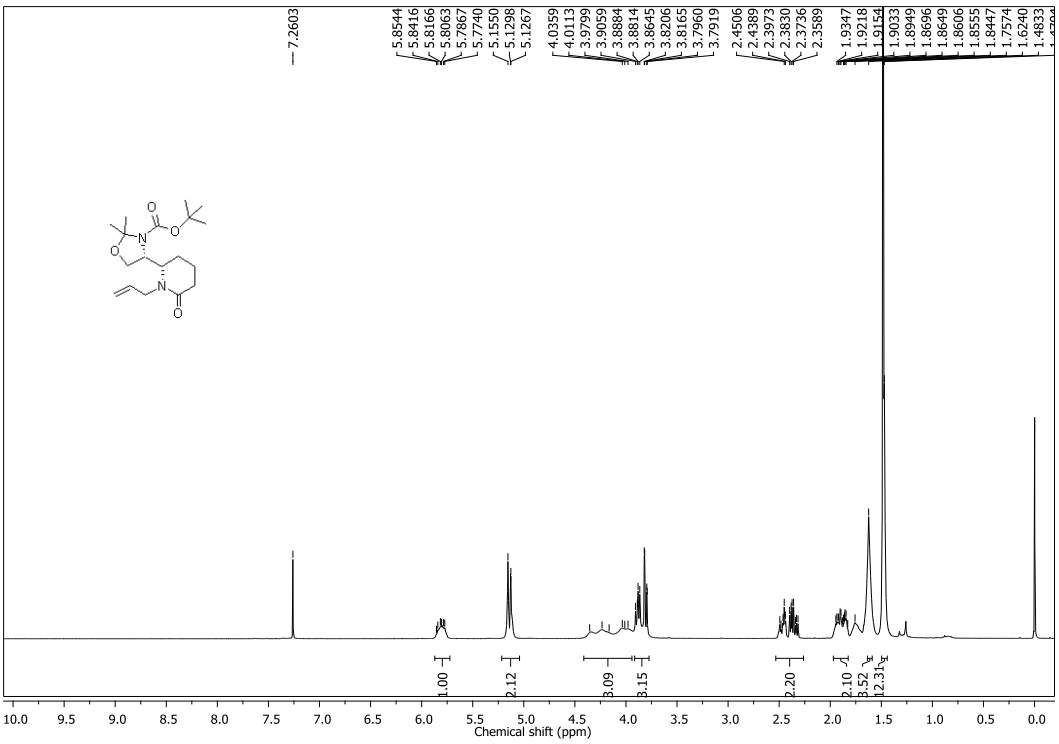


Figure 4.6: ^{1}H NMR spectra of **62a** in $CDCl_3$.

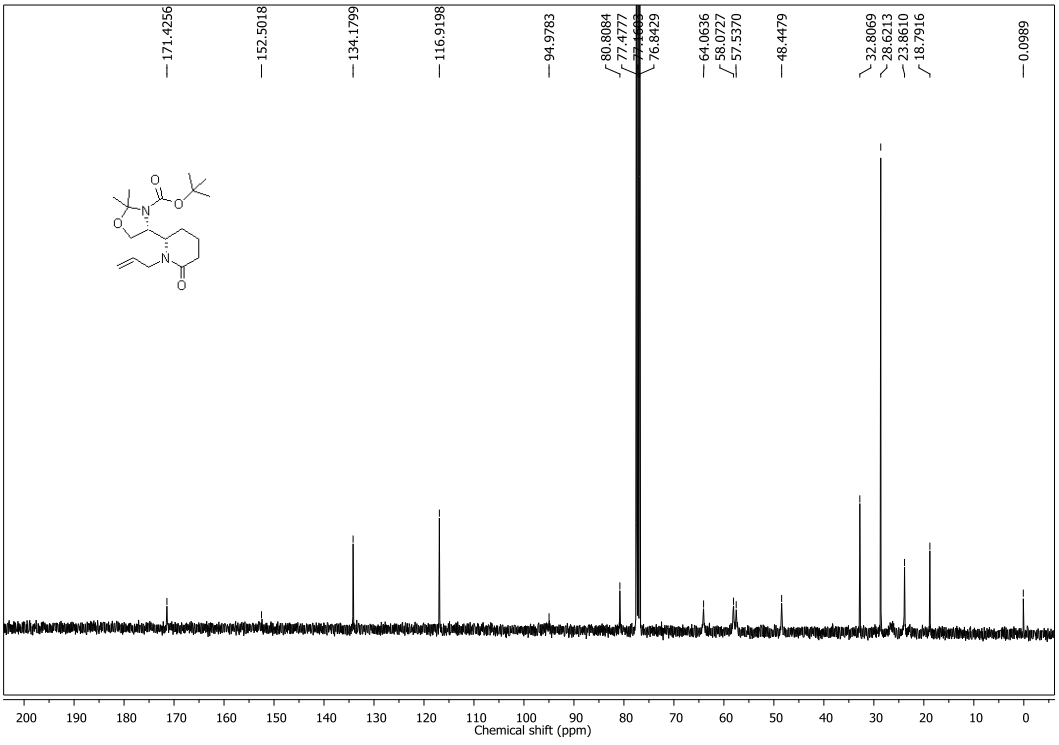


Figure 4.7: ^{13}C NMR spectra of **62a** in $CDCl_3$.

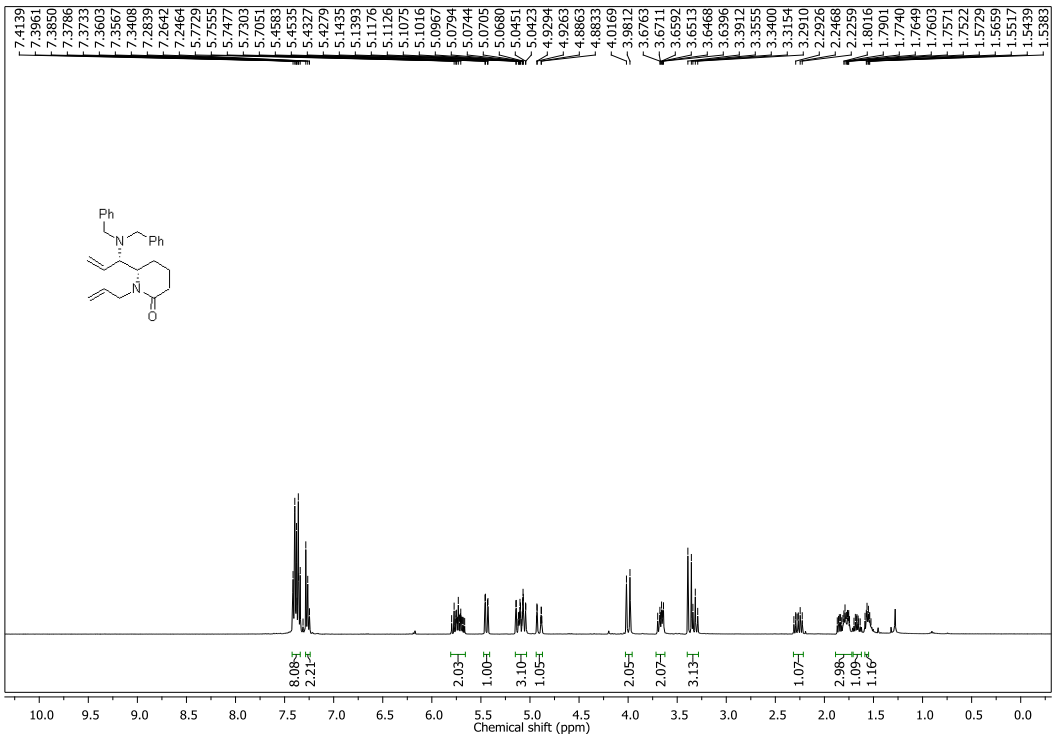


Figure 4.8: ^{1}H NMR spectra of **61a** in $CDCl_3$.

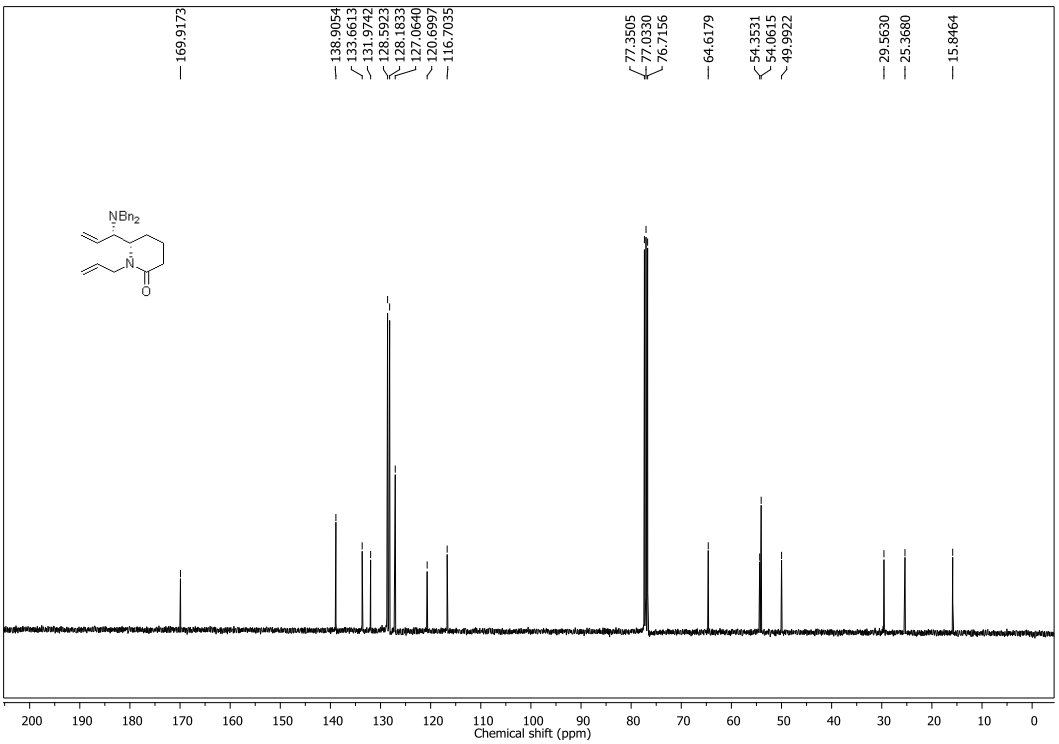


Figure 4.9: ^{13}C NMR spectra of **61a** in $CDCl_3$.

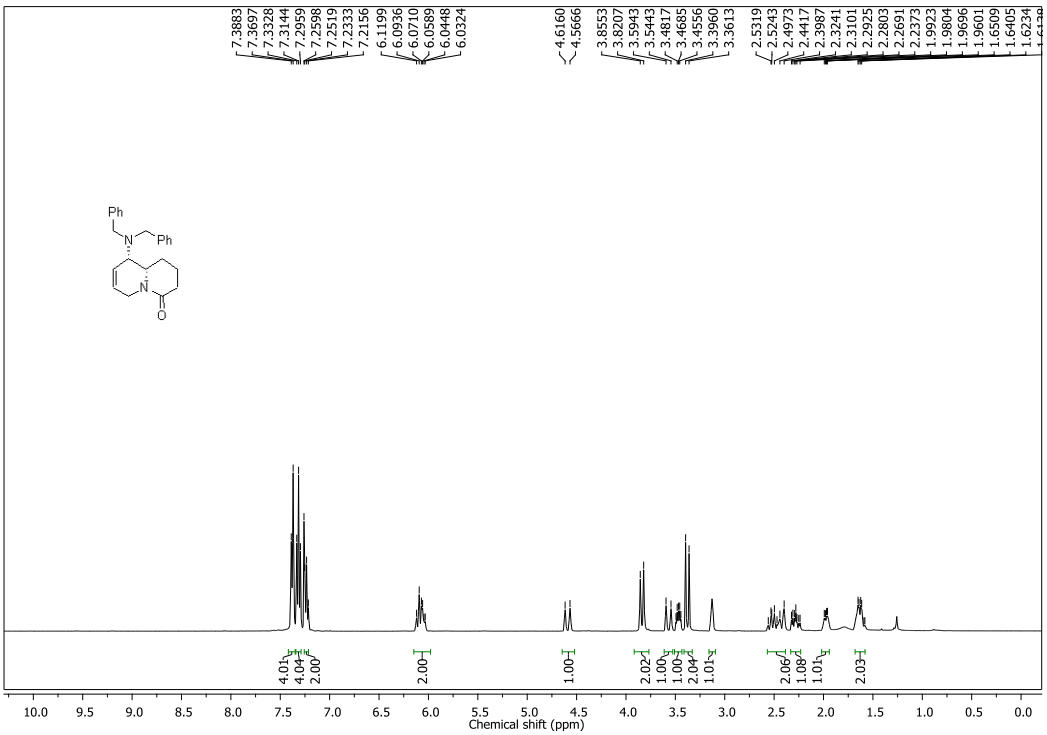


Figure 4.10: ^{1}H NMR spectra of **60a** in $CDCl_3$.

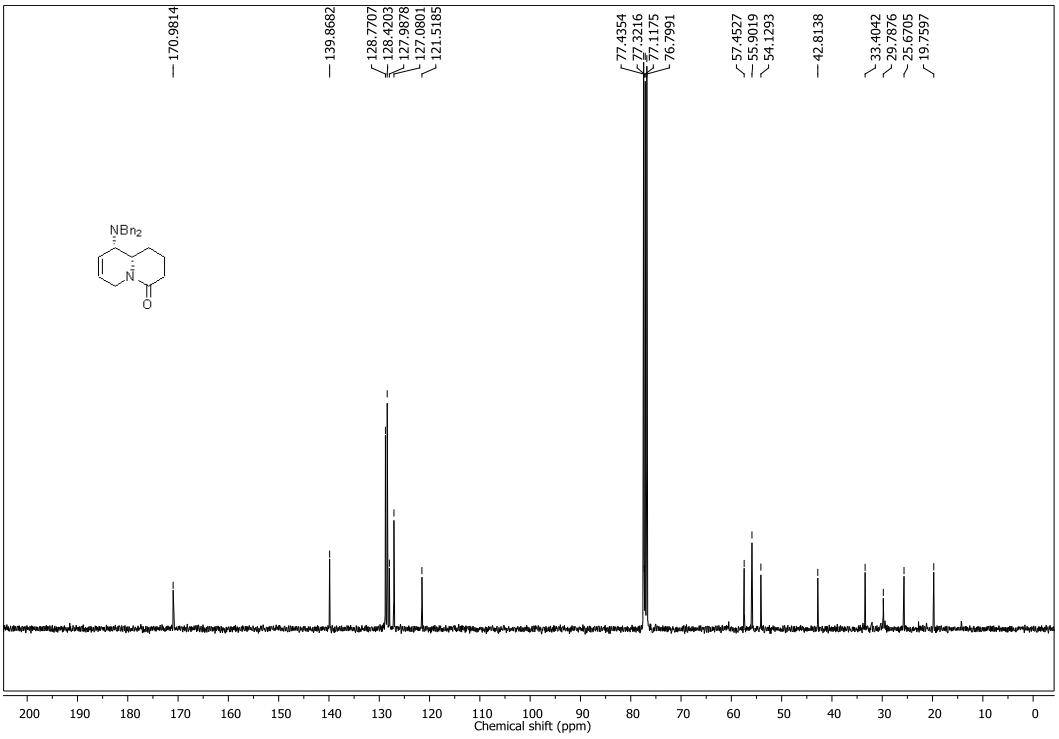


Figure 4.11: ^{13}C NMR spectra of **60a** in $CDCl_3$.

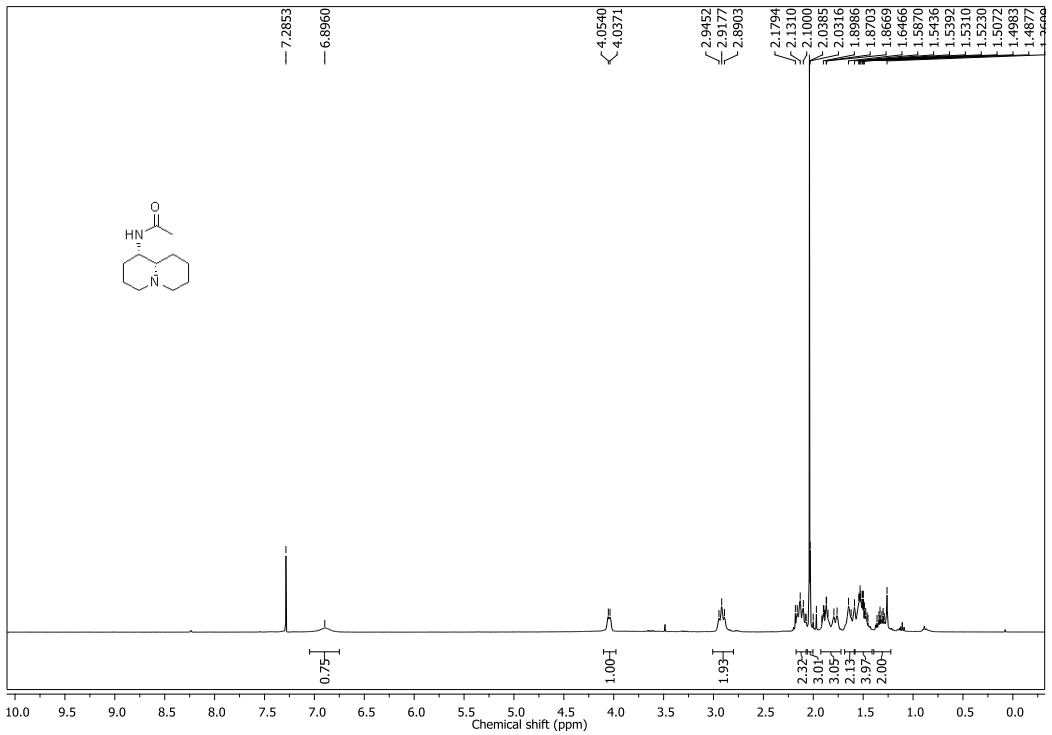


Figure 4.12: ^{1}H NMR spectra of **5** in $CDCl_3$.

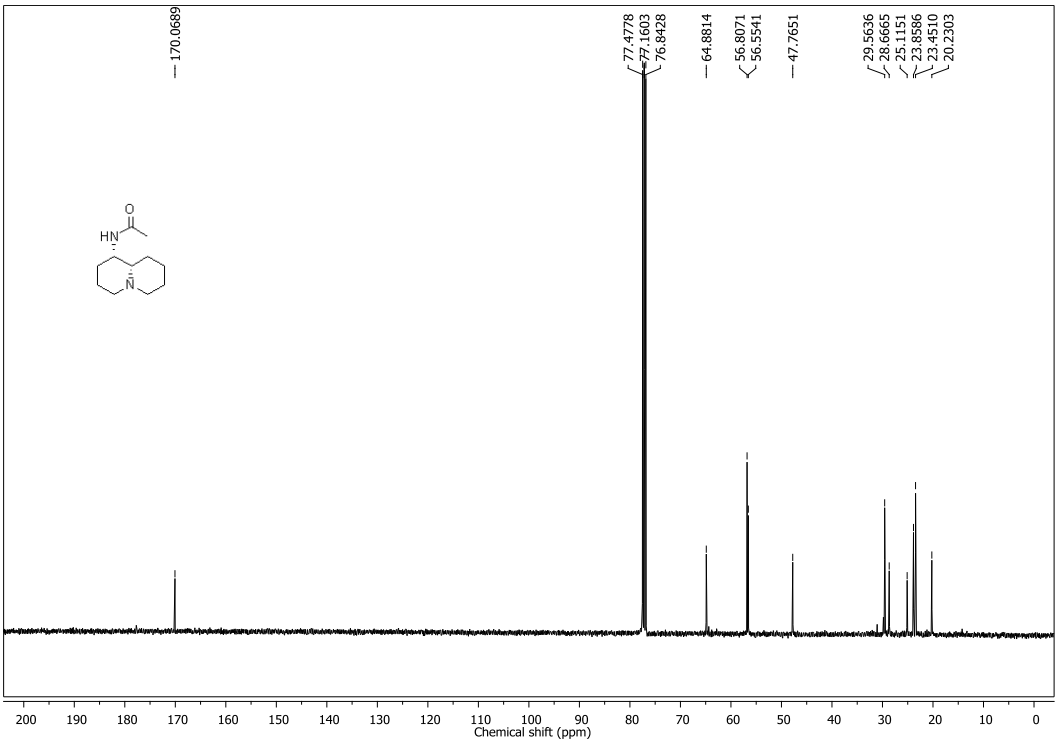


Figure 4.13: ^{13}C NMR spectra of **5** in $CDCl_3$.

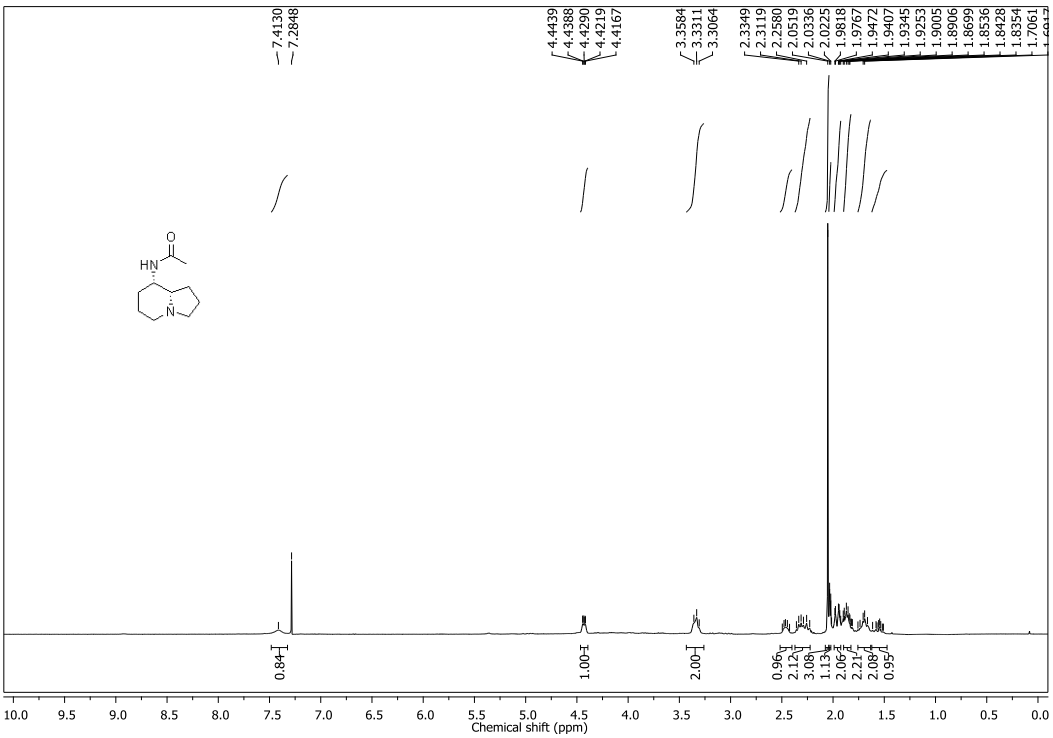


Figure 4.14: ^{1}H NMR spectra of **59** in $CDCl_3$.

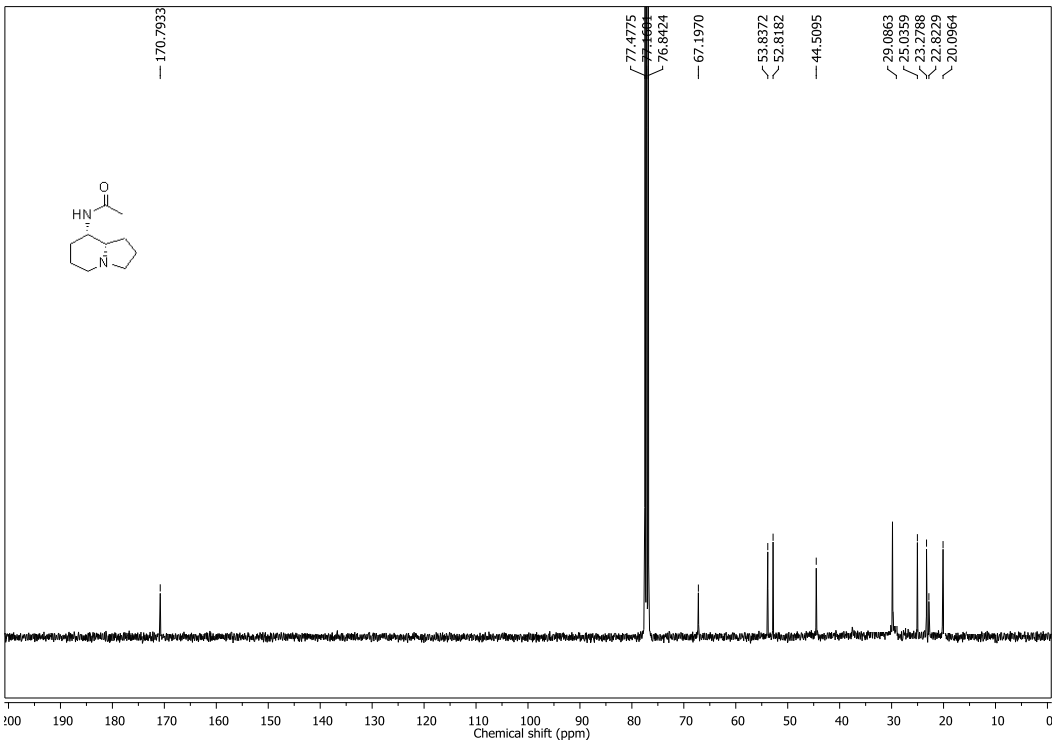


Figure 4.15: ^{13}C NMR spectra of **59** in $CDCl_3$.

4.9 References

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