Total Synthesis of Bioactive Natural Products Employing [3+2] Cycloaddition and Chiral Catalysts

Thesis Submitted in fulfillment of the

requirement of the degree of

Doctor of Philosophy

By

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Certificate

This is to certify that thesis entitled "**Total Synthesis of Bioactive Natural Products Employing [3+2] Cycloaddition and Chiral Catalysts**" being submitted by Ramandeep Kaur in the fulfillment of the requirement for the award of the Degree of Doctor of Philosophy to the School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, is a authentic record of candidate's own work carried out by her under my supervision and guidance. The matter presented in this thesis has not been submitted in part or full for the award of any degree in any other University or Institute.

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Candidate's Declaration

I, hereby declare that the work presented in the thesis entitled "**Total Synthesis of Bioactive Natural Products Employing [3+2] Cycloaddition and Chiral Catalysts**" in partial fulfillment of the requirement for the award of the Degree of Doctor of Philosophy, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, is an authentic record of my own work carried out under the supervision of Dr. Satyendra Kumar Pandey, Associate Professor, School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala, India. The matter embodied in this thesis has not been submitted in part or full to any other University or institute for the award of any degree in India or abroad.

Ramandeep Kaur

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DEDICATED TO

ALMIGHTY GOD

AND

MY BELOVED PARENTS

Acknowledgements

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Despite all this co-operation rendered generously by one and all, I am solely responsible for any and all the errors and short comings of this dissertation.

Besides this, I am thankful to the persons who knowingly and unknowingly helped me during the successful completion of this work.

May the Almighty God bless all of you.

Ramandeep Kaur

Ramandeep Kaur

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3.Me_2S$	-	Boron dimethyl sulfide complex
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-yl)phthalazine
DDQ	-	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	-	Diisobutylaluminium hydride
DMP	-	2,2-Dimethoxypropane
DMF	-	*N, N′*-Dimethylformamide
DMAP	-	*N,N′*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
de	-	Diastereomeric excess
eq.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether

EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
g	-	Grams
h	-	Hours
Hz	-	Hertz
m-CPBA	-	*m*-Chloroperbenzoic acid
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmol	-	Millimole
Ms	-	Methanesulfonyl
Me	-	Methyl
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
TsCl	-	*p*-Toluenesulphonyl chloride

GENERAL REMARKS

- ^{1}H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- Mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z.
- IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}.
- Optical rotations were measured on Automatic polarimeter AA-65 and concentrations of g/100 mL.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2, ninhydrin and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.
- Column chromatography were performed on silica gel (60-120, 100-200 and 230-400 mesh) using a mixture of hexane/ethyl acetate and dichloromethane/methanol as eluent.

ABSTRACT

The thesis entitled "**Total Synthesis of Bioactive Natural Products Employing [3+2] Cycloaddition and Chiral Catalysts**" is divided into six chapters.

Chapter 1: A brief account of [3+2] cycloaddition reactions, organocatalzyed Michael addition reactions, organocatalyzed aldol reactions, Jacobsen's Hydrolytic Kinetic Resolution (HKR) and Henry reaction.

Chapter 2: $InCl_3$ catalyzed diastereoselective approach for the syntheses of bisindole alkaloids flinderoles A-C and desmethylflinderole C.

Chapter 3: An enantioselective approach towards the synthesis of hydroxylated piperidines and its applications to the total syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine.

Chapter 4: Enantioselective approach towards the total synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram.

Chapter 5: An attempt towards total synthesis of antidepressant drug (*S*,*S*)-reboxetine.

Chapter 6: Conclusions and future Scope.

Chapter 1: A brief account of [3+2] cycloaddition reaction, organocatalzyed Michael addition reactions, organocatalyzed aldol reactions, Jacobsen's Hydrolytic Kinetic Resolution (HKR) and Henry reaction.

Bioactive natural products are rich source of novel therapeutics. Thus, the search for bioactive molecules from nature continues to play an important role in fashioning new medicinal agents.[1] Asymmetric synthesis of bioactive molecules is in the forefront of synthetic organic chemistry which allows the synthesis of complex, chiral, enantiomerically pure, polycyclic, natural products as well as natural product-like derivatives. In the last two decades, many powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds.[2] Asymmetric reactions have

revolutionised organic synthesis and found considerable applications in the sphere of sequential reactions. The construction and functionalization of these are central focus in organic synthesis and the transition-metal catalyzed multi-step cascade or sequential reactions have provided an effective alternative way for the synthesis of bioactive natural products.[3]

Catalytic asymmetric 1,3-dipolar cycloaddition is progressively growing by exploiting the concurrently developed organocatalysis, Lewis acid catalysis and transition metal catalysis.[4] 1,3-Dipolar cycloaddition reactions are straightforward but powerful tool for the construction of five membered heterocycles such as isoxazoles, isoxazolines, pyrazoles, pyrazolones and 1,2,4-oxadiazolines etc.[5] Cycloaddition reaction is a process in which two or more π systems combine to form a stable cyclic molecule, during which sigma bonds are formed between the termini of π systems without loss of any fragment, that follow a concerted mechanism.

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organocatalytic asymmetric synthesis has provided several new methods for obtaining chiral compounds. In this connection, proline and its derivatives available in both enantiomeric forms have emerged as the most practical and versatile organocatalyst for *α*-functionalization of carbonyl compounds for *e.g*. Michael addition of nitroalkanes to conjugated carbonyl and also the Michael addition of aldehydes to conjugated nitroalkenes.

Organocatalysis is an upcoming field in asymmetric synthesis. Barbas,[6a-c] Shibasaki[6d-e] and Trost[6f-g] have outlined the examples of enantioselective direct aldol reactions, an important class of metal- or proline-catalyzed transformations that do not require the pregeneration of enolates or enolate equivalents. Proline has been shown to be an effective organocatalyst in many asymmetric transformations such as aldol, Mannich and Michael reactions. MacMillan effectively reported the proline catalysed enantioselective direct aldol reactions of *α*-oxyaldehydes.[7]

The Jacobsen's Hydrolytic Kinetic Resolution (HKR) of terminal epoxides catalyzed by chiral (salen)Co(III) complex affords both recovered unreacted epoxide and 1,2-diol product in highly enantioenriched form. As such, the HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access, from inexpensive racemic materials. The reaction has several appealing features from a practical standpoint, including the use of H_2O as a reactant and low loadings (0.2-2.0 mol %) of a recyclable and

commercially available catalyst. In addition, the HKR displays extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to > or = 99% *ee*. The corresponding 1,2-diols were produced in good-to-high enantiomeric excess using 0.45 eq. of H_2O. Useful and general protocols are provided for the isolation of highly enantioenriched epoxides and diols, as well as for catalyst recovery and recycling.[8]

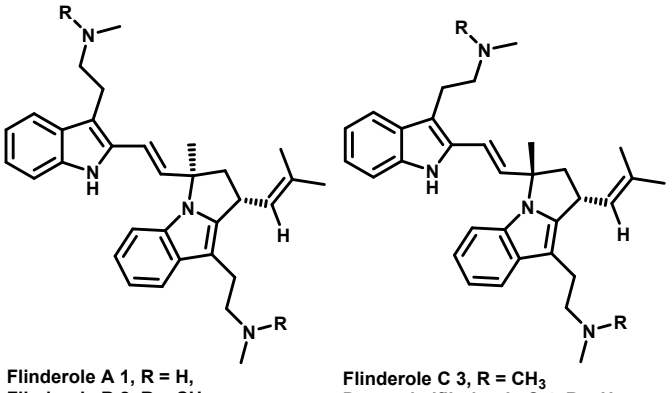
The Henry reaction is a base-catalyzed C-C bond forming reaction between nitroalkanes and aldehydes or ketones. It is similar to the aldol addition and also referred to as the nitro aldol reaction. Since the first report of Shibasaki and co-workers,[9] many efforts have been made continuously in the literature for the introduction of stereoselectivity into the Henry reaction (nitroaldol), using prochiral aldehydes and nitromethane in the presence of chiral complexes especially Cu-catalyzed Henry reaction has received much attention in recent years.

Keeping in view the above points, the following objectives have been designed.

1. Total synthesis of bioactive natural products employing chiral catalysts.
2. Total synthesis of stereoisomers of Flinderoles; a naturally ocurring antimalarial, employing [3+2] cycloaddition.
3. Jacobsen's HKR of terminal epoxide and its application to the total synthesis of bioactive natural products.

Chapter 2: $InCl_3$ catalyzed diastereoselective approach for the syntheses of bisindole alkaloids flinderoles A-C and desmethylflinderole C.

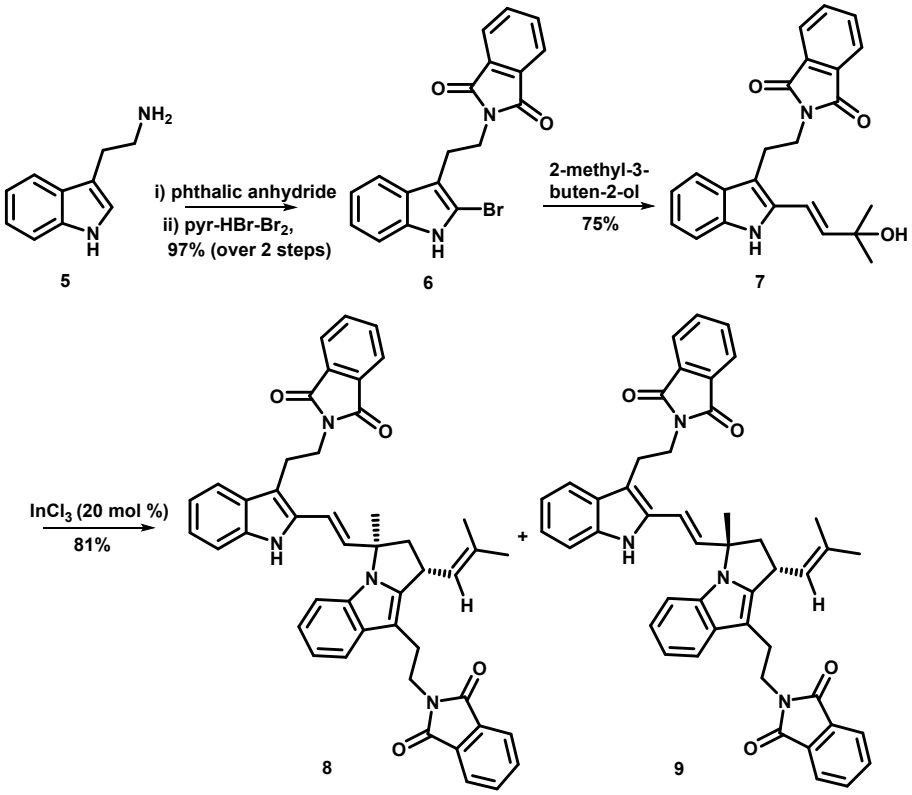
Natural products chloroquine, artemisinin and other frontline drugs for the treatment of malaria are becoming increasingly ineffective due to the development of drug resistance and therefore, the search for new antimalarial drugs is again of even greater significance. Bis-indole alkaloids flinderoles A-C (**1-3**) were isolated from the plant genus *Flindersia* along with the previously known natural products borrerine, borreverine, isoborreverine and dimethylisoborreverine.[10] The flinderoles A-C (**1-3**) alkaloids have been shown to possess significant selective growth inhibition against Dd2 (chloroquine-resistant) *P. falciparum* and exhibit antimalarial activity with IC_{50} values between 0.15-1.42 μM.[10] These alkaloids are fast acting and are currently the drugs of choice for the treatment of malaria through a different mechanism of action than that of chloroquine and other drugs by interrupting the parasitic hemoglobin.



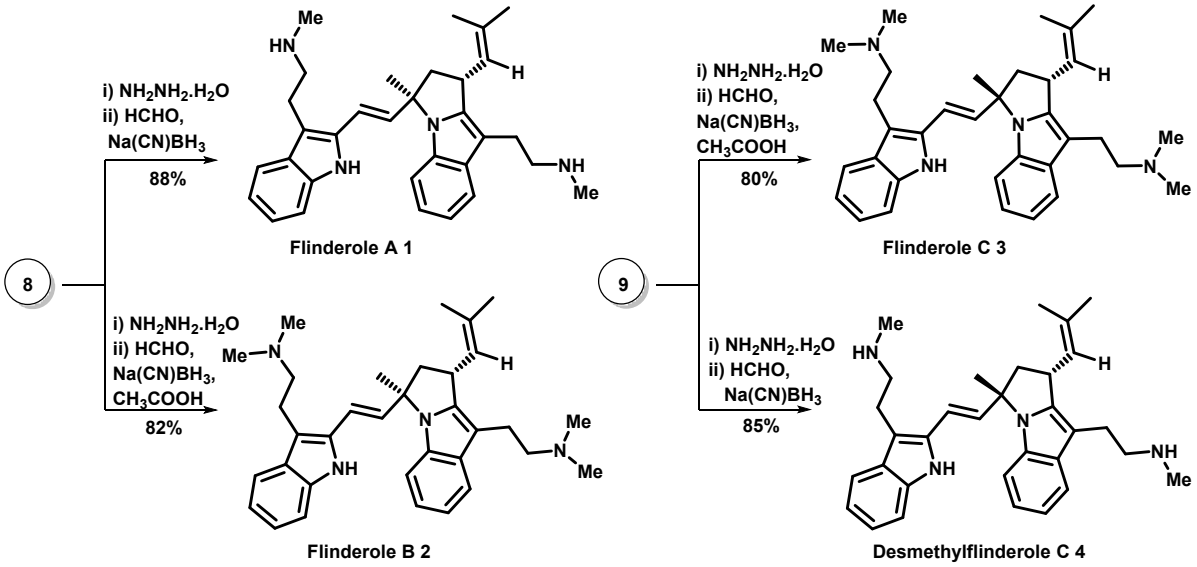
Flinderole A 1, R = H,
Flinderole B 2, R = CH_3,

Flinderole C 3, R = CH_3
Desmethylflinderole C 4, R = H

The synthesis of flinderole frameworks commenced with commercially available tryptamine **5** which was protected as a phthalimide and subsequent selective bromination at the C2 position of indole ring using pyridinium hydrogen perbromide furnished the bromide derivative **6**[11] in excellent yield. The bromo indole derivative **6** was subjected to a intermolecular Heck coupling reaction with 2-methyl-3-buten-2-ol in presence of tri-(*o*-tolyl)phosphine/$Pd(OAc)_2$ which afforded the alcohol derivative **7**.[12] The alcohol derivative **7** was subjected to $InCl_3$ catalyzed [3+2] cycloaddition[13] reaction which furnished the flinderole frameworks **8** and **9** with 81% yield in 3:2 diastereomeric ratios.

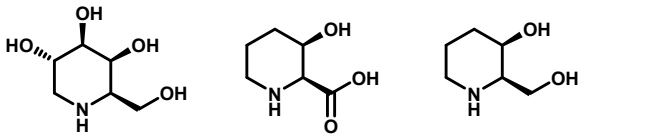


The cleavage of phthalimide group of compound **8** with hydrazine monohydrate furnished the bis-amine intermediate which on subsequent reductive amination with formaldehyde in presence of $Na(CN)BH_3$/Methanol at 0 ^oC-rt furnished the target compound flinderole A **1** in excellent yield. However, reductive amination of the bis-amine intermediate derived from compound **8** with formaldehyde in presence of $Na(CN)BH_3$/acetonitrile and acetic acid at 0 ^oC-rt afforded the flinderole B **2** in 82% yield. Flinderole C **3** and desmethylflinderole C **4** were synthesized from bis-amine intermediate derived from compound **9** following an analogous series of reactions.



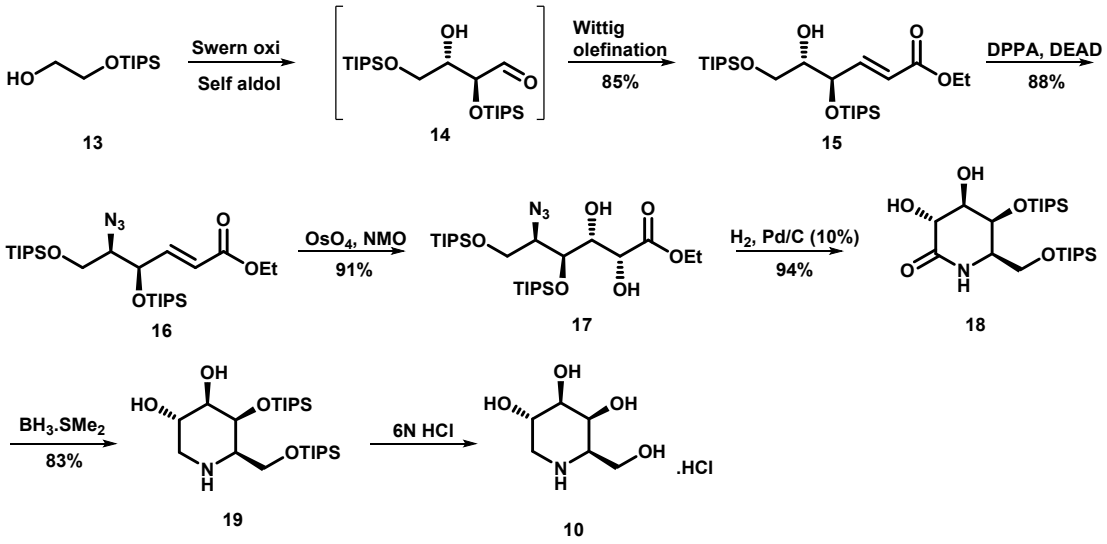
Chapter 3: An enantioselective approach towards the synthesis of hydroxylated piperidines and its applications to the total syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic Acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine.

Functionalized piperidines and their derivatives are one of the most important chemotherapeutic *N*-heterocyclic compounds whereas unnatural polyhydroxylated piperidines 1-deoxygalactonojirimycin **10** exhibits interesting potent glycosidase inhibitory activity[14] and currently undergoing phase II clinical trial for the treatment of Fabry's disease.[14] 3-hydroxypipecolic Acid **11** and its analogue, 3-hydroxy-2-hydroxymethylpiperidine **12**, are known as fagomine congeners due to their resemblance to the piperidine iminosugars which are promising glycosyltransferases and glycosidase inhibitor. The (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **12** is also found in the structure of the antimalarial isofebrifugine.



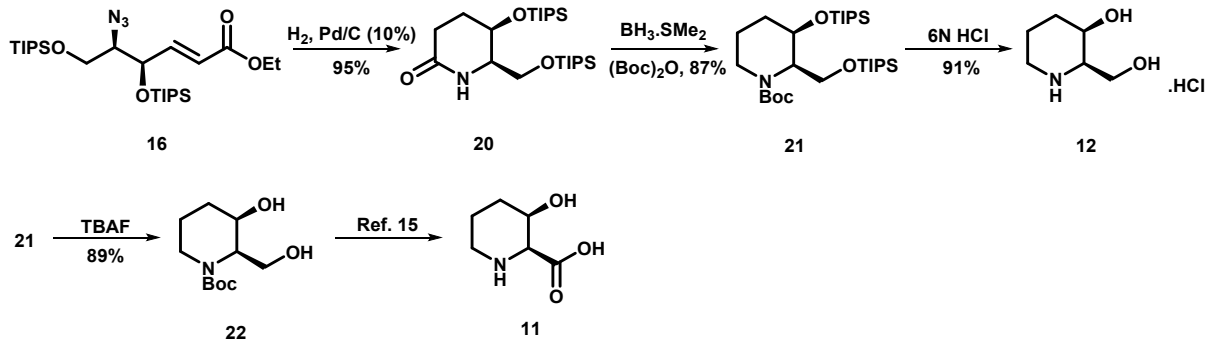
1-Deoxygalactonojirimycin 10 | *cis*-(-)-3-Hydroxy pipecolic acid 11 | (2*R*,3*R*)-3-Hydroxy-2-hydroxymethylpiperidine 12

The synthesis of 1-deoxygalactonojirimycin **10** commenced with readily available mono silylated ethylene glycol **13** which was exposed to Swern reaction conditions,[15] subsequently L-proline catalyzed MacMillan's self aldol reaction[7] furnished the aldol product **14** which on spontaneous treatment with wittig reagent afforded the *trans*-olefinic ester **15**.



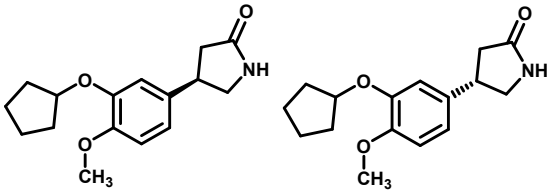
The hydroxyl group of **15** was converted into azide **16** under Mitsunobu conditions.[16] Then, azide **16** on dihydroxylation using OsO_4/NMO under Upjohn furnished the diol **17** as a single diastereomer.[17] The compound **17** was subjected to reductive lactamization under 1 atm H_2 pressure in the presence of catalytic amount of Pd/C under basic conditions which furnished the hydroxylated lactam **18** in excellent yield. The lactam **18** on $BH_3.SMe_2$ mediated reduction delivered the hydroxylated piperidine **19** in 83% yield. Finally, deprotection of silyl group of compound **19** using 6N HCl under reflux conditions delivered the 1-deoxygalactonojirimycin **10** as salt form.

The synthesis of *cis*-(-)-3-hydroxypipecolic acid **11** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **12** started with azide derivative **16**, which was subjected to hydrogenation in the presence of catalytic amount of Pd/C to deliver the lactam **20**.



The lactam **20** was then treated with $BH_3.SMe_2$ to afford the piperidine moiety, which on subsequent reaction with $(Boc)_2O$ furnished the *N*-Boc derivative **21**. Then global deprotection of *N*-Boc and *O*-TIPS of piperidine derivative **21** was performed *via* reflux under acidic conditions to deliver the (2*R*,3*R*)-3-hydroxymethylpiperidine **12** as salt form. On the other hand, cleavage of silyl group of compound **21** using TBAF afforded the diol **22**. The piperidine derivative **22** on oxidation and *N*-Boc deprotection would furnish the *cis*-(-)-3-hydroxypipecolic acid **11** using the known literature procedure.[18]

Chapter 4: Enantioselective approach towards the total synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram.

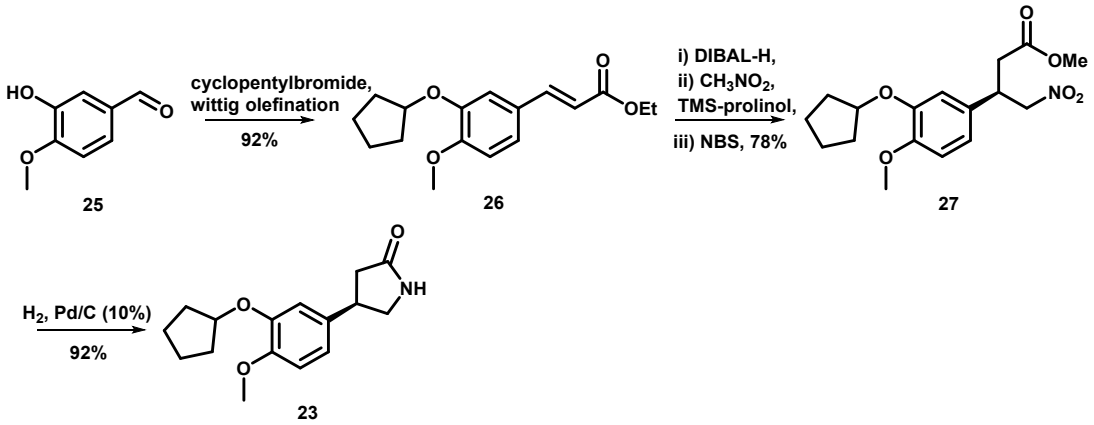


(*R*)-Rolipram 23 (*S*)-Rolipram 24

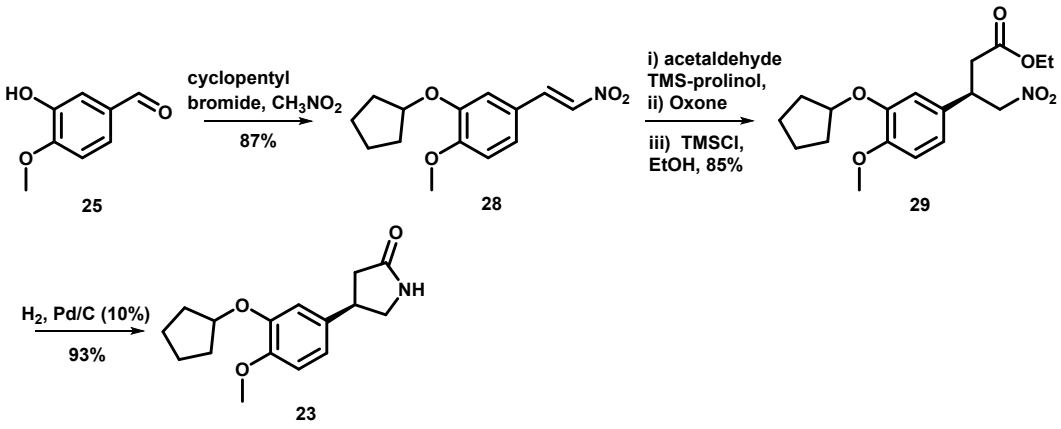
The rolipram (**23**-**24**) are simple cyclo-GABA derivative possessing a catechol type ring at chiral carbon (C-3). The (±)-rolipram was discovered and developed by Schering AG pharmaceutical company at Berlin, Germany in early 1990[19] and it acts as a selective phosphodiesterase-4 inhibitor and potential antidepressant drug. (*R*)-rolipram **23** has also been proposed as a antiinflammatory, immunosupressant, putative antiparkinsonian, neuroprotective, antipsychotic and has been suggested for the treatment of multiple sclerosis.[20]

The synthesis of (*R*)-rolipram **23** started with commercially available isovanillin **25** which on treatment with cyclopentylbromide under basic conditions followed by 2C-Wittig olefination afforded the *trans*-olefinic ester **26**. The DIBAL-H reduction of ester **26** at -78 ^oC afforded α,β-unsaturated aldehyde which was subsequently subjected to asymmetric Michael oxidative

esterification[21] with nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether (10 mol%) to furnish the nitro aldehyde adduct which on *in situ* treatment with NBS/MeOH furnished the *γ*-nitroester **27**. The compound **27** was then subjected to intramolecular reductive lactamization under hydrogenation conditions to furnish the (*R*)-rolipram **23**.

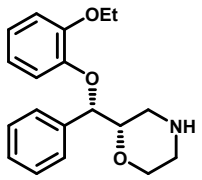


In another approach, the synthesis of (*R*)-rolipram **23** commenced with treatment of the isovanillin **25** with cyclopentylbromide under basic conditions followed by Henry condensation reaction with nitromethane to afford the nitro olefin **28**.[22] Asymmetric Michael addition of acetaldehyde to nitro olefin **28** in the presence of catalyst (*R*)-diphenylprolinol silyl ether (10 mol%) afforded the nitroaldehyde adduct, which on spontaneous oxidation with oxone and subsequent esterification using TMSCl/EtOH successfully furnished the ester derivative **29**. Nitroester **29** underwent hydrogenation in the presence of catalytic amount of Pd/C in EtOAc/Et_3N to deliver the target compound (*R*)-rolipram **23**. The (*S*)-rolipram **24** was also synthesized by following an analogous series of reactions using the (*S*)-diphenylprolinol ether catalyst during the asymmetric Michael addition step.



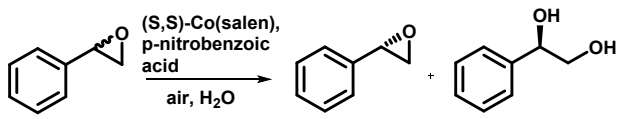
Chapter 5: An attempt towards total synthesis of antidepressant drug (*S*,*S*)-reboxetine.

Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has been widely studied for its pharmacological properties. Commercially available under the name Edronax, Prolift, Vestra, and Norebox, reboxetine is indicated in the treatment of depressive disorder and is marketed as a racemic mixture of the (*R*,*R*)- and (*S*,*S*)-enantiomers. However, the latter enantiomer has a greater affinity and selectivity for the norepinephrine transporter (NET).[23]



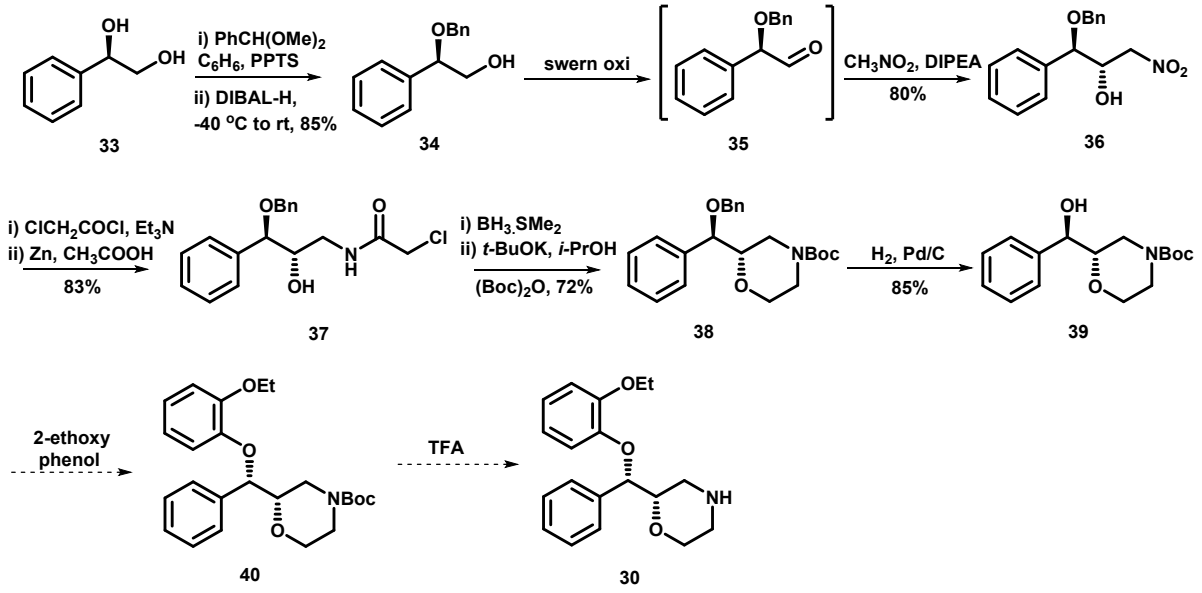
S,S-reboxetine, 30

The synthesis of (*S*,*S*)-reboxetine **30** started with commercially available recemic styrene oxide **31** which was subjected to Jacobsen's HKR[24] in the presence of catalytic amount of (*S*,*S*)-(salen)-Co-(salen) complex to afford (*S*)-styrene oxide **32** and (R)-styrene glycol **33**.



31 32 33

Styrene glycol **33** was then protected as 1,2-benzylidene acetal which on regioselective reductive opening with DIBAL-H afforded alcohol **34**. Oxidation of alcohol **34** under Swern conditions and subsequent treatment with nitomethane under Henry reaction conditions afforded the nitoalcohol **36** in diastereomeric ratio. Compound **36** on reduction with Zn/CH_3COOH followed by treatment with chloroacetyl chloride in presence of base afforded the compound **37**. The chloro derivative **37** on treatment with *t*-BuOK in *i*-PrOH and subsequent reduction of amide by using $BH_3.SMe_2$ afforded the corresponding amine which on subsequent reaction with $(Boc)_2O$ furnished the *N*-Boc derivative **38**. The compound **38** on hydrogenation under 1 atm pressure in the presence of catalytic amount of Pd/C (10%) furnished the amino alcohol **39**. We have optimized upto the intermediate **39**, however unfortunately the similar approach published for the same target molecule during progress of work.[25]



Characterization:

All the synthesized compounds were characterized by ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory. HRMS were recorded using Electron Spray Ionization. Optical rotations were measured on Automatic polarimeter AA-65. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of hexane/ethyl acetate and/or CH_2Cl_2/MeOH. The enantiomeric purity (%*ee*) was determined by Thermofisher HPLC analysis using chiralpak IA chiral column.

Conclusion:

We have described herein enantioselective approaches for the synthesis of bisindole alkaloids flinderoles A-C and desmethylflinderole C, hydroxylated piperidines and its applications to the total syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine, (-)-(*R*)- and (+)-(*S*)-rolipram respectively employed [3+2] cycloaddition reaction, organocatalyzed aldol reactions, organocatalzyed Michael addition reactions and Jacobsen's Hydrolytic Kinetic Resolution (HKR). The merits of these synthetic approaches are high enantio- and diastereoselectivity with high yielding reaction steps. All the new compounds were characterized by ^{1}H-NMR, ^{13}C NMR, HRMS, %*ee* by chiral HPLC and $[\alpha]_D^{25}$ for all new chiral compounds.

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List of Publications

1. Efficient synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram
   Ramandeep Kaur and Satyendra Kumar Pandey*
   ***Tetrahedron Lett.* 2017, *58*, 4333-4335.**
2. A short total synthesis of antimalarial flindersial alkaloids
   Ramandeep Kaur, Yuvraj Garg and Satyendra Kumar Pandey*
   ***ChemistrySelect* 2016, *1*, 4286-4288.**

3. Enantioselective synthesis of (1*S*,2*R*)-ephenamine
   Ramandeep Kaur and Satyendra Kumar Pandey*
   ***Tetrahedron Asymmtery* 2016, *27*, 338-340.**
4. Organocatalytic Asymmetric Tandem α-Aminooxylation-Henry Reactions for the Synthsis of 1,2-Diols: Total Synthesis of (-)-L-threo-Sphinganine
   Yuvraj Garg, **Ramandeep Kaur** and Satyendra Kumar Pandey*
   ***Eur. J. Org. Chem.* 2017, 6700-6707.**
5. Enantioselective Approach to Hydroxylated Piperidines: Total Syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine.
   Ramandeep Kaur and Satyendra Kumar Pandey*
   (*Manuscript Under preparation*)
6. Proline catalyzed asymmetric tandem aminoxylation reactions: Applications for the synthesis of bioactive natural products (Review Article)
   Yuvraj Garg, **Ramandeep Kaur** and Satyendra Kumar Pandey*
   (*Manuscript under preparation*)

Conferences

1. **Enantioselective synthesis of (1*S*,2*R*)-ephenamine**
   Ramandeep Kaur and Satyendra Kumar Pandey*
   Poster presentations at International conference FCASI 2016, University of Rajasthan, Jaipur, India.
2. **Enantioselective synthesis of (1*S*,2*R*)-ephenamine**
   Ramandeep Kaur and Satyendra Kumar Pandey*
   Poster presentations at the national conference "Recent Advancement in Drug Discovery and Development", 04th-05th February-2017, Geetanjali University, Udaipur, India.

CHAPTER 1

A brief account of [3+2] cycloaddition reactions, organocatalzyed Michael addition reactions, organocatalyzed aldol reactions, Jacobsen's Hydrolytic Kinetic Resolution (HKR) and Henry reaction

1.1 [3+2] cycloaddition reactions

1.1.1 Introduction

In this developing world, there is increase in demand for the chiral compounds, as these are found as a common motif in biologically active compounds. The development of efficient methods to provide enantiomerically enriched products is of great current interest to both academia and industry.[1] Among the various methods employed for this purpose, asymmetric catalysis provides an especially practical entry into the asymmetric world in terms of chiral economy and environmental considerations.[2] The vibrant dynamics of the pharmaceutical industry has lead to many novel technologies and innovative ideas for development of new chemical entities.

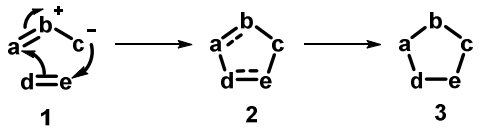
Over the past few years the pericyclic reactions like electrocyclic reaction, cycloaddition and sigmatropic rearrangement has gained importance among the scientists in relevant field. Among them, from the chemical and biological view point 1,3-dipolar cycloaddition reactions have came out as one of the important type of cycloaddition reactions.[3] Asymmetric 1,3-dipolar cycloaddition reactions are progressively growing by exploiting the concurrently developed organocatalysis, Lewis acid catalysis and transition metal catalysis.[4] Cycloaddition reaction is a process in which two or more π-systems combine to form a stable cyclic molecule, during which sigma bonds are formed between the termini of π-systems without loss of any fragment, that follow a concerted mechanism. These reactions are straightforward but powerful tool for the construction of five membered heterocycles such as pyrazoles, pyrazolones, isoxazoles, isoxazolines and 1,2,4-oxadiazolines etc.[5]

The Huisgen cycloaddition is basically the reaction of a dipolarophile with a 1,3-dipolar compound that leads to 5-membered heterocycles. The alkenes, alkynes and molecules that possess related heteroatom functional groups (such as carbonyls and nitriles) are examples of dipolarophiles. 1,3-Dipolar compounds contain one or more heteroatoms and can be described as having at least one mesomeric structure that represents a charged dipole. When two or more chiral centers are generated during the reaction, diastereomeric transition states and products can be obtained. In the Diels-Alder cycloaddition, the endo diastereoselectivity due to secondary orbital interactions is usually observed. In 1,3-dipolar cycloadditions, however, there are two forces that influence the diastereoselectivity: (i) the attractive π-interaction (resembling secondary orbital interactions in the Diels-Alder cycloaddition), (ii)

the repulsive steric interaction. Unfortunately, these two forces often cancel each other, causing poor diastereo-selectivity in 1,3-dipolar cycloaddition reactions.

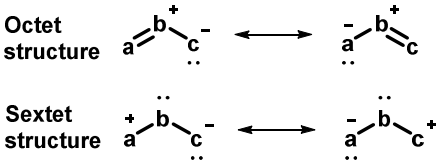
1,3-Dipolar cycloaddition reactions:

Huisgen and co-workers done an immense work by exploring the concept of 1,3-dipolar cycloaddition reactions, now known as Huisgen cycloaddition reactions.[6] Here, a five membered ring is constructed by the cycloaddition of 1,3-dipole molecule (a three atom entity; *a*-*b*-*c*) and dipolarophile (a two atom entity; *d*-*e*) (Scheme 1).



Scheme 1. General mechanism for 1,3-dipolar cycloaddition reaction.

1,3-Dipolar molecule is a species represented by Zwitter ionic octet and sextet structures as shown in Scheme 2. The three atoms can be a combination of C, O and N.

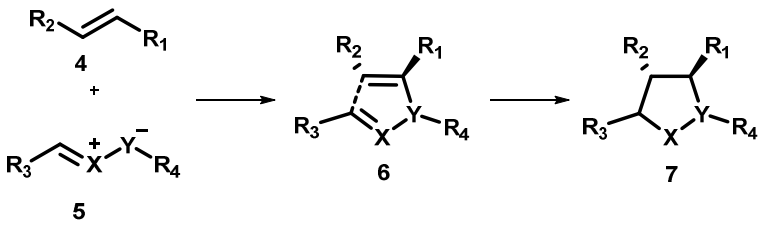


Scheme 2. Octet and sextet structures of 1,3-dipolar molecule species.

In all 1,3-dipoles, there are four electrons in three parallel π-orbitals and they are both nucleophilic and electrophilic in nature. This uncertainty of the 1,3-dipole is of key importance in understanding its reactivity. The nucleophilic behaviour of the 1,3-dipole may be stronger than its electrophilic nature. The cycloaddition of compounds such as diazomethane or nitrile ylides to electron deficient dipolarophiles, takes place with a faster rate than with electron rich multiple bonds. The opposite is true for ozone, which combines preferably with electron rich dipolarophiles.

1.1.2. Mechanism of 1,3-dipolar cycloaddition reactions

The 2π-electrons of the dipolarophile and 4π-electrons of the dipolar compound will participate in a pericyclic concerted shift. The addition is stereoconservative (suprafacial), therefore the reaction is [4s+2s] cycloaddition (Scheme 3), and is similar to the Diels-Alder reaction. A condition for such a reaction to take place is a certain similarity of the interacting HOMO and LUMO orbitals, depending on the relative orbital energies of both the dipolarophile and the dipole.

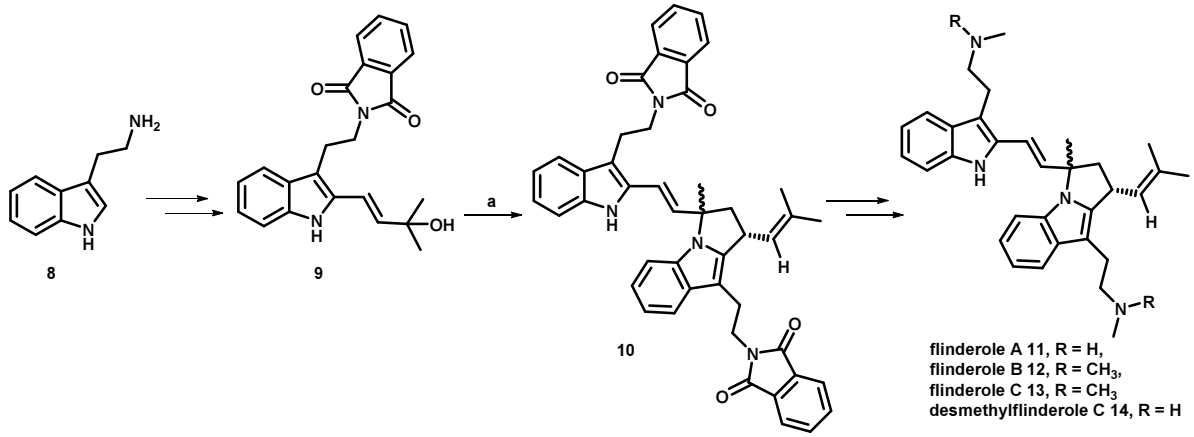


Scheme 3. General mechanism of 1,3-dipolar cycloaddition reaction.

Electron-withdrawing groups on the dipolarophile normally favor an interaction of the LUMO of the dipolarophile with the HOMO of the dipole that leads to the formation of the new bonds, where as electron donating groups on the dipolarophile normally favour the inverse of this interaction.

1.1.3 Application

We have applied the [3+2] cycloaddition reaction for the synthesis of pyrrolo[1,2-α]indoles framework and its application to the total syntheses of flindersial alkaloids as shown in Scheme 4. The synthesis of flinderole alkaloids commenced with commertially available tryptamine **8** which was converted into tertiary alcohol **9** *via* standard organic transformations. The alcohol **9** was subjected to $InCl_3$ catalyzed [3+2] cycloaddition reaction in toluene which afforded flinderole frameworks **10** with 81% yield in 3:2 diastereomeric ratios, which on further functional group manipulations furnished the target molecules flinderole A **11**, B **12**, C **13** and desmethylflinderole C **14**.



Scheme 4. *Reagents and conditions*: (a) $InCl_3$ (20 mol%), toluene, 0 °C-rt, 4 h, 81%.

1.2 Organocatalyzed aldol reactions

1.2.1 Introduction

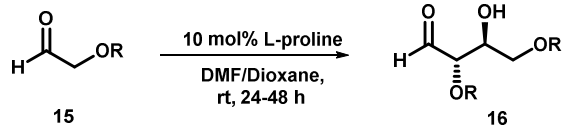
Organocatalysis is the acceleration of chemical reactions with substoichiometric quantities of organic molecules. Organocatalysis continues to be an important strand of research and the area is well established in the academic as well as in industrial sectors.[7] Recently, organocatalysis become one of the most powerful strategy for the asymmetric synthesis of chiral molecules. Organocatalysts are predominantly composed of carbon, hydrogen, sulfur and other non metal elements. Organocatalysts offers several advantages like metal free catalysis which contributes to green chemistry; it also reduces the organic waste involved in chemical transformation and saves time as well as cost of manufacturing pharmaceutical leads. Among various types of organocatalysts, L-proline, a naturally occurring cyclic amino acid, has been most extensively studied and catalyses various powerful asymmetric transformations such as α-functionalization, inter and intramolecular aldol reaction, Michael addition, mannich and Diels-Alder reactions. Development of catalytic methods that avoids the production of stoichiometric by-products while maintaining high levels of control available from stoichiometric processes provides an atom-economical alternative for the important transformations. Proline is referred as a "universal catalyst" due to its diversity of organic transformations and high utility.

Aldol reaction is an important synthetic method widely used in organic synthesis. Indeed, numerous catalysts for the aldol reaction have been reported in recent years, including enzymes, catalytic antibodies, organometals, organocatalysts and small molecules. Wiechert and coworkers in 1971, introduced the intramolecular aldol reaction known as Hajos-Parrish-Eder-Sauer-Wiechert reaction, where proline was used as a catalyst in organic transformation.[8] Later, in 1997, Barbas and coworkers synthesized Wieland-Miescher ketone *via* proline catalyzed Robinson annulation reaction.[9]

1.2.2 MacMillan's organocatalyzed direct aldol reactions of α-oxyaldehydes

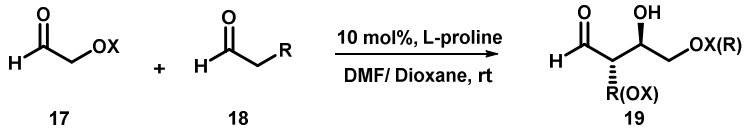
In 2004, MacMillan developed a first direct, enantioselective catalytic aldol reaction between α-oxyaldehydes as both the donor and acceptor and extended this transformation to the self and cross aldol reaction[10] as shown in Scheme 5 and 6 respectively. Significantly, the resulting α-oxyaldehyde products of this protocol were infact inert to *in situ* proline-catalyzed enolization or carbonyl addition. This stratergy allows a direct access to different enantioselective protected *anti*-1,2 diols and protected polyols. MacMillan examined the

organocatalytic self coupling of α-oxyaldehydes **15** in presence of 10 mol% L-proline in DMF/dioxane as a solvent afforded the desired aldol products **16** with both s*yn*-, *anti*- aldol selectivity with 42-92% yield and excellent 88-98% *ee* (Scheme 5).



Scheme 5. Self-aldol reactions of protected α-oxyaldehydes (R = TIPS, TBDPS, Bn, PMB, MOM, Ac, TBS).

Additionally, MacMillan performed cross-coupling between α-oxyaldehydes **17** and α-alkyl-substituted aldehydes **18** in presence of 10 mol% L-proline in DMF/dioxane which afforded *syn*-,*anti*- cross-aldol products **19** in 33-84% yield and good enantiomeric excess (94-99% *ee*) (Scheme 6).



Scheme 6. Cross-aldol reactions with protected α-oxyaldehydes (R = Me, *i*-Pr; OX = OTIPS, OTBDPS, OBn).

1.2.3 The mechanism of aldol reaction

A general mechanism of proline catalyzed asymmetric self/cross aldol reaction is explained in Figure 1. The aldehyde **20** on treatment with proline generates enamine intermediate **21**

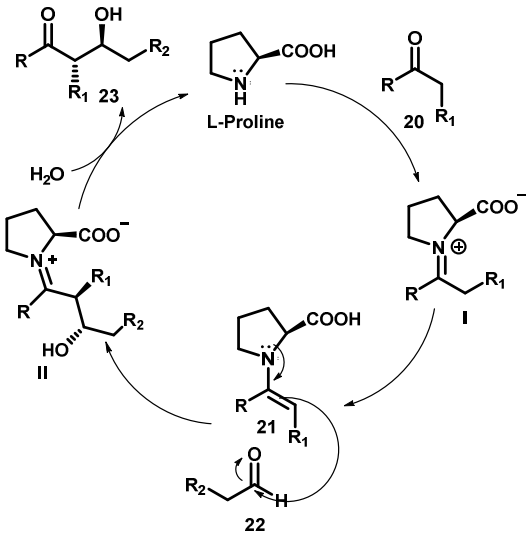


Figure 1. A general mechanism of proline-catalyzed self and cross aldol reactions.

which on nucleophilic addition to same or different aldehyde **22** synthesizes self/cross imine intermediate **II**. Finally, the imine intermediate **II** on hydrolysis generates the *β*-hydroxyaldehyde derivatives **23** with simultaneous release of organocatalyst.

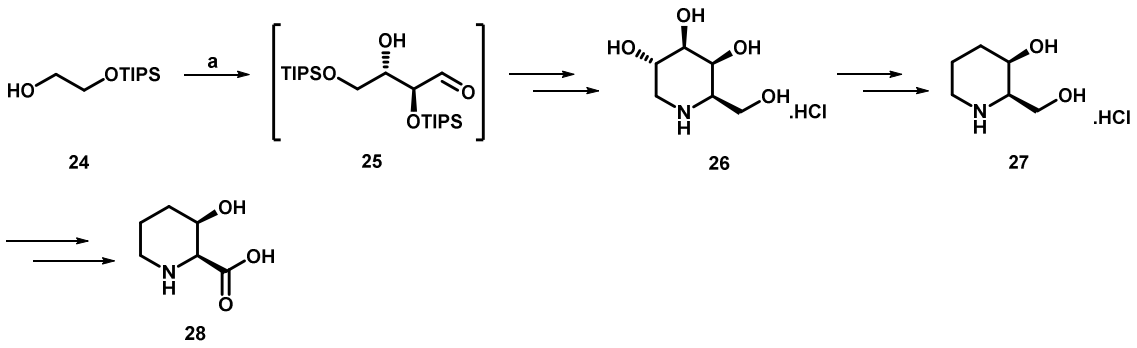
1.2.4 Reaction conditions

The self aldol reaction of *α*-oxyaldehyde (1 equivalent) in presence of 10 mol% L-proline in DMF or dioxane was carried out at room temperature.

Similarly, the asymmetric cross aldol reaction was performed in DMF or dioxane. Both acceptor (1 equivalent) and donor aldehydes (5 equivalents) were kept at 4 ^{o}C. A solution of donor aldehyde in DMF or dioxane was added dropwise to a mixture of acceptor aldehyde and 10 mol% L-proline in DMF or dioxane at 4 ^{o}C and resulting suspension was stirred for 24-48 h at 4 ^{o}C.

1.2.5 Application

We have applied the MacMillan's organocatalyzed direct aldol reactions for the synthesis of 1-deoxygalactonojirimycin **26**, (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** and (-)-3-hydroxypipecolic acid **28** as shown in Scheme 7. The synthesis of 1-deoxygalactonojirimycin, (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine and



Scheme 7. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^{o}C to rt, 2 h; ii) L-proline (10 mol%), DMF, rt, 24 h, 90%.

(-)-3-hydroxypipecolic acid **28** commenced with readily available monosilylated ethylene glycol **24** which on under Swern conditions and subsequent L-proline catalyzed MacMillan's self aldol reaction furnished the *anti*-diastereomer **25** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield which on further functional group manipulations furnished the target molecules.

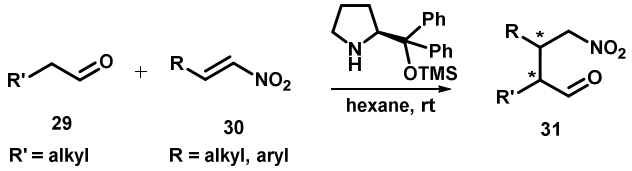
1.3 Organocatalzyed Michael addition reactions

1.3.1 Introduction

Asymmetric organocatalysis has now become one of the most active and developing field of research in asymmetric catalysis and it has been demonstrated a powerful tool for performing stereoselective transformations which were classically achieved by using transition-metal or enzymatic catalysis.[11] The Michael addition reaction is widely recognized as one of the most important carbon-carbon bond-forming reactions in organic synthesis.[12] Several reagent systems for this type of transformation that depends on asymmetric catalysts have been reported in the literature.[13-15] Organocatalyzed asymmetric Michael reactions with a diverse combination of Michael donors and acceptors is one of the significant method. In particular, the interest for environment-friendly and non-metal catalyzed asymmetric synthesis,[11] has focused considerable attention on the development of efficient organocatalyzed Michael reactions.[13,14]

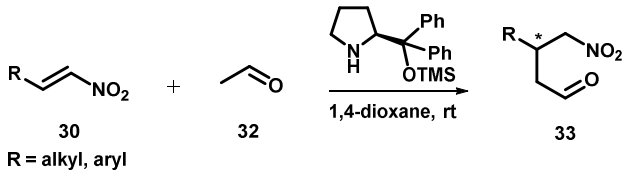
1.3.2 Organocatalzyed Michael addition reaction on conjugated nitro-olefins

The Michael addition reaction of a nucleophile with a conjugated acceptor is one of the useful approaches for the synthesis of nitroalkanes, which are important synthetic intermediates due to prevalence and various possible transformations of the aldehyde and nitro group to other useful functional groups. Recently, Hayashi and co-workers developed an organocatalyzed asymmetric Michael reaction of α-substituted aldehydes **29** with nitroalkenes **30** in the presence of catalytic amount of diphenylprolinol silyl ether to furnish the useful α-substituted-γ-nitro aldehydes **31** in high enantio- (upto 99% *ee*) and diastereoselectivity (upto 97:3 *syn*:*anti*) with good yield (upto 85%) (Scheme 8).[16]



Scheme 8. Organocatalyzed Michael addition reaction of aldehydes

More recently, Hayashi and co-workers described the organocatalytic asymmetric Michael addition reaction of acceptor nitroolefins **30** with acetaldehyde **32** in the presence of catalytic amount of diphenylprolinol silyl ether to afford the α-unsubstituted-γ-nitro aldehydes **33** in good yield (upto 77%) with excellent enantioselectivity (upto 99% *ee*) (Scheme 9).[17]



Scheme 9. Organocatalyzed Michael addition reaction of acetaldehyde

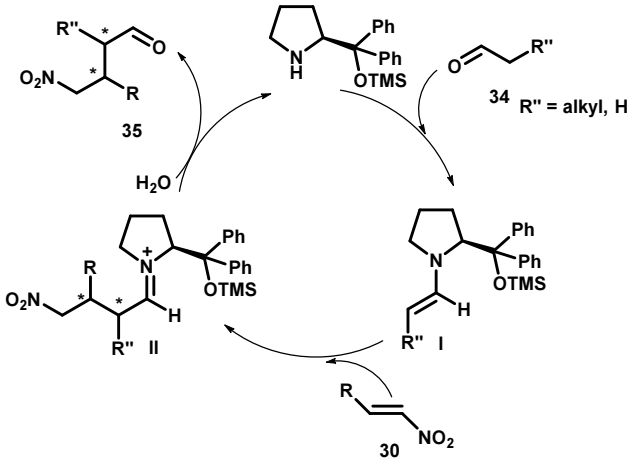


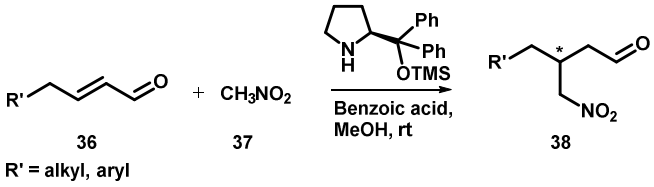
Figure 2. General mechanism for organocatalzyed Michael addition reaction

A plausible mechanism for the organocatalzyed asymmetric Michael addition reaction of aldehyde to conjugated nitro-olefins is described in Figure 2. Initially, aldehyde **34** on treatment with TMS-prolinol organocatalyst generates an enamine intermediate **I** which on nucleophilic addition to acceptor nitroolefin **30** furnish imine intermediate **II**. Finally, the intermediate **II** on hydrolysis generates the nitroaldehyde adduct **35** with simultaneous release of organocatalyst.

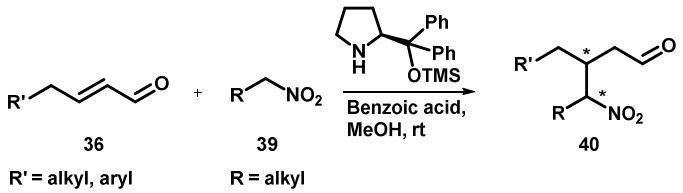
1.3.3 Organocatalzyed Michael addition reaction on conjugated aldehydes

The reverse combination of Michael addition reaction in which donor nitro-alkane and acceptor conjugated aldehyde reacts to form a nitro-aldehyde adduct which is also synthetically important, due to prevalence of these versatile synthetic intermediates in bioactive compounds and natural products.

Hayashi and co-workers described a synthetic methodology using Michael addition of nitromethane **37** to acceptor *trans*-olefinic aldehydes **36** in the presence of catalytic amount of TMS-prolinol to furnish the nitroaldehyde adduct **38** in good yield (up to 94%) and high enantioselectivity (up to 95% *ee*) (Scheme 10).[18]



Scheme 10. Organocatalyzed Michael addition reaction with nitromethane



Scheme 11. Organocatalyzed Michael addition reaction with nitroalkanes

Hayashi and co-workers also described the Michael addition of nitroalkane **39** with conjugated aldehydes **36** in the presence of catalytic amount of TMS-prolinol to afford the nitroaldehyde adduct **40** in high enantio- (upto 96% *ee*), diastereoselectivity of 1:1 *syn*:*anti* and good yield (upto 95%) (Scheme 11).[18]

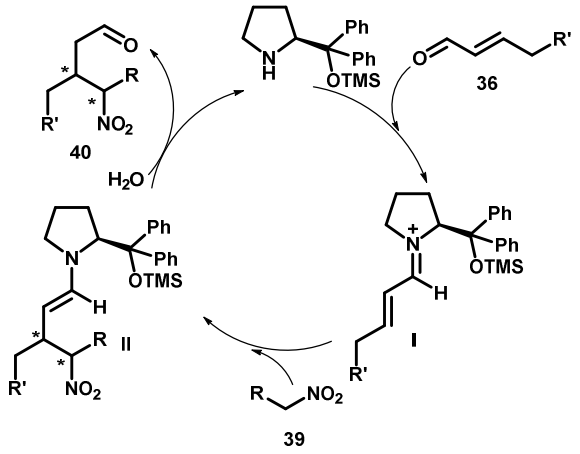


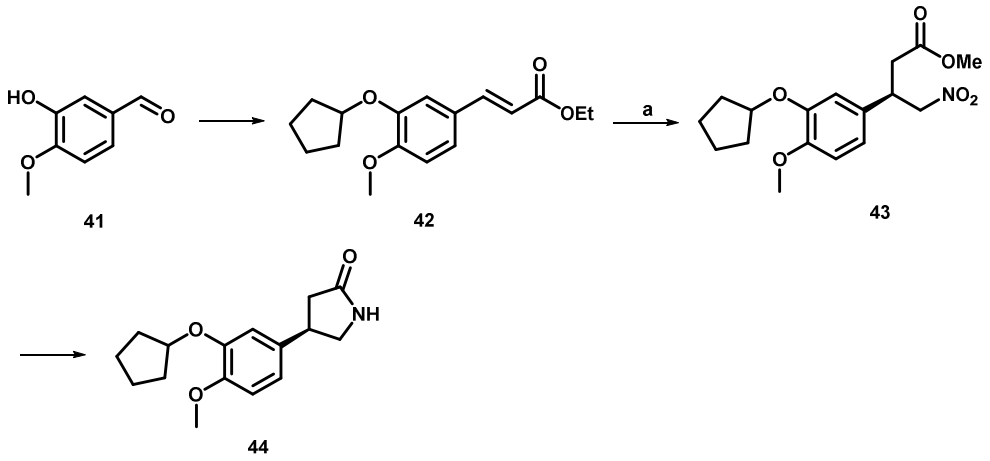
Figure 3. General mechanism for organocatalzyed Michael addition reaction.

A general mechanism for asymmetric organocatalyzed Michael addition reaction of nitroalkanes to conjugated aldehydes is described in Figure 3. Initially, the aldehyde **36** on reaction with TMS-prolinol generates an imine intermediate **I** which on addition of donor nitroalkane **39** forms enamine intermediate **II**. The intermediate **II** on hydrolysis forms the nitroaldehyde adduct **40** with simultaneous release of organocatalyst.

1.3.4 Application

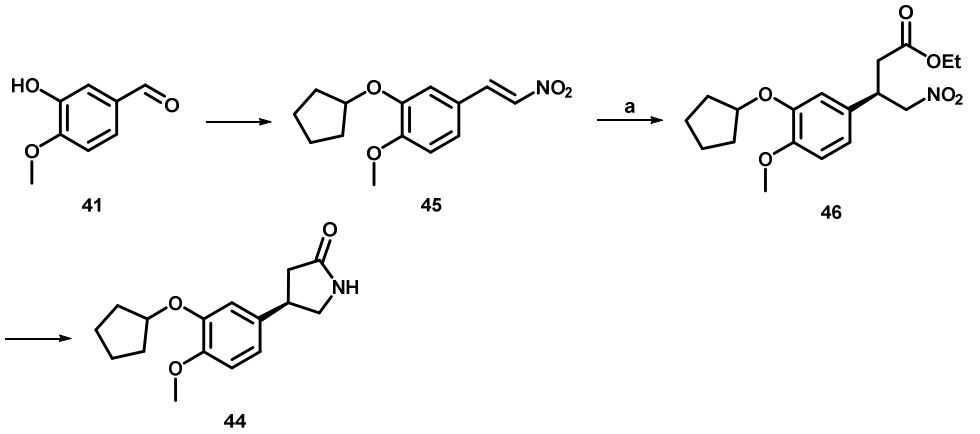
We have applied the organocatalzyed Michael addition reactions for the synthesis of (*R*)-rolipram **44** with two different stratergies. The synthesis of (*R*)-rolipram **44** started with commercially available isovanillin **41** which was converted into ester **42** *via* standard organic transformations (Scheme 12). The ester **42** on DIBAL-H reduction at -78 ^{o}C to *α,β*-unsaturated aldehyde and subsequent asymmetric Michael oxidative esterification with nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether (10 mol%) furnished the nitro aldehyde adduct which on *in situ* treatment with NBS/MeOH

furnished the γ-nitroester **43** in 78% yield which on further functional group manipulations furnished (*R*)-rolipram **44**.



Scheme 12. *Reagents and conditions*: (a) i) DIBAL-H, CH_2Cl_2, -78 ^oC, 1 h; ii) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, benzoic acid, MeOH, 16 h, rt; iii) NBS, 16 h, 4 ^oC, 78% (over three steps).

In another approach, isovanillin **41** was converted into nitro-olefin **45** *via* standard organic transformations (Scheme 13). The olefin **45** on asymmetric Michael addition reaction with acetaldehyde in the presence of catalyst (*R*)-diphenylprolinol silyl ether (10 mol%) in a sealed tube afforded the nitroaldehyde adduct, which on spontaneous oxidation with oxone and subsequent esterification using TMSCl/EtOH successfully furnished the ester derivative **46** in 85% yield which on further functional group manipulations furnished (*R*)-rolipram **44**.

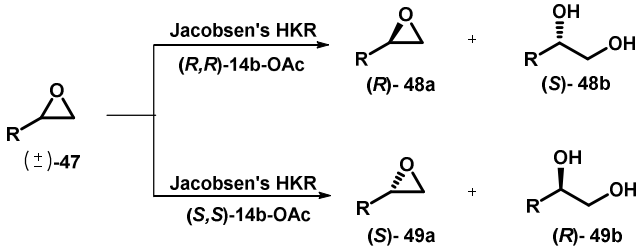


Scheme 13. *Reagents and conditions*: (a) i) acetaldehyde, (*R*)-diphenylprolinolsilyl ether, 1,4-dioxane, 4 ^oC to rt, 18 h; ii) oxone, DMF, rt, 12 h; iii) TMSCl, EtOH, rt, 12 h, 85% (over three steps).

1.4 Jacobsen's Hydrolytic Kinetic Resolution (HKR)

1.4.1 Introduction

Enantiomerically pure epoxides are extremely valuable chemical compounds due to controllable but high reactivity of epoxides coupled with the vast array of reactions they can undergo with retention of stereochemical integrity. One can envision a number of direct routes to asymmetric epoxides. Jacobsen's HKR has become one of rapid adoption in asymmetric catalytic reaction as the method of choice in organic chemistry with an impressive number of its applications in total synthesis of biologically active compounds and natural products documented in the literature.[19] The enantiopure terminal epoxides are versatile building blocks in organic synthesis, but no general and practical method was available for their synthesis in enantiomerically pure form. In 1997, Jacobsen's HKR has been emerged as a powerful tool for the preparation both terminal epoxides and their corresponding diols in enantioenriched form.[20] Racemic epoxides **47** were converted into chiral epoxides **48a** and **49a** along with their corresponding chiral 1,2-diols **48b** and **49b** in high enantiomeric excess using Jacobsen (salen) Co complex **50** (Scheme 14).



Scheme 14. Jacobsen's HKR of epoxide.

The Jacobsen's (salen) Co complex **50** (Figure 4) catalyzed the HKR of a variety of terminal epoxides in a highly efficient manner.[21] Therefore, the commercial

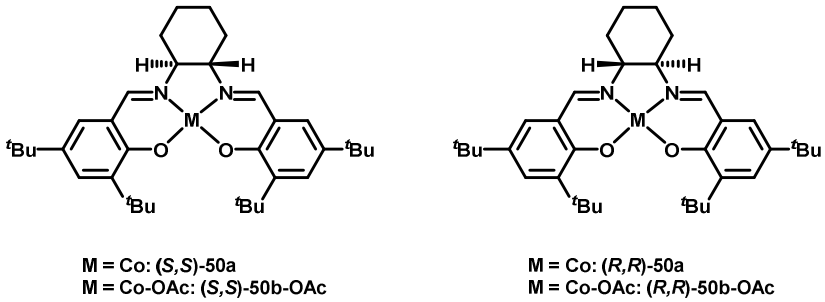


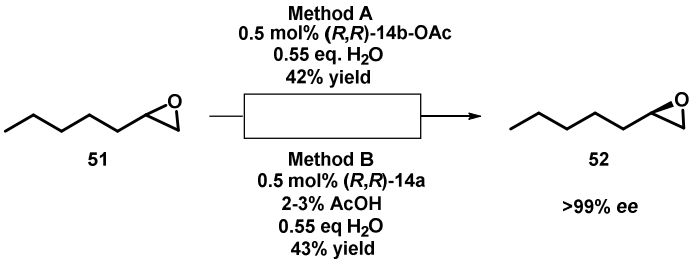
Figure 4. Structure of Jacobsen's catalysts.

synthesis of chiral epoxides such as propylene oxide, styrene oxide, glycidyl ether, butadiene monoepoxide and epichlorohydrin from racemic epoxides has been implemented successfully using Jacobsen's HKR by decreasing the cost of these chiral epoxides for suppliers.

1.4.2 Preparation of catalyst and general experimental conditions

Both the enantiomers of (salen)Co-II complex **50** are either commercially available or can be synthesized from the commercially available chiral ligands with $Co(OAc)_2$.[22] The Co(II) complex **50a** and **50b** (Figure 4) are inactive catalytically and requires the +3 oxidation state of cobalt prior to the HKR *via* one-electron oxidation, produced an anionic ligand (salen)Co-III complex which can be achieved easily by aerobic oxidation using a mild Bronsted acid. Only water was not found to mediate oxidation reaction, but a screen of additives revealed that acetic acid was effective and the corresponding Co(III) precatalyst-**50**-OAc (Figure 4) was found to be efficient in HKR reactions because of its easy preparation and reactivity. Thus, two mole of Co(II) pre-catalyst, two mole of acetic acid and a half mole of oxygen were converted into two mole of Co(III) catalyst and one mole of water.

However, two useful methods for the formation of complex-**50**-OAc (Scheme 15) have been developed. Method **A** constitutes the isolation of **50**.OAc as crude solid before the HKR. A solution of Co(II) complex **50** in toluene (ca. 1 M solution) was mixed with acetic acid (2 equivalents) and subjected to open air for 30 min at room temperature during which the color of the reaction mixture changed from orange to dark brown. The resulting crude was concentrated *in vacuo* to remove the volatile materials to afford the **50**.OAc as a brown solid which can be used without further purification. Method **B** constitutes the *in situ* preparation of **50**.OAc using HKR conditions by making a suspension of Co(II) complex **50** and epoxide or with epoxide/solvent followed by addition of AcOH under an aerobic conditions. The catalysts obtained by above methods **A** and **B** were then applied to a variety of epoxides. The catalyst synthesized by above two methods leads to approximately identical results when applied to 1-heptene oxide **50**. Catalyst prepared by method **B** is preferable in these situations as it avoids an extra solvent removal step. However with less reactive substrates, catalyst prepared by method **A** was found to be more effective. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method **B** after optimization of solvent and catalyst loading, then catalyst prepared by method **A** was employed as an alternative.



Scheme 15. Development of HKR methods

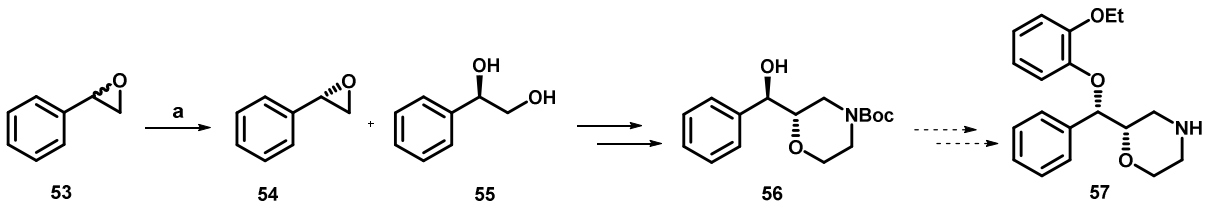
Aside from the procedure for the preparation of **50**.OAc, the other reaction parameters in Jacobsen's HKR for optimization were catalyst loading and choice of solvents for different type of substrates. In most of cases, 0.55 equivalent of H_2O relative to racemic epoxide afforded the epoxide in >99% *ee*. The epoxides with less solubility in water could undergo resolution in high enantiomeric excess without the addition of solvent. While, the HKR of high lipophilic epoxides provides chiral epoxides in high *ee*'s using water miscible organic solvents such as tetrahydrofuran (THF), isopropyl alcohol (IPA), or hexane-1,2-diol.

Generally, 1.0 equivalent of solvent relative to racemate was found to be sufficient for Jacobsen's HKR to a variety of substrates. However, the catalyst loadings in the amount of 0.5 mol% or less relative to racemic epoxide were found to be effective for most of the substrates, but saturated sterically hindered or unsaturated epoxides generally required up to 2 mol% of catalyst for achieving the complete resolution. Initially, the reaction generally started at 0 ^oC followed by stirring at room temperature for 12-18 h.

Thus, the salient features of the HKR method include the following: applicability to a wide range of racemic terminal epoxides; the high availability of racemic terminal epoxides; most of which are quite inexpensive; access to highly enantio-enriched products in close to theoretical yields; the low catalyst loading (0.2-2 mol%) and recyclability of HKR catalysts at low cost; a scaleable and practical protocol; the use of water as the nucleophile for epoxide ring opening and the ease of Jacobsen's HKR[24] products separation due to large polarity and boiling point differences.

1.3.4 Application

We have applied the Jacobsen's HKR reaction for the synthesis of (*S*,*S*)-reboxetine **57** (Scheme 16). The synthesis started with commercially available recemic styrene oxide **53** which was subjected to Jacobsen's HKR in the presence of catalytic amount of (*S*,*S*)-(salen)-Co-(salen) complex to afford (*S*)-styrene oxide **54** 34% with 99.6% *ee* and (*R*)-styrene glycol **55** in 47% with 93.9% *ee*, respectively, which was further subjected to standard organic transformations to furnish intermediate **56**.

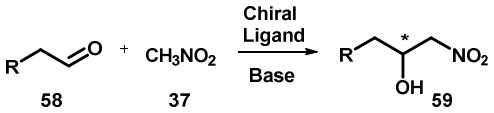


Scheme 16. *Reagents and conditions*: (a) (*S*,*S*)-Co(salen), *p*-nitrobenzoic acid, air, H_2O, **54** in 34% and **55** in 47%.

1.5 Asymmetric Henry reaction

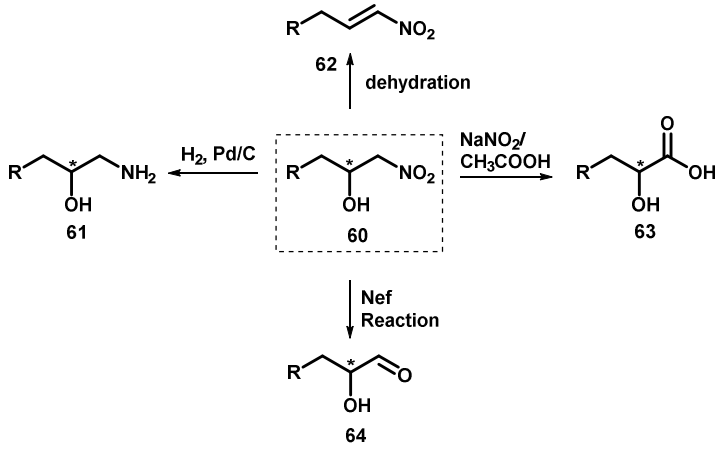
1.5.1 Introduction

The treatment of *in situ* generated nitronate species with the carbonyl compound, known as Henry (nitroaldol) reaction, is the most important and convenient carbon-carbon bond forming method in organic synthesis.[23] This method is a constructive and powerful tool for the synthesis of important *β*-nitroalcohols,[24] which facilitates the access to interesting and highly functionalized intermediates like nitroalkenes, nitroketones, *α,β*-unsaturated nitrocompounds, carbonyl compounds, 1,2-amino alcohols and α-hydroxy carboxylic acids.[25,26] In Henry (nitroaldol) reaction, commercially or readily available aldehydes **58** on reaction with nitromethane **37** gives the *β*-hydroxynitroalkane derivatives **59** in one step without any pretreatment (Scheme 17).[23,27]



Scheme 17. Asymmetric synthesis of *β*–hydroxynitroalkane derivatives.

Like all other catalytic asymmetric reactions, asymmetric Henry reaction has also been further divided into three main types of catalysts which include organocatalysts, metal complexes and biocatalysts. Among the three types of catalytic asymmetric Henry reaction, the metal complex catalyzed enantioslective Henry reaction is a powerful method in the synthesis of chiraly pure nitroalcohols. The resulting products, *β*-hydroxynitroalkane derivatives **60**, can be used further to many possible transformations of the nitro group such as to aminoalcohol derivative **61** by catalytic hydrogenation,[28] to alkene **62** by dehydration, to acid derivative **63** by oxidation,[29] to carbonyl compounds **64** by Nef reaction[30] and etc (Scheme 18).



Scheme 18. Selected synthetic utilities of chiral *β*-hydroxy nitroalkane derivatives

During recent years, the development of ligand based catalytic system towards the making of asymmetric protocols for Henry reaction has attracted many researchers as seen by many reports documented in the literature.[31]

In 1992, Sasai and co-workers reported the metal complex catalyzed asymmetric Henry reaction by using (*S*)-(2,2')-binaphthol in conjunction with lanthanum alkoxide,[32] various others complex catalytic systems have been successfully explored; for e.g. copper/bisoxazoline complexes,[33] and dinuclear zinc complex catalysts,[34] etc (Figure 5). In 1994, Najera and co-workers were first to published organocatalytic enantioselective example of Henry reaction by using enantiomerically pure guanidines as catalysts, affording enantiomeric excess upto 54%.[35] Also, several efforts have been aimed at making an asymmetric version of this catalytic process by using different metal ligands,[35] using organocatalysts,[37] optically active ligands, and bio-catalysts[38] from which most potential results have been obtained with copper-based catalytic complex systems. The design and synthesis of the novel ligands play an important role in the efficient metal-catalyzed asymmetric Henry reactions for the synthesis of optically active nitro-alcohol derivatives.

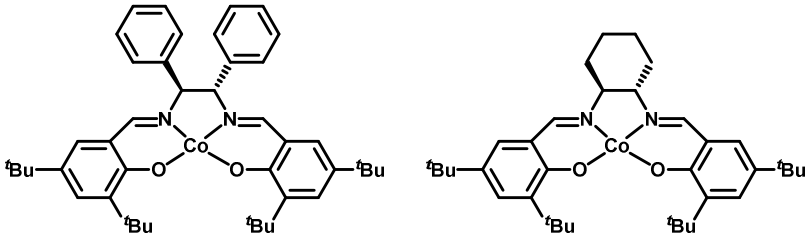
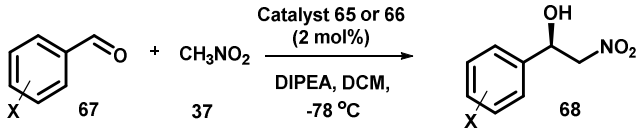


Figure 5. Some commercially available salen-cobalt complex

In a recent communication, it has been reported that asymmetric Henry reaction could be catalyzed by cobalt complexes of tertiary amine to afford *β*-hydroxynitroalkanes in high enantioselectivities with good yield.[31b] In another report, the Salen-cobalt complexes **65** and **66** which have been used previously for HKR were also found to be efficient catalysts for asymmetric Henry reactions using the amine as bases.

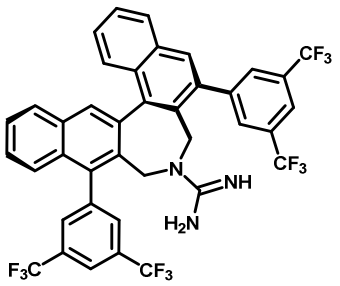


Scheme 19. Asymmetric synthesis of *β*–hydroxynitroalkane derivatives using salen ligands

Various derivatives aromatic aldehyde **67** was examined by using commercially available salen-cobalt complexs **65** and **66** for the asymmetric Henry reaction with nitromethane **37** using the DIPEA as base to furnish *β*-hydroxynitroalkane derivatives **68** in good yield upto

94% and excellent enantioselectivity (>98% *ee*) (Scheme 19). In 2008, Park and co-workers[39] developed a chiral bimetallic Co-(II)-salen catalyst assembled through hydrogen bonding, which results in effective rate acceleration and in 87% yield with excellent enantioselectivity (96% *ee*).

Terada and co-workers[40] synthesized a new axially chiral guanidine bases and applied it as efficient chiral Bronsted base catalyst in the Henry reaction between nitroalkanes and aldehydes (Figure 6). After an extensive screening of promising catalyst structures, catalyst **69**, having 3,5-bis(trifluoromethyl)phenyl groups introduced in the 3,3'-positions of the binaphthyl backbone, was found to be the best in terms of both catalytic activity and enantioselectivity.



69

Figure 6. Guanidine catalyst.

In addition, cinchona alkaloid derivatives have been also used as appropriate asymmetric catalysts in the Henry reaction (Figure 7). Hiemstra and co-workers[41] reported moderate results with the bifunctional structure **70**. Later on, it was found that the replacement of the phenol moiety in compound **70** with a better proton donor, such as a thiourea moiety, resulted in a more effective catalyst **71**.[42] With the use of this modified organocatalyst, the direct enantioselective nitroaldol reaction of aromatic and heteroaromatic aldehydes with nitromethane results in very good yield and with improving enantioselectivities.

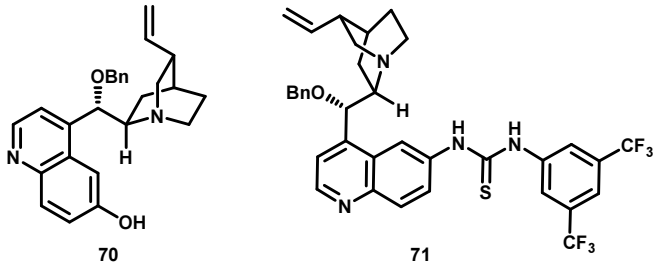
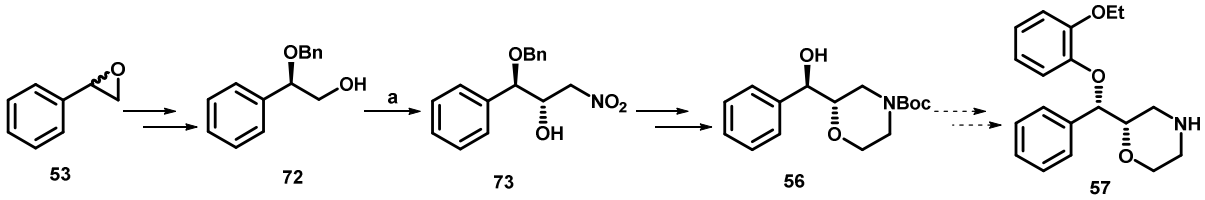


Figure 7. Cinchona alkaloid derivatives.

1.5.2 Application

We have applied the Henry (nitroaldol) reaction for the synthesis of (*S*,*S*)-reboxetine **57** (Scheme 20). The synthesis started with commercially available recemic styrene oxide **53** which was converted into alcohol **72** *via* number of organic transformations. The alcohol **72** on oxidation under Swern reaction conditions and subsequent treatment with nitomethane under Henry reaction conditions afforded the nitoalcohol **73** in 80% yield with 2:3 *syn*:*anti* diastereomeric ratio, which on further functional group manipulations furnished the intermediate **56**.



Scheme 20. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h; ii) CH_3NO_2, DIPEA, CH_3OH, rt, 1 h, 80%.

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CHAPTER 2

$InCl_3$ catalyzed diastereoselective approach for the syntheses of bisindole alkaloids flinderoles A-C and desmethylflinderole C

$InCl_3$ catalyzed diastereoselective approach for the syntheses of bisindole alkaloids flinderoles A-C and desmethylflinderole C

2.1 Introduction:

The Malaria is the most common, widespread life-threatening parasitic infectious disease in the tropic and sub-tropic reasons of the worlds today.[1] According to WHO report, there were an estimated 214 million new cases of malaria and approximately half million deaths in 2015 alone caused by *P. falciparum* and *P. vivax.* Natural products chloroquine, artemisinin and other frontline drugs for the treatment of malaria are becoming increasingly ineffective due to the development of drug resistance and therefore, the search for new antimalarial drugs is again of even greater significance. Bis-indole alkaloids flinderoles A-C (**11-13**) were isolated from the plant genus *Flindersia* along with the previously known natural products borrerine **74**, borreverine **75**, isoborreverine **76**, and dimethylisoborreverine **77** (Figure 8).[2] The flinderoles A-C (**11-13**) alkaloids have been shown to possess significant selective growth inhibition against Dd2 (chloroquine-resistant) *P. falciparum* and exhibit antimalarial activity with IC_{50} values between 0.15-1.42 μM.[2] These alkaloids are fast acting and are currently the drugs of choice for the treatment of malaria through a different mechanism of action than that of chloroquine and other drugs by interrupting the parasitic hemoglobin.[3] The flinderoles A-C (**11-13**) and desmethylflinderole C **14** have been synthetic targets of considerable interest due to its high antimalarial activity and with an array of functionalities.

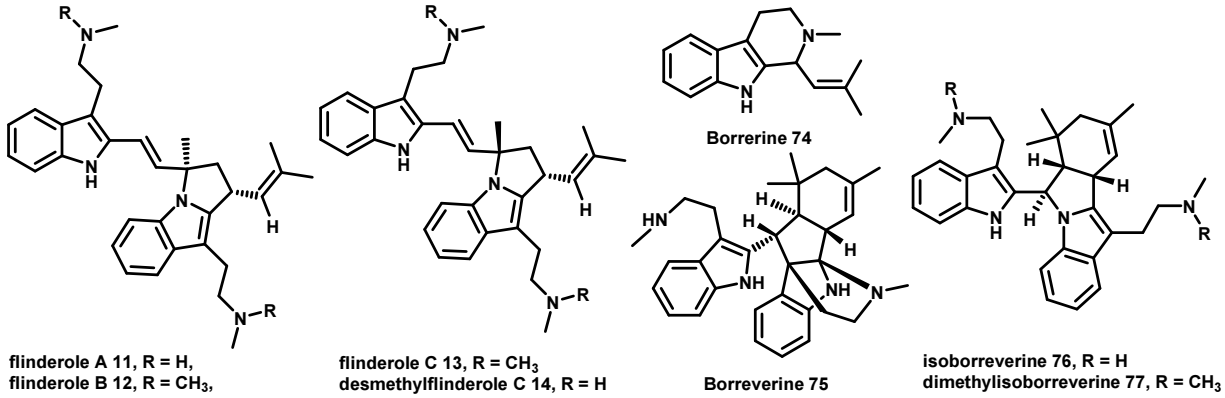


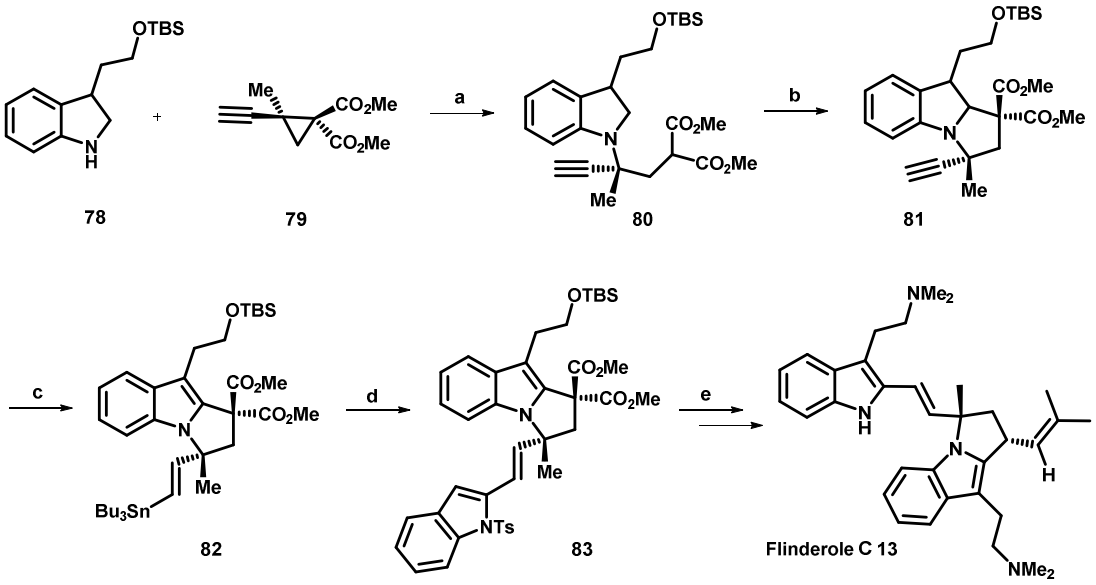
Figure 8. Structures of flinderole and borreverine alkaloids.

2.2 Review of Literature:

Various elegant syntheses for the flinderole alkaloids (**11**-**14**) have been documented in the literature.[4] Some of the recent syntheses of flindersial alkaloids (**11**-**14**) are described below.

Kerr, M. A. *et al.* (2016)[4a]

M. A. Kerr and co-workers reported the formal synthesis of flinderole C **13** using lewis acid mediated nucleophilic ring opening of cyclopropane **79** by indoline **78** as key step (Scheme 21). The acetylenic cyclopropane derivative **79** on treatment with *O*-TBS protected indoline **78** in the presence of $Sc(OTf)_3$ (10 mol%), as lewis acid catalyst afforded the indoline derivative **80** in 80% yield with 1:1 diaseteromeric ratio. The compound **80** underwent oxidative radical cyclization on treatment with $Mn(OAc)_3$ to furnish the pyrroloindoles **81** in 80% yield.

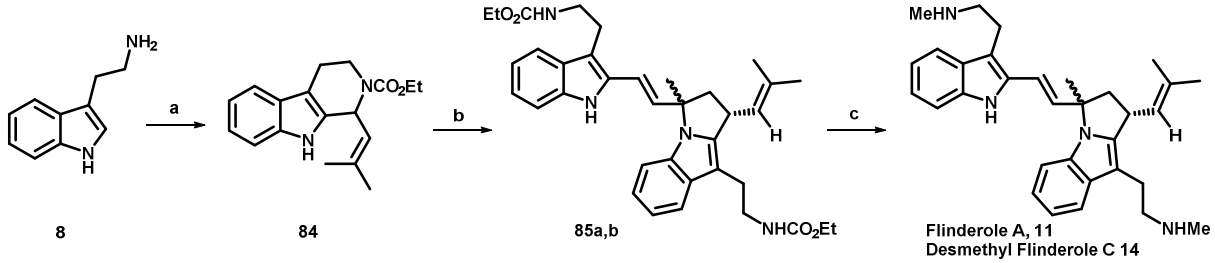


Scheme 21. *Reagents and conditions*: (a) $Sc(OTf)_3$ (10 mol%), toluene, 100 ^oC, 1.5 h, 80%; (b) $Mn(OAc)_3$, MeOH, 70 ^oC, 3 h, 80%; (c) $PdCl_2(PPh_3)_2$ (5 mol%), $HSnBu_3$, THF, 0 ^oC-rt, 30 min, 85%; (d) $Pd(PPh_3)_4$ (5 mol%), toluene, 110 ^oC, 24 h, 58%; (e) ref 4a.

Next, for the synthesis of flinderole moiety, the compound **81** on exposure to $HSnBu_3$ in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) afforded the vinylstannane **82** in 85% yield. The stannane derivative **82** under Stille coupling conditions with *N*-tosylated-2-bromoindole furnished the bisindole derivative **83** in 58% yield. With compound **83** in hand, a series of functional group manipulations were performed to afford the target molecule **13**.

Dethe, D. H. *et al.* (2014)[4b]

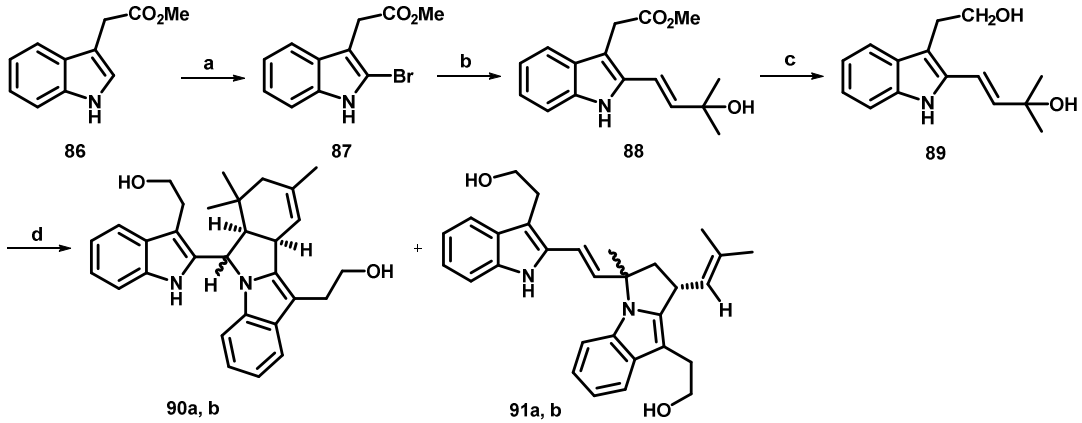
D. H. Dethe and co-workers reported the total synthesis of flinderole A **11** and desmethyl flinderole C **14** starting from commercially available tryptamine **8** in three steps (Scheme 22). The tryptamine **8** on coupling with 3-methylbut-2-enal followed by treatment with methyl chloro formate furnished the derivative **84** in 87% yield. The olefin **84** on treatment with TFA furnished the derivatives **85a**,**b** in 86% combined yield with 4:5 diastereomeric ratio. Then, LAH reduction of compound **85a**,**b** afforded the target compound flinderole A **11** and desmethyl flinderole C **14** in 83% and 86% yield, respectively.



Scheme 22. *Reagents and conditions*: (a) i) 3-methylbut-2-enal, CH_2Cl_2, 4 Å sieves, 22 ^oC, 16 h; ii) methyl chloro formate, pyridine, 0 ^oC-rt, 5 h 87% (over two steps); (b) TFA, CH_2Cl_2, rt, 30 min, 86%; (c) LAH, THF, rt, 3 h, 83% for **11** and 86% for **14**.

Dethe, D. H. *et al.* (2013)[4c]

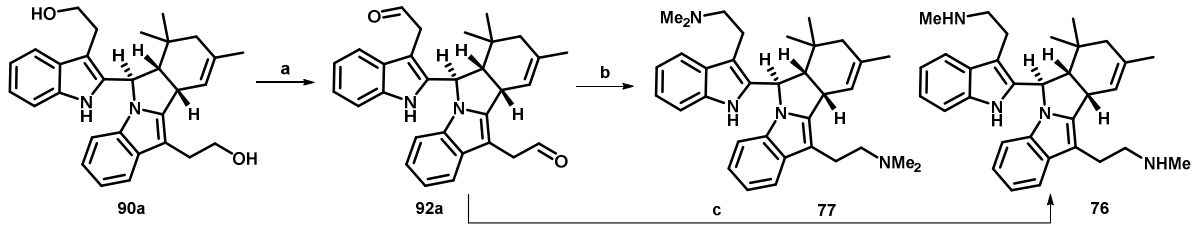
D. H. Dethe and co-workers reported the biomimetic total syntheses of borreverine and flinderole alkaloids (Scheme 23). The indole derivative **86** on bromination with NBS at C2



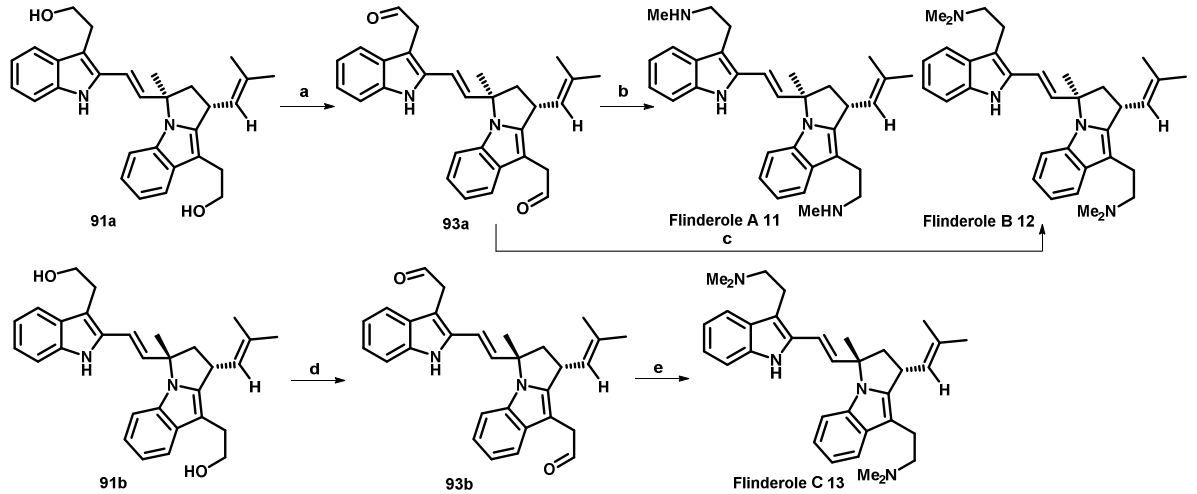
Scheme 23. *Reagents and conditions*: (a) NBS, CCl_4, reflux, 1 h, 67%; (b) 2-methyl-4-(tributyl-

stannyl)but-3-en-2-ol, $Pd(OAc)_2$, Bu_4NCl, DMF, reflux, 3 h, 77%; (c) $LiAlH_4$, Et_2O, 0 °C to rt, 3 h, 75%; (d) $BF_3 \cdot OEt_2$ (10 mol%), CH_2Cl_2, rt, 15 min, 82%.

position furnished the derivative **87** which on stille coupling with 2-methyl-4-(tributylstannyl)but-3-en-2-ol afforded the alcohol derivative **88** in 77% yield. The LAH reduction of ester **88** afforded the tertiary alcohol derivative **89** which on lewis acid mediated dimerization furnished the cyclized products **90a**,**b** and **91a**,**b** with a combined yield of 82% in 5:1 and 4:1 diastereomeric ratios, respectively. The alcohol **90a** on oxidation with IBX afforded the aldehyde **92a** which on subsequent reductive amination with $NHMe_2$ furnished dimethylisoborreverine **77** in 82% yield (Scheme 24). And reductive amination of above synthesized aldehyde in presence of $Fe(OTf)_3$ afforded the isoborreverine **76** in 89% yield.



Scheme 24. *Reagents and conditions*: (a) IBX, EtOAc, reflux, 1 h, 80%; (b) $NHMe_2$, $NaCNBH_3$,AcOH (cat.), MeOH, rt, 12 h, 82%; (c) NH_2Me, $NaBH_4$, $Fe(OTf)_3$, CH_2Cl_2, rt, 30 min, 89%.



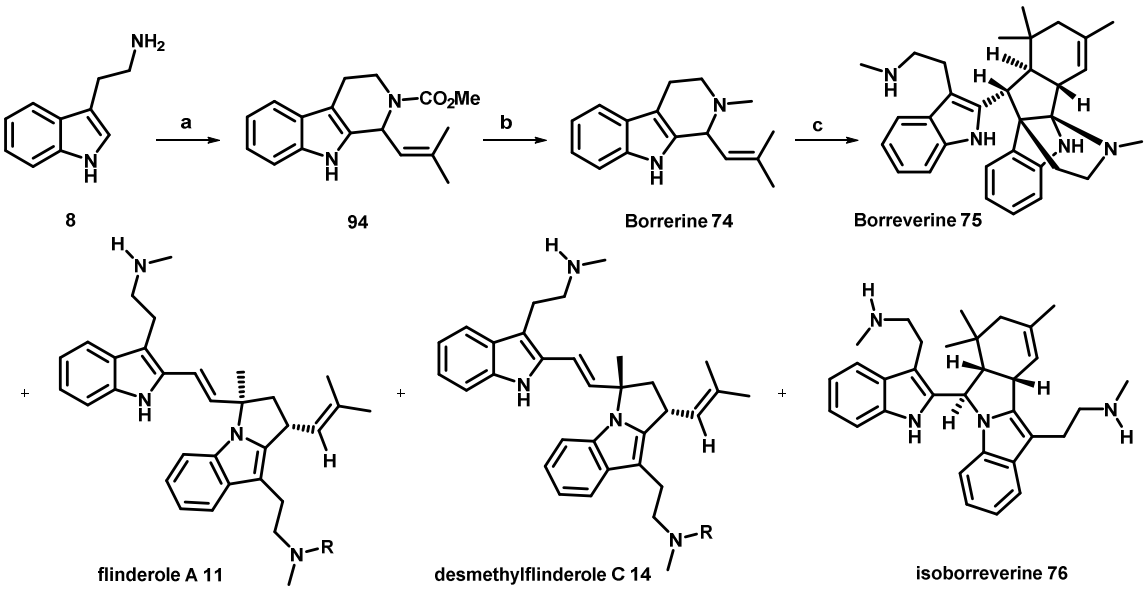
Scheme 25. *Reagents and conditions*: (a) IBX, EtOAc, reflux, 1 h, 74%; (b) NH_2Me, $NaBH_4$, $Fe(OTf)_3$, CH_2Cl_2, rt, 30 min, 75%; (c) $NHMe_2$, $NaCNBH_3$, AcOH (cat.), MeOH, rt, 12 h, 85%;

(d) IBX, EtOAc, reflux, 1 h, 81%; (e) $NHMe_2$, $NaCNBH_3$, AcOH (cat.), MeOH, rt, 12 h, 81%.

By following an analogous series of reactions flinderole A **11**, B **12** and C **13** were afforded in 17%, 85%, 81% yield, respectively (Scheme 25).

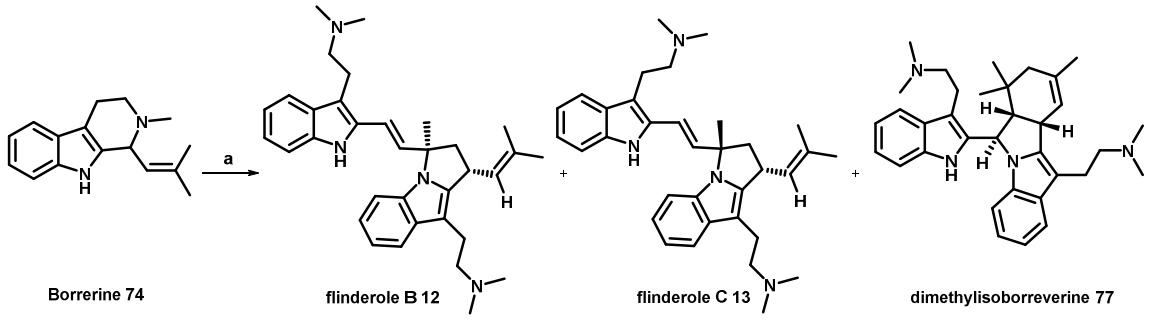
May, J. A. *et al.* (2012)[4d]

J. A. May and co-workers reported the total synthesis of flinderole A **11**, B **12**, and C **13**, desmethylflinderole C **14**, borreverine **75**, isoborreverine **76**, and dimethylisoborreverine **77** employed the acid-promoted dimerization of the natural product borrerine starting from commertially available tryptamine **8** (Scheme 26).



Scheme 26. *Reagents and conditions*: (a) i) 3-methylbut-2-enal, CH_2Cl_2, 4 Å sieves, 22 ^oC, 16 h; ii) methyl chloro formate, pyridine, 0 ^oC to rt, 5 h, 87% (over two steps); (b) LAH, THF, reflux, 2 h, 88%; (c) different conditions of acid, solvent, time, temperature.

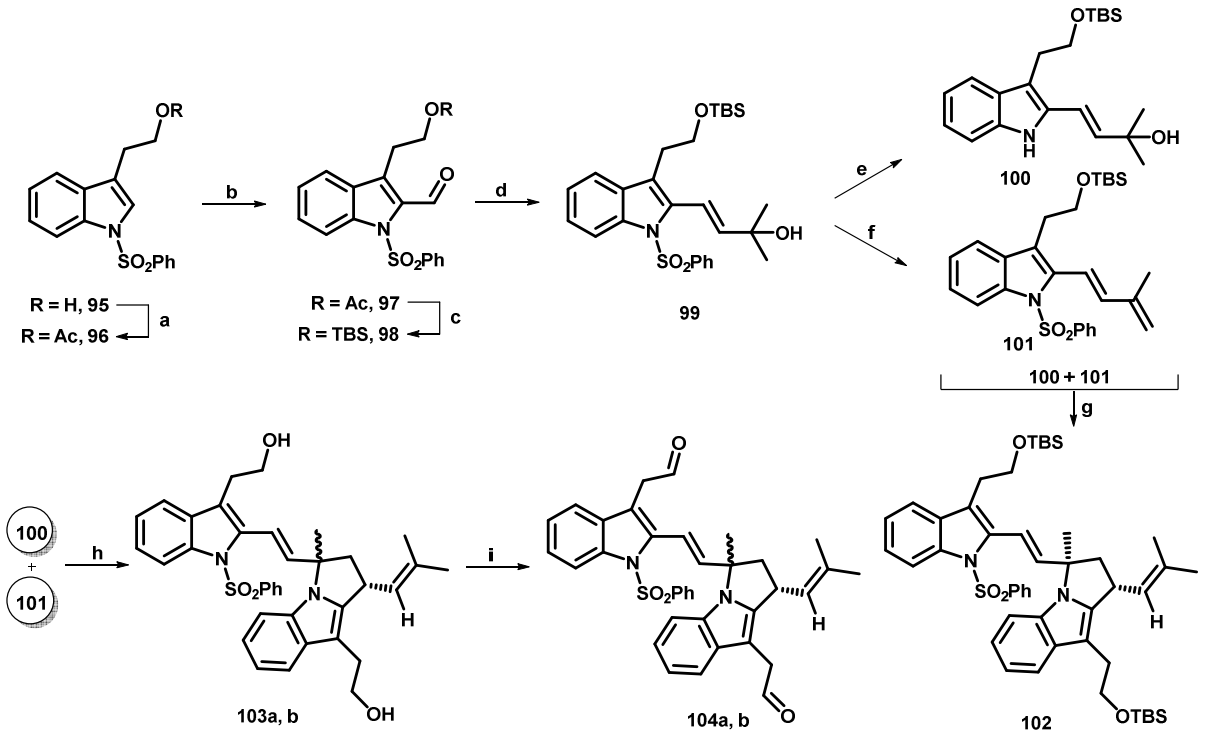
The reaction of tryptamine **8** with 3-methylbut-2-enal followed by treatment with methyl chloroformate furnished the amine derivative **94** which on LAH reduction afforded the borrerine **74** in 88% yield. The synthetic borrerine **74** on acid mediated dimerization under different conditions furnished the borreverine **75**, flinderoles A **11**, desmethylflinderole C **14** and isoborreverine **76** (Scheme 27). The treatment of borrerine **74** with methyl triflate in CH_2Cl_2 followed by reaction with TFA furnished the flinderole B **12** in 21%, flinderole C **13** in 19%, and dimethylisoborreverine **77** in 30% yield.



Scheme 27. *Reagents and conditions*: (a) i) MeOTf, CH_2Cl_2, 0 ^oC; ii) TFA, 0 ^oC-rt, 20 min (21% for **12**, 19% for **13**, 30% for **77**).

Dethe, D. H. *et al.* (2011)[4e]

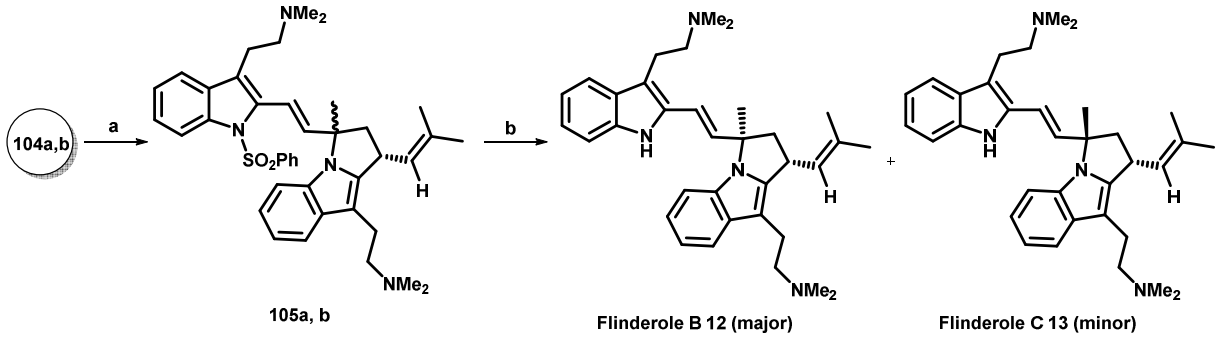
D. H. Dethe and co-workers in first report described the total synthesis of isomeric flinderoles B **12** and C **13** from protected tryptophol **95** as starting material (Scheme 28). The hydroxyl group of tryptophol **95** was acylated with acetic anhydride to synthesize compound **96** which on subsequent formylation with dichloromethyl methyl ether and stannic chloride afforded the aldehyde derivative **97** in 80% yield.



Scheme 28. *Reagents and conditions*: (a) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 6 h, 91%; (b) dichloromethyl methyl ether, stannic chloride, CH_2Cl_2, -78 to -10 ^oC, 1 h, 80%; (c) i) LiOH, H_2O, THF, rt, 3 h; ii) TBSCl, imidazole, CH_2Cl_2, 0 ^oC to rt, 6 h, 81% (over two steps); (d) i)

$Ph_3P{=}CHCO_2Et$,CH_2Cl_2, rt, 6 h, 91%; ii) MeI, Mg turnings, I_2 (cat.), Et_2O, 0 ^oC to rt, 2 h, 89%; (e) Na/Hg, Na_2HPO_4, MeOH, rt, 1 h, 97%; (f) MsCl, Et_3N, THF, 0 ^oC to reflux, 2 h, 81%; (g) $Cu(OTf)_2$, CH_2Cl_2, rt, 30 min, 62%; (h) $BF_3.OEt_2$, CH_2Cl_2, rt, 30 min, 78%; (i) IBX, EtOAc, reflux, 1 h, 84%.

The compound **97** on hydrolysis of acetate group and *O*-TBS protection furnished the compound **98** in 81% yield. The aldehyde **98** on 2C Wittig olefination and subsequent Grignard reaction with methylmagnesium iodide afforded the alcohol derivative **99** in good yield. The deprotection of phenylsulphonyl group of compound **99** with Na/Mg gave the alcohol intermediate **100** in 97% yield. The alcohol **99** was transformed into its mesylate followed by elimination reaction to afford the olefin **101**. The treatment of compound **100** and **101** with $Cu(OTf)_2$ afforded the TBS protected adduct **102**, whereas intermediate **100** and **101** on BF_3. OEt_2 mediated cyclization furnished the alcohol **103a** and **103b**.



Scheme 29. *Reagents and conditions*: (a) $NHMe_2$, $NaCNBH_3$, AcOH (cat.), MeOH, rt, 12 h, 91%; (b) Na/Hg, Na_2HPO_4, MeOH, rt, 1 h, 62% for **12**, 15% for **13**.

The mixture of alcohol **103a** and **103b** on oxidation with IBX furnished the aldehyde **104a,b** in 4:1 diastereomeric ratio, which on reductive amination with dimethylamine afforded the mixture of amines **105a** and **105b** in 91% combined yield (Scheme 29). Finally, deprotection of phenylsulphonyl group of **105a** and **105b** furnished the flinderoles B **12** and C **13** in 62% and 15% yield, respectively.

2.2.1 Table 1. Comparison with the previous reported syntheses of flindersial alkaloids.

Sr. No.	Syntheses	Key step	Overall yield	No. of steps
1.	***ChemistrySelect* 2016, *1*, 4286** (flinderoles A, B, and C, desmethylflinderole C)	**$InCl_3$ mediated [3 + 2] cycloaddition**	**51%**	**Three**
2.	*Org. Lett.* **2016**, *18*, 2142 (flinderole C)	lewis acid mediated nucleophilic ring opening of cyclopropane by indoline	-	formal synthesis
3.	*Org. Lett.* **2014**, *16*, 2764 (flinderoles A, desmethylflinderole C borreverine, caulindoles)	lewis acid mediated dimerization	62%	three
4.	*J. Org. Chem.* **2013**, *78*, 10106 (flinderoles A, B, C, dimethylisoborreverine, isoborreverine)	[3 + 2] cycloaddition and Diels-Alder reaction	12%	six
5.	*J. Am. Chem. Soc.* **2012**, *134*, 6936 (flinderoles A, B, C, desmethylflinderole C, isoborreverine, and dimethylisoborreverine)	acid-promoted dimerization	-	four
6.	*J. Am. Chem. Soc.* **2011**, *133*, 2864 (flinderole B and C)	$BF_3.OEt_2$ mediated [3 + 2] cycloaddition reaction	17%	eleven

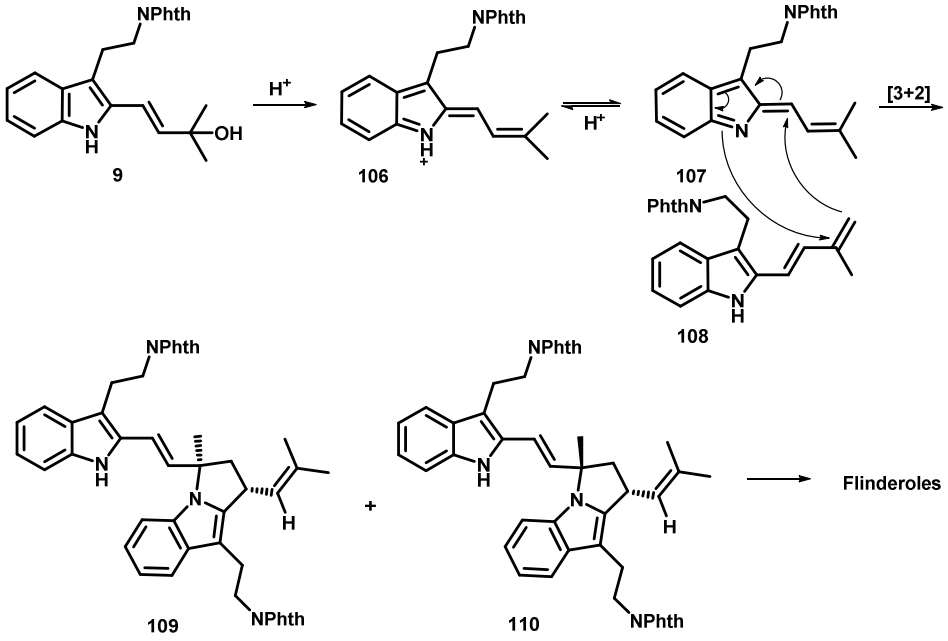
2.3 Present Work:

***Objective*:**

As part of our research programme aimed at developing new synthetic approaches for the synthesis of naturally occurring compounds, we became interested in developing a new, general and highly efficient synthetic approach for the synthesis of pyrrolo[1,2-α]indoles framework and its application to the total syntheses of flinderoles A-C (**11-13**) and desmethylflinderole C **14** employing [3+2] cycloaddition and Heck coupling reactions as a key steps.

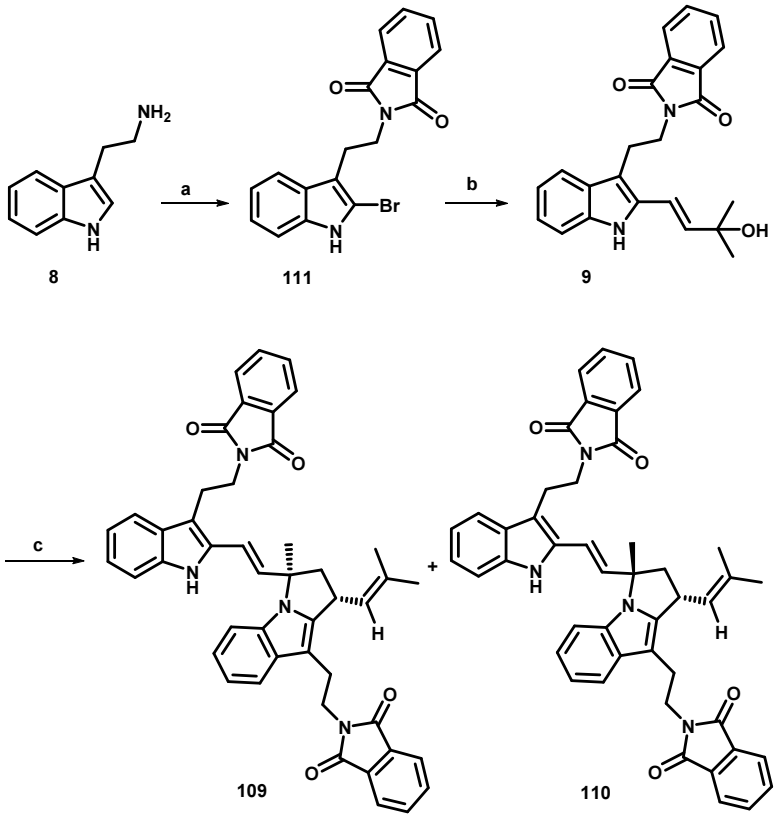
2.4 Results and Discussions:

Our hypothesis for the biosynthetic pathway began with that the flindersial alkaloids have tryptamine-isoprene based rearranged skeleton and therefore, flinderoles could be derived from monomeric tryptamine diene **1087** as a possible precursor.[4d] The flinderole frameworks could arise from dimerization reaction of tryptamine diene **106** or intermediate **107** *via* [3+2] cycloaddition reaction (Scheme 30).



Scheme 30. Proposed biosynthetic approach for the flinderoles.

As outlined in Scheme 31, the synthesis of flinderole frameworks commenced with readily available bromo compound **111**[5] which was prepared *via* a two step sequence of protection of tryptamine **8** as a phthalimide, and subsequent selective bromination at the C2 position of indole ring using pyridinium hydrogen perbromide. The bromo indole derivative **111** was subjected to a crucial intermolecular Heck coupling reaction and a number of reagent combinations (Table 1) were tested to optimize the yield. We were indeed happy to observed that tri-(*o*-tolyl)phosphine/$Pd(OAc)_2$/Et_3N combination in acetonitrile (Table 1, entry 5) afforded alcohol derivative **9** as a isolable product in 75% yield.[6] The IR spectrum of **9** showed hydroxyl absorption at 3383 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.72 (doublet, one proton) and δ 6.11 (doublet, one proton) with the coupling constants J = 16.0 and 16.5 Hz, respectively indicating *trans*-olefin.



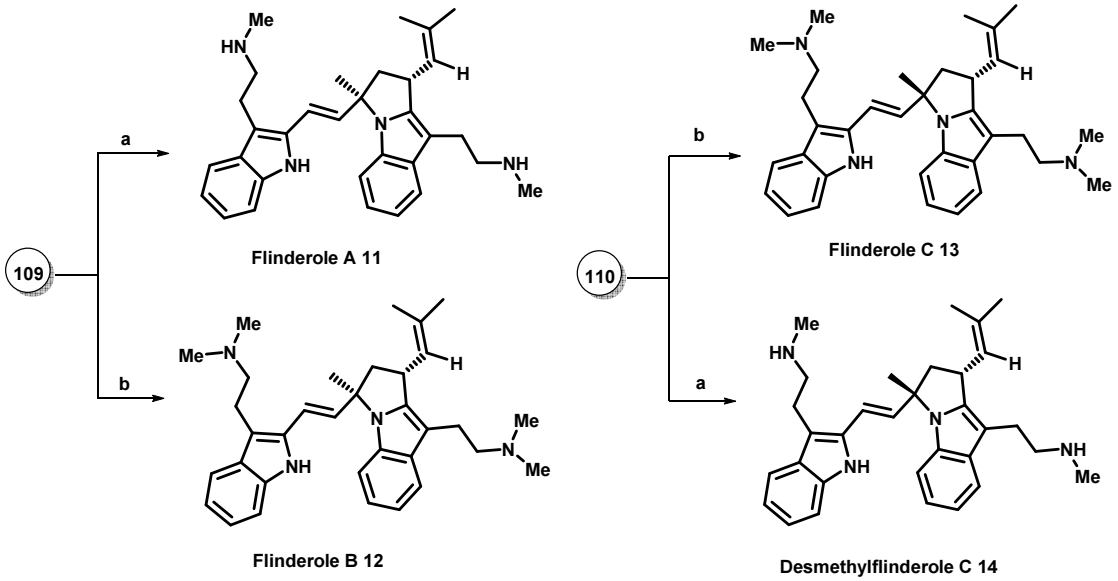
Scheme 31. *Reagents and conditions*: (a) i) phthalic anhydride, Et_3N, toluene, reflux, 12 h; ii) pyr-HBr-Br_2, $CHCl_3$:THF (1:1), -10 °C, 97% (over two steps); (b) 2-methyl-3-buten-2-ol, $Pd(OAc)_2$, tri-(*o*-tolyl)phosphine, Et_3N, sealed tube, 100 ^oC, 5 h, 75%; (c) $InCl_3$ (20 mol%), toluene, 0 °C-rt, 4 h, 81%.

Our next aim was to carry out cycloaddition reaction of alcohol derivative **9**. Towards this end, alcohol **9** was subjected to $InCl_3$ catalyzed [3+2] cycloaddition reaction[7] in toluene which furnished flinderole frameworks **109** and **110** with 81% yield in 3:2 diastereomeric ratios and were separated by careful silica gel column chromatography. The ^1H NMR spectrum of **109** gave olefin protons at 6.25 (doublet, one proton), 6.13 (doublet, one proton), with the coupling constant J = 16.0, 16.0 Hz respectively, indicating *trans*-olefin. The ^1H NMR spectrum of **110** gave olefin protons at 6.80 (doublet, one proton), 6.31 (doublet, one proton) with the coupling constant J = 16.5, 16.4 Hz respectively, indicating *trans*-olefin.

Table 2. Optimization of intermolecular Heck crosscoupling reaction.

Sr. No.	Reagents	Conditions	Time (h)	Yield (%)
1.	$Pd(PPh_3)_2Cl_2$, K_2CO_3, DMF:H_2O	90 ^oC	2	No discernible product
2.	$Pd(OAc)_2$, K_2CO_3, Toluene	Reflux	12	No discernible product
3.	$Pd(OAc)_2$, K_2CO_3, DMF:H_2O	90 ^oC	2	No discernible product
4.	$Pd(PPh_3)_4$, Cy_2NMe, Toluene	95 ^oC	48	Trace[a]
5.	Tri-(o-tolyl)phos-phine/ $Pd(OAc)_2$, Et_3N, acetonitrile	100 ^oC	5	75[a]

[a]Product identified by mass spectroscopy.



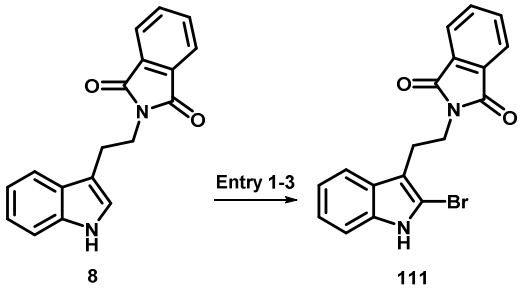
Scheme 32: *Reagents and conditions*: (a) i) $NH_2NH_2.H_2O$, *i*-PrOH, rt, 4 h; ii) HCHO, $Na(CN)BH_3$, MeOH, 0 ^oC-rt, 5 min, (88% for **11** and 85% for **14**, over two steps); (b) i) $NH_2NH_2.H_2O$, *i*-PrOH, 0 ^oC-rt, 4 h; ii) HCHO, $Na(CN)BH_3$, CH_3CN, acetic acid, 0 ^oC-rt, 10 h, (82% for **12** and 80% for **13**, over two steps).

The cleavage of phthalimide group of compound **109** with hydrazine monohydrate afforded the bis-amine intermediate which on subsequent reductive amination with formaldehyde in presence of $Na(CN)BH_3$/MeOH at 0 ^oC-rt furnished the target compound flinderole A **11** in excellent yield (Scheme 32).

However, reductive amination of the bis-amine intermediate derived from compound **109** with formaldehyde in presence of $Na(CN)BH_3$/acetonitrile and acetic acid at 0 ^oC-rt afforded the flinderole B **12** in 82% yield. Flinderole C **13** and desmethylflinderole C **14** were synthesized from bis-amine intermediate derived from compound **110** following an analogous series of reactions as shown in Scheme 32. The physical and spectroscopic data of flinderoles A-C (**11-13**) and desmethylflinderole C **14** were in full agreement with the literature data.[4]

2.5 Research and Development (R & D):

2.5.1 Table 3. Optimization of bromination at the C2 position of indole ring.

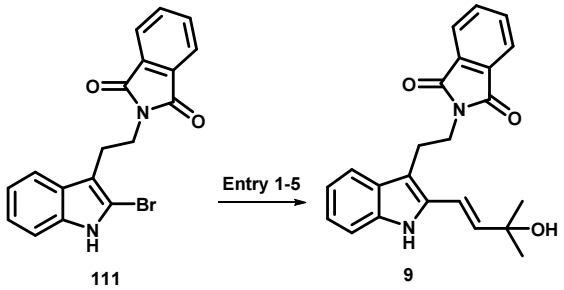


Entry	Reagents	Solvent	Temp. (^oC)	Time (h)	Result (% yield)
1	NBS	CCl_4	0 ^oC to rt	24	10
2	NBS	CCl_4	Reflux	30	20
3	pyridinium hydrogen perbromide (pyr-HBr-Br_2)	THF:$CHCl_3$	-10 ^oC	3	96

NBS = *N*-bromo succinimide, CCl_4 = Carbon tetrachloride

For the synthesis of bromo phthaloyl derivative **111**, we have optimized a few reaction conditions as described in table 3. First, indole derivative **8** on treatment with NBS in CCl_4 at 0 ^oC to rt for 24 h gave the compound **111** in only 10% yield (Table 3, entry 1). Next, indole derivative **8** on treatment with NBS in CCl_4 under reflux conditions for 30 h provided the compound **111** in only 20% yield (Table 3, entry 2). Finally, treatment of **8** with pyridinium hydrogen perbromide in THF:$CHCl_3$ at -10 ^oC for 3 h gave the desired compound **111** in good yield of 96% (Table 3, entry 3).

2.5.2 Table 4. Optimization for intermolecular Heck cross coupling reaction.



111 9

Entry	Reagents	Solvent	Temp. (^{o}C)	Time (h)	Result (% yield)
1	$Pd(PPh_3)_2Cl_2$, K_2CO_3	DMF:H_2O	90 ^{o}C	12	No discernible product
2	$Pd(OAc)_2$, K_2CO_3	Toluene	Reflux	20	No discernible product
3	$Pd(OAc)_2$, K_2CO_3	DMF:H_2O	90 ^{o}C	36	No discernible product
4	$Pd(PPh_3)_4$, Cy_2NMe	Toluene	95 ^{o}C	48	Trace
5	Tri-(*o*-tolyl)phos-phine/ $Pd(OAc)_2$, Et_3N	acetonitrile	100 ^{o}C	5	75

For the synthesis of tertiary alcohol derivative **9**, we have optimized few reaction conditions as described in table 4. Firstly, bromo indole derivative **111** on treatment with $Pd(PPh_3)_2Cl_2/K_2CO_3$ in DMF:H_2O at 90 ^{o}C for 12 h does not proceed (Table 4, entry 1). The bromo indole derivative **111** on treatment with $Pd(OAc)_2/K_2CO_3$ in toluene at reflux for 20 h was not fruitful (Table 4, entry 2). For the next trial by changing the solvent to DMF:H_2O was not successful (Table 4, entry 3). Then, changing the reagent to $Pd(PPh_3)_4/Cy_2NMe$ in toluene at 95 ^{o}C for 48 h, there was a trace of desired compound **9** (Table 4, entry 4). Finally, treatment of **111** with tri-(*o*-tolyl)phos-phine/ $Pd(OAc)_2/Et_3N$ in acetonitile at 100 ^{o}C for 5 h gave the desired tertiary alcohol **9** in 75% yield (Table 4, entry 5).

2.6 Conclusion:

In conclusion, a short and expeditious biomimetic divergent approach for the synthesis of pyrrolo[1,2-*α*]indoles framework and its application to the total syntheses of flindersial alkaloids has been developed employing the Heck reaction and [3+2] cycloaddition reaction as the key steps. As compared to the previous reported synthesis, we have achieved flinderoles A-C (**11**-**13**) and desmethylflinderole C **14** *via* $InCl_3$ mediated [3+2] cycloaddition as the key step. For the bromination at the C2 position of indole ring, pyridinium hydrogen perbromide was found to be the best reagent. Whereas, for the intermolecular Heck cross coupling reaction, only the combination of tri-(*o*-tolyl)phosphine/$Pd(OAc)_2$/Et_3N was the successful attempt. As compared to previous strategies, we have achieved the target compound in less number of steps with 51% overall yield starting from readily available phthalimide protected bromo-indole **111**. Moreover, the synthetic strategy described has significant potential for the syntheses of other analogues of flindersial alkaloids and isoborreverine with interesting pharmacological activities.

2.7. Experimental Section

2.7.1 General Experimental Details

All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. All the reagents were added either *via* syringe or cannula. Each distillation was performed under an inert atmosphere. All reactions have their respective temperatures within their respective schemes. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.

Chromatography

All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, then were stained by ninhydrin or anisaldehyde in ethanol or $KMnO_4$ in water as development reagents followed by brief heating with a heat gun. Column chromatography were performed on silica gel (60-120 and 100-200 mesh) using a mixture of ethyl acetate/hexane and methanol/ dichloromethane as eluent.

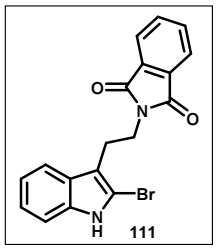
Reagents and solvents

Solvents were obtained commercially and were used without purification unless otherwise noted in experimentals. Distilled water was used for every aqueous reaction, work-up procedure, and in the preparation of every aqueous solution used in the work-up. For reaction solvent, CH_2Cl_2 was distilled from CaH_2, and THF was distilled under N_2 from sodium benzophenone ketyl, all immediately prior to use.

Spectroscopic Measurements

^1H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units (δ) downfield from TMS. Coupling constants, *J*, are listed in hertz (Hz). High resolution mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

2-(2-(2-Bromo-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione, 111[5]



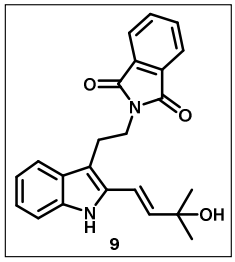
111

To a stirred solution of tryptamine **8** (650 mg, 4.16 mmol) in toluene (150 mL) was added Et_3N (0.86 mL, 6.24 mmol) followed by phthalic anhydride (0.73 g, 4.99 mmol) and refluxed for 12 h. Evaporation of the solvent under reduced pressure afforded the crude product which was used as such for the next step without further purification. [R_f = 0.50, ethyl acetate/hexane 1:1 v/v]; mp = 164-166 ^oC; IR (CH_2Cl_2): ν 3381, 2360, 1769, 1707, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (br s, 1H), 7.83-7.79 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.70-7.65 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 6.8 Hz, 1H), 7.11 (t, *J* = 6.8 Hz, 1H), 7.07 (s, 1H), 4.00 (t, *J* = 7.8 Hz, 2H), 3.14 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 136.1, 133.8, 132.0, 127.3, 123.1, 122.0, 122.0, 119.4, 118.7, 112.2, 111.0, 38.4, 24.4.

The residue thus obtained above was dissolved in $CHCl_3$: THF (1:1, 20 mL) and treated with pyridinium bromide perbromide (1.49 g, 4.65 mmol) at -10 ^oC. After completion of the reaction as monitored by TLC, the reaction was warmed to room temperature, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was

washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography of the crude product using (ethyl acetate/hexane 1:7 v/v) as eluent furnished the bromo compound **111** (1.43 g, 97% over two steps) as a light yellow solid. [R_f = 0.57, ethyl acetate/hexane 2:3 v/v]; mp = 168-170 ^oC; IR (CH_2Cl_2): *v* 3340, 2360, 1770, 1705, 1395, 743 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) : δ 8.11 (br s, 1H), 7.82-7.78 (m, 2 H), 7.70-7.66 (m, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.13 (td, *J* = 0.9, 6.8 Hz, 1H), 7.07 (td, *J* = 0.9, 7.8 Hz, 1H), 3.94 (t, *J* = 7.3 Hz, 2H), 3.10 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 136.5, 135.9, 133.9, 132.0, 127.5, 126.4, 123.1, 122.3, 120.1, 119.0, 117.9, 115.8, 113.4, 111.8, 110.4, 108.6, 37.4, 23.9; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{13}BrN_2O_2^+$ ([M + Na]$^+$) 391.0098; found 391.0096.

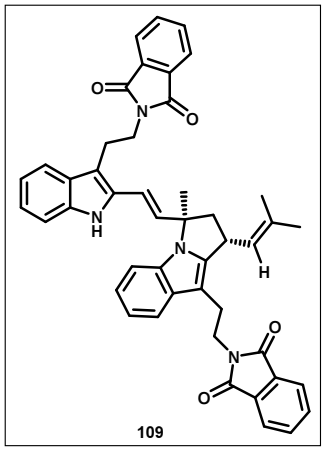
(*E*)-2-(2-(2-(3-Hydroxy-3-methylbut-1-enyl)-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione, 9



9

A mixture of bromo compound **111** (800 mg, 2.16 mmol), 2-methyl-3-buten-2-ol (0.28 mL, 2.70 mmol), palladium (II) acetate (24 mg, 5 mol%), tri-*o*-tolylphosphine (132 mg, 20 mol%), and triethylamine (0.38 mL, 2.70 mmol) in 5 mL of acetonitrile was purged with nitrogen gas for 10 minutes and heated at 100 ^oC in a sealed tube for 5 h. The mixture was then cooled to room temperature and evaporated solvent under reduced pressure. Silica gel column chromatography of the crude product using (ethyl acetate/hexane 1:4 v/v) as eluent furnished the alcohol **9** (600 mg, 75%) as a yellow oil. [R_f = 0.35, ethyl acetate/hexane 1:1 v/v]; IR (CH_2Cl_2): *v* 3383, 2920, 2360, 1770, 1705, 1396, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H), 7.84-7.79 (m, 2H), 7.71-7.66 (m, 3H), 7.28 (s, 1H), 7.16 (td, *J* = 0.9, 6.8 Hz, 1H), 7.09 (td, *J* = 0.9, 7.8 Hz, 1H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.11 (d, *J* = 16.5 Hz, 1H), 3.91 (t, *J* = 7.8 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 136.1, 136.0, 133.8, 132.3, 132.0, 128.5, 123.1, 122.8, 119.6, 118.5, 114.9, 111.5, 110.5, 71.0, 38.4, 29.6, 23.1; HRMS (ESI^+) *m/z* calcd for $C_{23}H_{22}N_2O_3^+$ ([M + Na]$^+$) 397.1498; found 397.1521.

2-(2-((1*R*,3*R*)-3-((*E*)-2-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1*H*-pyrrolo[1,2-α]indol-9-yl)ethyl)isoindoline-1,3-dione, 109

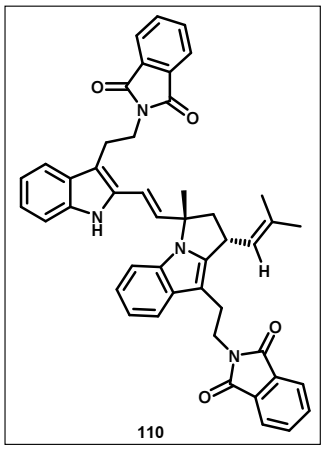


To a solution of alcohol **9** (300 mg, 0.80 mmol) in 36 mL of toluene was added $InCl_3$ (35 mg, 20 mol%) at 0 ^oC and stirred for 4 h at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate/hexane 1:2 v/v) to afford diastereomer **109** (168 mg, 46%) as yellow waxy solid. [R_f = 0.20, ethyl acetate/hexane 1:4 v/v]; IR (CH_2Cl_2): *v* 3378, 2924, 2360, 1769, 1703, 1394, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.83 (br s, 1H), 7.88-7.82 (m, 2H), 7.74-7.69 (m, 2H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.62-7.57 (m, 2H), 7.55-7.51 (m, 2H), 7.43 (d, *J* = 7.7 Hz, 1H) 7.21 (s, 1H), 7.19 (s, 1H), 7.13-7.05 (m, 2H), 6.90-6.86 (m, 1H), 6.83-6.79 (m, 1H), 6.25 (d, *J* = 16.0 Hz, 1H), 6.13 (d, *J* = 16.0 Hz, 1H), 5.27 (br d, *J* = 9.6 Hz, 1H), 4.23-4.11 (m, 1H), 3.98-3.83 (m, 4H), 3.18-3.09 (m, 3H), 3.02-2.96 (m, 1H), 2.66 (dd, *J* = 7.8, 12.4 Hz, 1H), 2.25 (dd, *J* = 9.16, 12.3 Hz, 1H), 2.00 (s, 3H), 1.83 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 168.2, 143.9, 135.9, 133.9, 133.8, 133.7, 133.1, 132.7, 132.3, 132.2, 131.9, 128.7, 124.2, 123.1, 122.8, 122.6, 120.2, 119.5, 118.7, 118.5, 118.1, 116.9, 110.5, 110.4, 110.0, 103.0, 63.9, 51.2, 38.8, 38.2, 34.7, 29.6, 25.7, 24.7, 23.6, 22.4, 18.1; HRMS (ESI^+) *m/z* calcd for $C_{46}H_{40}N_4O_4^+$ ($[M + Na]^+$) 735.2898; found 735.2906.

2-(2-((1*R*,3*S*)-3-((*E*)-2-(3-(2-(1,3-Dioxoisoindolin-2-yl)ethyl)-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1*H*-pyrrolo[1,2-α]indol-9-yl)ethyl)isoindoline-1,3-dione, 110

Further elution of the column (ethyl acetate/hexane 1:2 v/v) furnished another diastereomer **110** (112 mg, 35%) as yellow waxy solid. [R_f = 0.18, ethyl acetate/hexane 1:4 v/v]; IR (CH_2Cl_2): *v* 3364, 2360, 1765, 1707, 1396, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.30 (br s, 1H), 7.84 (dd, *J* = 2.7, 5.4 Hz, 2H), 7.78 (dd, *J* = 3.3, 5.4 Hz, 2H), 7.73-7.69 (m, 3H), 7.67 (dd, *J* = 3.2, 5.5 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.23 (s, 1H), 7.17 (td, *J* = 0.9, 6.8 Hz, 1H), 7.11 (m, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.85 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 16.5 Hz, 1H), 6.31 (d, *J* = 16.4 Hz, 1H),

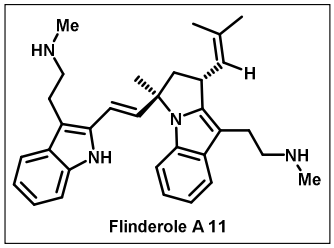
5.27 (br d, *J* = 9.1 Hz, 1H), 4.31-4.25 (m, 1H), 4.01-3.91 (m, 2H), 3.87-3.80 (m, 2H), 3.26-3.16 (m, 2H), 3.06-2.94 (m, 2H), 2.57 (dd, *J* = 8.2, 12.8 Hz, 1H), 2.27 (dd, *J* = 8.2, 12.8 Hz, 1H), 1.89 (s, 3H), 1.85 (s, 3H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 168.2, 143.0, 136.1, 133.9, 133.7, 133.2, 132.1, 132.1, 131.1, 128.5, 124.5, 123.1, 122.9, 120.2, 119.8, 118.8, 117.7, 111.9, 110.5, 109.6, 102.6, 62.9, 51.5, 38.6, 38.5, 35.2, 29.6, 25.8, 23.2, 23.0, 22.4, 18.2; HRMS (ESI^+) *m/z* calcd for $C_{46}H_{40}N_4O_4^+$ ($[M+Na]^+$) 735.2898; found 735.2909.



110

_N_-Methyl-2-((1_R_,3_R_)-3-methyl-3-((_E_)-2-(3-(2-(methylamino)ethyl)-1_H_-indol-2-yl)vinyl)-1-(2-methylprop-1-enyl)-2,3-dihydro-1_H_-pyrrolo[1,2-α]indol-9-yl)ethanamine, 11[4]

To a solution of compound **109** (30 mg, 0.04 mmol) in 1 mL of isopropyl alcohol was added hydrazine monohydrate (0.004 mL, 0.09 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 4 h. The resulting solution was filtered, washed with diethyl ether, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to furnish the crude bis-amine intermediate. [R_f = 0.20, MeOH/CH_2Cl_2 1:4 v/v]. The resulting crude product was used as such for the next step without further purification.



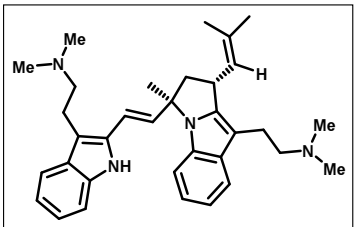
Flinderole A 11

To a methanolic solution (1 mL) of above crude product of bis-amine was added formaldehyde (37% w/w in H_2O, 0.03 mL, 0.42 mmol), Na(CN)BH_3 (4 mg, 0.07 mmol) and stirred for 5 minutes at room temperature. After completion of the reaction as monitored by TLC, the mixture was diluted with diethyl ether and the organic layer separated. The resulting organic phase was washed with brine, dried over anhydrousNa_2SO_4, and concentrated *in vacuo*. Silica gel column chromatography of the crude product using (MeOH/CH_2Cl_2 1:6 v/v) as eluent furnished the target compound flinderole A **11** (17 mg, 88% over two steps) as white waxy solid. [R_f = 0.30, MeOH/CH_2Cl_2 1:4 v/v]; IR (CH_2Cl_2): ν 3425, 2249, 2204, 1635, 1014, 994, 832, 756 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.94 (s, 1H), 7.49-7.42 (m, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.33-7.28 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.95-6.90 (m, 2H), 6.87 (t, *J* = 7.3 Hz, 1H), 6.36 (d, *J* = 16.0Hz, 1H), 6.08 (d, *J* = 16.0Hz, 1H), 5.21 (br d, *J* = 9.6 Hz, 1H), 4.17-4.10 (m, 1H), 3.43 (m, 1H), 2.78-2.64

(m, 8H), 2.57-2.50 (m, 2H), 2.33 (s, 3H), 2.24-2.21 (m, 1H), 2.18 (s, 3H), 1.87 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.6, 136.7, 133.2, 132.8, 132.3, 131.6, 131.4, 128.2, 125.2, 122.6, 120.5, 119.1, 118.7, 118.6, 116.6, 111.8, 111.1, 110.4, 102.7, 63.7, 60.5, 51.5, 51.0, 34.7, 34.6, 29.3, 25.8, 25.2, 22.4, 18.3; HRMS (ESI$^+$) *m/z* calcd for $C_{32}H_{40}N_4^+$ ($[M+H]^+$) 481.3353; found 481.3343.

2-((1*R*,3*R*)-3-((*E*)-2-(3(2-(Dimethylamino)ethyl-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1*H*-pyrrolo[1,2-α]indol-9-yl)-*N*,*N*-dimethylethanamine, 12[4]

To a solution of compound **109** (35 mg, 0.05 mmol) in 1 mL of isopropyl alcohol was added hydrazine monohydrate (0.005 mL, 0.10 mmol) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 4 h. The resulting solution was filtered, washed with diethyl ether, dried over Na_2SO_4 and concentrated *in vacuo* to furnish the crude compound, R_f = 0.2 (MeOH/CH_2Cl_2 1:4 v/v). The resulting crude was used as such for the next step without further purification due to high polar nature of the compound.

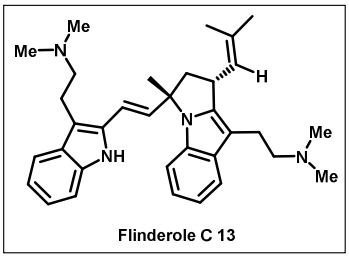


Flinderole B 12

To an acetonitrile solution (1 mL) of above crude product of bis-amine was added formaldehyde (37% w/w in H_2O, 0.039 mL, 0.49 mmol) followed by sodium cyanoborohydride (5 mg, 0.08 mmol) and acetic acid (0.05 mL) and stirred for 10 h at room temperature. TLC monitoring showed complete conversion. The mixture was diluted with diethyl ether and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The silica gel column chromatography of the crude product using (MeOH/CH_2Cl_2 1:9 v/v) as eluent furnished the target compound Flinderole B **12** (20 mg, 82% over two steps) as white waxy solid. R_f = 0.40 (MeOH/CH_2Cl_2 1:4 v/v); IR (CH_2Cl_2): *v* 3430, 2929, 1615, 1420, 1345, 1040, 745, 656; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.95 (s, 1H), 7.44-7.42 (m, 1H), 7.36-7.32 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.02-6.93 (m, 3H), 6.88 (t, *J* = 6.8 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.81 (d, *J* = 16.0 Hz, 1H), 5.27 (br d, *J* = 9.6 Hz, 1H), 4.14-4.07 (m, 1H), 2.75-2.67 (m, 3H), 2.43-2.22 (m, 5H), 2.17 (s, 6H), 2.13-2.03 (m, 2H), 1.98 (s, 6H), 1.91 (s, 3H), 1.75 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.3, 136.8, 133.1, 132.8, 132.0, 131.7, 131.4, 128.1, 125.2, 122.0, 120.0, 118.9, 118.7, 118.7, 116.4, 112.5, 111.2, 110.5,

103.6, 64.1, 60.6, 60.2, 50.8, 45.0, 44.7, 34.7, 25.9, 25.7, 21.4, 18.4; HRMS (ESI^+) *m/z* calcd for $C_{34}H_{44}N_4^+$ ($[M + H]^+$) 509.3644; found: 509.3656.

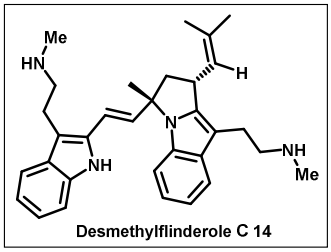
2-((1*R*,3*S*)-3-((*E*)-2-(3(2-(Dimethylamino)ethyl-1*H*-indol-2-yl)vinyl)-3-methyl-1-(2-methylprop-1-enyl)-2,3-dihydro-1*H*-pyrrolo[1,2-α]indol-9-yl)-*N*,*N*-dimethylethanamine, 13[4]



Flinderole C 13

Flinderole C **13** (20 mg, 80% over two steps) as white waxy solid. R_f = 0.40 ($MeOH/CH_2Cl_2$ 1:4 v/v); IR (CH_2Cl_2): *v* 3429, 2980, 2274, 2118, 1665, 1026, 824, 755; ^1H NMR (DMSO-d_6, 400 MHz): δ 10.97 (s, 1H), 7.41-7.36 (m, 2H), 7.23-7.15 (m, 2H), 7.05-6.99 (m, 1H), 6.93-6.87 (m, 3H), 6.52 (d, *J* = 16.0 Hz, 2H), 5.21 (br d, *J* = 9.6, 1H), 4.27 (dd, *J* = 7.8, 9.6 Hz, 1H), 2.80-2.62 (m, 6H), 2.30-2.22 (m, 4H), 2.15 (s, 6H), 2.10 (s, 6H), 1.78 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.1, 136.2, 133.2, 132.7, 131.5, 131.1, 130.6, 128.4, 124.9, 122.9, 120.4, 119.5, 118.7, 118.6, 118.5, 116.7, 113.5, 110.5, 110.1, 103.8, 63.8, 60.4, 59.9, 51.6, 44.9, 44.6, 36.2, 34.7, 25.8, 25.7, 22.6, 21.7, 21.6, 18.2; HRMS (ESI^+) *m/z* calcd for $C_{32}H_{40}N_4^+$ ($[M + H]^+$) 509.3644; found: 509.3654.

***N*-Methyl-2-((1*R*,3*S*)-3-methyl-3-((*E*)-2-(3-(2-(methylamino)ethyl)-1*H*-indol-2-yl)vinyl)-1-(2-methylprop-1-enyl)-2,3-dihydro-1*H*-pyrrolo[1,2-α]indol-9-yl)ethanamine, 14**[4]

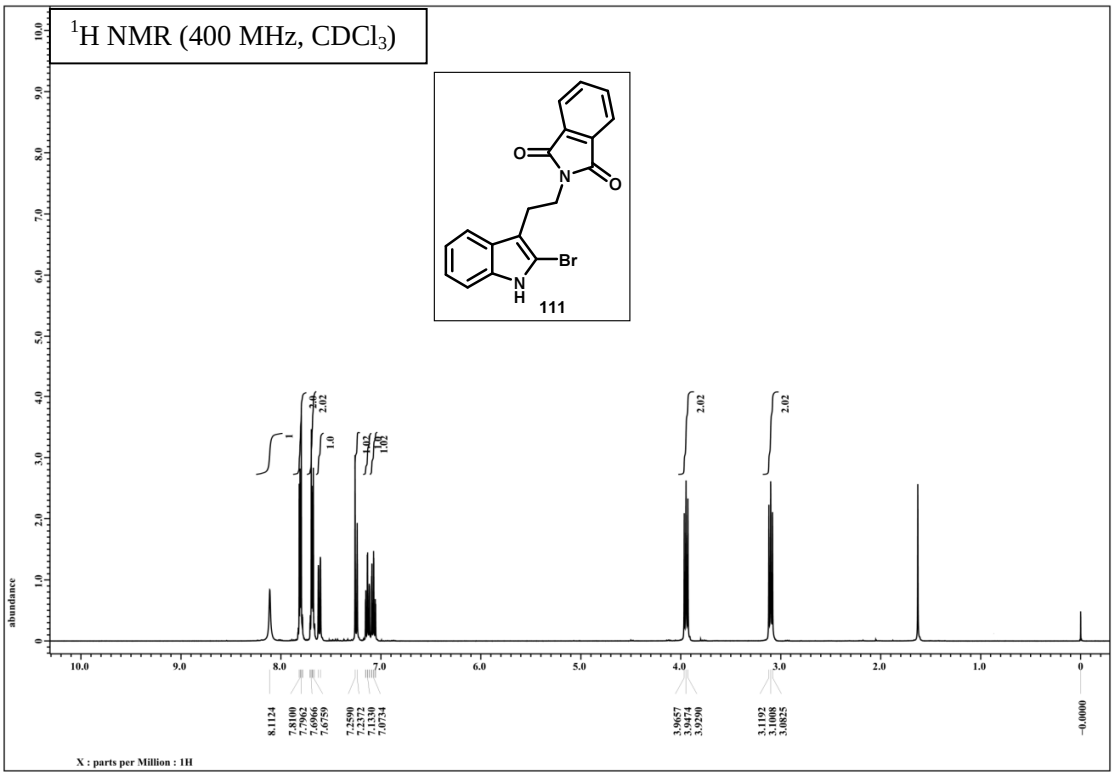


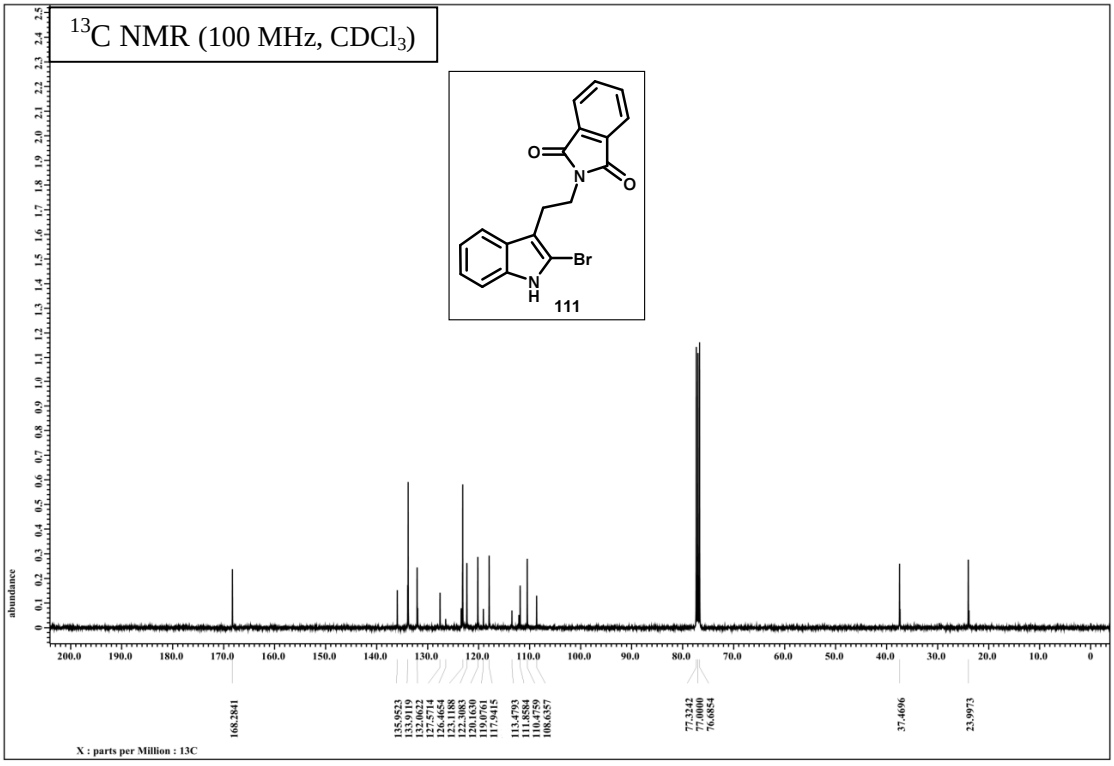
Desmethylflinderole C 14

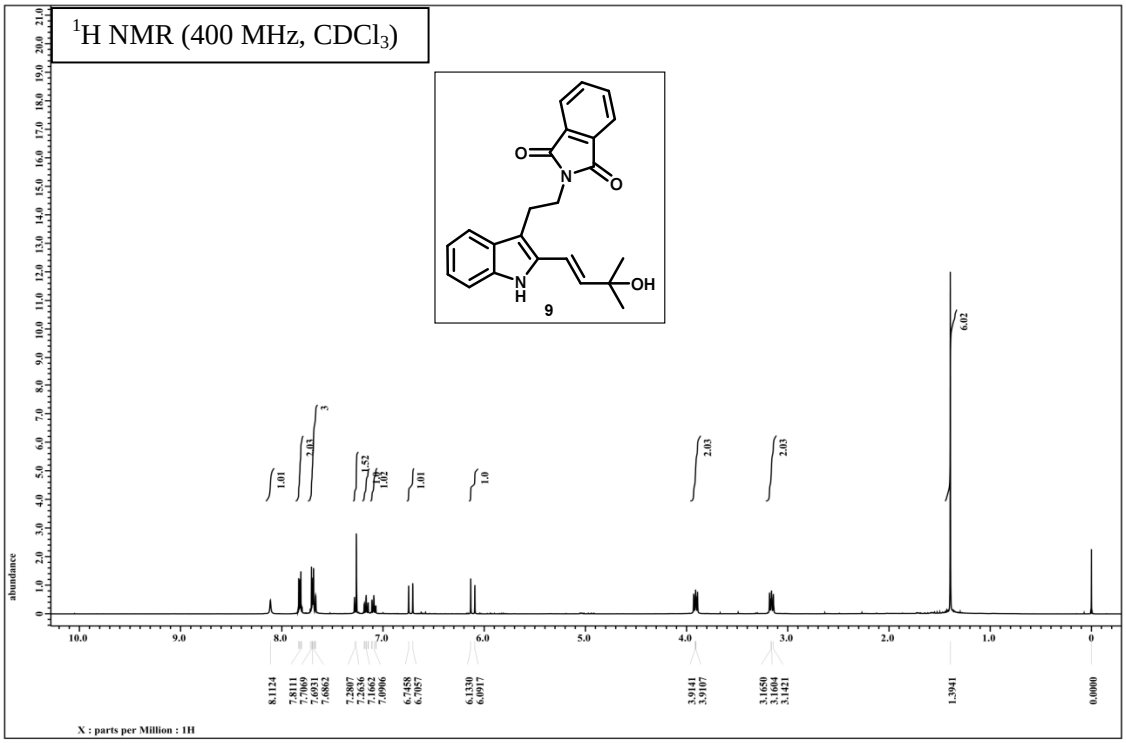
Desmethylflinderole C **14** (22 mg, 85% over two steps) as white waxy solid. R_f = 0.3 ($MeOH/CH_2Cl_2$ 1:4 v/v); IR (CH_2Cl_2): *v* 3435, 2935, 1580, 1448, 1365, 1275, 1104, 809, 742; ^1H NMR (DMSO-d_6, 400 MHz): δ 11.00 (s, 1H), 7.45-7.40 (m, 2H), 7.21-7.17 (m, 2H), 7.03-6.99 (m, 1H), 6.92-6.86 (m, 3H), 6.69 (d, *J* = 16.4 Hz, 1H), 6.52 (d, *J* = 16.4 Hz, 1H), 5.21 (br d, *J* = 9.6 Hz, 1H), 4.32-4.25 (m, 1H), 2.86-2.78 (m, 2H), 2.71-2.56 (m, 8H), 2.26 (s, 3H), 2.23 (s, 3H), 1.78 (s, 3H), 1.72 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 142.6, 136.5, 132.7, 132.5, 132.4, 132.0, 130.8, 128.1, 125.3, 122.2, 119.8, 118.6, 118.5, 118.3, 118.2, 117.9, 112.7, 110.7, 109.7, 103.4, 62.7, 52.2, 52.1, 50.9, 35.3, 34.7, 25.5, 23.3, 22.8, 18.0; HRMS (ESI^+) *m/z* calcd for $C_{32}H_{40}N_4^+$ ($[M + H]^+$) 481.3353; found 481.3337.

2.8 Spectra

1. ^{1}H and ^{13}C NMR spectra of **111**
2. ^{1}H and ^{13}C NMR spectra of **9**
3. ^{1}H and ^{13}C NMR spectra of **109**
4. ^{1}H and ^{13}C NMR spectra of **110**
5. ^{1}H and ^{13}C NMR spectra of **11**
6. ^{1}H and ^{13}C NMR spectra of **12**
7. ^{1}H and ^{13}C NMR spectra of **13**
8. ^{1}H and ^{13}C NMR spectra of **14**


^{1}H NMR (400 MHz, $CDCl_3$)
O
N
O
Br
N
H
111
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
O
N
O
Br
N
H
111
abundance
X : parts per Million : 13C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9
abundance
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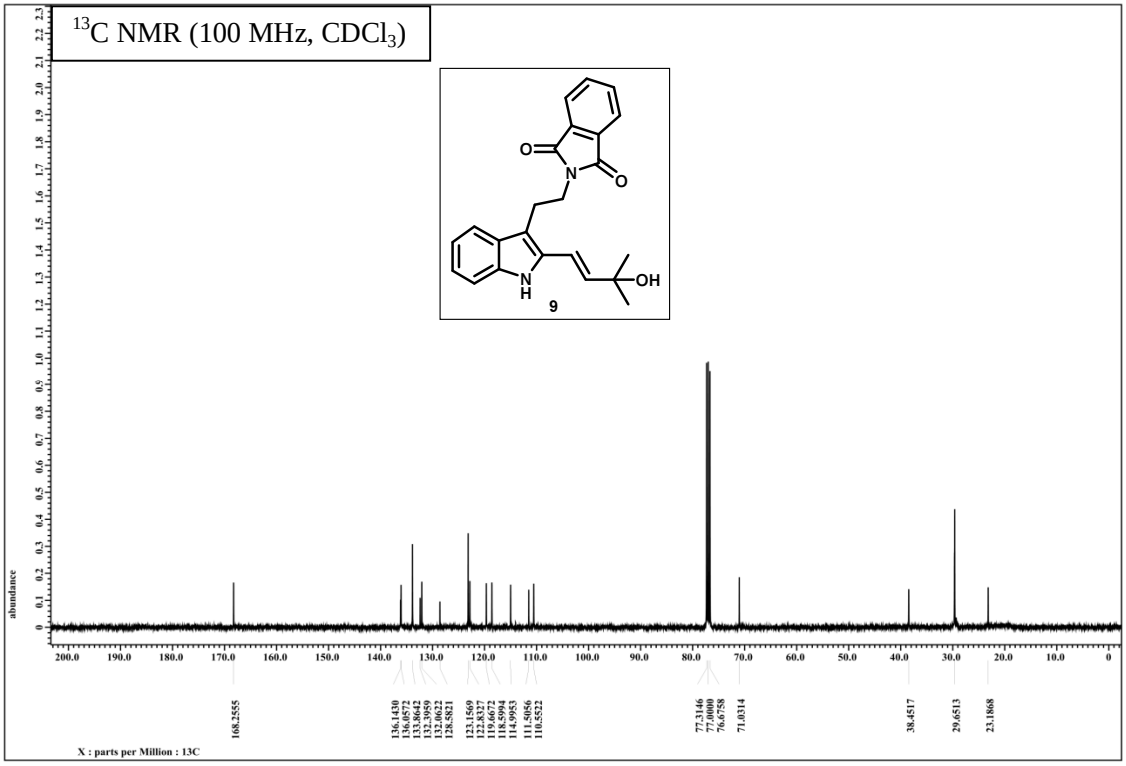
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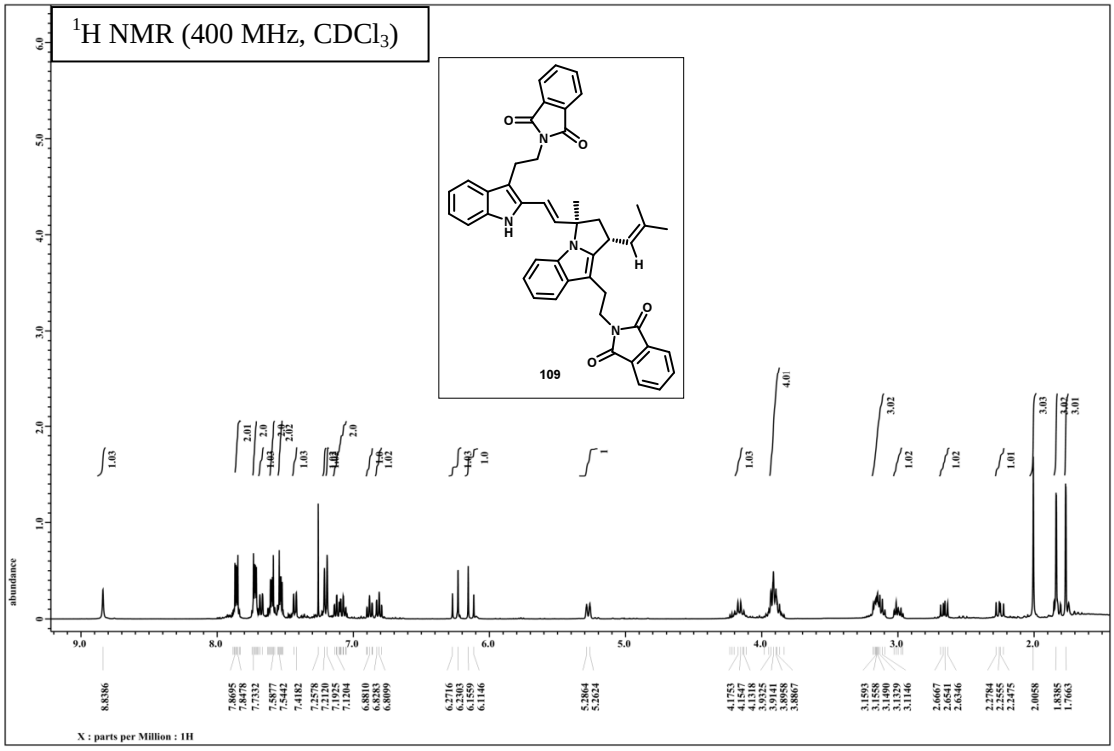
9
abundance
X : parts per Million : 13C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109
abundance
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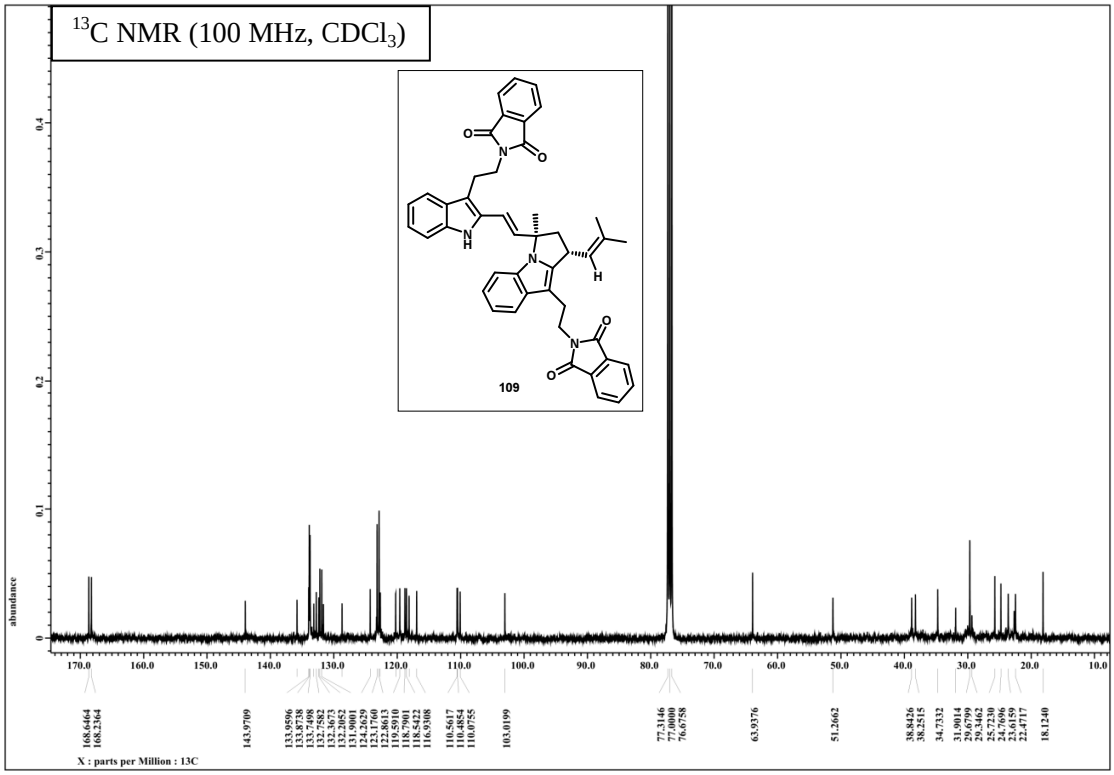
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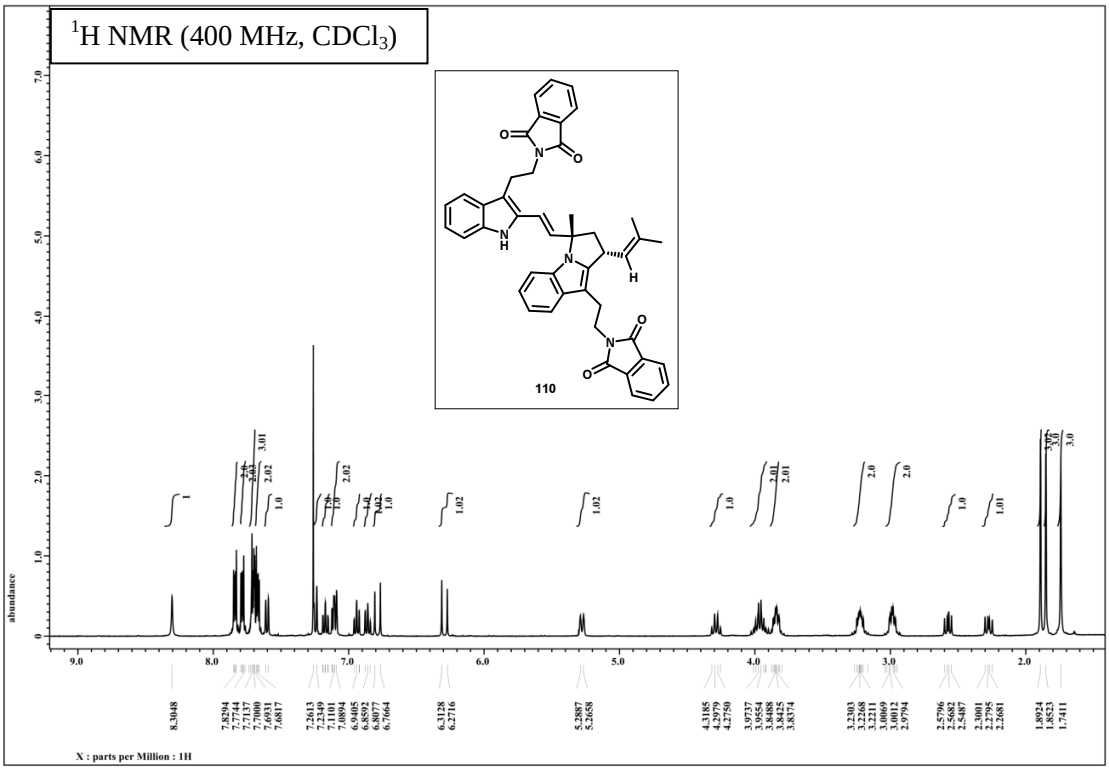
109
abundance
X : parts per Million : 13C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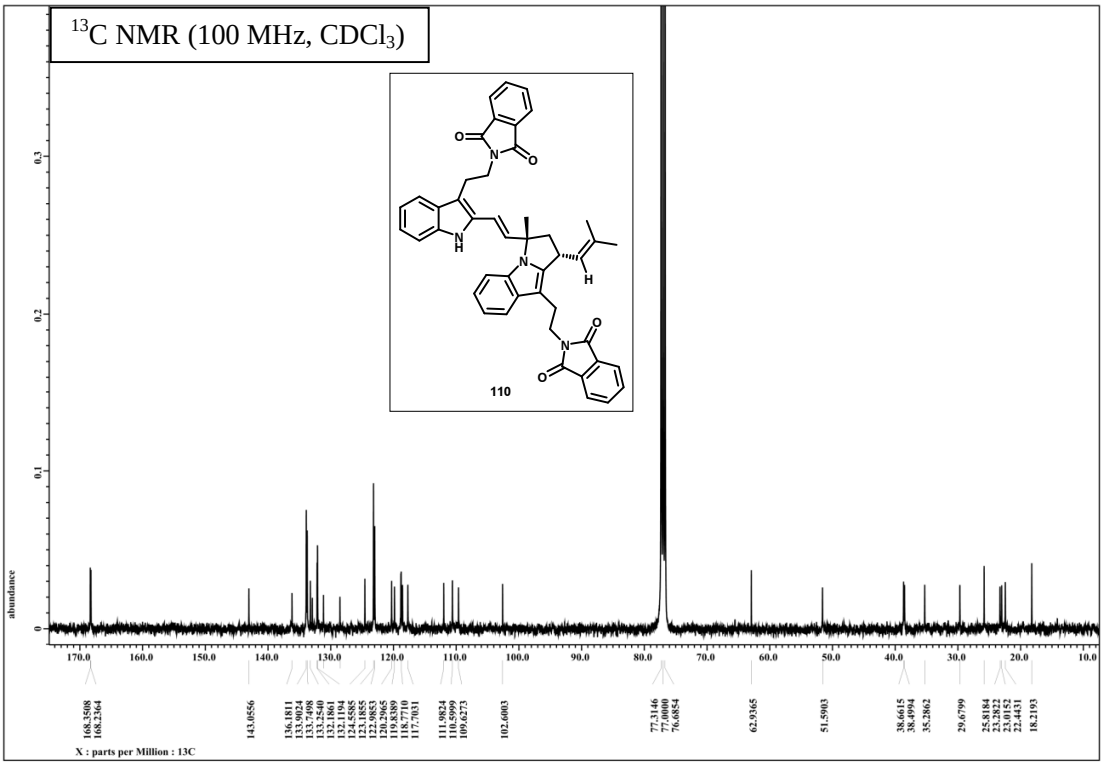
110
abundance
X : parts per Million : 1H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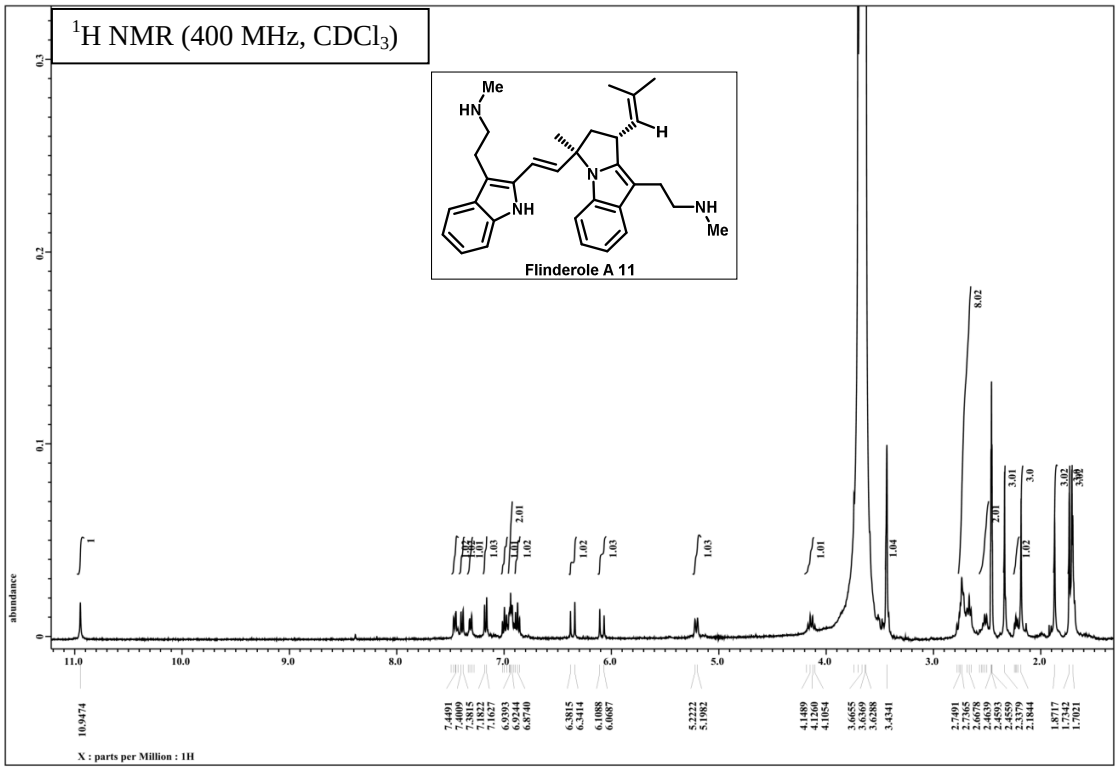
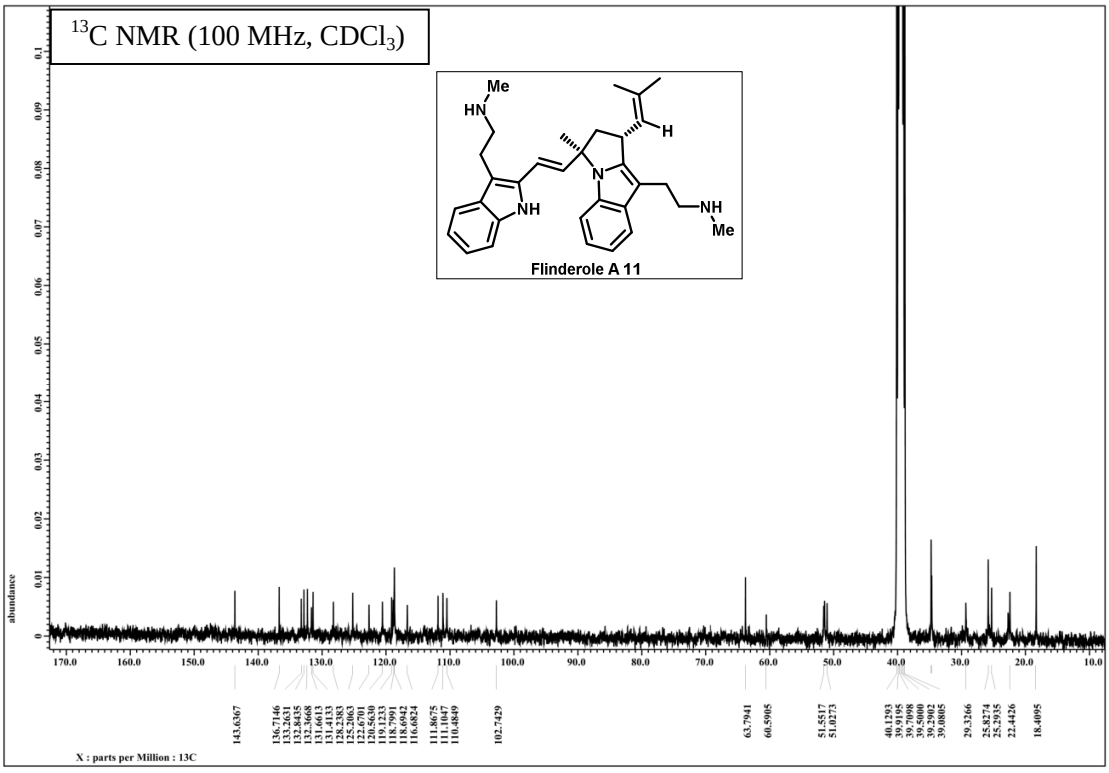
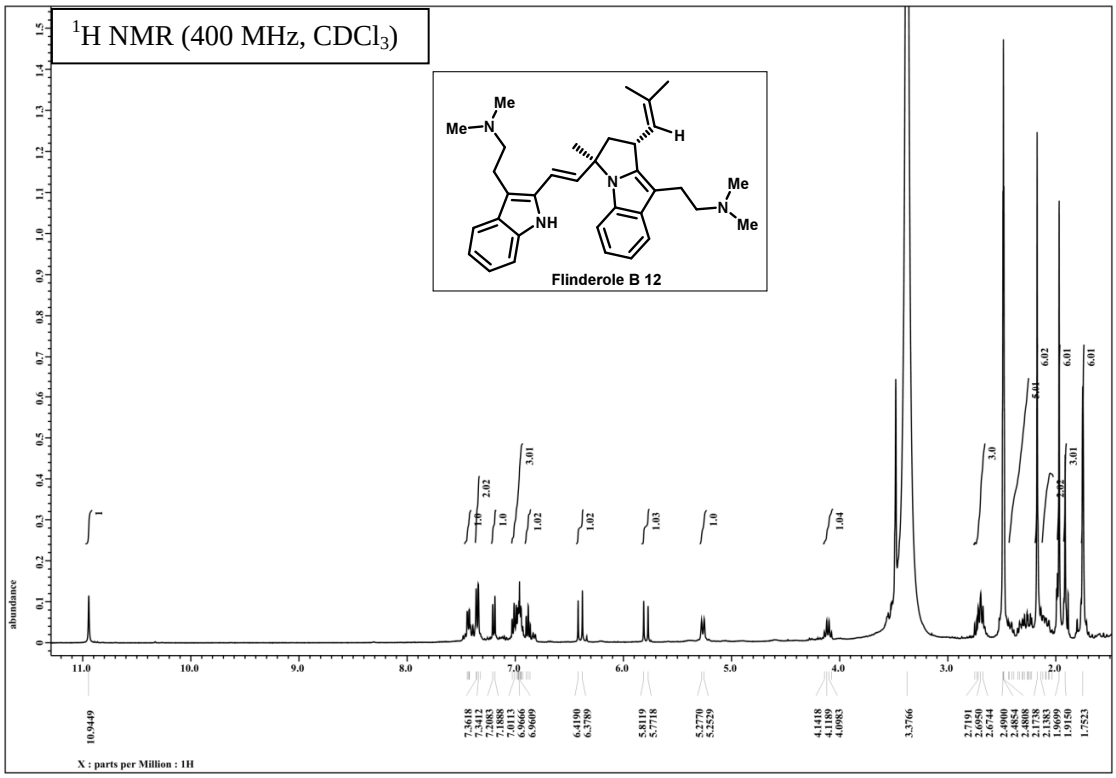
110
abundance
X : parts per Million : 13C


^{1}H NMR (400 MHz, $CDCl_3$)
Flinderole A 11
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
Flinderole A 11
abundance
X : parts per Million : 13C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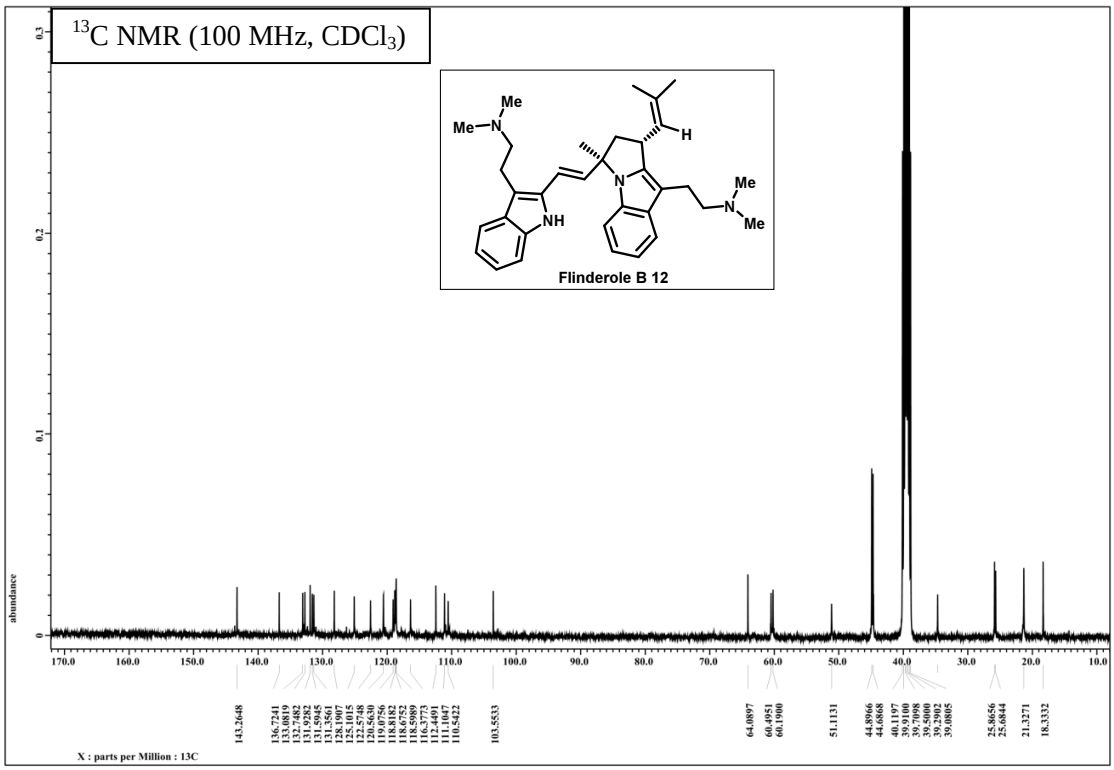
Flinderole B 12
abundance
X : parts per Million : 1H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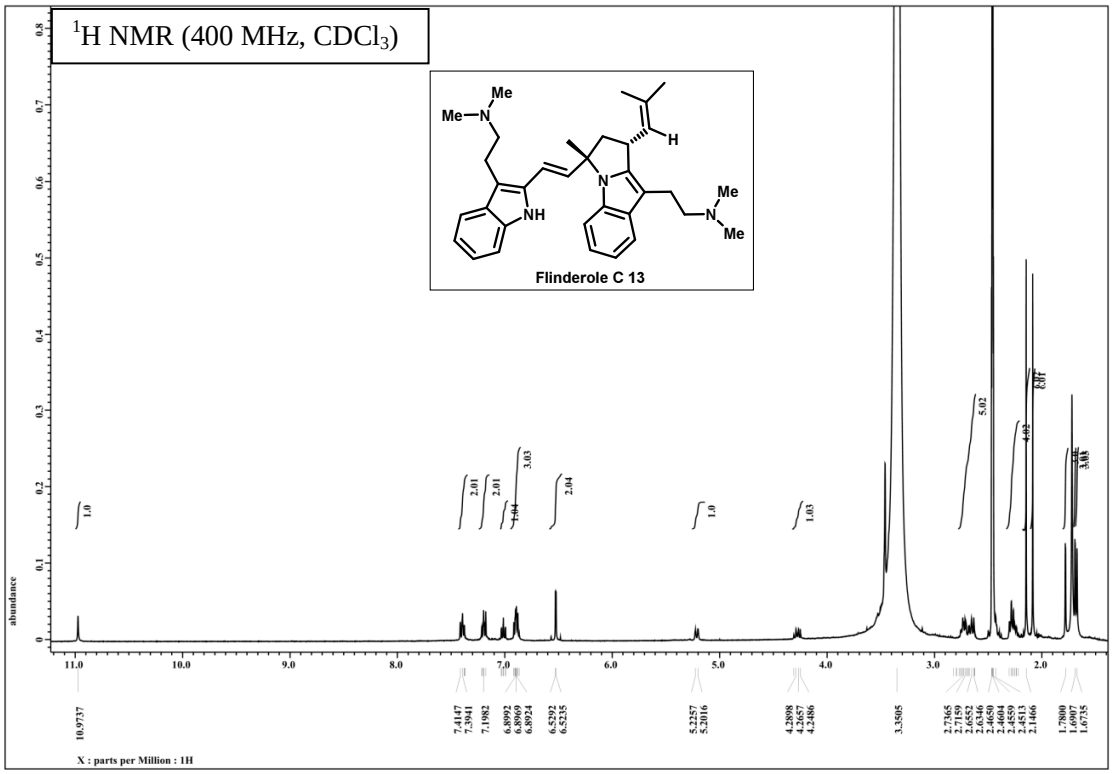
Flinderole B 12
abundance
X : parts per Million : 13C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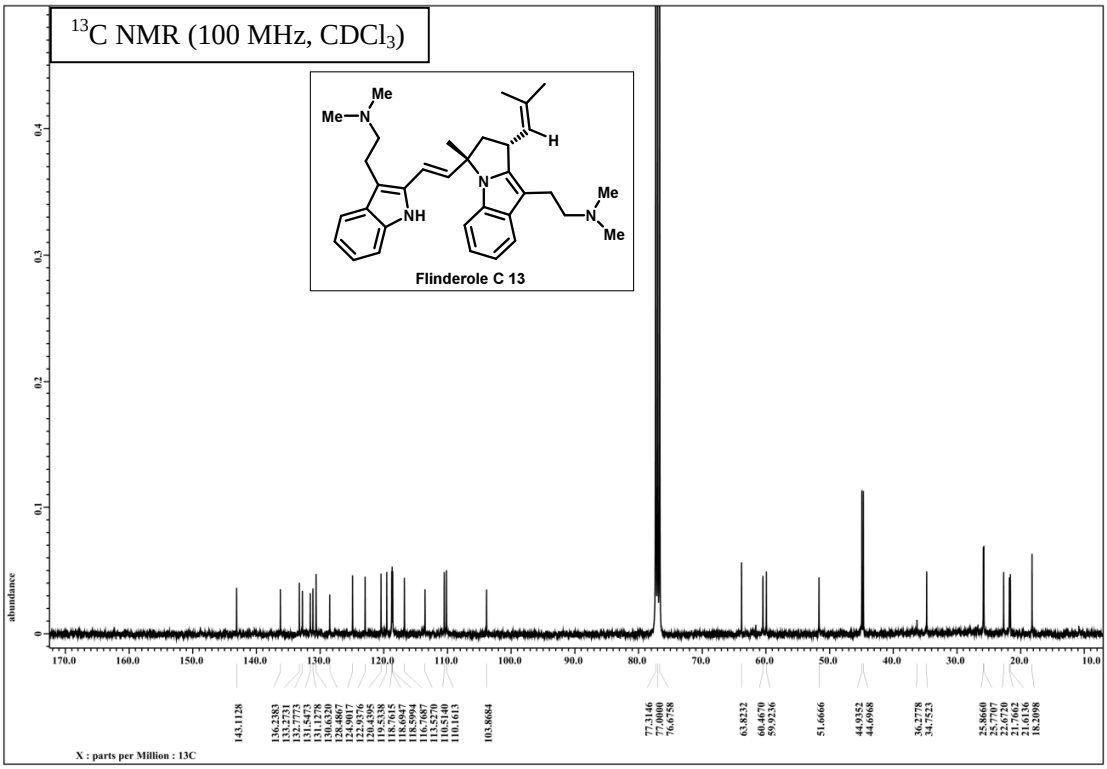
Flinderole C 13
abundance
X : parts per Million : 1H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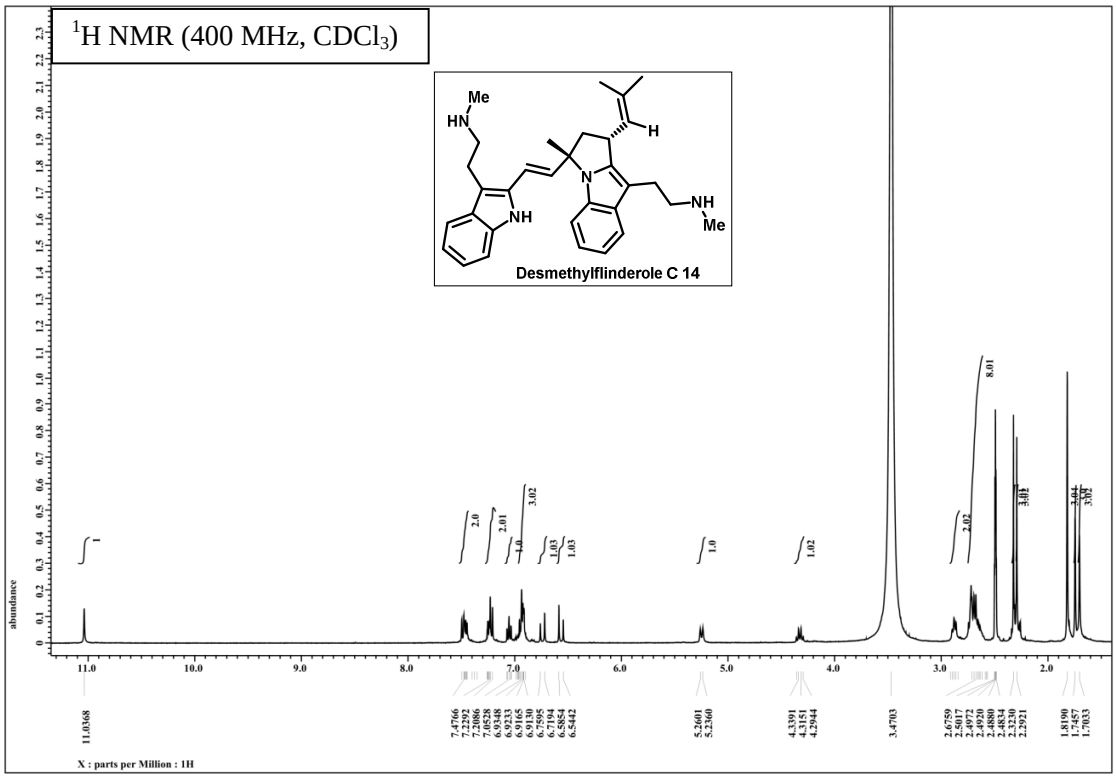
Flinderole C 13
abundance
X : parts per Million : 13C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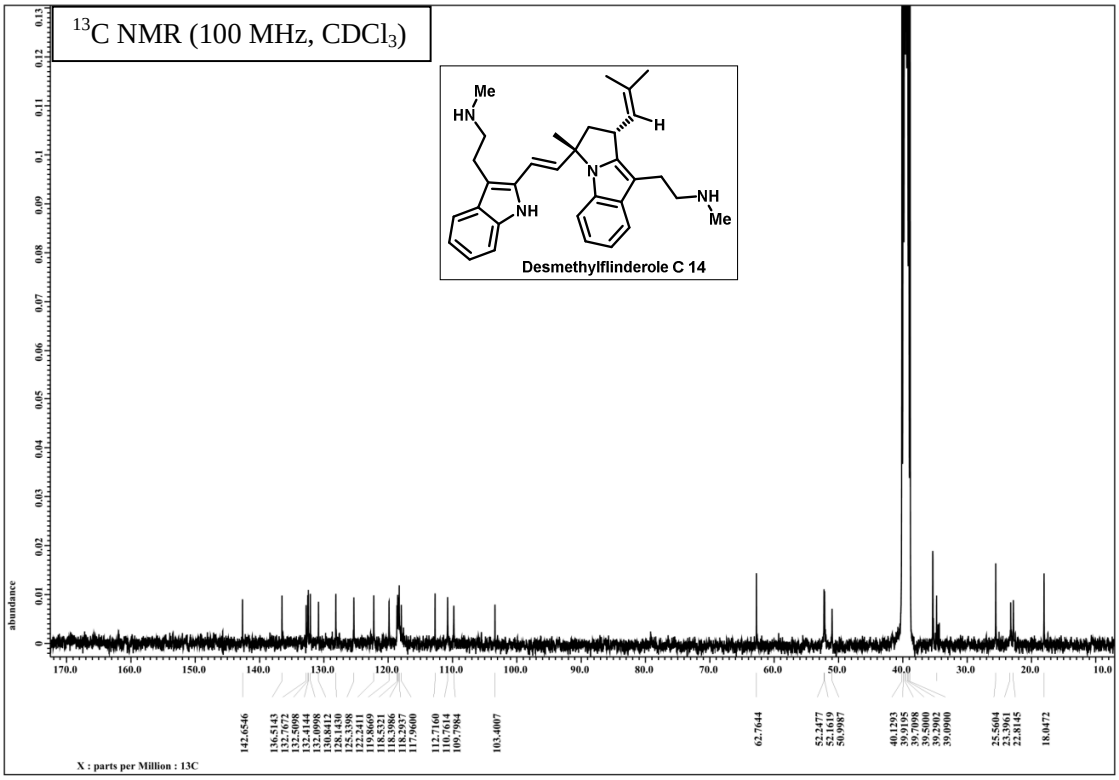
Desmethylflinderole C 14
abundance
X : parts per Million : 1H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Desmethylflinderole C 14
abundance
X : parts per Million : 13C

2.9 References:

1. Miller, L. H.; Ackerman, H. C.; Su, X. Z.; Wellems, T. E. *Nat. Med.* **2013**, *19*, 156; b) Alonso, P. L.; Tanner, M. *Nat. Med.* **2013**, *19*, 150; c) Cohen, J. M.; Woolsey, A. M.; Sabot, O.; Gething, J. P. W.; Tatem, A. J.; Moonen, B. *Science* **2012**, *338*, 612; d) Kappe, S. H. I.; Vaughan, A. M.; Boddey, J. A.; Cowman, A. F. *Science* **2010**, *328*, 862.
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CHAPTER 3

An enantioselective approach towards the synthesis of hydroxylated piperidines and its applications to the total syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine

An enantioselective approach towards the synthesis of hydroxylated piperidines and its applications to the total syntheses of 1-deoxygalactonojirimycin, (-)-3-hydroxypipecolic acid and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine

3.1 Introduction:

Hydroxylated piperidines and their derivatives are one of the most important chemotherapeutic *N*-heterocyclic compounds due to their ubiquitous structural features either as itself or as a part of more complex structural moiety in various biologically active compounds and natural products.[1] Among them, unnatural polyhydroxylated piperidines 1-deoxygalactonojirimycin **26** exhibits interesting potent glycosidase inhibitory activity[2] and currently undergoing phase II clinical trial for the treatment of Fabry's disease (Figure 9).[2] Due to their inherent biological activities, 1-deoxygalactonojirimycin **26** along with its other stereoisomers have been shown as potential therapeutics for different conditions including cancer, diabetes, HIV, and heritable diseases such as Gaucher's (lysosomal storage) disease.[3] Other hydroxylated piperidines such as *cis*-(-)-3-hydroxypipecolic acid **28** forms an important core of antitumor antibiotic tetrazomine **113**,[4] while its reduced analogue (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** forms an important core of potent antimalarial agent isofebrifugine **112** (Figure 9).[4]

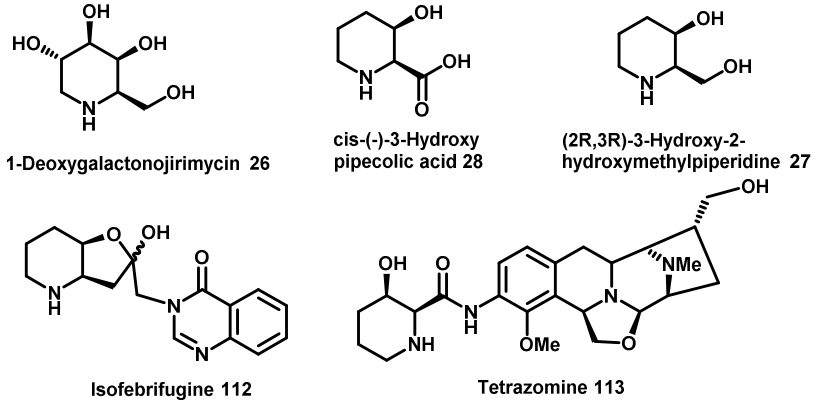


Figure 9. Structures of some hydroxylated piperidines and their derivatives.

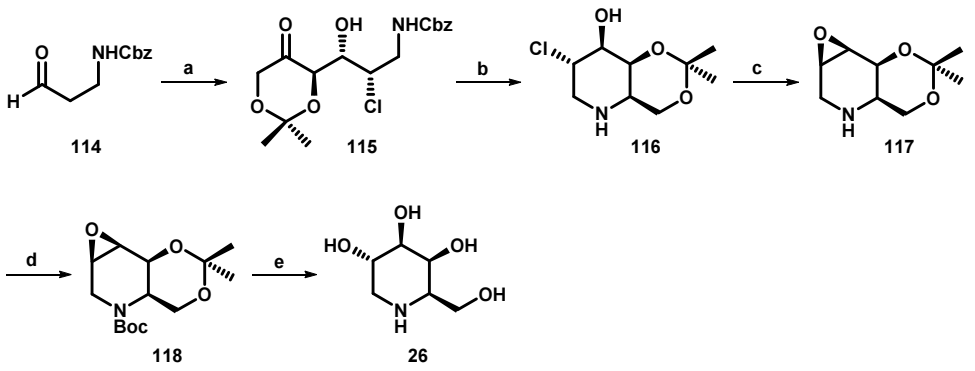
Additionally, six membered cyclic *cis*-(-)-3-hydroxypipecolic acid **28** and its stereoisomers have been used in ligand binding studies, peptide structure studies, used as organocatalysts and for the drug designing.[8c] Enantiomerically pure hydroxylated piperidines and derivatives have been synthetic targets of considerable interest owing to their wide range of important biological activities and with an array of functionalities.

3.2 Review of Literature:

Various asymmetric syntheses for hydroxylated piperidines alkaloids 1-deoxygalactonojirimycin **26**, *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** have been documented in the literature.[5-7] Most of the described asymmetric syntheses have employed chiral pool approach *viz.* started from sugars, tartaric acid, amino acids and heterocyclic compounds. Some of the recent syntheses of 1-deoxygalactonojirimycin **26**, *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** are described below.

Britton, R. *et al.* (2017)[5a]

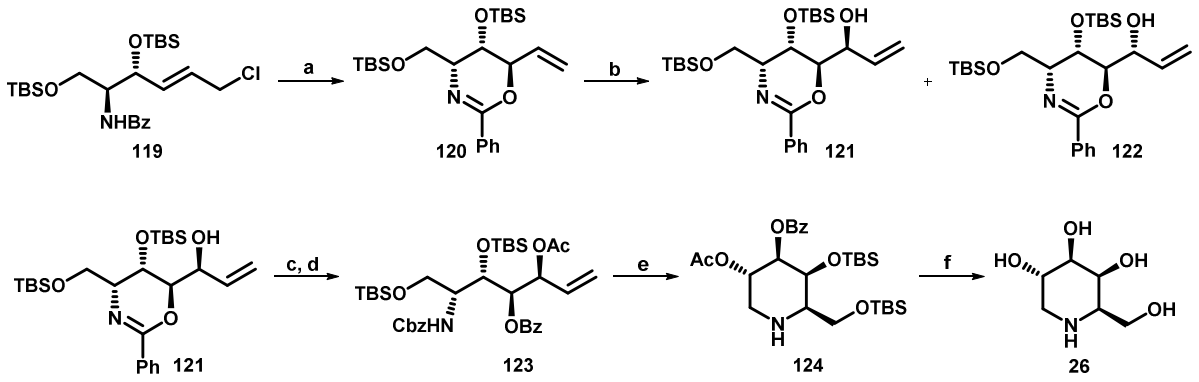
R. Britton and co-workers described the total synthesis of 1-deoxygalactonojirimycin **26** from readily available benzyl (3-oxypropyl)carbamate **114** in five steps (Scheme 33). The synthesis began with (*R*)-proline catalyzed α-chlorination of aldehyde **114** which on aldol reaction with dioxanone furnished the chlorohydrins **115** in 66% yield and 93% *ee*. The compound **115** on hydrogenation using Pd/C afforded the piperidine derivative **116** in 72% yield and 3:1 diastereomeric ratio. The treatment of chloropiperidine **116** with NaOH in ethanol furnished the epoxide derivative **117** in 93% yield which on subsequent treatment of free amine with $(Boc)_2O$ afforded the *N*-Boc protected compound **118** in 76% yield. The epoxide **118** on reaction with H_2SO_4 in dioxane and water delivered the target compound **26** in 87% yield.



Scheme 33. *Reagents and conditions*: (a) dioxanone, NCS, (*R*)-proline, CH_2Cl_2, rt, 24 h, 66%; (b) H_2, Pd/C, MeOH, rt, 12 h, 72%; (c) NaOH, EtOH, rt, 72 h, 93%; (d) Boc_2O, Et_3N, CH_2Cl_2, rt, 12 h, 76%; (e) H_2SO_4, 1,4-dioxane:H_2O, 100 ^oC, 3 h, 87%.

Ham, W. H. *et al.* (2016)[5b]

W. H. Ham and co-workers reported the stereoselective total synthesis of 1-deoxygalactonojirimycin **26** starting from oxazine in four steps with 44.4% overall yield (Scheme 34). The compound **119** on treatment with NaH in presence of palladium (0) catalyst furnished the olefin **120** in 89% yield. The olefin **120** on ozonolysis followed by Grignard reaction with vinylmagnesium bromide afforded the alcohol **121** and **122** in 72% combined yield with 10:1 diastereomeric ratio. The alcohol **121** on acetate protection and subsequent ring opening under Schotten-Baumann reaction conditions furnished the olefin **123** in 80% yield. The olefin **123** on ozonolysis and cyclization followed by Cbz deprotection delivered the cyclized amine **124** in 68% yield. Finally, the global deprotection with 6N HCl furnished the 1-deoxygalactonojirimycin **26** in 81% yield.

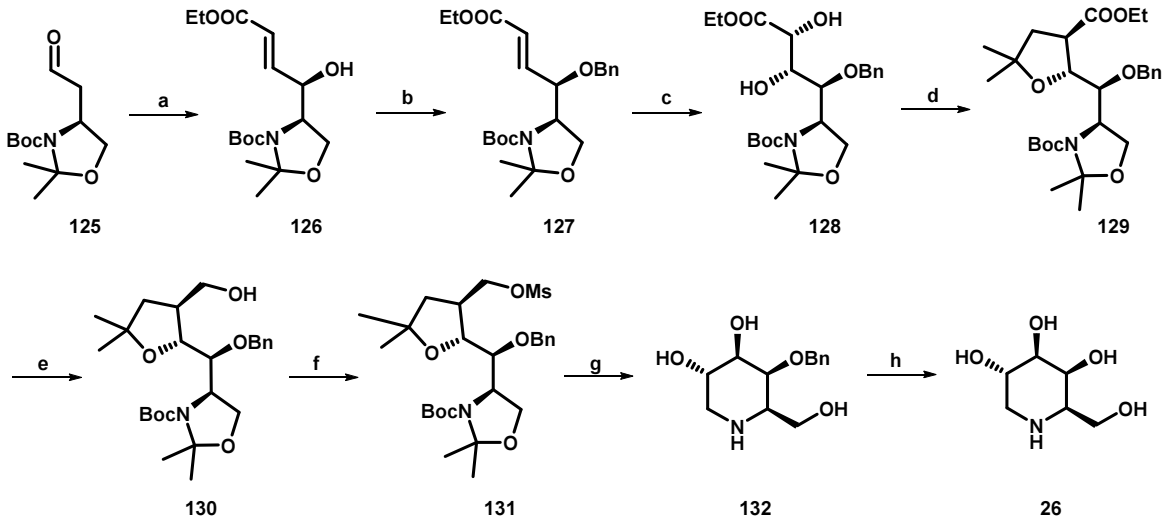


Scheme 34. *Reagents and conditions*: (a) NaH, TBAI, Pd(0) cat., 0 ^{o}C, 89%; (b) i) O_3, MeOH, Me_2S; ii) vinylmagnesium bromide, THF, -78 ^{o}C, 72%; (c) Ac_2O, 4-DMAP, pyridine, CH_2Cl_2; (d) CbzCl, $NaHCO_3$, CH_2Cl_2/H_2O (1:1) 80% (for two steps); (e) i) O_3, MeOH, -78 ^{o}C, then Me_2S; ii) $Pd(OH)_2/C$, H_2, MeOH; (f) 6 N HCl, reflux, then Dowex-50WX8, 81%.

Ramapanicker R. *et al.* (2015)[5c]

R. Ramapanicker and co-workers reported the diastereoselective synthesis of 1-deoxygalactonojirimycin **26** employed the proline catalyzed asymmetric *α*-aminoxylation as key step starting from higher homologue of Garner's aldehyde **125** (Scheme 35). The aldehyde **125** on *α*-aminoxylation with nitrosobenzene in presence of D-proline (20 mol%) followed by Wittig olefination and subsequent treatment with $Cu(OAc)_2$ in EtOH afforded the alcohol **126** in 69% yield. The alcohol **126** on *O*-Bn protection afforded the protected alcohol **127** in 94% yield followed by dihydroxylation under Upjohn reaction conditions furnished the diol **128** in 92% yield. The diol **128** on protection with 2,2- dimethoxypropane

afforded the ester **129** in 86% yield which on further reduction with LAH gave the alcohol derivative **130** in 96% yield. The compound **130** on *O*-Ms afforded the compound **131** in excellent yield. Acidolysis of compound **131** with HCl followed by treatment with K_2CO_3 furnished the cyclized amine **132** which on hydrogenation using Pd/C afforded the target compound **26** in 95% yield.

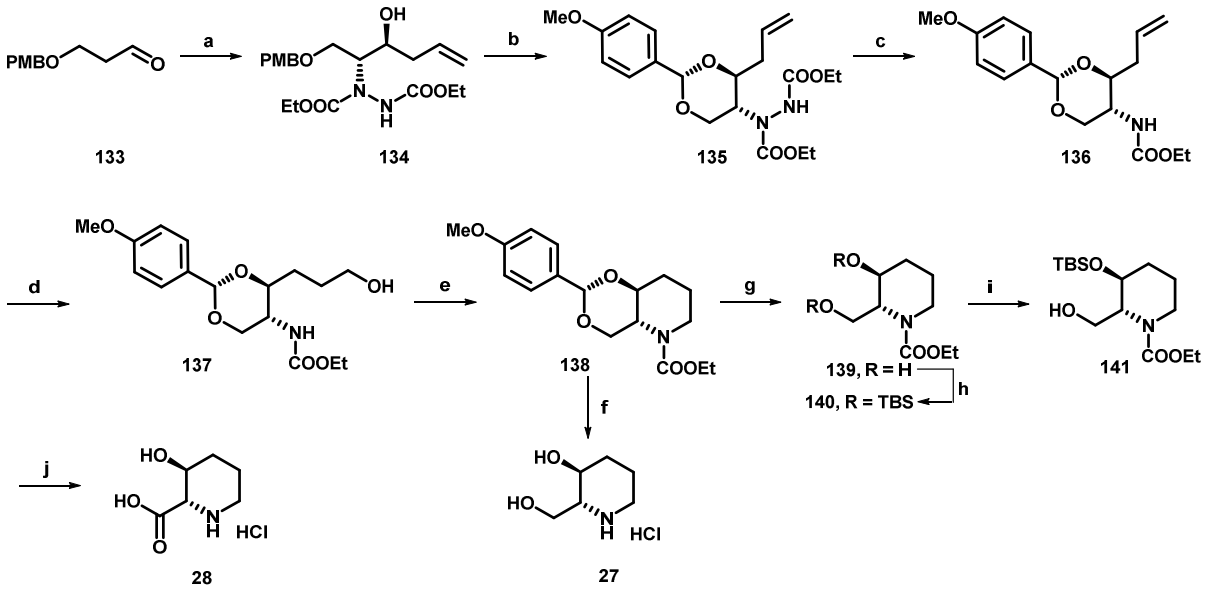


Scheme 35. *Reagents and conditions*: (a) i) D-proline, PhNO, DMSO, 15 ^oC, 3 h; ii) Ph_3P=CHCOOEt, DCM, rt, 3 h; iii) $Cu(OAc)_2$, EtOH, rt, 10 h, 69% (over three steps); (b) NaH, BnBr, TBAI, DMF, 0 ^oC-rt, 94%; (c) OsO_4, NMO, acetone:H_2O, 0 ^oC-rt, 24 h, 92%; (d) *p*-TSA, DMF, toluene, reflux, 1 h, 86%; (e) LAH, THF, rt, 3 h, 96%; (f) MsCl, Et_3N, DMAP, DCM, 0 ^oC, 30 min, 99%; (g) i) HCl, MeOH, 0 ^oC-rt, 2 h; ii) K_2CO_3, MeOH, 0 ^oC, 12 h, 76%; (h) Pd/C (10%), H_2, MeOH, rt, 12 h, 95%.

Sudalai, A. *et al.* (2016)[7a]

A. Sudalai and co-workers disclosed the enantioselective synthesis of 3-hydroxypipecolic acid **28** employed the L-proline catalyzed α-amination and Barbier allylation as the key steps (Scheme 36). The aldehyde **133** on proline catalyzed α-amination with diethyl azodicarboxylate followed by *in situ* Barbier allylation with allyl bromide in presence of Zn and NH_4Cl furnished the alcohol **134** in 80% yield. The alcohol **134** on DDQ mediated intramolecular oxidative acetalization with benzyl ether afforded the benzylidine acetal **135** in 95% yield. The acetal **135** on treatment with $BrCH_2CO_2Et$ in presence of Cs_2CO_3 furnished the olefin **136** which on hydroboration-oxidation delivered the primary alcohol **137** in 70% yield. The alcohol **137** was transformed into its mesylate which on subsequent intramolecular *N*-alkylation in presence of NaH afforded the piperidine derivative **138** followed by deprotection of acetal and carbamate ester group with 6N HCl furnished the compound **27** in

62% yield. The deprotection of benzylidine acetal group of **138** afforded the alcohol **139** in 95% yield and TBS protection of corresponding alcohol afforded the silyl ether **140** in 93% yield. The selective primary TBS group deprotection of **140** followed by oxidation of the primary alcohol and deprotection of the carbamate group afforded the target compound **28** in 65% yield.

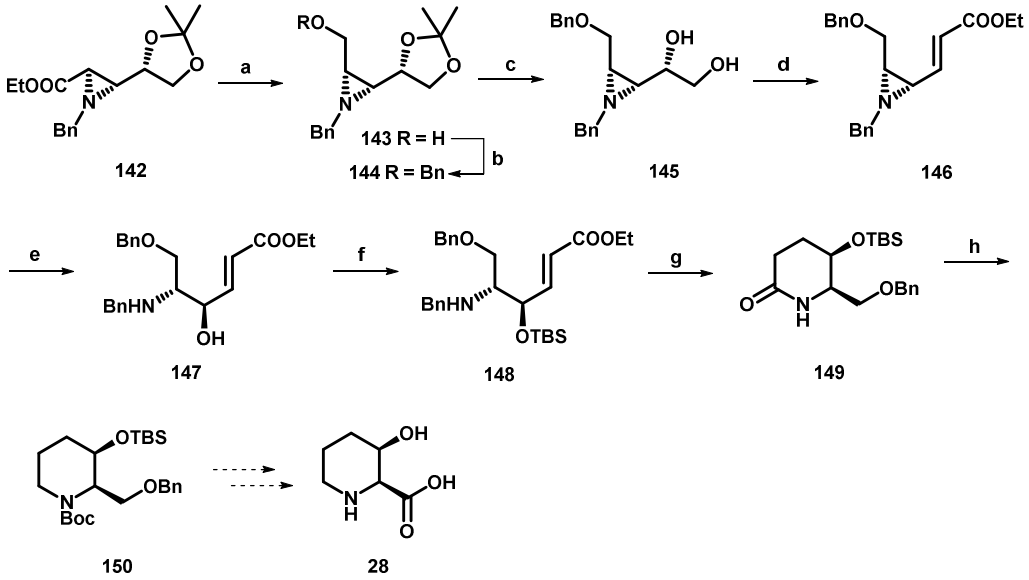


Scheme 36. *Reagents and conditions*: (a) i) DEAD, L-proline, CH_3CN, 0 ^oC, 3 h; ii) Zn, allyl bromide, NH_4Cl sat., 0 ^oC, 1 h, 80%; (b) DDQ, 4 Å MS, CH_2Cl_2, -30 ^oC, 6 h, 95%; (c) $BrCH_2CO_2Et$, Cs_2CO_3, CH_3CN, 80 ^oC, 6 h, 78%; (d) $BH_3.SMe_2$, THF, 0 ^oC, 1 h then, 10% aq. KOH, H_2O_2, 0 ^oC, 1 h, 70%; (e) i) MsCl, Et_3N, CH_2Cl_2, 0 ^oC, 2 h; ii) NaH, DMF, 0 ^oC, 3 h, 92% (over two steps); (f) 6N HCl, reflux, 24 h, 62% (g) CSA (cat.), CH_3OH, 0 ^oC, 1 h, 95%; (h) TBSCl, imidazole, DMF, 25 ^oC, 6 h, 93%; (i) CSA (cat.), CH_3OH, 0 ^oC, 1 h, 86%; (j) i) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/CH_3CN/H_2O$, 25 ^oC, 12 h; ii) 6N HCl, 24 h, 65% (over two steps).

Chavan, S. P. *et al.* (2014)[7f]

S. P. Chavan and co-workers reported the formal synthesis of *cis*-3-hydroxypipecoloc acid **28** starting from *cis*-aziridine-2-carboxylate employed the stereo and regioselective aziridine ring opening as key step (Scheme 37). The aziridine **142** was prepared from D-mannitol diacetonide which on reduction with LAH afforded the alcohol **143** in 90% yield and subsequent protection with benzyl bromide furnished the compound **144** in 95% yield. Then **144** on treatment with PTSA in MeOH afforded the acetonide deprotected compound **145** which on oxidative cleavage with sodium metaperiodate and subsequent 2C Wittig olefination of the corresponding aldehyde furnished the ester **146** in 85% yield. The ester **146**

on regio and stereoselective ring opening of aziridine moiety under acidic conditions gave the amino alcohol **147** in 85% yield. The compound **147** on *O*-TBS protection followed by cyclization under hydrogenation reaction conditions furnished the lactam **149** in 88% yield. The reduction of lactam **149** using BH_3.DMS and subsequent protection with $(Boc)_2O$ afforded the compound **150** in 80% yield. The target compound **28** could be obtained from **150** by following the known literature procedure.[7o]

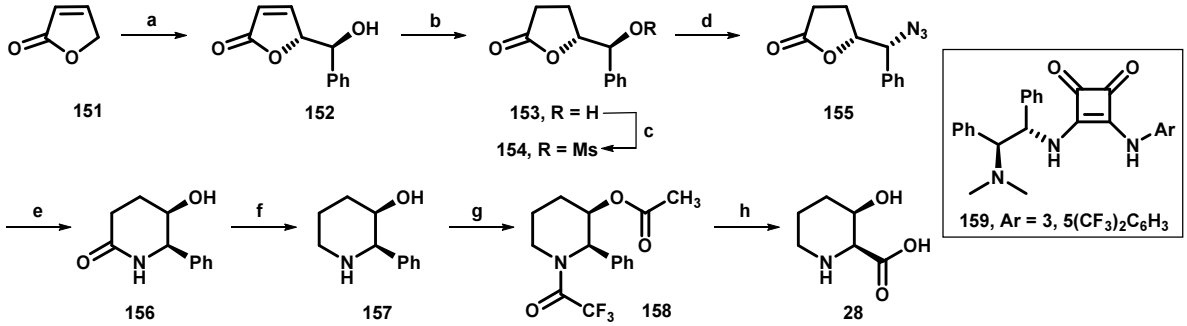


Scheme 37. *Reagents and conditions*: (a) LAH, THF, 0 ^oC, 1 h, 90%; (b) BnBr, NaH, TBAI, DMF, 95%; (c) PTSA, CH_3OH, 85%; (d) i) $NaIO_4$, $(CH_3)_2CO/H_2O$ (2:1); ii) Ph_3PCHCO_2Et, $PhCO_2H$, PhMe, reflux, 85% (over two steps); (e) TFA, CH_3CN/H_2O (9:1), 85%; (f) TBSCl, Imidazole, DMAP, CH_2Cl_2, reflux, 90%; (g) H_2, 10% $Pd(OH)_2/C$, EtOH, 88%; (h) i) BH_3.DMS, THF; ii) $(Boc)_2O$, CH_2Cl_2, Et_3N, 80% (over two steps).

Pansare, S. V. *et al.* (2012)[7i]

S. V. Pansare and co-workers reported the synthesis of (2*S*,3*R*)-3-hydroxypipecolic acid **28** starting from commercially available lactone **151** in eight steps (Scheme 38). The lactone **151** on vinylogous aldol reaction with benzaldehyde in presence of catalyst **159** provided the alcohol **152** in 74% yield. The alcohol **152** under hydrogenation reaction conditions afforded the butyrolactone **153** which on subsequent *O*-mesylation of the secondary alcohol followed by nucleophilic displacement with NaN_3/DMF furnished the azido derivative **155**. The azide derivative **155** on cyclization under hydrogenation reaction conditions using K_2CO_3/MeOH afforded the lactam **156** in 79% yield. The amide **156** on reduction with BH_3.THF furnished the piperidine derivative **157** in 96% yield. The piperidine derivative **157** was first converted to the *N*,*O*-bistrifluoroacetyl derivative and the trifluoroacetate ester was replaced with an

acetate to deliver **158** in 89% yield. The compound **158** on oxidation of the phenyl ring with $RuCl_3/NaIO_4$ followed by methanolysis of trifluoroacetamide and acetate afforded the target compound **28** in 58% yield.



Scheme 38. *Reagents and conditions*: (a) PhCHO, **159**, CH_2Cl_2, rt, 192 h, 74%; (b) H_2, Pd/C, rt, 4 h, 99%; (c) MsCl, Et_3N, 0 ^oC, 1 h; (d) NaN_3, DMF, 80 ^oC, 4 h; (e) Pd/C, H_2, K_2CO_3, MeOH, rt, 4 h, 79%; (f) BH_3.THF, reflux, 5 h, 96%; (g) i) $(CF_3CO)_2O$, dimethylamino-pyridine, Et_3N, CH_2Cl_2, 0 ^oC-rt, 12 h; ii) K_2CO_3, THF, rt, 36 h; iii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, rt, 12 h (89% over three steps); (h) i) $RuCl_3/NaIO_4$, $CCl_4/CH_3CN/H_2O$, rt, 24 h; ii) K_2CO_3, MeOH, rt, 12 h, 58% (over two steps).

3.2.1 Table 5. Comparison with the previous reported syntheses of 1-deoxygalactonojirimycin **26**, *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27**.

Sr. No.	Syntheses	Key step	Overall yield	No. of steps
1.	***Under manuscript preparation*** (1-deoxygalactonojirimycin, (2R,3R)-3-hydroxy-2-hydroxymeth ylpiperidine & 3-hydroxypipecolic acid)	organocatalyzed self aldol reaction	**46% & 56%**	**Six & five**
2.	*Can. J. Chem.* **2017**, 1 (1-deoxygalactonojirimycin)	*α*-chlorination and aldol reaction	29%	five
3.	*J. Org. Chem.* **2016**, *81*, 7432 (1-deoxygalactonojirimycin)	Stereoselective addition to *syn,anti*-oxazine	44%	Four
4.	*J. Org. Chem.* **2015**, *80*, 4776 (1-deoxygalactonojirimycin)	*α*-aminoxylation	35%	eight

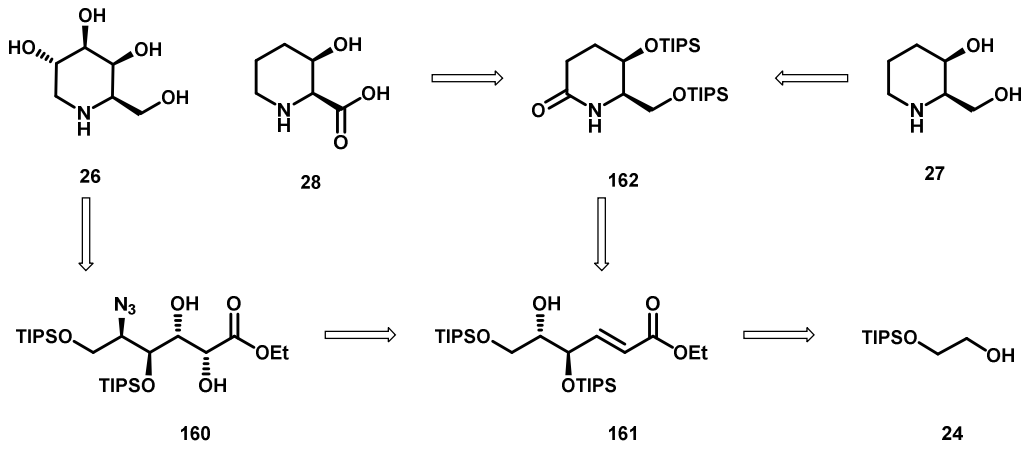
5.	*Tetrahedron Lett.* **2016**, *57*, 2021 (3-hydroxypipecolic acid & (2R,3R)-3-hydroxy-2-hydroxymeth ylpiperidine)	L-proline catalyzed sequential *a*-amination	18 & 23%	eight
6.	*Tetrahedron Lett.*, **2014**, *55*, 6423 (3-hydroxypipecolic acid)	regioselective aziridine ring opening	24%	ten
7.	*Org. Biomol. Chem.* **2012**, *10*, 2119 (3-hydroxypipecolic acid)	vinylogous aldol reaction	28%	eight

3.3 Present Work:

Herein, we are reporting a novel and flexible access to the synthesis of 1-deoxygalactonojirimycin **26**, *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** employing the proline catalyzed MacMillan's asymmetric aldol reaction, Mitsunobu inversion and Upjohn reaction as key steps.

3.4 Results and Discussion:

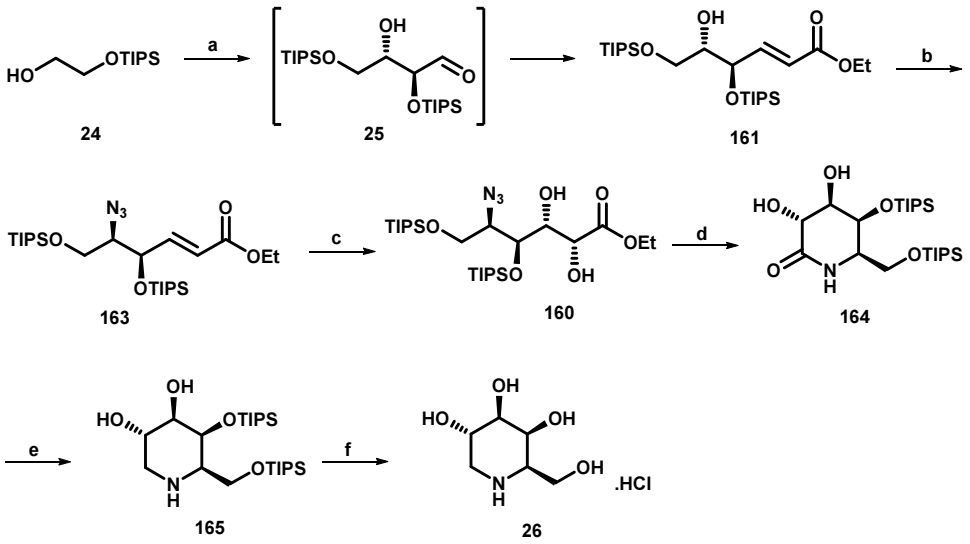
Our synthetic approach towards the synthesis of hydroxylated piperidines and derivatives was envisaged *via* the retrosynthetic route as outlined in Scheme 39. The azido derivative **160** was visualized as a synthetic intermediate from which 1-deoxygalactonojirimycin **26** could be synthesized *via* catalytic hydrogenation followed by reduction of amide functionality and following standard organic transformations. The azide **160** in turn could be accessed from ester **161** by Mitsunobu inversion followed by asymmetric dihydroxylation reaction.



Scheme 39. Retrosynthetic analysis for hydroxylated piperidines and their derivatives.

The *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** could be obtained from common derivative **162** through amide reduction followed by standard functional group manipulations. The lactam **162** in turn could be easily accessed from ester **161** *via* Mitsunobu inversion followed by catalytic hydrogenation. The key intermediate ester **161** could easily be assembled from readily available mono-silyl ether protected terminal alcohol **24** *via* oxidation followed by MacMillan's self aldol and Wittig olefination reactions.

The synthetic endeavour for 1-deoxygalactonojirimycin **26** commenced with readily available monosilylated ethylene glycol **24**, which can be easily synthesized from base catalyzed selective protection of ethylene glycol with TIPS-Cl (Scheme 40). Exposure of alcohol **24** under Swern conditions[8] and subsequent L-proline catalyzed MacMillan's self aldol reaction following the literature[9] procedure furnished the *anti*-diastereomer **25** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield, the ^{1}H NMR spectrum of **25** gave aldehyde protons at δ 9.68 (singlet, one proton), which on spontaneous treatment with (ethoxycarbonylmethylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester **161** in excellent yield. The IR spectrum of **161** showed hydroxyl absorption at 3450 cm^{-1} and C=O stretching at 1720 cm^{-1}.



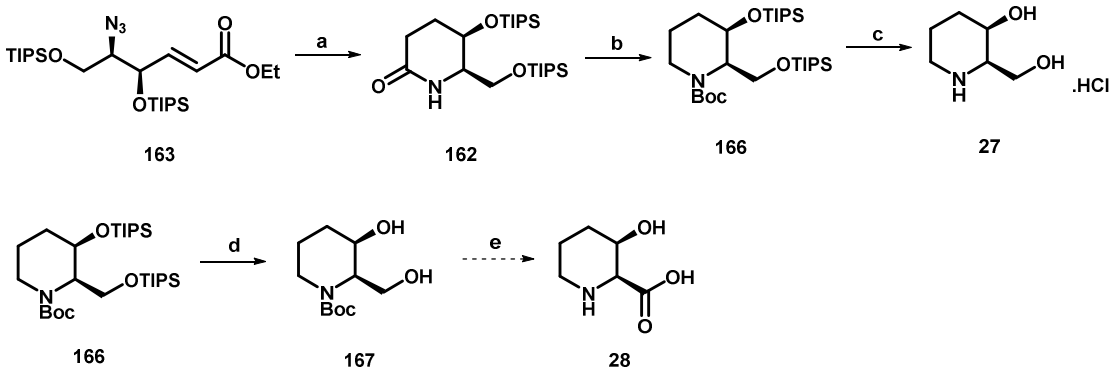
Scheme 40. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, -78 ^oC to rt, 2 h; ii) L-proline (10 mol%), DMF, rt, 24 h, *syn*-isomer in 16% and *anti*-isomer in 74%; iii) $PPh_3CHCOOEt$, THF, rt, 12 h, 85%; (b) DPPA, DEAD, TPP, THF, rt, 1 h, 88%; (c) OsO_4, NMO, acetone:water (8:1), 0 ^oC-rt, 24 h, 91%; (d) H_2, Pd/C (10%), Et_3N, EtOAc, rt, 12 h, 94%; (e) $BH_3.SMe_2$, THF, 5 ^oC, 12 h, 83%; (f) 6N HCl, reflux, 12 h, 88%.

The ^{1}H NMR spectrum of **161** gave olefin protons at δ 6.98 (doublet of doublet, one proton) with the coupling constant J = 6.0 and 15.6 Hz and δ 6.06 (doublet, one proton) with the coupling constant J = 16.0 Hz, indicating *trans*-olefin and shows absence of aldehyde protons.

Next, our attempt for conversion of free hydroxyl group of compound **161** *via O*-mesylate followed by nucleophilic displacement with NaN_3/DMF to azide **163** was sluggish. Therefore, we performed the conversion of hydroxyl group of **161** *via* DPPA/DEAD under Mitsunobu conditions[10] which proceeded well to furnish the azide **163** in 88% yield. The IR spectrum of **163** showed strong azide absorption at 2102 cm^{-1}. With enantiomerically pure azide **163** in hand, we then performed dihydroxylation using OsO_4/NMO under Upjohn conditions[11] which furnished the diol **160** as a solitary diastereomer.[5c] The ^{1}H NMR of diol **160** indicated the absence of olefin protons.

Our next aim was to carry out the synthesis of hydroxylated piperidine moiety. Towards this end, compound **160** was subjected to reductive lactamization under 1 atm H_2 pressure in the presence of catalytic amount of Pd/C under basic conditions which furnished the hydroxylated lactam **164** in 94% yield. The lactam **164** on $BH_3.SMe_2$ mediated reduction under anhydrous conditions afforded the hydroxylated piperidine **165** in 83% yield. Finally, *O*-TIPS deprotection of compound **165** using 6N HCl under reflux conditions delivered the 1-deoxygalactonojirimycin **26** as salt form in 88% yield. The physical and spectroscopic data of 1-deoxygalactonojirimycin **26** were found to be in consonance with those reported in the literature.[5a,c,d]

Next, we moved further to extend the above developed strategy towards the synthesis of other analogues of hydroxylated piperidines such as *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** (Scheme 41). The synthesis of *cis*-(-)-3-hydroxypipecolic acid **28** and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** started with azide derivative **163**, which was subjected to hydrogenation in the presence of catalytic amount of Pd/C under basic conditions to deliver the lactam **162** in 95% yield (Scheme 41). The lactam **162** was then treated with $BH_3.SMe_2$ under anhydrous conditions to afford the piperidine moiety, which on subsequent reaction with $(Boc)_2O/Et_3N$ synthesized the *N*-Boc derivative **166** in 87% yield.

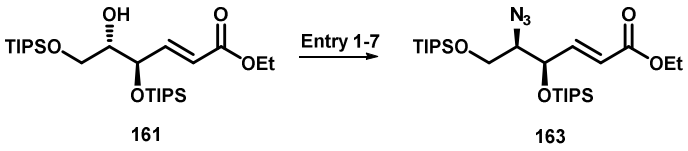


Scheme 41. *Reagents and conditions*: (a) H_2, Pd/C (10%), Et_3N, EtOAc, rt, 12 h, 95%; (b) (i) $BH_3.SMe_2$, THF, 5 ^oC, 12 h; (ii) $(Boc)_2O$, Et_3N, DCM, rt, 12 h, 87%; (c) 6N HCl, reflux, 12 h, 91%; (d) TBAF, THF, rt, 12 h, 89%; (e) Ref. 12.

Finally, the concomitant global deprotection of *N*-Boc and *O*-TIPS of piperidine derivative **166** was achieved in one pot *via* reflux under acidic conditions which successfully delivered the (2*R*,3*R*)-3-hydroxymethylpiperidine **27** as salt form in 91% yield. The physical and spectroscopic data of (2*R*,3*R*)-3-hydroxymethylpiperidine **166** were found to be in consonance with those reported in the literature.[6] On the other hand, cleavage of triisopropyl silyl group of compound **166** using TBAF afforded the diol **167** in 89% yield. Finally compound **167** on oxidation and *N*-Boc deprotection would furnish the *cis*-(-)-3-hydroxypipecolic acid **28** using the known literature procedure.[12]

3.5 Research and Development (R & D):

3.5.1 Table 6. Optimization of conversion of alcohol to azide.



Entry	Reagents	Solvent	Temp. (^oC)	Time (h)	Result (%yield)
1	i) MsCl, Et_3N	DCM	0 ^oC to rt	20 min	No desired product
	ii) NaN_3	DMF	80 ^oC	12	
2	i) MsCl, Et_3N	DCM	0 ^oC to rt	20 min	No reaction
	ii) NaN_3	DMSO	120 ^oC	48	

3	i) TsCl, Et_3N	DCM	0 ^oC to rt	1	No reaction
	ii) NaN_3	DMF	80 ^oC	24	
4	i) TsCl, DIPEA, DMAP	DCM	0 ^oC to rt	2	No reaction
	ii) NaN_3	DMSO	80 ^oC	12	
5	DPPA, DBU	Toluene	0 ^oC to rt	24	No reaction
6	DPPA, Et_3N	DMF	100 ^oC	24	No reaction
7	TPP, DPPA, DEAD	THF	rt	1	88

DEAD = Diethylazodicarboxylate, DPPA = Diphenylphosphoryl azide, TPP = Triphenylphosphine

For the synthesis of azide derivative **163**, we have optimized few reaction conditions as described in table 6. The conversion of free hydroxyl group of compound **161** *via O*-mesylate followed by nucleophilic displacement with NaN_3 in DMF at 80 ^oC for 12 h was not successful as ^1H-NMR predicts the presence of mesyl group and deprotection of one of the TIPS protecting group (table 6, entry 1). Similarly, by changing solvent DMF to DMSO was also not successful (table 6, entry 2). Then, conversion of hydroxyl group *via O*-Ts followed treatment with NaN_3 in DMF at 80 ^oC for 24 h was sluggish (table 6, entry 3). Similarly, conditions in entry 4 were also not working (table 6, entry 4). Then, treatment of alcohol with DPPA/DBU in toluene at 0 ^oC to rt for 24 h was not fruitful (table 6, entry 5). Similarly, treatment of alcohol with DPPA/Et_3N in DMF at 100 ^oC for 24 h was sluggish (table 6, entry 6). Lastly, reaction of alcohol with TPP/DPPA/DEAD in THF at rt for 1 h gave the azido derivative **163** in 88% yield (table 6, entry 7).

3.6 Conclusion:

In conclusion, we have developed a simple and efficient approach for the synthesis of hydroxylated piperidines and its applications to the total synthesis of 1-deoxygalactonojirimycin **26**, (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** and formal synthesis of *cis*-(-)-3-hydroxypipecolic acid **28** employing the proline catalyzed MacMillan's asymmetric aldol reaction, Mitsunobu inversion and Upjohn reaction as key steps. We have

used MacMillan's organocatalyzed self aldol reaction as the source of chirality. For azide formation of alcohol **161**, DPPA/TPP/DEAD in THF was found to be the successful attempt with good yield. We have achieved the synthesis of 1-deoxygalactonojirimycin **26** in six steps with 46% overall yield and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** in five steps with 56% overall yield. Moreover, the described synthetic strategy has significant potential for further stereochemical variations at all the possible positions to synthesize the other hydroxylated piperidine alkaloids.

3.7 Experimental Section:

3.7.1 General Experimental Details:

All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. All the reagents were added either *via* syringe or cannula. Each distillation was performed under an inert atmosphere. All reactions have their respective temperatures within their respective schemes. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.

Chromatography

All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, then were stained by ninhydrin or anisaldehyde in ethanol or $KMnO_4$ in water as development reagents followed by brief heating with a heat gun. Column chromatography were performed on silica gel (60-120 and 100-200 mesh) using a mixture of ethyl acetate/hexane as eluent.

Reagents and solvents

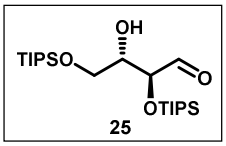
Solvents were obtained commercially and were used without purification unless otherwise noted in experimentals. Distilled water was used for every aqueous reaction, work-up procedure, and in the preparation of every aqueous solution used in the work-up. For reaction solvent, CH_2Cl_2 was distilled from CaH_2, and THF was distilled under N_2 from sodium benzophenone ketyl, all immediately prior to use.

Spectroscopic Measurements

^{1}H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units (δ) downfield from TMS. Coupling

constants, *J*, are listed in hertz (Hz). Optical rotations were measured on Automatic polarimeter AA-65 and concentrations of g/100mL. High resolution mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

(2*S*,3*S*)-3-hydroxy-2,4-bis((triisopropylsilyl)oxy)butanal, 25[9]

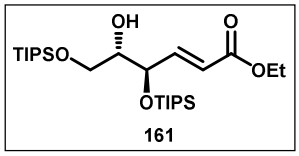


25

To a stirred solution of oxalyl chloride (2.36 mL, 27.46 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added DMSO (4.02 mL, 56.72 mmol) in CH_2Cl_2 (20 mL) dropwise over 15 min and stirred for additional 30 min at -78 ^oC. A solution of the monosilylated ethylene glycol **24** (4.0 g, 18.31 mmol) in CH_2Cl_2 (40 mL) was added dropwise to the above reaction mixture and stirred for another 30 min at -78 ^oC. Then Et_3N (11.20 mL, 80.52 mmol) in CH_2Cl_2 (30 mL) was added slowly at -78 ^oC and stirred for 1 h at room temperature. The mixture was diluted with water and organic layer separated. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude aldehyde, which was used as such for the next step without further purification.

To a DMF (110 mL) solution of above crude aldehyde was added L-proline (210 mg, 1.83 mmol) and stirred for 24 h at room temperature. The resulting solution was diluted with ethyl acetate (50 mL), washed successively with water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, concentrated in vacuo to afford the anti/syn-diastereomeric mixture as pale yellow liquid. The *anti*-/*syn*-diastereomers were separated and purified by silica gel column chromatography using EtOAc/hexane 1:99 v/v as eluent to give the *anti*-diastereomer **25** (5.8 g, 74%) as pale yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 4.26-4.24 (m, 1H), 4.00-3.96 (m, 1H), 3.84 (dd, J = 9.8, 6.5 Hz, 1H), 3.78 (dd, J = 9.5, 5.9 Hz, 1H), 2.40 (d, J = 3.04 Hz, 1H), 1.11-1.03 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.3, 78.9, 74.2, 69.6, 62.6, 17.9, 17.8, 12.2, 11.8.

Ethyl(4*R*,5*S*,*E*)-5-hydroxy-4,6-bis((triisopropylsilyl)hex-2-enoate, 161

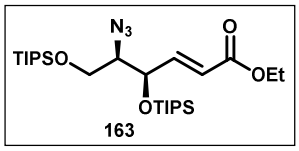


161

To a stirred solution of (ethoxycarbonylmethylene)triphenyl phosphorane (4.83 g, 13.86 mmol) in dry THF (30 mL) was dropwise added a solution of the above aldehyde **25** (4.0 g, 9.24 mmol) in dry THF (30 mL) and stirred for 12 h at room temperature. The reaction mixture

was then concentrated *in vacuo* and purified by silica gel column chromatography using (EtOAc/hexane 1:49 v/v) as eluent to furnish the olefin **161** (3.9 g, 85%) as a thick yellow liquid. [R_f = 0.20, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -41.0 (c 2.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3450, 2943, 1720, 1364, 1174, 985, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.98 (dd, *J* = 6.0, 15.6 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 4.62-4.60 (m, 1H), 4.19 (q, *J* = 7.6, 14.4 Hz, 2H), 3.85-3.78 (m, 2H), 3.69-3.66 (m, 1H), 2.53 (s, 1H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.33-1.03 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.0, 146.4, 122.7, 74.8, 73.1, 63.5, 60.5, 60.3, 17.9, 17.9, 14.2, 12.3, 11.8; HRMS (ESI), calcd for $C_{26}H_{55}O_5Si_2$ $[M + H]^+$ 503.3583; found 503.3581.

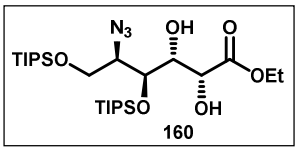
Ethyl(4*R*,5*R*,*E*)-5-azido-4,6-bis((triisopropylsilyl)oxy)hex-2-enoate, 163



163

To a dry THF (15 mL) solution of alcohol **161** (3.5 g, 6.96 mmol) were sequentially added triphenylphosphine (3.65 g, 13.92 mmol), diethyl azodicarboxylate (2.20 mL, 13.92 mmol), diphenyl phosphorazidate (3.01 mL, 13.92 mmol) dropwise at room temperature and stirred for 1 h at the same temperature. The reaction mixture was then concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane 1:99 v/v) to afford the azide **163** (3.2 g, 88%) as a yellow oil. [R_f = 0.6, EtOAc/hexane 1 : 19 v/v]; $[\alpha]_D^{25}$ +9.6 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) ν: 2924, 2866, 2102, 1717, 1462, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.93 (dd, *J* = 6.0, 15.6 Hz, 1H), 6.03 (d, *J* = 16.0 Hz, 1H), 4.58-4.55 (m, 1H), 4.21 (q, *J* = 6.8, 14.0 Hz, 2H), 4.02 (dd, *J* = 3.6, 10.8 Hz, 1H), 3.74-3.69 (m, 1H), 3.51-3.47 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.12-1.04 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9, 146.4, 122.2, 71.9, 67.7, 62.9, 60.5, 29.6, 17.9, 17.8, 14.1, 12.3, 11.8; HRMS (ESI), calcd for $C_{26}H_{54}N_3O_4Si_2$ $[M + H]^+$ 528.3648; found 528.3628.

Ethyl(2*R*,3*R*,4*S*,5*R*)-5-azido-2,3-dihydroxy-4,6-bis((triisopropylsilyl)oxy)hexanoate, 160

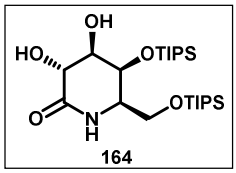


160

To an acetone/water (18 mL, 8:1) solution of the alkene **163** (1.0 g, 1.89 mmol) were added 0.1 M solution of OsO_4 in toluene (0.94 mL, 5 mol %) and 50% solution of *N*-methylmorpholine *N*-oxide (0.88 mL, 3.78 mmol) sequentially at 0 ^oC. After completion of the reaction as monitored by TLC, sodium sulfite (238 mg, 1.89 mmol) was added at 0 ^oC and stirred for additional 1 h. The crude product was then extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by silica gel column chromatography (EtOAc/hexane 1:9 v/v) to provide the diol **160** (960 mg, 91%) as a white solid. [R_f = 0.4,

EtOAc/hexane 1:4 v/v]; mp = 172-175 ^{o}C; $[\alpha]_D^{25}$ +6.2 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3320, 2950, 2102, 1734, 1680, 1632, 1452, 858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.33-4.23 (m, 4H), 4.11-4.09 (m, 1H), 4.05 (d, *J* = 5.2 Hz, 2H), 3.97 (t, *J* = 7.2 Hz, 1H), 3.84-3.81 (m, 1H), 3.14-3.12 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14-1.05 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 74.0, 71.0, 70.1, 65.7, 62.7, 62.0, 18.0, 17.8, 14.0, 13.0, 11.8; HRMS (ESI), calcd for $C_{26}H_{56}N_3O_6Si_2$ $[M + H]^+$ 562.3702; found 562.3703.

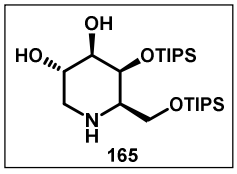
(3*R*,4*R*,5*S*,6*R*)-3,4-Dihydroxy-5-((triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl) piperidin-2-one, 164



164

To an EtOAc (25 mL) solution of azide **160** (800 mg, 1.42 mmol) were added catalytic amount of Et_3N and 10% Pd/C (100 mg) at room temperature. The reaction mixture was then subjected to hydrogenation under 1 atmosphere pressure for 12 h. After this time, the solution was filtered through Celite pad and washed with methanol. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (EtOAc/hexane 1:4 v/v) to furnish the lactam **164** (650 mg, 94%) as a yellow liquid. [R_f = 0.3, EtOAc/hexane 2:3 v/v]; $[\alpha]_D^{25}$ -5.7 (c 1.5, $CHCl_3$); IR (CH_2Cl_2) *v*: 1680, 1409, 1390, 885 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.16 (br s, 1H), 4.40-4.36 (m, 2H), 3.90-3.84 (m, 4H), 3.55-3.51 (m, 1H), 2.90 (br s, 1H), 1.18-1.03 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 73.4, 69.7, 69.5, 64.2, 57.3, 18.2, 17.8, 12.9, 11.7; HRMS (ESI), calcd for $C_{24}H_{52}NO_5Si_2$ $[M + H]^+$ 490.3379; found 490.3364.

(3*S*,4*R*,5*S*,6*R*)-5-((Triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)piperidine-3,4-diol, 165

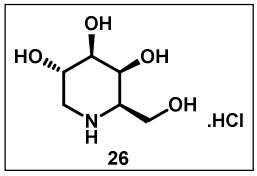


165

To a dry THF (15 mL) solution of lactam **164** (600 mg, 1.22 mmol) was added $BH_3.SMe_2$ (0.43 mL, 4.89 mmol) dropwise under argon at 0 ^{o}C and warmed to room temperature for 12 h. The reaction mixture was then quenched by slow addition of MeOH (8 mL) over 4 h. The reaction mixture was then evaporated, diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 2:3 v/v) to afford amine **165** (515 mg, 89%) as a white solid. [R_f = 0.3, EtOAc/hexane 3:2 v/v]; mp = 181-183 ^{o}C; $[\alpha]_D^{25}$ -46.0 (c 1.0, $CHCl_3$); IR (CH_2Cl_2) *v*: 3310, 1645, 1390, 878 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.31 (t, *J* = 3.6 Hz, 1H), 3.96 (t, *J* = 8.8 Hz, 1H), 3.85-3.81 (m, 1H), 3.70-3.66 (m, 1H), 3.62 (br s, 1H), 3.24-3.20 (m, 1H), 2.89 (br s, 1H), 2.52-2.47 (m, 1H), 1.88 (br s, 3H), 1.19-1.02 (m, 42H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 79.9, 74.9, 69.6, 69.4, 60.5, 47.2, 18.2, 17.9, 12.6, 11.9; HRMS (ESI), calcd for $C_{24}H_{54}NO_4Si_2$ $[M + H]^+$ 476.3586; found 476.3563.

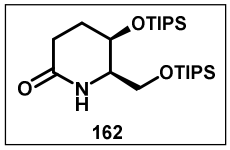
1-Deoxygalactonojirimycin, 26[5]



26

A freshly prepared 6N HCl (10 mL) solution was added to amine **165** (200 mg, 0.42 mmol) and refluxed for 12 h. The reaction mixture was cooled to room temperature and washed with CH_2Cl_2 (10 mL) to remove organic soluble impurities. The aqueous layer layer was then concentrated under high vacuum followed by overnight drying under high vacuum furnished the target compound 1-deoxygalactonojirimycin **26** in salt form as a light brown oil (57 mg, 85%). $[\alpha]_D^{25}$ -54.5 (c 0.155, H_2O)]; [lit.[5d] $[\alpha]_D^{25}$ -54.8 (c 0.155, H_2O)]; IR (neat) ν: 3358, 3045, 2962, 1657, 1556, 1290, 1164, 1056, 998, 736 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ: 4.14 (br s, 1H), 4.08-4.01 (m, 1H), 3.87-3.75 (m, 2H), 3.63-3.60 (m, 1H), 3.48 (dd, J = 5.6, 12.4 Hz, 1H), 3.40-3.37 (m, 1H), 2.84 (t, J = 11.9 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ: 72.9, 66.9, 64.6, 60.0, 59.1, 46.1.

(5*R*,6*R*)-5-((Triisopropylsilyl)oxy)-6-(((triisopropylsilyl)oxy)methyl)piperidin-2-one, 162



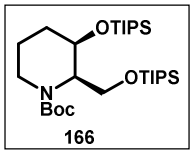
162

To an EtOAc (25 mL) solution of azide **163** (1.0 g, 1.89 mmol) were added catalytic amount of Et_3N and 10% Pd/C (50 mg) at room temperature. The reaction mixture was then subjected to hydrogenation under 1 atmosphere pressure for 12 h. After this time, the solution was filtered through Celite pad and washed with methanol. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 1:4) to furnish lactam **162** (820 mg, 95%) as a semi solid. [R_f = 0.3, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ -24.6 (c 0.9, $CHCl_3$); IR (CH_2Cl_2) ν: 1670, 1415, 1390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.06 (br s, 1H), 4.25-4.22 (m, 1H), 3.90-3.79 (m, 2H), 3.53-3.49 (m, 1H), 2.65-2.57 (m, 1H), 2.37-2.28 (m, 1H), 2.07-1.99 (m, 1H), 1.90-1.81 (m, 1H), 1.12-1.02 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.0, 65.2, 64.5, 59.0, 28.1, 27.0, 18.0, 17.8, 12.5, 11.7; HRMS (ESI), calcd for $C_{24}H_{52}NO_3Si_2$ $[M + H]^+$ 458.3480; found 458.3483.

***tert*-Butyl(2*R*,3*R*)-3-((triisopropylsilyl)oxy)-2(((triisopropylsilyl)oxy)methyl)piperidine-1-carboxylate, 166**

To a dry THF (15 mL) solution of lactam **162** (800 mg, 1.74 mmol) was added $BH_3.SMe_2$ (0.46 mL, 5.24 mmol) dropwise under argon at 0 ^oC and warmed to room temperature for 12

h. The reaction mixture was then quenched by slow addition of MeOH (8 mL) over 4 h. The reaction mixture was then evaporated, diluted with water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by silica gel column chromatography (EtOAc/hexane 3:7) to afford amine derivative which was used as such for the next step without further purification.

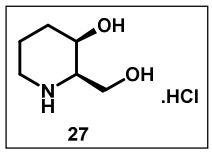


166

To a CH_2Cl_2 (10 mL) solution of above synthesized amine were added triethylamine (0.53 mL, 4.05 mmol) followed by di(tert-butyl)dicarbonate (0.65 mL, 2.70 mmol) and stirred for 12 h at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 1:99) to afford **166** (675 mg, 92%) as a colorless oil; [R_f = 0.65, EtOAc/hexane 1:19 v/v]; $[\alpha]_D^{25}$ -32.5 (c 0.5, $CHCl_3$); IR (CH_2Cl_2) *v*: 2938, 1685, 1523, 1249, 885 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.45-4.41 (m, 1H), 4.11-3.93 (m, 3H), 3.86-3.76 (m, 2H), 1.80-1.51 (m, 4H), 1.43 (s, 9H), 1.12-1.00 (m,42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.2, 79.1, 69.8, 58.1, 57.5, 37.1, 29.7, 28.3, 24.2, 18.0, 12.1, 11.8; HRMS (ESI), calcd for $C_{29}H_{62}NO_4Si_2$ $[M+H]^+$ 544.4212; found 544.4220.

(2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine, 27[6c]

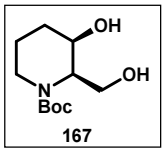
A freshly prepared 6N HCl (10 mL) solution was added to compound **166** (200 mg, 0.36 mmol) and refluxed for 12 h. The reaction mixture was cooled to room temperature and washed with CH_2Cl_2 (10 mL) to remove organic soluble impurities. The aqueous layer layer was then concentrated under high vacuum followed by overnight drying under high vacuum furnished the target compound (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** as a brown waxy solid (38 mg, 80%). $[\alpha]_D^{25}$ -13.1 (c 2.5 , H_2O); [lit.[6c] $[\alpha]_D^{25}$ -13.2 (c 2.51 , H_2O); ^1H NMR (400 MHz, D_2O) δ: 4.14 (br s, 1H), 3.83-3.79 (m, 1H), 3.74-3.69 (m, 1H), 3.41-3.37 (m, 1H), 3.31-3.25 (m, 1H), 3.03-2.96 (m, 1H), 2.04-1.90 (m, 2H), 1.75-1.67 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ: 62.6, 60.4, 59.9, 44.2, 28.4, 16.4.



27

***tert*-Butyl(2*R*,3*R*)-3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate, 167[7d]**

To a dry THF (5 mL) solution of the compound **166** (0.2 mL, 0.36 mmol) was added TBAF (1.10 mL, 1.0 M in THF, 1.10 mmol) at room temperature and stirred for 12 h. The reaction mixture was diluted with ethyl acetate, washed with water, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel



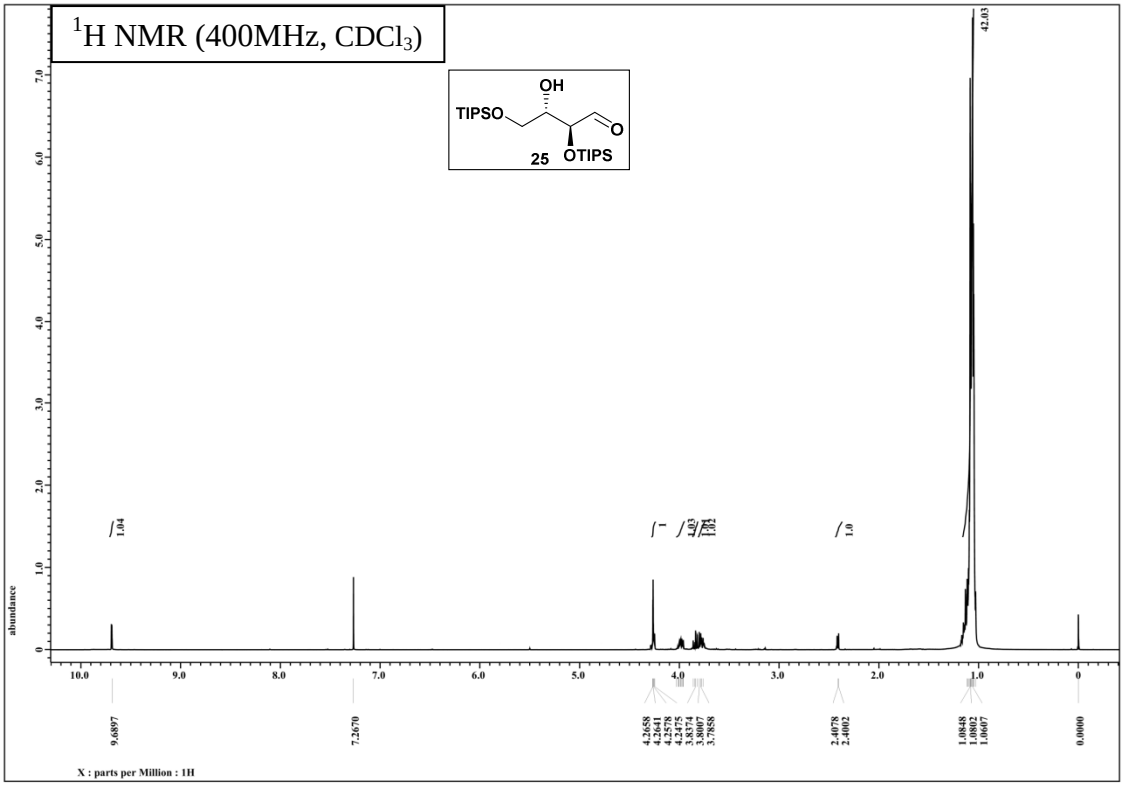
167

column chromatography (EtOAc/hexane 1:1 v/v) to afford the compound **167** (75 mg, 89%) as a white solid. [R_f = 0.4, pure EtOAc v/v]; mp = 115-117 ^{o}C {$[\alpha]_D^{25}$ -24.3 (c 0.7, MeOH)}, {lit.[7d] $[\alpha]_D^{25}$ -24.0 (c 0.7, MeOH)}; IR (CH_2Cl_2) ν: 3315, 1720, 1680, 1435 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.44-4.40 (m, 1H), 4.15-4.10 (m, 1H), 3.96-3.91 (m, 1H), 3.84-3.69 (m, 3H), 1.88-1.83 (m, 1H), 1.75-1.68 (m, 1H), 1.66-1.59 (m, 1H), 1.52-1.48 (m, 1H), 1.45 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.6, 80.2, 69.4, 59.3, 55.9, 39.6, 29.6, 28.3, 23.6; HRMS (ESI) calcd for $C_{11}H_{22}NO_4$ $[M + H]^+$ 232.1544; found 232.1544.

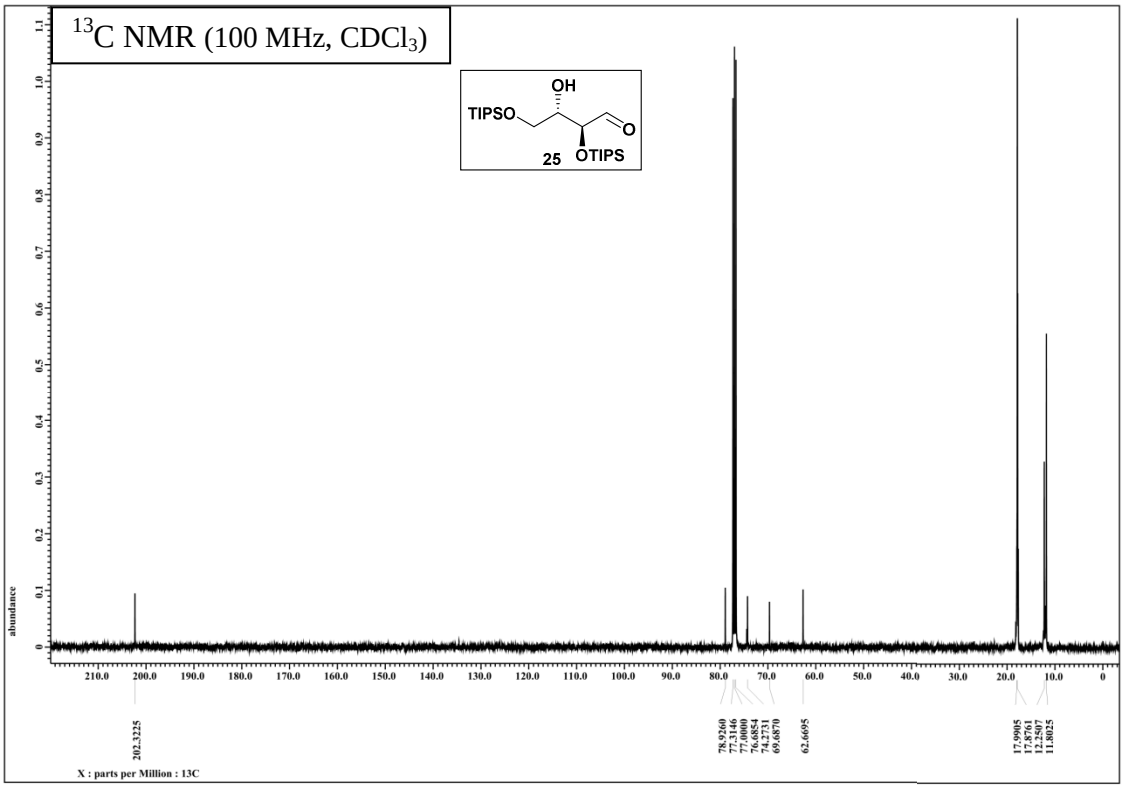
3.8 Spectra:

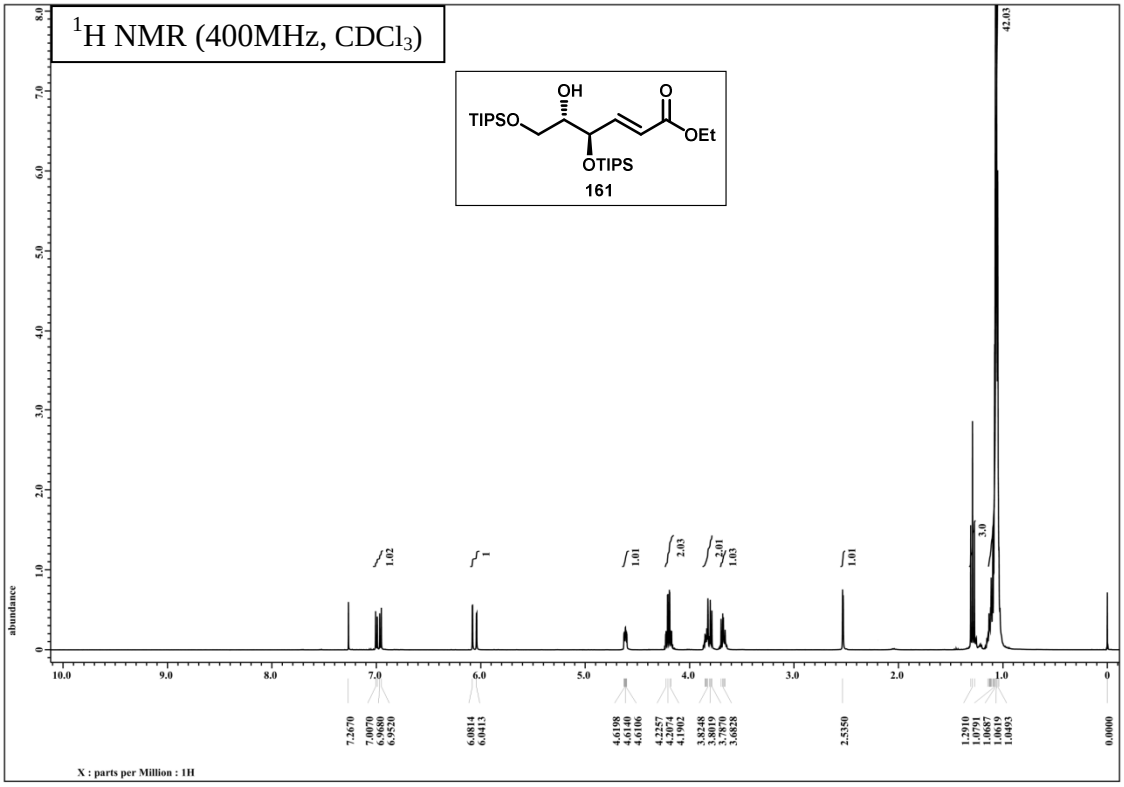
1. ^{1}H and ^{13}C NMR spectra of **25**
2. ^{1}H and ^{13}C NMR spectra of **161**
3. ^{1}H and ^{13}C NMR spectra of **163**
4. ^{1}H and ^{13}C NMR spectra of **160**
5. ^{1}H and ^{13}C NMR spectra of **164**
6. ^{1}H and ^{13}C NMR spectra of **165**
7. ^{1}H and ^{13}C NMR spectra of **26**
8. ^{1}H and ^{13}C NMR spectra of **162**
9. ^{1}H and ^{13}C NMR spectra of **166**
10. ^{1}H and ^{13}C NMR spectra of **27**
11. ^{1}H and ^{13}C NMR spectra of **167**

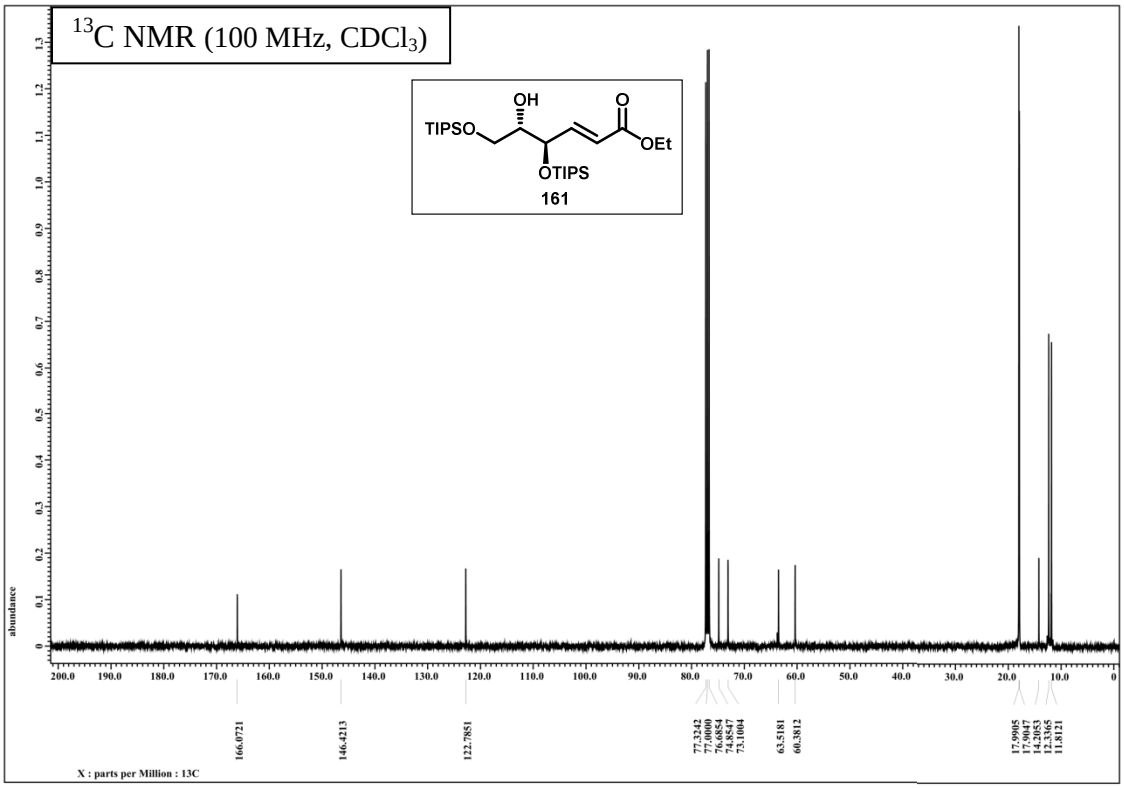
^{1}H NMR (400MHz, $CDCl_3$)

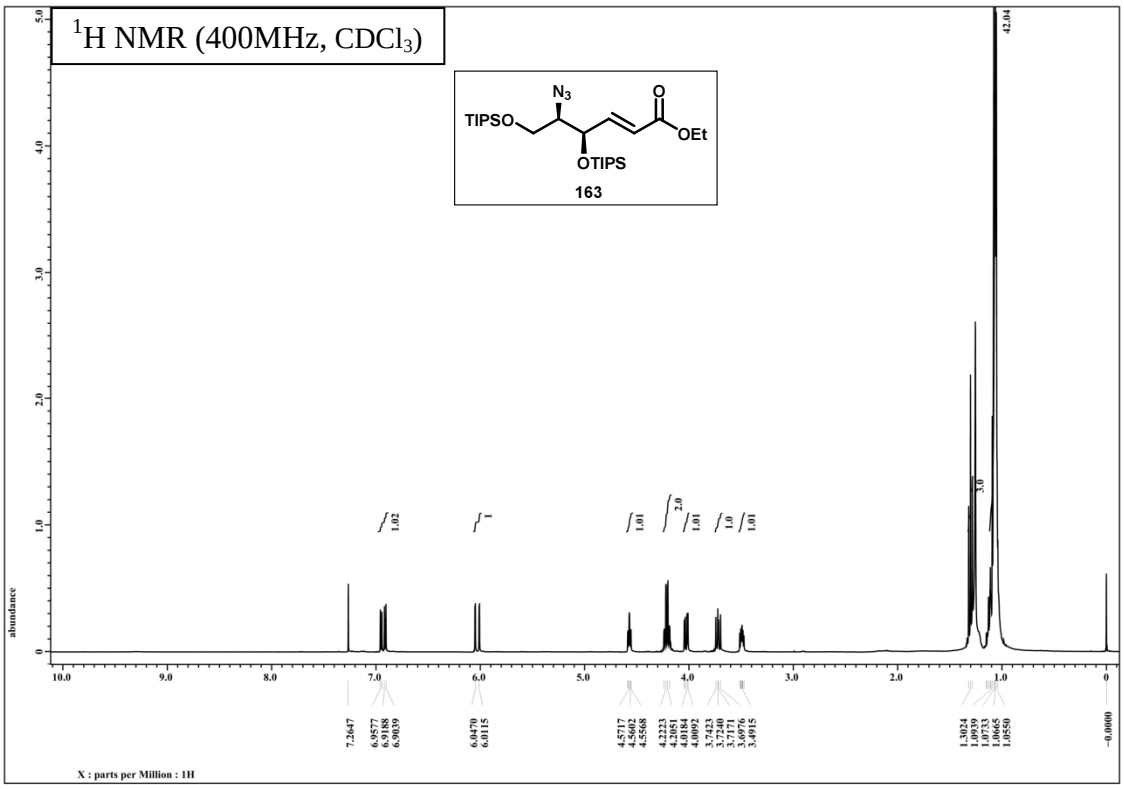


^{13}C NMR (100 MHz, $CDCl_3$)




^{1}H NMR (400MHz, $CDCl_3$)
OH
O
TIPSO
OEt
OTIPS
161
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
OH
O
TIPSO
OEt
OTIPS
161
abundance
X : parts per Million : 13C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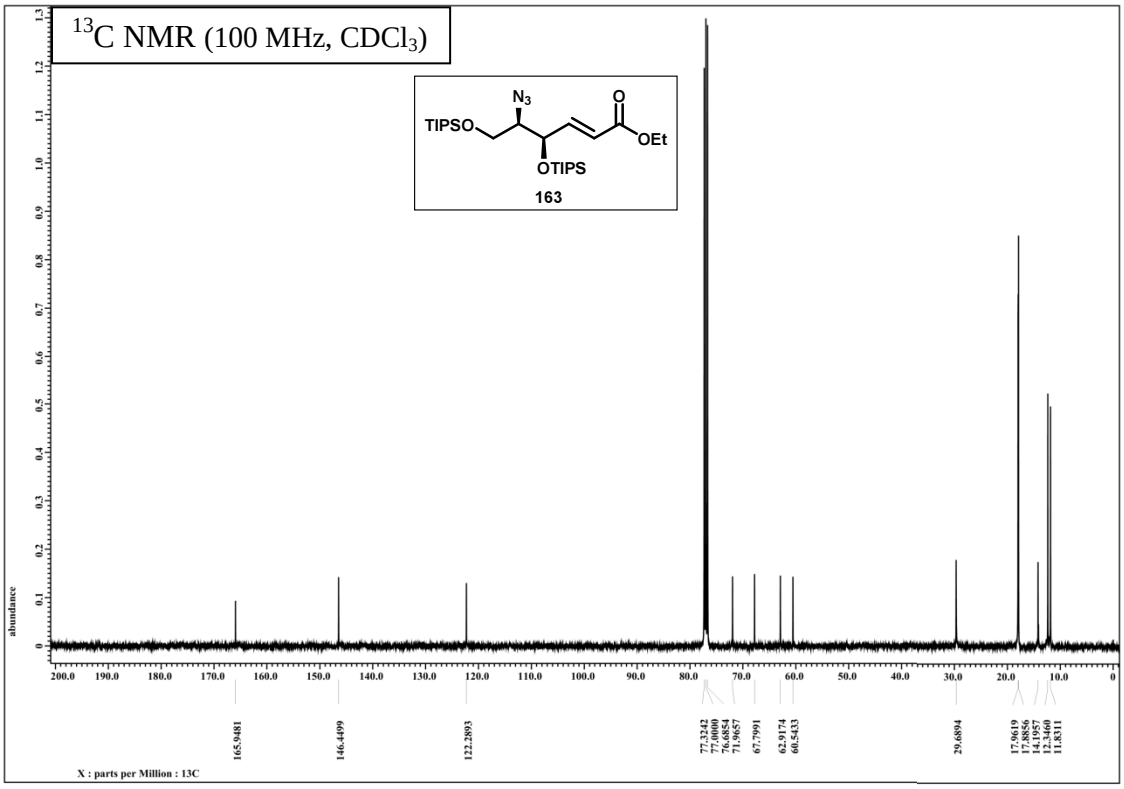
N3
O
OEt
OTIPS
163
abundance
X : parts per Million : 1H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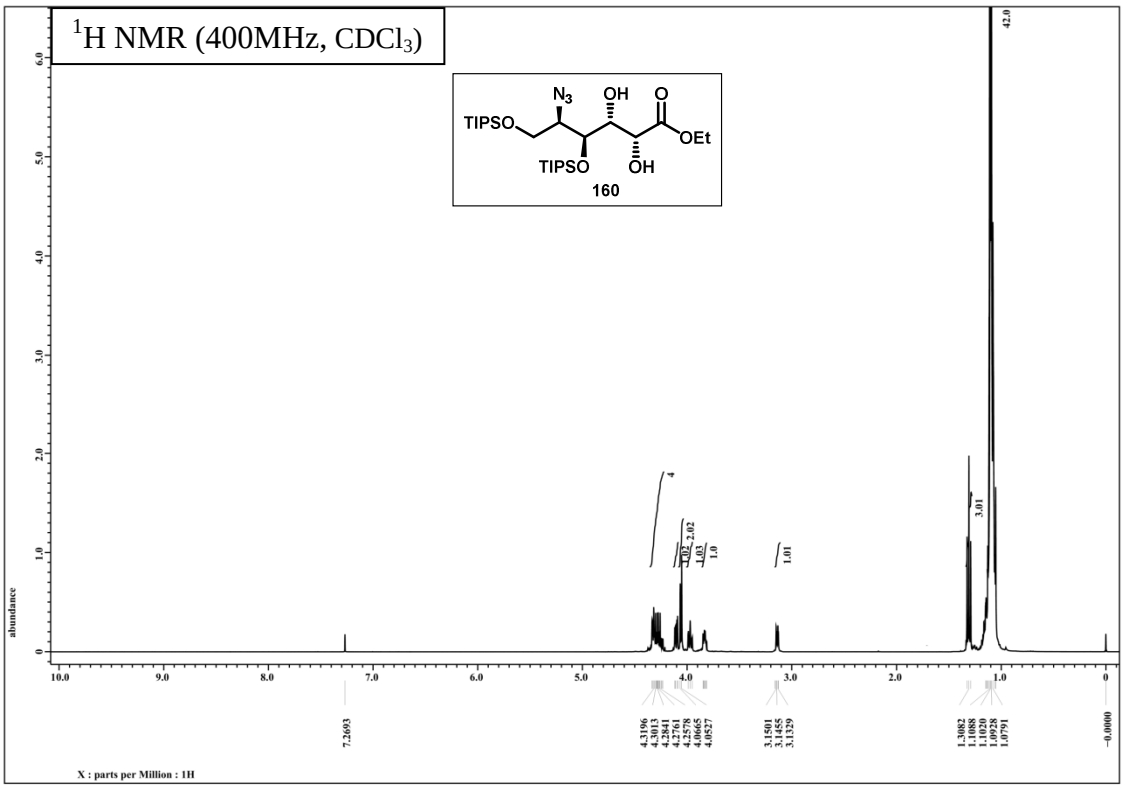
N3
O
OEt
OTIPS
163
abundance
X : parts per Million : 13C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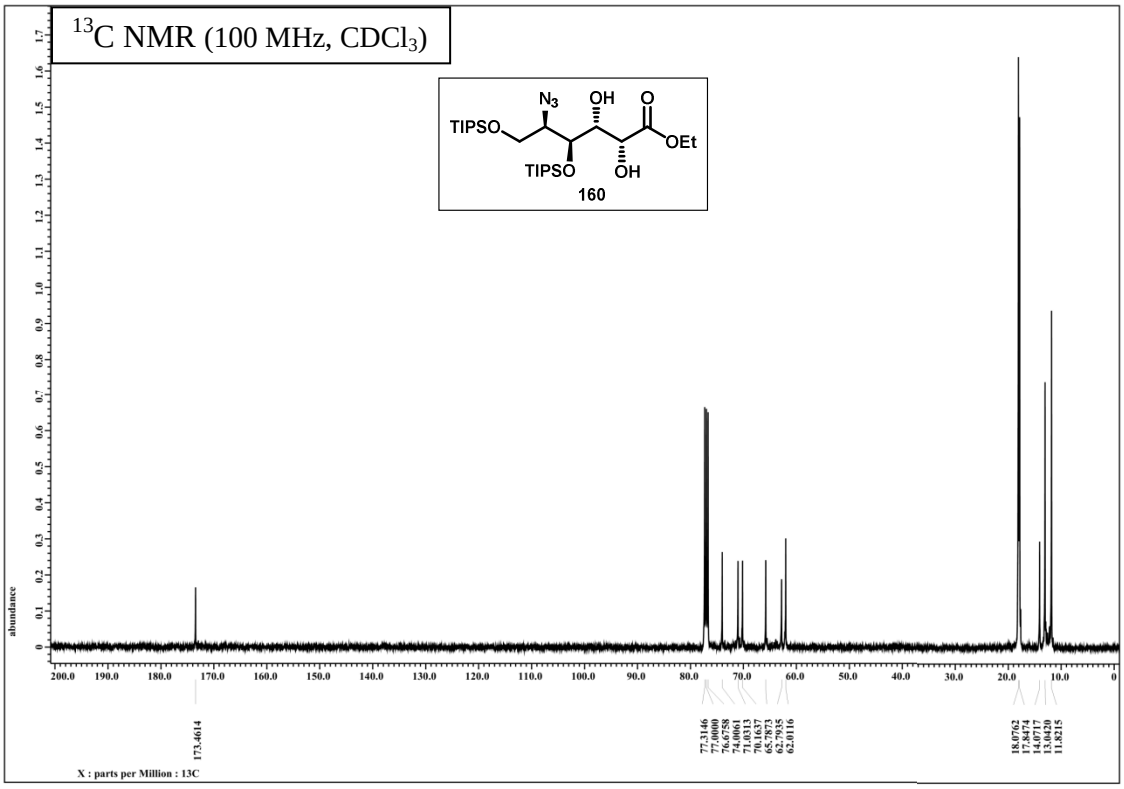
N3
OH
O
OEt
TIPSO
OH
160
abundance
X : parts per Million : 1H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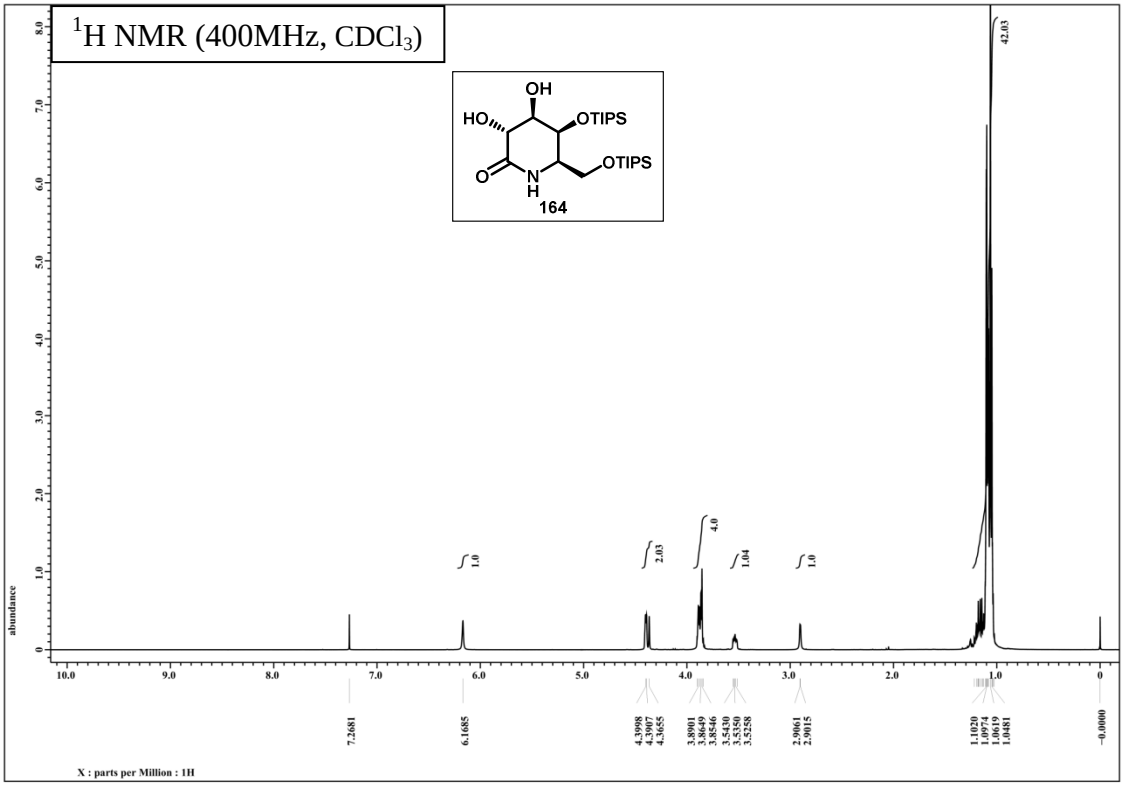
N3
OH
O
OEt
TIPSO
OH
160
abundance
X : parts per Million : 13C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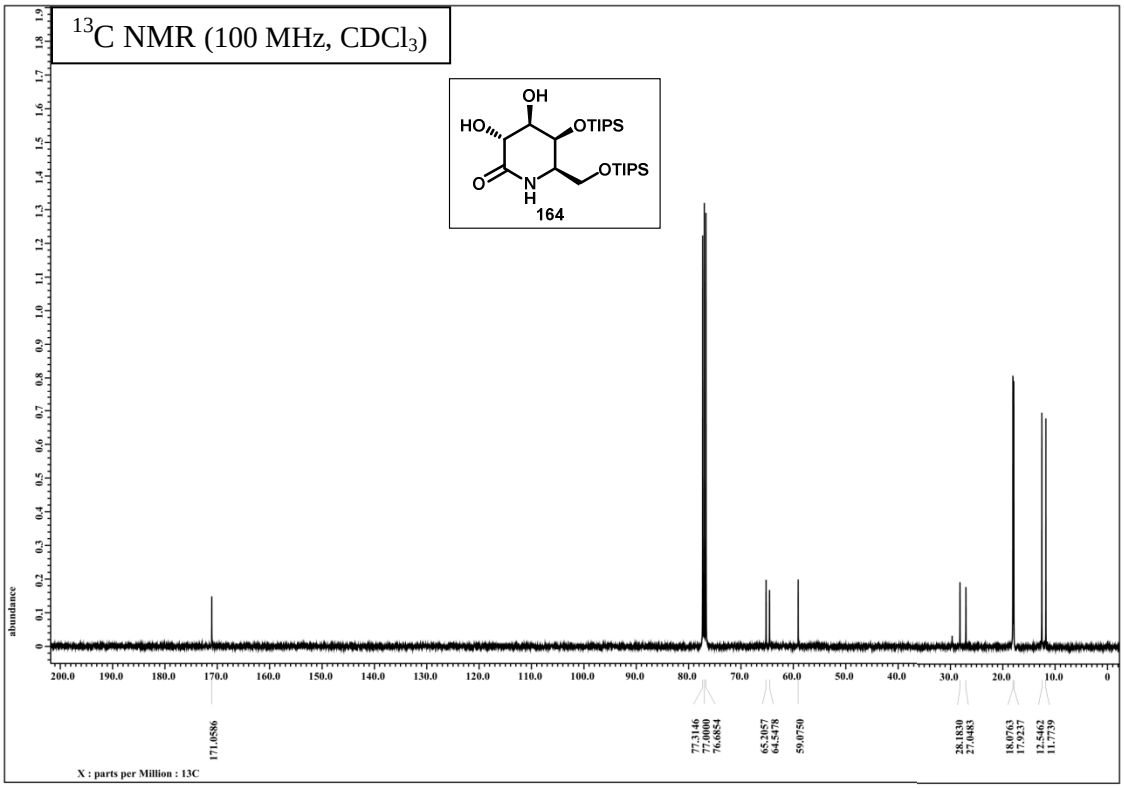
OH
HO
OTIPS
OTIPS
O
N
H
164
42.03
1.0
2.03
4.0
1.04
1.0
abundance
X : parts per Million : 1H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OH
HO
OTIPS
OTIPS
O
N
H
164
abundance
X : parts per Million : 13C

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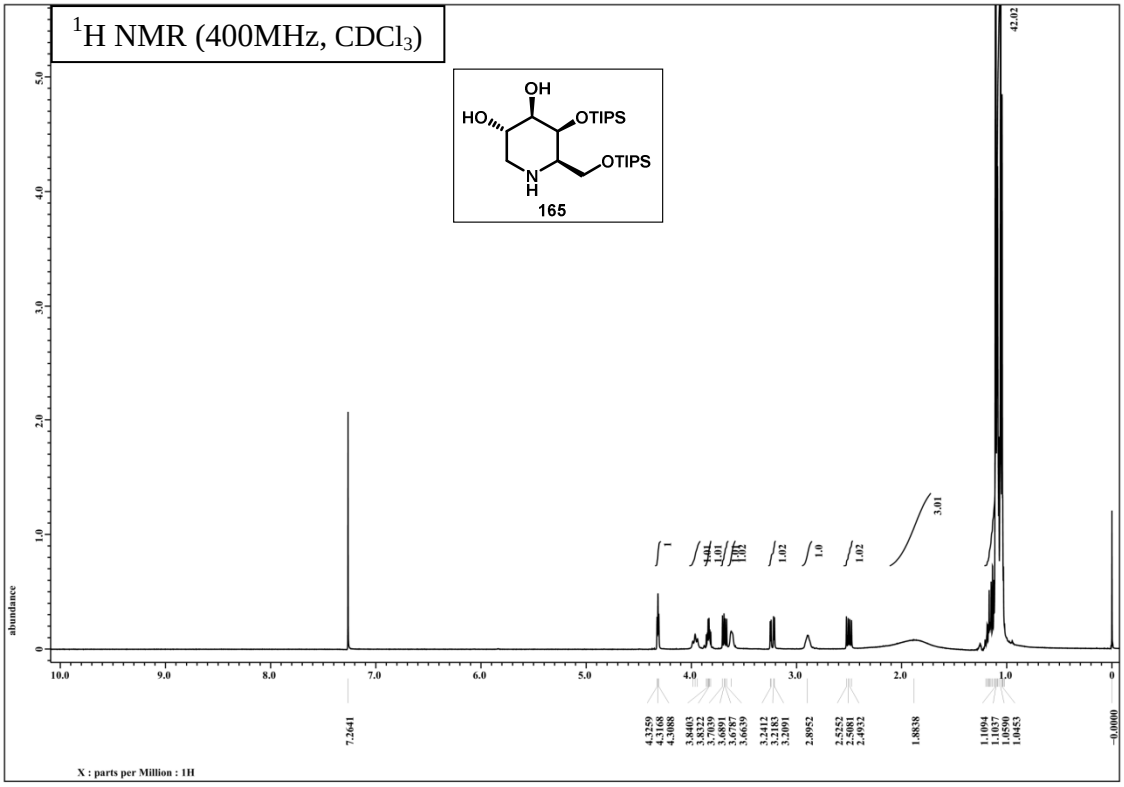

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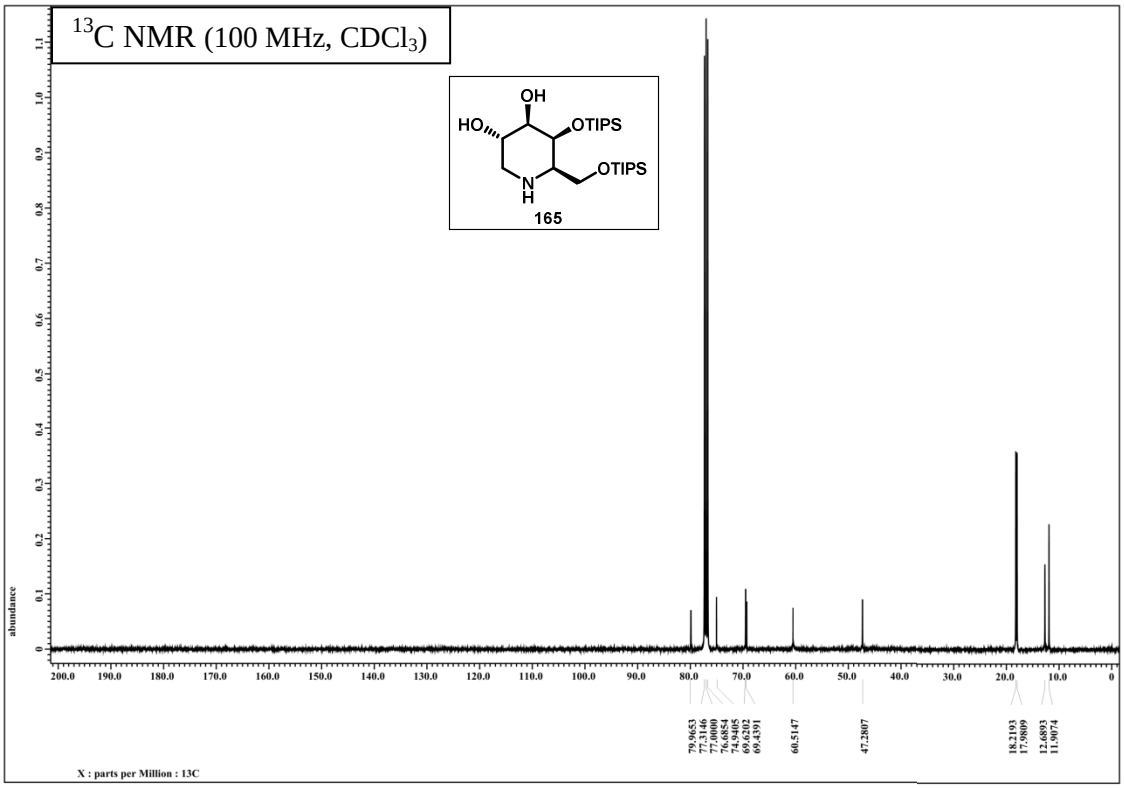
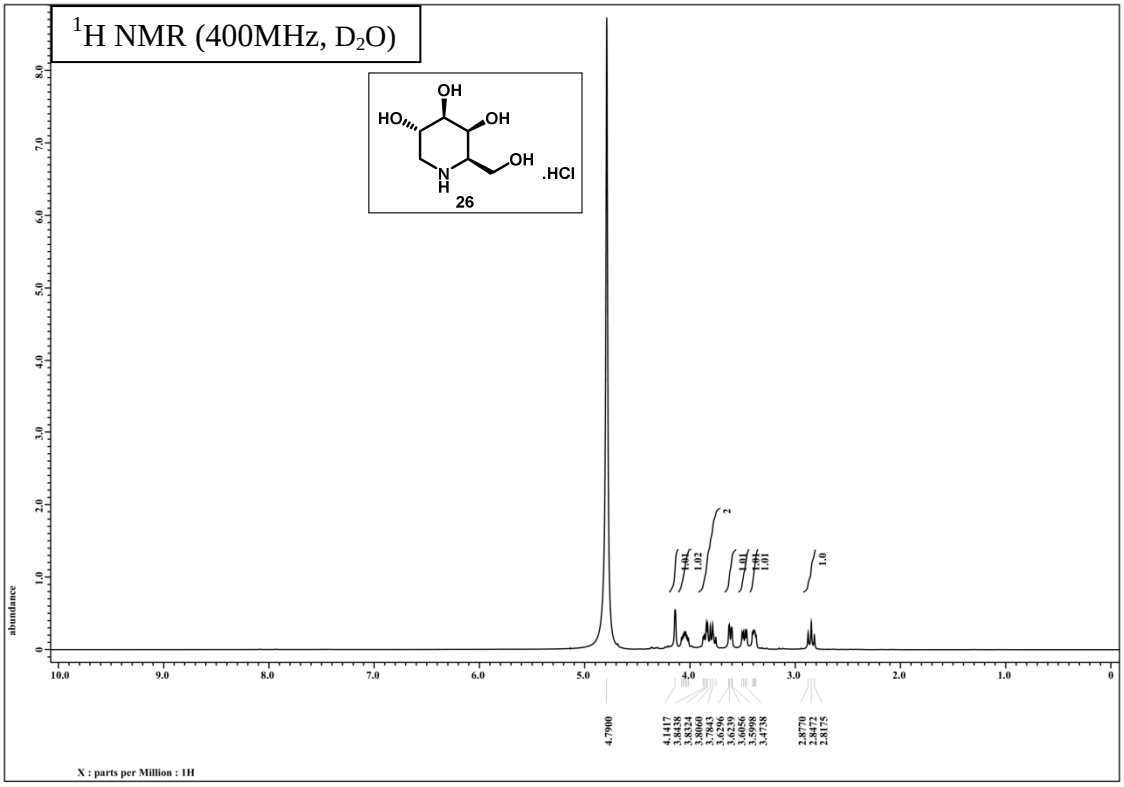
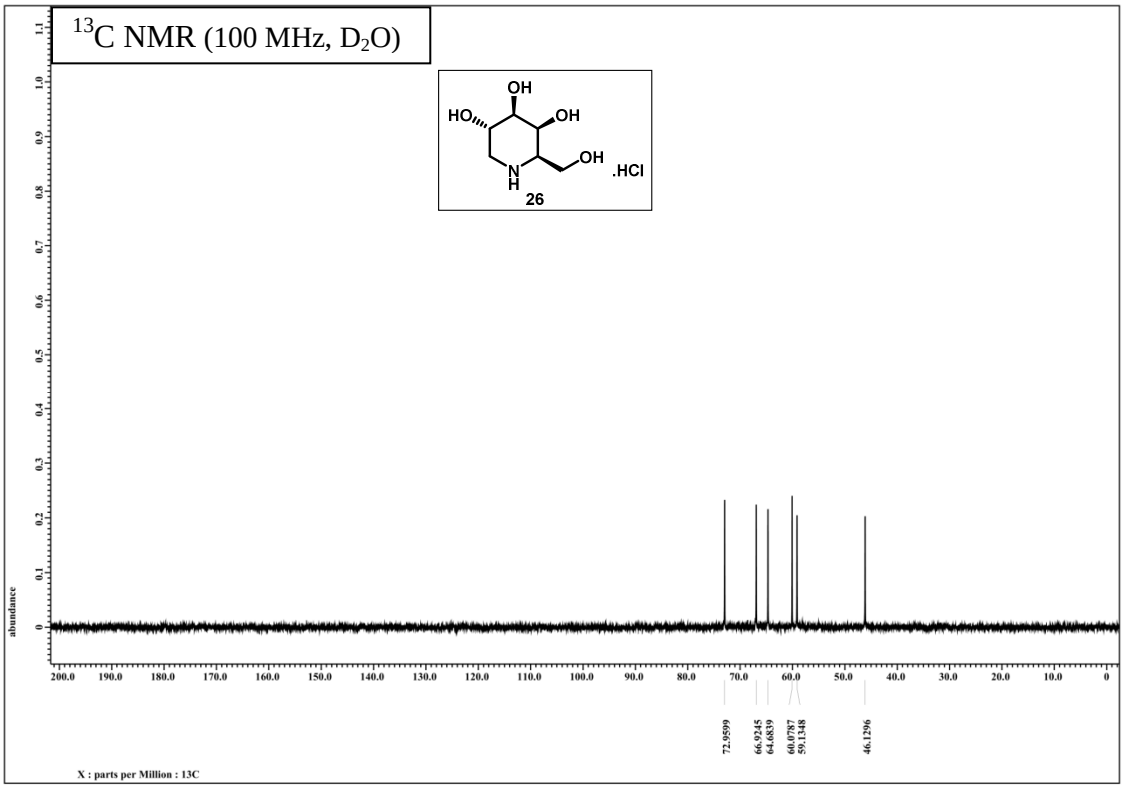
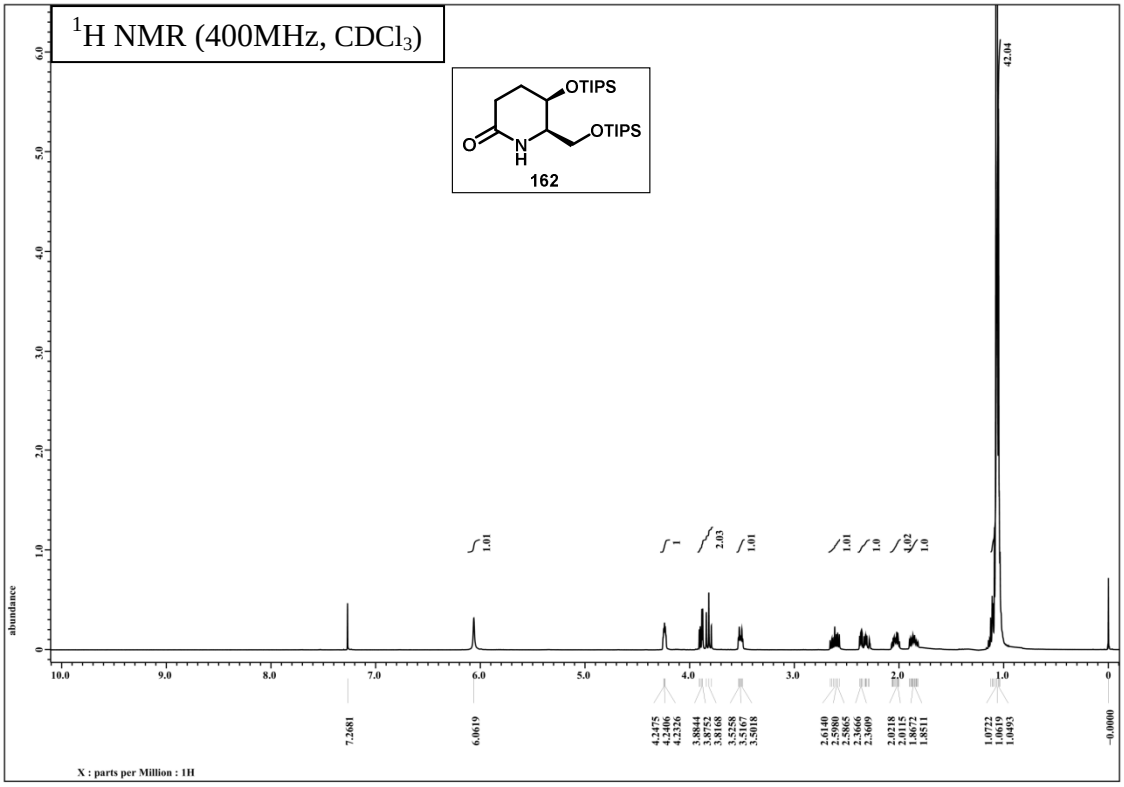



^{1}H NMR (400MHz, D_2O)
OH
HO
OH
OH
N
H
.HCl
26
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, D_2O)
OH
HO
OH
OH
N
H
.HCl
26
abundance
X : parts per Million : 13C

^{1}H NMR (400MHz, $CDCl_3$)



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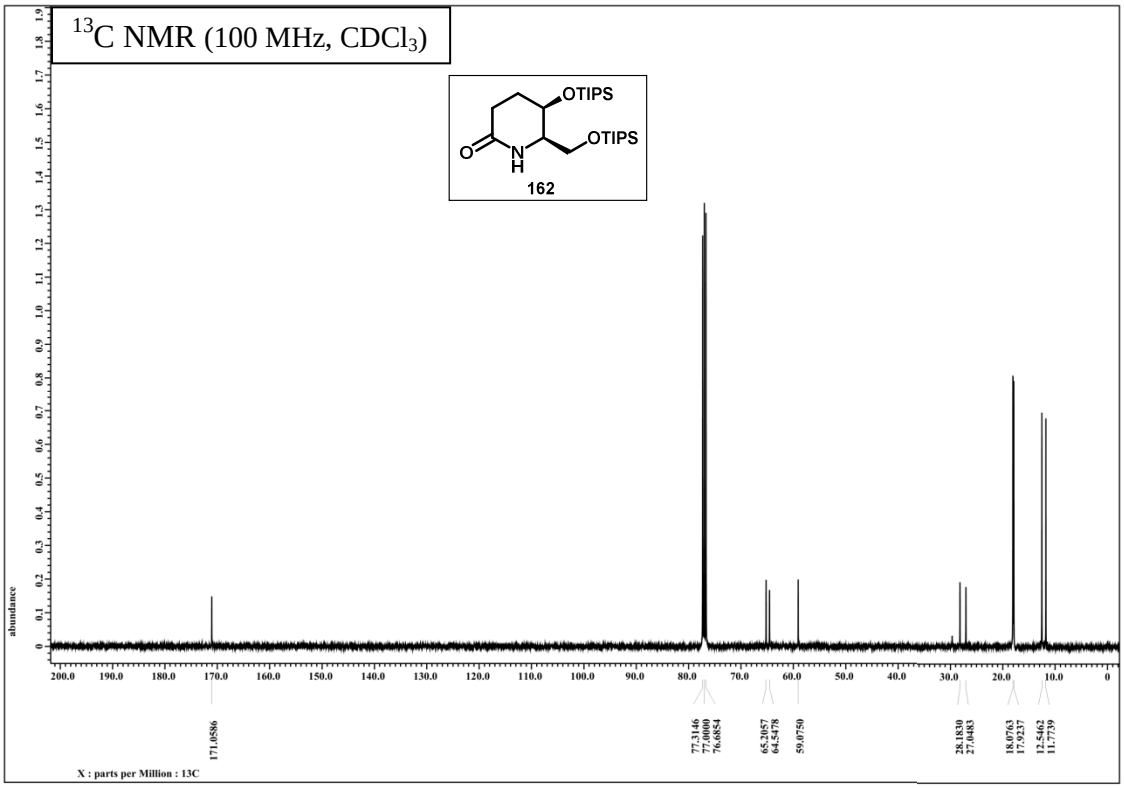
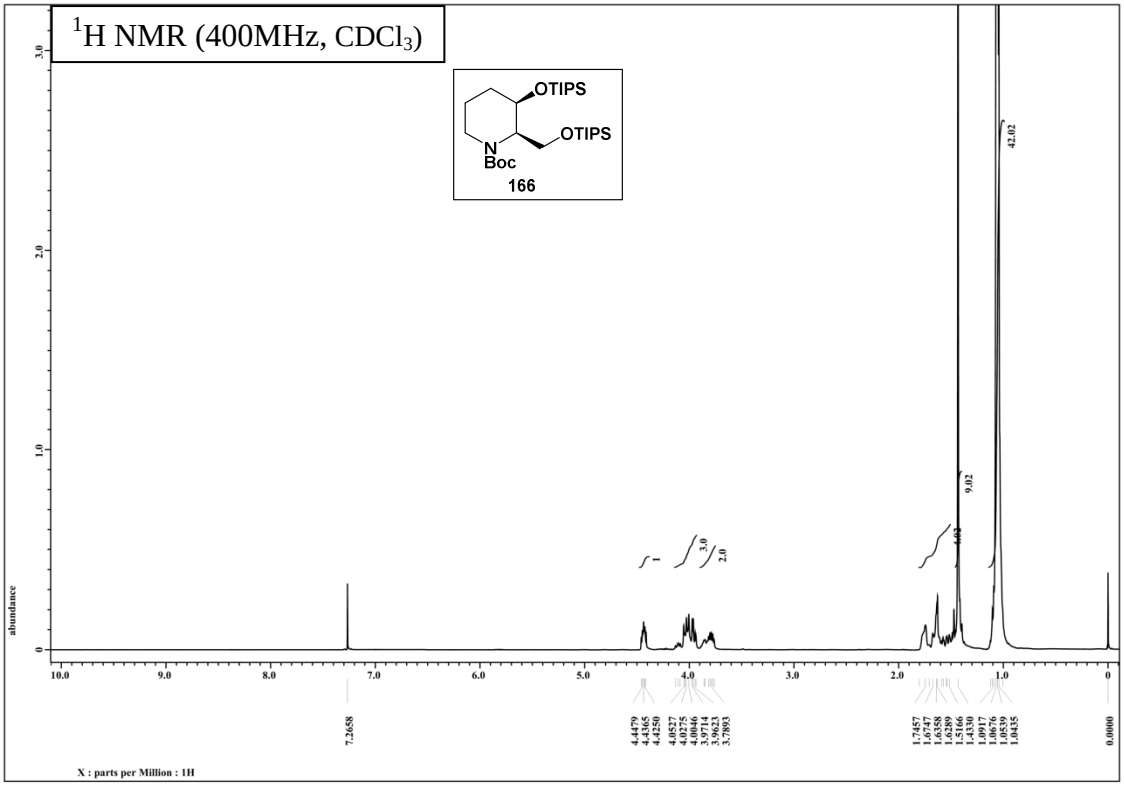


^{1}H NMR (400MHz, $CDCl_3$)



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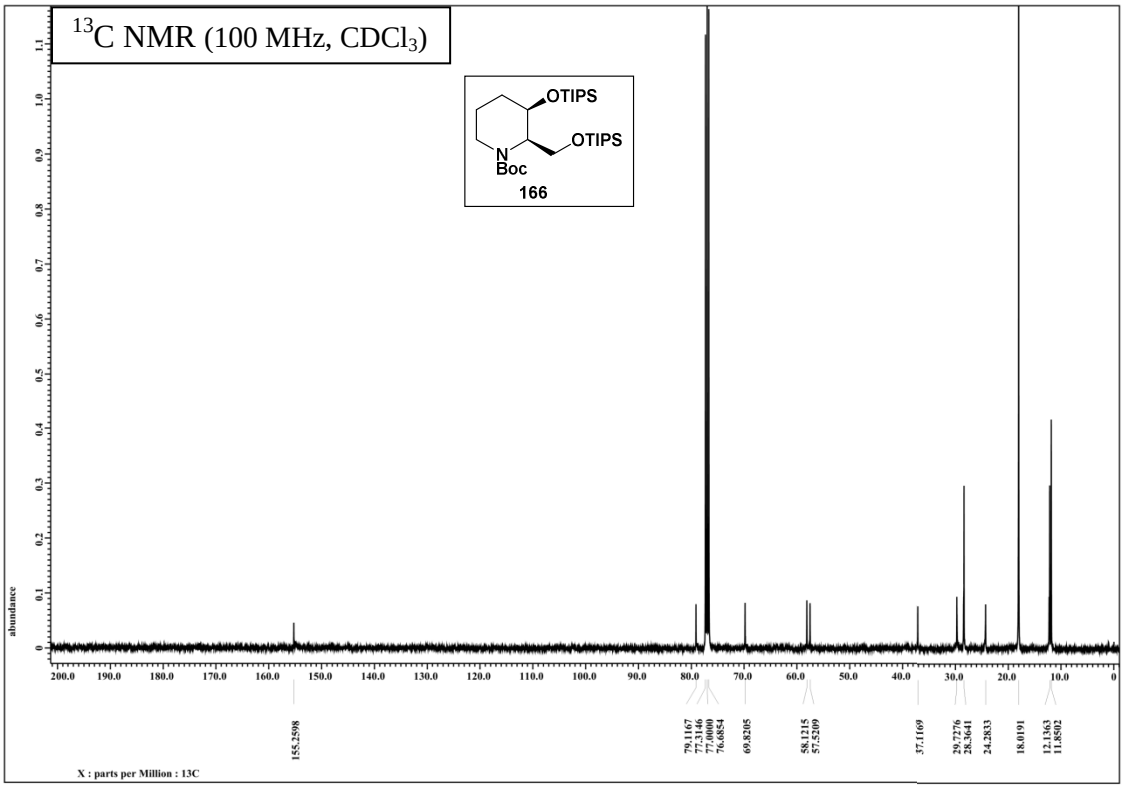
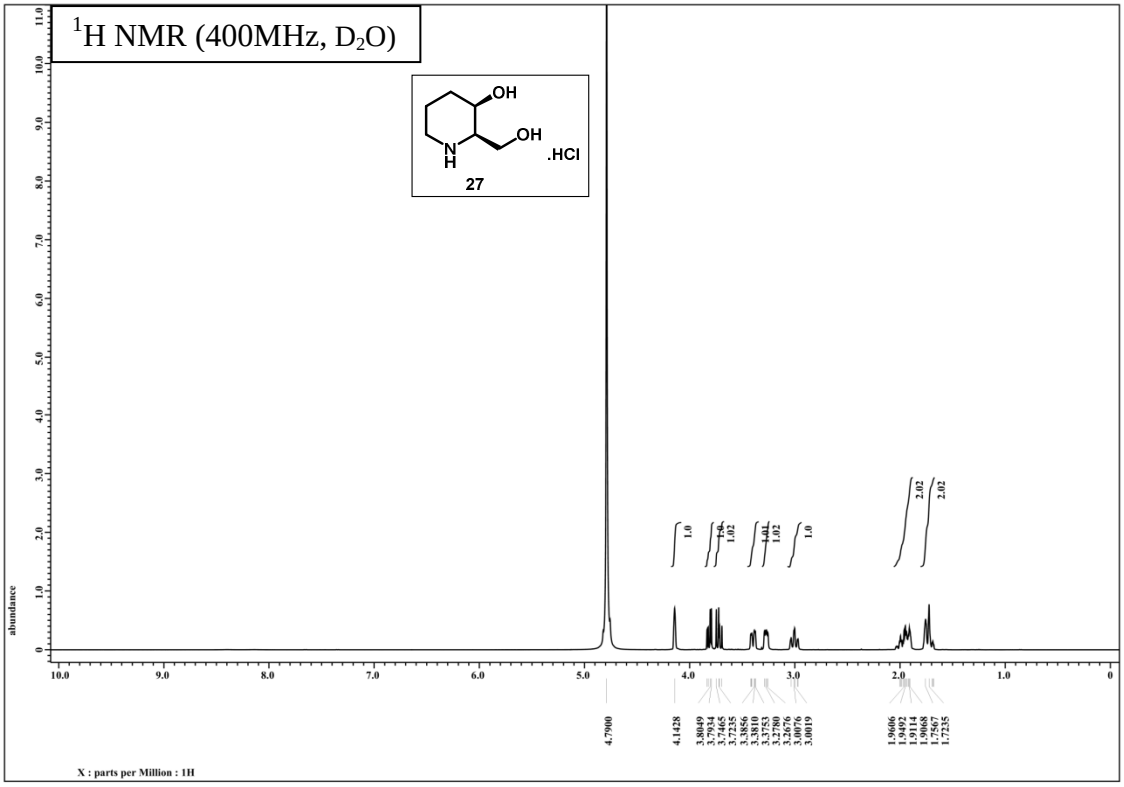
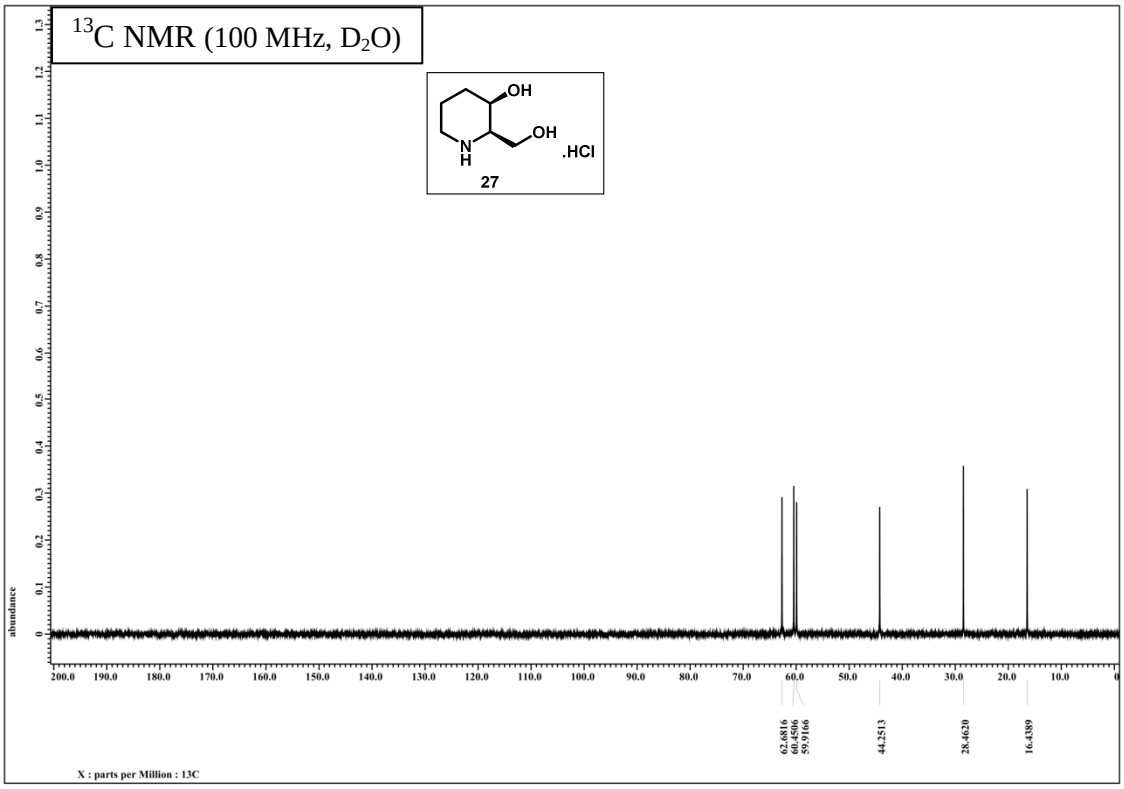
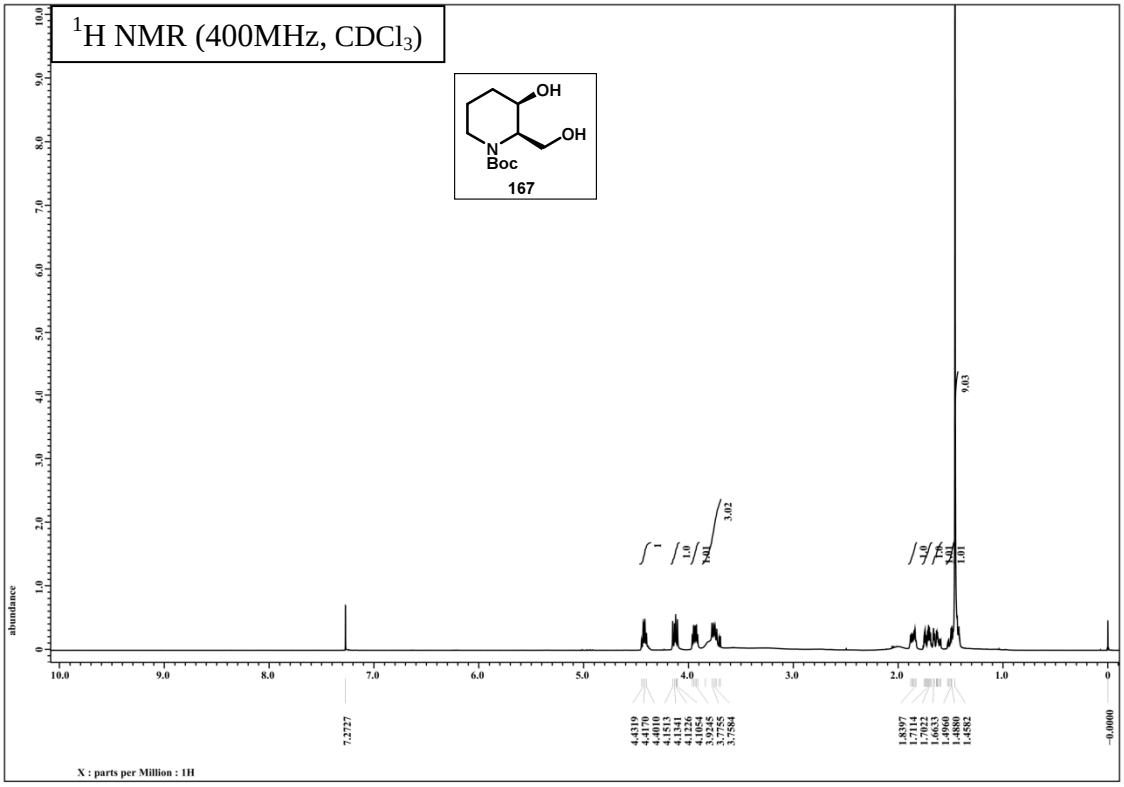
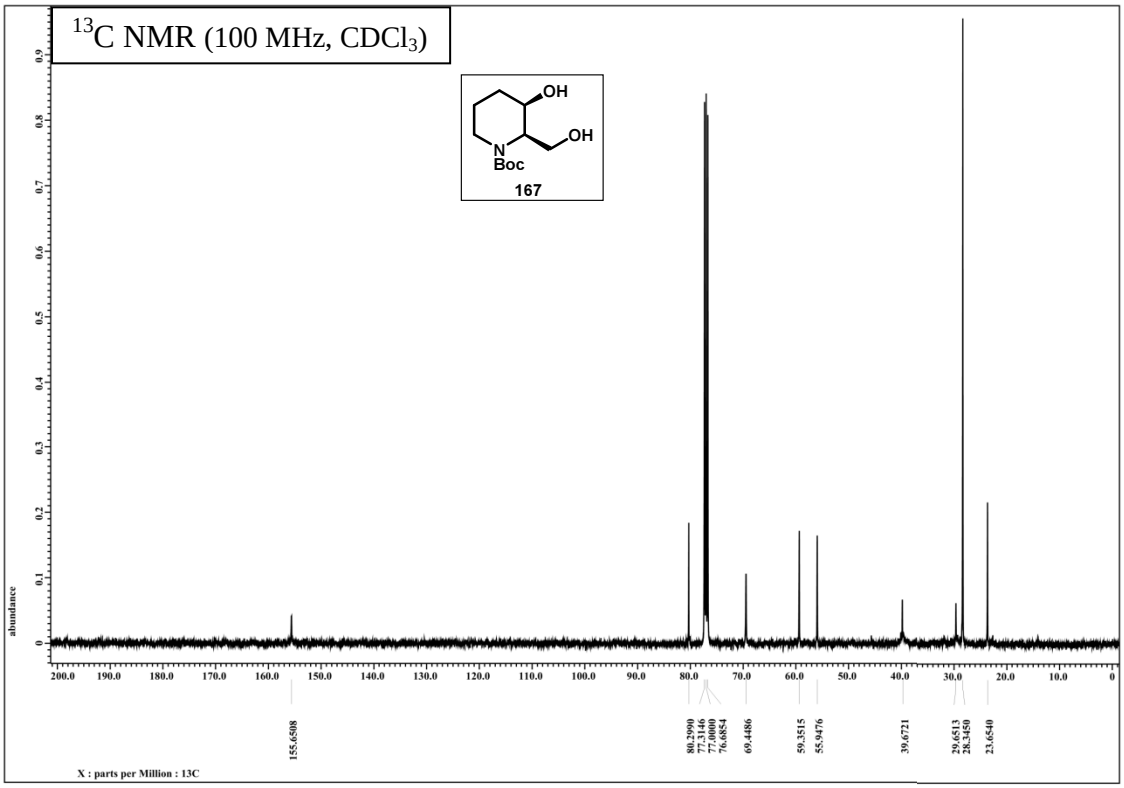



^{1}H NMR (400MHz, D_2O)
OH
OH
N
H
.HCl
27
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, D_2O)
OH
OH
N
H
.HCl
27
abundance
X : parts per Million : 13C


^{1}H NMR (400MHz, $CDCl_3$)
OH
OH
N
Boc
167
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
OH
OH
N
Boc
167
abundance
X : parts per Million : 13C

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CHAPTER 4

Enantioselective approach towards the total synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram

Enantioselective approach towards the total synthesis of (-)-(*R*)- and (+)-(*S*)-rolipram

4.1 Introduction:

Chirally branched pyrrolidones are among the most bioactive heterocyclic compounds in organic chemistry due to their ubiquitous structural motifs in natural and unnatural products with varied biological activity.[1] Among them, γ-aminobutyric acid (GABA) and its analogues rolipram (**44a**-**44b**), brivaracetam **168** and (*S*)-pregabalin **169** are useful division of compounds possessing interesting pharmacological activities (Figure 10).[2] The rolipram (**44a**-**44b**) are simple cyclo-GABA derivative possessing a catechol type ring at chiral carbon (C-3).[3] The (±)-rolipram was discovered and developed by Schering AG pharmaceutical company at Berlin, Germany in early 1990[4] and it acts as a selective phosphodiesterase-4 inhibitor and potential antidepressant drug. The most active enantiomer (*R*)-rolipram **44a** is an advanced novel class of effective antidepressant drug with additional possible emetic,[5] which act as selective inhibitor for cardiac cyclic AMP phosphodiesterase, present in brain tissue and mainly effective for the PDE4B and subtype of PDE4.[6] Additionally, (*R*)-rolipram **44a** has also been proposed as a antiinflammatory,[7] immunosupressant,[7] putative antiparkinsonian,[8] neuroprotective,[9] antipsychotic[10] and has been suggested for the treatment of multiple sclerosis.[10] The (*R*)-**44a** and (*S*)-rolipram **44b** have been synthetic target of considerable interest for academia and pharmaceutical industries due to its high antidepressant activity combined with attractive structural features.

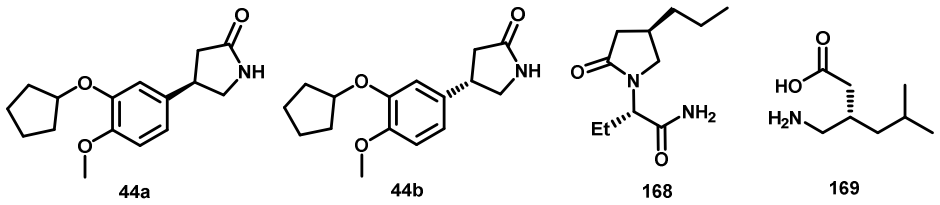


Figure 10. Some structures of GABA derivatives (**44a**-**44b**).

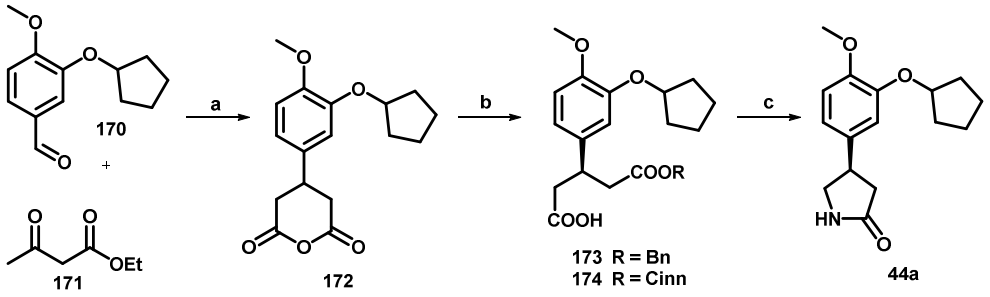
4.2 Review of Literature:

Various elegant studies and syntheses of (*R*)-**44a** and (*S*)-rolipram **44b** have been documented in the literature.[11] Most of the synthesis described employed the bifunctional catalyst mediated asymmetric Michael addition of malonate nucleophiles, desymmetrization of glutaric anhydride

and the chiral heterogeneous catalysts as key step. Some of the recent syntheses of (*R*)-**44a** and (*S*)-rolipram **44b** are described below.

Hamersak, Z. (2013)[11c]

Z. Hamersak and co-workers reported the enantioselective synthesis of (*R*)-**44a** and (*S*)-rolipram **44b** by cinchona alkaloid catalyzed opening of cyclic anhydride (desymmetrization of glutaric anhydride) as key step (Scheme 42). The aldehyde intermediate **170** was obtained from commercially available isovanillin *via O*-alkylation with cyclopentylbromide in 95% yield. The aldehyde **170** on condensation with ethylacetoacetate **171** followed by hydrolysis with concentrated alkali afforded the glutaric acid intermediate which on subsequent treatment with acetic anhydride furnished the anhydride **172** in 93% yield. The quinine mediated opening of anhydride **172** with benzyl alcohol or cinnamyl alcohol furnished ester **173** in 98% yield or **174** in 95% yield, respectively. The corresponding ester on treatment with DPPA afforded the azide derivative which was thermally rearranged into an unstable isocyanate intermediate and reacts with a nucleophile to afford *N*-protected aminoester followed by thermal decarboxylation to furnish the cyclized product (*R*)-rolipram **44a** in 51% yield. The synthesis of (*S*)-rolipram **44b** was performed by following an analogous series of reactions as described in Scheme 42.

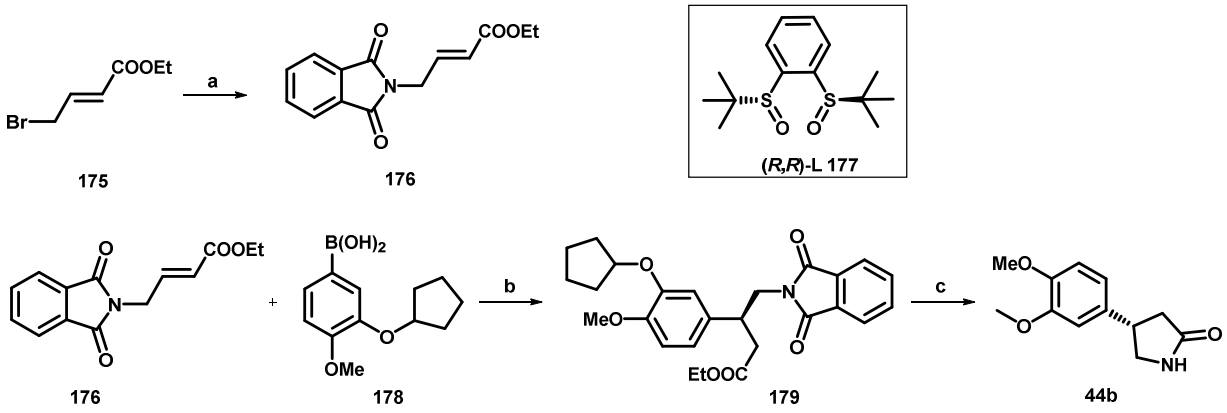


Scheme 42. *Reagents and conditions*: (a) i) piperidine, EtOH, rt, 2 days, 73%; ii) KOH, H_2O:EtOH, rt, 4 days, 74%; iii) Ac_2O, 110 ^oC, 30 min, 93%; (b) quinine, BnOH or CinnOH, rt, 3 days, 98% for **173** and 95% for **174**; (c) DPPA, Et_3N, toluene, 90 ^oC, 30 min, 51%.

Liao, J. (2011)[11d]

J. Liao and co-workers reported the total synthesis of (*S*)-rolipram **44b** employed the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to ethyl-*γ*-phthalimidocrotonate by using bis-sulfoxide ligands as key step (Scheme 43). The (*E*)-ethyl-4-bromobut-2-enoate **175** on treatment with phthalimide potassium salt afforded the ethyl-*γ*-phthalimidocrotonates **176** in

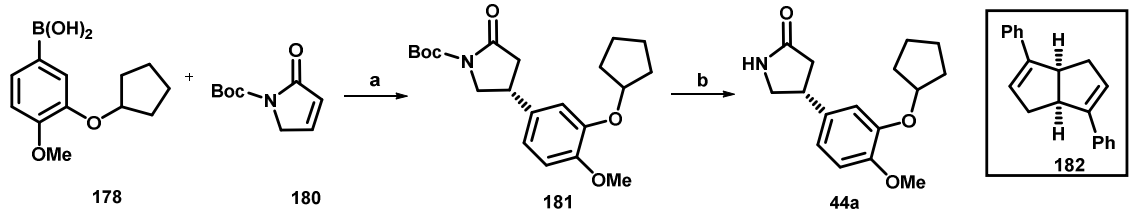
excellent yield. The compound **176** which on treatment with 3-cyclopentoxy-4-$MeOC_6H_3$-boronic acid **178** in the presence of ligand (*R*,*R*)-L **177** furnished the phthalimide intermediate **179** in 85% yield. The ester derivative **179** on phthalimide deprotection with hydrazine hydrate and cyclization under basic conditions afforded the target compound (*S*)-rolipram **44b** in 78% yield.



Scheme 43. *Reagents and conditions*: (a) Potassium phtahlimide, DMF, rt, 12 h, 90%; (b) [(*R*,*R*)L**177**-RhCl]$_2$ (2.5 mol%), CH_2Cl_2:H_2O, KOH (50 mol%), 40 ^oC, 1.5 h, 85%; (c) i) NH_2NH_2, THF, 0 ^oC-rt, 5 h; ii) Et_3N, toluene, reflux, 20 h, 78% (over two steps).

Lin, G. Q. (2011)[11e]

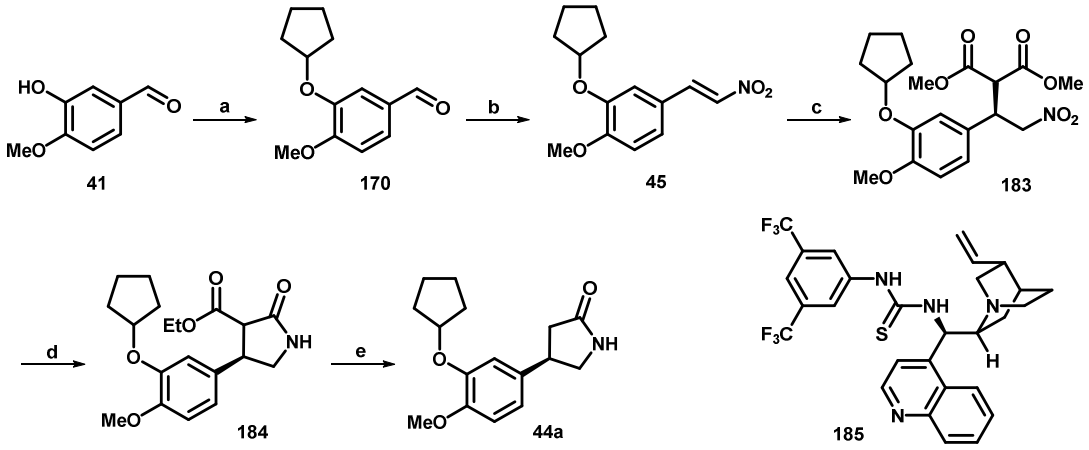
G. Q. Lin and co-workers described the asymmetric synthesis of (*R*)-rolipram **44a** employed the rhodium/diene-catalyzed asymmetric addition of arylboronic acids to *α*,*β*-unsaturated *γ*-lactams (Scheme 44). The boronic acid derivative **178** on enantioselective addition to lactam **180** in the presence of rhodium complex **182** afforded the *N*-Boc protected lactam derivative **181** in 98% yield with 99% ee (after single crystallization). The compound **181** on *N*-Boc deprotection with TFA furnished the final compound (*R*)-rolipram **44a** in quantitative yield.



Scheme 44. *Reagents and conditions*: (a) [$RhCl(C_2H_4)_2]_2$/**182** (3 mol% Rh), toluene/H_2O, Et_3N, 60 ^oC, 98%; (b) TFA, CH_2Cl_2, 0 ^oC-rt, quantitative.

Dixon. D. J. (2008)[11f]

D. J. Dixon and co-workers reported the synthesis of (*R*)-rolipram **44a** employed the enantioselective Michael addition of malonate nucleophiles as key step (Scheme 45). Isovanillin **41** on *O*-alkylation with cyclopentylbromide in presence of base funished the aldehyde **170** in 87% yield which on Henry condensation reaction afforded the nitro olefin **45** in 92% yield. The olefin **45** on treatment with dimethyl malonate under enantioselective Michael addition using **185** furnished the ester **183** in 96% yield with 94% *ee*. The nitro group of **183** on reduction with nickel boride afforded the *γ*-lactam **184** in 96% yield followed by hydrolysis/thermolysis furnished the decarboxylated product (*R*)-rolipram **44a** in 94% yield.



Scheme 45. *Reagents and conditions*: (a) cyclopentylbromide, K_2CO_3, DMF, 100 ^oC, 30 h, 87%; (b) $MeNO_2$, NH_4OAc, 130 ^oC, 24 h, 92%; (c) **185**, dimethyl malonate, CH_2Cl_2, -20 to 0 ^oC, 96 h, 96%; (d) $NiCl_2.H_2O$, $NaBH_4$, EtOH, 0 ^oC, 2 h, 96%; (e) i) $LiOH.H_2O$, THF, rt, 2 h; ii) PhMe, reflux, 12 h, 94%.

4.2.1 Table 7. Comparison with the previous reported syntheses of (*R*)-**44a** and (*S*)-rolipram **44b**.

Sr. No.	Syntheses	Key step	Overall yield	No. of steps
1.	***Tetrahedron Lett.* 2017, *58*, 4333** [(*R*)-rolipram]	**diphenylprolinol silyl ether catalyzed Michael addition**	**66% & 69%**	**Three**
2.	*Tetrahedron: Asymmetry* **2013**, *24*, 217 [(*R*)-rolipram]	desymmetrization of glutaric anhydride	25%	five

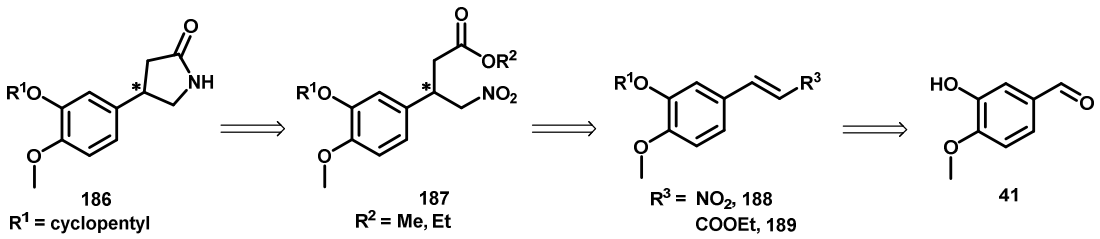
3.	*Tetrahedron Lett.* **2011**, *52*, 830 [(*S*)-rolipram]	Rh/(*R*,*R*)-1,2-bis(tert-butylsulfinyl)benzene complex	59%	three
4.	*Org. Lett.* **2011**, *13*, 788 [(*R*)-rolipram]	Rh/diene catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated γ-lactams	-	two
5.	*Org. Lett* **2008,** *10*, 1389 [(*R*)-rolipram]	Michael addition of malonate	63%	six

4.3 Present Work:

As part of research programme directed towards the asymmetric synthesis of biologically active compounds, we became interested in developing a short and efficient route to (*R*)-**44a** and (*S*)-rolipram **44b** with two different strategies employing the organocatalyzed asymmetric Michael addition, Henry condensation, Wittig olefination and reductive lactamization reactions as the key steps.

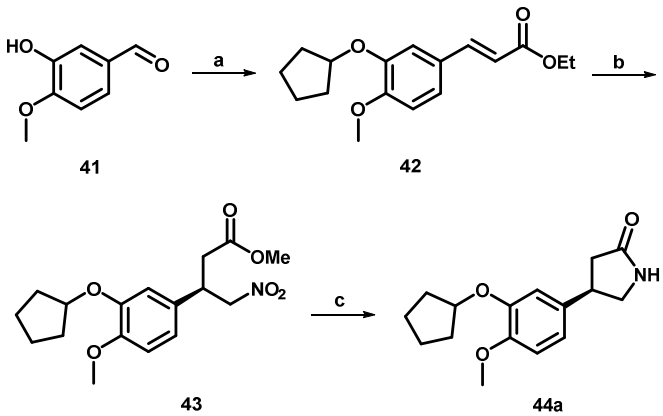
4.4 Results and Discussion:

Our synthetic approach for the enantioselective synthesis of pyrrolidone skeleton **186** was envisioned *via* the retrosynthetic route as depicted in Scheme 46. The ester derivative **187** was visualized as a synthetic intermediate from which pyrrolidone **186** and rolipram (**44a**-**44b**) could be easily synthesized *via* intramolecular cyclization under hydrogenation conditions. The ester derivative **187** in turn could be synthesized from olefin **188** or **189** by means of (*R*)- and (*S*)-diphenylprolinolsilyl ether mediated asymmetric Michael addition reactions followed by standard organic transformations. The nitro olefin derivative **188** could be derived from commercially available isovanillin **41** through base catalyzed *O*-alkylation and Henry condensation reaction, whereas olefinic ester **189** could be easily synthesized from isovanillin **41** *via O*-alkylation and 2C-Wittig olefination. Thus, in principle, both the enantiomers of rolipram (**44a**-**44b**) along with different substitutions at *O*-site could be accessed by two different approaches.



Scheme 46. Retrosynthesis of pyrrolidone skeleton **187**.

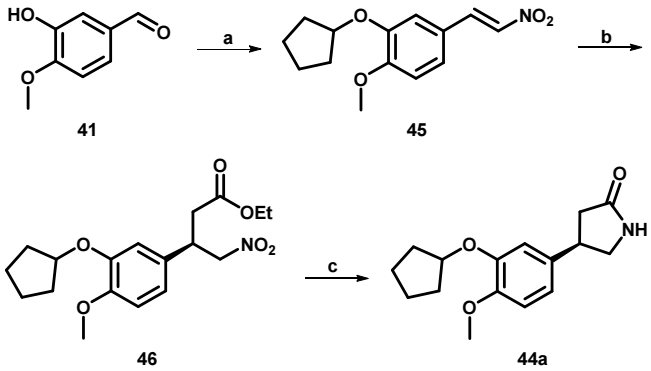
The synthesis of (*R*)-rolipram **44a** started with commercially available isovanillin **41** which on treatment with cyclopentylbromide under basic conditions followed by 2C-Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester **42** in 92% yield (Scheme 47). The IR spectrum of **42** showed olefin C=O stretching at 1730 cm^{-1}. The ^1H NMR spectrum of **42** gave olefin protons at δ 7.62 (doublet, one proton) and δ 6.29 (doublet, one proton) with the coupling constant J = 16.0 and 16.0 Hz, respectively indicating *trans*-olefin. The DIBAL-H reduction of ester **42** at -78 ^oC to α,β-unsaturated aldehyde and subsequent asymmetric Michael oxidative esterification[12] with nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether (10 mol%) furnished the nitro aldehyde adduct which on *in situ* treatment with NBS/MeOH furnished the γ-nitroester **43** in 78% yield.
With enantiomerically pure ester **43** in hand, it was then subjected to intramolecular reductive lactamization under 1 atm H_2 pressure in presence of catalytic amount of Pd/C in EtOAc/Et_3N to furnish the (*R*)-rolipram **44a** in 92% yield and >99% *ee*[13] {$[\alpha]_D^{25}$ -31.1 (*c* 1.05, CH_3OH), [lit.[11f] $[\alpha]_D^{25}$ -31 (*c* 1.05, CH_3OH)]}. The spectroscopical and physical data of (*R*)-rolipram **44a** were found to be in full agreement with the literature data.[11c-f,i-j]



Scheme 47. *Reagents and conditions*: (a) i) cyclopentylbromide, K_2CO_3, DMF, 100 ^oC, 30 h; ii) $PPh_3CHCOOEt$, THF, rt, 12 h, 92% (over two steps); (b) i) DIBAL-H, CH_2Cl_2, -78 ^oC, 1 h; ii)

(*R*)-diphenylprolinol silyl ether, CH_3NO_2, benzoic acid, MeOH, 16 h, rt; iii) NBS, 16 h, 4 ^oC, 78% (over three steps); (c) H_2, Pd/C (10%), Et_3N, EtOAc, rt, 12 h, 92%.

In another approach, the synthesis of (*R*)-rolipram **44a** commenced with treatment of the isovanillin **41** with cyclopentylbromide under basic conditions followed by Henry condensation reaction with nitromethane to afford the nitro olefin **45** in 87% yield (Scheme 48).[11f] The IR spectrum of **45** showed olefin C=C stretching at 1650 cm^{-1}. The ^1H NMR spectrum of **45** gave olefin protons at δ 7.96 (doublet, one proton) and δ 7.51 (doublet, one proton) with the coupling constants J = 13.6 and 13.6 Hz, respectively indicating *trans*-olefin. Asymmetric Michael addition of acetaldehyde to nitro olefin **45** in the presence of catalyst (*R*)-diphenylprolinol silyl ether[14] (10 mol%) in a sealed tube afforded the nitroaldehyde adduct,[15] which on spontaneous oxidation with oxone[16] and subsequent esterification using TMSCl/EtOH[17] successfully furnished the ester derivative **46** in 85% yield. Our next endeavour was to carry out the intramolecular reductive lactamization at the nitro group site. Towards this end, nitroester **46** underwent hydrogenation in the presence of catalytic amount of Pd/C in EtOAc/Et_3N to deliver the target compound (*R*)-rolipram **44a** in 93% yield and >99% *ee*[18] {$[\alpha]_D^{25}$ -31.1 (*c* 1.05, CH_3OH), [lit.[11f] {$[\alpha]_D^{25}$ -31 (*c* 1.05, CH_3OH)]}. The spectral and physical data of (*R*)-rolipram **44a** was found to be in consonance with those reported in the literature.[11c-f,i-j]



Scheme 48. *Reagents and conditions*: (a) i) cyclopentylbromide, K_2CO_3, DMF, 100 ^oC, 30 h; ii) CH_3NO_2, NH_4OAc, 130 ^oC, 24 h, 87% (over two steps); (b) i) acetaldehyde, (*R*)-diphenylprolinolsilyl ether, 1,4-dioxane, 4 ^oC to rt, 18 h; ii) oxone, DMF, rt, 12 h; iii) TMSCl, EtOH, rt, 12 h, 85% (over three steps); (c) H_2, Pd/C, Et_3N, EtOAc, rt, 12 h, 93%.

The (*S*)-rolipram **44b** was also synthesized in >99% *ee*[19] {$[\alpha]_D^{25}$ +31.8 (*c* 0.6, CH_3OH) [lit.[11j] $[\alpha]_D^{rt}$ +31 (*c* 0.6, CH_3OH)]} following an analogous series of reactions as shown in Scheme 48

using the (*S*)-diphenylprolinol ether catalyst during the asymmetric Michael addition step. The spectral and physical data of (*S*)-rolipram **44b** was found to be in accordance with the literature data.[11c-d,j]

4.5 Conclusion:

In conclusion, we have disclosed a novel, short and protecting group free enantioselective syntheses of (*R*)-**44a** and (*S*)-rolipram **44b** from commercially available isovanillin as a starting material employing the (*R*)- and (*S*)-diphenylprolinol silyl ether mediated asymmetric Michael addition reaction as key step. We have used diphenylprolinol silyl ether catalyzed Michael addition reaction as the source of chirality. As compared to the previous synthesis we have achieved the target compound (*R*)-rolipram **44a** in high overall yield, 66% and 69% with two different strategies after three column chromatographic purification steps. The merits of our synthesis are high enantioselectivity (i.e. >99% *ee*) and high yielding reaction steps. The synthetic approach also has significant potential for the variation at *O*-alkyl site to synthesize various *γ*-pyrrolidone derivatives with expected increase in biological activities.

4.6 Experimental Section:

4.6.1 General Experimental Details:

All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. All the reagents were added either *via* syringe or cannula. Each distillation was performed under an inert atmosphere. All reactions have their respective temperatures within their respective schemes. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.

Chromatography

All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, then were stained by ninhydrin or anisaldehyde in ethanol or $KMnO_4$ in water as development reagents followed by brief heating with a heat gun. Column chromatography were performed on silica gel (60-120 and 100-200 mesh) using a mixture of ethyl acetate/hexane and methanol/ dichloromethane as eluent.

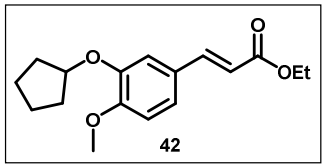
Reagents and solvents

Solvents were obtained commercially and were used without purification unless otherwise noted in experimental. Distilled water was used for every aqueous reaction, work-up procedure, and in the preparation of every aqueous solution used in the work-up. For reaction solvent, CH_2Cl_2 was distilled from CaH_2, and THF was distilled under N_2 from sodium benzophenone ketyl, all immediately prior to use.

Spectroscopic Measurements

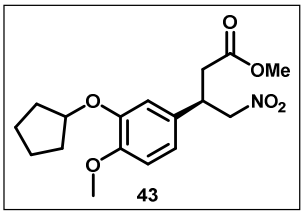
^1H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units (δ) downfield from TMS. Coupling constants, *J*, are listed in hertz (Hz). High resolution mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. The enantiomeric purity (*ee*) was determined by Thermofisher HPLC analysis using chiralcel IA chiral column (5 μM, 4 x 250 mm).

Ethyl (*E*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)acrylate, 42



To a THF (10 mL) solution of (ethoxycarbonylmethylene)triphenyl phosphorane (1.7 g, 4.92 mmol) was added dropwise a solution of cyclopentyl substituted aldehyde synthesized from isovanillin **41** in THF (5 mL) and stirred for 12 h at room temperature. The reaction mixture was then concentrated *in vacuo* and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *trans*-olefin **42** (875 mg, 92%) as a thick yellow liquid. IR (CH_2Cl_2) *v*: 2241, 1730, 1374 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 16.0 Hz, 1H), 7.08-7.05 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.29 (d, *J* = 16.0 Hz, 1H), 4.82-4.76 (m, 1H), 4.25 (q, *J* = 6.8, 14.0, 2H), 3.84 (s, 3H), 1.99-1.78 (m, 6H), 1.66-1.56 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 151.8, 147.6, 144.5, 127.0, 122.1, 115.4, 112.9, 111.3, 80.2, 60.1, 55.8, 32.6, 32.6, 24.0, 23.9, 14.2; HRMS (ESI), calcd for $C_{17}H_{23}O_4^+$ $[M + H]^+$ 291.1591; found 291.1576.

Methyl (*R*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate, 43

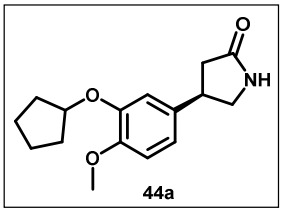


43

To a CH_2Cl_2 (10 mL) solution of ester **42** (400 mg, 1.37 mmol) was added DIBAL-H (0.85 mL, 1.51 mmol, 1.75 M in toluene) at -78 ^oC and stirred for 1 h at the same temperature. The reaction mixture was quenched with saturated aqueous solution of sodium potassium tartrate and stirred for additional 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give *α,β*-unsaturated aldehyde as a yellow liquid, which was used as such for the next step without further purifcation.

To a CH_3OH (0.5 mL) solution of above aldehyde was added nitromethane (0.2 mL, 4.13 mmol), (*R*)-diphenyltrimethylsiloxymethylpyrrolidine (9 mg, 0.02 mmol) and benzoic acid (33 mg, 0.27 mmol) at room temperature. After stirring the mixture for 16 h, reaction mixture was then cooled to 4 °C, *N*-bromosuccinimide (730 mg, 4.13 mmol) was added and the mixture was stirred for additional 16 h. Then, the reaction mixture was filtered through a pad of celite, washed with EtOAc, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane 1:9) to furnish the methylester **43** (450 mg, 78%) as a yellow liquid. $[\alpha]_D^{25}$ -20.5 (*c* 0.8, CH_3OH); IR (CH_2Cl_2) *v*: 1726, 1525, 1360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 6.81 (d, *J* = 7.6 Hz, 1H), 6.74-6.71 (m, 2H), 4.77-4.67 (m, 2H), 4.62-4.57 (m, 1H), 3.94-3.87 (m, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 2.74 (d, *J* = 7.6 Hz, 2H), 1.97-1.77 (m, 6H), 1.66-1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 171.1, 149.6, 147.7, 130.3, 119.0, 114.2, 112.0, 80.4, 79.6, 55.9, 51.9, 39.7, 37.6, 32.7, 32.7, 24.0; HRMS (ESI), calcd for $C_{17}H_{24}NO_6^+$ $[M + H]^+$ 338.1598; found 338.1582.

(*R*)-Rolipram, 44a[11f]



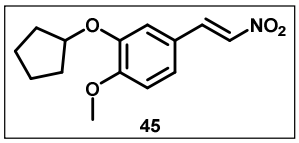
44a

To an EtOAc (25 mL) solution of methylester **43** (100 mg, 0.30 mmol) were added 10% Pd/C (30 mg) and catalytic amount of Et_3N at room temperature. The reaction mixture was then subjected to hydrogenation under 1 atmosphere pressure for 12 h. After the completion of reaction, the solution was filtered through Celite pad and washed with methanol. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc) to furnish the (*R*)-rolipram **44a** (68 mg, 92%) as a white solid with >99% *ee*. [R_f = 0.2, pure EtOAc]; mp = 130-132 ^oC; {$[\alpha]_D^{25}$ -31.1 (*c* 1.05, CH_3OH), [lit.[11f] $[\alpha]_D^{25}$ -31 (*c* 1.05, CH_3OH)]}. IR (CH_2Cl_2) *v*:

3450, 1535, 1280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.85-6.71 (m, 3H), 6.01 (brs, 1H), 4.79-4.74 (m, 1H), 3.83 (s, 3H), 3.77-3.72 (m, 1H), 3.68-3.60 (m, 1H), 3.40-3.36 (m, 1H), 2.76-2.64 (m, 1H), 2.47 (dd, *J* = 9.2, 16.8 Hz, 1H), 1.97-1.79 (m, 6H), 1.64-1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.5, 149.0, 147.8, 134.3, 118.7, 113.6, 112.0, 80.4, 56.0, 49.6, 39.9, 37.9, 32.7, 24.0; HRMS (ESI), calcd for $C_{16}H_{22}NO_3^+$ $[M + H]^+$ 276.1594; found 276.1595.

The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.668 min, (*S*)-enantiomer: t_r = 36.624 min.

(*E*)-2-(Cyclopentyloxy)-1-methoxy-4-(2-nitrovinyl)benzene, 45[11f]

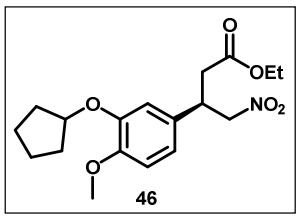


45

To a DMF (70 mL) solution of isovanillin **41** (500 mg, 3.28 mmol) was added K_2CO_3 (680 mg, 4.92 mmol), cyclopentylbromide (0.45 mL, 4.27 mmol) and heated at 100 ^oC for 30 h. After the completion of reaction as monitored by TLC, the mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 x 40 mL). The organic extracts were combined, washed with water, dried over anhydrous Na_2SO_4, concentrated *in vacuo* to give cyclopentylaldehyde as a brown liquid, which was directly used for the next step without further purification.

To a stirred solution of the above crude aldehyde was added nitromethane (15 mL), ammonium acetate (250 mg, 3.28 mmol) and heated at 130 ^oC for 24 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, dissolved in a mixture of CH_2Cl_2/H_2O (1:1) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by silica gel chromatography (EtOAc/hexane 1:19) as eluent to furnish the compound **45** (750 mg, 87% yield) as a light yellow solid. [R_f = 0.6, EtOAc/hexane 1:9 v/v]; mp = 138-140 ^oC; IR (CH_2Cl_2) *v*; 1650, 1522, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.96 (d, *J* = 13.6 Hz, 1 H), 7.51 (d, *J* = 13.6 Hz, 1 H), 7.16-7.13 (m, 1 H), 7.01 (br d, *J* = 1.6 Hz, 1 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 4.82-4.78 (m, 1 H), 3.91 (s, 3 H), 2.02-1.79 (m, 6 H), 1.70-1.64 (m, 2 H); ^{13}H NMR ($CDCl_3$, 100 MHz) δ: 153.7, 148.0, 139.5, 134.9, 124.2, 122.5, 113.5, 111.6, 80.6, 56.0, 32.7, 24.0; HRMS (ESI), calcd for $C_{14}H_{18}NO_4^+$ $[M + H]^+$ 264.1231; found 264.1233.

Ethyl (*R*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-4-nitrobutanoate, 46



46

To a 1,4-dioxane (0.3 mL) solution of catalyst (*R*)-diphenyltrimethylsiloxymethylpyrrolidine (30 mg, 0.09 mmol, 10 mol%) was added compound **45** (250 mg, 0.94 mmol) and acetaldehyde (0.53 mL, 9.49 mmol) in a sealed tube at 4 ^{o}C. After stirring the reaction mixture for 18 h at room temperature, the reaction mixture was quenched with 1N HCl (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude aldehyde which was used as such for the next step without further purifcation.

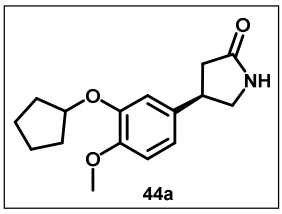
To a DMF solution of above synthesized aldehyde was added oxone (580 mg, 1.89 mmol) and stirred at room temperature for 12 h. The resulting reaction mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo* to obtain the crude acid which was used as such for the next step without further purification due to more polar nature of the compound.

To an ethanolic solution (4 mL) of above crude acid was added trimethylsilyl chloride (0.24 mL, 1.89 mmol) and stirred at room temperature for 12 h. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc (3 x 10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel chromatography using (EtOAc/hexane 1:9) as eluent to give nitroester **46** (280 mg, 85%) as a yellow liquid. $[\alpha]_D^{25}$ -23.7 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*: 1668, 1520, 1390, 1205 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.80 (d, *J* = 8.0 Hz, 1H), 6.75-6.72 (m, 2H), 4.76-4.67 (m, 2H), 4.62-4.57 (m, 1H), 4.08 (q, *J* = 6.8, 14.0 Hz, 2H), 3.94-3.86 (m, 1H), 3.81 (s, 3H), 2.73 (d, *J* = 7.6 Hz, 2H), 1.94-1.80 (m, 6H), 1.63-1.59 (m, 2H), 1.18 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.6, 149.5, 147.7, 130.4, 119.1, 114.2, 112.0, 80.3, 79.6, 60.8, 55.9, 39.7, 37.8, 32.7, 32.6, 23.9, 14.0; HRMS (ESI), calcd for $C_{18}H_{26}NO_6^+$ $[M + H]^+$ 352.1755; found 352.1734.

(*R*)-Rolipram, 44a[11f]

To an EtOAc (25 mL) solution of ethylester **46** (100 mg, 0.28 mmol) were added 10% Pd/C (30 mg) and catalytic amount of Et_3N at room temperature. The reaction mixture was then subjected to hydrogenation under 1 atmosphere pressure for 12 h. After the completion of reaction, the solution was filtered through Celite pad and washed with methanol. The filtrate was concentrated

in vacuo and purified by silica gel column chromatography (EtOAc) to furnish the (*R*)-rolipram **1** (70 mg, 93%) as a white solid, >99% *ee*. [R_f = 0.2, pure EtOAc]; mp = 130-132 ^oC; {$[\alpha]_D^{25}$ -31.1 (*c* 1.05, CH_3OH), [lit.[11f] $[\alpha]_D^{25}$ -31 (*c* 1.05, CH_3OH)]}.

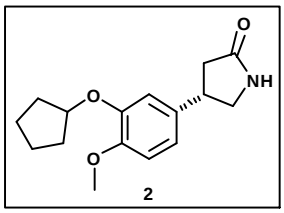


44a

The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.768 min, (*S*)-enantiomer: t_r = 36.994 min.

(*S*)-Rolipram, 44b[11j]

White solid, >99% *ee*. [R_f = 0.2, pure EtOAc]; mp = 131-134 ^oC; {$[\alpha]_D^{25}$ +31.8 (*c* 0.6, CH_3OH) [lit.[11j] $[\alpha]_D^{rt}$ +31 (*c* 0.6, CH_3OH)]}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.83-6.71 (m, 3H); 6.08 (brs, 1H), 4.79-4.74 (m, 1H), 3.83 (s, 3H), 3.77-3.72 (m, 1H), 3.67-3.59 (m, 1H), 3.40-3.36 (m, 1H), 2.76-2.60 (m, 1H), 2.48 (dd, *J* = 9.1, 16.9 Hz, 1H), 1.97-1.79 (m, 6H), 1.64-1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6, 149.1, 147.8, 134.3, 118.7, 113.6, 112.0, 80.5, 56.1, 49.7, 39.9, 37.9, 32.7, 24.0; HRMS (ESI), calcd for $C_{16}H_{22}NO_3^+$ $[M + H]^+$ 276.1594; found 276.1589.

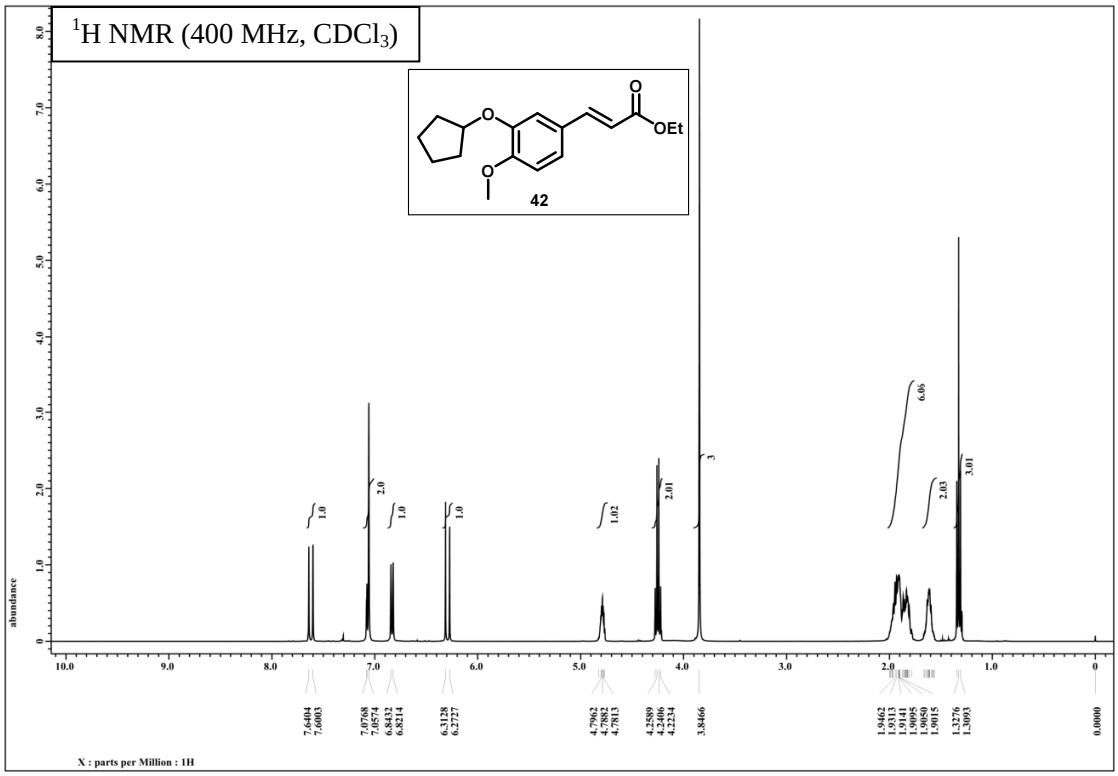


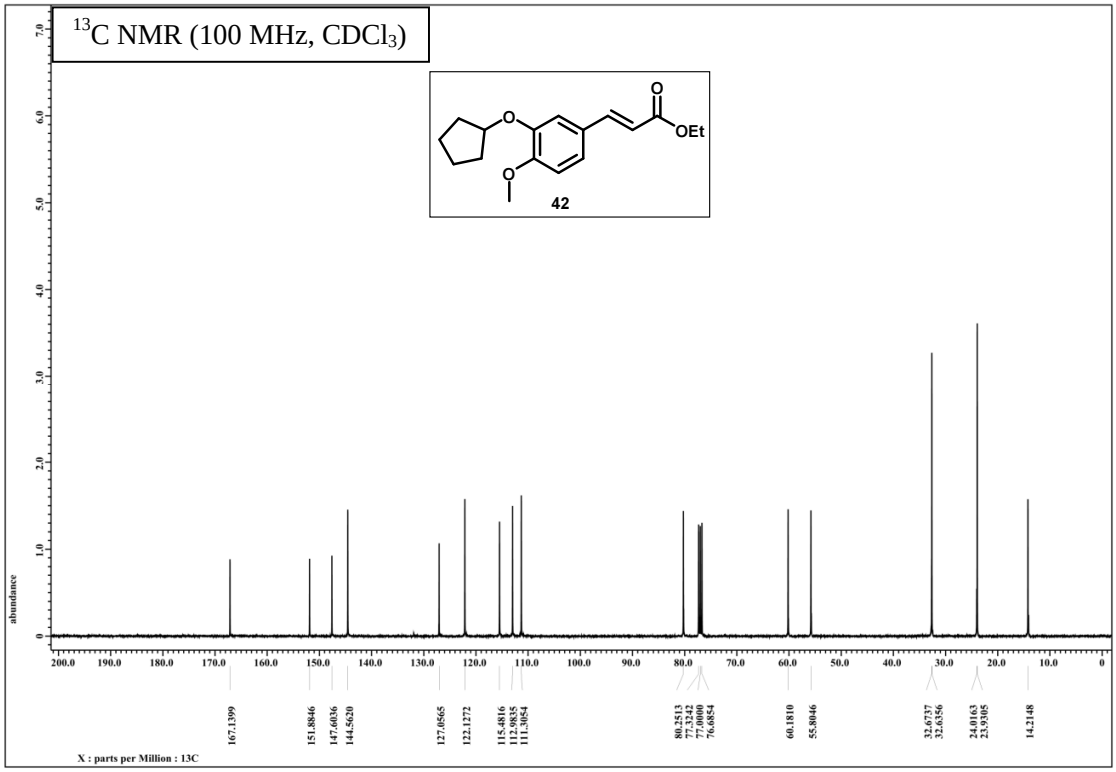
2

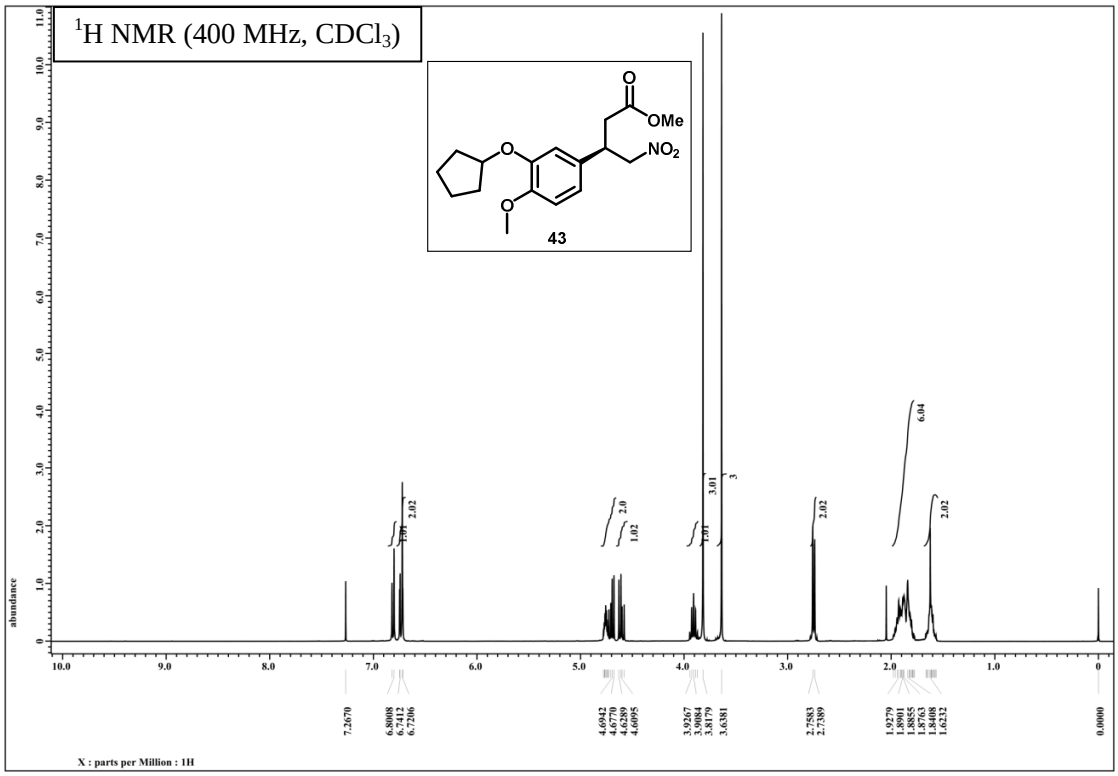
The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.521 min, (*S*)-enantiomer: t_r = 35.654 min.

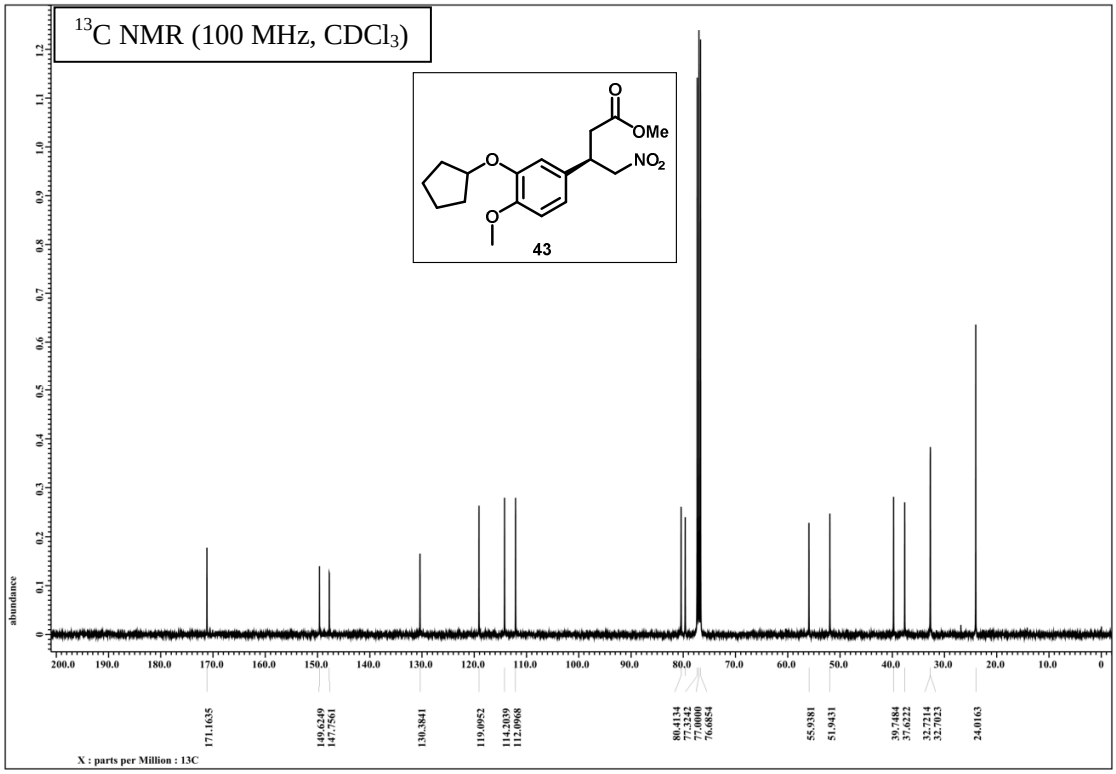
4.7 Spectra:

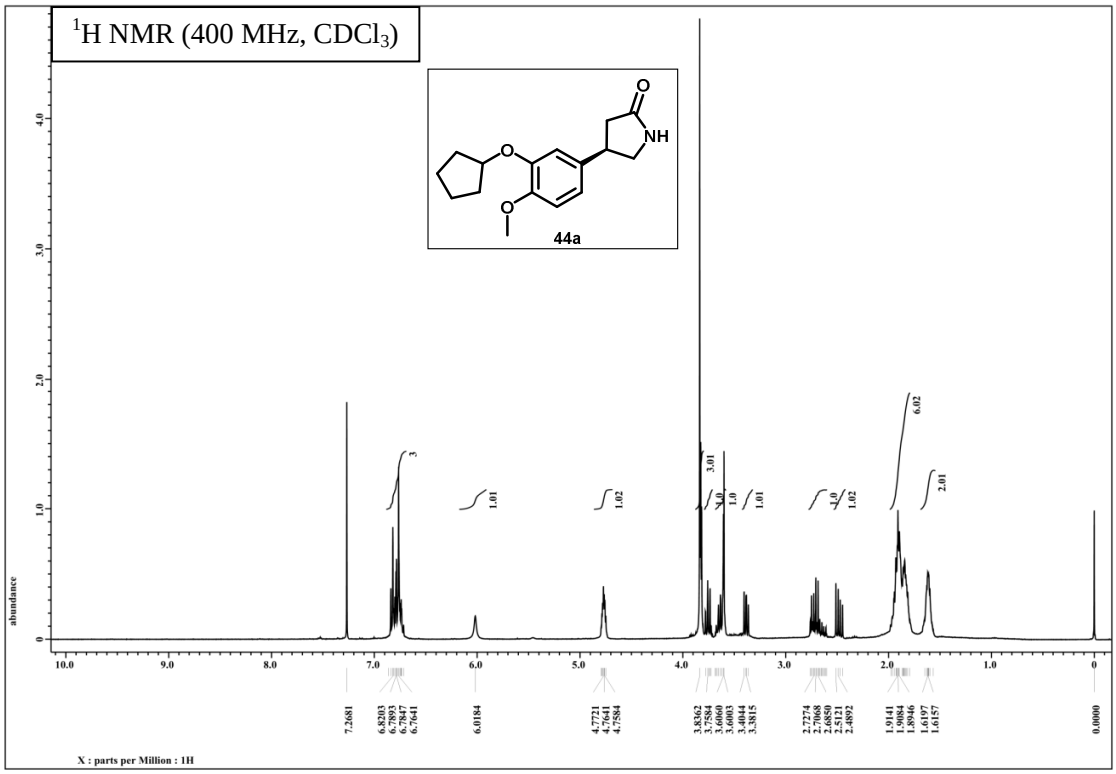
1. ^1H and ^{13}C NMR spectra of **42**
2. ^1H and ^{13}C NMR spectra of **43**
3. ^1H and ^{13}C NMR spectra of **44a**
4. ^1H and ^{13}C NMR spectra of **45**
5. ^1H and ^{13}C NMR spectra of **46**
6. ^1H and ^{13}C NMR spectra of **44b**
7. HPLC data of **44a** and **44b**

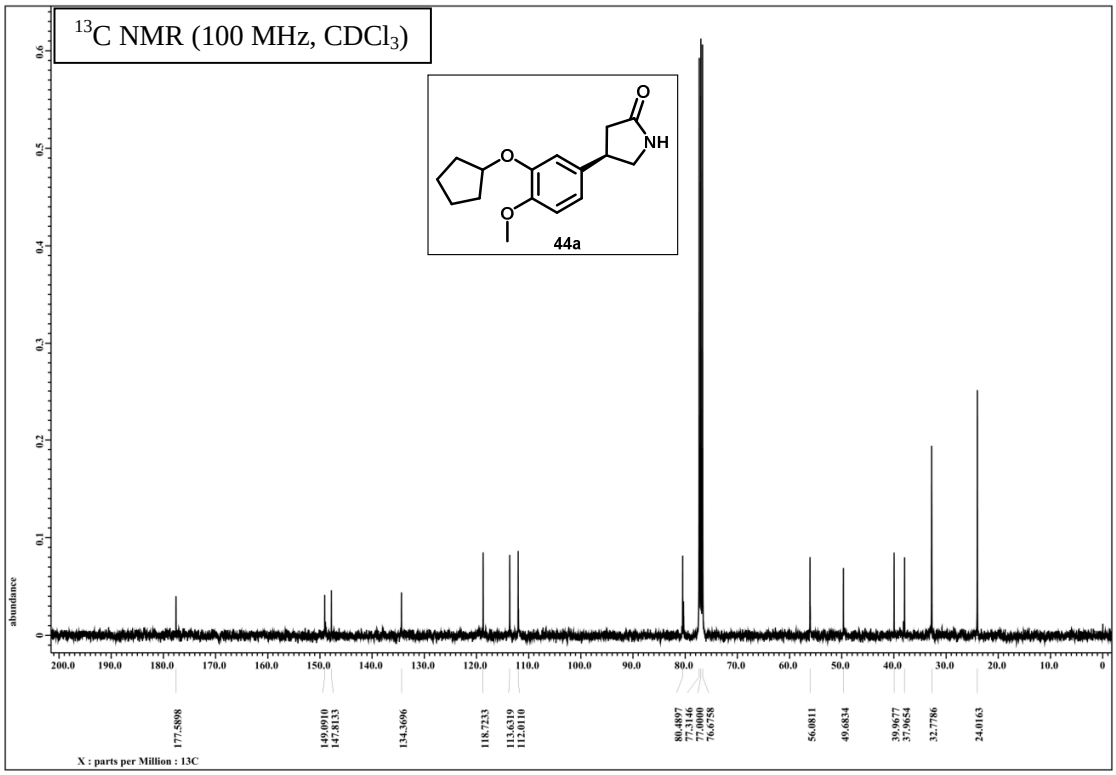

^{1}H NMR (400 MHz, $CDCl_3$)
O
OEt
O
O
42
abundance
X : parts per Million : 1H

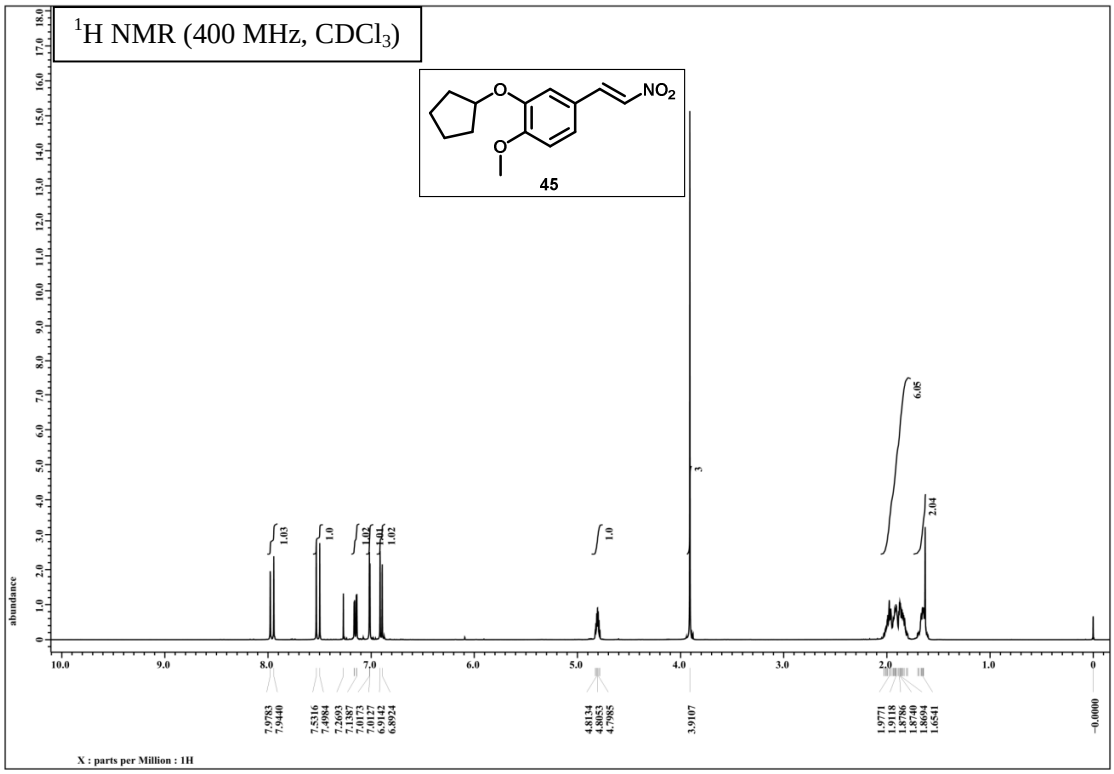

^{13}C NMR (100 MHz, $CDCl_3$)
O
OEt
O
O
42
abundance
X : parts per Million : 13C

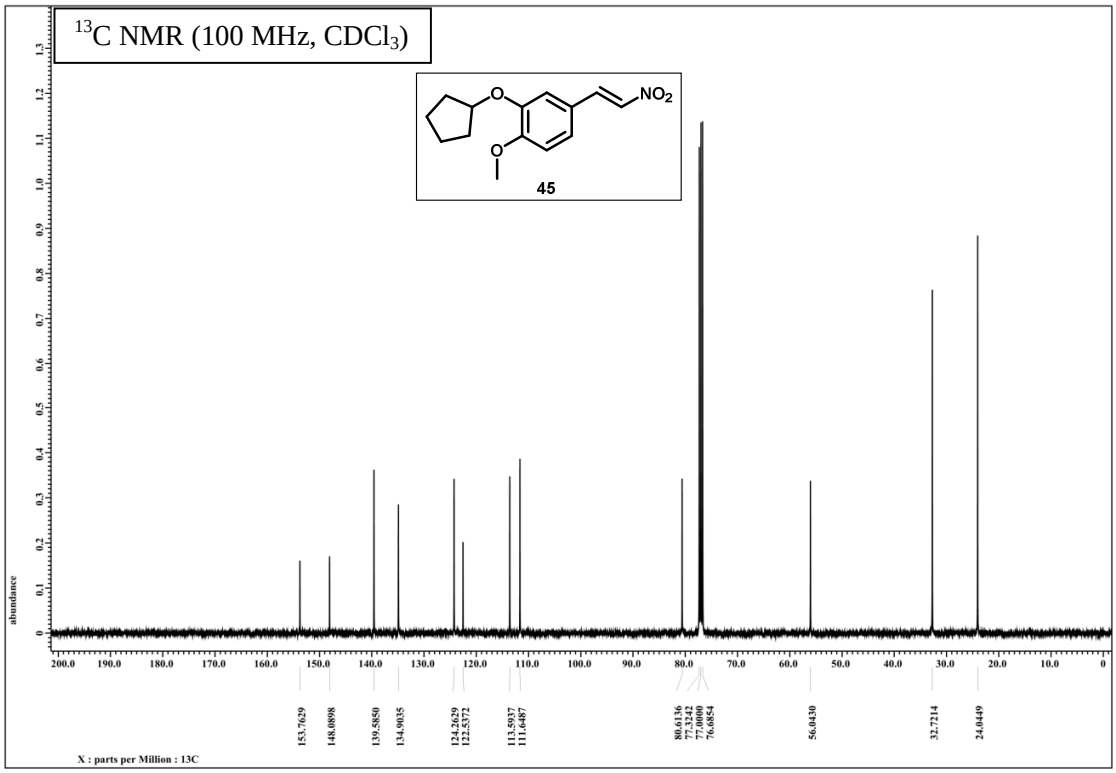

^{1}H NMR (400 MHz, $CDCl_3$)
OMe
NO_2
43
abundance
X : parts per Million : 1H

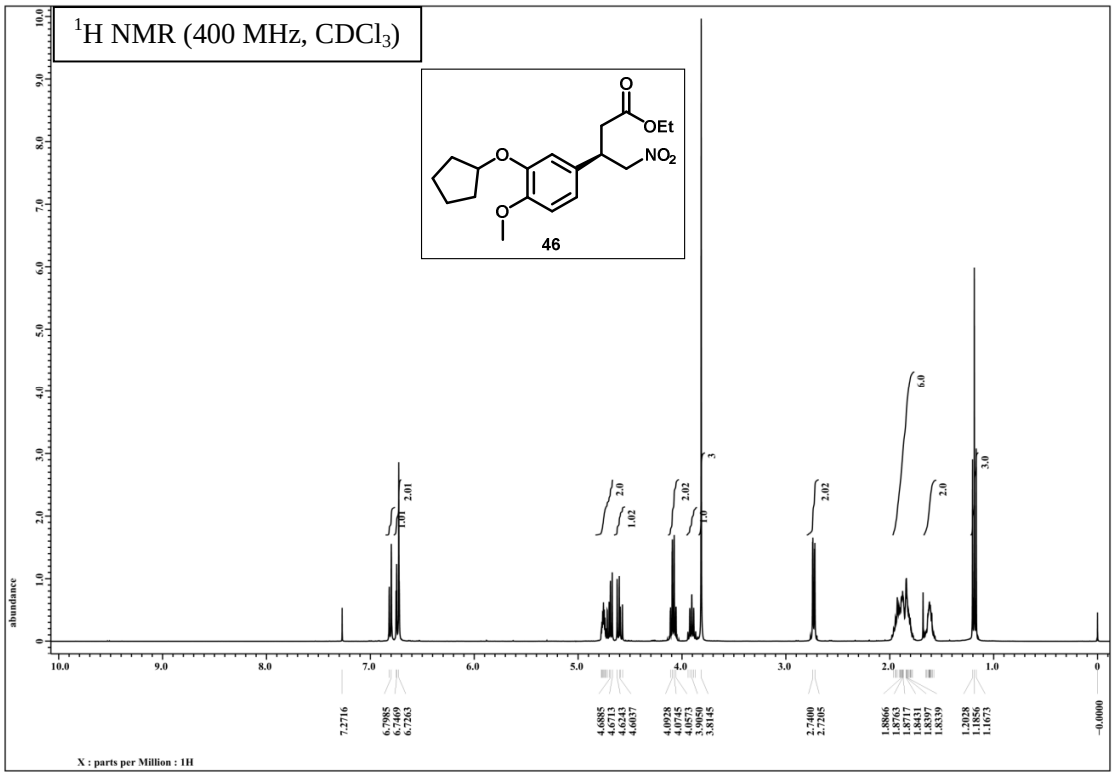

^{13}C NMR (100 MHz, $CDCl_3$)
OMe
NO_2
43
abundance
X : parts per Million : 13C

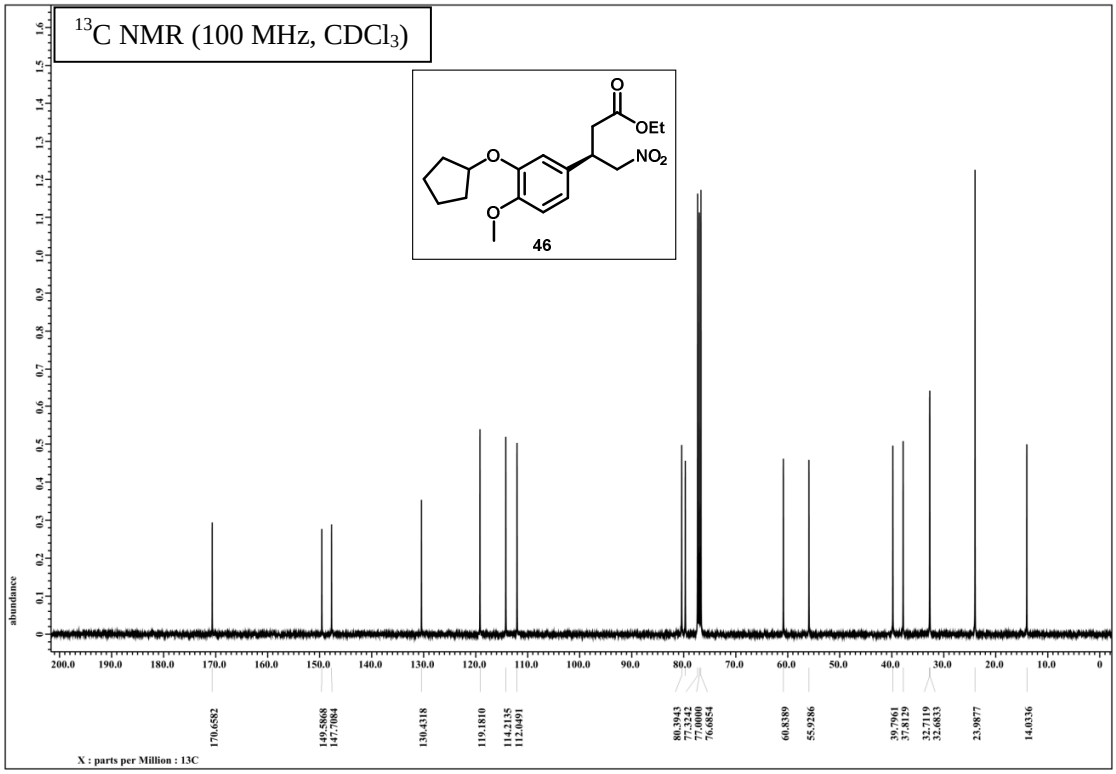

^{1}H NMR (400 MHz, $CDCl_3$)
44a
abundance
X : parts per Million : 1H

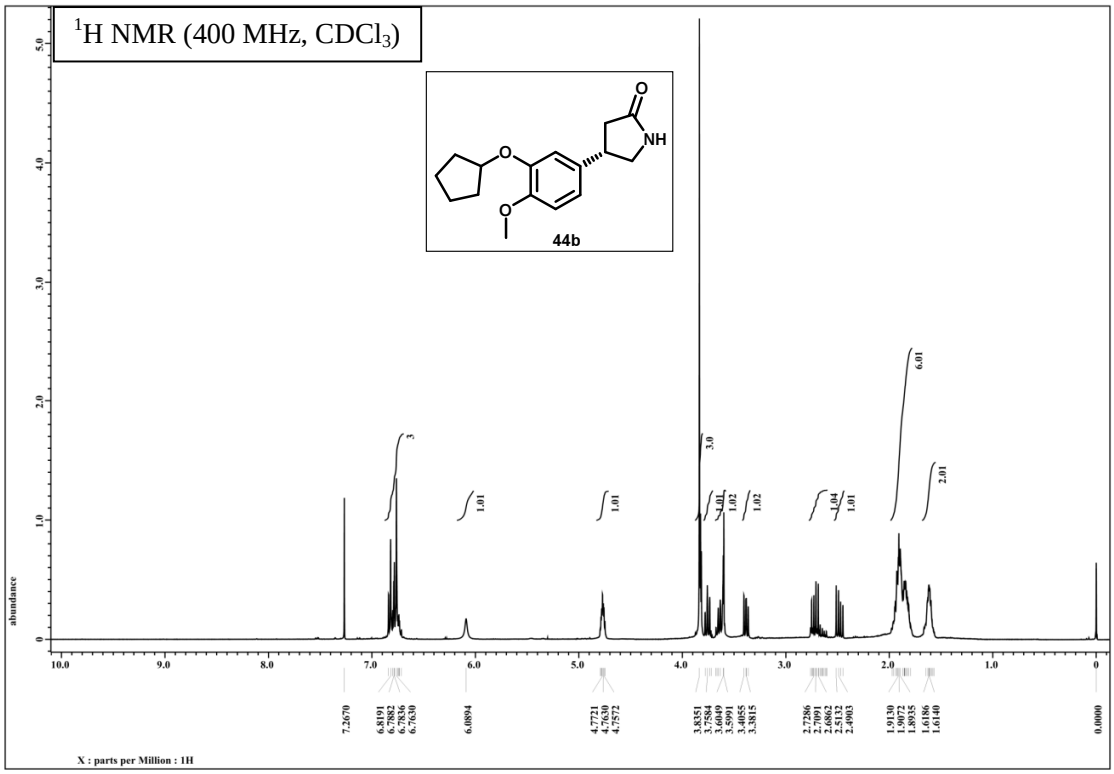

^{13}C NMR (100 MHz, $CDCl_3$)
44a
abundance
X : parts per Million : 13C

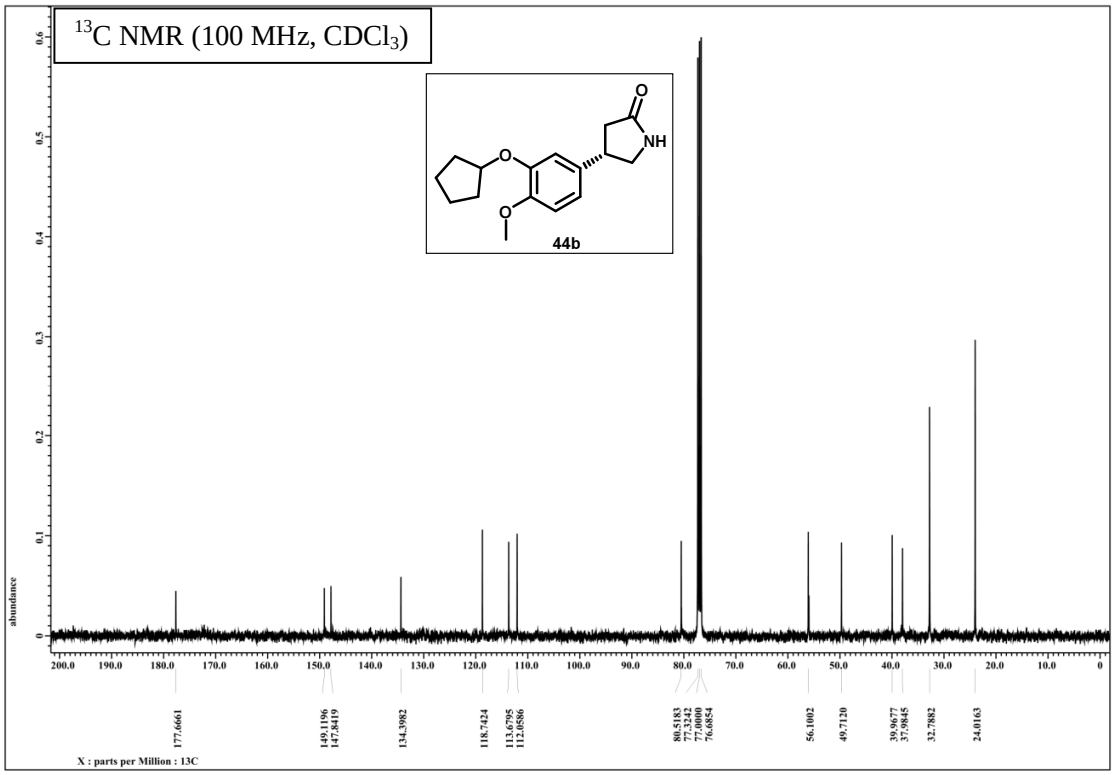

^{1}H NMR (400 MHz, $CDCl_3$)
45
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
45
abundance
X : parts per Million : 13C


^{1}H NMR (400 MHz, $CDCl_3$)
OEt
NO_2
46
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
OEt
NO_2
46
abundance
X : parts per Million : 13C


^{1}H NMR (400 MHz, $CDCl_3$)
44b
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
44b
abundance
X : parts per Million : 13C

Thermofisher HPLC System Report

Application: HPLC

Column: Chiralcel IA (5 µM, 4 x 250 mm)

Sample Name: RoliRaman (Racemic)

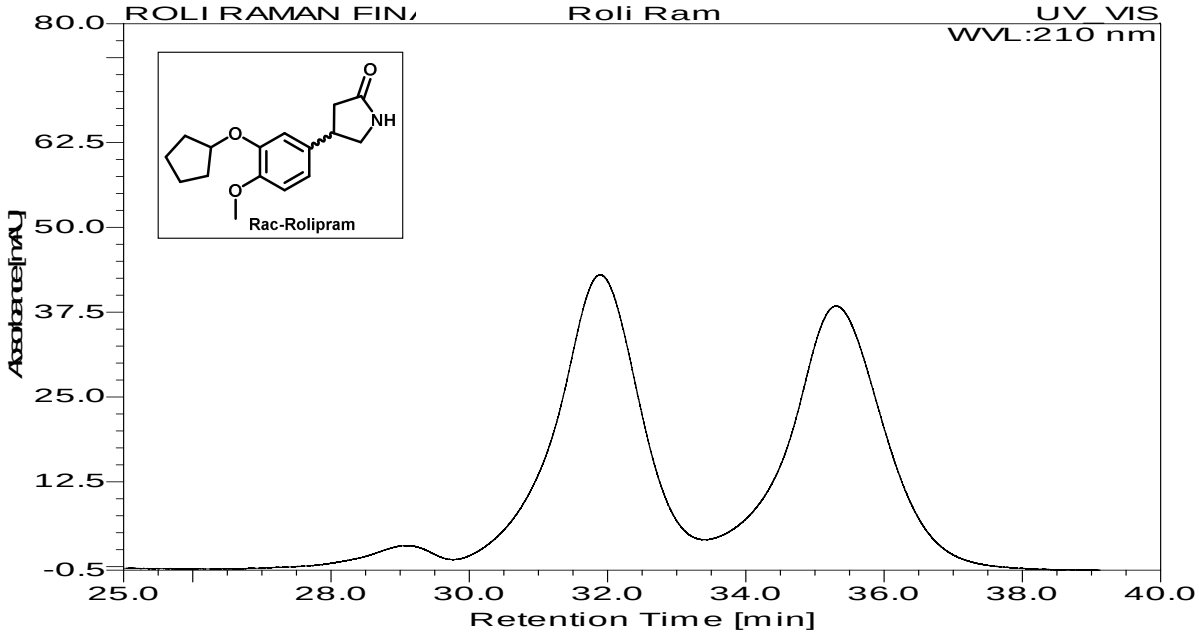
Wavelength: 210 nm

Mobile Phase: hexane/*i*-PrOH (96:4)

Flow Rate: 1 mL/min

Injection Volume: 20 µL

Sample Conc: 1 mg/mL



No.	RT (min)	Height mAU	Area mAU*min	Area %
1	31.89	39.816	50.668	52.88
2	35.31	33.902	45.150	47.12
		73.718	95.818	100

Thermofisher HPLC System Report

Application: HPLC

Column: Chiralcel IA (5 µM, 4 x 250 mm)

Sample Name: RoliRaman (*R*-Rolipram)

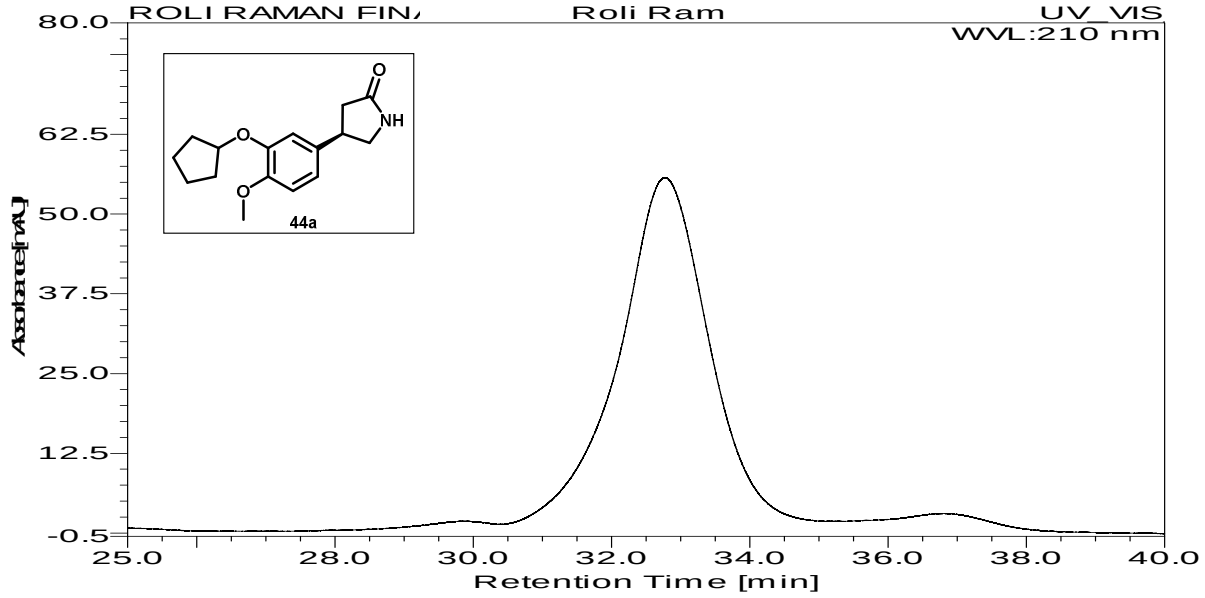
Wavelength: 210 nm

Mobile Phase: hexane/*i*-PrOH (96:4)

Flow Rate: 1 mL/min

Injection Volume: 20 µL

Sample Conc: 1 mg/mL



No.	RT (min)	Height mAU	Area mAU*min	Area %
1	32.768	51.063	36.79	99.97
2	36.994	0.019	0.01	0.03
		51.082	36.80	100

Thermofisher HPLC System Report

Application: HPLC

Column: Chiralcel IA (5 µM, 4 x 250 mm)

Sample Name: RoliRaman (*S*-Rolipram)

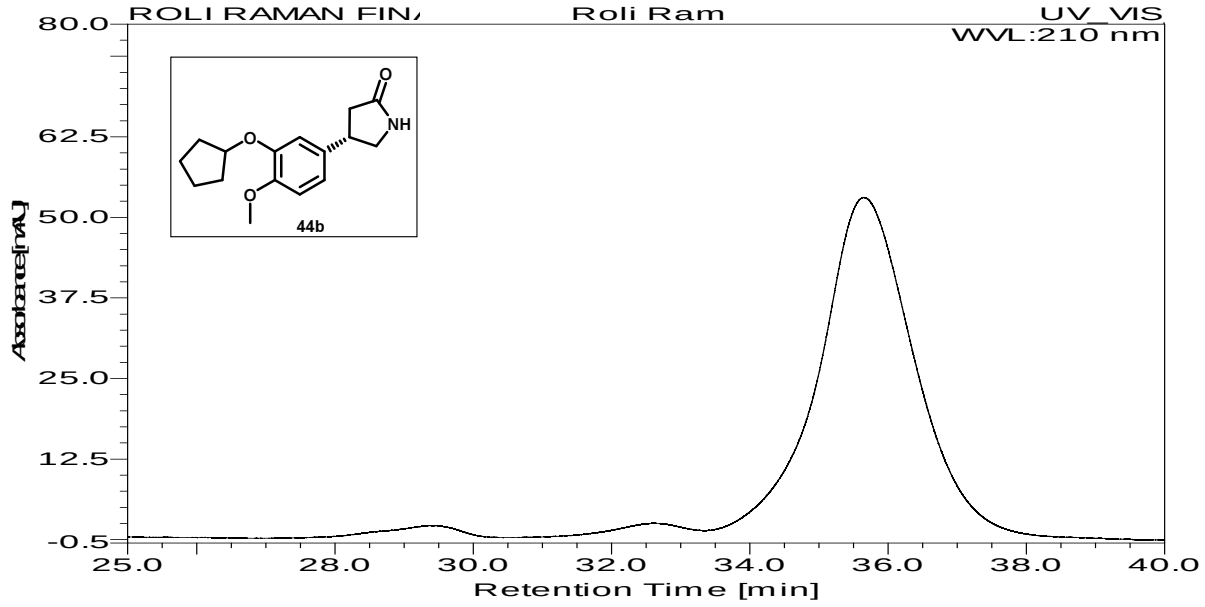
Wavelength: 210 nm

Mobile Phase: hexane/*i*-PrOH (96:4)

Flow Rate: 1 mL/min

Injection Volume: 20 µL

Sample Conc: 1 mg/mL



No.	RT (min)	Height mAU	Area mAU*min	Area %
1	32.521	0.017	0.01	0.02
2	35.654	51.108	50.21	99.98
		51.125	50.22	100

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13. HPLC spectral data of (*R*)-rolipram **44a**: The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.668 min, (*S*)-enantiomer: t_r = 36.624 min.
14. (*R*)-Diphenylprolinol silyl ether was prepared from (*R*)-diphenylprolinol and TMSCl using a known procedure; see: Hayashi, Y.; Gotoh, H.; Hayashi. T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
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18. HPLC spectral data of (*R*)-rolipram **44a**: The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.768 min, (*S*)-enantiomer: t_r = 36.994 min.
19. HPLC spectral data of (*S*)-rolipram **44b**: The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralpak IA chiral column (4.6 x 250 mm) using mobile phase of (24:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 210 nm): (*R*)-enantiomer: t_r = 32.521 min, (*S*)-enantiomer: t_r = 35.654 min.

CHAPTER 5

An attempt towards total synthesis of antidepressant drug (*S*,*S*)-reboxetine

5.1 Introduction:

Morpholine ring structures are among the most biologically active heterocyclic compounds in organic chemistry due to their ubiquitous structural motifs in natural and unnatural products with varied range of biological activity.[1] Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has been extensively studied for its pharmaceutical properties and used as medicine for the treatment of hyperactivity disorder and depression (Figure 11). Reboxetine has been commercialised under the name of Vestra, Norebox, Prolift, Integrex, Edronax for the treatment of depression, narcolepsy and cocaine dependence disorder and as a racemic mixture of the (*S*,*S*)-**57** and (*R*,*R*)-**190** enantiomers. However, (*S*,*S*)-**57** enantiomer is by far the more effective one and highly selective for the norepinephrine transporter (NET).[2]

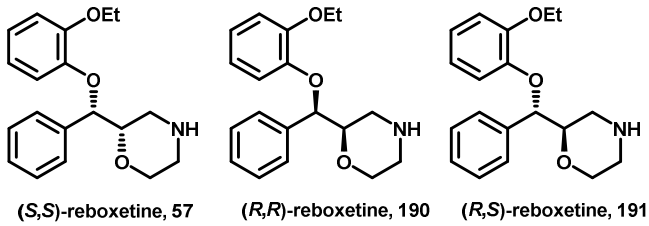


Figure 11. Structures of (*S*,*S*)-**57**, (*R*,*R*)-**190** and (*R*,*S*)-reboxetine **191**.

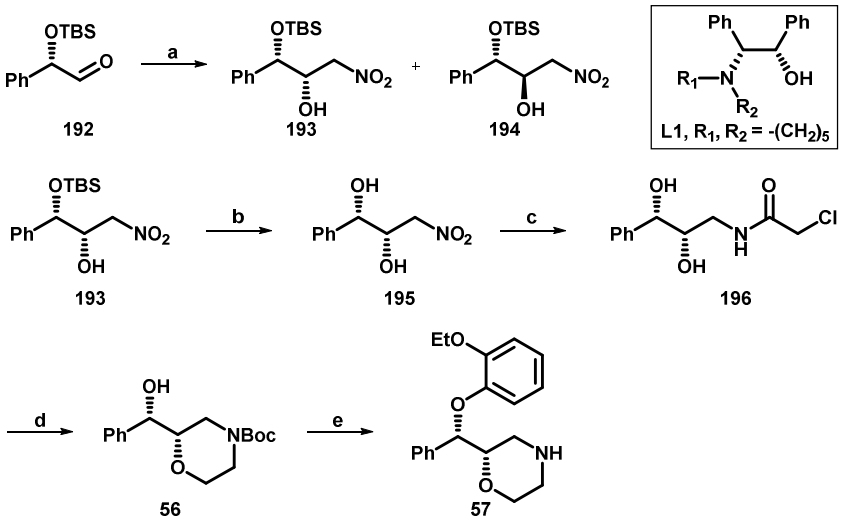
5.2 Review of Literature:

Various elegant synthesis for (*S*,*S*)-reboxetine **57** have been documented in the literature based on optically active starting materials,[3] chemical resolution,[4] asymmetric epoxidation,[4] hydrolytic kinetic resolution,[5] asymmetric transfer hydrogenation[6] and dihydroxylation.[7] Some of the recent synthesis of (*S*,*S*)-reboxetine **57** are described below.

Chen, H. B. (2017)[3a]

H. B. Chen and co-workers reported the strereodivergent synthesis of reboxetine **57** from the readily available aldehyde **192** employed the chiral amino alcohol-copper (II) catalyzed diastereoselective nitroaldol reaction as the key step (Scheme 49). The aldehyde **192** on treatment with nitromethane in presence of catalyst **L1** furnished the nitroaldol adduct **193** and **194** (*syn*/*anti* 10.4:1) in 86% yield. The *O*-TBS protected compound **193** on deprotection with 3N HCl afforded the diol **195** which on hydrogenation using Pd/C followed by treatment with chloroacetyl chloride in the presence of base afforded the chloroacetamide derivative

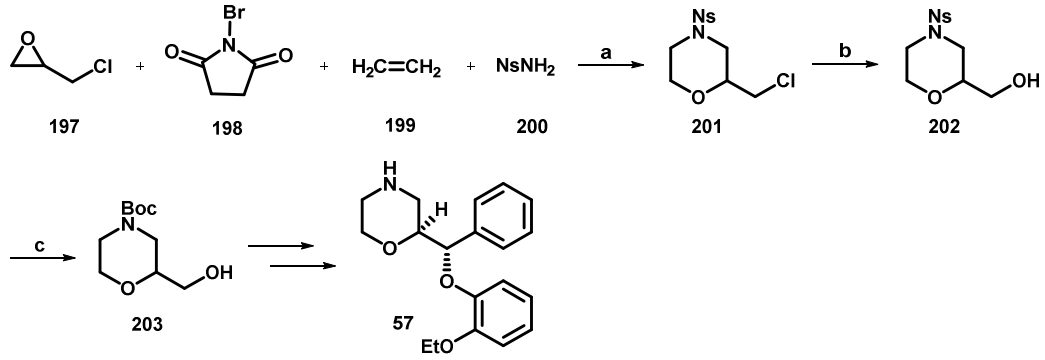
196 in 71% yield. The amide derivative **196** was subjected to cyclization using *t*-BuOK followed by amide reduction with LAH and subsequent *N*-Boc protection furnished the morpholine derivative **56** in 70% yield. Finally, the derivative **56** was transformed to reboxetine **57** in 85% yield by following the known literature method. [5,6a]



Scheme 49. *Reagents and conditions*: (a) $CuOAc.H_2O$, **L1**, $MeNO_2$, rt, 3 d, 86%; (b) 3N HCl, MeOH, rt, 3 h, 84%; (c) i) 10% Pd/C, H_2, MeOH, rt, 12 h; ii) $ClCH_2COCl$, K_2CO_3, 0 ^oC, 1 h, 71%; (d) i) *t*-BuOK, *t*-BuOH, rt, 2 h; ii) LAH, THF, 0 ^oC-reflux, 6 h; iii) $(Boc)_2O$, THF, rt, 12 h, 70%; (e) i) CBr_4, PPh_3, imidazole, DCM, rt, 2 h; ii) 2-ethoxyphenol, *t*-BuOK, *t*-BuOH/THF, reflux, 12 h; iii) TFA, DCM, rt, 6 h, 85%.

Yeung, Y. Y. *et al.* (2014)[3b]

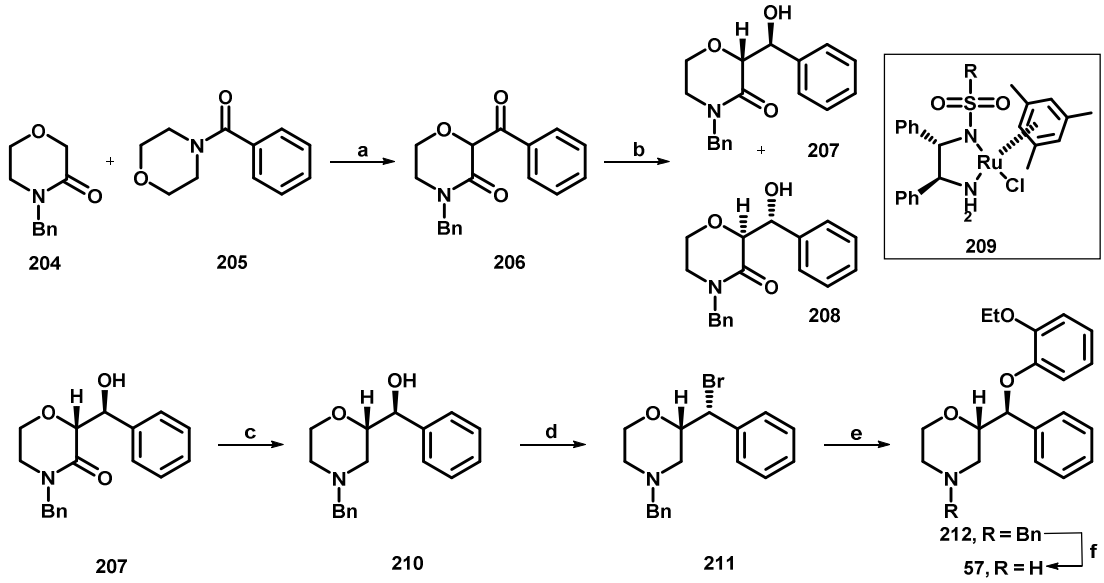
Y. Y. Yeung and co-workers reported the formal synthesis of reboxetine **57** starting from commercially available epichlorohydrin **197** employed the *N*-bromosuccinimide induced electrophilic multicomponent reaction as key step (Scheme 50). The epichlorohydrin **197** on treatment with ethylene **199**, NBS **198** and $NsNH_2$ **200** at -30 ^oC and subsequent treatment with base afforded the morpholine derivative **201** in 66% yield. The compound **201** on substitution with acetate followed by hydrolysis furnished the alcohol derivative **202** in 93% yield. The alcohol **202** on deprotection of nosyl amide group and subsequent treatment with $(Boc)_2O$ afforded the *N*-Boc protected derivative **203** in 80% yield. Finally, the compound **203** was converted into final target compound reboxetine **57** by following the known literature method.[3e]



Scheme 50. *Reagents and conditions*: (a) i) -30 ^{o}C, 24 h; ii) K_2CO_3, MeCN, 25 ^{o}C, 66% (over two steps); (b) i) AcOK, DMF, 90 ^{o}C, 16 h, 81%; ii) K_2CO_3, MeOH/H_2O, 25 ^{o}C, 16 h, 93%; (c) i) *n*-PrSH/LiOH, CH_3CN, 25 ^{o}C, 8 h; ii) $(Boc)_2O$, NaOH, CH_2Cl_2/H_2O, 25 ^{o}C, 4 h, 80% (over two steps).

Lee, H. K. *et al.* (2013)[6a]

H. K. Lee and co-workers reported the stereoselective synthesis of reboxtine **57** employed the dynamic kinetic resolution mediated asymmetric transfer hydrogenation reaction (ATH) of 2-benzoylmorpholin-3-ones as key step (Scheme 51). The *N*-benzyl-3-morpholinone **204** on condensation reaction with *N*-aroylmorpholines **205** in the presence of LDA furnished the *N*-benzyl-2-aroylmorpholin-3-one **206** in 93% yield. The dynamic kinetic resolution mediated ATH reaction of **206** with catalyst (*S*,*S*)-**209** afforded the alcohol (2*R*,3*S*)-**207** and (2*S*,3*R*)-**208** in 90% combined yield.

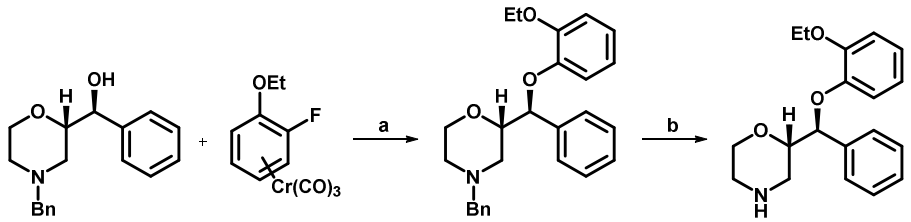


Scheme 51. *Reagents and conditions*: (a) LDA, THF, -78 to 10 ^{o}C, 93%; (b) **209**, HCOOH, Et_3N, CH_2Cl_2, 35 ^{o}C, 24 h, 99%; (c) BH_3.THF, THF, 60 ^{o}C, 2 h, then MeOH, 97%; (d) Ph_3PBr_2, CH_2Cl_2, 50 ^{o}C, 95%; (e) 2-EtO-phenol, *t*-BuOK, *t*-BuOH/THF (3:1), 80 ^{o}C, 24 h,

91%; (f) α-chloroethyl chloroformate, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 50 ^oC, 4 h, then MeOH, reflux, 2 h, 86%.

The lactam **207** on reduction with $BH_3 \cdot THF$ delivered the morpholine benzyl alcohol **210** in 97% yield which on subsequent treatment with Ph_3PBr_2 synthesized the corresponding morpholine bromide derivative **211** in 95% yield. The compound **211** on bromide displacement with 2-ethoxyphenol in the presence of *t*-BuOK afforded the *N*-benzyl-protected derivative **212** in 91% yield. The compound **212** on treatment with α-chloroethyl chloroformate and subsequent methanolysis furnished the target molecule (*S,S*)-reboxetine **57** in 86% yield.

In another approach, the 2-ethoxyphenyl group was directly incorporated in compound **210** with retention of configuration at the benzylic position (Scheme 52). Thus, reaction of benzyl alcohol **210** with the tricarbonylchromium complex of 1-ethoxy-2-fluorobenzene **213** in the presence of NaH, which on subsequent oxidative dechromination with iodine afforded the *N*-Bn protected reboxetine derivative **212** in 88% yield. The *N*-Bn derivative **212** on reaction with α-chloroethyl chloroformate followed by methanolysis furnished the target molecule (*S,S*)-reboxetine **57** in 86% yield.



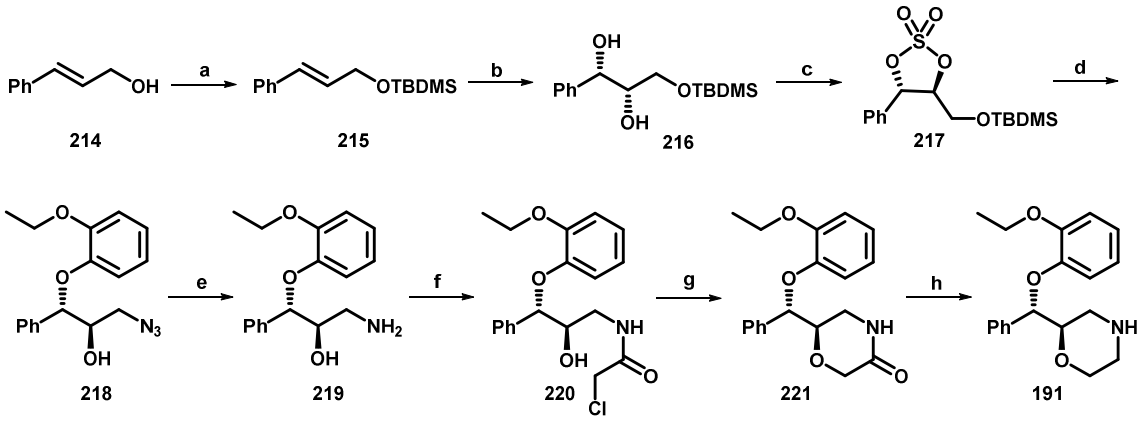
210 213 212 57

Scheme 52. *Reagents and conditions*: (a) i) NaH, DMF, rt, 2 h; ii) I_2, THF, 0 ^oC to rt, 1 h, 88%; (b) α-chloroethyl chloroformate, $(i\text{-Pr})_2NEt$, CH_2Cl_2, 50 ^oC, 4 h, then MeOH, reflux, 2 h, 86%.

Ko, S. Y. *et al.* (2012)[6b]

S. Y. Ko and co-workers described the synthesis of (*R,S*)-reboxeine **191** starting from *trans*-cinnamyl alcohol in nine steps and with 43% overall yield (Scheme 53). The *trans*-cinnamyl alcohol **214** on protection with TBDMSCl afforded the compound **215** which on Sharpless AD reaction furnished the diol **216** in 95% yield. The compound **216** on thionyl chloride followed by oxidation with $RuCl_3.H_2O$ furnished the cyclic sulfate **217** in excellent yield. The compound **217** on TBDMS deprotection with TBAF followed by nucleophilic displacement

with sodium azide and subsequent treatment with 2-ethoxyphenol afforded the azide **218** in 84% yield. The azido alcohol derivative **218** on reduction under hydrogenation conditions furnished the amine **219** in 88% yield. The amine intermediate **219** on treatment with chloroacetyl chloride afforded the chloroacetamide derivative **220** in 84% yield. Finally, the compound **220** on cyclization using *t*-BuOK delivered the amine **221** which on BH_3.DMS mediated amide reduction furnished the (*R*,*S*)-reboxetine **191** in 73% yield.



Scheme 53. *Reagents and conditions*: (a) TBDMSCl, imidazole, DMF, rt, 12 h, 100%; (b) AD-mix-*α*, methanesulfonamide, *t*-BuOH/H_2O, 0 ^oC, 9.5 h, 95%; (c) i) $SOCl_2$, Et_3N, CH_2Cl_2; ii) $NaIO_4$, $RuCl_3.H_2O$, $CCl_4/H_2O/CH_3CN$, 0 ^oC, 1 h, 100%; (d) i) TBAF, THF, rt, 30 min; ii) NaN_3, THF, H_2O, 70 ^oC, 21 h; iii) 2-$EtOC_6H_4OH$, NaOH, H_2O, reflux, 5 h, 84%; (e) H_2, Pd/C, EtOAc, 30 min, 88%; (f) $ClCH_2COCl$, Et_2O, aq $NaHCO_3$, -10 ^oC-rt, 10 min, 84%; (g) *t*-BuOK, *t*-BuOH, rt, 1 h, 99%; (h) BH_3.DMS, THF, 0 ^oC to reflux, 20 h, 73%.

5.2.1 Table 8. Comparison with the previous reported syntheses of (*S*,*S*)-reboxetine **57**.

Sr. No.	Syntheses	Key step	Overall yield	No. of steps
1.	-	**HKR and Henry reaction**	-	-
2.	*Org. Biomol. Chem.* **2017**, *15*, 5395	copper (II) catalyzed nitroaldol reaction	30%	five
3.	*J. Org. Chem.* **2014**, *79*, 4644	NBS induced electrophilic multicomponent reaction	-	nine
4.	*J. Org. Chem.* **2013**, *78*, 8396	dynamic kinetic resolution mediated asymmetric transfer hydrogenation reaction of 2-benzoylmorpholin-3-ones	66%	six

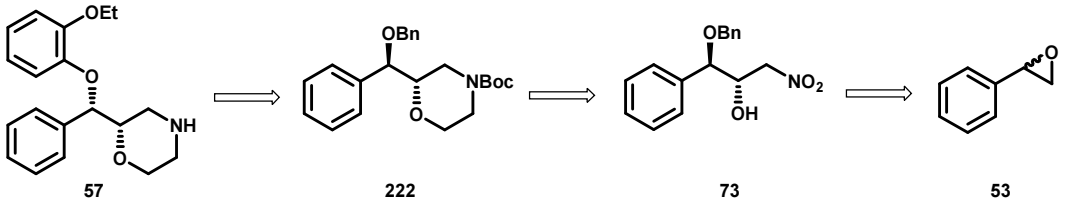
5.	*Tetrahedron: Asymmetry* **2012**, *23*, 650	Asymmetric dihydroxylation	43%	nine

5.3 Present Work:

Herein, we have attempted a new synthetic strategy for the (*S*,*S*)-reboxetine **57** employing Jacobsen's HKR and Henry reaction as key steps.

5.4 Results and Discussion:

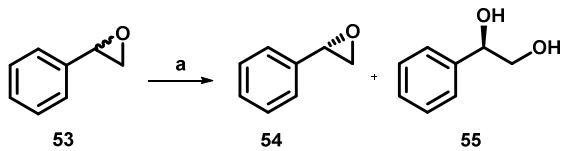
Our retrosynthetic approach for the synthesis of (*S*,*S*)-reboxetine **57** is outlined in Scheme 54. Accordingly, we envisioned that the (*S*,*S*)-reboxetine **57** could be obtained from the amine protected derivative **222** by mitsunobu inversion with 2-ethoxyphenol



Scheme 54. Retrosynthetic approach to (*S*,*S*)-reboxetine **57**.

followed by *N*-Boc deprotection. The derivative **222** in turn could be synthesized from nitro-alcohol **73** *via* hydrogenation followed by standard organic transformations. The nitro derivative **73** could be obtained from recemic styrene oxide **53** *via* Jacobsen's HKR followed by *in situ* Henry reaction.

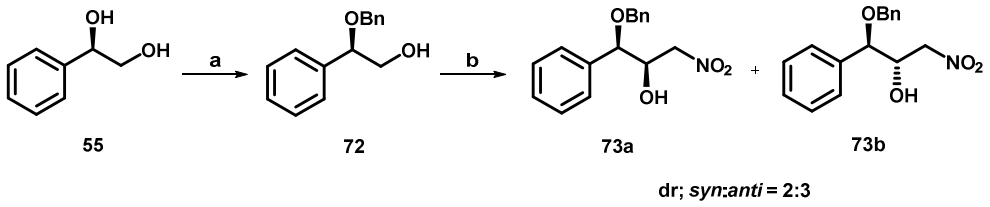
The synthesis of (*S*,*S*)-reboxetine **57** started with commercially available recemic styrene oxide **53** which was subjected to Jacobsen's HKR[8] in the presence of catalytic amount of (*S*,*S*)-Co-(salen) complex to afford the (*S*)-styrene oxide **54** along with (*R*)-styrene glycol **55** in 34% and 47% yield, respectively (Scheme 55).



Scheme 55. *Reagents and conditions*: (a) (*S*,*S*)-Co(salen), *p*-nitrobenzoic acid, air, H_2O, 12 h, **54** in 34% and **55** in 47%.

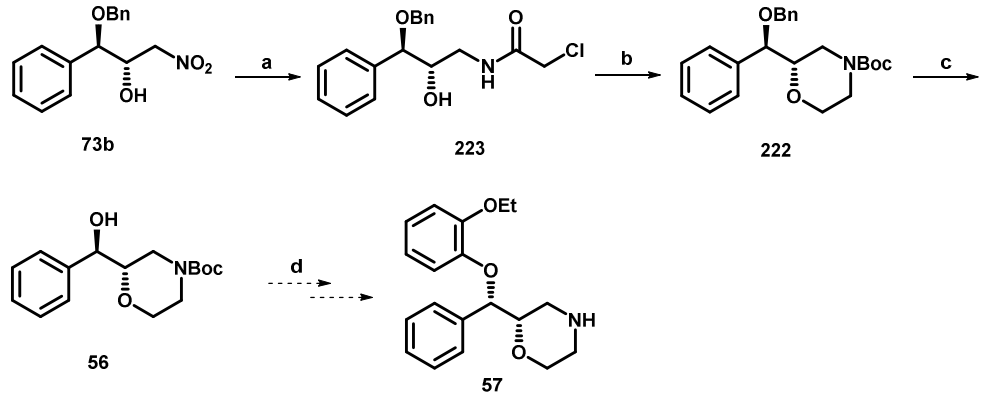
The styrene glycol **55** on protection with benzaldehyde dimethyl acetal in presence of catalytic amount of PPTS and subsequent regioselective reductive opening with DIBAL-H at -40 ^oC afforded the monobenzyl protected alcohol **72** in 85% yield (Scheme 56). The alcohol

72 on oxidation under Swern reaction conditions[10] and subsequent treatment with nitomethane under Henry reaction conditions afforded the nitoalcohol **73a** and **73b** in 80% combined yield with 2:3 *syn*:*anti* diastereomeric ratio which were separated by silica gel column chromatography.



Scheme 56. *Reagents and conditions*: (a) i) $PhCH(OMe)_2$, C_6H_6, PPTS, reflux, 1 h, 88%; ii) DIBAL-H, -40 ^oC to rt, 2 h, 85%; (b) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h; ii) CH_3NO_2, DIPEA, CH_3OH, rt, 12 h, **73a** in 32% and **73b** in 48%.

The nitro derivative **73b** on reduction with Zn/CH_3COOH followed by treatment with chloroacetyl chloride[3d] in presence of base furnished the chloro derivative **223** in 83% yield (Scheme 57). The compound **223** on cyclization in the presence of *t*-BuOK afforded the amide derivative which on reduction with BH_3.DMS and subsequent treatment with $(Boc)_2O$ furnished the *N*-Boc protected derivative **222** in 72% yield. The derivative **222** on debenzylation using Pd/C under hydrogenation conditions furnished the amino alcohol **56** in 85% yield. We have optimized upto the intermediate **56**, however unfortunately the similar approach published for the same target compound in due course of current work.[3a]



Scheme 57. *Reagents and conditions*: (a) i) Zn, CH_3COOH, H_2O, 0 ^oC to rt, 3 h; ii) $ClCH_2COCl$, Et_3N, CH_2Cl_2, 45 min, 83%; (b) i) *t*-BuOK, *i*-PrOH, rt, 2 h; ii) $BH_3.SMe_2$, THF, 0 ^oC to rt, 6 h; iii) $(Boc)_2O$, NaOH, $THF:H_2O$, rt, 4 h, 72%; (c) H_2, Pd/C, MeOH, rt, 12 h, 85%; (d) i) 2-ethoxyphenol; ii) TFA.

5.5 Conclusion:

In conclusion, a simple and flexible enantioselective total synthesis of (*S*,*S*)-reboxetine **57** has been attempted employing the Jacobsen's HKR and Henry reaction as key steps. We have optimized upto the intermediate **56**, however unfortunately the similar approach became published for the same target molecule during progress of work. As compared to previous reported synthesis for (*S*,*S*)-reboxetine, the merits of our synthesis are high regio- and enantioselectivity with high yielding reaction steps.

5.6 Experimental Section:

5.6.1 General Experimental Details:

All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. All the reagents were added either *via* syringe or cannula. Each distillation was performed under an inert atmosphere. All reactions have their respective temperatures within their respective schemes. All evaporations were carried out under reduced pressure on Heidolph rotary evaporator below 40 °C.

Chromatography

All reactions were monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, then were stained by ninhydrin or anisaldehyde in ethanol or $KMnO_4$ in water as development reagents followed by brief heating with a heat gun. Column chromatography were performed on silica gel (60-120 and 100-200 mesh) using a mixture of ethyl acetate/hexane and methanol/ dichloromethane as eluent.

Reagents and solvents

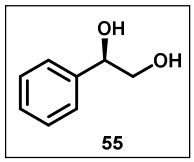
Solvents were obtained commercially and were used without purification unless otherwise noted in experimentals. Distilled water was used for every aqueous reaction, work-up procedure, and in the preparation of every aqueous solution used in the work-up. For reaction solvent, CH_2Cl_2 was distilled from CaH_2, and THF was distilled under N_2 from sodium benzophenone ketyl, all immediately prior to use.

Spectroscopic Measurements

^{1}H NMR and ^{13}C NMR spectra were recorded on on JEOL ECS spectrometer operating at 400 and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard.

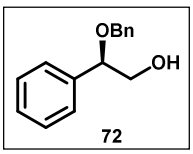
Chemical shifts have been expressed in ppm units (δ) downfield from TMS. Coupling constants, *J*, are listed in hertz (Hz). Optical rotations were measured on Automatic polarimeter AA-65 and concentrations of g/100mL. High resolution mass spectra were obtained by using electron spray ionization (ESI) and mass values are expressed as m/z. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory and peaks are reported in cm^{-1}. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

(*R*)-1-Phenylethane-1,2-diol, 55[8]



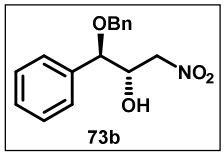
A mixture of styrene oxide **53** (5.0 g, 41.61 mmol), (*S*,*S*)-Co(salen) (125 mg, 0.20 mmol), H_2O (1.49 g, 83.22 mmol) and *p*-nitrobenzoic acid (70 mg, 0.41mmol) was stirred at room temperature for 12 h. The resulting reaction mixture was purified by silica gel column chromatography (EtOAc/hexane 1:4 v/v) to afford the (*R*)-**55** (2.3 g, 47%, 93.9% *ee*) as dark liquid. [R_f = 0.3, EtOAc/hexane 1:1 v/v]; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.28 (m, 5H), 4.81-4.78 (m, 1H), 3.81 (brs, 1H), 3.70-3.63 (m, 1H), 2.82 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.6, 128.4, 127.9, 126.0, 74.5, 67.8.

(*R*)-2-(Benzyloxy)-2-phenylethan-1-ol, 72



To a stirred mixture of diol **55** (2.0 g, 14.47 mmol) in benzene (50 mL) was added benzaldehyde dimethylacetal (2.20 g, 14.47 mmol), PPTS (361 mg, 1.44 mmol) and refluxed for 1 h. The Et_3N (1 mL) was added to the mixture followed by solvent evaporation *in vacuo*. The resulting mixture was purified by silica gel column chromatography (EtOAc/hexanes 1:49 v/v) to afford the 1,2-benzylidene acetal (2.8 g, 88%). To a solution of above 1,2-benzylidene acetal in dry CH_2Cl_2 (30 mL) at -40 ^{o}C was added DIBAL-H (12.4 mL, 21.71 mmol, 1.75 M in toluene) dropwise and the reaction mixture was warmed to room temperature over a period of 2 h, then re-cooled to 0 ^{o}C and treated with saturated aq solution of potassium sodium tartrate. The solid material was filtered through a pad of Celite and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:4 v/v) as eluent afforded monobenzyl protected alcohol **72** (2.4 g, 85%) as a yellow liquid. [R_f = 0.2, EtOAc/hexane 1:9 v/v]; IR ($CHCl_3$) *v*: 3327, 1856, 1680, 1605, 1365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.28 (m, 10H), 4.54-4.50 (m, 2H), 4.31 (d, *J* = 11.4 Hz, 1H), 3.74-3.69 (m, 1H), 3.63-3.57 (m, 1H), 2.55 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 137.8, 128.5, 128.4, 128.1, 127.8, 127.7, 126.9, 82.2, 70.6, 67.2.

(1*R*,2*S*)-1-(Benzyloxy)-3-nitro-1-phenylpropan-2-ol, 73b

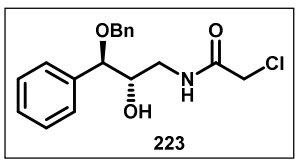


73b

To a stirred solution of oxalyl chloride (1.87 g, 1.26 mL, 14.73 mmol) in dry CH_2Cl_2 (20 mL) at -78 ^oC was added dropwise DMSO (2.37 g, 2.10 mL, 30.44 mmol) in CH_2Cl_2 (15 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of benzyl protected alcohol **72** (2.20 g, 9.82 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -60 °C and then Et_3N (4.36 g, 5.70 mL, 43.20 mmol) was added dropwise and stirred for 1 h. The reaction was quenched with aq $NaHCO_3$ (30 mL) solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used as such for the next step without further purification.

To the methanolic (5 mL) solution of the above synthesized aldehyde, DIPEA (1.90 g, 2.50 mL, 14.73 mmol) and nitromethane (710 mg, 0.63 mL, 11.78 mmol) were added. The reaction mixture was stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was evaporated, diluted with water, extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography (EtOAc/hexane 1:5 v/v) to furnish the *syn*-**73a** (800 mg, 32%) and further elution of the column furnished the *anti*-**73b** diastereomer (1.32 g, 48%) as a pale yellow liquid. [R_f = 0.35, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{20}$ +35.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3177, 2930, 1705, 1476, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.42-7.30 (m, 10H), 4.65-4.54 (m, 2H), 4.51-4.142 (m, 2H), 4.38-4.31 (m, 1H), 4.29-4.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 137.0, 136.3, 128.9, 128.5, 128.0, 128.0, 127.9, 127.6, 127.4, 127.3, 81.4, 77.4, 72.2, 70.9.

***N*-((2*S*,3*R*)-3-(Benzyloxy)-2-hydroxy-3-phenylpropyl)-2-chloroacetamide, 223**



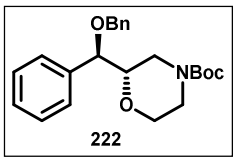
223

To an ice-cooled solution of **73b** (1.5 g, 5.22 mmol) in AcOH:H_2O (30 mL, 1:1 v/v) was added Zn dust (8.1 g, 125.3 mmol) and the mixture was vigorously stirred for 3 h at room temperature. After completion of reaction as monitored by TLC, reaction was quenched with aq $NaHCO_3$. The organic phase was separated, dried over Na_2SO_4, filtered, concentrated *in vacuo* and used further without purification.

To a solution of above synthesized amine in MeCN/CH_2Cl_2 (1:9, 100 mL) at 0 °C was added Et_3N (1.03 mL, 7.83 mmol) and chloroacetyl chloride (450 µL, 5.74 mmol) dropwise. After

being stirred at room temperature for 45 min, the reaction was quenched with a solution of 1N HCl (20 mL), extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography by using MeOH:CH_2Cl_2 (1:49 v/v) to afford the compound **223** (1.35 g, 83%) as a yellow liquid. [R_f = 0.2, MeOH/ CH_2Cl_2 1:9 v/v]; $[\alpha]_D^{20}$ = -20.8 (*c* 1.5, $CHCl_3$) ; IR ($CHCl_3$) *v*: 3250, 2960, 1655, 1609, 1420, 1310, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.28 (m, 10H), 7.05 (brs, 1H), 4.53-4.47 (m, 1H), 4.36 (d, *J* = 6.0 Hz, 1H), 4.27-4.22 (m, 1H), 3.95 (s, 2H), 3.89-3.83 (m, 1H), 3.31-3.24 (m, 1H), 3.20-3.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 137.6, 128.7, 128.7, 128.4, 128.0, 127.9, 127.8, 127.5, 82.6, 73.7, 70.8, 42.4, 41.3.

***tert*-Butyl (*S*)-2-((*R*)-(benzyloxy)(phenyl)methyl)morpholine-4-carboxylate, 222**



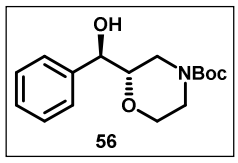
222

To a solution of **223** (1.0 g, 2.99 mmol) in *i*-PrOH (100 mL) at 0 ^oC was added dropwise *t*-BuOK (840 mg, 7.48 mmol) solution in *i*-PrOH (50 mL). After being stirred at room temperature for 2 h, the reaction mixture was quenched with a 1N HCl solution (20 mL) and the aqueous layer was extracted with EtOAc (3 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

To a dry THF (10 mL) solution of above synthesized lactam was added $BH_3.SMe_2$ (4.50 mL, 8.98 mmol) dropwise under nitrogen at 0 ^oC and warmed to room temperature for 6 h. The reaction mixture was then quenched by slow addition of MeOH (8 mL) over 4 h. The reaction mixture was then evaporated, diluted with water and extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and used as such for the next step without purification.

To a THF:H_2O (10 mL) solution of above synthesized amine were added NaOH (239 mg, 5.99 mmol), di(*tert*-butyl)dicarbonate (1.3 g, 5.99 mmol) and stirred for 4 h at room temperature. The reaction mixture was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 1:9 v/v) to afford **222** (820 mg, 72%) as a colorless pale yellow liquid. [R_f = 0.4, EtOAc/hexane 1:4 v/v]; $[\alpha]_D^{20}$ = -55.2 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) *v*: 3547, 3420, 2801, 1680, 1425, 1416, 1236, 1203 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ*:* 7.39-7.28 (m, 10H), 4.69 (s, 1H), 4.58-4.53 (m, 1H), 4.35-4.26 (m, 2H), 3.96-3.90 (m, 1H), 3.77-3.71 (m, 1H), 3.64-3.60 (m, 1H), 3.52-3.46 (m, 1H), 2.95-2.87 (m, 1H), 2.69 (t, *J* = 12.1, 23.8 Hz, 1H), 1.47-1.39 (m, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ*:* 154.7, 140.8, 137.7, 128.5, 128.5, 128.3, 127.9, 127.7, 127.6, 126.9, 79.9, 78.3, 70.5, 66.5, 65.3, 48.5, 42.8, 28.2.

***tert*-Butyl (*S*)-2-((*R*)-hydroxy(phenyl)methyl)morpholine-4-carboxylate, 56[3d]**



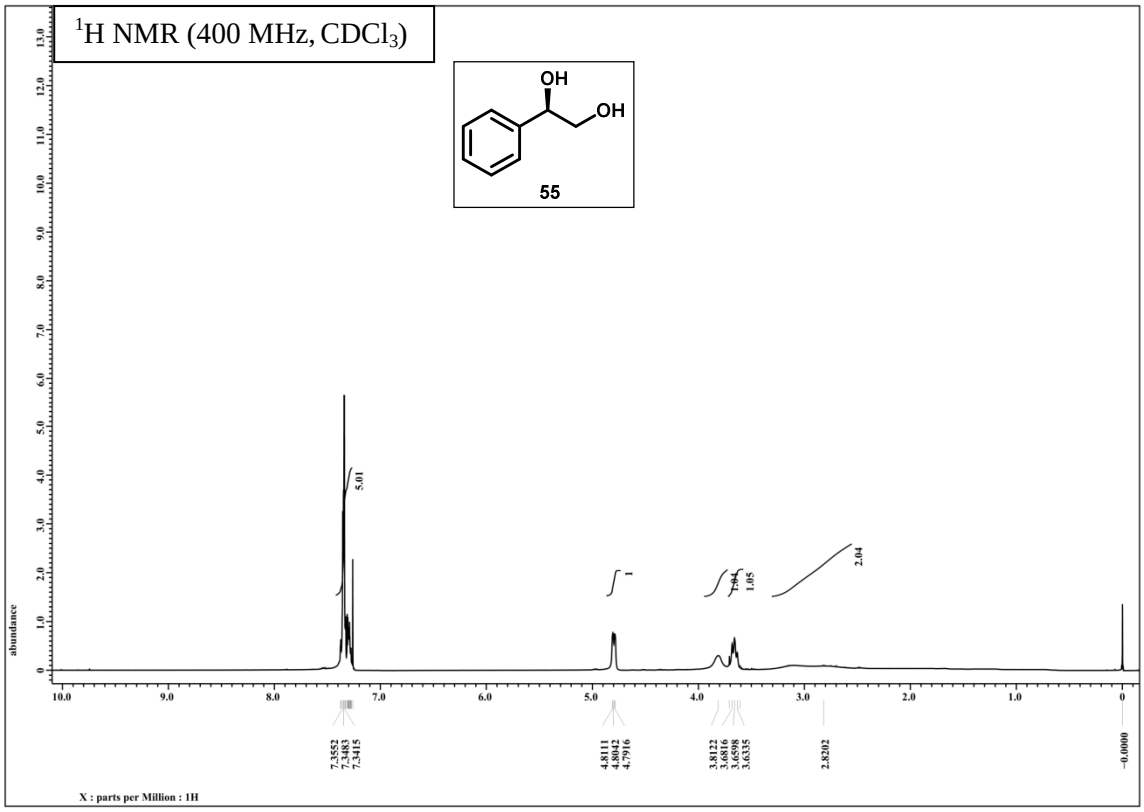
56

To a solution of **222** (500 mg, 1.30 mmol) in MeOH (10 mL) was added catalytic amount of Pd/C and the mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 1:4 v/v) to furnish **56** (320 mg, 85%) as a white solid. [R_f = 0.1, EtOAc/hexane 2:3 v/v]; mp = 150-152 ^oC; {$[\alpha]_D^{20}$ = +3.5 (*c* 2.35, $CHCl_3$), [Lit.[3d] {$[\alpha]_D^{20}$ +3.45 (*c* 2.35, $CHCl_3$); IR ($CHCl_3$) *v*: 3635, 3420, 2870, 1650, 1410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ:* 7.39-7.29 (m, 5H), 4.53 (d, *J* = 7.7 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.59-3.47 (m, 4H), 3.00-2.93 (m, 2H), 2.69 (brs, 1H), 1.49-1.39 (m, 9H); ^{13}C NMR (100MHz, $CDCl_3$) *δ:* 154.6, 140.0, 128.5, 128.4, 126.8, 80.0, 79.2, 78.4, 66.3, 44.7, 43.5, 28.2.

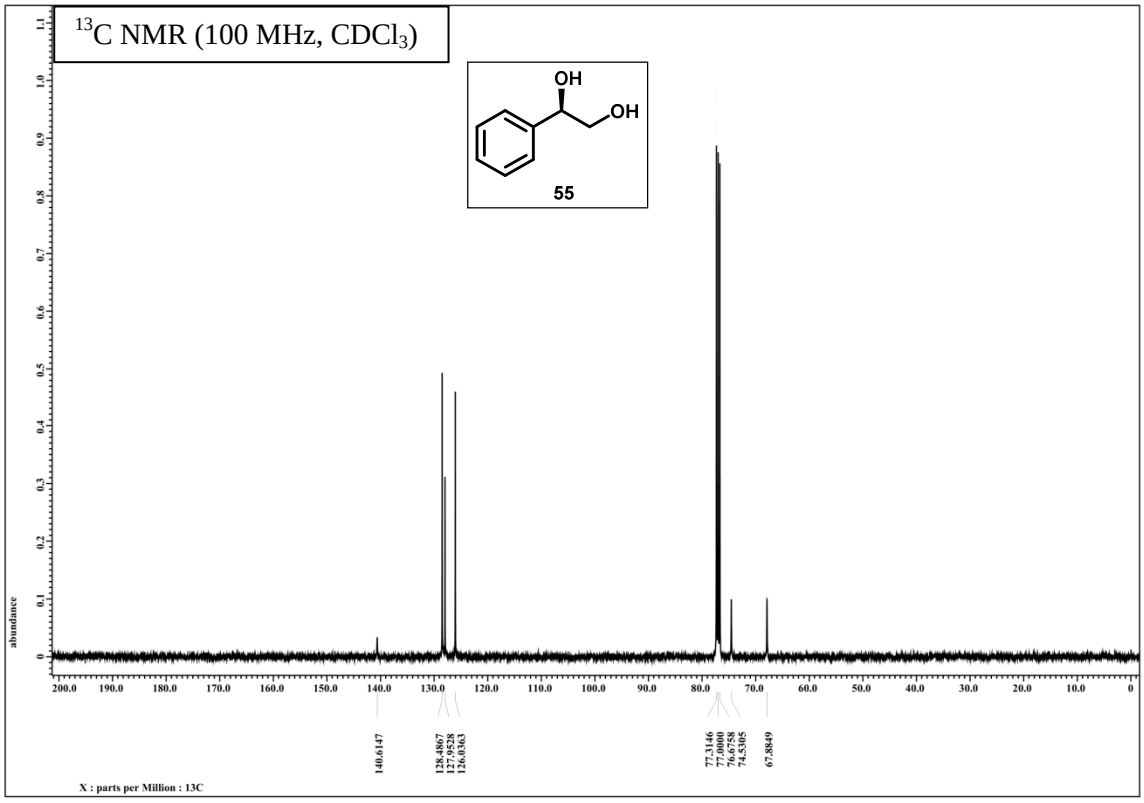
5.7 Spectra:

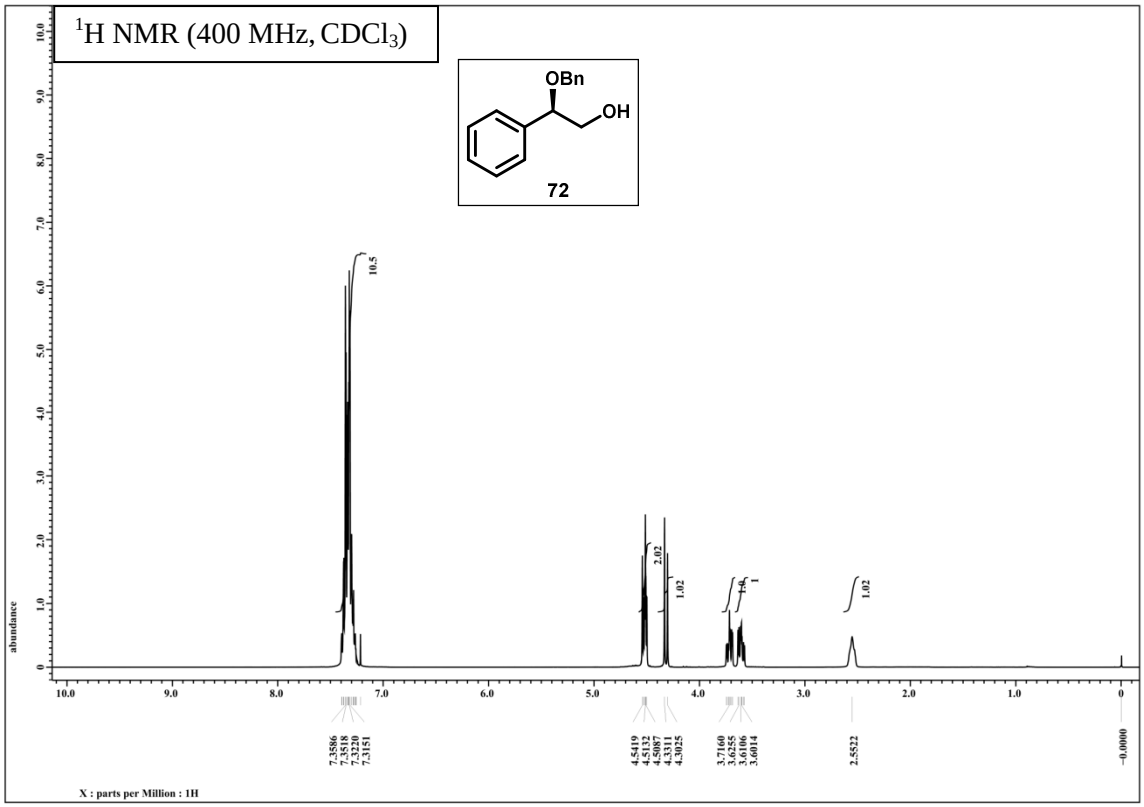
1. ^{1}H and ^{13}C NMR spectra of **55**
2. ^{1}H and ^{13}C NMR spectra of **72**
3. ^{1}H and ^{13}C NMR spectra of **73b**
4. ^{1}H and ^{13}C NMR spectra of **223**
5. ^{1}H and ^{13}C NMR spectra of **222**
6. ^{1}H and ^{13}C NMR spectra of **56**

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

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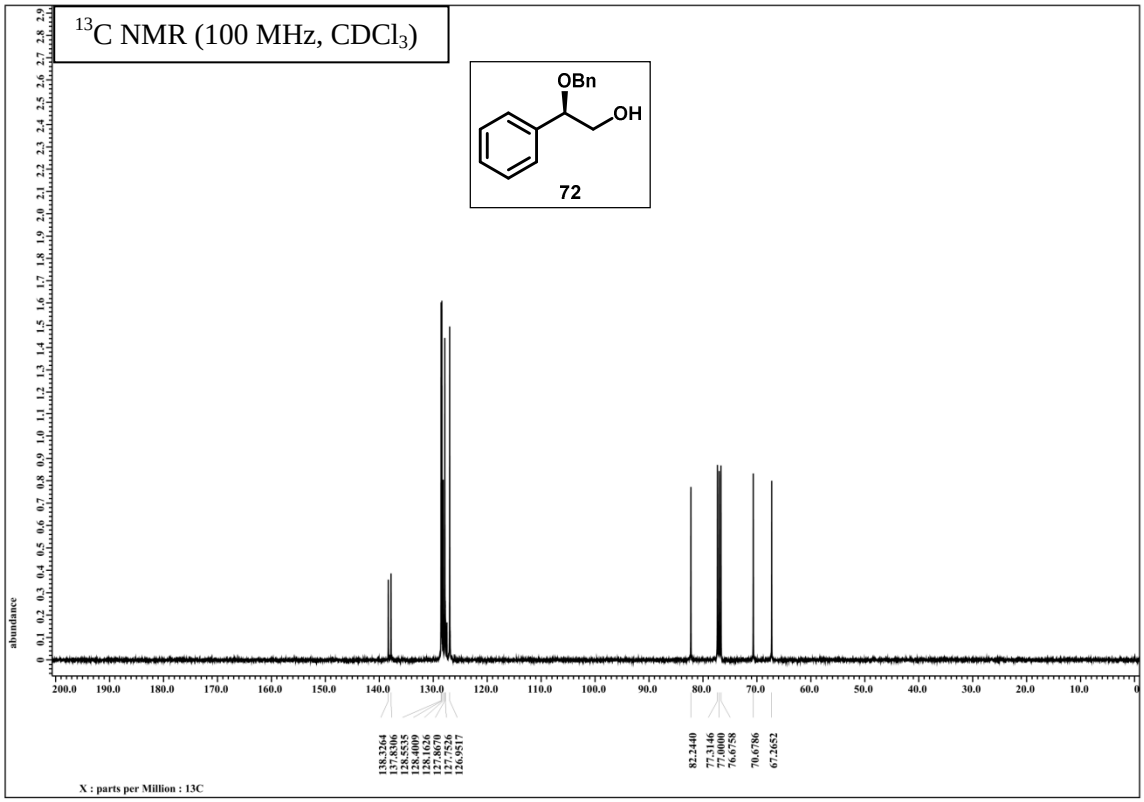
OBn
OH
72
abundance
X : parts per Million : 1H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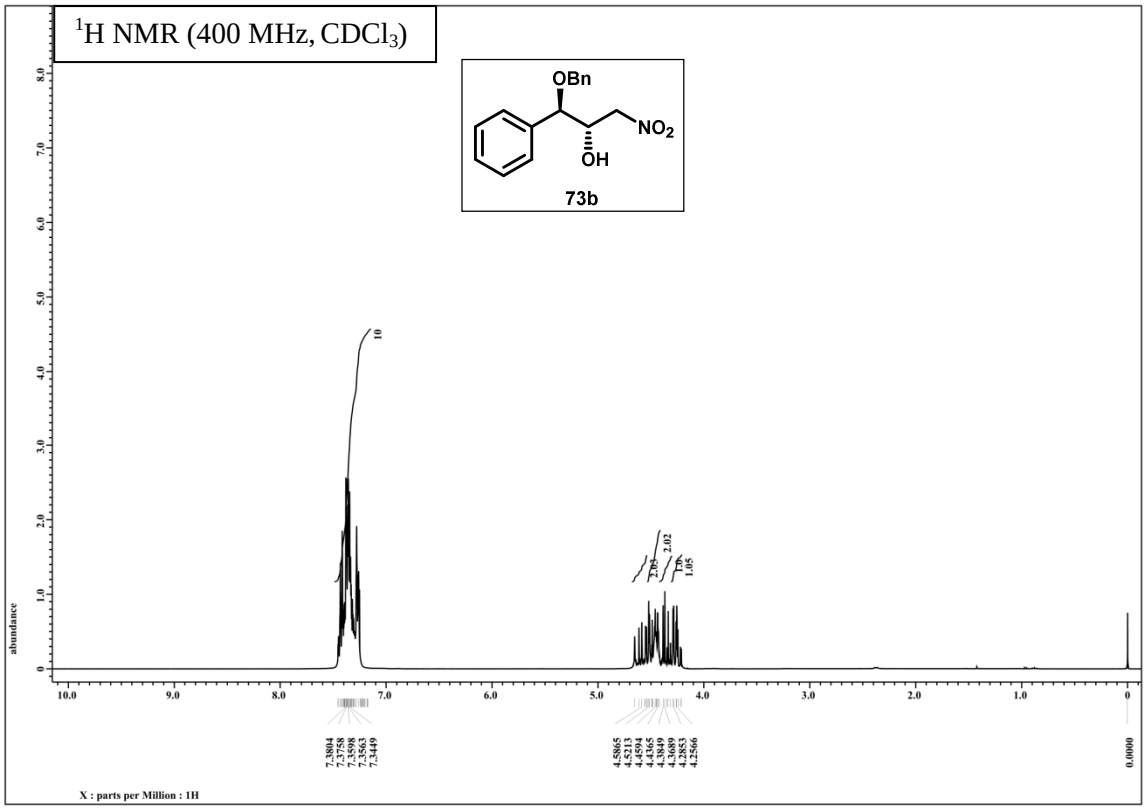
OH
72
abundance
X : parts per Million : 13C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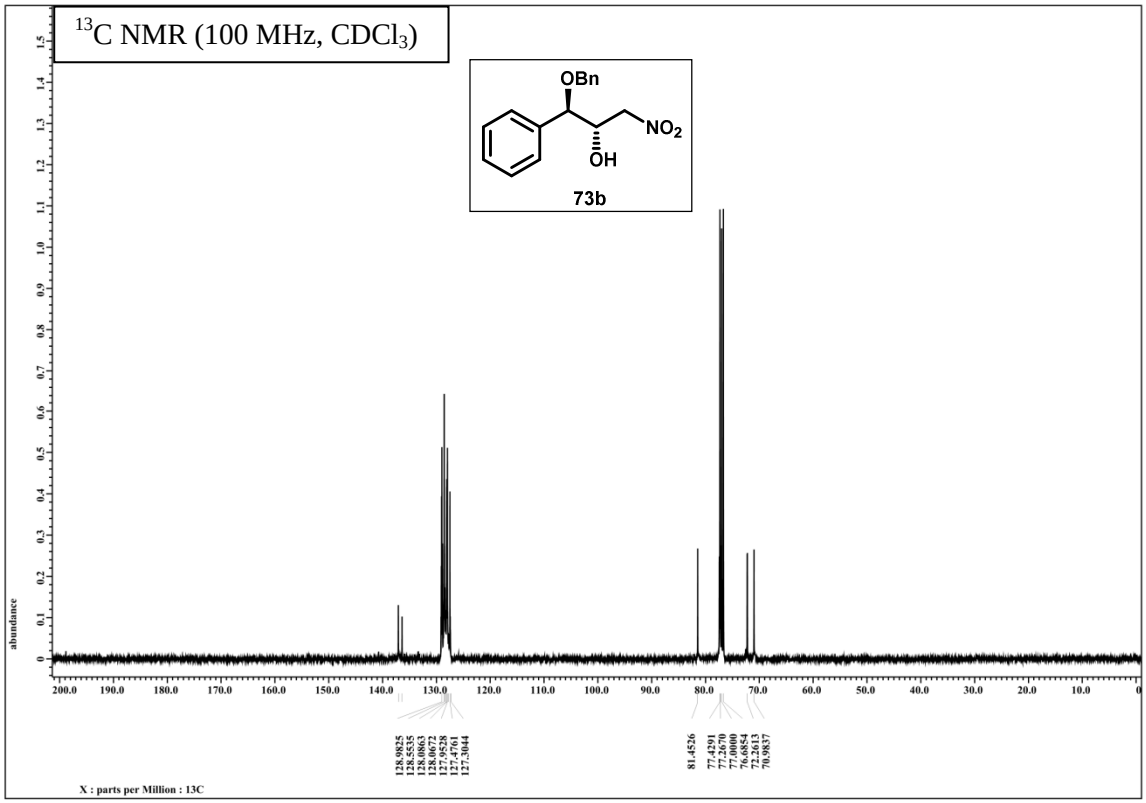
NO2
OH
73b
abundance
X : parts per Million : 1H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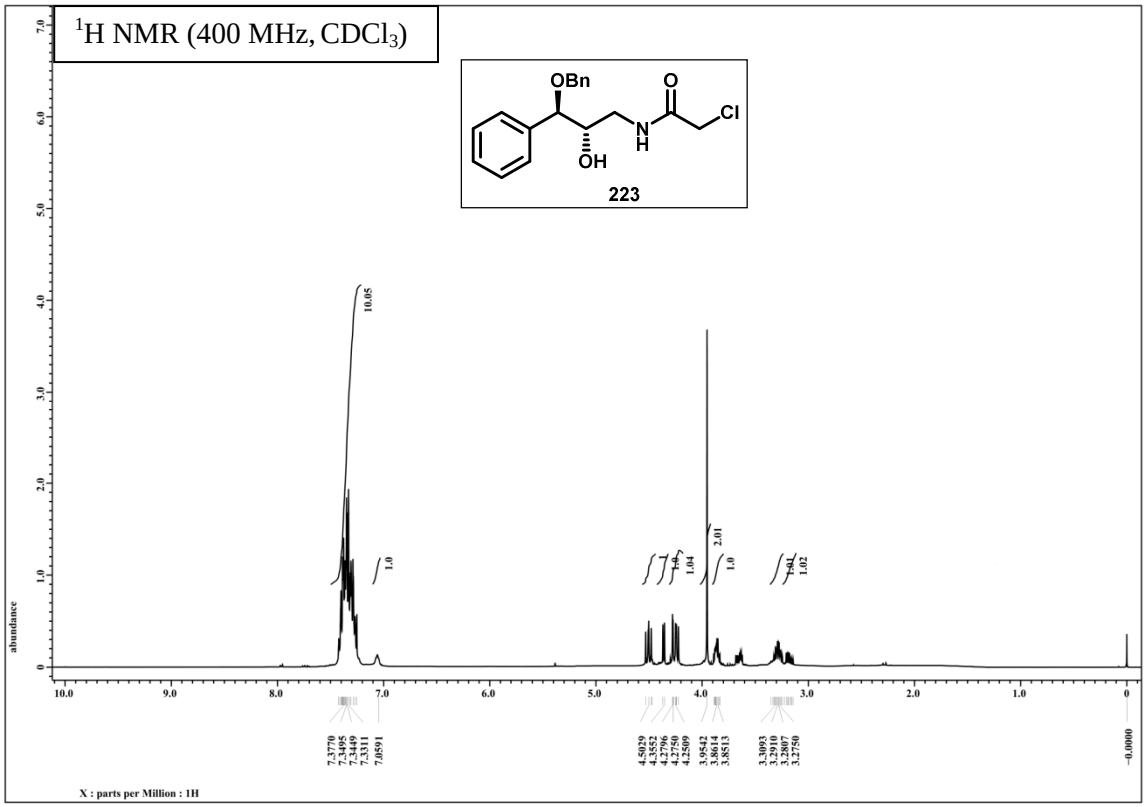
OBn
NO2
OH
73b
abundance
X : parts per Million : 13C


^{1}H NMR (400 MHz, $CDCl_3$)
OBn
O
Cl
N
H
OH
223
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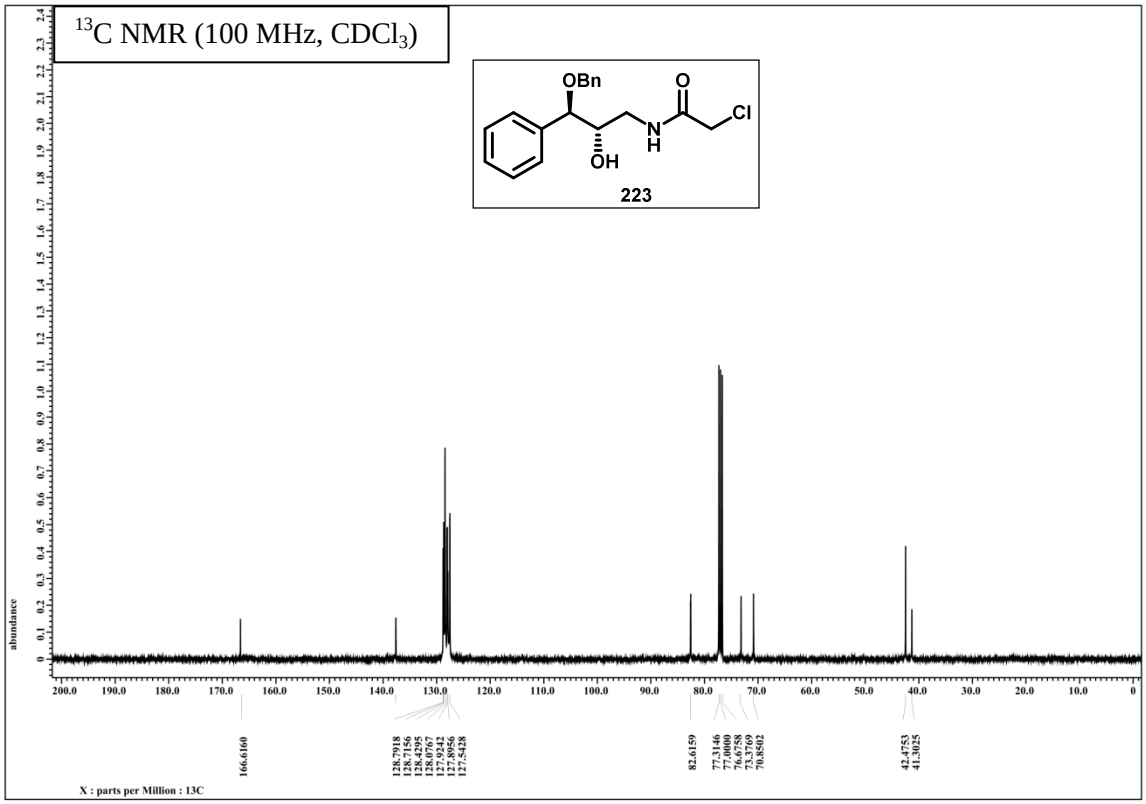
1.0
2.01
1.04
1.0
1.02
abundance
X : parts per Million : 1H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Cl
N
H
OH
223
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127.8956
127.5428
82.6159
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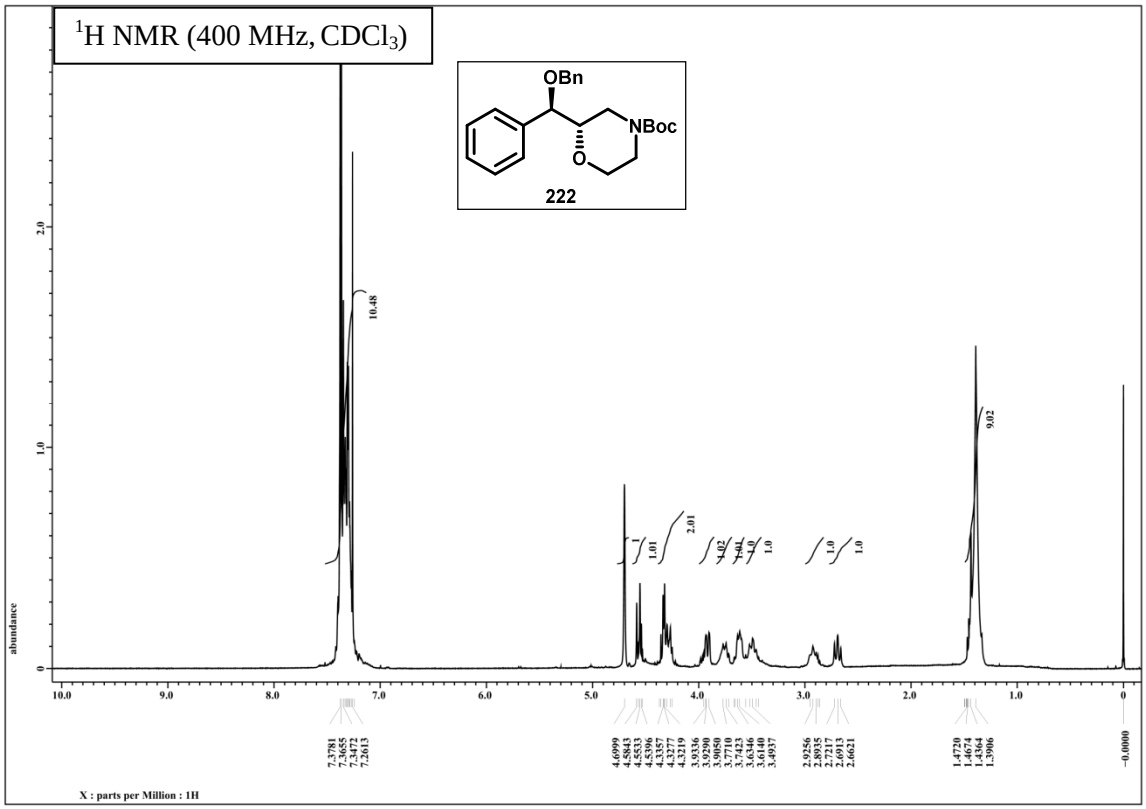
73.1760
70.8502
42.4753
41.3025
abundance
X : parts per Million : 13C


^{1}H NMR (400 MHz, $CDCl_3$)
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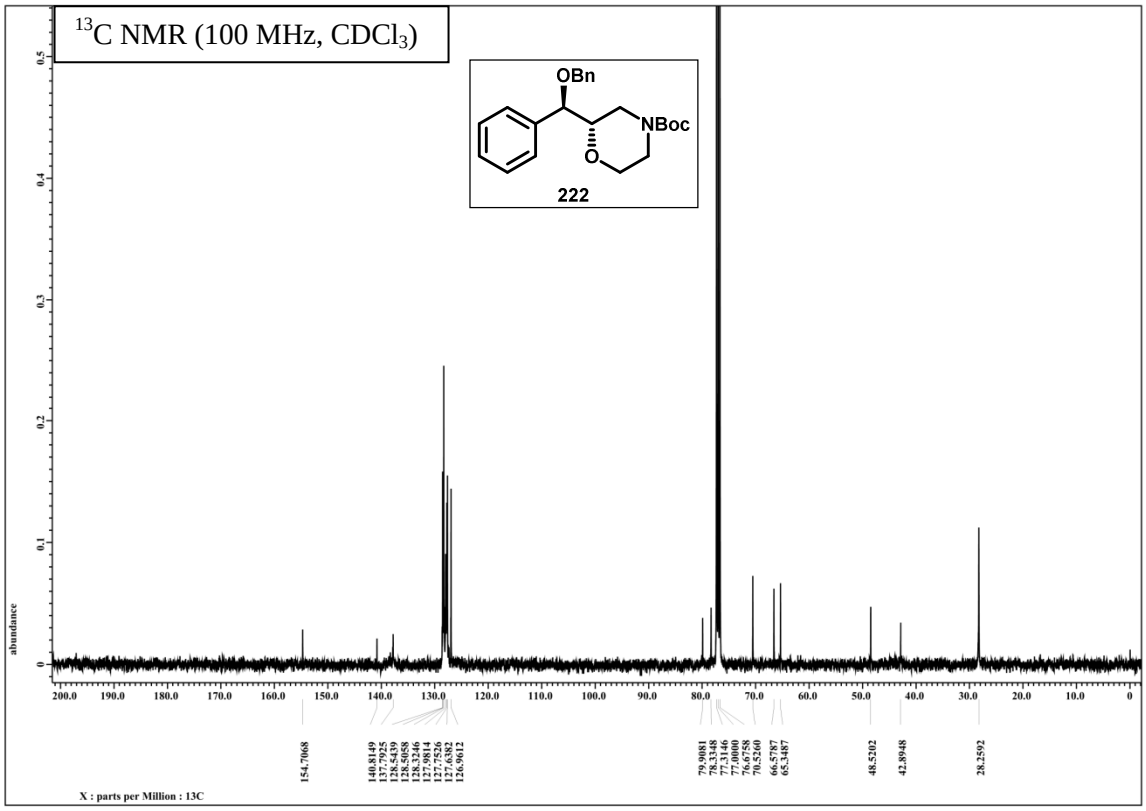
NBoc
O
222
abundance
X : parts per Million : 1H


^{13}C NMR (100 MHz, $CDCl_3$)
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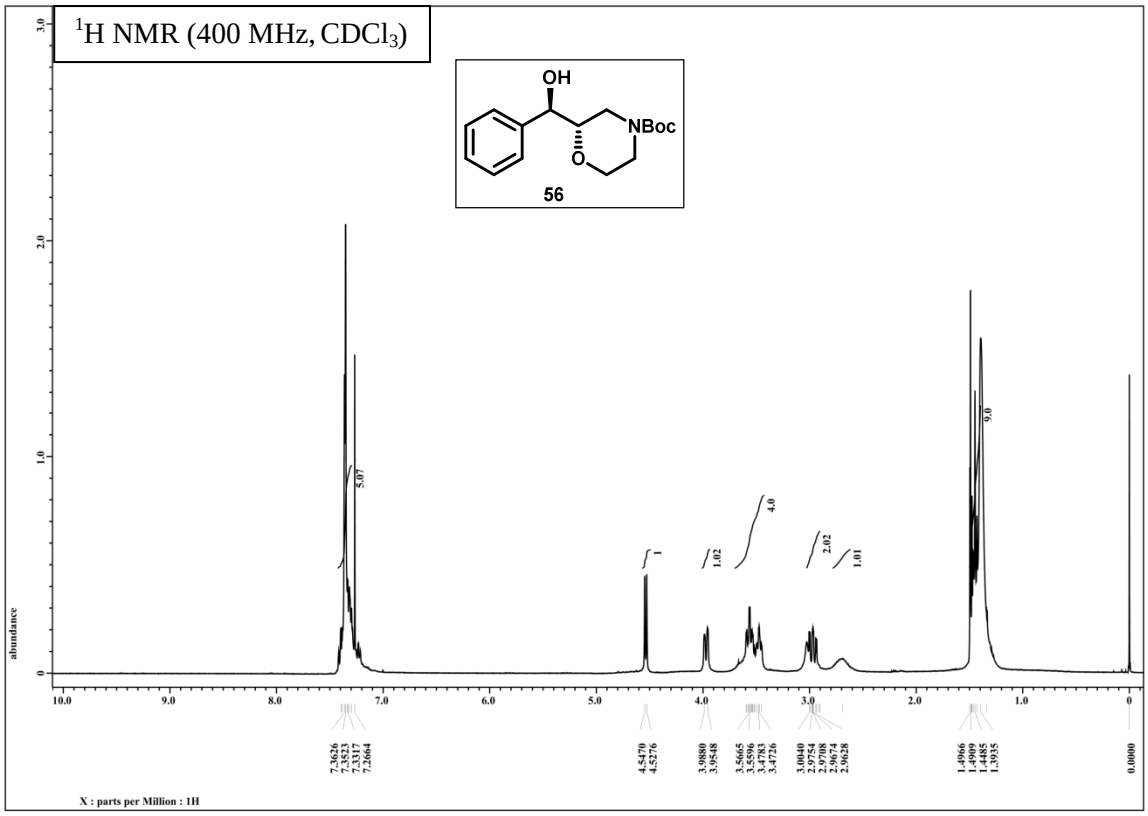
NBoc
O
222
abundance
X : parts per Million : 13C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NBoc
O
56
abundance
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1.02
4.0
2.02
1.01
9.0
7.3626
7.3513
7.3317
7.2664
4.5470
4.5276
3.9880
3.9548
3.5665
3.5496
3.4788
3.4726
3.0040
2.9754
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2.9628
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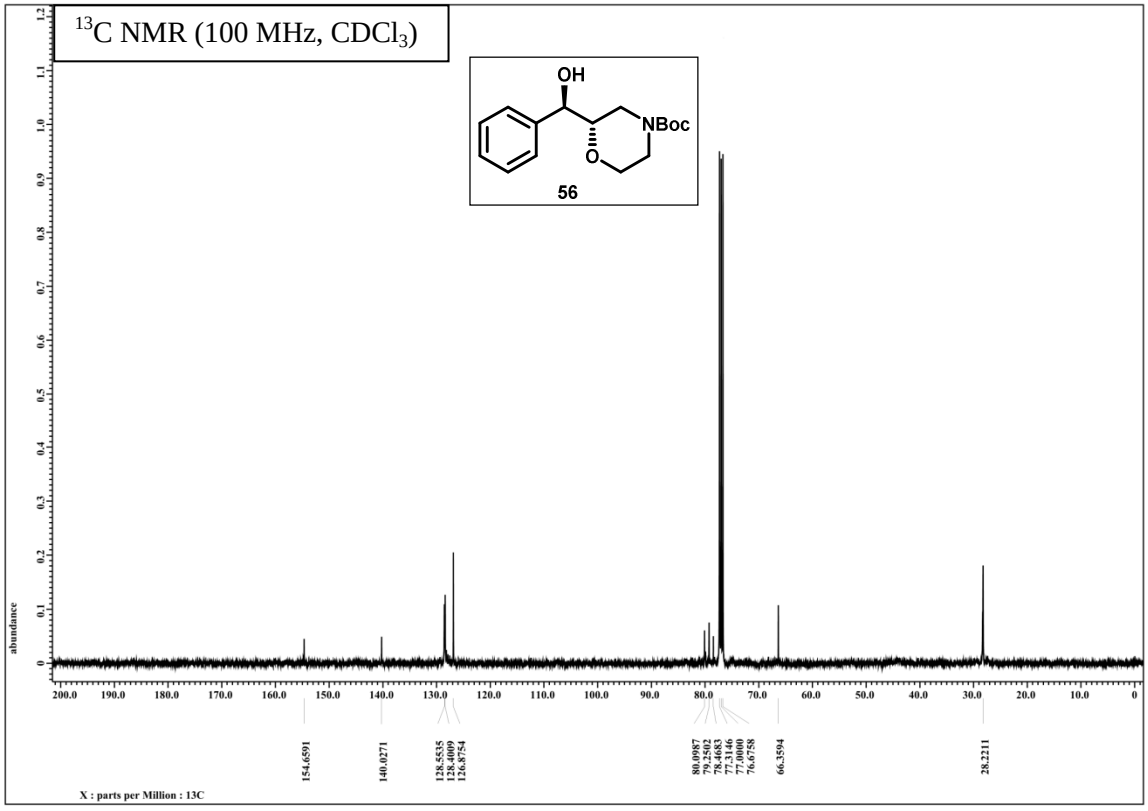
1.4900
1.4485
1.3935
0.0000
X : parts per Million : 1H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OH
NBoc
O
56
abundance
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140.0271
128.5535
128.4009
126.8754
80.0987
78.4683
77.3146
77.0000
76.6758
66.3594
28.2211
X : parts per Million : 13C

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CHAPTER 6

Conclusions and future Scope

6.1 Conclusions

In conclusion, we have described the total synthesis of flinderoles A-C (**11**-1**3**), desmethylflinderole C **14**, 1-deoxygalactonojirimycin **26**, (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27**, formal synthesis of *cis*-(-)-3-hydroxypipecolic acid **28**, (*R*)-**44a**, (*S*)-rolipram **44b** and also made an attempt to synthesize (*S*,*S*)-reboxetine **57**. Herein, a short and expeditious biomimetic divergent approach for the synthesis of functionalized pyrrolo[1,2-α] indoles framework, along with its application to the total syntheses of flindersial alkaloids have been described employed Heck cross coupling and [3 + 2] cycloaddition reactions as the key step. The overall yield for flinderoles A-C (**11**-1**3**) and desmethylflinderole C **14** were 51% in three steps starting from readily available phthalimide protected bromo-indole **111**. Moreover, the synthetic strategy described has significant potential for the syntheses of other analogues of flindersial alkaloids and isoborreverine with interesting pharmacological activities. The synthesis of hydroxylated piperidines and its applications to the total synthesis of 1-deoxygalactonojirimycin **26**, (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** and formal synthesis of *cis*-(-)-3-hydroxypipecolic acid **28** were achieved by employing the proline catalyzed MacMillan's asymmetric aldol reaction, Mitsunobu inversion and Upjohn reaction as key steps. The 1-deoxygalactonojirimycin **26** was synthesized in six steps with 46% overall yield and (2*R*,3*R*)-3-hydroxy-2-hydroxymethylpiperidine **27** synthesized in five steps with 56% overall yield. Moreover, the described synthetic strategy has significant potential for further stereochemical variations at all the possible positions to synthesize the other hydroxylated piperidine alkaloids. Next, a short and protecting group free enantioselective syntheses of (*R*)-**44a** and (*S*)-rolipram **44b** were achieved from commercially available isovanillin **41** employing the (*R*)- and (*S*)-diphenylprolinol silyl ether mediated asymmetric Michael addition reaction as key step. The overall yields for the (*R*)-rolipram **44a** were 66% and 69% with two different strategies after three column chromatographic purification steps. The merits of our synthesis are high enantioselectivity (i.e. >99% *ee*) and high yielding reaction steps. The synthetic approach also has significant potential for the variation at *O*-alkyl site to synthesize various γ-pyrrolidone derivatives with expected increase in biological activities. Also, an attempt towards a simple and

flexible enantioselective total synthesis of (*S*,*S*)-reboxetine **57** was made by employing Jacobsen's HKR and Henry reaction as key steps. The merits of this synthesis are high regio- and enantioselectivity with high yielding reaction steps. All the new compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS, %*ee* by chiral HPLC and $[\alpha]_D^{25}$ for all new chiral compounds.

6.2 Future scope of the work

Few futuristic suggestions related with the present work are listed below:

1. The synthetic strategy described in chapter 2, has significant potential for the syntheses of other derivatives of flindersial alkaloids, isoborreverine and other potent antimalarial natural products with interesting pharmacological activities.
2. The described synthetic strategy in chapter 3, has importance for further stereochemical variations at all the possible positions to synthesize the other hydroxylated piperidine alkaloids as well as further extension to other stereoisomers and analogues by simply changing the L- or D-proline in MacMillan's self aldol reaction.
3. The synthetic approach described in chapter 4, also has significant potential for the variation at *O*-alkyl site to synthesize various *γ*-pyrrolidone derivatives with expected increase in biological activities. The (*S*)- or (*R*)-configuration of GABA derivative could be manipulated by simply changing the (*S*)- and (*R*)-configuration of the catalyst diphenylprolinol silyl ether during asymmetric Michael addition step.
4. The synthetic strategy explained in chapter 5, could be used for the synthesis of structurally diverse stereoisomers of antidepressant reboxitine and highly potent norepinephrine reuptake inhibitors (NRI) by screening the different catalysts in asymmetric Henry reaction.

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Enantioselective synthesis of (1*S*,2*R*)-ephenamine

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ABSTRACT

A short and efficient enantioselective synthesis of (1*S*,2*R*)-ephenamine is described employing Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of a cyclic sulfite as the key steps.

1. Introduction

(1*S*,2*R*)-Ephenamine **1**, (1*S*,2*S*)-pseudoephenamine **2**, and their aminoalcohol analogues (1*S*,2*R*)-1,2-diphenyl-2-aminoethanol **3** and (1*S*,2*S*)-1,2-diphenyl-2-aminoethanol **4**, respectively, have been used as chiral auxiliaries in diastereoselective alkylation reactions, providing easy access to enantiomerically pure alcohols, carboxylic acids, α-methyl α-amino acids,[1] and Williams amino acid synthesis.[2] The biological activity of ephenamine and pseudoephenamine analogues significantly varies and depends on the substituents present at the amino functional group. Therefore, the introduction of *N*-substituents in ephenamine and pseudoephenamine analogues is of great importance for the syntheses of pharmaceuticals and chiral auxiliaries.[3] Ephenamine has been used to resolve penicillin and glycine derivatives,[4] and also in a salt form of penicillin G, an antibiotic additive used to stimulate growth in livestock and poultry.[5] Ephenamine-glutamine salts have been used to provide effective amounts of glutamine for human consumption[6] (Fig. 1).

Various methods for the syntheses of (1*S*,2*R*)-ephenamine **1** and (1*S*,2*R*)-**3** in their different stereoisomeric forms, mainly based on chiral pool or auxiliary supported approaches, have been documented in the literature.[7] In continuation of our research program toward the asymmetric syntheses of bioactive compounds,[8] the Sharpless asymmetric dihydroxylation and cyclic sulfite methodology were envisioned as powerful tools for synthetic functional group transformations. Herein we report a new and short synthesis of (1*S*,2*R*)-ephenamine by employing Sharpless asymmetric dihydroxylation as the source of chirality and cyclic sulfite methodology as the key steps.

2. Results and discussion

As outlined in Scheme 1, the synthesis of (1*S*,2*R*)-ephenamine **1** began with commercially available *trans*-stilbene **5**, which upon treatment with osmium tetraoxide and potassium ferricyanide as the co-oxidant, in the presence of $(DHQ)_2PHAL$ under Sharpless asymmetric dihydroxylation conditions[9] furnished diol **6** in 97% yield (99% ee) {$[\alpha]_D^{25}$ = +95.5 (*c* 1.28, C_2H_5OH) [Lit.[10] $[\alpha]_D^{25}$ = +95.2 (*c* 1.28, C_2H_5OH)]}.

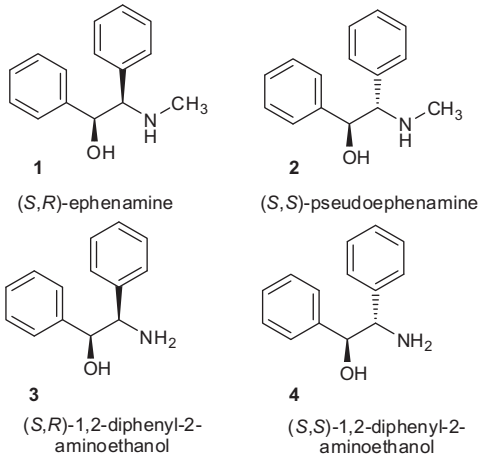

Figure 1. Structures of 1,2-diphenyl-2-aminoalcohols.

With enantiomerically pure (1*S*,2*S*)-1,2-diphenylethane-1,2-diol **6** in hand, we then subjected it to treatment with thionyl chloride in the presence of Et_3N as the base to afford **7**, which upon subsequent treatment with NaN_3 furnished azido alcohol derivative **8** in 89% yield. Concomitant one-pot reduction of the azide group and Boc protection of the resulting amino alcohol were carried out via hydrogenation in the presence of catalytic amounts of Pd–C (20%) and Boc_2O to afford Boc protected amino alcohol derivative **9** in excellent yield. The Boc protected derivative via LAH reduction furnished (1*S*,2*R*)-ephenamine **1** as a white crystalline solid in 83% yield, {$[\alpha]_D^{25}$ = +32.7 (*c* 0.5, C_2H_5OH)

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E-mail address: skpandey@thapar.edu (S.K. Pandey).

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0957-4166/

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Organic & Supramolecular Chemistry

A Short Total Synthesis of the Antimalarial Flindersial Alkaloids

Ramandeep Kaur, Yuvraj Garg, and Satyendra Kumar Pandey*[a]

A short, efficient and novel approach for the syntheses of bis-indole alkaloids flinderoles A–C, and desmethylflinderole C, is being described. The synthesis utilizes the optimized intermolecular Heck coupling and $InCl_3$ catalyzed stereo- and regioselective [3 + 2] annulation reactions as the key steps.

Introduction

Malaria is the most common, widespread and life-threatening parasitic infectious disease in the tropic and sub-tropic regions of the worlds today.[1] According to WHO report, there were an estimated 214 million new cases of malaria and approximately half million deaths in 2015 alone caused by *P. falciparum* and *P. vivax*. Natural products chloroquine, artemisinin and other frontline drugs for the treatment of malaria are becoming increasingly ineffective due to the development of drug resistance and therefore, the search for new antimalarial drugs is again of even greater significance. Very recently, Avery and coworkers isolated bis-indole alkaloids flinderoles A–C (**1**-**3**) from the plant genus *Flindersia* along with the previously known natural products borrerine **5**, borreverine **6**, isoborreverine **7** and dimethylisoborreverine **8** (Figure 1).[2]

The Flinderoles A–C (**1**-**3**) alkaloids have been shown to possess significant selective growth inhibition against Dd2 (chloroquine-resistant) *P. falciparum* and exhibit antimalarial activity with IC_{50} values between 0.15-1.42 μM.[2] These alkaloids are fast acting and are currently the drugs of choice for the treatment of malaria through a different mechanism of action than that of chloroquine and other drugs by interrupting the parasitic hemoglobin.[3] The flinderoles A–C (**1**-**3**) and desmethylflinderole C **4** with pyrrolo[1,2-α]indoles skeleton have been synthetic targets of considerable interest due to its high antimalarial activity and with an array of functionalities. Therefore, in order to achieve flinderole alkaloids and their analogues in larger quantities for further biological evaluation, it is highly desirable to develop a short and efficient synthetic approach. More recently, various elegant syntheses for the flinderole alkaloids have been documented in the literature.[4] As part of our research on the syntheses of bioactive compounds,[5] astonishing biological properties and attractive structural features prompted us towards the short total syntheses of flinderoles A–C (**1**-**3**) and desmethylflinderole C **4.** Herein, we wish to report a new, short and efficient synthetic approach for the flinderoles A–C (**1**-**3**) and desmethylflinderole C **4**, employing Heck coupling and $InCl_3$ mediated [3 + 2] annulation reactions as the key steps.

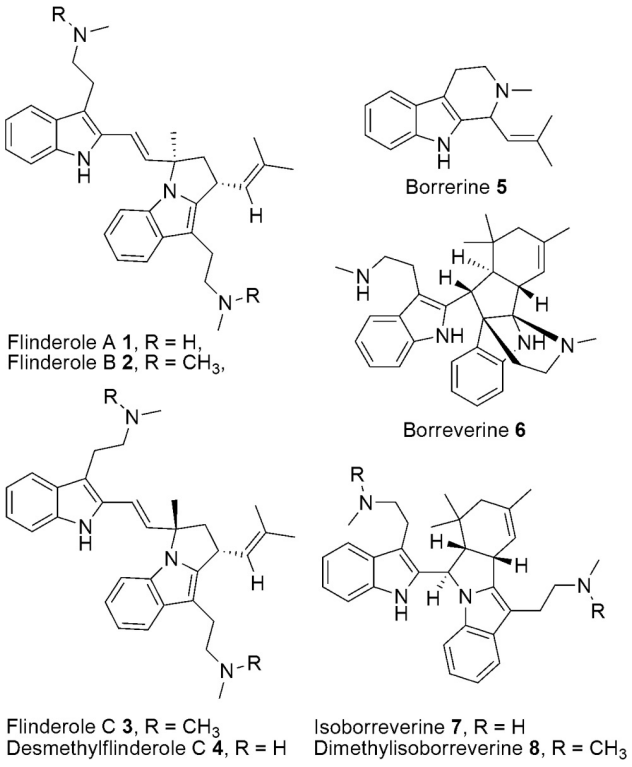

Figure 1. Structures of borreverine and flinderole alkaloids.

Our hypothesis for the biosynthetic pathway began with that the flindersial alkaloids have tryptamine-isoprene based rearranged skeleton and therefore, flinderoles could be derived from monomeric tryptamine diene **11** as a possible precursor.[4d] The flinderole frameworks could arise from dimerization reaction of tryptamine diene **11** with intermediate **12** *via* [3 + 2] annulation reaction (Scheme 1).

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Efficient synthesis of (−)-(*R*)- and (+)-(*S*)-rolipram

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ABSTRACT

A novel, efficient and protecting group free enantioselective synthetic approach of (−)-(*R*)-**1** and (+)-(*S*)-rolipram **2** is described employing the organocatalyzed asymmetric Michael addition, Henry condensation, Wittig olefination and reductive lactamization reactions as key steps.

Introduction

Chirally branched pyrrolidones are among the most bioactive heterocyclic compounds in organic chemistry due to their ubiquitous structural motifs in natural and unnatural products with varied biological activity.[1] Among them, γ-aminobutyric acid (GABA) and its analogues rolipram (**1**–**2**), brivaracetam **3** and (*S*)-pregabalin **4** are useful division of compounds possessing interesting pharmacological activities (Fig. 1).[2] The rolipram (**1**–**2**) are simple cyclo-GABA derivative possessing a catechol type ring at chiral carbon (C-3).[3] The (±)-rolipram was discovered and developed by Schering AG pharmaceutical company at Berlin, Germany in early 1990[4] and it acts as a selective phosphodiesterase-4 inhibitor and potential antidepressant drug.

The most active enantiomer (*R*)-rolipram **1** is an advanced novel class of effective antidepressant drug with additional possible emetic,[5] which act as selective inhibitor for cardiac cyclic AMP phosphodiesterase, present in brain tissue and mainly effective for the PDE4B and subtype of PDE4.[6] Additionally, (*R*)-rolipram **1** has also been proposed as a antiinflammatory,[7] immunosupressant,[7] putative antiparkinson-ian,[8] neuroprotective,[9] antipsychotic[10] and has been suggested for the treatment of multiple sclerosis.[10] The (*R*)-**1** and (*S*)-rolipram **2** have been synthetic target of considerable interest for academia and pharmaceutical industries due to its high antidepressant activity combined with attractive structural features. Various elegant studies and syntheses of (*R*)-**1** and (*S*)-rolipram **2** have been documented in the literature.[11]

In 2008, Dixon and co-workers[11f] reported an enantioselective total synthesis of (*R*)-rolipram in six steps employed the bifunctional catalyst mediated asymmetric Michael addition of malonate nucleophiles as key step. Recently, Kobayashi and co-workers[11a] described the continuous flow asymmetric synthesis of (*R*)- and (*S*)-rolipram employed the chiral heterogeneous catalysts as key step. As part of our ongoing research programme directed towards the asymmetric synthesis of biologically active compounds,[12] we became interested in developing a short and efficient route to (*R*)-**1** and (*S*)-rolipram **2** with two different strategies employing the organocatalyzed asymmetric Michael addition, Henry condensation, Wittig olefination and reductive lactamization reactions as the key steps.

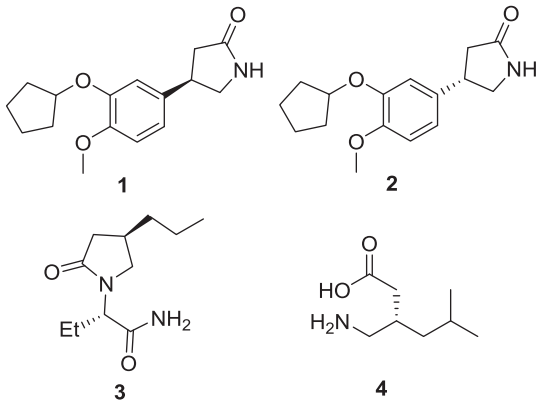

Fig. 1. Some structures of GABA derivatives (**1**–**4**).

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Tandem Reactions

Organocatalytic Asymmetric Tandem α-Aminooxylation–Henry Reactions for the Synthesis of 1,2-Diols: Total Synthesis of (–)-L-*threo*-Sphinganine

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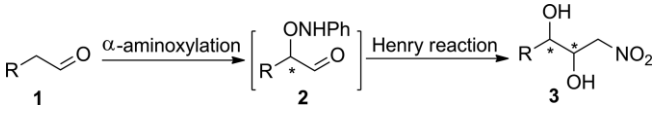
Dedicated to Professor Radhey M Singh, Department of Chemistry, Institute of Science, BHU on his 65th Birthday

Abstract: A new and rapid asymmetric synthesis of *anti*- and *syn*-β,γ-dihydroxynitroalkanes through an organocatalytic tandem α-aminooxylation–Henry reaction is described. The target diol derivatives were synthesized in good yields, with excellent enantioselectivities, and low to moderate diasteroselectivities, under mild conditions. The synthesis of the antineoplastic and antipsoriatic drug (–)-L-*threo*-sphinganine demonstrates the synthetic utility of the building blocks generated in the developed reaction.

Introduction

Enantiopure 1,2-diols are versatile chiral building blocks, and they have been used widely as starting materials for the asymmetric synthesis of drugs and biologically active natural products.[1] Various methods for the synthesis of 1,2-diols have been documented in the literature.[2,3] The Sharpless asymmetric dihydroxylation (AD) of *trans* olefins[3] is one of the most efficient reactions, leading to *syn* 1,2-diols with high enantiomeric excesses (*ee*'s); *cis* olefins give rise to *anti* 1,2-diols with low enantioselectivity.[3b] Recent developments in asymmetric catalysis have included organocatalytic α-aminooxy-group-directed tandem reactions; these reactions lead to enantiopure compounds in a rapid and atom-economical one-pot catalytic process.[4] We envisioned that a reactive α-aminooxy aldehyde intermediate **2**, generated from the organocatalytic α-aminooxylation[2l–2n] of an aldehyde **1**, could undergo in-situ trapping with nitromethane under Henry reaction conditions,[5] followed by cleavage of the phenylamine moiety to give a β,γ-dihydroxynitroalkane **3** [Equation (1)].

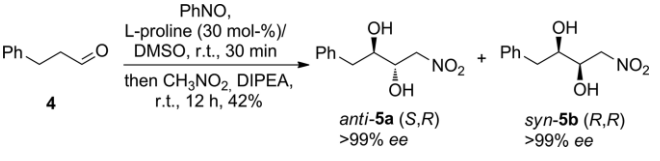


(1)

Based on this idea, we describe in this paper a highly enantioselective one-pot tandem approach to β,γ-dihydroxynitroalkanes, containing a nonterminal 1,2-diol unit. The reaction involves the organocatalytic α-aminooxylation of aldehydes followed by an in-situ Henry reaction.

Results and Discussion

In our preliminary experiments, we used 3-phenylpropionaldehyde (**4**) as a model substrate, nitrosobenzene, DMSO as the solvent, and L-proline as the catalyst (Scheme 1).



Scheme 1. Strategy for in-situ trapping of reactive α-aminooxylated aldehyde intermediates.

Nitromethane and the base DIPEA (diisopropylethylamine) were used in the second step, and were added to the α-aminooxylation reaction mixture when all the nitrosobenzene had been consumed. Pleasingly, the tandem reaction proceeded smoothly to give products *anti*-**5a** and *syn*-**5b** in 42 % yield, along with the expected *O*-NHPh-protected derivative of **5** in low yield (12 %). It is known that partial N–O bond cleavage may occur in situ during α-aminooxylation reactions.[2i] Also, removal of the *N*-phenylamino group could be achieved either by catalytic hydrogenation[2n] or by Cu^{II}-catalysed reactions.[6] Compounds *anti*-**5a** and *syn*-**5b** were separated by silica gel column chromatography. We found that there was no diastereoselectivity in the second step (*anti*-**5a**/*syn*-**5b**, 1:1), but

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701289.