Asymmetric Total Synthesis of Biologically Active Natural Products Employing Chiral Catalysts

Thesis Submitted in fulfillment of the

requirement of the degree of

Doctor of Philosophy

By

Yuvraj

(Regn. No. 901309007)

Under the supervision of

Dr. Satyendra Kumar Pandey

Associate Professor

SCHOOL OF CHEMISTRY AND BIOCHEMISTRY

THAPAR UNIVERSITY

PATIALA-147004

PUNJAB, INDIA

Certificate

This is to certify that thesis entitled "**Asymmetric Total Synthesis of Biologically Active Natural Products Employing Chiral Catalysts**" being submitted by Yuvraj in the fulfillment of the requirement for the award of the Degree of Doctor of Philosophy to the School of Chemistry and Biochemistry, Thapar University, Patiala, is a authentic record of candidate's own work carried out by him 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.

(Supervisor)

Dr. Satyendra Kumar Pandey

Associate Professor

School of Chemistry and Biochemistry

Thapar University, Patiala - 147 004

Punjab (India)

(Head)

Dr. Amjad Ali

Associate Professor & Head

School of Chemistry and Biochemistry

Thapar University, Patiala - 147 004

Punjab (India)

Candidate's Declaration

I, hereby declare that the work presented in the thesis entitled "**Asymmetric Total Synthesis of Biologically Active Natural Products Employing Chiral Catalysts**" in partial fulfillment of the requirement for the award of the Degree of Doctor of Philosophy, School of Chemistry and Biochemistry, Thapar University, 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 University, 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.

Yuvraj

(Supervisor)

Dr. Satyendra Kumar Pandey

Associate Professor

School of Chemistry and Biochemistry

Thapar University, Patiala - 147 004

Punjab (India)

Dedicated

To My

Beloved Grandmother

Father, Mother,

Sister & Brother

Acknowledgements

Any human accomplishment is the culmination of numerous contributions and endeavors.

The present thesis is no exception. I take this opportunity to thank the special people whose kind support was the reason I could complete the task with confidence.

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My sincere thanks to **Dr. Amjad Ali**, Associate Professor and Head, **Dr. Bonamali Pal**, Professor and former Head, School of Chemistry and Biochemistry, Thapar University, Patiala for his support and encouragement. I extend my gratitude to my doctoral committee members **Dr. Ranjana Prakash**, **Dr. Kamaldeep Paul** and **Dr. Siddharth Sharma** for their fruitful discussion and endless encouragement, constructive criticism and inspirations. The kind help extended by the NMR facility fraternity **Mr. Mukesh Aggarwal**, SAI labs, is gratefully acknowledged. My sincere thanks also go to **Mr. Chander Thakur** and office staff **Mr. Mayank** for their cooperation, support and help.

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I gratefully acknowledge University Grants Commission for UGC-JRF (NET) scheme for providing me financial support during my Ph.D. research work.

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.

Yuvraj

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ABBREVIATIONS

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
Bn	-	Benzyl
BnBr	-	Benzyl bromide
$BH_3 \cdot Me_2S$	-	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
er	-	Enantiomeric ratio
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
Ph	-	Phenyl
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*par*a-Toluenesulfonic acid
RCM	-	Ring closing metathesis
TEA	-	Triethylamine
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/100mL.
- All reactions are 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 "**Asymmetric Total Synthesis of Biologically Active Natural Products Employing Chiral Catalysts**" is divided into five chapters.

Chapter 1: A brief account of Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT), Jacobsen's Hydrolytic Kinetic Resolution (HKR), Henry reaction, organocatalzyed α-aminoxylation and Michael addition reactions.

Chapter 2: Enantioselective general approaches towards the synthesis of functionalized amino acids and 2-alkyl substituted tetrahydroquinolines with their applications to the total synthesis of (*R*)-lacosamide and (+)-angustureine, respectively. This chapter is divided into two sections.

Chapter 3: Enantioselective approaches towards the synthesis of α-phenyl-β^2-amino acids and 3-substituted pyrrolidines with their applications to the total synthesis of (*S*)-nakinadine B and pyrrolidine core unit of serotonin norepinephrine reuptake inhibitors, respectively. This chapter is divided into two sections.

Chapter 4: Development of stereocontrolled organocatalyzed tandem α-aminoxylation/Henry reactions approach towards the asymmetric synthesis of β,γ-dihydroxynitroalkanes from aldehydes and its application to the total synthesis of L-*threo*-sphinganine (safingol). This chapter is divided into two sections.

Chapter 5: Two different enantioselective approaches for the total synthesis of (+)-disparlure, a lepidopteran sex pheromone. This chapter is divided into two sections.

Chapter 1: A brief account of Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT), Jacobsen's Hydrolytic Kinetic Resolution (HKR), Henry reaction, organocatalzyed α-aminoxylation and Michael addition reactions.

Stereo- and enantioselective organic synthesis is a powerful discipline that allows the synthesis of complex, chiral, enantiomerically pure and polycyclic natural products as well as natural product-like bioactive 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. Asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents either employing chiral transition-metal complexes or chiral organocatalysts.

A number of transition metal-mediated methods such as Trost's DYKAT, Jacobsen's HKR and Henry reactions have emerged as a powerful tool for asymmetric reactions. A common feature of most of these processes is the phenomenon of ligand acceleration, wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand. This causes the reaction to be funneled through the ligated pathway with the additional consequence that the ligand may leave its 'imprint' on the selectivity determining step. Hence, the ligand can influence the chemo-, regio-, and stereoselectivity of the above reactions in a profound way.

The Trost's DYKAT of racemic butadiene monoepoxide catalyzed by η^3-C_3H_5PdCl and chiral ligands (*R,R*)-/(*S,S*)-DACH (1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-1-naphthoyl) followed by regioselectively ring-opening of epoxide by phthalimide as nucleophile provides vinyl glycinol in high enantiomeric purity.[1]

The Jacobsen's HKR of terminal epoxides catalyzed by chiral salen/Co(III)-OAc complex affords both recovered epoxide and 1,2-diol products in highly enantioenriched form.[2] In many cases there exist no practical alternatives for accessing these valuable chiral building blocks from inexpensive racemic materials.

Since the first report of Shibasaki and co-workers,[3] 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 metal ligand complexes especially Cu-catalyzed Henry reaction has received much attention in recent years.

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.

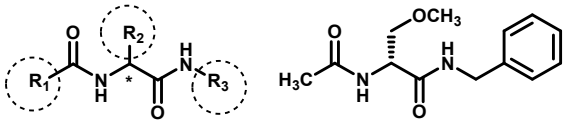
In this chapter, the development of Trost's DYKAT, Jacobsen's HKR, stereocontrolled Henry reaction, organocatalzyed α-aminoxylation and Michael addition with their mechanisms, reaction conditions, various ligands used and its applications will be covered.

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

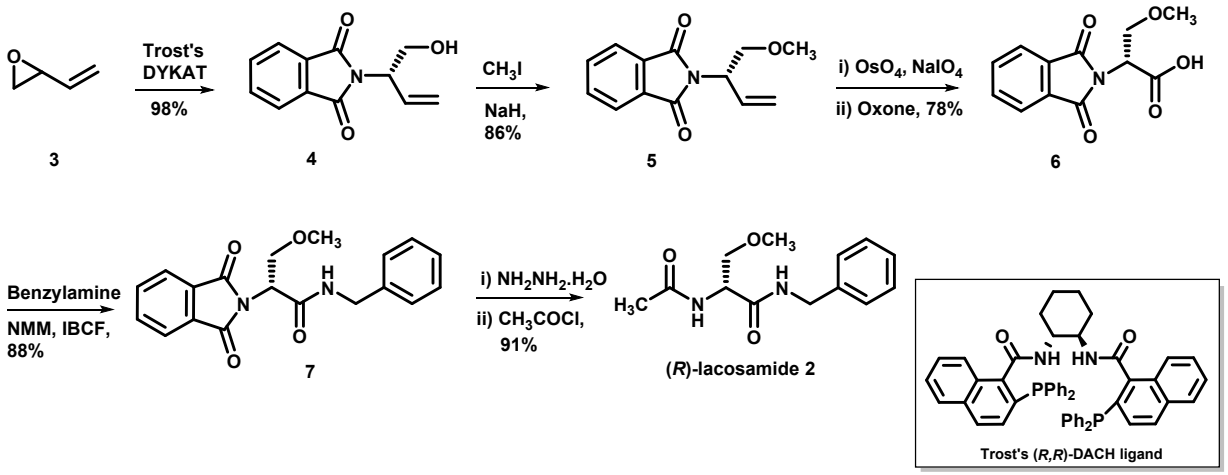
1. Asymmetric synthesis of bioactive natural products employing organocatalysts and ligand based {(*R*,*R*) & (*S*,*S*)-DACH and Jacobsen's catalysts} asymmetric synthesis.
2. Characterization of asymmetric compounds and determination of enantiomeric excess, and optical rotation $[\alpha]_D^{25}$.

Chapter 2: Enantioselective general approaches towards the synthesis of functionalized amino acids and 2-alkyl substituted tetrahydroquinolines with their applications to the total synthesis of (*R*)-lacosamide and (+)-angustureine, respectively. This chapter is divided into two sections.

Section A: An enantioselective approach to functionalized amino acids: total synthesis of antiepileptic drug (*R*)-lacosamide

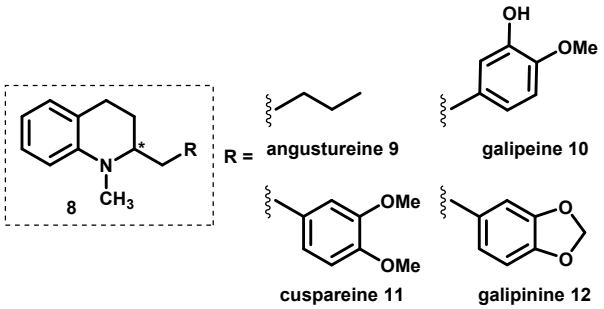


Functionalized amino acids (FAAs) **1** are advanced novel class of anticonvulsant agents, from which (*R*)-lacosamide **2** emerged as a best antiepileptic drug (AED) and has been suggested for the treatment of partial-onset seizures in patients with epilepsy and as add-on treatment in brain tumor patients.[4] (*R*)-lacosamide **2** has been a synthetic target of considerable interest due to its anticonvulsant activity with an array of functionalities.

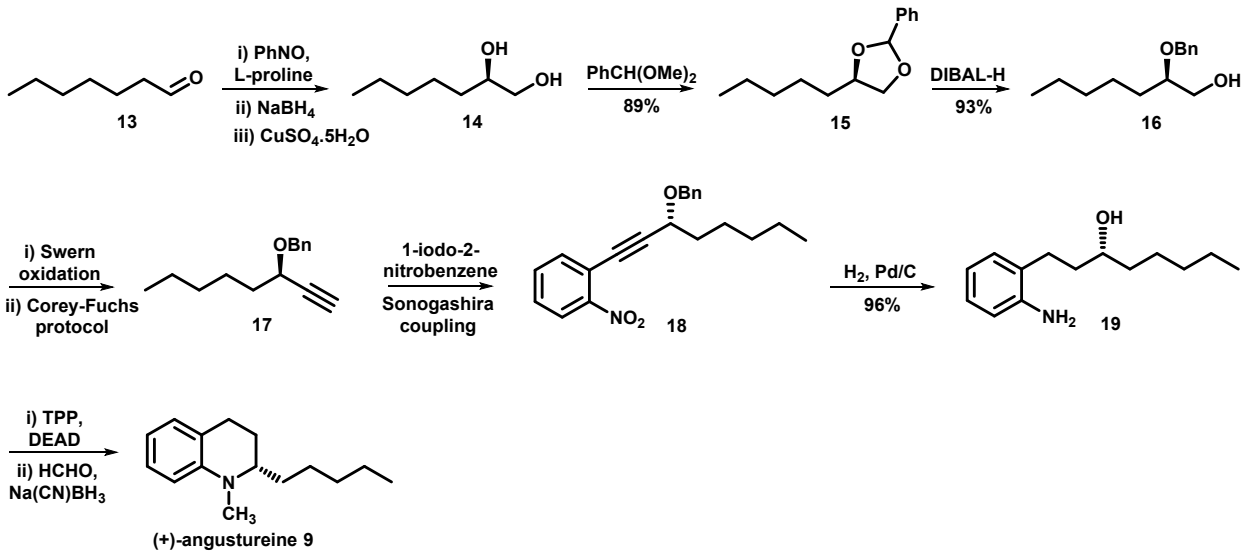


The synthesis of (*R*)-lacosamide **2** started from the commercially available racemic butadiene monoepoxide **3**, which on palladium catalyzed Trost's DYKAT in the presence of (*R*,*R*)-DACH, $[\eta^3\text{-}C_3H_5PdCl]_2$, and phthalimide afforded alcohol **4** as a single enantiomer.[1] The alcohol **4** was subjected to *O*-methylation with MeI to afford methyl ether **5** which on oxidative cleavage in the presence of $OsO_4/NaIO_4$ followed by oxidation with oxone furnished the phthaloyl acid **6**. The acid (*R*)-**6** on amide bond formation with benzylamine using NMM/IBCF afforded the phthaloyl amide **7** which on cleavage of phthalimide group with hydrazine monohydrate followed by *N*-acetylation using acetyl chloride furnished the target compound (*R*)-lacosamide **2** in excellent yield.

Section B: An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine



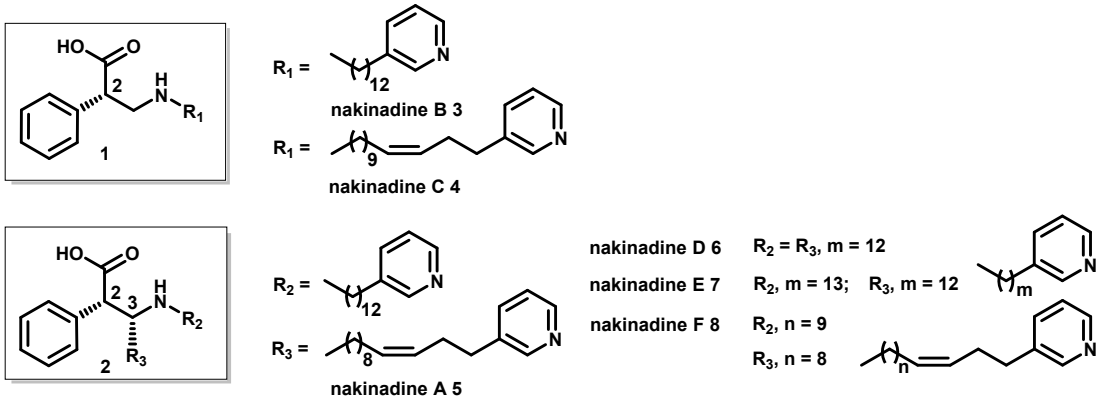
Enantiomerically pure 2-alkyl substituted tetrahydroquinolines alkaloids **8** from which angustureine **9**, galipeine **10**, cuspareine **11**, and galipinine **12** were first extracted from the bark of *Galipea Officinalis* Hancock shrub tree found in the mountains of Venezuela.[5]



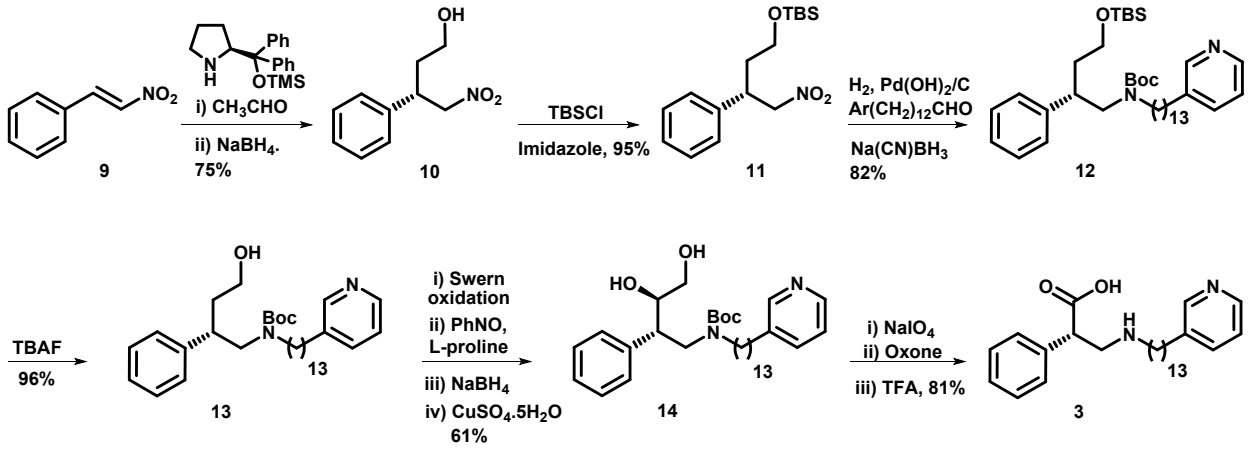
These alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities. The synthesis of (+)-angustureine **9** started from the commercially available *n*-heptanal **13**, which on treatment with nitrosobenzene in the presence of catalytic amount of L-proline (10 mol %) afforded *α*-aminoxylated aldehyde which on subsequent reduction with $NaBH_4/CH_3OH$ followed by aniline cleavage with $CuSO_4.5H_2O$ afforded the required diol **14**.[6] It was then protected as 1,2-benzylidene acetal **15** which on regioselective reductive opening with DIBAL-H afforded alcohol **16**. Oxidation of alcohol **16** under Swern conditions and subsequent treatment with CBr_4/TPP followed by *n*-BuLi under Corey-Fuchs protocol[7] afforded the terminal alkyne **17**. The alkyne **17** under Sonogashira coupling conditions[8] with 1-iodo-2-nitrobenzene afforded the 2-nitrobenzene-alkyne derivative **18** which on hydrogenation under 1 atm pressure in the presence of catalytic amount of Pd/C (10%) furnished the amino alcohol **19**. Cyclization of amino alcohol **19** under Mitsunobu conditions[9] (DEAD, PPh_3) and subsequent methylation with formaldehyde in presence of $Na(CN)BH_3$ afforded the target compound (+)-angustureine **9** in excellent yield.

Chapter 3: Enantioselective approaches towards the synthesis of *α*-phenyl-*β*^{2}-amino acids and 3-substituted pyrrolidines with their applications to the total synthesis of (*S*)-nakinadine B and pyrrolidine core unit of serotonin norepinephrine reuptake inhibitors, respectively. This chapter is divided into two sections.

Section A: Enantioselective organocatalyzed Michael addition/aminoxylation approach to the total synthesis of (*S*)-nakinadine B



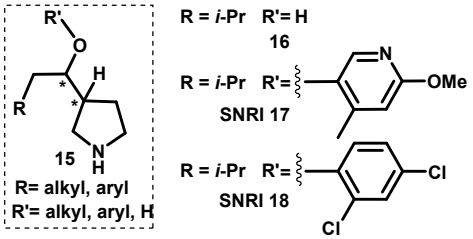
The nakinadine A-F (**3**-**8**) alkaloids were recently isolated from an Okinawan marine sponge *Amphimedon sp*.[10] The nakinadine A-F (**3**-**8**) have been synthetic targets of considerable interest due to its high cytotoxic activity and with an array of functionalities.



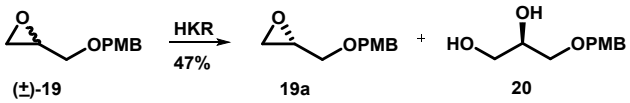
The synthesis of (*S*)-nakinadine B **3** commenced with commercially available nitrostyrene **9**, which on asymmetric Michael addition with acetaldehyde in the presence of catalytic amount of (*S*)-diphenylprolinol silyl ether followed by reduction with $NaBH_4$ delivered the nitroalcohol derivative **10** as a single enantiomer.[11] It was then protected as *O*-TBS derivative **11** which was subjected to hydrogenation in the presence of catalytic amount of $Pd(OH)_2/C$ followed by reductive *N*-alkylation with 13-(pyridin-30-yl)tridecanal using $Na(CN)BH_3$ and *N*-Boc protection afforded the *N*-alkylated amine derivative **12**. The cleavage of silyl ether in compound (*S*)-**12** with TBAF afforded the alcohol derivative **13** quantitatively which on oxidation under Swern conditions, subsequent treatment of aldehyde with nitrosobenzene in the presence of catalytic amount of L-proline (20 mol %) furnished α-aminoxylated aldehyde, which on spontaneous

reduction with $NaBH_4$ and cleavage of phenylamine moiety with $CuSO_4.5H_2O$ afforded the diol **14** as a single diastereomer. The diol **14** on smooth oxidative cleavage in the presence of $NaIO_4$ followed by oxidation with oxone and finally deprotection of *N*-Boc with TFA furnished the sponge metabolite (*S*)-nakinadine B **3** in quantitative yield.

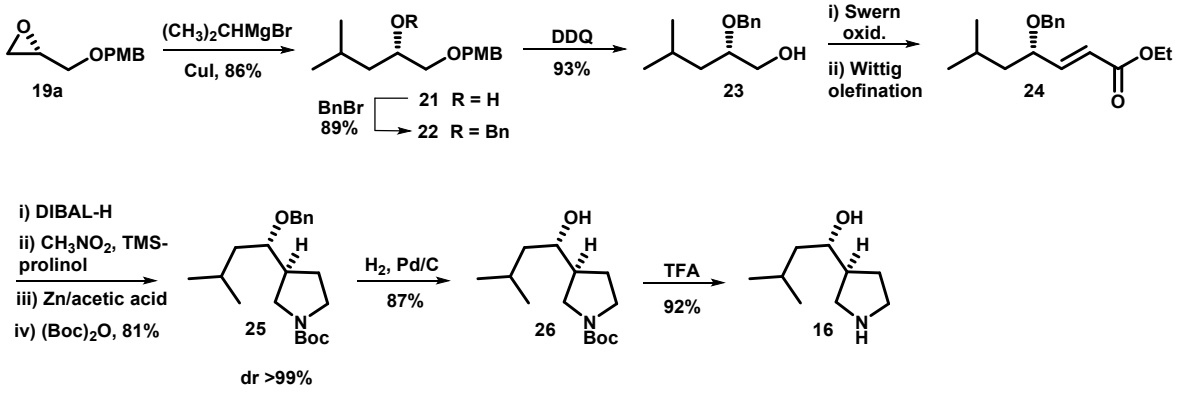
Section B: An efficient enantioselective approach towards the synthesis of 3-substituted pyrrolidines: asymmetric synthesis of pyrrolidine core of serotonin norepinephrine reuptake inhibitors (SNRIs)



We report a novel and efficient general synthetic approach to enantiopure 3-substituted pyrrolidines **15** and its application to the asymmetric synthesis of pyrrolidine core **16** of serotonin norepinephrine reuptake inhibitors (SNRIs) **17** and **18**.[12] Johansson and co-workers reported the discovery of novel 3-substituted pyrrolidine ether SNRI **17** with improved norepinephrine transporter activity, acceptable metabolic stability and exhibiting minimal drug to drug interaction.[12] Stangeland and co-workers reported the discovery of novel 3-substituted pyrrolidine ether SNRI **18** which showed inhibition of the serotonin and/or norepinephrine transporter, for the treatment of neuropathic pain with reduced side effects such as nausea.[13]



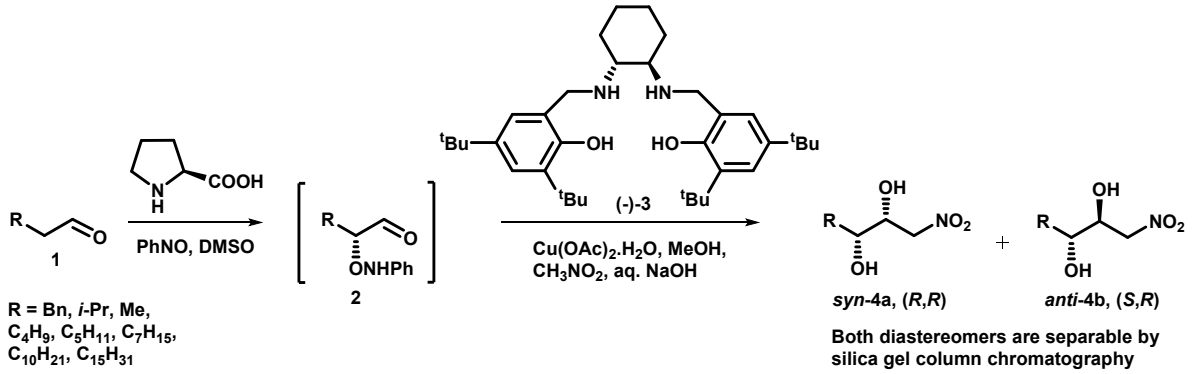
The synthesis of pyrrolidine core unit for SNRIs **17** and **18** commenced with readily available racemic PMB-protected glycidyl ether **19** which was subjected to Jacobsen's HKR[2] in the presence of catalytic amount of (*S*,*S*)-(salen)-Co-(OAc) complex to afford (*S*)-PMB-protected glycidyl ether **19a** as a single enantiomer and (*R*)-PMB protected triol **20**.



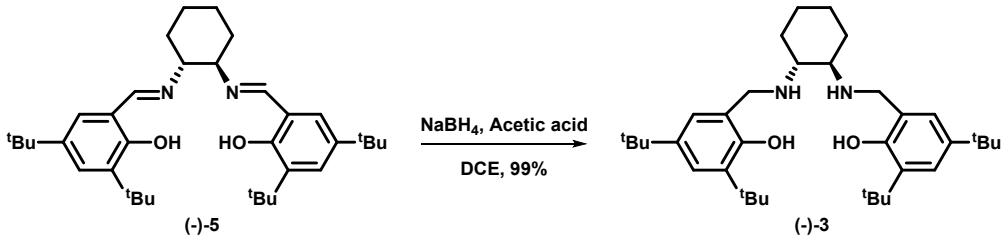
Epoxide **19a** on Cu(I)-catalysed regioselective ring-opening reaction with *i*-propylmagnesium bromide furnished the PMB protected alcohol (*S*)-**21** which on treatment with BnBr followed by selective deprotection of *O*-PMB ether group afforded the terminal alcohol derivative (*S*)-**23**. The alcohol (*S*)-**23** on oxidation under Swern conditions and subsequent treatment with (ethoxycarbonylmethylene)triphenylphosphorane afforded the conjugated ester (*S*)-**24**. The olefinic ester (*S*)-**24** on reduction with DIBAL-H to aldehyde and subsequent asymmetric Michael addition[14] reaction with nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether followed by intramolecular reductive amination with Zn/CH_3COOH and Boc protection furnished *N*-Boc-pyrrolidine **25** as a single diastereomer. The pyrrolidine **25** was then subjected to debenzylation under 1 atm. pressure in the presence of a catalytic amount of Pd/C to afford alcohol **26** which upon S_NAr reaction with commercially available 6-chloro-2-methyl-pyridine followed by *N*-Boc deprotection with TFA and methoxide moiety addition using the literature route could afford SNRI **17**.[12] On the other hand, the *N*-Boc deprotection of derivative **26** with TFA furnished the pyrrolidine core unit **16** which could be used for the synthesis of SNRI **18** by S_NAr reaction with commercially available 1,3-dichloro-4-fluorobenzene following the literature route.[13]

Chapter 4: Development of stereocontrolled organocatalyzed tandem *α*-aminoxylation/Henry reactions approach towards the asymmetric synthesis of *β,γ*-dihydroxynitroalkanes from aldehydes and its application to the total synthesis of L-*threo*-sphinganine (safingol). This chapter is divided into two sections.

Section A: Stereocontrolled organocatalyzed tandem *α*-aminoxylation/Henry reaction approach for the asymmetric synthesis of *β,γ*-dihydroxynitroalkanes from aldehydes

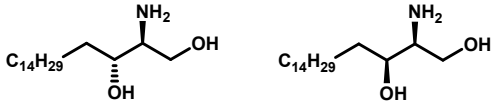


We have describe herein a one pot strategy for the synthesis of versatile and highly enantiopure *β,γ*-dihydroxynitroalkane derivatives **4** *via* proline-catalyzed asymmetric *α*-aminoxylation[15] of aldehydes **1** to *α*-aminoxylated aldehyde intermediate **2** followed by its *in situ* utilization employing chiral ligand **3**/transition-metal complex catalyzed Henry reaction. Optically active *β,γ*-dihydroxynitroalkanes **4** are valuable chiral building blocks and potential precursors to chiral *α,β*-dihydroxyaldehyde, *α,β*-dihydroxyacid, and 1-amino-2,3-diol derivatives which are common structural features found in numerous biologically active natural products.[16]



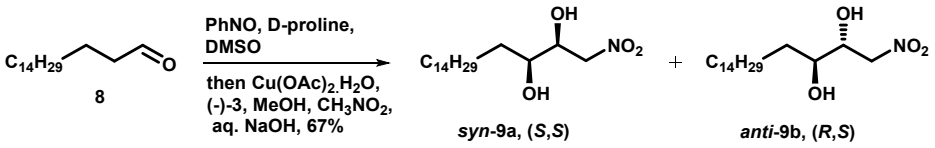
A series of Cu (I) catalysts, such as CuI, CuBr, CuCl, CuCN, CuOAc and Cu (II) catalysts, such as $CuCl_2.2H_2O$, $Cu(OTf)_2$, $CuSO_4.5H_2O$ were employed in the presence of ligand (-)-**3** and (-)-**5**. A diamine ligand (-)-**3** was synthesized from the reduction of Jacobsen's ligand (-)-**5** with $NaBH_4$/acetic acid in DCE for the control of diastereoselectivity. Among them, $Cu(OAc)_2.H_2O$ turned out to be the best choice for subsequent reactions which provided highest *syn*/*anti* ratio. Among the screened solvents, best yield, enantio- and diastereoselectivity were observed when the reaction was performed in methanol. Among the screened bases, aqueous alkali bases NaOH exhibited good reactivity and diastereoselectivity for the *anti* product. After optimal reaction conditions in hand, we then explored the scope of this tandem approach to a variety of *α*-aminoxylated aldehyde intermediates of aromatic and aliphatic aldehydes.

Section B: Enantioselective total synthesis of L-*threo*-sphinganine (safingol) *via* organocatalyzed tandem α-aminoxylation/Henry reactions.



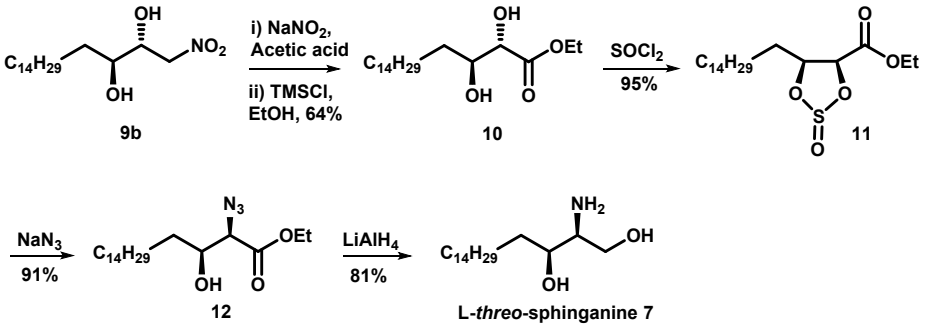
D-*erythro*-sphinganine 6 L-*threo*-sphinganine 7

Sphingolipids were isolated from membranes of plants, mammals, yeast, fungi, viruses and some prokaryotic organisms.[17] Among the natural D-*erythro*-sphinganine **6** and three other unnatural isomers of sphingoid bases, L-*threo*-sphinganine (safingol) **7** illicit a myriad of biological activities that includes antineoplastic, antipsoriatic, inhibit protein kinase C and acts as synergistic with anticancer drugs.[18]



dr; *anti*:*syn* = 1.64:1

The synthesis of safingol **7** commenced with *n*-heptadecanal **8**, which on treatment with nitrosobenzene in the presence of catalytic amount of D-proline (30 mol %) furnished α-aminoxylated aldehyde which on subsequent treatment with nitromethane using a complex of (-)-**3**/$Cu(OAc)_2.H_2O$ and aqueous NaOH followed by cleavage of phenylamine moiety with $Cu(OAc)_2.H_2O$ delivered the column chromatography separable mixture of β,γ-dihydroxynitrooctadecane **9a** and **9b**.

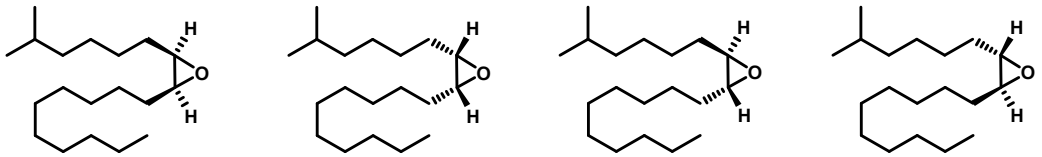


The *anti* diastereomer **9b** was then subjected to oxidation using $NaNO_2$/acetic acid in DMSO to afford acid[16] which on spontaneous ester formation with TMSCl/EtOH[19] afforded the α,β-dihydroxy ester **10**. The diol **10** on treatment with thionyl chloride furnished the cyclic sulfite **11** which on regiospecific nucleophilic opening at the α-carbon position with NaN_3/DMF afforded

the azido ester **12**. Finally, the concomitant reduction of both ester and azide groups of derivative **12** with $LiAlH_4$ afforded the target safingol **7** in excellent yield.

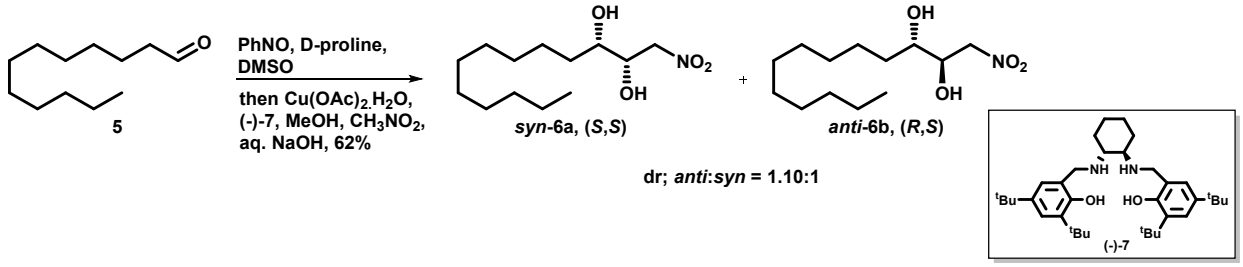
Chapter 5: Two different enantioselective approaches for the total synthesis of (+)-disparlure, a lepidopteran sex pheromone. This chapter is divided into two sections.

Section A: Enantioselective synthesis of (+)-disparlure *via* organocatalyzed tandem α-aminoxylation/Henry reactions.

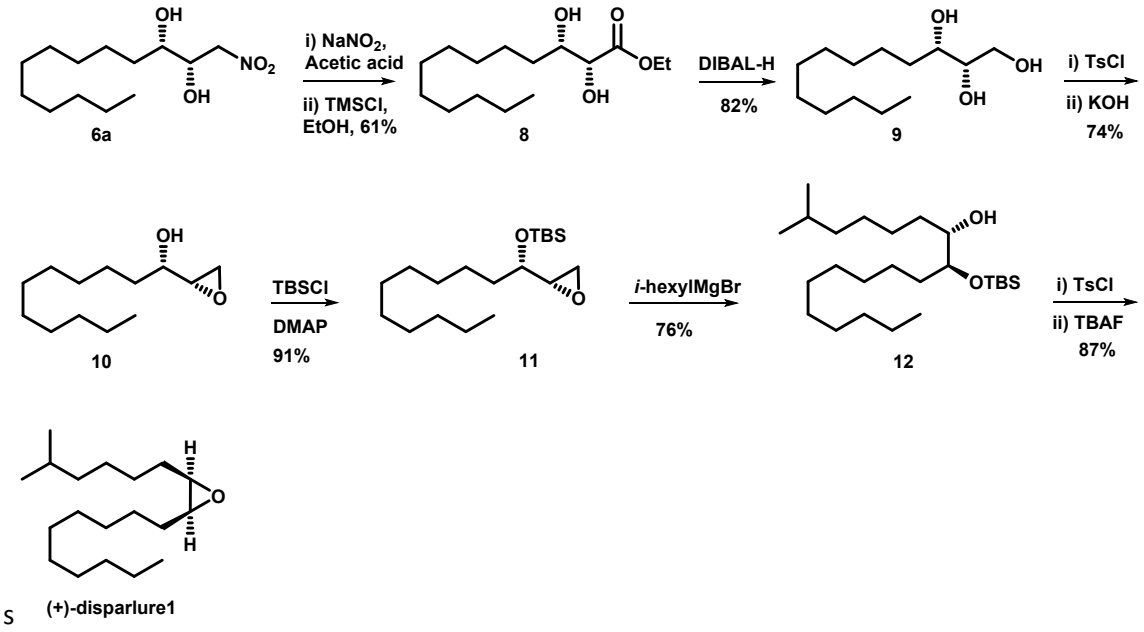


The novel straight chain lepidopteran sex pheromone *cis*-(+)-disparlure **1** was isolated from the female gypsy moth, *Porthetria disar L.*, a widespread pest causing damage to wild ecosystem.[20] *cis*-(+)-Disparlure **1** and its analogues (**2**-**4**) have been synthetic targets of considerable interest for academia and industries due to their astonishing biologically properties combined with attractive structural features with an array of functionalities.

In the first approach for the synthesis of *cis*-(+)-disparlure **1**, we have used the stereocontrolled tandem organocatalyzed α-aminoxylation/Henry reaction developed in our laboratory as the key step.



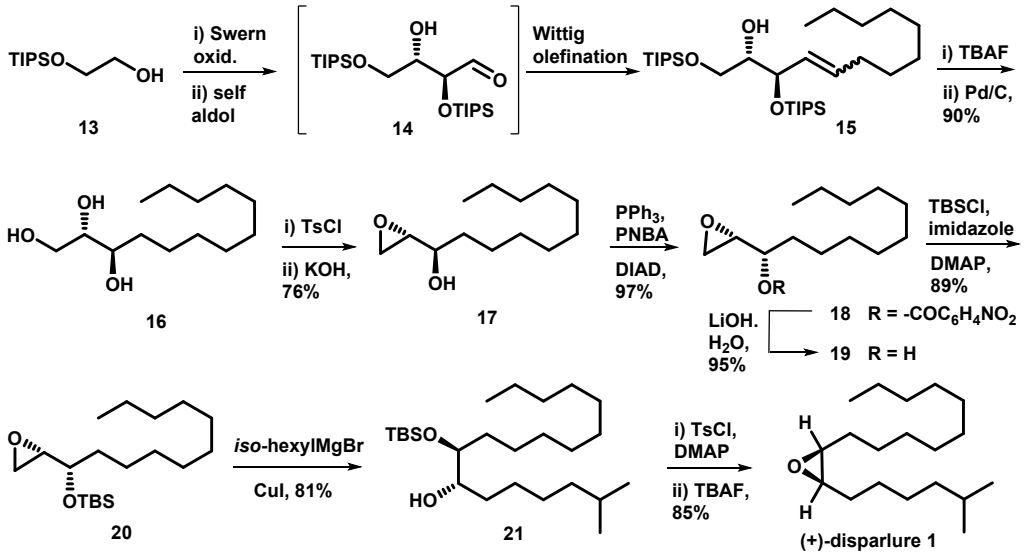
The synthesis of (+)-disparlure **1** commenced with *n*-dodecanal **5**, which was subjected to α-aminoxylation using nitrosobenzene and D-proline as a catalyst to afford *O*-*N*-phenylaminoxyaldehyde which on subsequent treatment with nitromethane using a complex of (-)-**7**/$Cu(OAc)_2.H_2O$ under basic conditions of aqueous NaOH followed by cleavage of phenylamine moiety with $Cu(OAc)_2.H_2O$ delivered the mixture of β,γ-dihydroxynitrotridecane **6a** and **6b**.



S

The *syn* diastereomer **6a** on oxidation using $NaNO_2$/acetic acid[16] in DMSO to acid followed by treatment with TMSCl/EtOH[19] afforded the ester derivative **8**. The DIBAL-H reduction of dihydroxy ester **8** to corresponding triol **9** was achieved which on selective tosylation using $TsCl/NEt_3$ in the presence of catalytic amount of dibutyltin oxide followed by base treatment furnished the terminal epoxide **10** in quantitative yield. The free alcohol **10** was protected with TBSCl using imidazole/DMAP to afford epoxide derivative **11** which on CuI catalysed regioselective ring-opening of epoxide with *i*-hexylmagnesium bromide afforded the TBS protected diol derivative **12**. Finally, the alcohol **12** was treated with TsCl/DMAP to produce *O*-tosylated diol which on *O*-TBS deprotection using TBAF furnished the sex pheromone (+)-disparlure **1** in excellent yield.

Section B: Enantioselective synthesis of (+)-disparlure *via* asymmetric organocatalysis.



In another approach, synthesis of (+)-disparlure **1** commenced with monosilylated ethylene glycol **13**, which on oxidation under Swern conditions, subsequent L-proline catalyzed asymmetric Macmillan's self aldol reaction[21] afforded aldehyde **14** which on further Wittig olefination with (nonyl)triphenylphosphonium bromide furnished olefin **15**. The cleavage of silyl ether in compound **15** with TBAF and subsequent hydrogenation under 1 atm pressure in the presence of a catalytic amount of Pd/C furnished the triol derivative **16**. Triol **16** on base catalyzed selective monotosylation with TsCl/Bu_2SnO followed by base treatment furnished the epoxide **17** in 76% yield. The free hydroxyl group of compound **17** on treatment with *p*-nitrobenzoic acid (PNBA) and diisopropyl azodicarboxylate (DIAD) under the Mitsunobu esterification conditions successfully furnished the ester **18**, which on basic hydrolysis synthesized the inverted alcohol **19** in 95% yield. Treatment of alcohol **19** with TBSCl using imidazole/DMAP successfully synthesized the TBS protected derivative **20** in excellent yield which on Cu(I)-catalyzed regioselective ring-opening with *iso*-hexylmagnesium bromide afforded the TBS protected alcohol **21**. Finally, the free hydroxyl group of alcohol **21** was subjected to *O*-tosylation using TsCl/DMAP and subsequent silyl ether cleavage using TBAF delivered the sex pheromone (+)-disparlure **1** in excellent yield.

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 excess (%*ee*) of chiral compounds was determined by HPLC on chiral phase OD-H and Chiradex columns.

Conclusion:

We have described herein enantioselective approaches for the synthesis of functionalized amino acids, 2-alkyl substituted tetrahydroquinoline, α-phenyl-β^2-amino acid and 3-substituted pyrrolidines, along with their applications to the total synthesis of (*R*)-lacosamide, (+)-angustureine, (*S*)-nakinadine B and pyrrolidine core of serotonin norepinephrine reuptake inhibitors respectively employed Trost's DYKAT, organocatalzyed α-aminoxylation, Michael addition and Jacobsen's HKR reactions as key steps. We have also developed a new stereocontrolled tandem organocatalyzed α-aminoxylation/Henry reaction approach for the asymmetric synthesis of β,γ-dihydroxynitroalkanes from aldehydes and described its applications to the total synthesis of (-)-safingol. In addition to the above, we have also described two new different approaches for enantioselective total syntheses of (+)-disparlure, a lepidopteran sex pheromone *via* asymmetric organocatalysis. 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. An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (*R*)-Lacosamide
   Yuvraj Garg and Satyendra Kumar Pandey*
   J. Org. Chem. **2015**, *80*, 4201-4203.
2. An Enantioselective Approach to 2-Alkyl Substituted Tetrahydroquinolines: Total Synthesis of (+)-Angustureine
   Yuvraj Garg, Suraksha Gahalawat and Satyendra Kumar Pandey*
   RSC Adv., **2015**, *5*, 38846-38850.
3. Total Synthesis of (+)-Petromyroxol, a Marine Natural Product
   Suraksha Gahalawat, **Yuvraj Garg** and Satyendra Kumar Pandey*
   Asian J. Org. Chem. **2015**, *4*, 1025-1029.
4. Enantioselective Total Synthesis of (*S*)-Nakinadine B
   Yuvraj Garg and Satyendra Kumar Pandey*
   RSC Adv., **2016**, *6*, 25913-25917.
5. A Short Total Synthesis of the Antimalarial Flindersial Alkaloids
   Ramandeep Kaur, **Yuvraj Garg** and Satyendra Kumar Pandey*
   ChemistrySelect **2016**, *1*, 4286-4288.
6. Enantioselective total synthesis of *cis*-(+)- and *trans*-(+)-disparlure
   Yuvraj Garg, Anand Kumar Tiwari and Satyendra Kumar Pandey*
   Tetrahedron Lett. **2017**, *58*, 3344-3346.
7. An Enantioselective Approach to 3-Substituted Pyrrolidines: Asymmetric Synthesis of Pyrrolidine Core of Serotonin Norepinephrine Reuptake Inhibitors
   Yuvraj Garg and Satyendra Kumar Pandey*
   Tetrahedron Lett. **2017**, *58*, 3493-3495.
8. Organocatalytic Asymmetric Tandem α-Aminoxylation-Henry Reactions for the Synthesis of 1,2-Diols: Total Synthesis of (-)-L-*threo*-Sphinganine
   Yuvraj Garg and Satyendra Kumar Pandey*
   (**Manuscript Communicated**)
9. An Efficient Total Synthesis of (+)-Disparlure *via* Tandem α-Aminoxylation-Henry Reaction

Yuvraj Garg and Satyendra Kumar Pandey*

(**Manuscript Communicated**)

10. 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**)

Patents

1. Process for the Synthesis of (*R*)-Lacosamide

   March **2016**; US patent: US 9,284,263 B1

   Satyendra Kumar Pandey and **Yuvraj Garg**
2. Improved Process for the Synthesis of (*R*)-Lacosamide

   August **2016**; WO patent: WO 2016/125178

   Satyendra Kumar Pandey and **Yuvraj Garg**
3. Improved process for the preparation of (*R*)-Lacosamide

   August 2016; **IPO: 324/DEL/2015 A**

   Satyendra Kumar Pandey* and **Yuvraj Garg**

Conferences

1. Asymmetric Synthesis of Antiepileptic Drug (*R*)-Lacosamide (Vimpat)

   Yuvraj Garg and Satyendra Kumar Pandey

   Poster presentation, 17th CRSI National Symposium in Chemistry, 2015 at CSIR-NCL, Pune.
2. Total syntheses of (*R*)-lacosamide, (+)-angustureine and (*S*)-nakinadine B

   Yuvraj Garg and Satyendra Kumar Pandey

   Poster presentations at International conference FCASI 2016, University of Rajasthan, Jaipur, India.
3. Short and Efficient Asymmetric Total Synthesis of Drugs and Bioactive Natural Products

   Yuvraj Garg 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 Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT), Jacobsen's Hydrolytic Kinetic Resolution (HKR), Henry reaction, organocatalzyed α-aminoxylation and Michael addition reactions.

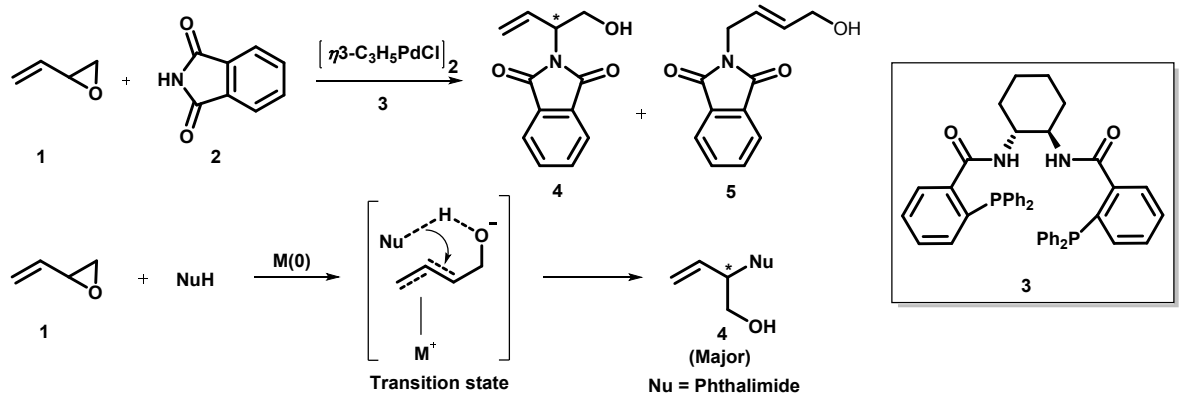
1.1 Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT)

1.1.1 Introduction

Recently, B. M. Trost and co-workers described the dynamic kinetic asymmetric transformation (DYKAT) by using a Pd-catalyzed asymmetric allylic alkylation (AAA) on a racemic butadiene monoepoxide which helps in the conversion of both the enantiomers of epoxide to a single enantiomeric product.[1] This strategy was also successfully applied for the asymmetric synthesis of vinylglycinol by nucleohilic opening of racemic butadiene monoepoxide with phthalimide as the nitrogen source in quantitative yield with >99% *ee*, which demonstrates the excellent ability of the newly designed chiral ligands to control both the regio- and enantioselectivity in this methodology for the generation of a quaternary center asymmetrically.

1.1.2 Optimization of experimental conditions

The optimization of the reaction conditions commenced with an equimolar mixture of both butadiene monoepoxide **1** and phthalimide **2** which on addition to a catalyst synthesized *in situ* from π-allylpalladium chloride dimer and a ligand **3** in THF furnished the phthaloyl alcohol **4** and **5** with 16:1 ratio, *ee* 77% (er 88.5:11.5) in a good regioselective manner while favoring the attack at the more hindered allyl terminus as summarized in Scheme 1.[1] In case of triphenylphosphine as ligand in solvent THF, compound **4** and **5** were achieved only in 4:1 ratio with 71% yield.



Scheme 1. Trost's DYKAT (Dynamic Kinetic Asymmetric Transformation)

The terminal alcohol on *o*-methylmandelate ester formation allowed the determination of *de* by both ^{1}H NMR and chiral HPLC. The doublet of doublets for the methylene group in ^{1}H NMR

clearly distinguishes both compounds at δ 4.387 for compound **4** and δ 4.515 for the another compound **5**. However, the HPLC analysis (using Dynamax, 15% EtOAc/hexane) first elutes the compound **5** followed by the compound **4**. On the other hand, chiral HPLC (using Chiracel OD, 90:10 heptane/IPA) also helped in clear resolution of the both enantiomers of alcohol **4**. Further, switching to another ligand containing diphenyl system **6** significantly improved the regioselectivity of **4** and **5** in the ratio of 19:1 and enantioselectivity of 83% *ee* (er of 91.5:8.5) (Figure 1).

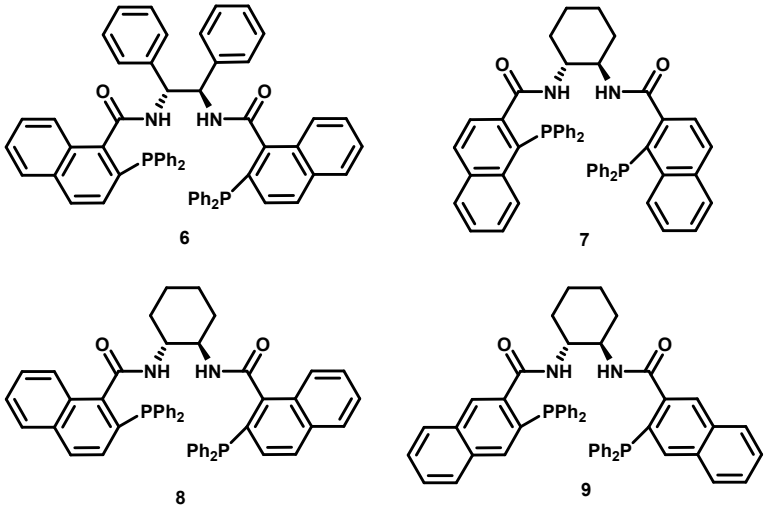


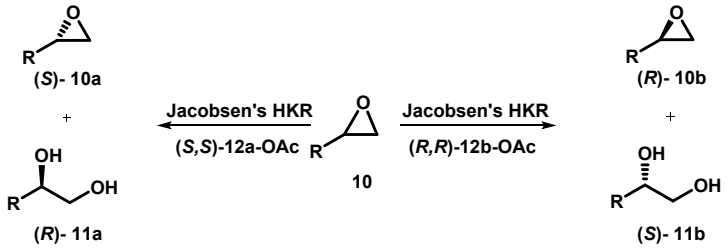
Figure 1. Newly designed chiral ligands **6-9**

Also, a set of optimized condition using the palladium complex (2.5 mol%), ligand **7-9** (7.5 mol%) and sodium carbonate (5 mol%) as an initiator was selected (Figure 1). Among them, ligand **7** generally provides low *ee* in all the reactions, so was not used further in this process. The conformationally rigidified ligand **8** furnished alcohol **4** and **5** in 75:1 ratio of regioselectivity, enantioselectivity of 98% *ee* with 99:1 *er*, and with 99% yield when the reaction was performed in methylene chloride as solvent. On the other side, the ligand **9** furnishes alcohol **4** in low enantioselectivity (55-66% *ee*), although the yield was satisfactorily (94-99%).

1.2 Jacobsen's Hydrolytic Kinetic Resolution (HKR)

1.2.1 Introduction

During recent years, Jacobsen's HKR has become one of the most important asymmetric catalytic reaction in organic chemistry with an impressive number of its applications in total synthesis of biologically active compounds and natural products documented in the literature.[2] The applications of this advantageous methodology for the conversion of commercially and readily available racemic epoxides **10** to chiral epoxides **10a** and **10b** along with corresponding chiral 1,2-diols **11a** and **11b** in high enantiomeric excess using the (salen)Co complex **12** made it a choice for the reasearchers to prepare a variety of terminal epoxides in high enantioselectivity (Scheme 2).



Scheme 2. Jacobsen's HKR of epoxide

The Jacobsen's (salen)Co complex **12** catalyzed the hydrolytic kinetic resolution of a variety of terminal epoxides in a highly efficient manner (Figure 2).[3] Therefore, the commercial synthesis of chiral epoxides such as propylene oxide, glycidyl ether and epichlorohydrin from racemic epoxides has been implemented successfully using Jacobsen's HKR by decreasing the cost of these chiral epoxides for suppliers.

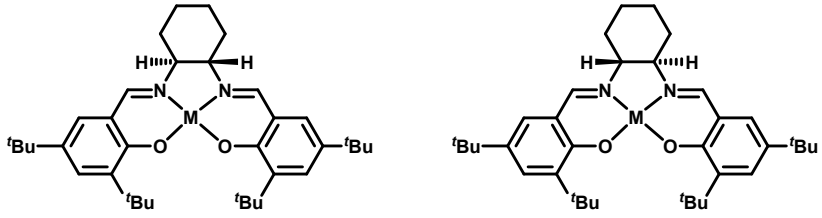
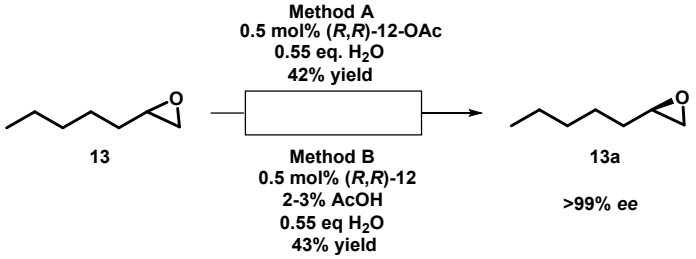


Figure 2. Jacobsen's catalysts

1.2.2 Preparation of catalyst and general experimental conditions

Both the enantiomers of (salen)Co-II complex **12** are either commercially available or can be synthesized from the commercially available chiral ligands with $Co(OAc)_2$. The Co(II) complex **12a** and **12b** (Figure 2) are inactive catalytically, however if subjected to one-electron oxidation, it produced an anionic ligand (salen)Co-III complex prior to the HKR which can be performed easily by aerobic oxidation using a mild Bronsted acid. Only water was not found to mediate this oxidation reaction, but another additive acetic acid was also effective and and the corresponding Co(III) precatalyst-**12**-OAc (Figure 2) was found to be stable and efficient for HKR reactions due to its easy preparation and high reactivity.

Towards this end, two useful methods have been developed for the preparation of complex-**12**-OAc (Scheme 3). Method A constitutes the isolation of **12**.OAc as crude solid before the HKR. A toluene solution of Co(II) complex **12** (ca. 1 M solution) is mixed with acetic acid (2 eq) followed by stirring in open air for 30 min at room temperature, and the color of the reaction mixture changes from dark orange to dark brown. The resulting crude was concentrated *in vacuo* to remove the volatile materials to afford the **12**.OAc as a brown solid residue which can be used further without purification. Method B constitutes the *in situ* formation of **12**.OAc using HKR conditions by making a suspension of Co(II) complex **12** and epoxide or with epoxide/solvent followed by addition of AcOH under aerobic conditions. The catalysts obtained by above methods **A** and **B** were then applied to a variety of epoxides. The catalyst synthesized by either of two methods leads to approximately identical results when applied to 1-heptene oxide **13** which furnished chiral epoxide **13a** in high enantiomeric excess (Scheme 3).



Scheme 3. Development of HKR methods

In these situations, *in situ* catalyst synthesized by method **B** is more recommendable since the method avoids an additional solvent removal step. On the other side, the catalyst synthesized by method **A** was applicable to variety of less reactive substrates. Thus, if HKR do not provide epoxide in >99% *ee* with catalyst synthesized by method **B** under optimized conditions of

catalyst loading and solvent, then catalyst synthesized by method **A** could be used as an alternative.

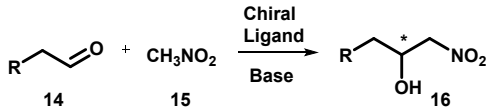
Aside from the procedure for the synthesis of **12**.OAc, the other reaction parameters in Jacobsen's HKR for optimization were catalyst loading and type of solvents for different type of substrates. In some cases, the epoxide could be obtained in >99% *ee* by using 0.55 eq H_2O relative to racemic epoxide. The epoxides with good 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 organic solvents which are miscible with water such as tetrahydrofuran (THF), isopropyl alcohol (IPA), or hexane-1,2-diol.

Generally, 1.0 eq of solvent relative to racemate was found to be sufficient for doing HKR efficiently to a variety of substrates. However, the catalyst loadings in the amount of 0.5 mol% or less relative to racemate were found to be efficient for all substrates, but saturated sterically hindered or unsaturated epoxides generally required more amount of catalyst (up to 2 mol%) for achieving the complete resolution. Initially, the reaction generally started at 0 °C followed by stirring at room temperature for 12-18 h.

1.3 Asymmetric Henry reaction

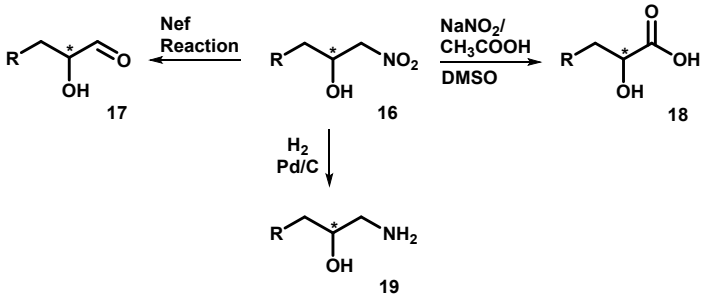
1.3.1 Introduction

The Henry (nitroaldol) reaction is one of the most convenient and atom-economical reaction for C-C bond-formation to afford *β*-hydroxynitroalkane derivatives **16** from commercially available aldehydes **14** on reaction with nitromethane **15** in one step without any pretreatment (Scheme 4).[4]



Scheme 4. Asymmetric synthesis of *β*–hydroxynitroalkane derivatives

The resulting products, *β*-hydroxynitroalkane derivatives **16**, can be used further to many possible transformations of the nitro group such as to carbonyl compounds **17** by Nef reaction,[5] to acid derivative **18** by oxidation[6] and to aminoalcohol derivative **19** by catalytic hydrogenation[7] etc. (Scheme 5). 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.[8]



Scheme 5. Selected synthetic utilities of chiral *β*-hydroxy nitroalkane derivatives

Since the first report on catalytic enantioselective version of this reaction through using the heterobimetallic lanthanide with BINOL catalyst systems,[9] various others complex catalytic systems have been successfully explored; for e.g. dinuclear zinc complex catalysts,[10] and copper/bisoxazoline complexes,[11] etc. Also, many efforts have been aimed at making an asymmetric version of this catalytic process by using optically active ligands, different metal containing (such as rare-metal, Cu, Zn, Co, Cr, Mg) ligands,[12] using organocatalysts,[13] and bio-catalysts[14] from which most promising 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 *β*-hydroxynitroalkane derivatives.

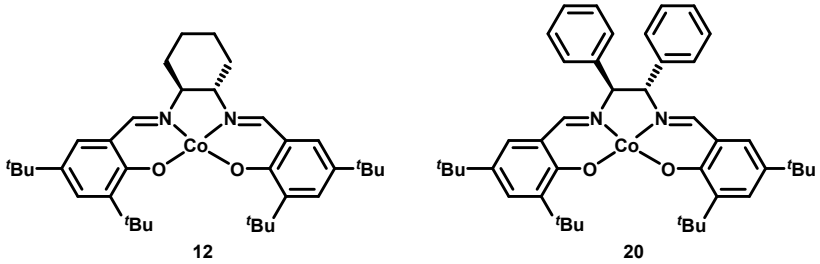
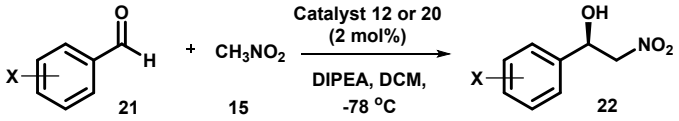


Figure 3. Some commercially available salen-cobalt complex

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.[8b] In another report, the salen-cobalt complexes **12** and **20** used previously for hydrolytic kinetic resolution were also found to be compatible and efficient catalysts for asymmetric Henry reactions using the amine as bases. In the report, it has been described that the asymmetric Henry reaction catalyzed by the chiral salen-cobalt complexes could furnish the *β*-hydroxynitroalkanes in high enantioselectivities with good yield. The commercially available salen-cobalt complex **12** and **20** (Figure 3) have been examined which worked as the efficient catalytic system for the asymmetric Henry reaction. A variety of aromatic aldehydes **21** were examined by applying optimized conditions of this asymmetric Henry reaction with nitromethane **15** using the diisopropylethylamine as base to furnish *β*-hydroxynitroalkane derivatives **22** in good enantioselectivity (upto 98% *ee*) and yield (upto 94%) (Scheme 6).

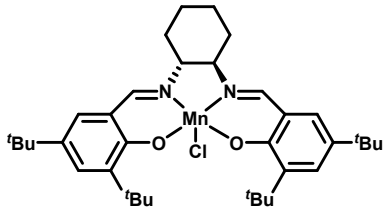


Scheme 6. Asymmetric synthesis of *β*–hydroxynitroalkane derivatives using salen ligands

In continuation, Schiff base ligands are reactive to coordinate with metals through imine nitrogen and other group such as alcohol etc., to synthesize efficient catalytic systems for asymmetric Henry reactions. In these days, many chemists have been designing novel and active Schiff bases, which could be considered as ‘‘privileged ligands’’ in enantioselective Henry reaction. The Schiff bases have also the ability of stabilizing metals in different oxidation states, thus

improving the ability of metals to a catalyzed asymmetric Henry reaction in a more efficient way.

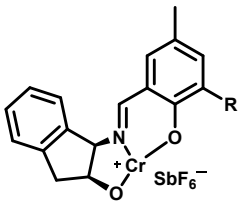
The optically active Salen-Mn complexes were first described by Jacobsen using simple methods and reactions.[15] The manganese complex **23** (Figure 4) was prepared by using $Mn(OAc)_2$ followed by oxidation of the intermediate Salen-Mn(II) under the atmosphere of air. These Chiral Salen-Mn complexes are found to be efficient catalysts in the asymmetric catalytic transformations.



23

Figure 4. Mn(salen)Cl complex

The optically active chromium Schiff base complexes have also found to possess some interesting applications in asymmetric transformation reactions exemplified by complex **24** (Figure 5).[16] The presence of bulky groups at the *ortho* position relative to phenoxy group makes it a highly efficient catalytic system using transition metals.



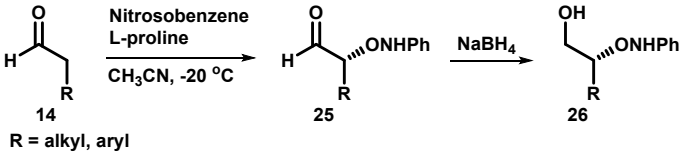
24

Figure 5. Cr/Schiff base complex

1.4 Organocatalzyed α-aminoxylation reactions

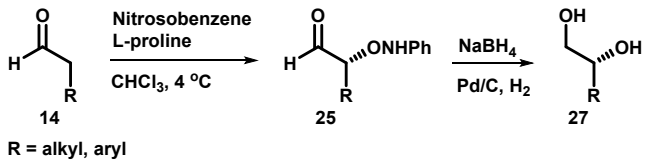
1.4.1 Introduction

The enantioselective synthesis of terminal optically active 1,2-diols are of considerable interest due to prevalence of this structural moiety in biologically active compounds and natural products.[17] A number of strategies have been developed for their synthesis of *syn*- and *anti*-1,2-diols of which Sharpless asymmetric dihydroxylation (SAD) of olefins is commonly used.[17,18] Another potential strategies for the asymmetric synthesis of terminal 1,2-diols are the i) asymmetric *in situ* α-hydroxylation of aldehydes followed by reduction, ii) transformation from chiral pool materials such as from amino acids, sugars, and chiral α-hydroxy acids, iii) diastereoselective reactions *via* nucleophilic addition to the chiral glyoxal derivatives, or alkylation of chiral hydrazones.[19] Very recently, Hayashi and co-workers described a first, direct and asymmetric strategy for the synthesis of α-hydroxyaldehydes **25** from the corresponding aldehyde **14** under the optimized conditions of chiral proline as catalyst with electrophilic nitrosobenzene as an aminooxylating agent in high yield (upto 81%) and excellent enantioselectivity (upto 99% *ee*) (Scheme 7).[20]



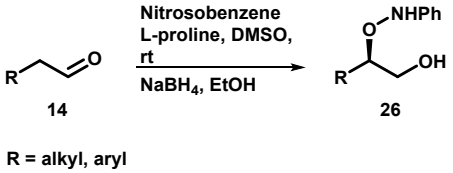
Scheme 7. Direct proline catalyzed α-aminoxylation reactions

In this strategy, the L-proline on treatment with aldehyde **14** and nitrosobenzene furnished optically active α-aminoxylated aldehydes **25** which on subsequent reduction with $NaBH_4$ furnished the α-aminoxylated alcohol **26** in good yield and high enantioselectivity. MacMillan and co-workers also reported the direct catalytic asymmetric α-carbonyl oxidation with high levels of asymmetric induction (Scheme 8).[21]



Scheme 8. Proline catalyzed asymmetric α-aminoxylation reactions

In this route, the aldehyde **14** on treatment with nitrosobenzene in the presence of catalytic amount of L-proline afforded α-aminoxylated aldehyde derivatives **25** under given optimized conditions which on further reduction using $NaBH_4$ and *O*-NHPh deprotection *via* hydrogenation in the presence of Pd/C furnished chiral 1,2-diols **27** in high yield (upto 95%) and excellent enantioselectivity (upto 99% *ee*).



Scheme 9. Enantioselective proline catalyzed asymmetric α-aminoxylation reactions

G. Zhong also reported the direct catalytic asymmetric α-aminoxylation of aldehydes by using nitrosobenzene as the oxygen source and chiral proline in catalytic amount under given optimized conditions (Scheme 9).[22] In this strategy, the aldehyde **14** on treatment with nitrosobenzene in the presence of catalytic amount of L-proline at room temperature followed by *in situ* reduction using $NaBH_4$/EtOH furnished α-aminoxylatedalcohol derivatives **26** in high yield (upto 86%) and excellent enantioselectivity (upto 99% *ee*).

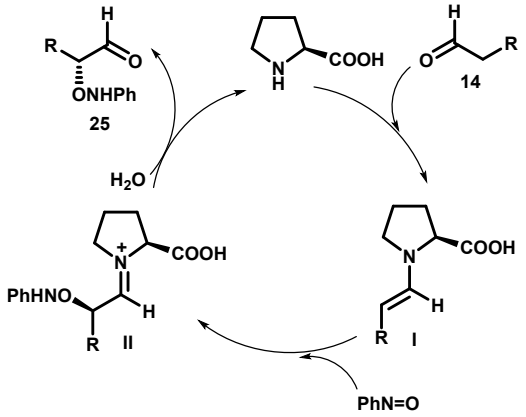


Figure 6. A general mechanism for proline catalzyed *a*-aminoxylation

A general mechanism of proline catalyzed asymmetric *a*-aminoxylation of aldehydes **14** for the synthesis of optically active α-aminoxylated aldehyde derivatives **25** is explained in Figure 6. The aldehyde **14** on reaction with proline generates enamine intermediate **I** which on nucleophilic addition to nitrosobenzene synthesizes imine intermediate **II**. Finally, the imine intermediate **II** on hydrolysis furnish the α-aminoxylated aldehyde derivatives **25** with simultaneous release of proline molecule.

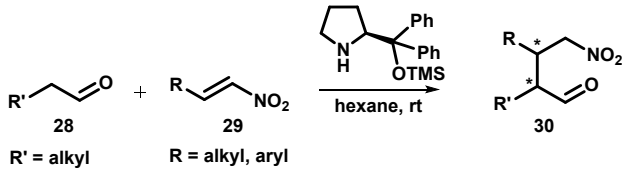
1.5 Organocatalzyed Michael addition reactions

1.5.1 Introduction

The Michael addition reaction is one of the most important reactions for carbon-carbon bond-formation, which could be catalyzed enantioselectively by organocatalysts. The Michael addition reaction of a nucleophile with a conjugated acceptor is one of the useful methods 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. However, the need of an environment friendly and metal-free reaction made the organocatalyst as an alternative for Michael addition reaction of aldehyde to nitroalkenes and Michael addition of nitroalkanes to conjugated aldehydes.

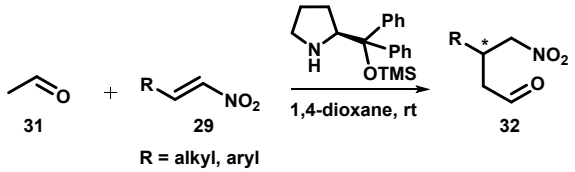
1.5.2 Organocatalzyed Michael addition reactions on conjugated nitro-olefins

Recently, Hayashi and co-workers developed an organocatalyzed asymmetric Michael reaction of α-substitutedaldehydes **28** with nitroalkenes **29** in the presence of catalytic amount of diphenylprolinol silyl ether to furnish the useful α-substituted-γ-nitro aldehydes **30** in high enantio- (upto 99% *ee*) and diastereoselectivity (upto 97:3 *syn*:*anti*) with good yield (upto 85%) (Scheme 10).[23]



Scheme 10. Organocatalyzed Michael addition reaction of aldehydes

More recently, Hayashi and co-workers described the organocatalytic asymmetric Michael addition reaction of acetaldehyde **31** with acceptor nitroolefins **29** in the presence of catalytic amount of diphenylprolinol silyl ether to afford the α-unsubstituted-γ-nitro aldehydes **32** in good yield (upto 77%) with excellent enantioselectivity (upto 99% *ee*) (Scheme 11).[24]



Scheme 11. Organocatalyzed Michael addition reaction of acetaldehyde

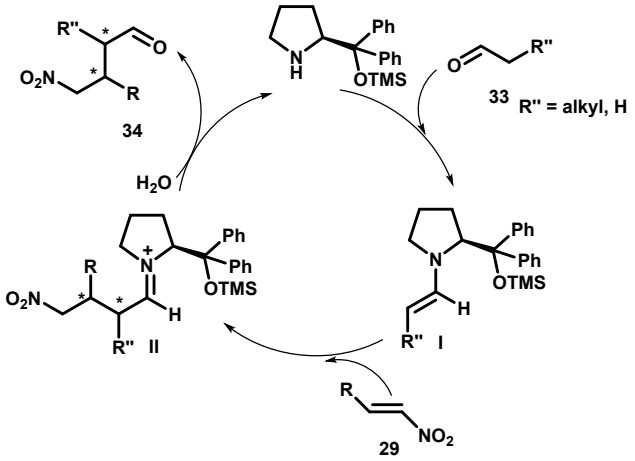


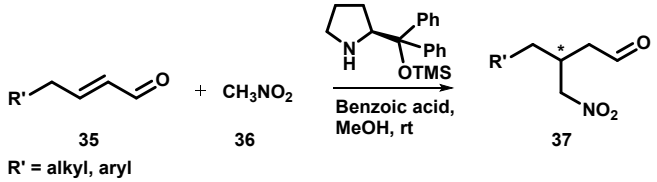
Figure 7. General mechanism for organocatalzyed Michael addition reaction

A plausible mechanism for the organocatalzyed asymmetric Michael addition reaction of aldehyde to conjugated nitro-olefins is described in Figure 7. Initially, aldehyde **33** on treatment with TMS-prolinol organocatalyst generates an enamine intermediate **I** which on nucleophilic addition to acceptor nitroolefin **29** furnish imine intermediate **II**. Finally, the intermediate **II** on hydrolysis generates the nitroaldehyde adduct **34** with simultaneous release of organocatalyst.

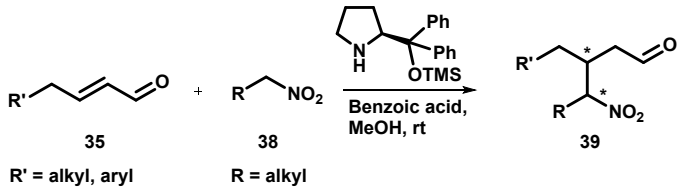
1.5.3 Organocatalzyed Michael addition reactions on conjugated aldehydes

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 **36** to acceptor *trans*-olefinic aldehydes **35** in the presence of catalytic amount of TMS-prolinol to furnish the nitroaldehyde adduct **37** in good yield (up to 94%) and high enantioselectivity (up to 95% *ee*) (Scheme 12).[25]



Scheme 12. Organocatalyzed Michael addition reaction with nitromethane



Scheme 13. Organocatalyzed Michael addition reaction with nitroalkanes

Hayashi and co-workers also described the Michael addition of nitroalkane **38** with conjugated aldehydes **35** in the presence of catalytic amount of TMS-prolinol to afford the nitroaldehyde adduct **39** in high enantio- (upto 96% ee), diastereoselectivity of 1:1 *syn*:*anti* and good yield (upto 95%) (Scheme 13).[25]

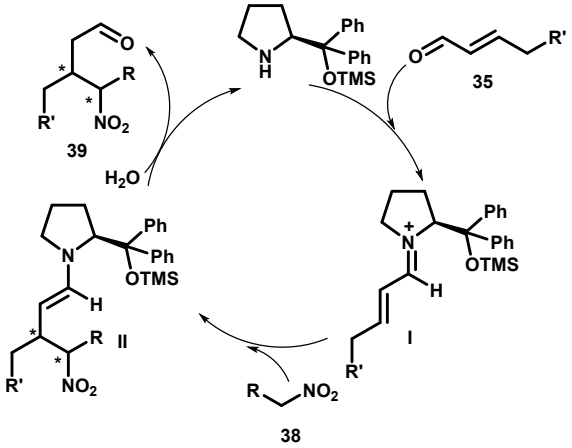


Figure 8. General mechanism for organocatalzyed Michael addition reaction

A general mechanism for asymmetric organocatalyzed Michael addition reaction of nitroalkanes to conjugated aldehydes is described in Figure 8. Initially, the aldehyde **35** on reaction with TMS-prolinol generates an imine intermediate **I** which on addition of donor nitroalkane **38** forms enamine intermediate **II**. The intermediate **II** on hydrolysis forms the nitroaldehyde adduct **39** with simultaneous release of organocatalyst.

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CHAPTER 2

Enantioselective general approaches towards the synthesis of functionalized amino acids and 2-alkyl substituted tetrahydroquinolines with their applications to the total synthesis of (*R*)-lacosamide and (+)-angustureine, respectively. This chapter is divided into two sections.

2.1 Section A

An enantioselective approach to functionalized amino acids: total synthesis of antiepileptic drug (*R*)-lacosamide

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2.1.1 Introduction:

Functionalized amino acids (FAAs) **1** are advanced novel class of anticonvulsant agents, from which (*R*)-lacosamide **2** emerged as a best antiepileptic drug (AED) and has been suggested for the treatment of partial-onset seizures in patients with epilepsy and as add-on treatment in brain tumor patients (Figure 1).[1] Currently, (*R*)-lacosamide **2** (Vimpat®) is marketed in US and Europe with its worldwide expected sale in 2015-2020 is € 1.2 billion (UCB pharma). Epilepsy is a chronic neurological disorder that arise from dysregulations and hypersynchronous neuronal firing which is affecting almost over 10 million people in India and 50 million people worldwide.[2] The precise mechanism of action of (*R*)-lacosamide **2** in humans has not yet been fully elucidated, but it enhances the slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.[3] Additionaly, (*R*)-lacosamide **2** is also under clinical trials for the treatment of neuropathic pains.[4] (*R*)-Lacosamide **2** has been a synthetic target of considerable interest due to its anticonvulsant activity with an array of functionalities.

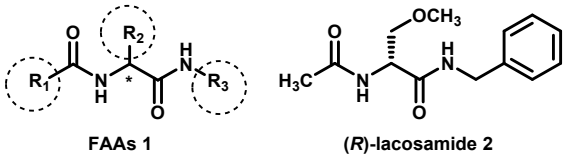


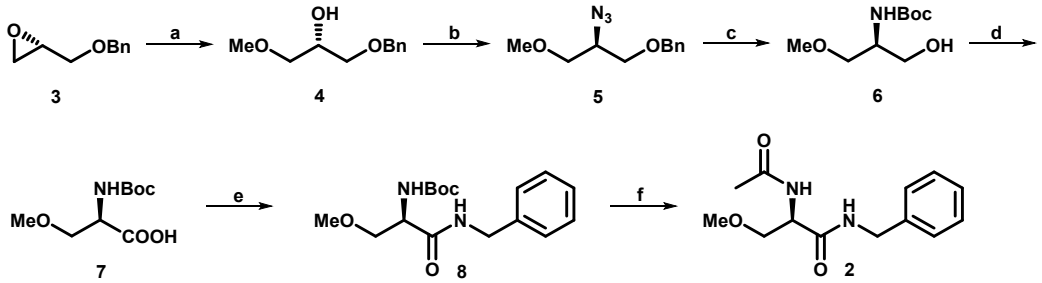
Figure 1. Structure of FAAs and (*R*)-lacosamide

2.1.2 Review of Literature:

Various methods for the synthesis of (*R*)-lacosamide **2** have been documented in the literature from pharmaceutical industries and academia.[5-6] Most of the synthesis described employed chiral pool approach and started from unnatural amino acid D-serine and derivatives. Some of the recent syntheses of (*R*)-lacosamide **2** are described below.

Muthukrishnan, M. *et al*. (2011)[5f]

M. Muthukrishnan and co-workers reported the asymmetric synthesis of (*R*)-lacosamide **2** from chiral *O*-benzyl glycidyl ether **3** resolved by Jacobsen's HKR as key step (Scheme 1). The epoxide **3** was subjected to base catalyzed regioselective ring opening with methanol followed by reaction with DPPA under Mitsunobu conditions afforded the azide derivative **5** in 83% yield. Next, the azido compound **5** on $Pd(OH)_2$ catalyzed hydrogenation/hydrogenolysis and concomitant *N*-Boc protection afforded compound **6** which on oxidation using TEMPO and $NaOCl/NaClO_2$ furnished acid **7** in 83% yield. Finally, the acid **7** on amide bond formation with benzyl amine, subsequent *N*-Boc deprotection and *N*-acetylation furnished the target (*R*)-lacosamide **2** in 80% yield.

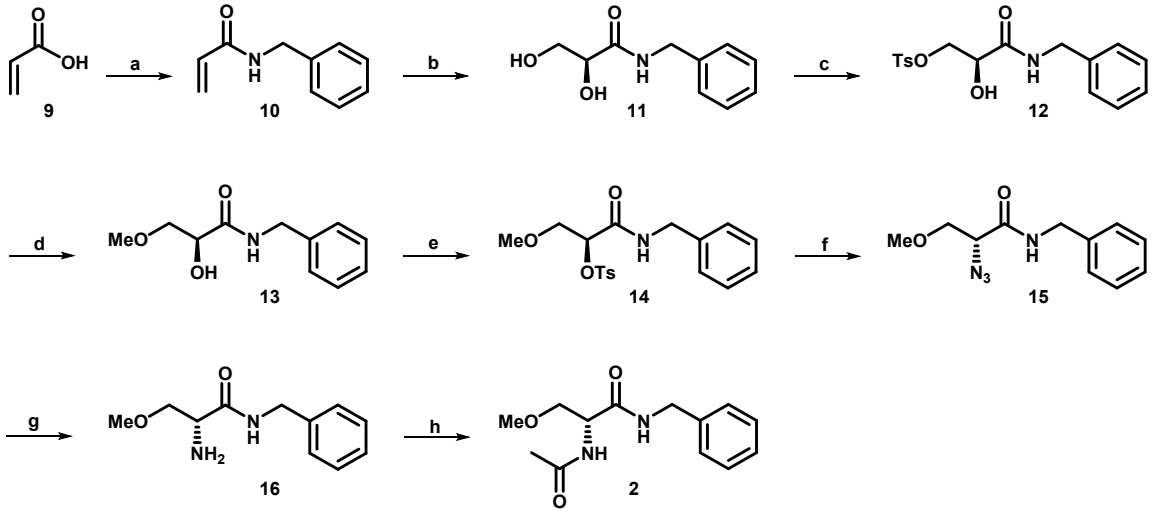


Scheme 1. *Reagents and conditions*: (a) KOH, MeOH, 0 °C to rt, 8 h, 98%; (b) DPPA, DIAD, Ph_3P, toluene, -20 °C to rt, 10 h, 83%; (c) $Pd(OH)_2$, H_2, $(Boc)_2O$, EtOAc, 36 h, 86%; (d) TEMPO, buffer, $NaOCl/NaClO_2$, CH_3CN, 35 °C, 6 h, 83%. (e) IBCF, NMM, $BnNH_2$, THF, -78 °C, 1 h, 90%; (f) CF_3CO_2H, CH_2Cl_2, 0 °C to rt, overnight; (ii) CH_3COCl, Na_2CO_3, toluene, 5 °C, 1 h, 80% (over two steps).

Narsaiah, A. V. *et al*. (2013)[5g]

A. V. Narsaiah and co-workers reported the asymmetric synthesis of (*R*)-lacosamide **2** from commercially available acrylic acid **9** in eight steps using Sharpless asymmetric dihydroxylation as a key step (Scheme 2). The synthesis of (*R*)-lacosamide **2** commenced with peptide bond formation of acrylic acid **9** with benzylamine in the presence of EDCI/HOBt to afford amide **10** in 70% yield. The compound **10** was subjected to Sharpless asymmetric dihydroxylation to afford diol **11** in 93% *ee* which on treatment with $TsCl/Bu_2SnO$ followed by base treatment in methanol (**12→13**) afforded amide **13** in 90% yield. The alcohol **13** on tosylation with TsCl/DMAP (**13→14**) followed by nucleophilic replacement with sodium azide (**14→15**) furnished azide derivative **15** in 87% yield. Finally, the reduction of azide **15** with

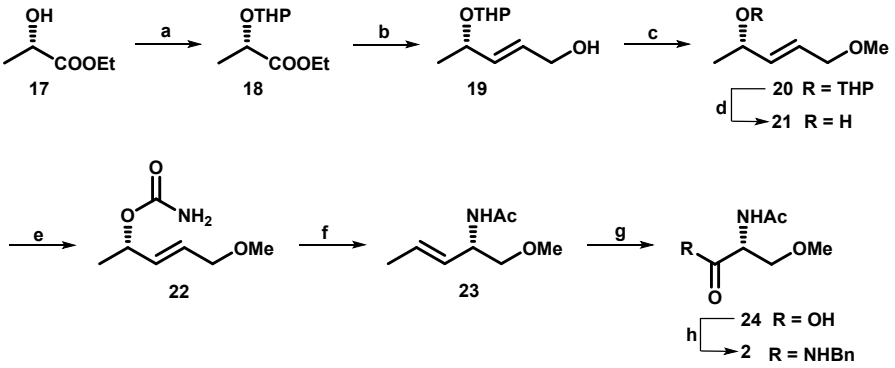
triphenylphosphine in THF/H_2O followed by *N*-acylation afforded the target molecule (*R*)-lacosamide **2** in 90% yield.



Scheme 2. *Reagents and conditions*: (a) $BnNH_2$, HOBt, EDCI, Et_3N, CH_2Cl_2, 0 °C to - rt, 8 h, 70%; (b) AD-mix-ß, $MsNH_2$, *t*-BuOH:H_2O (1:1), 0 °C, 80%; (c) Bu_2SnO, TsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 95%; (d) K_2CO_3, MeOH, 0 °C, 8 h, 90%; (e) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 92%; (f) NaN_3, DMF, 70 °C, 6 h, 87%; (g) Ph_3P, THF:H_2O (9:1), 50 °C, 12 h, 85%; (h) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 1 h, 90%.

Stecko, S. *et al*. (2014)[5h]

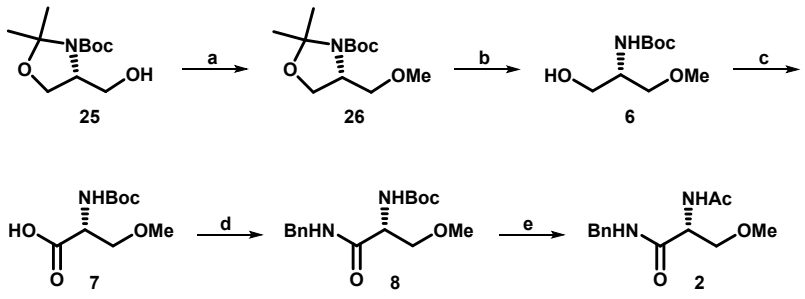
S. Stecko reported the total synthesis of **2** employed stereospecific allylcyanate-to-isocyanate rearrangement, which proceeds with chirality transfer starting from ethyl L-lactate **17** (Scheme 3). The reaction of ethyl L-lactate **17** on *O*-THP protection using DHP/PPTS, subsequent reduction with DIBAL-H followed by Horner Wadsworth Emmons reagent generated from triethyl phosphonoacetate/NaH furnished allylic alcohol derivative **19**. Next, the compound **19** was subjected to methylation, followed by deprotection of the *O*-THP protecting group furnished the allyl alcohol derivative **21**. The compound **21** on reaction with trichloroacetyl isocyanate (TCA-NCO), followed by hydrolysis furnished the derivative **22** in 82% yield. The compound **22** on dehydration, subsequent [3,3] sigmatropic rearrangement followed by Grignard reaction afforded the *N*-acetylated allyl amine **23**. Finally, allyl **23** on oxidative cleavage of the double bond using $RuCl_3/NaIO_4$ followed by amide bond formation using NMM/IBCF furnished the target (*R*)-lacosamide **2** in 82% yield.



Scheme 3. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2, rt, 95%; (b) i) DIBAL-H, CH_2Cl_2, -78 °C; ii) NaH, $(EtO)_2P(O)CH_2COOEt$, THF, 0 °C; iii) DIBAL-H, CH_2Cl_2, -78 °C, 75% (over three steps); (c) NaH, MeI, THF, rt; (d) AcCl, MeOH, rt, 78% (over two steps); (e) i) TCA-NCO, CH_2Cl_2, 0 °C, 1 h; ii) aq. K_2CO_3, MeOH, rt, 2 h, 82% (over two steps); (f) i) TFAA, Et_3N, THF, 0 °C, 30 min; ii) MeMgBr, THF, -10 °C to rt, 74% (over three steps); (g) $RuCl_3 \cdot H_2O$, $NaIO_4$, acetone/water (5:1), 79%; (h) IBCF, NMM, $BnNH_2$, THF, -20 °C to rt, 82%.

Bhattacharya, A. K. *et al.* (2015)[5i]

A. K. Bhattacharya and co-workers described the asymmetric synthesis of (*R*)-lacosamide **2** from *N*-Boc-*N*,*O*-isopropylidene-L-serinol **25** as starting material (Scheme 4). The serinol derivative **25** on treatment with MeI in the presence of base, followed by acid catalyzed deprotection of acetonide afforded the alcohol derivative **6** in 86% yield. The alcohol **6** on oxidation with TEMPO (**6**→**7**) followed by amide bond formation with benzylamine using NMM/IBCF furnished the amide derivative **8** in 90% yield. Finally, compound **8** on *N*-Boc deprotection and subsequent *N*-acetylation furnished the target (*R*)-lacosamide **2** in 80% yield.



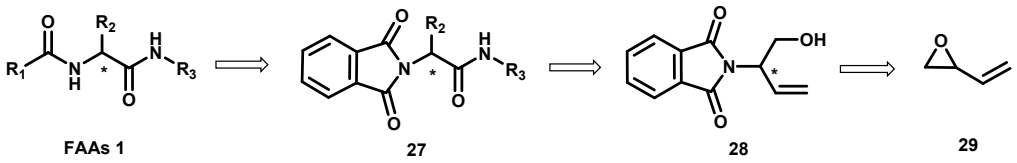
Scheme 4. *Reagents and conditions*: (a) NaH, MeI, THF, rt, 30 min, 88%; (b) PTSA, MeOH, rt, 5 h, 86%; (c) TEMPO, $NaOCl/NaClO_2$, CH_3CN, rt, 3 h, 99%; (d) $BnNH_2$, NMM, IBCF, THF, -78 °C to rt, 1 h, 90%; (e) (i) TFA, CH_2Cl_2, rt, overnight; (ii) Ac_2O, DMAP, CH_2Cl_2, rt, 4 h, 80% (over two steps).

2.1.3 Present Work:

As part of our research programme aimed at developing enatioselective synthesis of naturally occurring compounds, we aimed towards a new, general and highly efficient synthetic approach for FAAs **1** and its application to the total synthesis of (*R*)-lacosamide **2** employing Trost's DYKAT as a key step.[7]

2.1.4 Results and Discussion:

Our synthetic approach for the synthesis of (*R*)-lacosamide **2** was envisioned *via* the retrosynthetic route as shown in Scheme 5. The phthalimide derivative **27** was visualized as a synthetic intermediate from which FAAs **1** and (*R*)-lacosamide **2** could be synthesized *via* phthalimide cleavage and acylation. The phthalimide derivative **27** in turn could be obtained from the phthaloyl alcohol derivative **28** through base catalyzed alkylation. The terminal double bond of derivative **28** could be available for the functional group manipulation *via* standard organic transformations.



Scheme 5. Retrosynthetic approach to FAAs **1**

Enantiopure phthaloyl alcohol derivative **28** could be easily prepared from the racemic butadiene monoepoxide **29** by means of Trost's DYKAT. The (*S*)- and (*R*)- configuration of the derivative **28** could be manipulated by simply changing chiral ligands (*R,R*)-DACH and (*S,S*)-DACH (Figure 2) respectively in the Trost's DYKAT step.

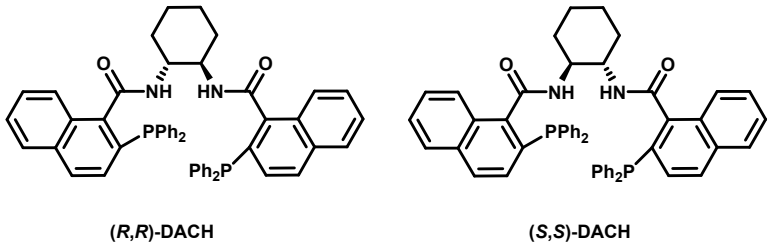
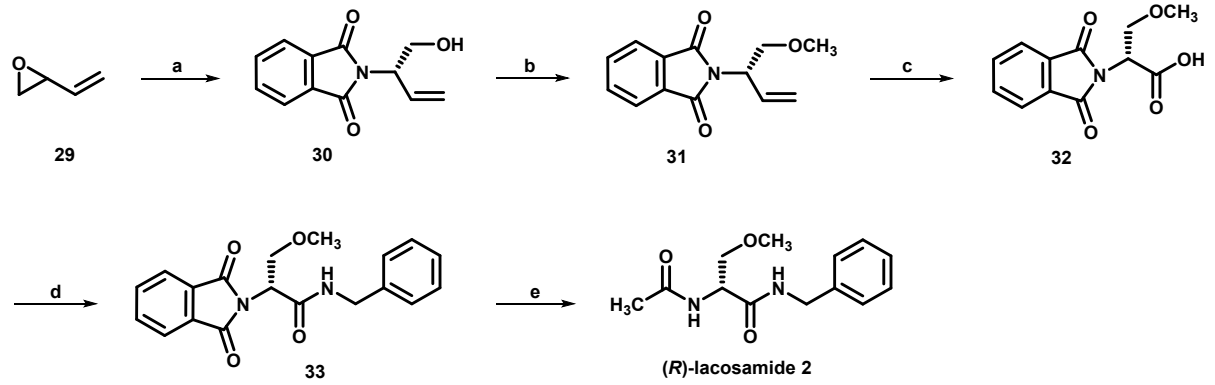


Figure 2. Structures of (*R,R*)- and (*S,S*)-DACH ligands

The synthesis of (*R*)-lacosamide **2** started from the commercially available racemic butadiene monoepoxide **29**, which can easily be synthesized from silver-catalyzed oxidation of 1,3-butadiene (Scheme 6).[8] Deracemisation of butadiene monoepoxide **29** with palladium catalyzed

Trost's DYKAT in the presence of 1.2 mol% (*R*,*R*)-DACH and 0.4 mol% [η^3-$C_3H_5PdCl]_2$, phthalimide and Na_2CO_3 afforded asymmetric allylic alkylation (AAA) product phthaloyl alcohol **30** as a single enantiomer in 98% yield with ≥ 99% *ee* {$[\alpha]_D^{25}$-72.2 (*c* 2.02, CH_2Cl_2) [Lit.[7] -72.2 (*c* 2.02, CH_2Cl_2)]}. The IR spectrum of **30** showed hydroxyl absorption at 3467 cm^{-1} and olefin C=C stretching at 1698 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.91 (doublet of doublet of doublet, one proton) and δ 5.27-5.30 (multiplet, two protons).



Scheme 6. *Reagents and conditions*: (a) Phthalimide, Na_2CO_3, 1.2 mol% (*R*,*R*)-DACH, 0.4 mol% [η^3-$C_3H_5PdCl]_2$, dry CH_2Cl_2, rt, 14 h, 98%; (b) MeI, NaH, DMF, 0 ^oC to rt, 3 h, 86%; (c) (i) OsO_4, $NaIO_4$, 2,6-lutidene, dioxane: water (3:1 v/v), 0 ^oC to rt, 2 h; (ii) Oxone, DMF, rt, 12 h (78% over two steps); (d) $C_6H_5CH_2NH_2$, NMM, IBCF, THF, -78 ^oC to rt, 1 h, 88%; (e) (i) $NH_2NH_2.H_2O$, isopropyl alcohol, 0 ^oC to rt, 2 h; (ii) CH_3COCl, Na_2CO_3, dry toluene, 0 to 5 ^oC, 1 h, (91% over two steps).

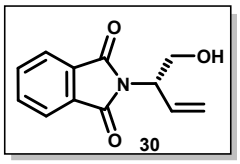
With enantiomerically pure alcohol **30** in hand, we then subjected it to *O*-methylation with MeI in presence of NaH which afforded methyl ether **31** in 86% yield. Our next aim was to carry out the amide formation at terminal double bond site. To this end, compound (*S*)-**31** on oxidative cleavage in the presence of OsO_4 and sodium periodate followed by oxidation with oxone at room temperature furnished the phthaloyl acid **32**.[9-10] The ^1H NMR indicated absence of olefin protons. The treatment of acid (*R*)-**32** with benzylamine in presence of isobutylchloroformate and *N*-methyl morpholine in THF at -78 ^oC afforded the phthaloyl amide **33** in 88% yield. An alternative method for the amide formation with benzylamine using HOBt and EDCI-HCl furnished phthaloyl amide **33** in 61% yield. Finally, the cleavage of phthalimide group of amide (*R*)-**33** with hydrazine monohydrate in presence of isopropyl alcohol followed by *N*-acetylation using acetyl chloride under basic conditions furnished the target compound (*R*)-lacosamide **2** in

91% yield {$[\alpha]_D^{25}$ +16.1 (*c* 1, MeOH) [Lit. +16.2 (*c* 1, MeOH),[5g] +16.1 (*c* 1.2, MeOH)[5h]]}. The physical and spectroscopic data of (*R*)-lacosamide **2** were in full agreement with literature data.[5-6]

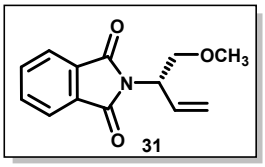
2.1.5 Conclusions:

In conclusion, a simple, flexible and highly efficient synthetic approach for FAAs **1** and its application to the total synthesis of (*R*)-lacosamide **2** has been developed. The overall yield for (*R*)-lacosamide **2** was 52% in five steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps, protection free synthesis, catalyst regenerability and cost effective strategy. Moreover, the synthetic strategy has significant potential for variation of substituents at the amide site, 2-aza and 3-oxy sites to synthesize various FAAs **1** with expected increase in anticonvulsant activities.

2.1.6 Experimental Section:



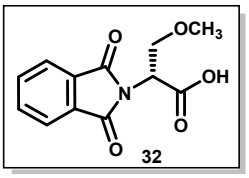
(*S*)-2-(Isoindolin-2-yl)but-3-en-1-ol (30): A mixture of π-allylpalladium chloride dimer 0.4 mol% (20 mg, 53 μmol), 1.2 mol% (*R,R)*-DACH ligand (125 mg, 158 μmol), Na_2CO_3 (70 mg, 0.66 mmol) and phthalimide (1.94 g, 13.20 mmol) in 100 mL of dry CH_2Cl_2 was purged with nitrogen for 1 h. The resulting mixture was stirred for 10 min at room temperature to which butadiene monoepoxide **29** (920 mg, 13.2 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h, concentrated *in vacuo* and purified by silica gel column chromatography using EtOAc/hexane (3:7) as eluent furnished 2.8 g (98%) yield of (*S*)-**30** as a crystalline white solid. mp 61-63 °C; [R_f= 0.21, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$-72.2 (*c* 2.02, CH_2Cl_2) [Lit.[7] -72.2 (*c* 2.02, CH_2Cl_2)]; IR (CH_2Cl_2) *v*: 3467, 1773, 1698, 1467, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.8 (m, 2H), 7.7 (m, 2H), 6.1 (ddd, *J* = 17.4, 10.56, 6.88 Hz, 1H), 5.27-5.30 (m, 2H), 4.9 (m, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 2.7 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.5, 134.2, 131.9, 131.7, 123.4, 118.8, 62.8, 55.9.



(*S*)-2-(1-Methoxybut-3-en-2-yl)isoindoline (31): To a solution of (*S*)-**30** (2.0 g, 9.20 mmol) in 40 mL DMF was successively added NaH (442 mg, 18.40 mmol) at 0 °C, stirred for ten minutes followed by addition of MeI (1.73 mL, 27.60 mmol) and then the reaction mixture was stirred at room temperature for 3 h.

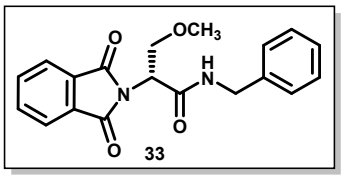
The reaction mixture was quenched by addition of ice cold water, extracted with diethyl ether, washed with brine and dried over anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* and purified by silica gel column chromatography using EtOAc/hexane (1:9) as eluent to furnish 1.83 g (86%) yield of (*S*)-**31** as a crystalline white solid. [R_f = 0.56, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$-75.1 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v*: 1773, 1708, 1468, and 1384 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.80 (m, 2H), 7.68 (m, 2H), 6.1 (ddd, *J* = 17.44, 10.56, 7.36 Hz, 1H), 5.25-5.34 (m, 2H), 5.0 (m, 1H), 4.0 (m, 1H), 3.6 (m, 1H), 3.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 168.0, 133.9, 132.1, 131.9, 123.2, 119.0, 71.3, 58.7, 52.8; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{13}NO_3Na$ [M+Na^+] 254.080; found 254.079.

(*R*)-2-(Isoindolin-2-yl)-3-methoxypropanoic acid (32): To a solution of compound (*S*)-**31** (1.5 g, 6.50 mmol) in dioxane-water (3:1, 40 mL) was added 2,6-lutidine (1.5 mL, 13.00 mmol), OsO_4 (0.1 M solution in toluene, 1.3 mL, 0.13 mmol) and $NaIO_4$ (2.78 g, 13 mmol). The reaction was stirred at 25 ^oC for 2 h. After completion of reaction, water (10 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give crude aldehyde which was used as such for the next step without further purification.



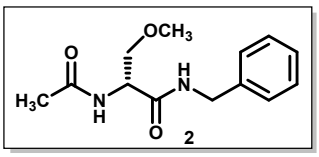
The above aldehyde was dissolved in DMF and oxone (2.0 g, 6.50 mmol) was added in one portion and stirred at room temperature for 12 h. The resulting solution was diluted with water, filtered through a celite pad, washed and extracted with diethyl ether (3 x 20 mL). The organic extract was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to obtain the crude product (*R*)-**32** which was used as such for the next step without further purification due to more polar nature of acid compound (*R*)-**32** (1.26 g, 78% yield determined by ^1H NMR). The analytical sample was obtained by preparative chromatography on silica gel (CH_2Cl_2/MeOH, 9:1 v/v) as yellow oil. $[\alpha]_D^{25}$ +66.5 (*c* 0.1, MeOH); IR (CH_2Cl_2) *v*: 2896, 1775, 1699, 1604 and 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 3.36 (s, 3H), 4.0 (m, 1H), 4.17 (t, *J* = 10.08 Hz, 1H), 5.17-5.19 (m, 1H), 7.7 (dd, 2H), 7.8 (dd, 2H), 8.05 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 58.6, 60.5, 70.1, 119.0, 123.3, 128.6, 131.9, 133.8, 168.1, 171.2; HRMS (ESI-TOF) m/z calcd for $C_{12}H_{11}NO_5Na$ [M+Na^+] 272.050; found 272.053.

(*R*)-*N*-Benzyl-2-(isoindolin-2-yl)-3-methoxypropanamide (33):



To a crude acid (*R*)-**32** (1.25 g, 5.00 mmol) in dry THF was added *N*-methylmorpholine (0.66 mL, 6.0 mmol) at -78 ^{o}C under an argon atmosphere. After 5 min, isobutyl chloroformate (0.78 mL, 6.0 mmol) was added and stirred for another 5 min. To this reaction mixture benzylamine (0.65 mL, 6.0 mmol) was added at -78 ^{o}C after which the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was filtered through a celite pad, washed with ethyl acetate, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude product was subjected to silica gel column chromatography (EtOAc/Hexane 4:6 v/v) to afford 1.48 g (88%) of (*R*)-**33** as a crystalline solid. [R_f = 0.26, EtOAc/hexane 4:6 v/v]; $[\alpha]_D^{25}$ +81.8 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 1718, 1685, 1535, and 1387 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.8 (m, 2H), 7.7 (m, 2H), 7.27-7.3 (m, 5H), 7.2 (bs, 1H), 5.0 (m, 1H), 4.4 (m, 2H), 4.3 (t, *J* = 9.64 Hz, 1H), 3.7 (m, 1H), 3.4 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.9, 167.3, 137.9, 134.1, 131.8, 128.6, 128.4, 127.4, 127.4, 127.3, 123.5, 70.1, 58.9, 51.7, 43.5; HRMS (ESI-TOF) m/z calcd for $C_{19}H_{18}N_2O_4Na$ [M+Na$^+$] 361.120; found 361.116.

(*R*)-Lacosamide (2): To a solution of compound (*R*)-**33** (1.4 g, 4.10 mmol) in 20 mL of isopropyl alcohol was added hydrazine monohydrate (0.22 mL, 4.50 mmol) at 0 ^{o}C under nitrogen atmosphere. The reaction was stirred at 25 ^{o}C for 2 h. The resulting solution was filtered, washed with diethyl ether, brine, dried over magnesium sulphate and concentrated *in vacuo* to furnish the crude compound (R_f = 0.36, CH_2Cl_2/MeOH 9:1 v/v). The resulting crude was used as such for the next step without further purification.

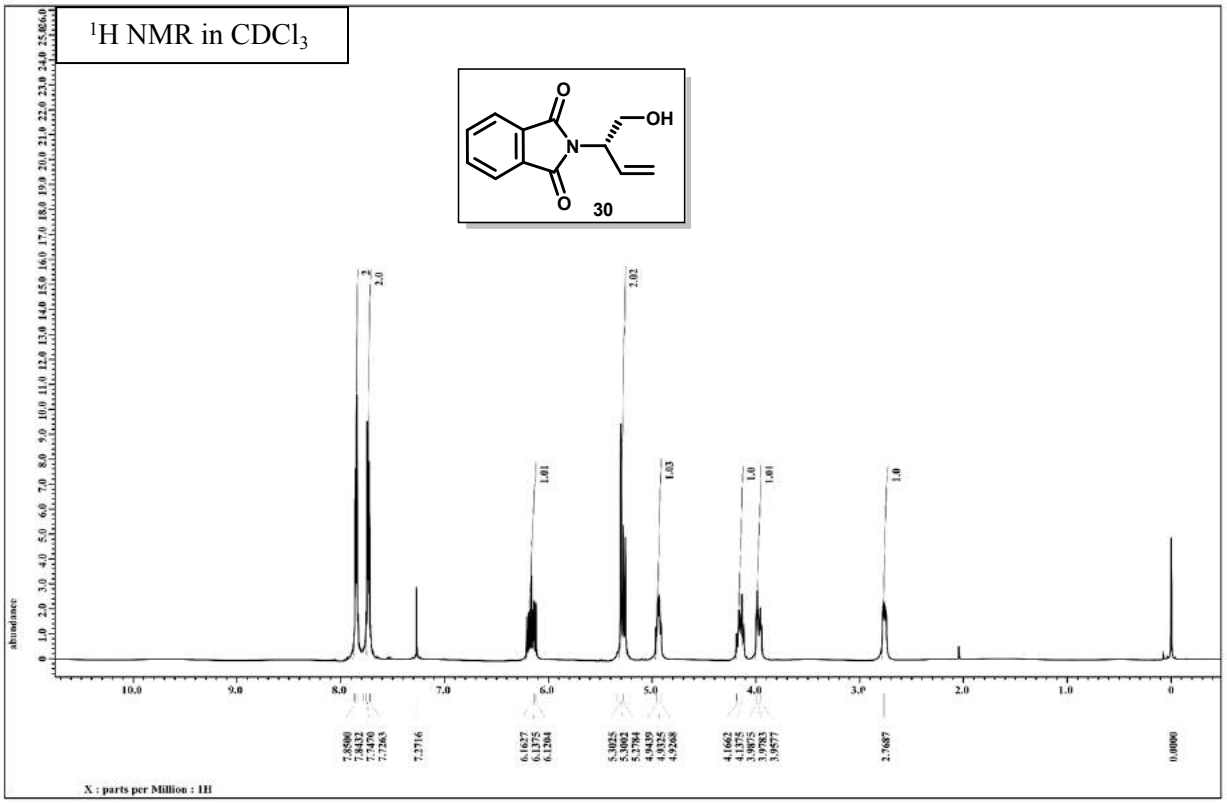


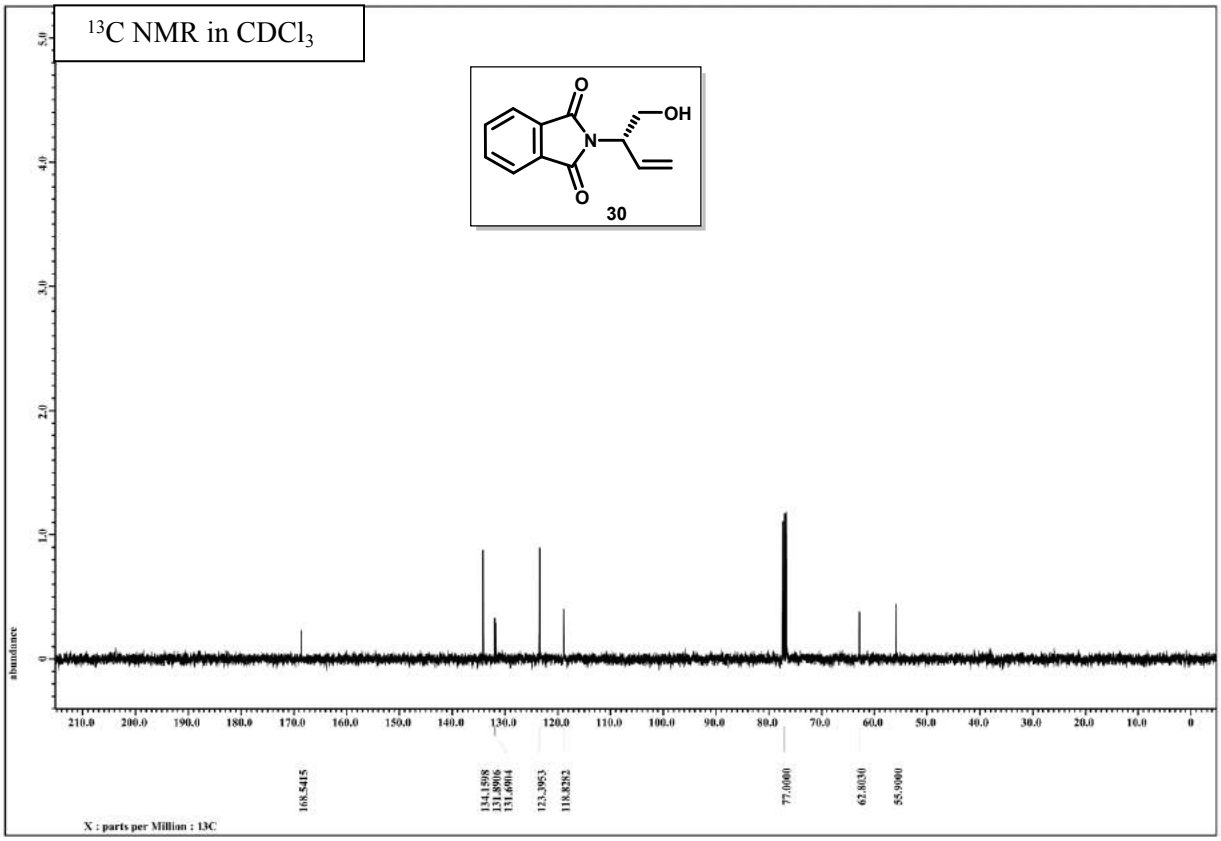
The residue was then dissolved in dry toluene followed by addition of Na_2CO_3 (1.3 g, 12.30 mmol). The reaction mixture was cooled to 0 ^{o}C after which acetyl chloride (0.33 mL, 4.5 mmol) was slowly added and the solution stirred at 5 ^{o}C for 1 h. After completion of the reaction, the solid was filtered through a celite pad and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 19:1 v/v) to afford 935 mg (91%) yield of (*R*)-lacosamide **2** as white solid. [R_f = 0.47, CH_2Cl_2/MeOH 9:1 v/v]; mp 143-144 °C [Lit. 140-141 °C,[5g] 142-143 °C[5h]]; $[\alpha]_D^{25}$ +16.1 (*c* 1, MeOH) [Lit. +16.2 (*c* 1, MeOH),[5g] +16.1 (*c* 1.2, MeOH)[5h]]; IR (CH_2Cl_2) *v*: 3054, 2928, 1650, 1529, 1372, 1264, and 1118 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24-7.68 (m, 5H), 6.86 (s, 1H), 6.54 (s, 1H), 4.5 (m,

1H), 4.4 (m, 2H), 3.80 (dd, J = 9.2, 4.1 Hz, 1H), 3.4 (m, 1H), 3.37 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 169.9, 137.8, 128.7, 127.5, 127.4, 71.6, 59.0, 52.3, 43.5, 23.2. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{18}N_2O_3Na$ [M+Na^+] 273.1215; found 273.1212.

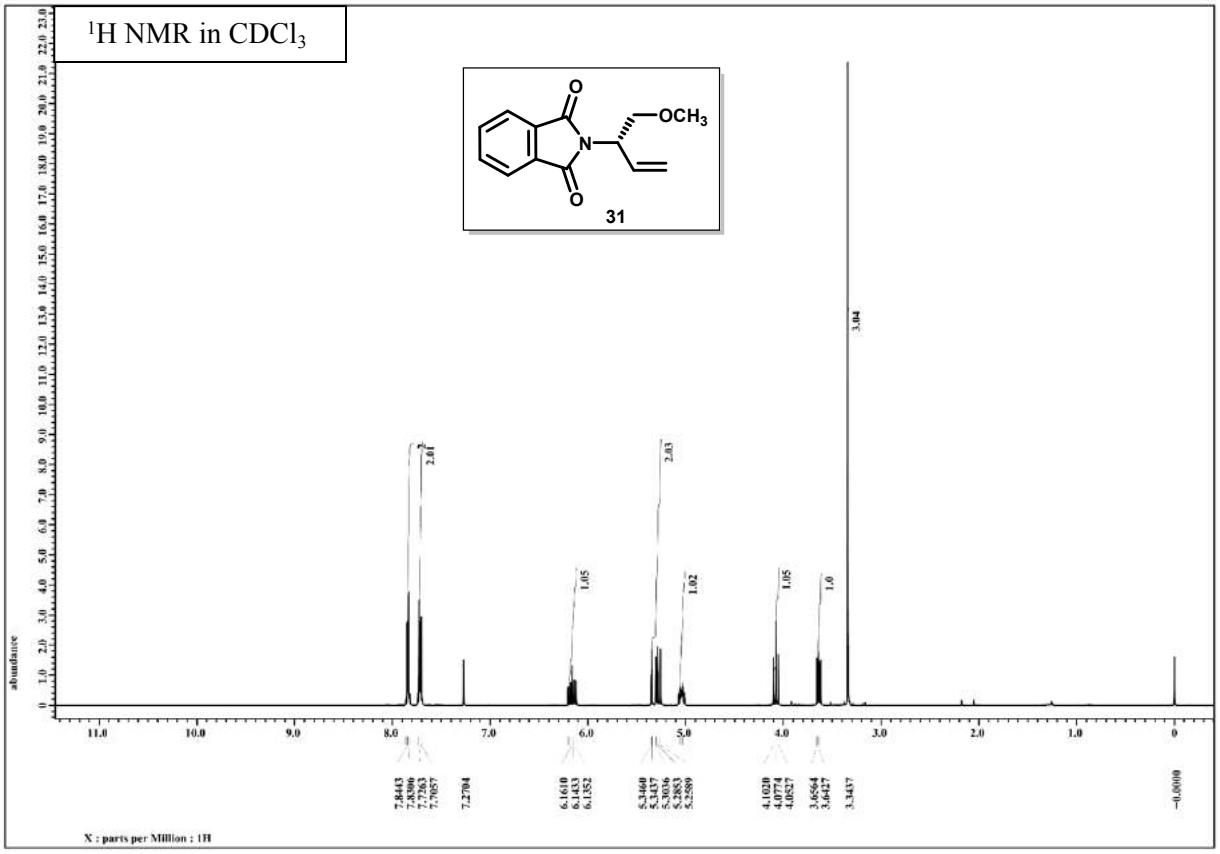
2.1.7 Spectra:

1. ^{1}H and ^{13}C NMR spectra of **30**
2. ^{1}H and ^{13}C NMR spectra of **31**
3. ^{1}H and ^{13}C NMR spectra of **32**
4. ^{1}H and ^{13}C NMR spectra of **33**
5. ^{1}H and ^{13}C NMR spectra of **2**

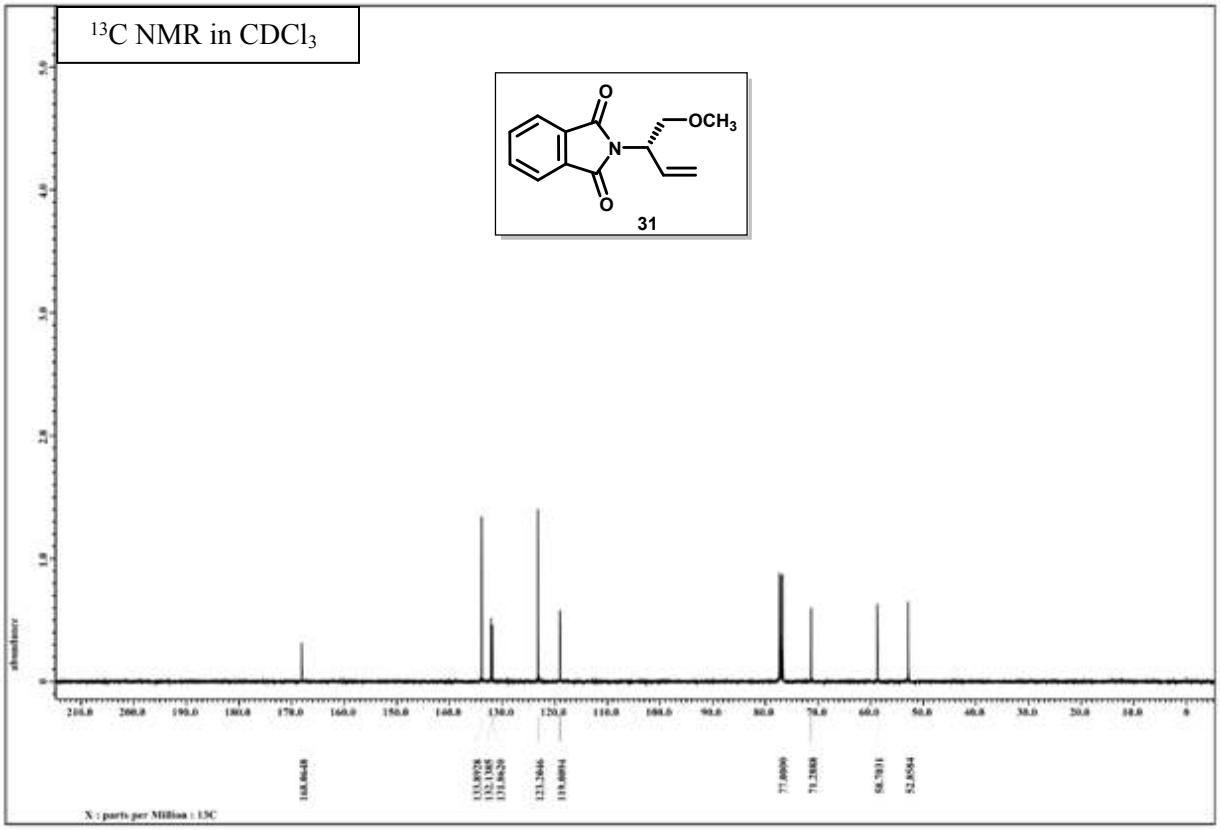

^{1}H NMR in $CDCl_3$
OH
30
abundance
X : parts per Million : 1H

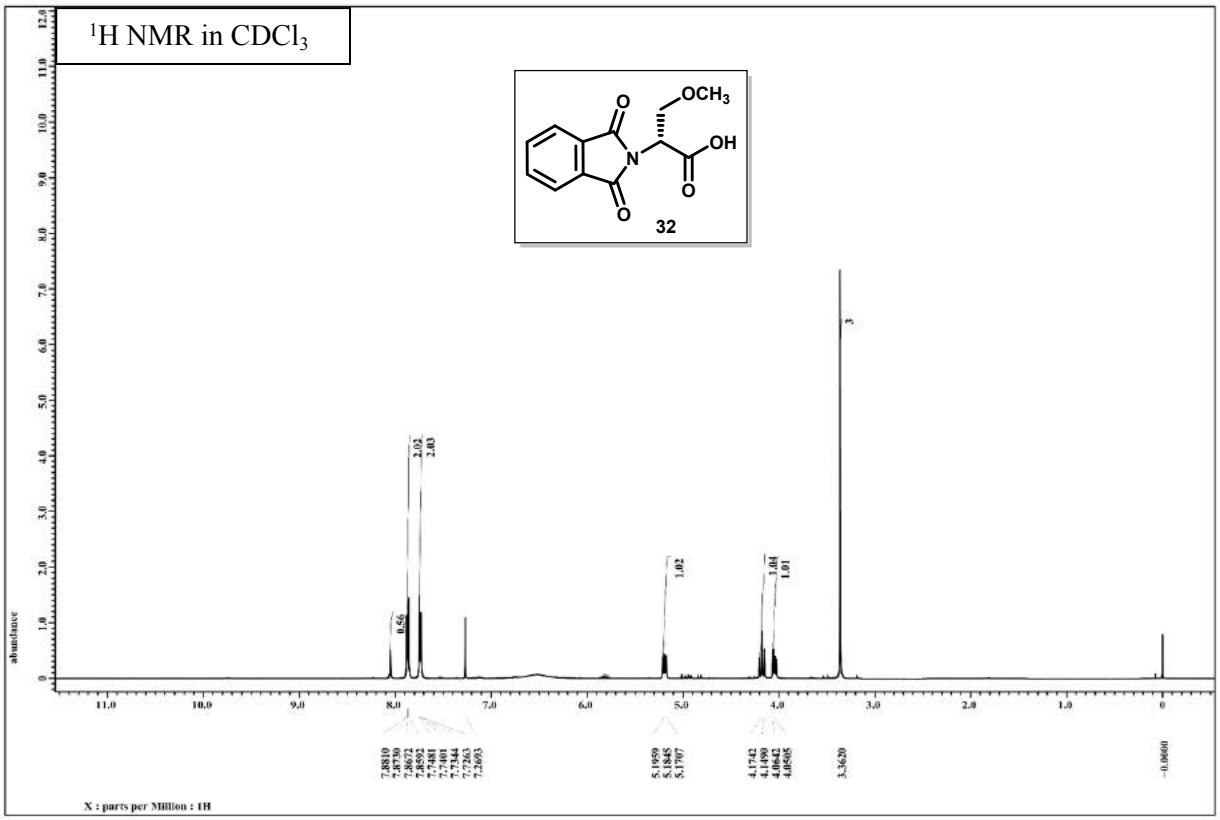

^{13}C NMR in $CDCl_3$
OH
30
abundance
X : parts per Million : 13C

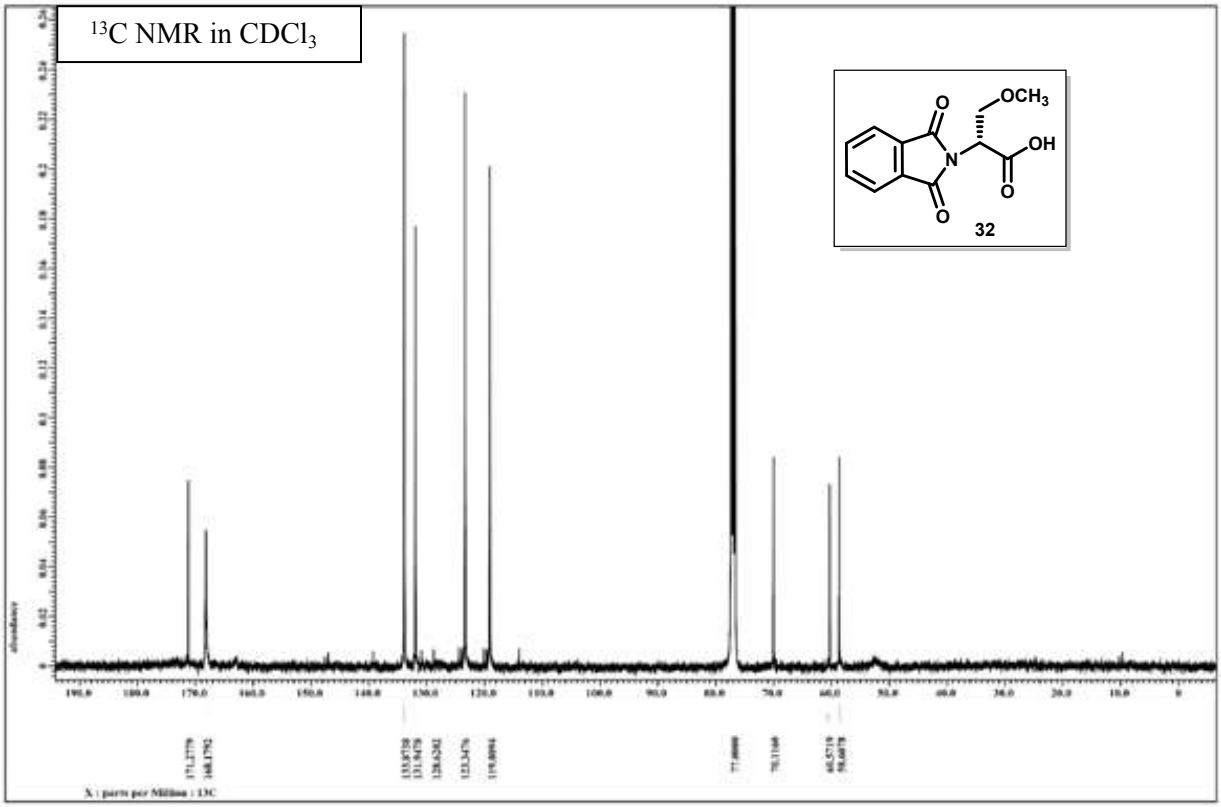
^{1}H NMR in $CDCl_3$

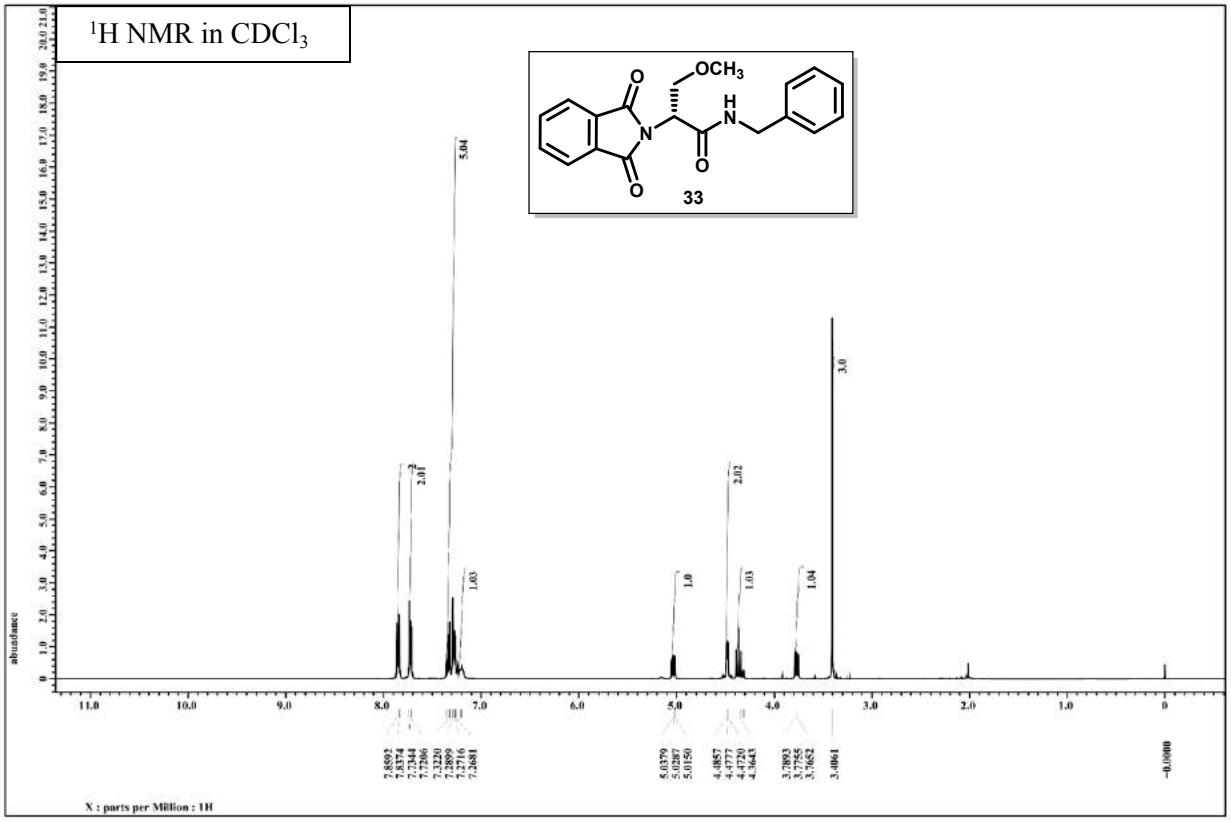


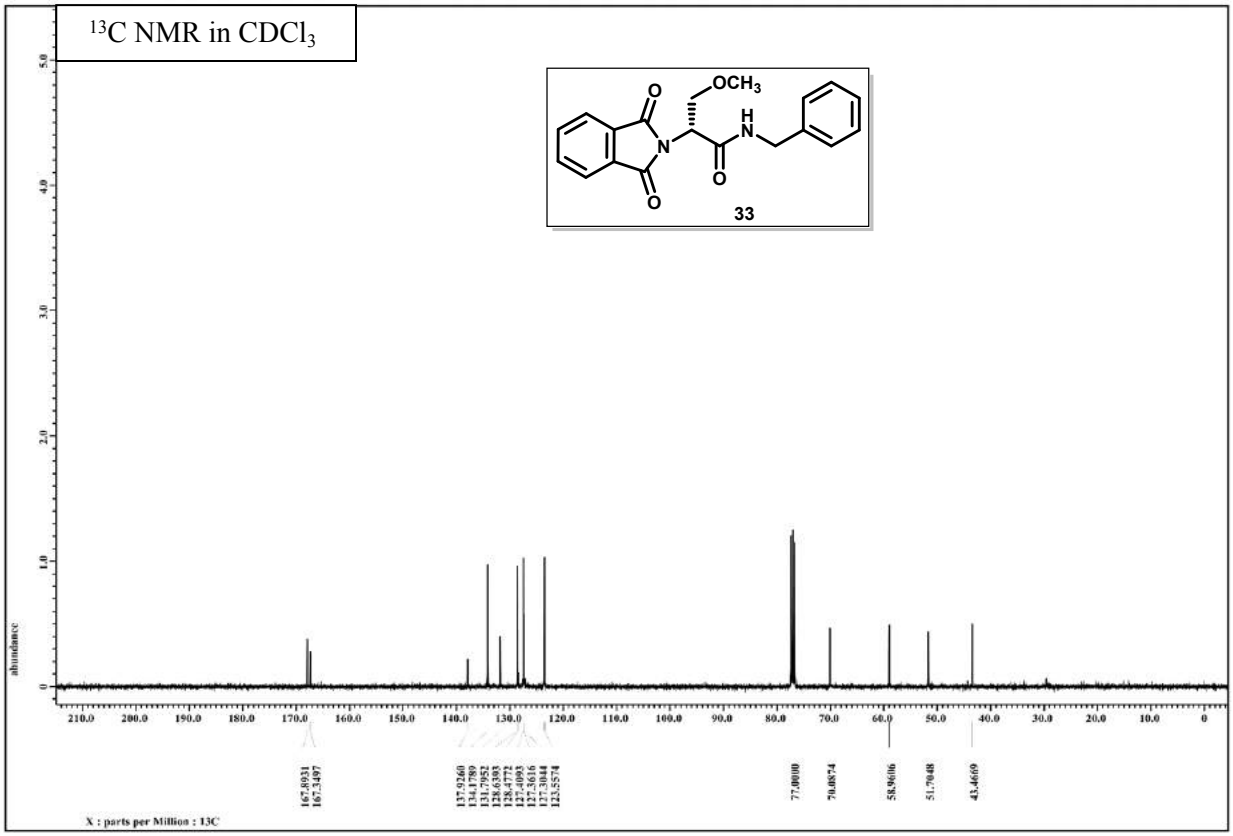
^{13}C NMR in $CDCl_3$

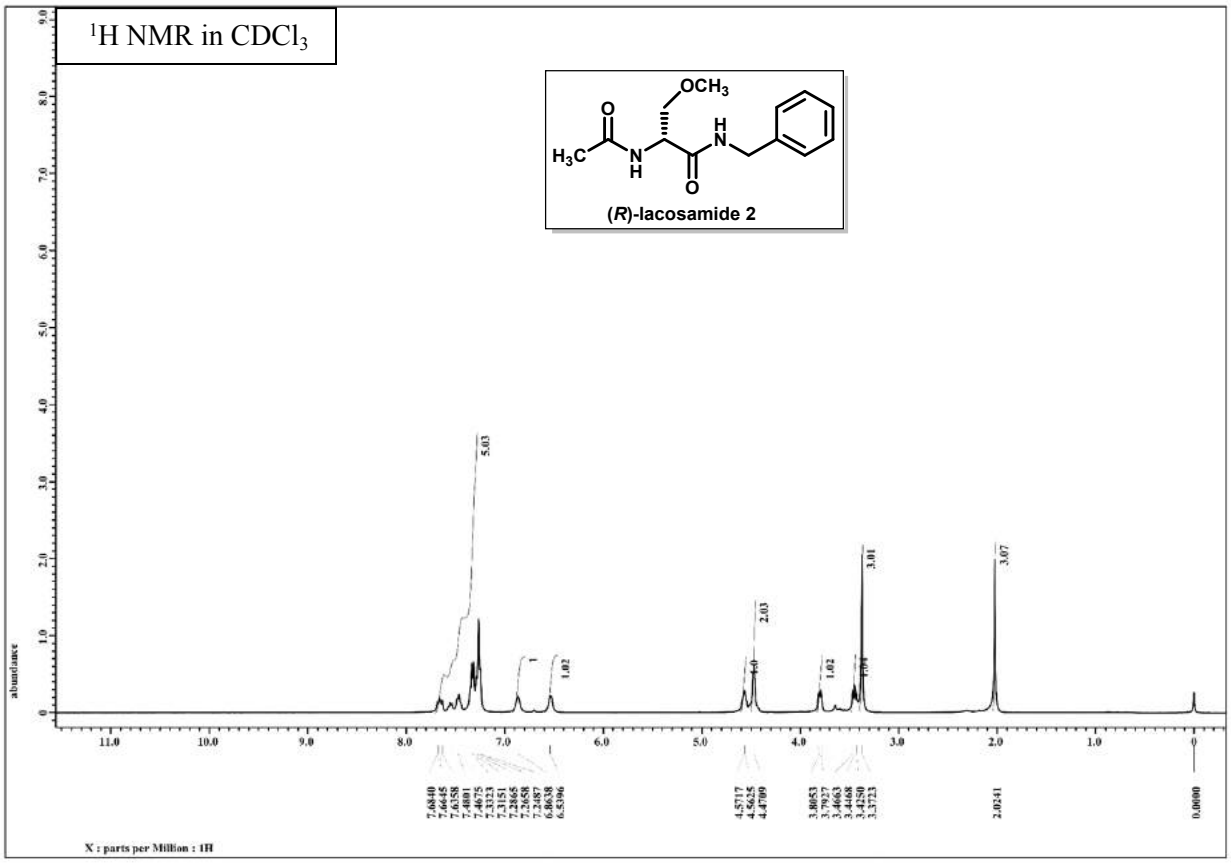


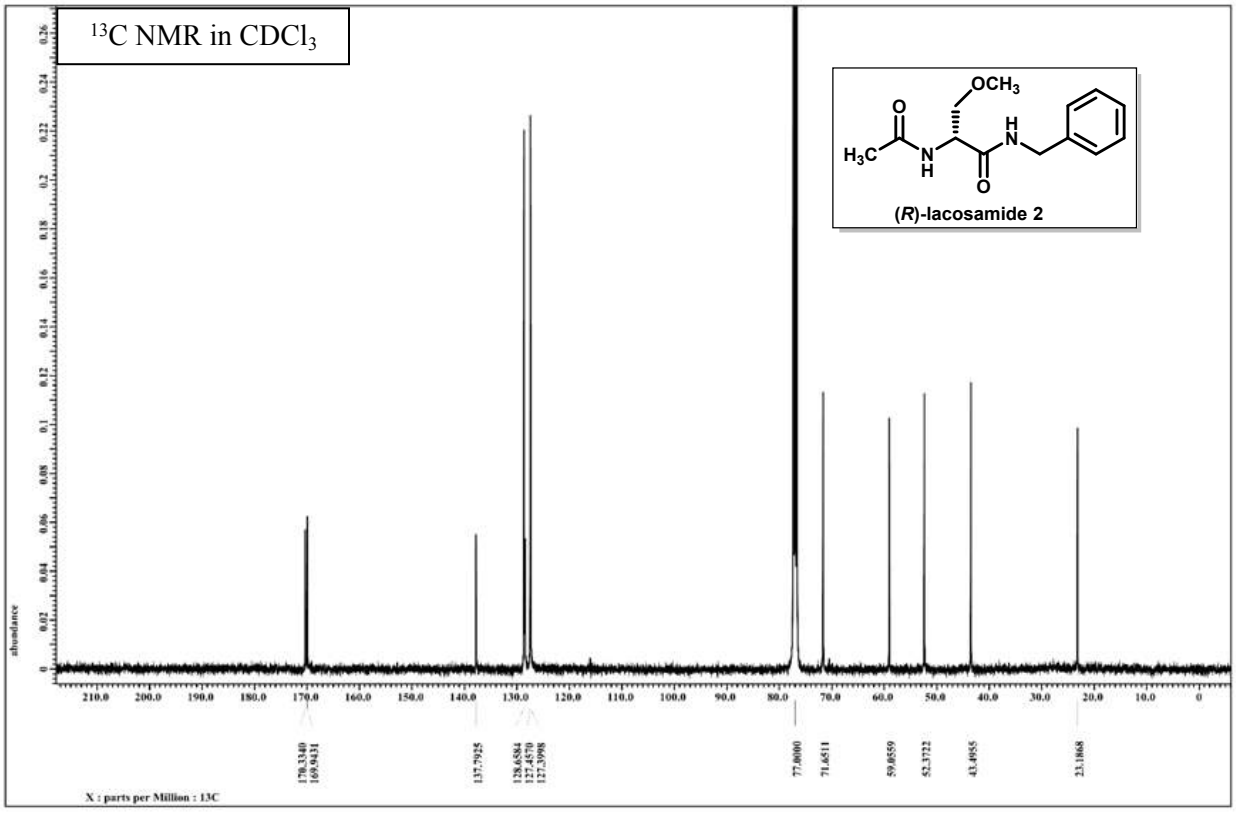

^{1}H NMR in $CDCl_3$
OCH3
OH
O
N
O
O
O
32
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OCH3
OH
O
N
O
O
32
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OCH3
H
N
O
33
5.04
2.01
2.02
1.03
1.0
1.04
3.0
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OCH3
H
N
O
33
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
(*R*)-lacosamide 2
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
(*R*)-lacosamide 2
X : parts per Million : 13C

2.2 Section B

An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine

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2.2.1 Introduction:

Quinoline and tetrahydroquinolines alkaloids are found abundantly in nature and most of them exhibits interesting biological activity.[11] Enantiomerically pure 2-alkyl substituted tetrahydroquinolines alkaloids **34** from which angustureine **35**, galipeine **36**, cuspareine **37** and galipinine **38** were first extracted from the bark of *Galipea Officinalis* Hancock shrub tree found in the mountains of Venezuela[12] (Figure 3). These alkaloids exhibits anti-malarial, anti-tuberculous, cytotoxic, and antiplasmodial activities.[13] *Galipea* species have also been used in folk medicine for the treatment of dysentery, dyspepsia, chronic diarrhea, spinal motor nerve problems and fevers.[14] These alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities.

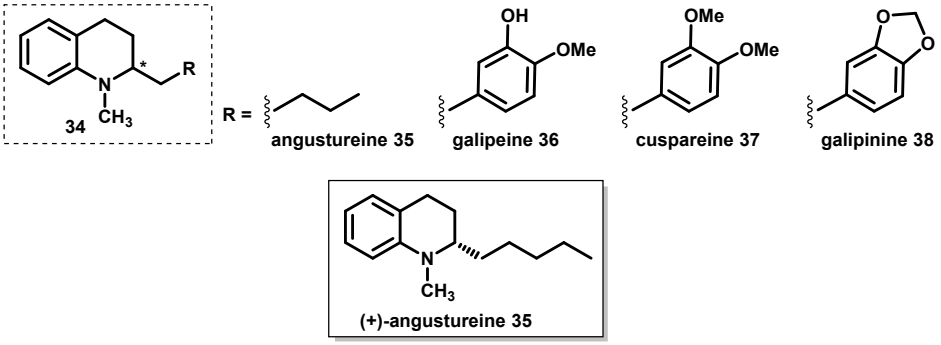


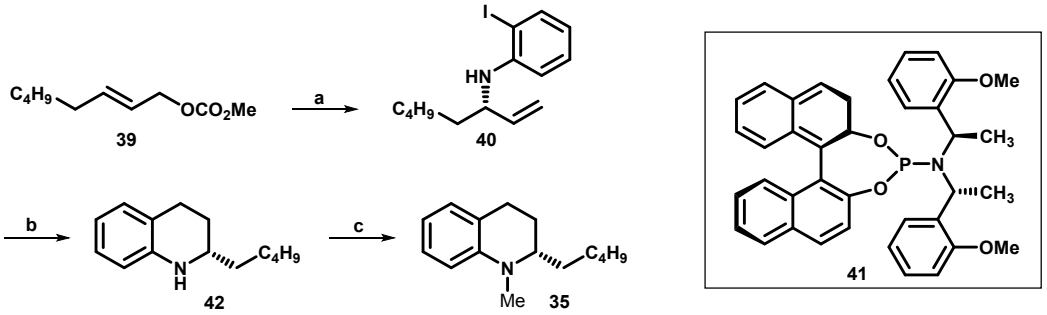
Figure 3. Some naturally occurring 2-alkyl substituted tetrahydroquinoline alkaloids.

2.2.2 Review of Literature:

Various methods for the synthesis of (+)-angustureine **35** and others **36-38** have been documented in the literature.[15] Some of the recent syntheses of (+)-angustureine **35** are described below.

Helmchen, G. *et al*. (2011)[15r]

G. Helmchen and co-workers described the asymmetric synthesis of (+)-angustureine **35** using a highly regio- and enantioselective intermolecular iridium-catalyzed allylic amination, hydroboration and intramolecular Suzuki-Miyaura cross coupling reactions as key steps (Scheme 7). The synthesis of (+)-angustureine **35** commenced with methyl cinnamyl carbonate which on allylic amination with commercially available *o*-iodoaniline using a complex of {[Ir(COD)Cl]$_2$/**41** (4 mol%) and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene, 8 mol%) furnished the allylic amine derivative **40** in 53% yield. The amine derivative **40** on hydroboration using 9-BBN followed by palladium catalyzed Suzuki-Miyaura cross-coupling reaction afforded tetrahydroquinoline derivative **42** in 81% yield which on *N*-methylation using paraformaldehyde/Na(CN)BH$_3$ furnished the target (+)-angustureine **35** in 94% yield.

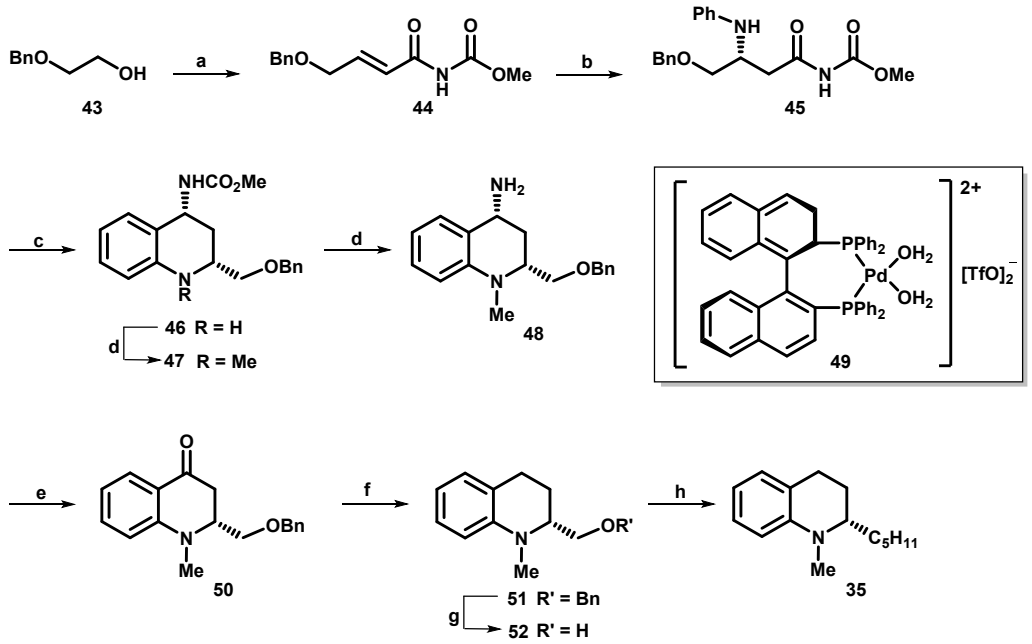


Scheme 7. *Reagents and conditions*: (a) *o*-iodoaniline, [Ir(COD)Cl]$_2$/**41**, TBD, THF, 50 ^{o}C, 4 h, 53%; (b) 9-BBN, THF, Pd(dppf)Cl$_2$, AsPh$_3$, Cs$_2$CO$_3$, DMF/H$_2$O (15:1), 80 ^{o}C, 20 h, 81%; (c) (CH$_2$O)$_n$/AcOH, Na(CN)BH$_3$, CH$_3$CN, rt, 17 h, 94%.

Hii, K. K. *et al*. (2012)[15t]

K. K. Hii and co-workers reported the multisteps synthesis of (*S*)-angustureine **35** from monoprotected ethylene glycol **43** using a Pd-catalyzed aza-Michael reaction to induce chirality as key step (Scheme 8). Oxidation of **43** under Swern conditions and subsequent Horner Wadsworth Emmons olefination reaction using phosphonium ylide afforded α,β-conjugated amide **44** in 53% yield. The amide derivative **44** on Michael addition with aniline using a chiral palladium catalyst **49** furnished derivative **45** in good yield. The reductive cyclization of **45** to afford tetrahydroquinoline derivative **46** and subsequent *N*-methylation followed by deprotection of *N*-ester furnished compound **48**, which on transamination using Rapoport's reagent afforded **50**. The derivative **50** on reduction using LiAlH$_4$ and the *O*-benzyl deprotection using nickel

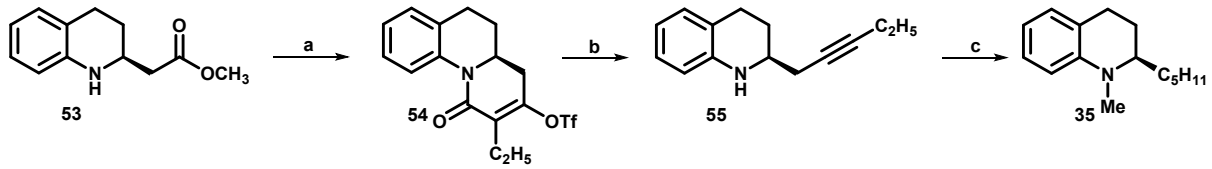
sponge furnished derivative **52**. The alcohol derivative **52** on oxidation and subsequent Wittig olefination followed by catalytic hydrogenation furnished the alkaloid (*S*)-angustureine **35** in 44% overall yield.



Scheme 8. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 ^oC; ii) PPh_3=CHCONHCOOBn, THF, 53%; (b) **49**, toluene, 61%; (c) i) $MgCl_2$, $NaBH_4$, EtOH:THF, -10 °C, 87%; ii) HCHO, $NaCNBH_3$, AcOH:CH_3CN, 0 °C, 88%; (d) TMSI, CH_3CN, 78%; (e) i) 4-formyl-1-methylpyridinium benzenesulfonate, DBU, DCM:DMF, rt; ii) oxalic acid, 75%; (f) $LiAlH_4$, $AlCl_3$, THF, 87%; (g) RANEY® Ni, H_2, EtOH:THF, reflux, 71%. (h) i) PPh_3=CHC_3H_7, THF; ii) H_2, Pd/C.

Dudley, G. B. *et al*. (2013)[15u]

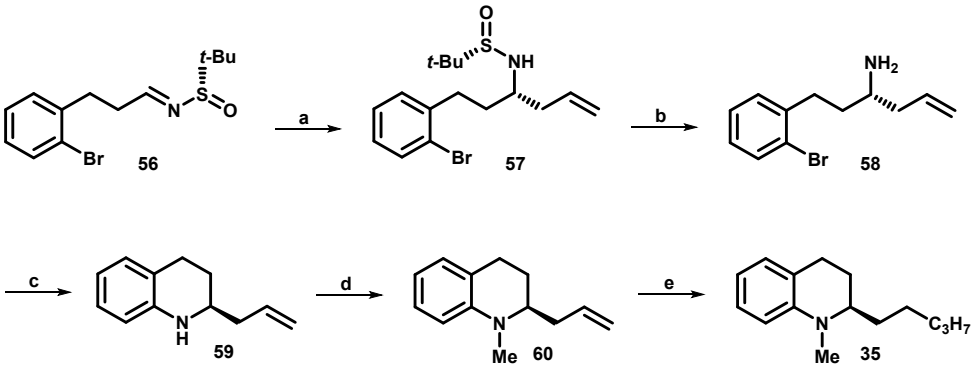
G. B. Dudley and co-workers disclosed the enantioselective synthesis of (-)-angustureine **35** employed an annulations and domino fragmentation sequence started from (*S*)-*β*-amino ester **53** synthesized by enzymatic kinetic resolution (Scheme 9). The ester **53** on three step sequence *i.e*. annulation, acylation of amine followed by Reformatsky type cyclocondensation and enol triflation afforded the conjugated amide derivative **54** in 72% yield. The derivative **54** on base treatment furnished amine derivative **55** which on hydrogenation using Pd/C in the atmosphere of H_2 followed by *N*-methylation furnished the final target compound (-)-angustureine **35** in 96% yield.



Scheme 9. *Reagents and conditions*: (a) (i) $BrCOCHBrC_2H_5$, DMAP, CH_2Cl_2, 60 °C; (ii) *t*-BuMgCl, THF, 60 °C, 2 h; (iii) Tf_2O, Et_3N, CH_2Cl_2, -78 °C, 1 h, 72%; (b) MeLi, $PhCH_3$, rt, 30 min, 67%; (c) (i) H_2, Pd/C, CH_2Cl_2, rt, 3 h; (ii) CH_3I, K_2CO_3, acetone, rt, overnight, 96%.

Yus, M. *et al*. (2014)[15v]

M. Yus and co-workers described the asymmetric synthesis of (*R*)-angustureine **35** employed diastereoselective addition of an allylic indium intermediate to the chiral sulfinyl imine **56** and an intramolecular *N*-arylation using Ullmann type reaction conditions as key steps (Scheme 10). The allylation of imines **56** with allyl bromide in the presence of indium metal produced the homoallylamine derivatives **57** in 81% yield. Removal of the *tert*-butylsulfinyl unit in homoallylamine derivatives **57** under acidic conditions afforded amine derivative **58** which on palladium catalyzed reaction furnished tetrahydroquinoline derivative **59** in 100% yield. Tetrahydroquinoline derivative **59** was converted to *N*-methyltetrahydroquinoline **60** using paraformaldehyde and $NaBH_3CN$ which on cross-metathesis with (*Z*)-hex-3-ene and *in situ* hydrogenation of the resulting olefin furnished the target compound (*R*)-angustureine **35** in 54% yield.



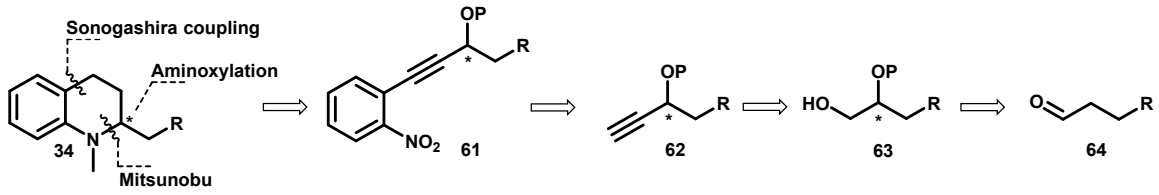
Scheme 10. *Reagents and conditions*: (a) In, THF, 60 °C, 6 h, 81%; (b) HCl (6M), THF, 0 °C to 23 °C, 1 h, 100%; (c) $Pd(OAc)_2$, PPh_3, $CsCO_3$, PhMe, 110 °C, 21 h, 100%; (d) $(HCHO)_n$, $NaBH_3CN$, AcOH, MeCN, 23 °C, 12 h, 95%; (e) (i) $CH_3CH_2CH{=}CHCH_2CH_3$, Hoveyda-Grubbs cat., CH_2Cl_2, 40 °C, 2h; (ii) H_2, Pd/C, MeOH, 23 °C, 12 h, 54%.

2.2.3 Present work:

Various methods for the synthesis of (+)-angustureine **35** and others **36-38** have been documented in the literature.[15] These alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities. In continuation of our research program aimed towards syntheses of bioactive compounds we became interested in developing a general and highly efficient synthetic approach for enantiopure 2-alkylsubstituted tetrahydroquinolines **34** and its application to the total synthesis of (+)-angustureine **35** employing proline catalyzed asymmetric aminoxylation, Corey-Fuchs protocol, palladium catalyzed Sonogashira coupling, and Mitsunobu reaction as key steps.

2.2.4 Results and Discussion:

Our retrosynthetic approach for the synthesis of 2-alkyl substituted tetrahydroquinolines **34** and (+)-angustureine **35** is outlined in Scheme 11. We envisioned that the aryl nitro-alkyne derivative **61** from which 2-alkyl substituted tetrahydro-quinolines **34** and (+)-angustureine **35** could be synthesized *via* hydrogenation, Mitsunobu intramolecular ring closer in S_N2 fashion followed by alkylation. The aryl nitro-alkyne derivative **61** could be obtained from the monoprotected alkyne derivative **62** through palladium catalyzed Sonogashira coupling reaction with suitable aromatic nitro-halides. The alkyne derivative **62** in turn could be obtained by means of Corey-Fuchs protocol from the aldehyde synthesized from oxidation of monoprotected alcohol **63**.

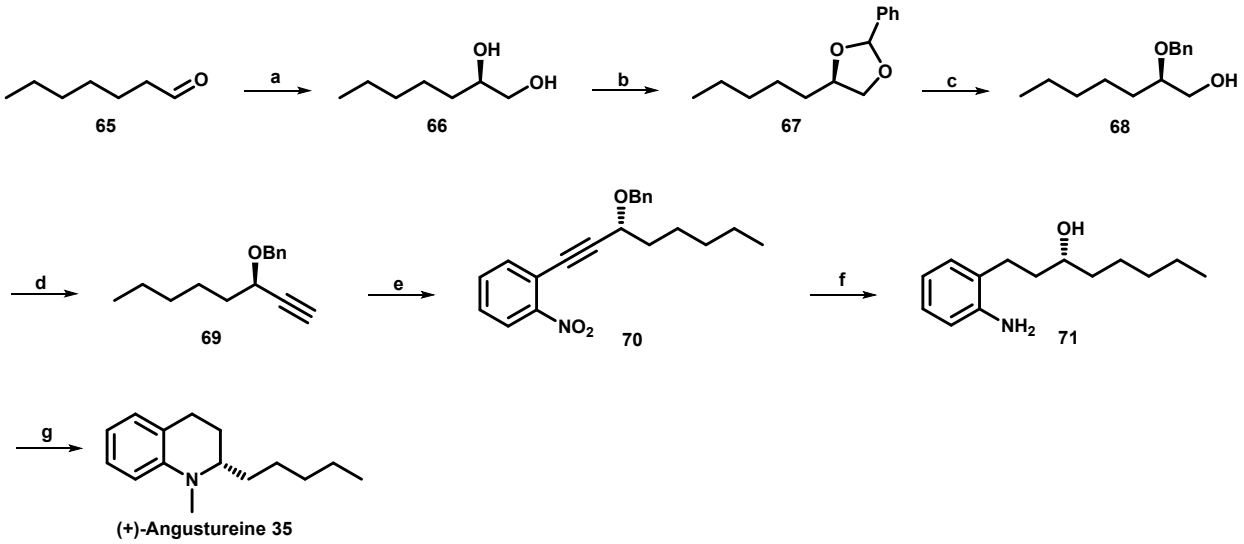


Scheme 11. Retrosynthetic approach to 2-alkyl substituted tetrahydroquinolines

Enantiomerically pure monoprotected alcohol **63** could be obtained from the commercially available aldehydes **64** *via* proline catalyzed aminoxylation followed by standard organic transformation. The (*S*)- and (*R*)- configuration of the 2-alkyl substituted tetrahydroquinolines **34** and (+)-angustureine **35** could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step.

The synthesis of (+)-angustureine **35** started from the commercially available *n*-heptanal **65**, which on treatment with nitrosobenzene in the presence of catalytic amount of L-proline (10 mol

%) in DMSO at room temperature afforded α-aminoxylated aldehyde (Scheme 12) which on subsequent reduction with $NaBH_4/CH_3OH$ followed by aniline cleavage with $CuSO_4.5H_2O$ afforded the required diol **66** in 71% yield over three steps with >99% *ee*.[16] $\{[\alpha]_D^{25}$-14.4 (*c* 1, CH_3OH). The IR spectrum of **66** showed hydroxyl absorption at 3359 cm^{-1}.



Scheme 12. *Reagents and conditions*: (a) (i) Nitrosobenzene, L-proline, DMSO, rt, 12 h; (ii) $NaBH_4$, CH_3OH, 0 ^oC, 15 min; (iii) $CuSO_4.5H_2O$, CH_3OH, 0 ^oC to rt, 12 h, 71% (one pot, three steps); (b) $PhCH(OMe)_2$, C_6H_6, PPTS, reflux, 1 h, 89%; (c) DIBAL-H, CH_2Cl_2, -40 ^oC to rt, 2 h, 93%; (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h; (ii) CBr_4, PPh_3, CH_2Cl_2, 0 ^oC, 30 min; (iii) *n*-BuLi, THF, -78^oC to rt, 3 h, 86% (over three steps); (e) 1-iodo-2-nitrobenzene, 2 mol% $Pd(PPh_3)_2Cl_2$, 1 mol% CuI, Et_3N, DMF, reflux, 3 h, 95%; (f) H_2, Pd/C (10%), EtOAc, rt, 24 h, 96%; (g) (i) PPh_3, DEAD, CH_2Cl_2, rt, 12 h; (ii) HCHO, $Na(CN)BH_3$, AcOH, CH_3CN, rt, 10 h, 88% (over two steps).

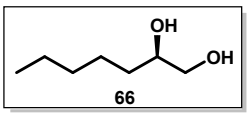
With enantiomerically pure diol **66** in hand, we then subjected it to protection with benzaldehyde dimethyl acetal in presence of catalytic amount of PPTS, which furnished 1,2-benzylidene acetal **67** in 89% yield.[17] Compound **67** showed acetal proton at δ 5.92 (singlet) and aromatic protons appeared at δ 7.35-7.48 (multiplet, five protons) in the ^1H NMR spectrum. Regioselective reductive opening of 1,2-benzylidene acetal **67** with DIBAL-H afforded monobenzyl protected alcohol **68** in 93% yield. Oxidation of alcohol **68** under Swern conditions[18] and subsequent treatment with CBr_4/TPP followed by treatment with *n*-BuLi under Corey-Fuchs protocol[19] afforded the terminal alkyne **69** in 86% yield. The IR spectrum of **69** showed alkyne stretching at 3302 cm^{-1}. The terminal alkyne **69** under Sonogashira coupling conditions[20] with commercially

available 1-iodo-2-nitrobenzene in the presence of Et_3N as a base afforded the 2-nitrobenzene-alkyne derivative **70** in excellent yield (95%). Concomitant reduction of the triple bond, nitro group to amine and deprotection of benzyl group of 2-nitrobenzene-alkyne derivative **70** was achieved in one pot *via* hydrogenation under 1 atm pressure in presence of catalytic amount of Pd/C (10%) which furnished the key intermediate amino alcohol **71** in 96% yield. The IR spectrum of **71** showed hydroxyl absorption at 2935 cm^{-1}. Cyclization of amino alcohol **71** under Mitsunobu conditions[21] (DEAD, PPh_3, CH_2Cl_2, rt) afforded the tetrahydroquinoline (norangustureine), and subsequent methylation using reductive amination with formaldehyde in presence of $Na(CN)BH_3$ afforded the target compound (+)-angustureine **35** in 88% yield. {$[\alpha]_D^{25}$ +7.6 (*c* 0.4, $CHCl_3$) [Lit. +7.5 (*c* 0.4, $CHCl_3$, 94% ee),[15t] -7.16 (*c* 1, $CHCl_3$, natural product for (-)-angustureine)[15l]]}. The physical and spectroscopic data were in full agreement with those documented in literature.[15]

2.2.5 Conclusions:

In conclusion, a simple, flexible and highly efficient synthetic approach for 2-alkyl substituted tetrahydroquinolines **34** and its application to the total synthesis of (+)-angustureine **35** has been developed. The overall yield for alkaloid (+)-angustureine **35** was 41% in seven steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps and cost effective strategy. The synthetic strategy described has significant potential for stereochemical variation and further extension to 2-alkyl substituted tetrahydroquinolines derived natural products with interesting pharmacological activities.

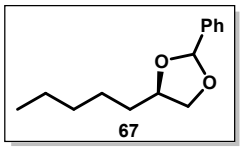
2.2.6 Experimental Section:



(*R*)-Heptane-1,2-diol (66): To a DMSO solution (60 mL) of L-proline (168 mg, 1.46 mmol) were added *n*-heptanal **65** (5.0 g, 43.86 mmol) and nitrosobenzene (1.56 g, 14.60 mmol) successively at room temperature. After stirring the reaction mixture for 12 h, MeOH (20 mL) and $NaBH_4$ (835 mg, 22.00 mmol) were added and the reaction mixture was stirred for 15 min at 0 ^oC. The reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate (3x10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue thus obtained above was dissolved in MeOH (15 mL) and subjected to treatment with $CuSO_4.5H_2O$ (913 mg, 3.65 mmol) at 0 ^oC and warm to room temperature over 12 h.

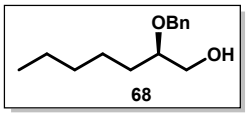
After completion of reaction as monitored by TLC, it was quenched with aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes 1:1 v/v) to afford the desired diol **66** (1.35 g, 71%). {$[\alpha]_D^{25}$ -14.4 (*c* 1, CH_3OH) [Lit.[22] -14.1 (*c* 1, CH_3OH)]}; IR (CH_2Cl_2) *v*; 3359, 2941, 2853, 1462, 1312, 1062, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.6 (m, 2H), 3.4 (m, 1H), 2.67 (bs, 2H), 1.29-1.43 (m, 8H), 0.9 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 72.3, 66.8, 33.1, 31.8, 25.2, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_7H_{16}O_2Na$ [M+Na^+] 155.110; found 155.104.

(4*R*)-4-Pentyl-2-phenyl-1,3-dioxolane (67): To a benzene solution (50 mL) of diol **66** (1.35 g, 10.4 mmol) was added benzaldehydedimethylacetal (1.58 g, 10.4 mmol) and catalytic amount of PPTS (260 mg, 1.04 mmol).

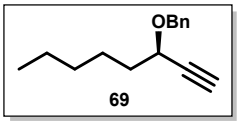


The mixture was then heated to reflux with a Dean-Stark apparatus. After 1 h, triethylamine (1 mL) was added to the mixture, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (EtOAc/hexanes 1:99 v/v) to afford the 1,2-benzylidene acetal **67** (2.0 g, 89%). $[\alpha]_D^{25}$ -11.5 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*; 1478, 1366, 1260, 1120, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.48 (m, 5H), 5.92 (s, 1H), 4.2 (m, 2H), 3.59-3.67 (m, 1H), 1.31-1.75 (m, 8H), 0.9 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4, 129.0, 128.3, 126.4, 103.0, 70.8, 33.3, 31.8, 25.4, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{21}O_2$ [M+H^+] 221.158; found 221.153.

(*R*)-2-(Benzyloxy)heptan-1-ol (68): To a solution of 1,2-benzylidene acetal **67** (2.0 g, 9.2 mmol) in dry CH_2Cl_2 (30 mL) at -40 °C was added dropwise DIBAL-H (6.3 mL, 11.1 mmol, 1.75 M in toluene) through a syringe. The reaction mixture was allowed to warm at room temperature over a period of 2 h, then re-cooled to 0 °C and treated with saturated aqueous 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 (3:7 v/v) as eluent furnished monobenzyl protected alcohol **68** (1.9 g, 93%) as a pale yellow oil. $[\alpha]_D^{25}$ -44.7 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*; 2957, 2902, 2820, 1609, 1505, 772 cm^{-1}; ^1H NMR ($CDCl_3$,



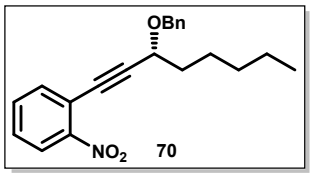
400 MHz) δ: 7.33-7.36 (m, 5H), 4.56 (s, 2H), 3.8 (m, 1H), 3.5 (m, 1H), 3.3 (m, 1H), 2.4 (s, 1H), 1.28-1.43 (m, 8H), 0.9 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.9, 128.4, 127.8, 127.7, 74.6, 73.3, 70.4, 33.0, 31.8, 25.2, 22.5, 14.0. HRMS (ESI) m/z calcd for $C_{14}H_{22}O_2Na$ [M+Na^+] 245.150; found 245.151.



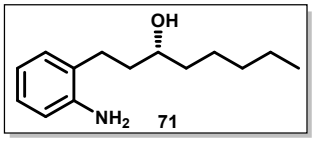
(*R*)-((Oct-1-yn-3-yloxyl)methyl)benzene (69): To a solution of oxalyl chloride (1.63 g, 1.1 mL, 12.84 mmol) in dry CH_2Cl_2 (30 mL) at -78 °C was added dropwise DMSO (2.07 g, 1.9 mL, 26.53 mmol) in CH_2Cl_2 (10 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of monobenzyl protected alcohol **68** (1.9 g, 8.56 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -60 °C and then Et_3N (3.80 g, 5.20 mL, 37.7 mmol) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (50 mL) and the organic layer 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 a solution of CBr_4 (5.68 g, 17.12 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added PPh_3 (8.97 g, 34.24 mmol) and stirred for 15 min at 0 °C. To this reaction mixture, a solution of crude aldehyde obtained above in dry CH_2Cl_2 (20 mL) was added dropwise and stirred for 15 min at 0 °C. The reaction mixture was quenched with water and aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude dibromo olefin, which was used as such for the next step without further purification. To a solution of above crude dibromo olefin in dry THF (30 mL) at -78 °C was added *n*-BuLi (6.85 mL, 17.12 mmol, 2.5 M in hexane). The reaction mixture was stirred for 1 h at -78 °C and 2 h at 0 °C. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:19 v/v) as eluent furnished the corresponding terminal alkynes **69** (1.59 g, 86% over three steps) as a pale yellow oil. $[\alpha]_D^{25}$ +34.2 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*; 3302, 2952, 2851, 2125, 1362, 1172, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.36 (m, 5H), 4.8 (m, 1H), 4.5 (m, 1H), 4.0 (m, 1H), 2.46 (d, J = 1.84 Hz, 1H), 1.28-1.78 (m, 8H), 0.9 (t, J = 6.88 Hz, 3H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ: 137.9, 128.4, 128.0, 127.7, 83.0, 73.7, 70.5, 68.5, 35.6, 31.4, 24.9, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{21}O$ [M+H$^+$] 217.158; found 217.158.

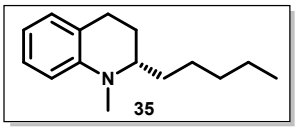


(*R*)-1-(3-(Benzyloxy)oct-1-ynyl)-2-nitrobenzene (70): A mixture of 1-iodo-2-nitrobenzene (1.67 g, 6.7 mmol), $Pd(PPh_3)_2Cl_2$ (94 mg, 0.134 mmol, 2 mol %), CuI (13 mg, 0.067 mmol, 1 mol %), Et_3N (60 mL) and **69** (1.45 g, 6.7 mmol) in 20 mL DMF was purged with nitrogen for 10 min. The resulting mixture was then stirred at 100 ^oC for 3 h. It was then concentrated, diluted with water, extracted with ether, dried over sodium sulfate and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:19 v/v) as eluent gave the coupled product **70** (2.15 g, 95%) as a yellow oil. $[\alpha]_D^{25}$ -121.3 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*; 2935, 2850, 1362, 1172, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.0 (m, 1H), 7.6 (m, 2H), 7.26-7.42 (m, 6H), 4.9 (d, *J* = 11.5 Hz, 1H), 4.6 (d, *J* = 11.9 Hz, 1H), 4.3 (t, *J* = 6.8 Hz, 1H), 1.84-1.88 (m, 2H), 1.5 (m, 2H), 1.3 (m, 4H), 0.9 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.8, 137.9, 134.9, 132.8, 128.7, 128.4, 128.2, 127.7, 124.6, 118.3, 97.0, 81.1, 70.8, 69.1, 35.5, 31.5, 25.0, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_3$ [M+H$^+$] 338.178; found 338.177.



(*R*)-1-(2-Aminophenyl)octan-3-ol (71): To a solution of **70** (1.0 g, 2.96 mmol) in EtOAc (12 mL) was added catalytic amount of HCl followed by addition of 10% Pd/C (150 mg, 5 mol%). The reaction mixture was subjected to hydrogenation under 1 atm H_2 pressure for 24 h. After this time, a solution of saturated Na_2CO_3 was added to the reaction mixture, filtered through a pad of Celite and the pad was washed with additional EtOAc (30 mL) and organic layer separated. The resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography purification (EtOAc/hexanes 1:1 v/v) of the crude product furnished amino alcohol **71** (630 mg, 96%) as a yellow oil. $[\alpha]_D^{25}$ -94.5 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*; 2935, 2850, 1362, 1172, 937 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.0 (m, 2H), 6.7 (m, 2H), 3.5 (m, 1H), 3.2 (bs, 2H), 2.6 (m, 2H), 2.1 (bs, 1H), 1.7 (m, 2H), 1.25-1.28 (m, 8H), 0.87 (t, *J* = 6.88 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0, 129.6, 127.0, 119.2, 116.1, 70.9, 37.7, 37.0, 31.9, 27.0, 25.4, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{23}NONa$ [M+Na$^+$] 244.170; found 244.172.

(+)-Angustureine (35): To a solution of amino alcohol **71** (400 mg, 1.8 mmol) in dry CH_2Cl_2 (6.0 mL) was slowly added triphenylphosphine (520 mg, 1.98 mmol) in portion wise at room temperature. To the resulting solution, diethylazodicarboxylate (345 mg, 1.98 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise and stirred at room temperature for 12 h. After this time, the solution was quenched with water, diluted with CH_2Cl_2 and organic layer 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 afford the crude tetrahydroquinolone (norangustureine), which was used as such for next step without further purification. To a acetonitrile solution (6 mL) of above crude tetrahydroquinolone (norangustureine) was added formaldehyde (37% w/w in H_2O, 1.5 mL, 18 mmol), sodium cyanoborohydride (1.13 g, 18 mmol) and acetic acid (1 mL, 18 mmol) and stirred for 10 h at room temperature. TLC monitoring showed complete conversion {hexane/ethyl acetate 19:1 v/v, $R_f = 0.60$}. The mixture was diluted with diethyl ether and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:99 v/v) as eluent furnished the target (+)-angustureine **35** (345 mg, 88% over two steps) as pale yellow oil. {$[\alpha]_D^{25}$ +7.6 (*c* 0.4, $CHCl_3$) [Lit. +7.5 (*c* 0.4, $CHCl_3$),[15t] -7.16 (*c* 1, $CHCl_3$,[15l]]}; IR (CH_2Cl_2) *v*; 2935, 2850, 1362, 1172, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.1 (t, J = 7.2 Hz, 1H), 6.9 (d, J = 7.2 Hz, 1H), 6.57 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 3.2 (m, 1H), 2.92 (s, 3H), 2.66 (m, 1H), 2.62 (m, 1H), 1.8 (m, 2H), 1.56 (m, 1H), 1.25-1.3 (m, 7H), 0.9 (t, J = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.3, 128.6, 127.0, 121.8, 115.1, 110.3, 58.9, 37.9, 32.0, 31.1, 25.7, 24.3, 23.5, 22.7, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{24}N$ [$M+H^+$] 218.188; found 218.190.

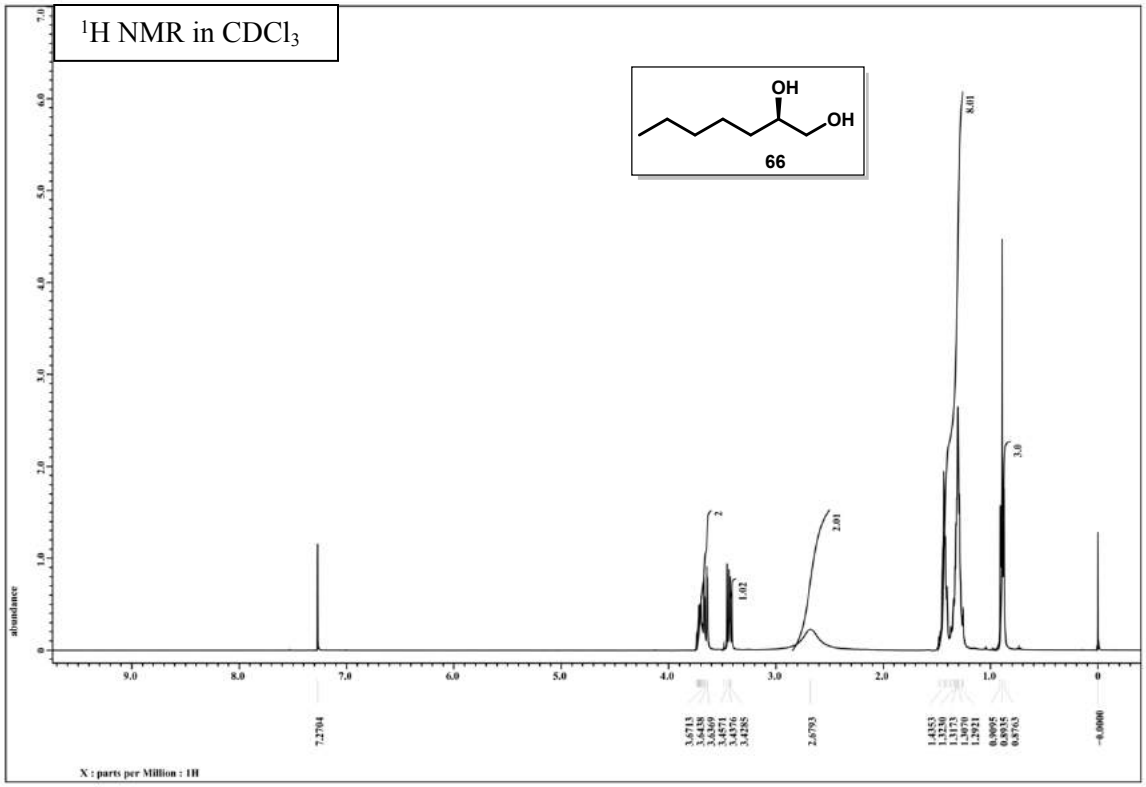


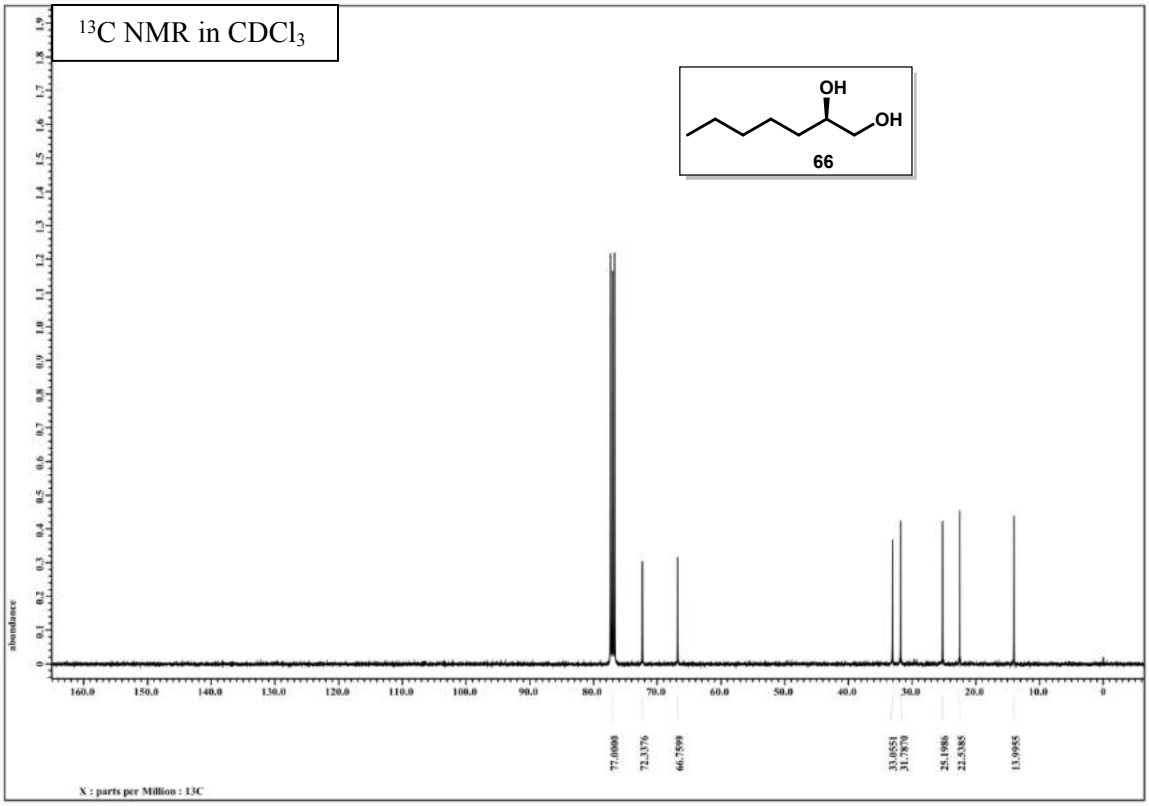
2.2.7 Spectra:

1. ^1H and ^{13}C NMR spectra of **66**
2. ^1H and ^{13}C NMR spectra of **67**
3. ^1H and ^{13}C NMR spectra of **68**
4. ^1H and ^{13}C NMR spectra of **69**
5. ^1H and ^{13}C NMR spectra of **70**

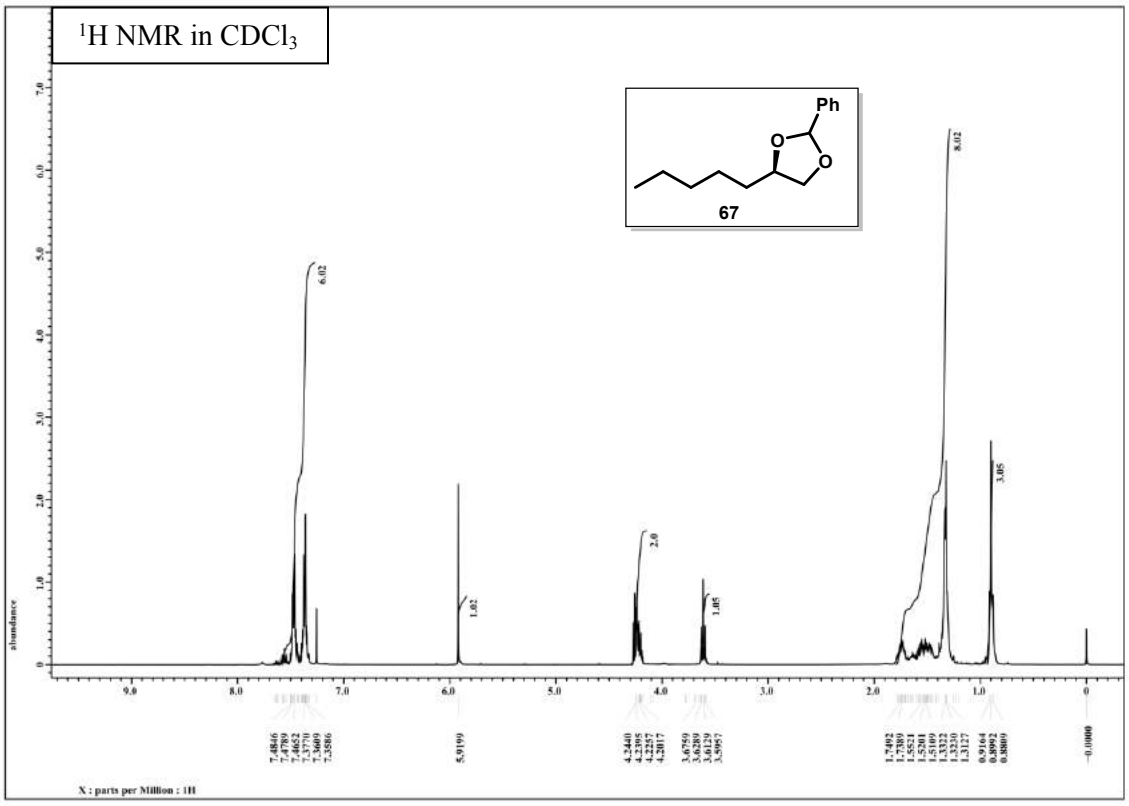
6. ^{1}H and ^{13}C NMR spectra of **71**

7. ^{1}H and ^{13}C NMR spectra of **35**

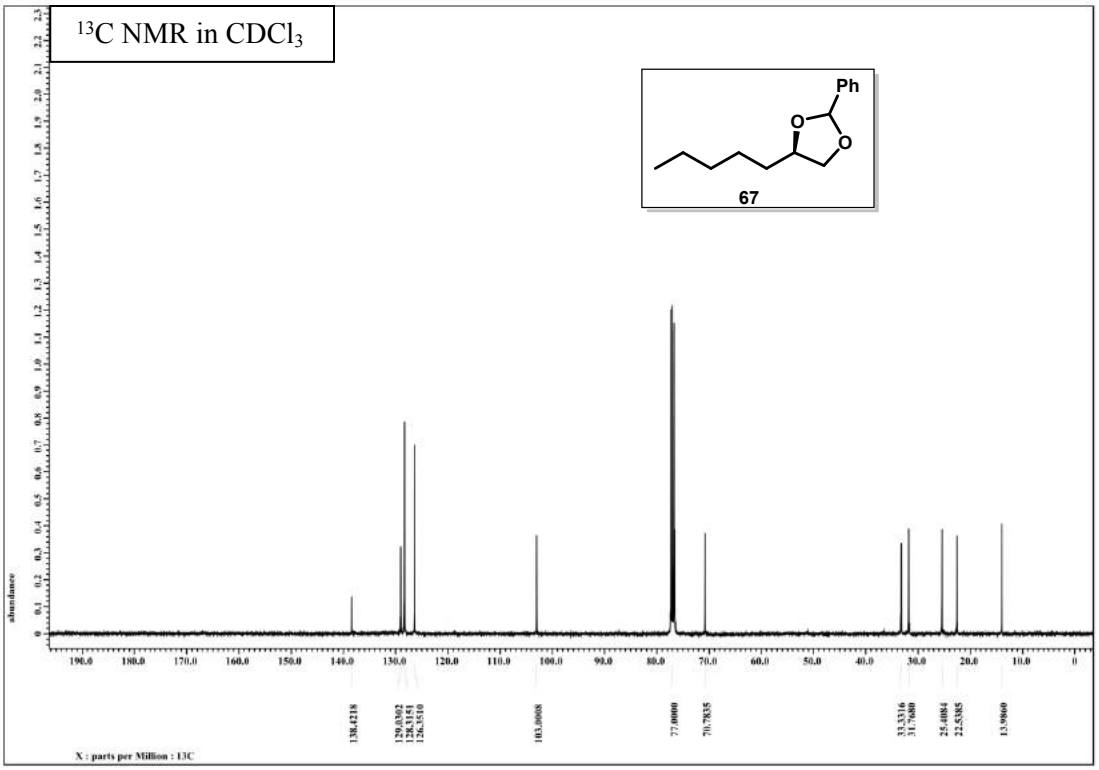

^{1}H NMR in $CDCl_3$
OH
OH
66
X : parts per Million : 1H

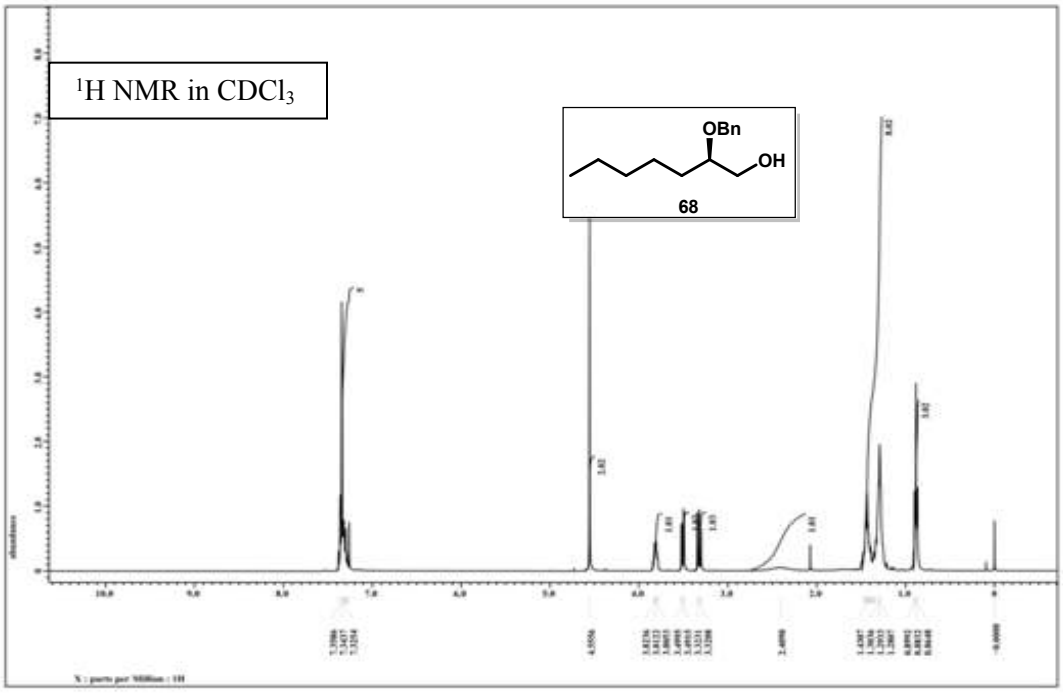

^{13}C NMR in $CDCl_3$
OH
OH
66
X : parts per Million : 13C

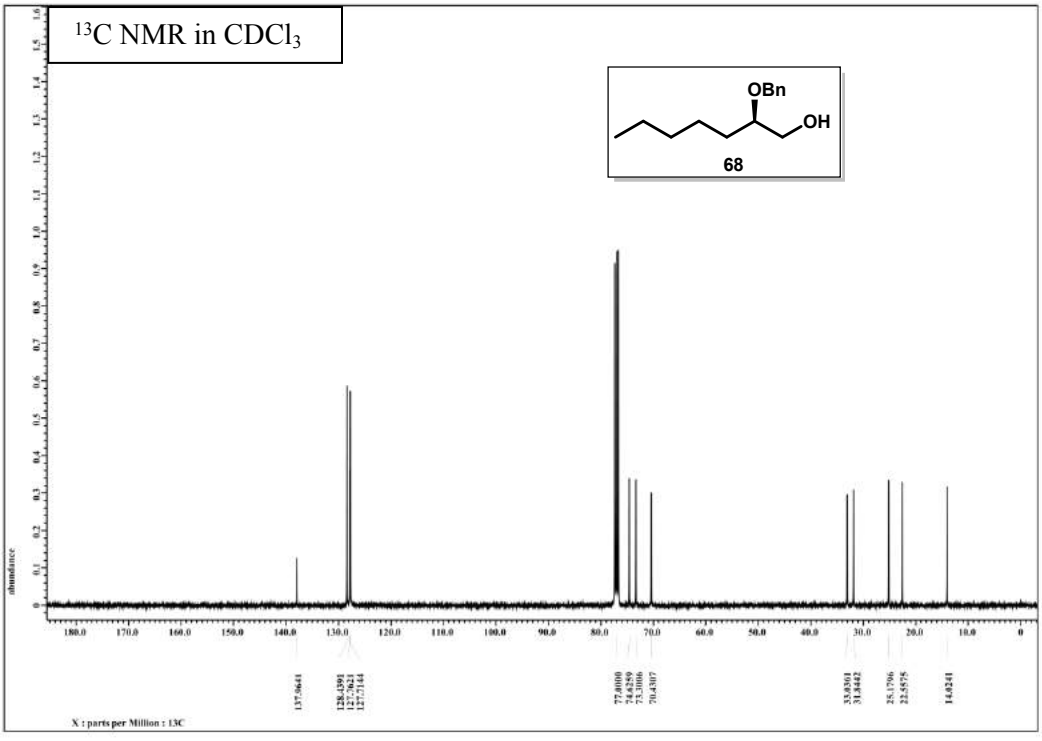
^{1}H NMR in $CDCl_3$

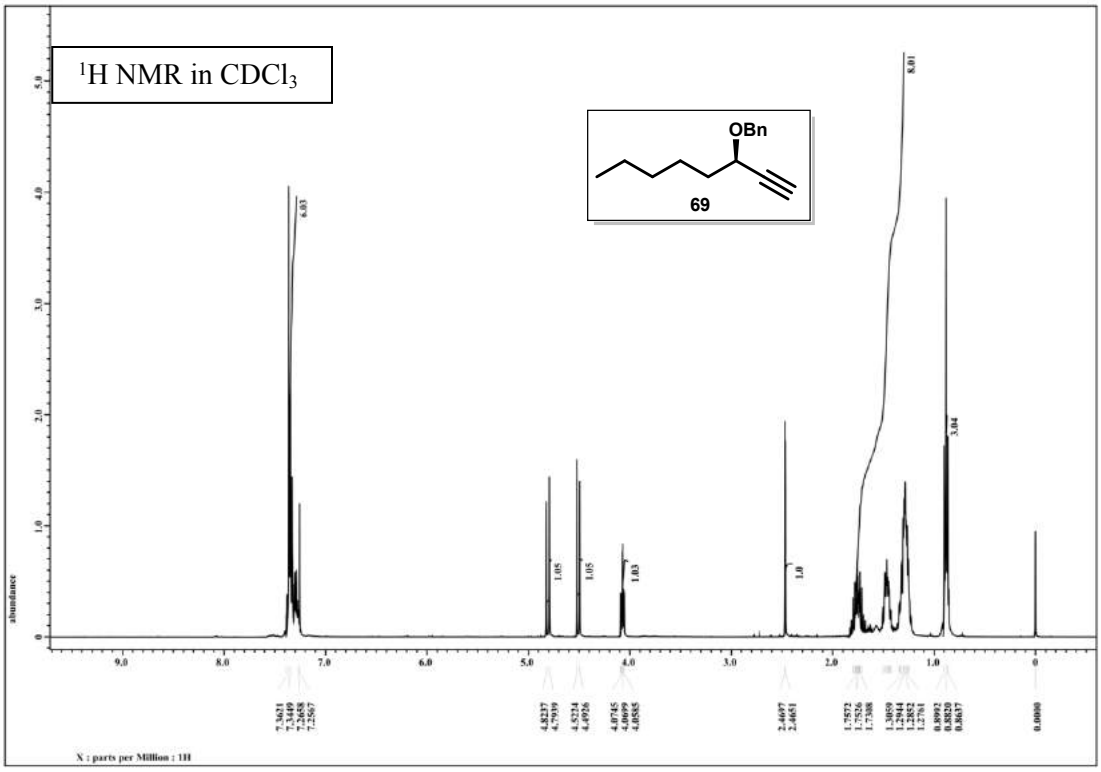


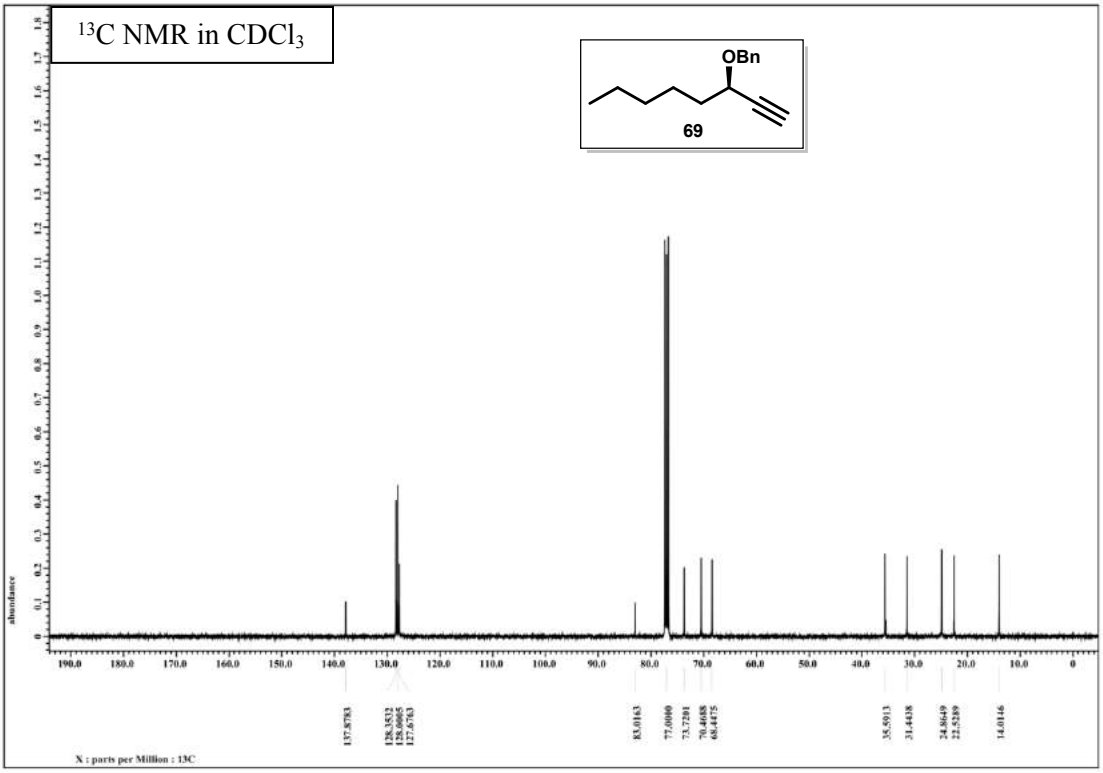
^{13}C NMR in $CDCl_3$

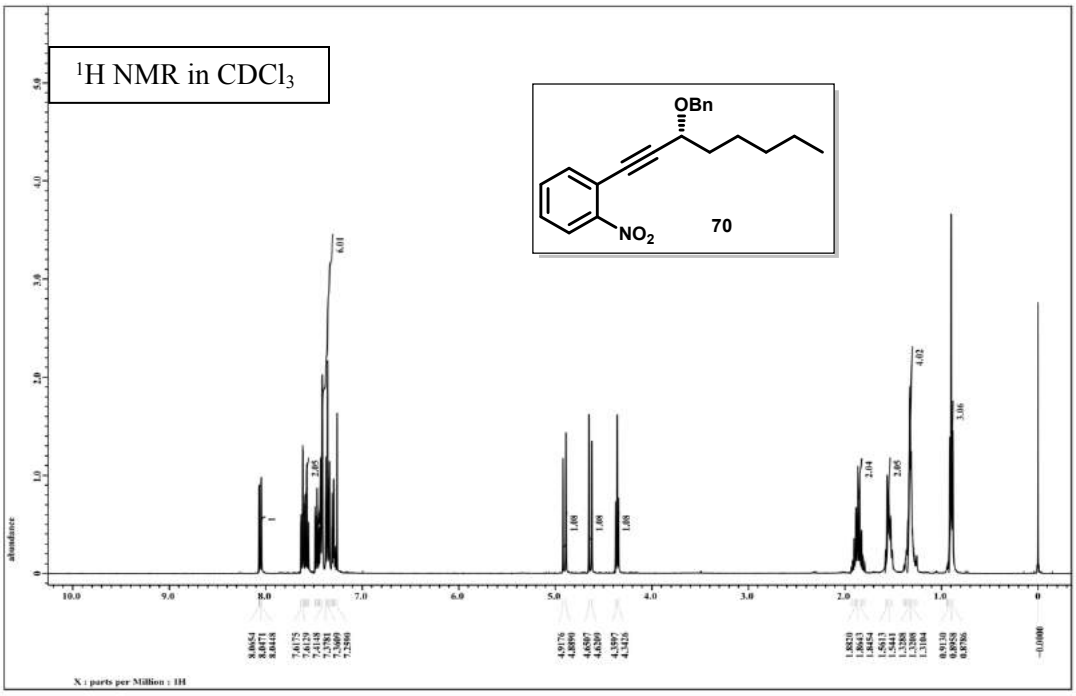


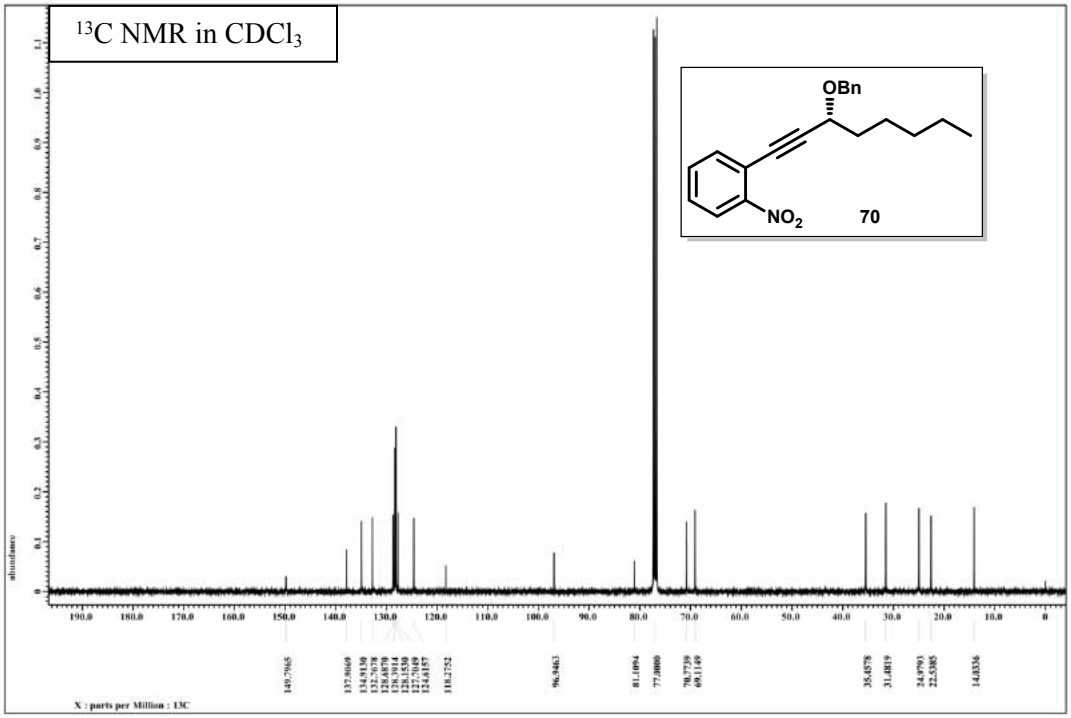

^{1}H NMR in CDCl$_3$
OBn
OH
68

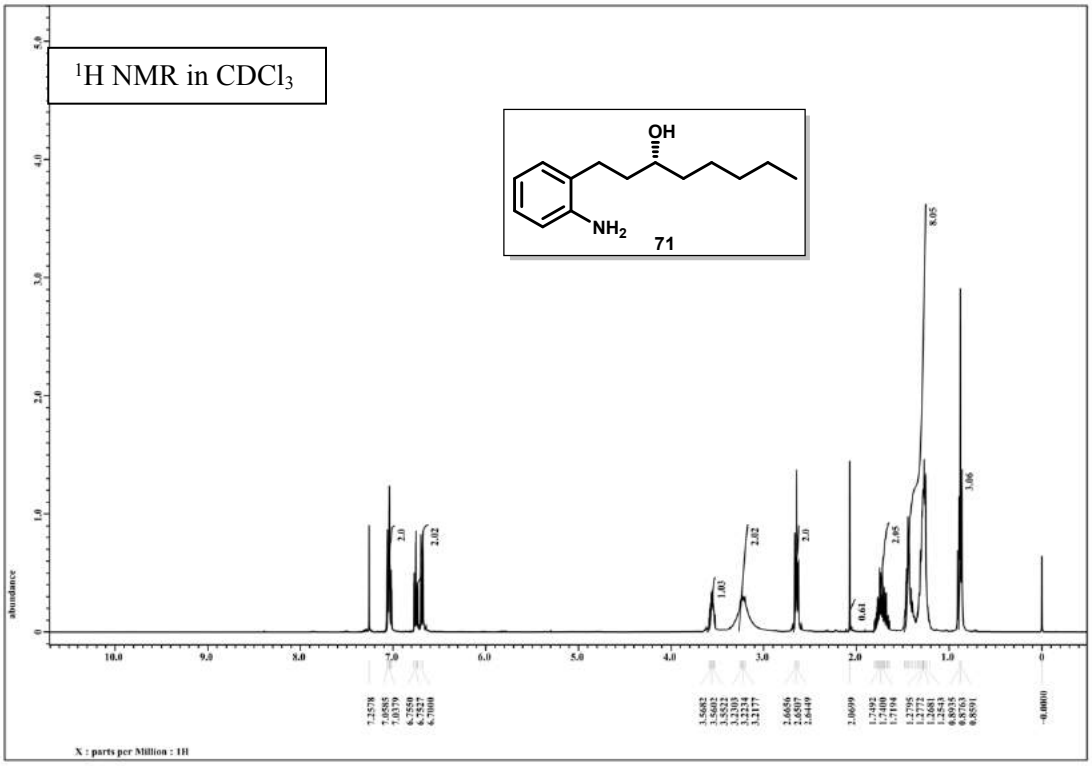

^{13}C NMR in CDCl$_3$
OBn
OH
68

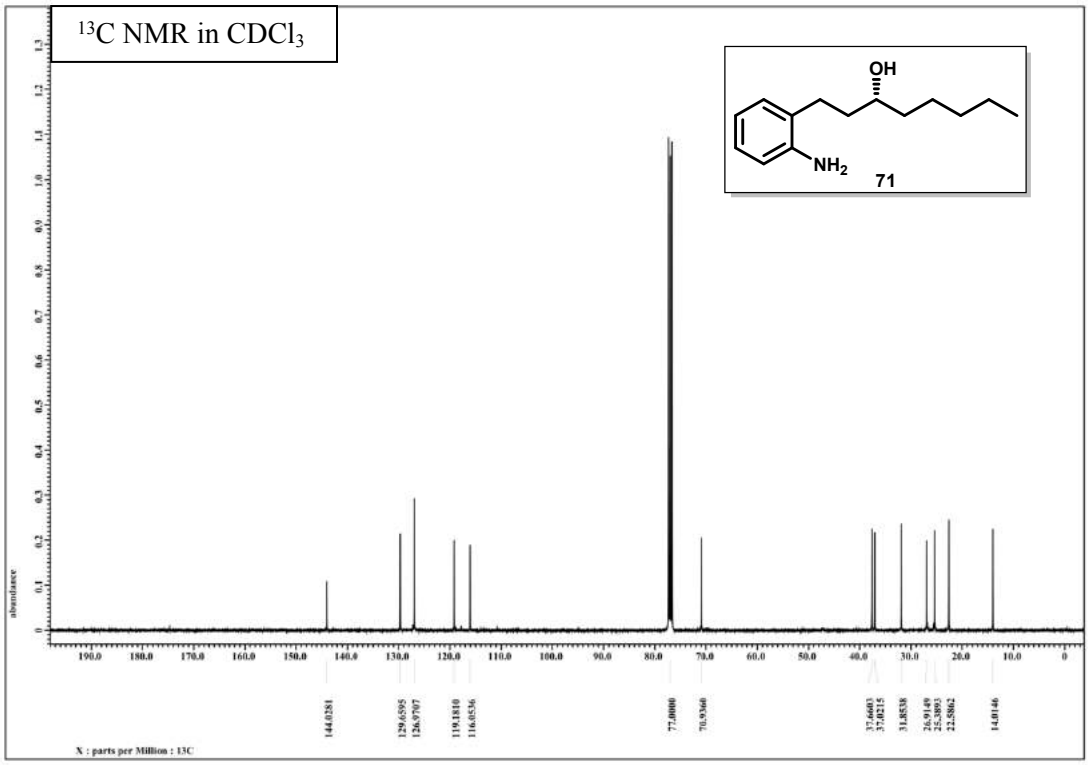

^{1}H NMR in $CDCl_3$
OBn
69
X : parts per Million : 1H

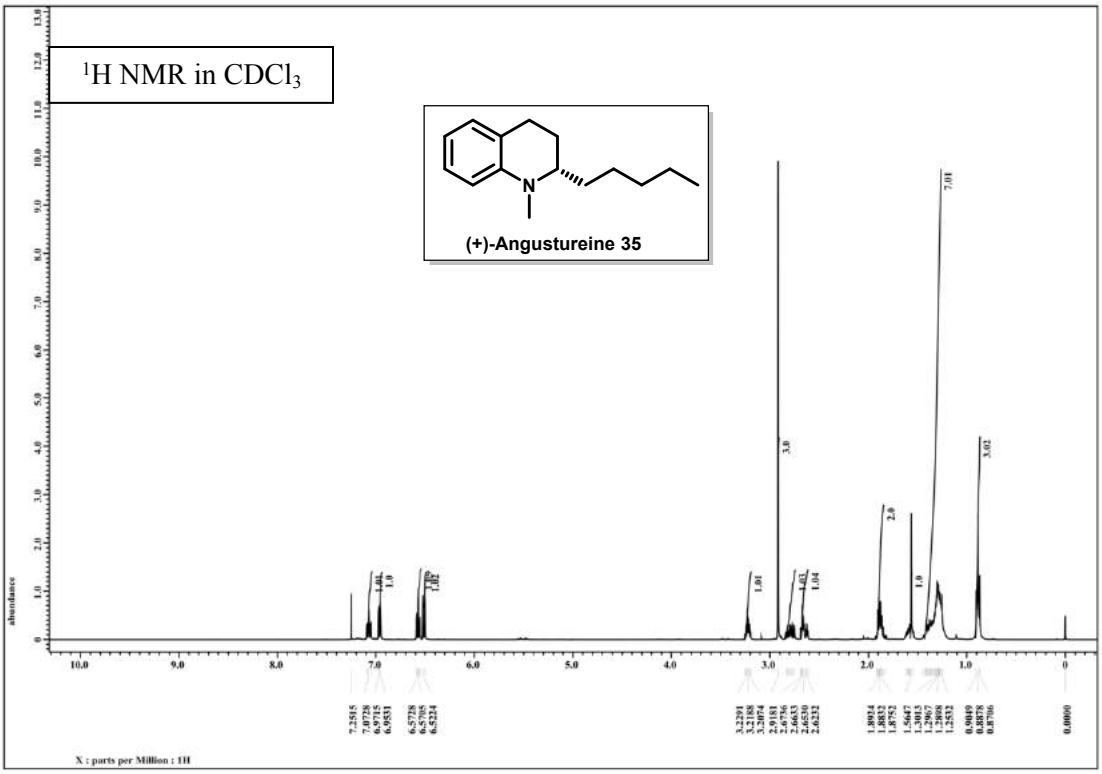

^{13}C NMR in $CDCl_3$
OBn
69
X : parts per Million : 13C

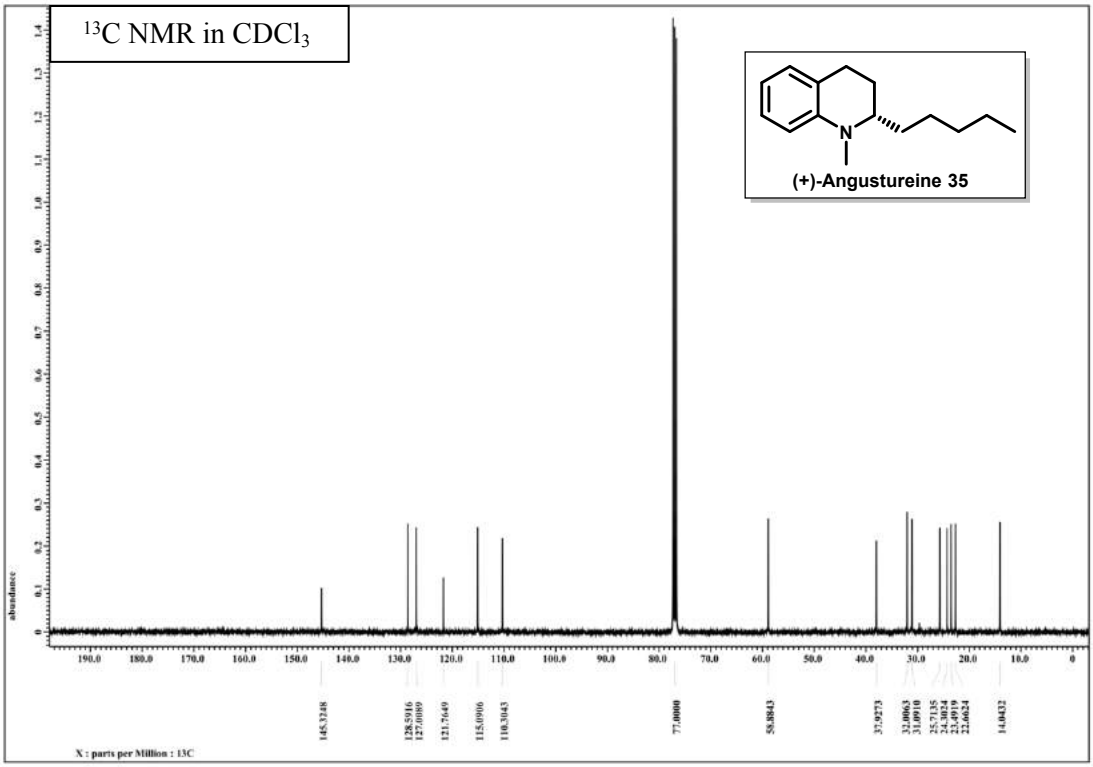

^{1}H NMR in $CDCl_3$
OBn
NO_2
70


^{13}C NMR in $CDCl_3$
OBn
NO_2
70


^{1}H NMR in $CDCl_3$
OH
NH_2
71
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
NH_2
71
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
(+)-Angustureine 35
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
(+)-Angustureine 35
abundance
X : parts per Million : 13C

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CHAPTER 3

Enantioselective approaches towards the synthesis of *α*-phenyl-*β*^{2}-amino acids and 3-substituted pyrrolidines with their applications to the total synthesis of (*S*)-nakinadine B and pyrrolidine core unit of serotonin norepinephrine reuptake inhibitors, respectively. This chapter is divided into two sections.

3.1 Section A

Enantioselective organocatalyzed Michael addition/aminoxylation approach to the total synthesis of (*S*)-nakinadine B

3.1.1 Introduction:

During recent years, marine sponges have been recognized as a rich source of bioactive natural products with fascinating chemical structures. The nakinadine A-F (**3**-**8**) alkaloids were recently isolated from an Okinawan marine sponge *Amphimedon sp*. (SS-1059) (Figure 1).[1] Metabolites from an Okinawan marine sponge family illicit a myriad of biological activities that includes antimicrobial, cardiotonic, cytotoxic and antitumor activities.[2] The nakinadine alkaloids possess an *α*-phenyl-*β*-amino acid moiety with a long chain *N*-alkyl substituent capped by a terminal 3-pyridyl moiety.

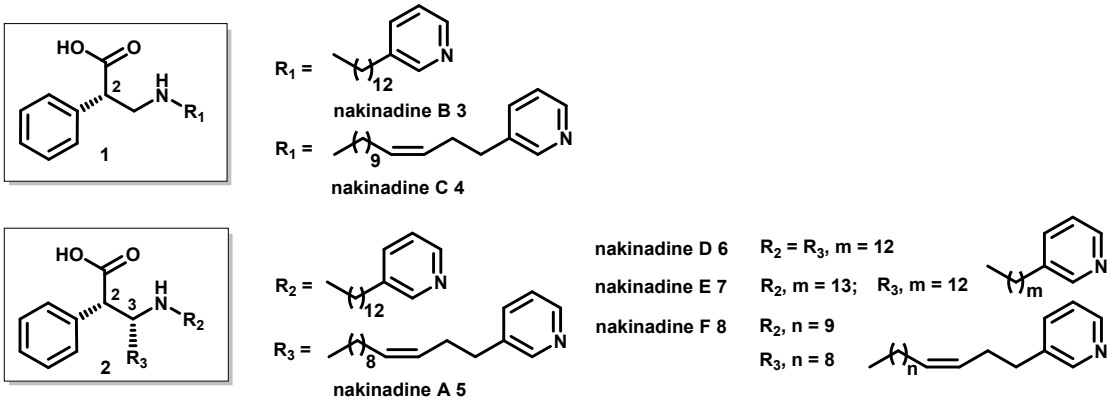


Figure 1. Structures of nakinadine A-F alkaloids

The nakinadine B **3** and C **4** possess an *α*-phenyl-*β*^{2}-amino acid core unit **1** which is different from the nakinadines A **5** and D-F (**6**-**8**) having an *α*-phenyl-*β*^{2,3}-amino acid core unit **2**. The nakinadine A-C (**3**-**5**) alkaloids have been shown to possess significant cytotoxicity against a variety of tumour cell lines including L1210 murine leukaemia and KB human epidermoid carcinoma cells.[1] The absolute configurations of (*S*)-nakinadine B **3** were determined by Kobayashi and co-workers with the help of 2D NMR spectroscopic studies.[1] The paucity of the material in isolation has hampered further studies of the biochemistry of (*S*)-nakinadine A-F **(3-8)**.[1] Therefore, in order to achieve nakinadine A-F **(3-8)** alkaloids in larger quantities for further biological evaluation, it is highly desirable to develop a general, convergent and enantiopure

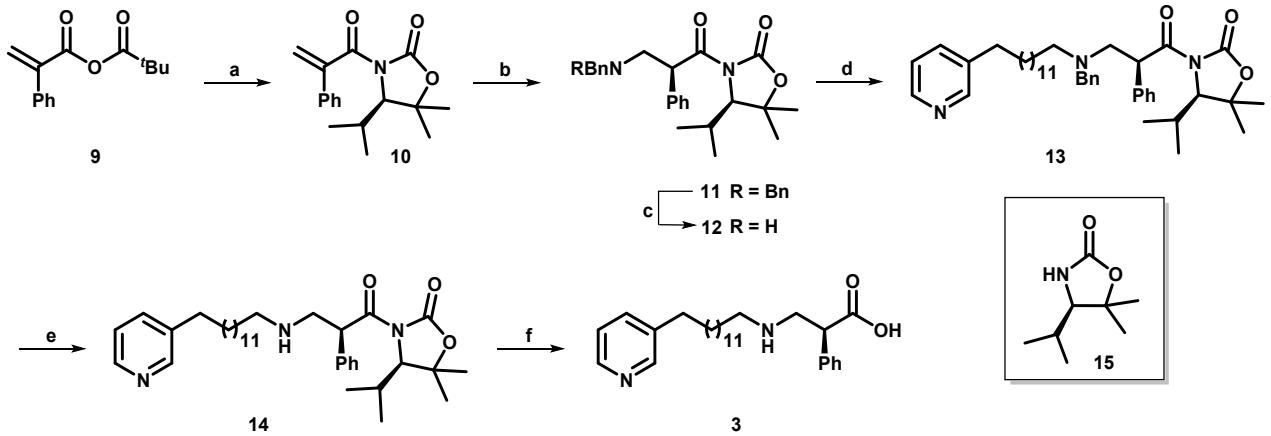
synthetic route which involves stable intermediates. The nakinadine A-F (**3**-**8**) have been synthetic targets of considerable interest due to its high cytotoxic activity and with an array of functionalities.[3]

3.1.2 Review of Literature:

Very recently, Davies and co-workers reported the first total synthesis for each of nakinadine B **3** and nakinadine C **4** employed a common strategy to both the alkaloids which are summarised below.[3a-b]

Davies, S. G. *et al*. (2012)[3a]

S. G. Davies and co-workers reported the first asymmetric synthesis of (-)-(*S*)-nakinadine B **3** in 9 steps and 17% overall yield from mixed anhydride **9** synthesized from commercially available atropic acid (Scheme 1). The D-valine derived SuperQuat **15** on *N*-acylation with anhydride **9** furnished amide derivative **10** which on conjugate addition of $LiNBn_2$ followed by diastereoselective enolate protonation afforded amide derivative **11** in 87:13 diastereomeric ratio. The major diastereomer **11** on *N*-debenzylation using CAN furnished derivative **12** which on reductive *N*-alkylation with 13-pyridinyltridecanal using $NaBH(OAc)_3$ afforded pyridine derivative **13**. The derivative **13** on debenzylation using CAN afforded amine derivative **14** in 71% yield. The derivative **14** on *N*-Boc protection followed by amide hydrolysis using $LiOH/aq.H_2O_2$ and subsequent *N*-Boc deprotection furnished the final target (*S*)-nakinadine B **3** in 73% yield.

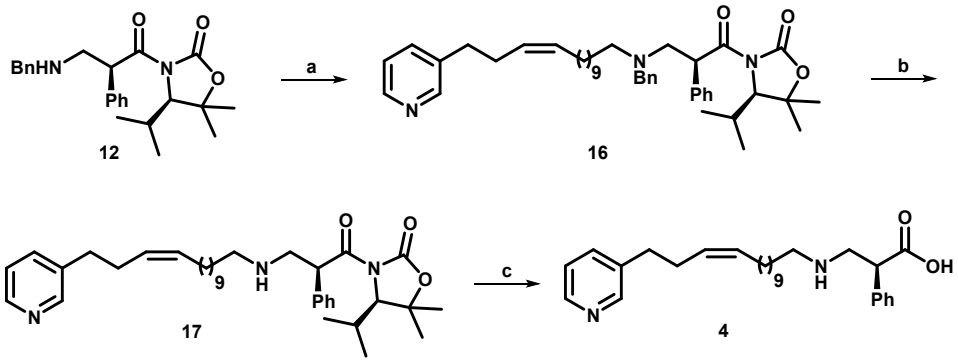


Scheme 1. *Reagents and conditions*: (a) *n*-BuLi, THF, -78 °C, 10 min, **15**, -78 °C to rt, 2 h, 81%; (b) *n*-BuLi, $NHBn_2$, THF, -78 °C to rt, 20 h, 63%; (c) CAN, MeCN, H_2O, rt, 16 h, 76%; (d) $Ar(CH_2)_{12}CHO$, $NaBH(OAc)_3$, AcOH, DCE, rt, 16 h, 85%; (e) CAN, MeCN, H_2O, rt, 16 h, 71%;

(f) (i) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt, 16 h; (ii) LiOH, aq. H_2O_2, THF, 0 °C to rt, 16 h; (iii) HCl (2.0 M in Et_2O), rt, 30 min, 73%.

Davies, S. G. *et al*. (2013)[3b]

S. G. Davies and co-workers also reported the first asymmetric synthesis of (-)-(*S*)-nakinadine C **4** in 9 steps with 13% overall yield from amine derivative **12** (Scheme 2) used in the previously described approach for (-)-(*S*)-nakinadine B **3** (Scheme 1). The derivative **12** on reductive *N*-alkylation with *cis*-pyridinyltetradecanal using $NaBH(OAc)_3$/DCE furnished protected amine derivative **16** in 85% yield. The amine derivative **16** on *N*-debenzylation using CAN afforded amine compound **17** in 71% yield. The amine derivative **17** on *N*-Boc protection, subsequent amide hydrolysis using LiOH/aq.H_2O_2 followed by *N*-Boc deprotection in acidic conditions furnished target compound (-)-(*S*)-nakinadine C **4** in 73% yield.



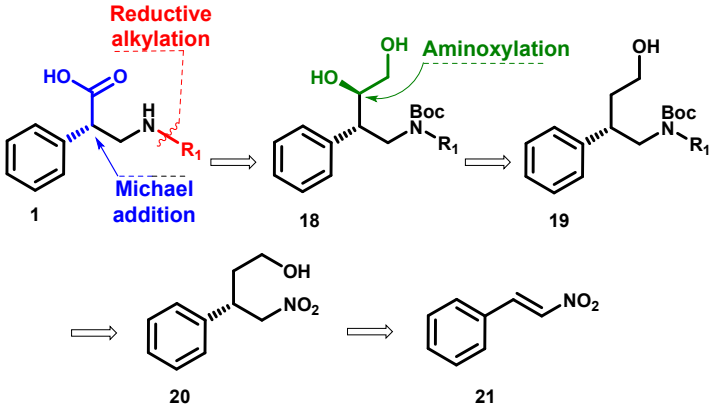
Scheme 2. *Reagents and conditions*: (a) $ArCH_2CH_2CH{=}CH(CH_2)_9CHO$, $NaBH(OAc)_3$, AcOH, DCE, rt, 16 h, 85%; (b) CAN, MeCN, H_2O, rt, 16 h, 71%; (c) (i) Boc_2O, $NaHCO_3$, EtOH, 0 °C to rt, 16 h; (ii) LiOH, aq. H_2O_2, THF, 0 °C to rt, 16 h; (iii) HCl (2.0 M in Et_2O), rt, 30 min, 73%.

3.1.3 Present Work:

As part of our research on the asymmetric synthesis of bioactive compounds, we wish to report herein, a new, general and highly efficient synthetic approach for enantiopure α-phenyl-β^2-amino acid core unit **1** and its application to the total synthesis of (*S*)-nakinadine B **3** employing diphenylprolinol silyl ether mediated asymmetric Michael addition and proline catalyzed aminoxylation reactions as key steps.

Our synthetic approach for the synthesis of α-phenyl-β^2-amino acid core unit **1** and (*S*)-nakinadine B **3** was envisioned *via* the retrosynthetic route as shown in Scheme 3. The diol **18** was visualized as a synthetic intermediate from which α-phenyl-β^2-amino acid

core unit **1** could be synthesized by oxidative cleavage followed by oxidation of the intermediate aldehyde. The diol **18** in turn could be synthesized from alcohol derivative **19** through proline catalyzed α-aminoxylation of aldehyde derived from **19** followed by standard organic transformations. The alcohol **19** could be obtained from nitroalcohol derivative **20** by employing hydrogenation to get amine intermediate followed by reductive *N*-alkylation.



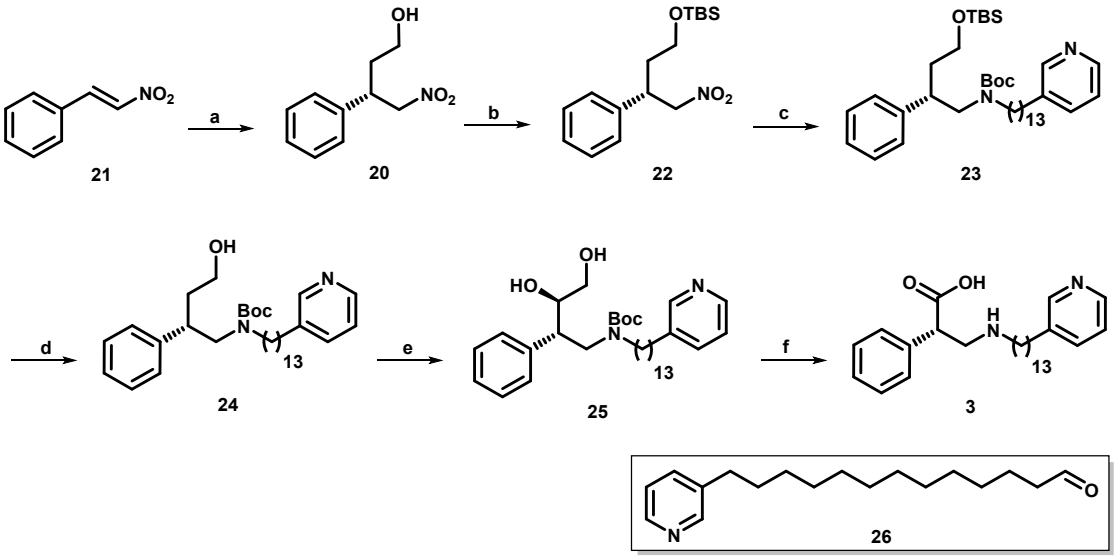
Scheme 3. Retrosynthetic approach for the asymmetric synthesis of α-phenyl-β^2-amino acid core unit **1** and (*S*)-nakinadine B **3**.

The key intermediate nitroalcohol **20** could be easily prepared from commercially available nitrostyrene **21** *via* diphenylprolinol silyl ether mediated asymmetric Michael addition with acetaldehyde. The (*S*)- and (*R*)- configuration of α-phenyl-β^2-amino acid core unit **1** could be manipulated by simply changing the (*S*)- and (*R*)- configuration of the catalyst diphenylprolinol silyl ether during asymmetric Michael addition step.

3.1.4 Results and Discussion:

As outlined in Scheme 4, the synthesis of (*S*)-nakinadine B **3** commenced with commercially available nitrostyrene **21**, which can be easily synthesized from base catalyzed condensation of benzaldehyde with nitromethane.[4] Asymmetric Michael addition of acetaldehyde with nitrostyrene **21** in the presence of catalytic amount of (*S*)-diphenylprolinol silyl ether[5] in a sealed tube afforded the nitroaldehyde adduct,[6] which on subsequent reduction with $NaBH_4$ delivered the nitroalcohol derivative **20** as a single enantiomer in 75% yield with 96% ee {$[\alpha]_D^{25}$ -13.8 (*c* 0.5, CH_2Cl_2) [Lit.[7] $[\alpha]_D^{25}$ -13.7 (*c* 0.5, CH_2Cl_2)]. The IR spectrum of **20** showed hydroxyl absorption at 3378 cm^{-1} and N-O stretching for nitro group at 1549 cm^{-1}. With enantiomerically

pure nitroalcohol **20** in hand, we then performed base catalyzed silyl ether protection of free alcohol which afforded the TBS protected alcohol derivative **22** in 95% yield.



Scheme 4. *Reagents and conditions*: (a) (i) Acetaldehyde, (*S*)-diphenylprolinol silyl ether, 1,4-dioxane, 4 ^{o}C to rt, 18 h; (ii) $NaBH_4$, CH_3OH, 0 ^{o}C, 15 min, 75% (over two steps); (b) TBSCl, imidazole, dry CH_2Cl_2, 0 ^{o}C to rt, 6 h, 95%; (c) (i) H_2, $Pd(OH)_2/C$ (20%), CH_3OH, rt, 6 h; (ii) $Ar(CH_2)_{12}CHO$ **26**, $Na(CN)BH_3$, Na_2SO_4, C_2H_5OH, 0 ^{o}C to rt, 48 h; (iii) $(Boc)_2O$, NaH, DMAP, dry DMF, 0 ^{o}C to rt, 12 h, 82% (over three steps); (d) TBAF, THF, rt, 6 h, 96%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^{o}C, 3 h; (ii) Nitrosobenzene, L-proline, DMSO, rt, 30 min; (iii) $NaBH_4$, CH_3OH, 0 ^{o}C, 15 min; (iv) $CuSO_4.5H_2O$, CH_3OH, 0 ^{o}C to rt, 12 h, 61% (over four steps); (f) (i) $NaIO_4$, dioxane:water (3:1 v/v), rt, 3 h; (ii) Oxone, DMF, rt, 12 h; (iii) TFA, CH_2Cl_2, rt, 12 h, 81% (over three steps).

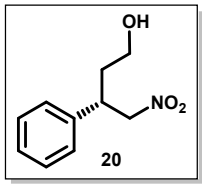
Our next aim was to carry out *N*-alkylation at terminal nitro group site. To this end, compound (*S*)-**22** was subjected to hydrogenation in the presence of catalytic amount of $Pd(OH)_2$ to afford the terminal amine intermediate. Reductive *N*-alkylation of the synthesized amine intermediate with 13-(pyridin-30-yl)tridecanal[8] **26** using $Na(CN)BH_3$ afforded the *N*-alkylated amine intermediate which on subsequent protection with $(Boc)_2O$ in the presence of NaH and catalytic amount of DMAP furnished the Boc protected derivative **23** in 82% yield. The cleavage of silyl ether in compound (*S*)-**23** with TBAF afforded the alcohol derivative **24** quantitatively. Oxidation of alcohol (*S*)-**24** to aldehyde under Swern conditions,[9] subsequent treatment of

aldehyde with nitrosobenzene in the presence of catalytic amount of L-proline (20 mol%) in DMSO at room temperature furnished α-aminoxylated aldehyde, which on spontaneous reduction with $NaBH_4$ and cleavage of phenylamine moiety with $CuSO_4.5H_2O$ afforded the diol **25** as a single diastereomer in 61% yield.[10] The IR spectrum of **25** showed hydroxyl absorption at 3369 cm^{-1}. The diol **25** on smooth oxidative cleavage in the presence of $NaIO_4$[11] followed by oxidation with oxone[12] and finally deprotection of *N*-Boc with TFA furnished the sponge metabolite (*S*)-nakinadine B **3** in 81% yield {$[\alpha]_D^{25}$ -6.4 (*c* 1, $CHCl_3$) [Lit.[3a] $[\alpha]_D^{20}$ -6.3 (*c* 1, $CHCl_3$)]}. The physical and spectroscopic data of (*S*)-nakinadine B **3** were found in full agreement with those reported in the literature.[1,3a]

3.1.5 Conclusions:

In conclusion, we have described an expeditious approach for the synthesis of α-phenyl-β^2-amino acid core unit **1** and its application to the total synthesis of (*S*)-nakinadine B **3** employing diphenylprolinol silyl ether mediated asymmetric Michael addition and proline catalyzed aminoxylation reactions as key steps. The overall yield for (*S*)-nakinadine B **3** was 28% after six column chromatography steps. Moreover, the synthetic strategy described has significant potential for stereochemical variation of substituents at the 2-aryl and *N*-alkyl sites to synthesize other analogues of nakinadine alkaloids.

3.1.6 Experimental Section:

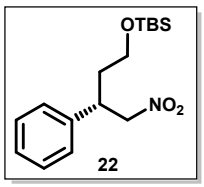


(*S*)-4-Nitro-3-phenylbutan-1-ol (20): To a 1,4-dioxane (2.0 mL) solution of (*S*)-diphenyltrimethylsiloxymethyl pyrrolidine (265 mg, 0.81 mmol, 10 mol%) and nitrostyrene **21** (1.2 g, 8.05 mmol) was added acetaldehyde (4.5 mL, 80.5 mmol) in a sealed tube at 4 ^oC. The reaction mixture was stirred at room temperature for 18 h and then quenched with 1N HCl (10 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL) washed with brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and used as such for the next step without further purification.

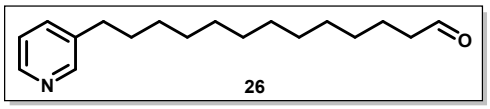
To the above crude product were added MeOH (20 mL), $NaBH_4$ (460 mg, 12.1 mmol) and the reaction mixture stirred for 15 min at 0 ^oC. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 3:7 v/v) as eluent to afford the nitro alcohol **20** (1.18 g, 75%). {$[\alpha]_D^{25}$ -13.8 (*c* 0.5, CH_2Cl_2)

[Lit.[7] -13.7 (*c* 0.5, CH_2Cl_2)]; IR (CH_2Cl_2) *v*: 3378, 2940, 2415, 1549, 1379, 1265, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.23-7.34 (m, 5H), 4.61-4.65 (m, 2H), 3.66-3.74 (m, 1H), 3.59-3.64 (m, 1H), 3.46-3.52 (m, 1H), 1.87-2.04 (m, 2H), 1.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.7, 129.0, 127.7, 127.5, 80.6, 59.8, 41.0, 35.5. HRMS (ESI^+) m/z calcd for $C_{10}H_{13}NO_3Na^+$ ($[M+Na^+]$) 218.0800; found 218.0784.

(*S*)-*tert*-Butyldimethyl(4-nitro-3-phenylbutoxy)silane (22): To a solution of nitro alcohol **20** (1.0 g, 5.13 mmol) in CH_2Cl_2 (20 mL) was added imidazole (525 mg, 7.7 mmol) followed by *tert*-butyldimethylsilyl chloride (940 mg, 6.2 mmol) at 0 °C. The reaction was then stirred under N_2 for 6 h at room temperature, after which it was quenched by adding saturated aqueous NH_4Cl (20 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), organic layer separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:9 v/v) as eluent furnished TBS protected alcohol derivative **22** (1.5 g, 95%) as pale yellow oil. $[\alpha]_D^{25}$ -71.2 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3012, 2945, 2932, 2402, 1552, 1362, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.20-7.36 (m, 5H), 4.58-4.72 (m, 2H), 3.68-3.74 (m, 1H), 3.56-3.61 (m, 1H), 3.42-3.47 (m, 1H), 1.83-1.97 (m, 2H), 0.89 (s, 9H), 0.009 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.1, 128.8, 127.6, 80.6, 59.9, 41.1, 35.8, 25.8, 18.1, -5.5. HRMS (ESI^+) m/z calcd for $C_{16}H_{28}NO_3Si^+$ ($[M+H^+]$) 310.1800; found 310.1833.

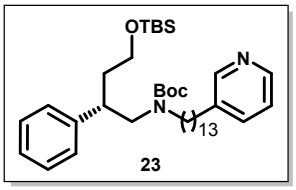


13-(Pyridin-3-yl)tridecanal (26): To a solution of oxalyl chloride (685 mg, 460 µL, 5.4 mmol) in dry CH_2Cl_2 (10 mL) at -78 °C was added dropwise DMSO (870 mg, 790 µL, 11.2 mmol) in CH_2Cl_2 (10 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of 13-(pyridin-3-yl)tridecan-1-ol (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at same temperature, then added Et_3N (1.6 g, 2.2 mL, 15.84 mmol) in CH_2Cl_2 (10 mL) dropwise and stirred for 3 h. The reaction mixture was diluted with water (20 mL), organic layer separated, extracted with CH_2Cl_2 (3 x 20 mL) washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:1 v/v) as eluent afforded aldehyde derivative **26** (940 mg, 95%) as pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 9.76 (t, *J* = 1.84



Hz, 1H), 8.42-8.43 (m, 2H), 7.48-7.50 (m, 1H), 7.19-7.22 (m, 1H), 2.60 (t, J = 7.32 Hz, 2H), 2.42 (td, J = 1.80, 7.76 Hz, 2H), 1.59-1.64 (m, 4H), 1.25-1.30 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 149.7, 146.9, 137.9, 135.8, 123.2, 43.8, 32.9, 31.1, 29.5, 29.4, 29.4, 29.3, 29.2, 29.0, 22.0.

(*S*)-*tert*-Butyl-4-(tert-butyldimethylsilyloxy)-2-phenylbutyl(13-(pyridin-3-yl)tridecyl)carbamate (23): To a solution of compound **22** (750 mg, 2.42 mmol) in MeOH (12 mL) was added catalytic amount of 20% $Pd(OH)_2/C$. The reaction mixture was then subjected to hydrogenation under 1 atm pressure for 6 h. After this time, the reaction mixture was filtered through a pad of Celite and washed with additional MeOH (30 mL). The resulting organic layer was concentrated *in vacuo*, which was used as such for the next step without further purification.



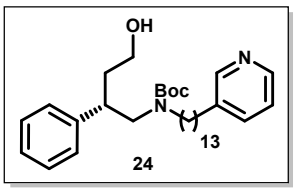
23

Pyridyl aldehyde **26** (665 mg, 2.42 mmol) in ethanol (10 mL) was added to above synthesized TBS-protected amine intermediate in ethanol (10 mL) followed by addition of anhydrous Na_2SO_4 (2.1 g, 14.6 mmol) at 0 ^oC. The reaction mixture was then stirred at room temperature for 36 h. After this time, $Na(CN)BH_3$ (305 mg, 4.84 mmol) was added to the reaction mixture at 0 ^oC and the reaction mixture was stirred at room temperature for additional 12 h. The ethanol from the reaction mixture was evaporated *in vacuo*. The reaction mixture was then diluted with water and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and used as such for the next step without further purification.

NaH (87 mg, 3.63 mmol) was added to the solution of above coupled amine derivative in 20 mL of dry DMF at 0 °C. After the solution was stirred for 10 min, di-*tert*-butyl dicarbonate (790 mg, 3.63 mmol) and DMAP (150 mg, 1.2 mmol) were added at the same temperature. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction as monitored by TLC, the reaction was quenched with water and extracted with diethyl ether (3 x 20 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (EtOAc/hexane 1:9 v/v) as eluent furnished the compound **23** (1.27 g, 82%) as yellow oil. $[\alpha]_D^{25}$ -45.2 (*c* 0.8, CH_2Cl_2); IR (CH_2Cl_2) ν: 3075, 2982, 2431, 1567, 1383, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45-8.47 (m, 2H), 7.51-7.54 (dt, J = 1.84, 7.76 Hz, 1H), 7.29-7.33 (m, 3H),

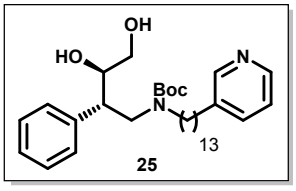
7.17-7.25 (m, 3H), 3.39-3.64 (m, 3H), 3.02-3.30 (m, 3H), 2.85-2.91 (m, 1H), 2.63 (t, J = 8.28 Hz, 2H), 1.84-1.96 (m, 4H), 1.61-1.68 (m, 2H), 1.44 (s, 9H), 1.19-1.34 (m, 18H), 0.89 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8, 147.0, 142.6, 137.9, 135.7, 128.3, 128.2, 128.0, 126.4, 123.2, 79.0, 60.9, 60.7, 53.4, 52.7, 47.3, 41.3, 40.7, 35.8, 32.9, 31.1, 29.5, 29.5, 29.3, 29.1, 28.3, 28.1, 27.7, 26.8, 25.8, 18.2, -5.4. HRMS (ESI)$^+$ m/z calcd for $C_{39}H_{67}N_2O_3Si^+$ ([M+H$^+$]) 639.4900; found 639.4921.

(*S*)-*tert*-Butyl-4-hydroxy-2-phenylbutyl(13-(pyridin-3-yl)tridecyl)carbamate (24):



To a solution of compound **23** (1.0 g, 1.56 mmol) in THF (10 mL) was added TBAF solution (3.12 mL, 1.0 M in THF, 3.12 mmol) dropwise *via* syringe. The reaction mixture was stirred for 6 h at room temperature, after which the reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane 4:6 v/v) as eluent gave the alcohol derivative **24** (770 mg, 96%) as light yellow oil. $[\alpha]_D^{25}$ -55.8 (*c* 0.5, CH_2Cl_2); IR (CH_2Cl_2) v: 3362, 2961, 1589, 1269, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40-8.42 (m, 2H), 7.48-7.50 (dt, J = 1.40, 7.32 Hz, 1H), 7.27-7.31 (m, 2H), 7.18-7.24 (m, 4H), 3.48-3.72 (m, 3H), 2.86-3.25 (m, 4H), 2.59 (t, J = 7.76 Hz, 2H), 1.81-1.88 (m, 5H), 1.57-1.64 (m, 2H), 1.42 (s, 9H), 1.22-1.30 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.6, 146.8, 138.0, 135.9, 128.4, 127.8, 126.5, 123.2, 79.2, 60.6, 52.8, 47.8, 41.3, 35.7, 32.9, 31.0, 29.6, 29.5, 29.4, 29.4, 29.3, 29.0, 28.3, 28.1, 26.7, 22.6, 14.0. HRMS (ESI)$^+$ m/z calcd for $C_{33}H_{53}N_2O_3^+$ ([M+H$^+$]) 525.4000; found 525.4104.

***tert*-Butyl(2*S*,3*R*)-3,4-dihydroxy-2-phenylbutyl(13-(pyridin-3-yl)tridecyl)carbamate (25):**

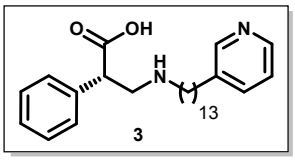


To a solution of oxalyl chloride (100 mg, 68 µL, 0.78 mmol) in dry CH_2Cl_2 (5 mL) at -78 °C was added dropwise DMSO (125 mg, 115 µL, 1.6 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of alcohol **24** (270 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min, then Et_3N (230 mg, 320 µL, 2.3 mmol) in CH_2Cl_2 (5 mL) dropwise and stirred for 3 h. The reaction mixture was diluted with water and the organic layer separated. The aqueous layer was

extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used in the next step without further purification.

To a DMSO solution (5 mL) of L-proline (12 mg, 0.104 mmol, 20 mol %) was added above synthesized aldehyde and nitrosobenzene (62 mg, 0.572 mmol) successively at room temperature. After stirring the reaction mixture for 30 min, MeOH (5 mL) and $NaBH_4$ (30 mg, 0.78 mmol) were added and the reaction mixture was stirred for 15 min at 0 ^oC. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue thus obtained above was dissolved in MeOH (5 mL) and subjected to treatment with $CuSO_4.5H_2O$ (33 mg, 0.13 mmol) at 0 ^oC to room temperature for 12 h. After completion of reaction as monitored by TLC, it was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes 7:3 v/v) as eluent to afford the diol **25** (170 mg, 61%). $[\alpha]_D^{25}$ -42.2 (*c* 1.02, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3369, 2942, 2855, 1467, 1312, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.43 (m, 2H), 7.48-7.50 (m, 1H), 7.22-7.31 (m, 6H), 4.18-4.24 (m, 1H), 3.87 (bs, 1H), 3.20-3.48 (m, 3H), 2.77-2.98 (m, 3H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.59-1.61 (m, 4H), 1.48 (s, 9H), 1.25-1.29 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 149.7, 146.9, 138.8, 135.9, 129.0, 128.3, 127.0, 80.5, 70.4, 65.1, 49.0, 47.6, 46.7, 32.9, 31.1, 29.6, 29.5, 29.5, 29.3, 29.2, 29.1, 28.3, 26.8, 14.1. HRMS (ESI^+) m/z calcd for $C_{33}H_{53}N_2O_4^+$ ($[M+H^+]$) 541.4000; found 541.4012.

(*S*)-Nakinadine B (3): To a solution of diol **25** (100 mg, 0.185 mmol) in dioxane-water (3:1, 2 mL) was added $NaIO_4$ (80 mg, 0.37 mmol). The reaction was stirred at 25 ^oC for 3 h. After completion of reaction, water (5 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated *in vacuo* to give crude aldehyde which was used as such for the next step without further purification.



3

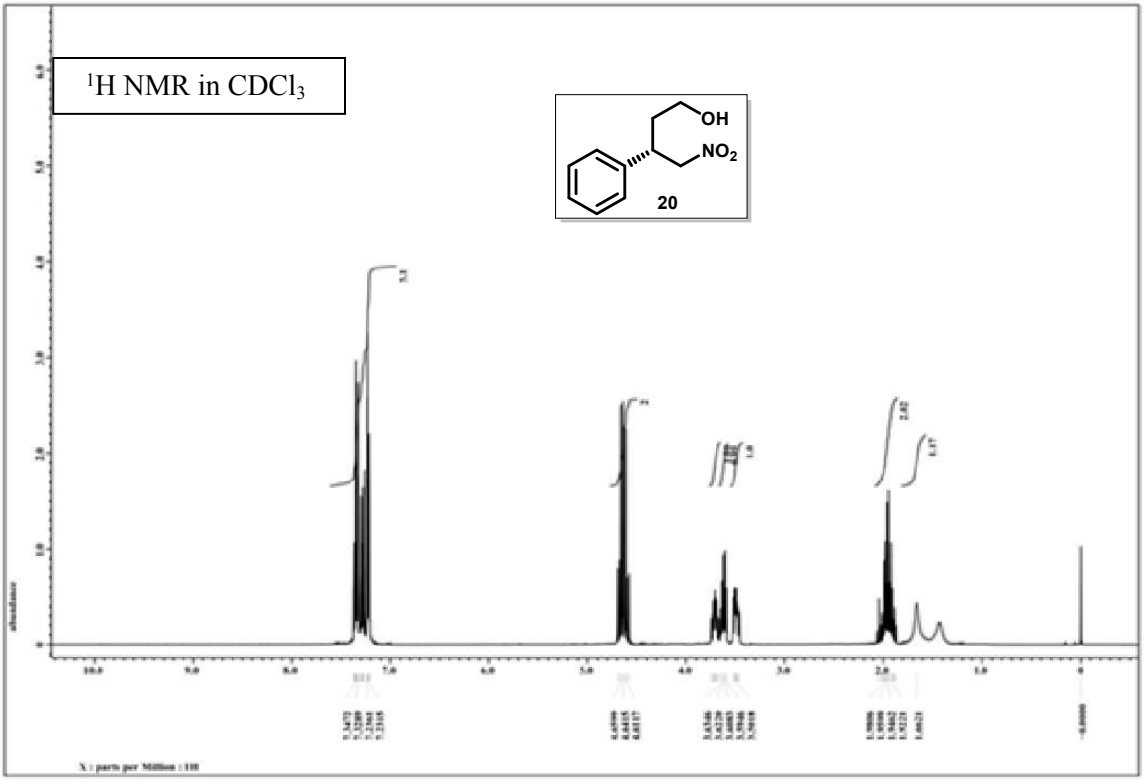
The above aldehyde was dissolved in DMF followed by addition of oxone (57 mg, 0.185 mmol) and stirred at room temperature for 12 h. The resulting solution was diluted with water, filtered

through a celite pad, washed and extracted with diethyl ether (3 x 10 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo* to obtain the crude product which was used for the next step without further purification.

To the above acid product in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL) and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography using (CH_3OH/CH_2Cl_2 1:9 v/v) as eluent to give title compound **3** (63 mg, 81%) as a white solid compound. mp 120-122 °C {$[\alpha]_D^{25}$ -6.4 (*c* 1, $CHCl_3$) [Lit.[3a] -6.3 (*c* 1, $CHCl_3$)]} IR (CH_2Cl_2) *v*: 3032, 2925, 2853, 1652, 1562 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 8.41-8.42 (m, 2H), 7.47-7.49 (m, 1H), 7.12-7.34 (m, 6H), 3.99 (m, 1H), 3.38-3.48 (m, 1H), 2.78-2.87 (m, 3H), 2.57-2.61 (t, *J* = 7.56 Hz, 2H), 1.57-1.67 (m, 4H), 1.20-1.29 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 173.2, 149.8, 147.0, 138.0, 137.8, 135.8, 128.7, 128.1, 127.2, 123.2, 52.3, 51.1, 47.8, 32.9, 31.1, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 29.1, 29.1, 26.7, 25.7. HRMS (ESI^+) m/z calcd for $C_{27}H_{41}N_2O_2^+$ ([$M+H^+$]) 425.3163; found 425.3163.

3.1.7 Spectra:

1. ^1H and ^{13}C NMR spectra of **20**
2. ^1H and ^{13}C NMR spectra of **22**
3. ^1H and ^{13}C NMR spectra of **26**
4. ^1H and ^{13}C NMR spectra of **23**
5. ^1H and ^{13}C NMR spectra of **24**
6. ^1H and ^{13}C NMR spectra of **25**
7. ^1H and ^{13}C NMR spectra of **3**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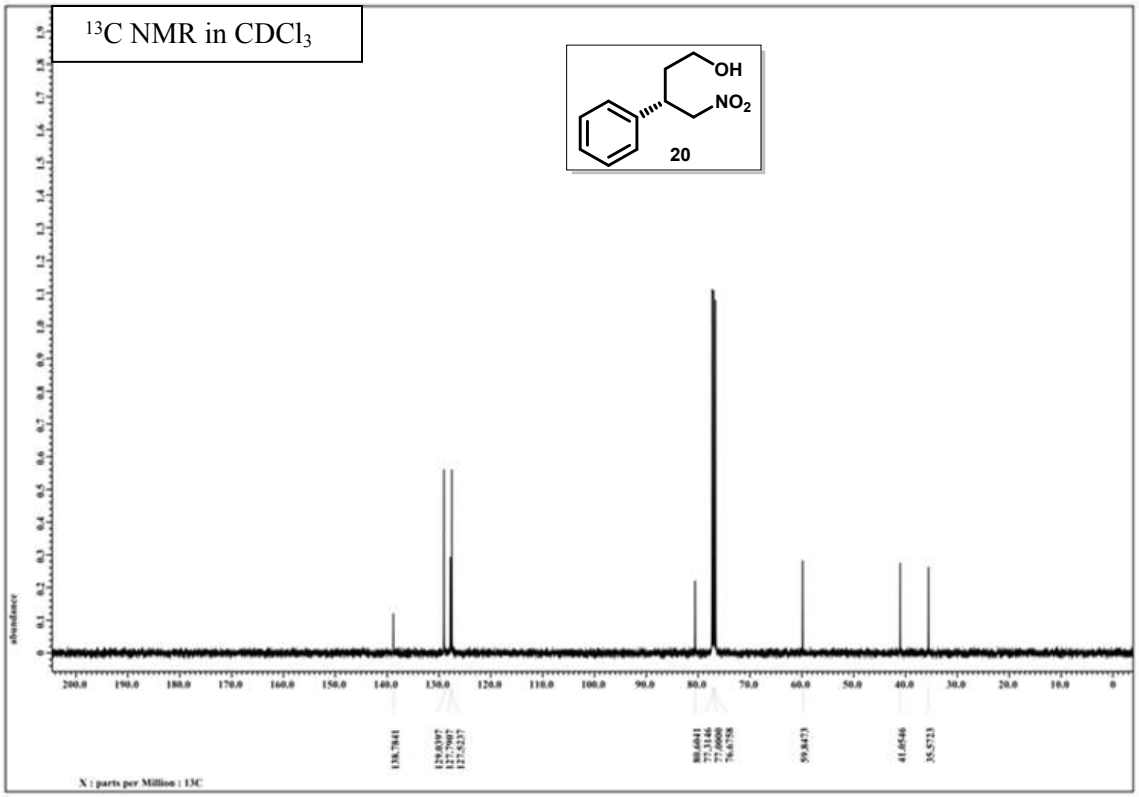
NO_2
20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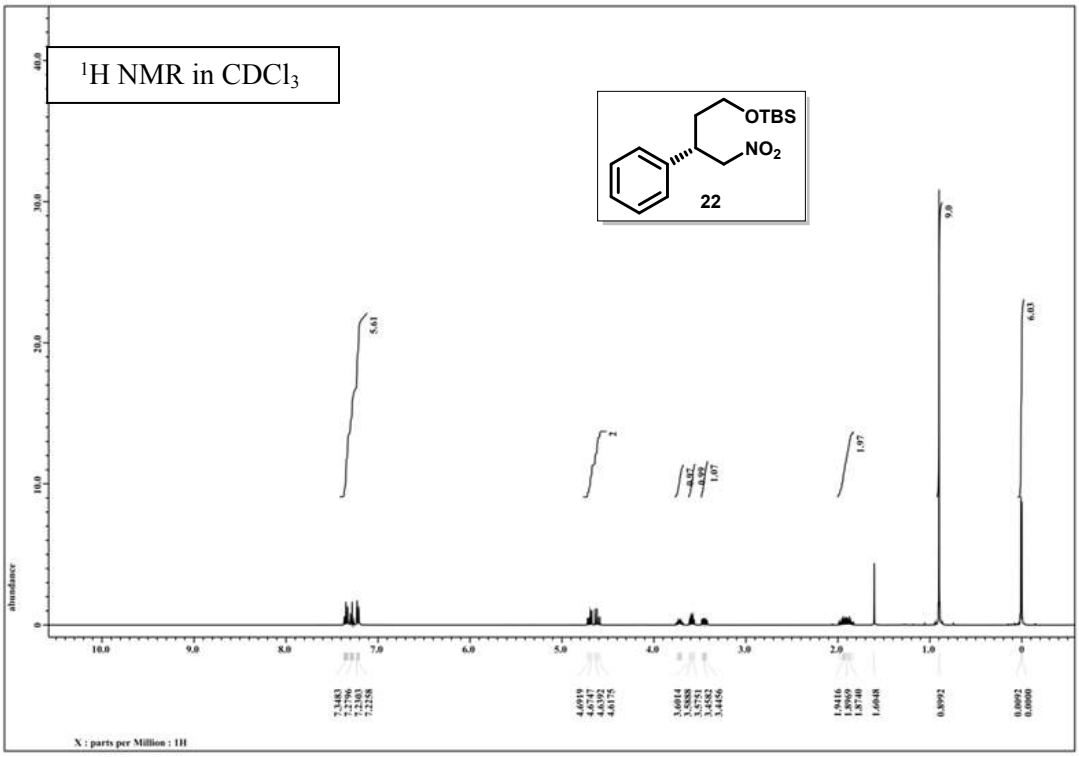
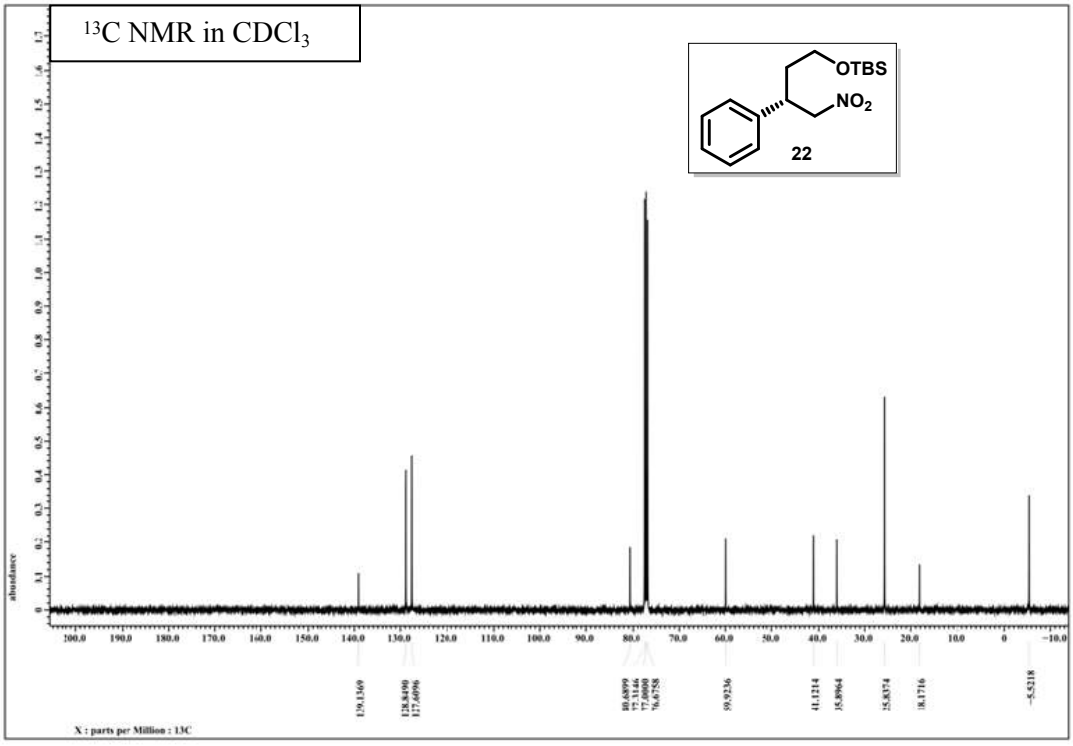
OH
NO_2
20


^{1}H NMR in $CDCl_3$
OTBS
NO_2
22
X : parts per Million : 1H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OTBS
NO_2
22
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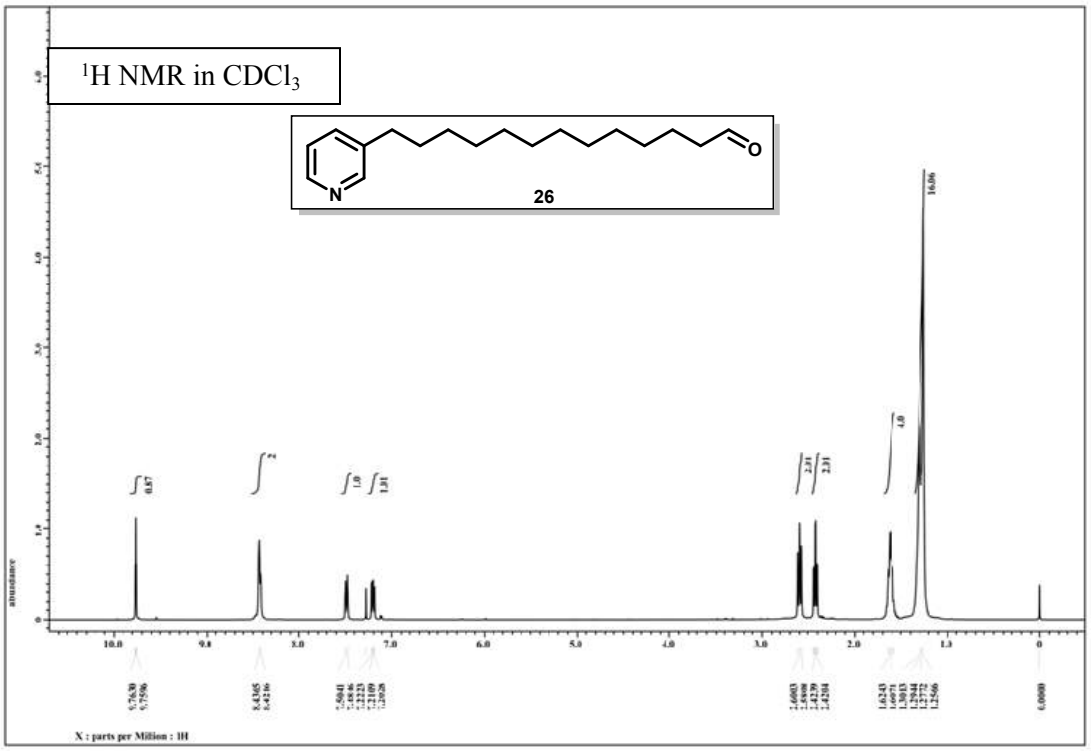
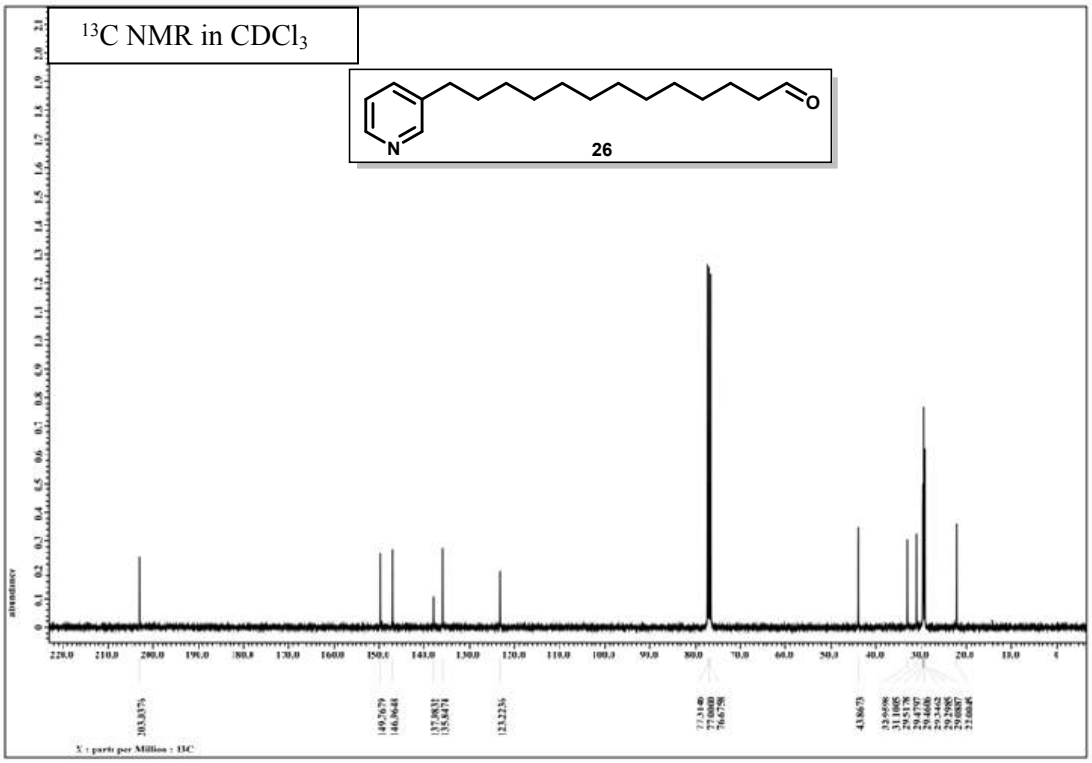
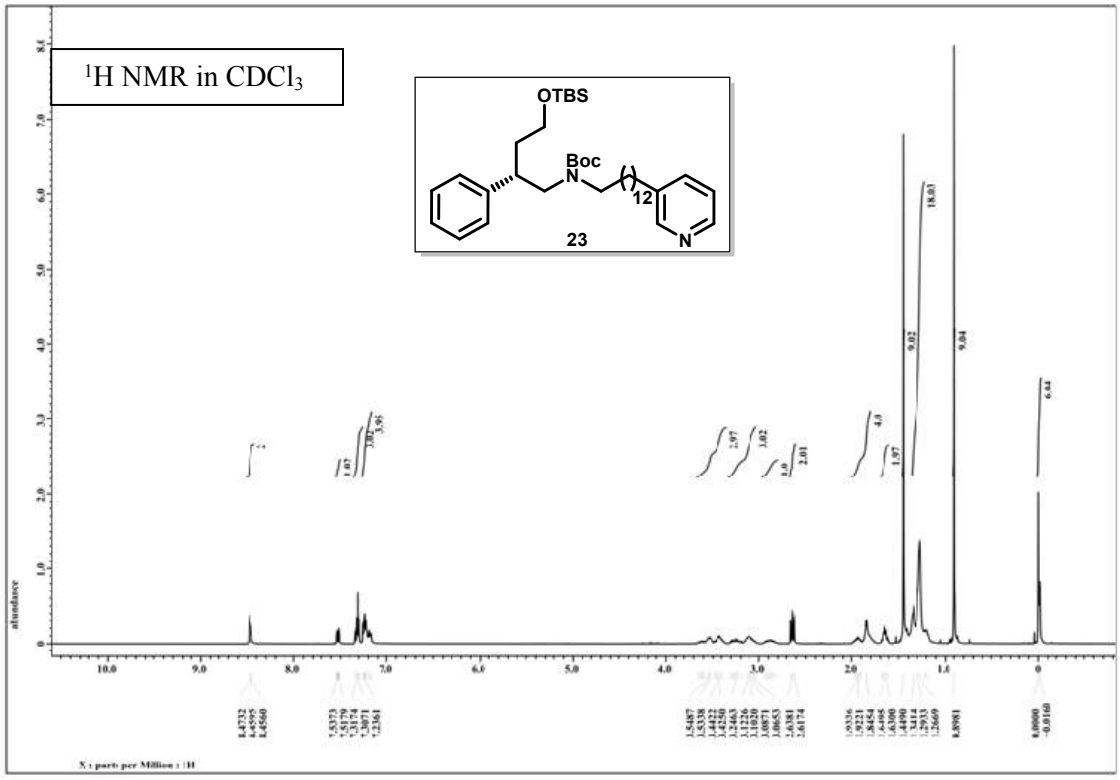
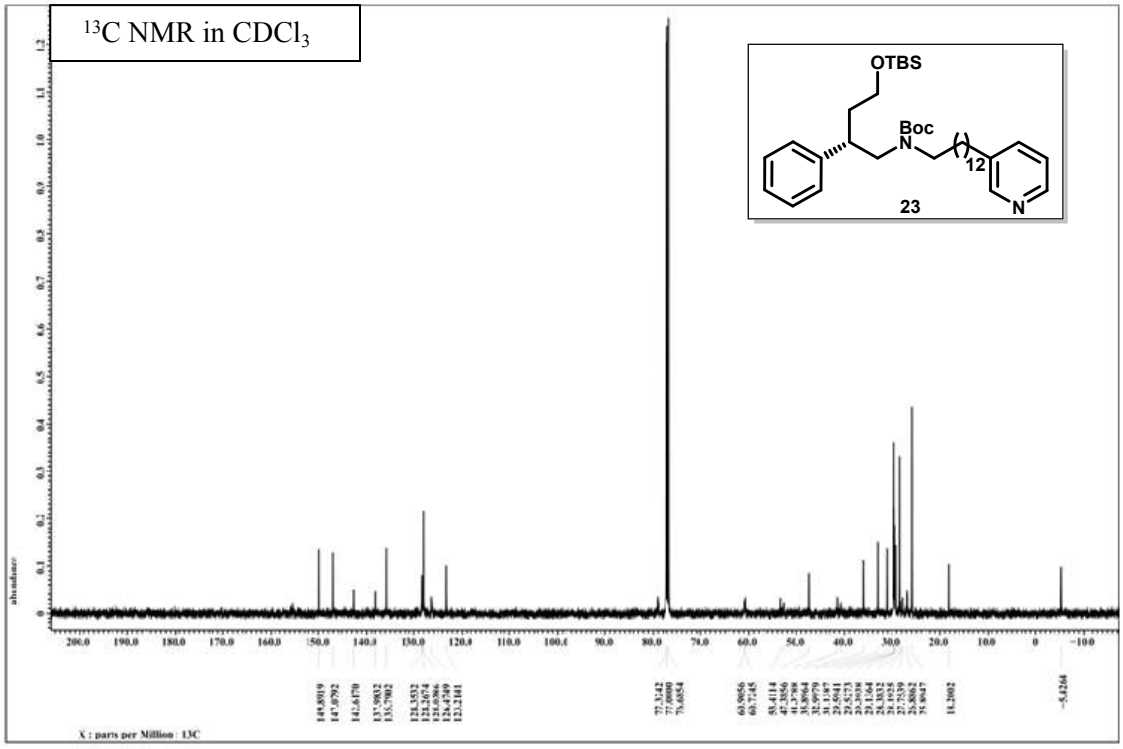

^{1}H NMR in $CDCl_3$
O
N
26
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
O
N
26
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OTBS
Boc
N
12
N
23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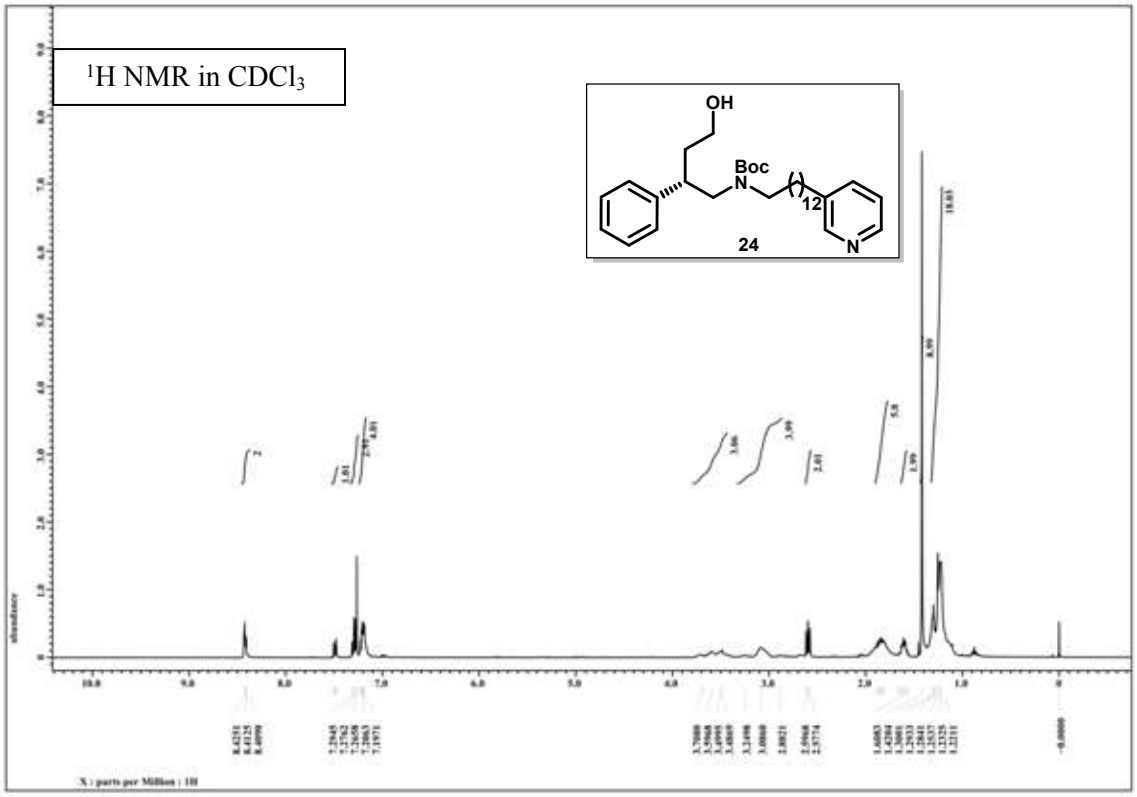
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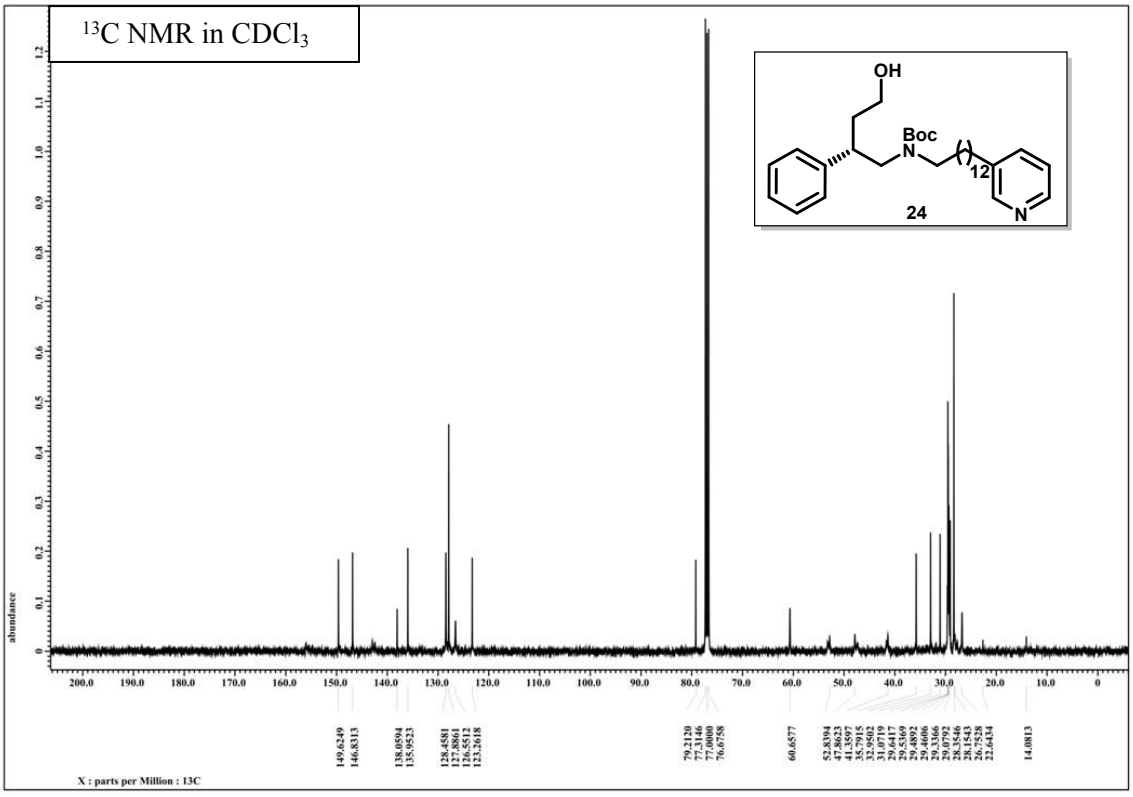
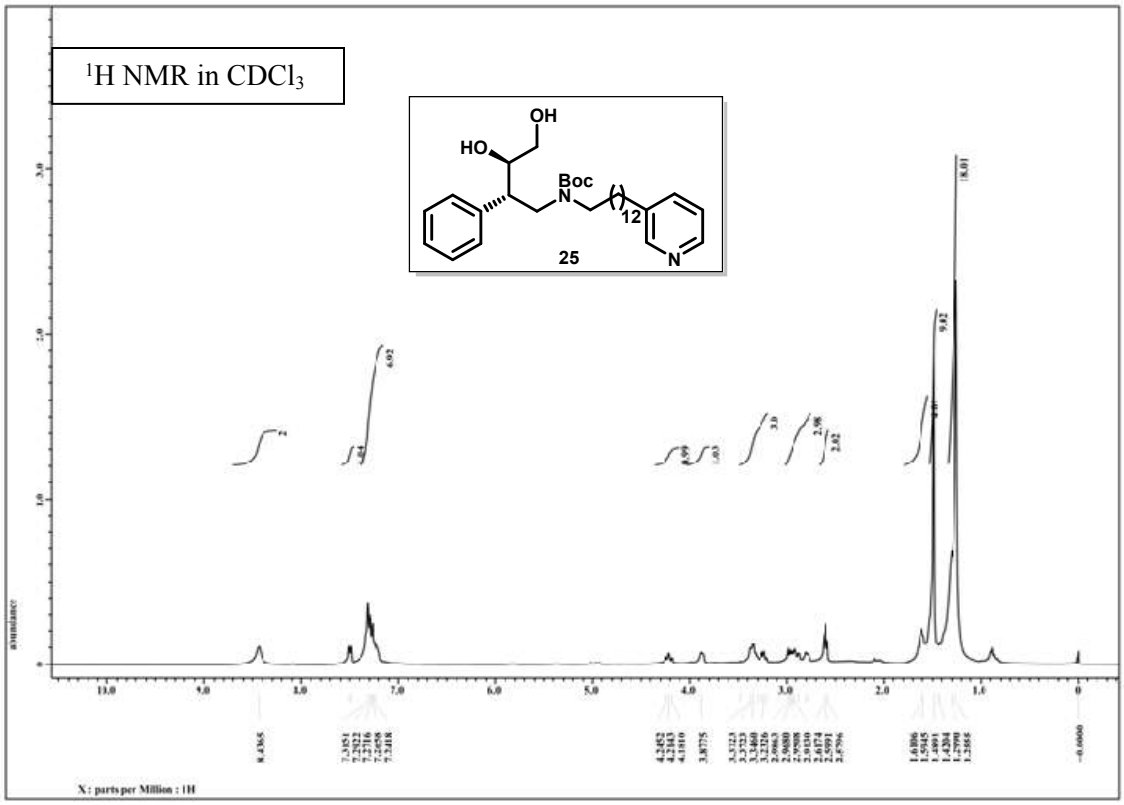

^{13}C NMR in $CDCl_3$
OH
Boc
N
12
N
24
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
HO
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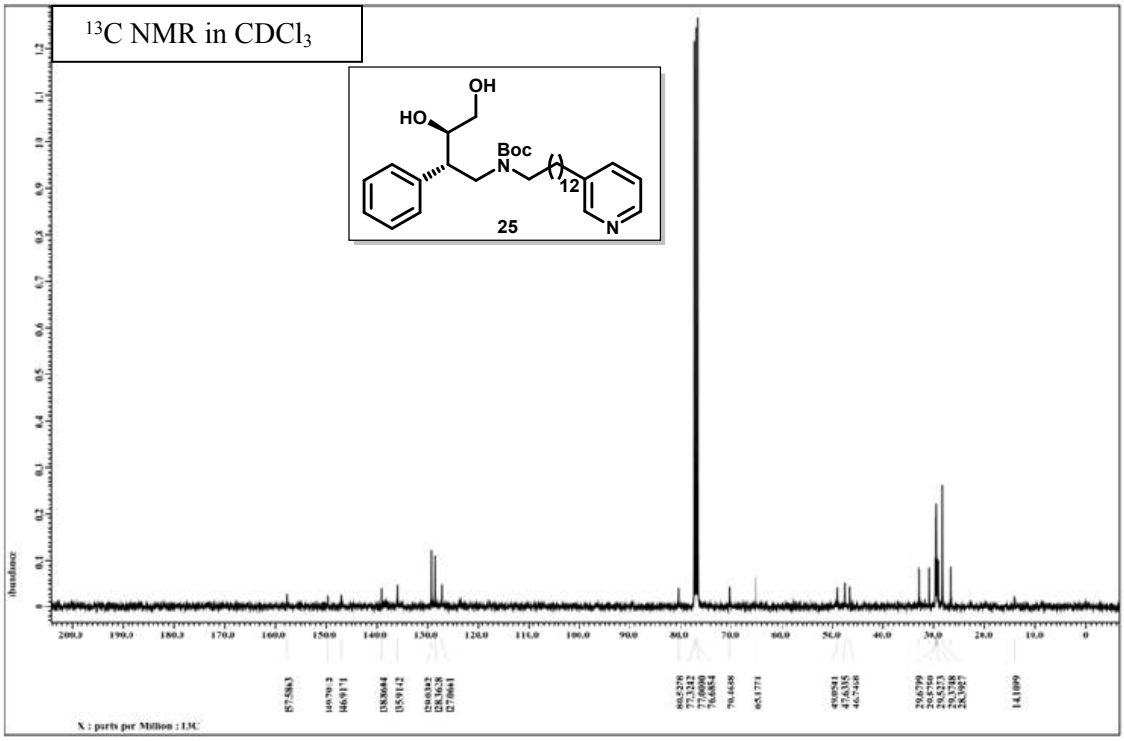
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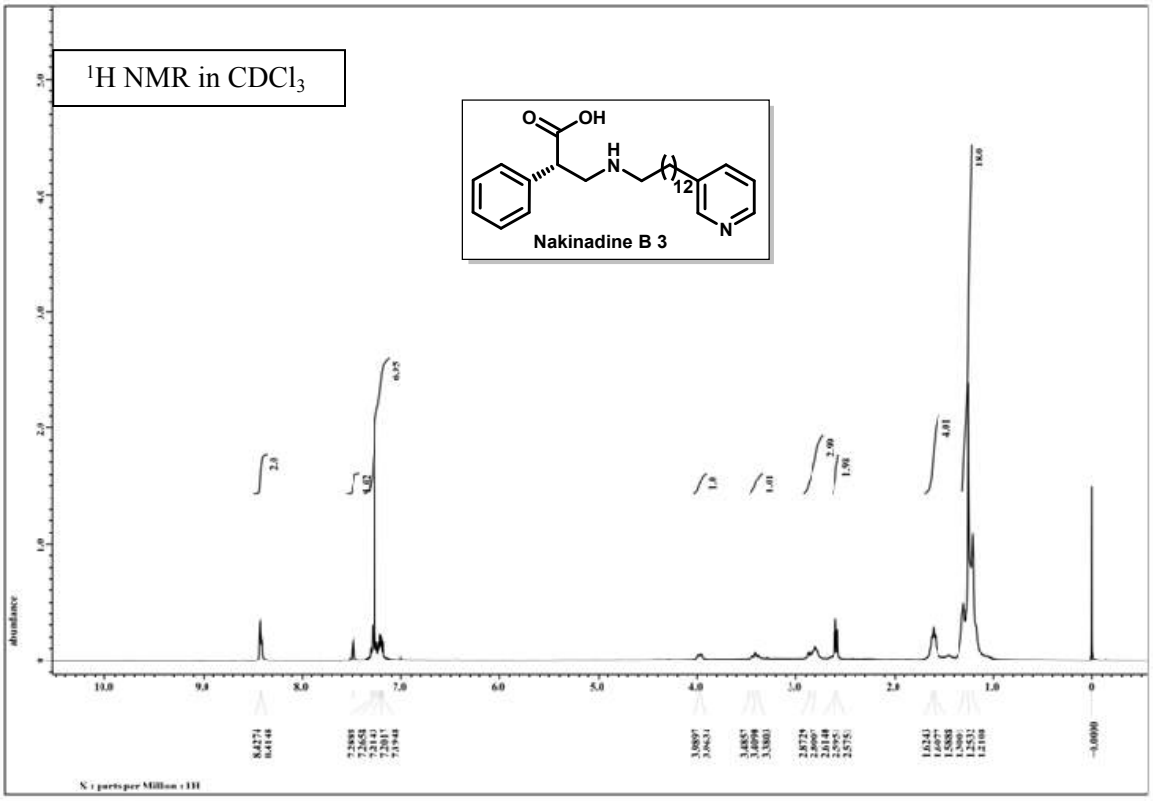
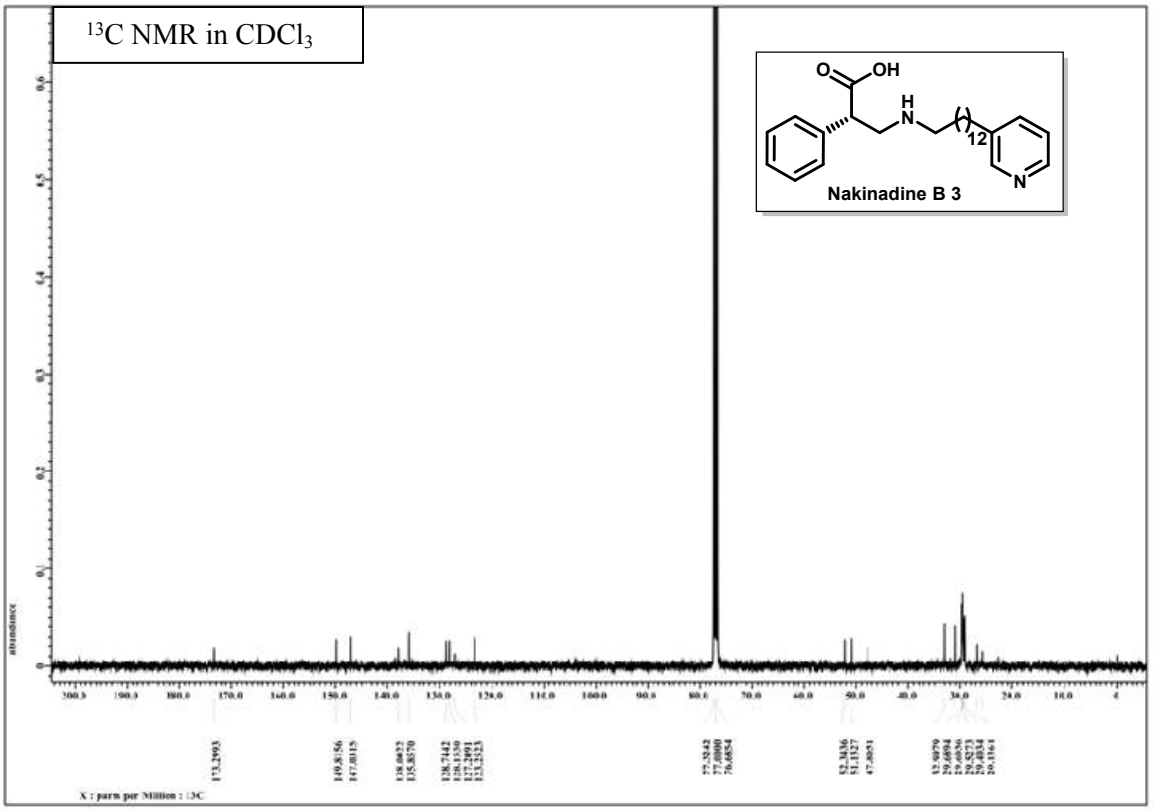

^{1}H NMR in $CDCl_3$
Nakinadine B 3


^{13}C NMR in $CDCl_3$
Nakinadine B 3

3.2 Section B

An enantioselective approach to 3-substituted pyrrolidines: asymmetric synthesis of pyrrolidine core of serotonin norepinephrine reuptake inhibitors (SNRIs)

3.2.1 Introduction:

Pyrrolidines and their substituted derivatives are among the most bioactive *N*-heterocyclic compounds in organic chemistry due to prevalence of these structural motifs either as itself or as a part of a more complex structural moiety in a large number of biologically active molecules and natural products.[13] Among them, enantiomerically pure 3-substituted pyrrolidines and their derivatives (**27**-**28**) are important subclass of compounds possessing interesting pharmacological activities.[14] Serotonin-norepinephrine reuptake inhibitors (SNRIs) are advanced novel class of antidepressant drugs which have been suggested for the treatment of several central nervous disorders including chronic painful conditions such as diabetic peripheral neuropathic pain and fibromyalgia.[17] The precise mechanism of action of SNRIs has not yet been fully elucidated, but it is believed to be mainly caused by decreasing the levels of serotonin and norepinephrine in the synaptic cleft, resulting erratic signalling.[18] Currently, several SNRIs marketed worldwide have proven to be safe and effective drugs in chronic painful conditions and mood disorders but the search for new SNRIs has always been of greater significance upon past drugs in regards to efficacy, tolerability and fewer side effects. In 2013, Johansson and co-workers[15] reported the discovery of novel 3-substituted pyrrolidine ether SNRI **29**, which is the first example showing improved norepinephrine transporter activity, acceptable metabolic stability and exhibiting minimal drug to drug interaction (Figure 2). Additionally, SNRI **29** has also been explored as a selective serotonin-norepinephrine reuptake inhibitor *in vitro* and *in vivo* that retains pain inhibiting activity in a previously proven model of pain behaviour responsive to clinically used SNRIs and possesses favourable ADME properties for its use in treatment of various pain conditions.[15] Stangeland and co-workers have also reported previously the discovery of an another novel 3-substituted pyrrolidine ether SNRI **30** which showed inhibition of the serotonin

and/or norepinephrine transporter, for the treatment of neuropathic pain with reduced side effects such as nausea (Figure 2).[16]

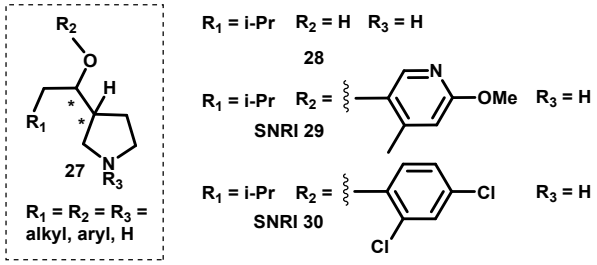


Figure 2. Structures of 3-substituted pyrrolidines

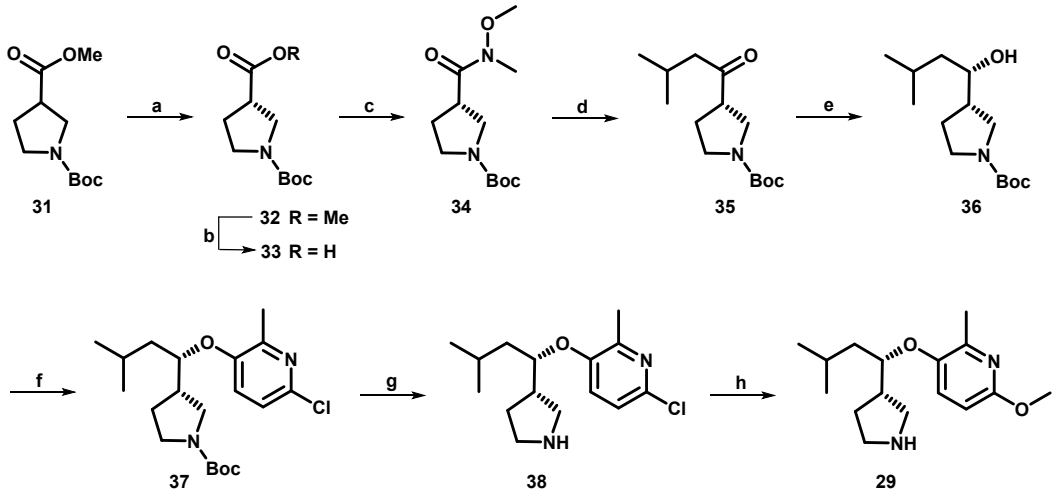
The SNRIs **29** and **30** have been synthetic targets of considerable interest for pharmaceutical industries and academia due to their utility in treatment of central nervous disorders with an array of functionalities.[15,16]

3.2.2 Review of Literature:

Only two approaches for the synthesis of 3-substituted pyrrolidine **27** have been documented in the literature.[15,19] These strategies employed chiral pool approach starting from protected pyrrolidine derivatives which are described below.[15,19]

Johansson, A. M. *et al.* (2013)[15]

A. M. Johansson and co-workers accomplished the synthesis of SNRi **29** starting from *N*-Boc pyrrolidine ester derivative **31** which on enzymatic resolution gave the (*S*)-methyl ester **32** which on hydrolysis using LiOH afforded acid derivative **33** (Scheme 5).



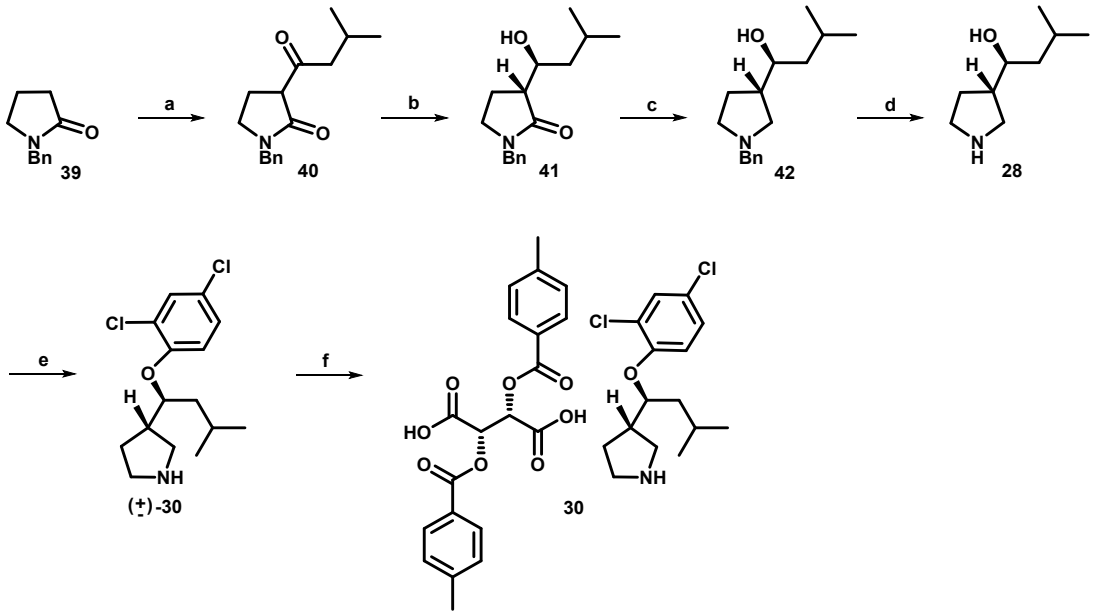
Scheme 5. *Reagents and conditions*: (a) lipase AS, buffer phosphate, K_2CO_3, rt, 20.5 h, 43%; (b) LiOH, THF, 22 ^oC, overnight, 74%; (c) *N*,*O*-dimethylhydroxyl-amine HCl, CDI, DCM, rt, 72 h,

92%; (d) *i*BuMgCl, THF, 22 °C, 2 h, 94%; (e) $NaBH_4$, MeOH, 30 °C, 4 h, 98%; (f) NaH, 6-chloro-3-fluoro-2-methyl-pyridine, DMA, 30 °C, 44 h, 87%; (g) TFA, anisole, 45 °C, overnight; (h) NaOMe, DMSO, 100 °C, 50 h, 90%.

The derivative **33** was converted to Weinreb amide **34** which on Grignard reaction with *iso*-butylmagnesium bromide afforded ketone derivative **35**. The derivative **35** was reduced to the alcohol derivative **36** using $NaBH_4$, subsequently introduced 2-methyl-6-chloro-pyridine *via* base catalyzed nucleophilic aromatic substitution reaction to afford derivative **37**. Finally, the derivative **37** on *N*-Boc deprotection followed by methoxide addition furnished compound **29** in 90% yield.

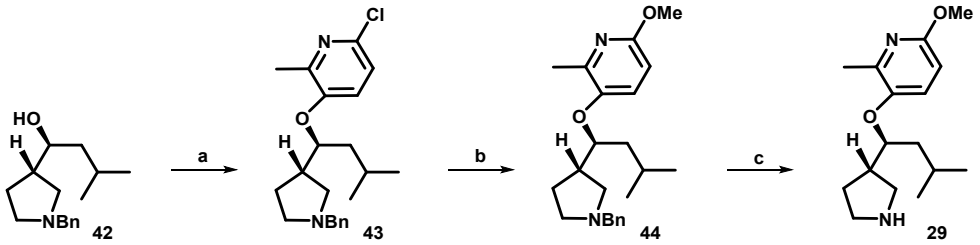
Magnus, N. A. *et al*. (2013)[19]

N. A. Magnus and co-workers reported the synthesis of SNRi **30** starting with *N*-benzyl-*γ*-lactam **39** which on treatment with ethyl isovalerate using LDA afforded *β*-keto-*γ*-lactam **40** as an oil (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) LDA, 2-MeTHF, ethyl 3-methylbutanoate, - 10 °C to 5 °C, 3 h, 79%; (b) $RuCl_2(PPh)_3$, H_2, MeOH, 50 °C, 24 h, 77%; (c) vitride, PhMe, 22 °C, 22 h, 100%; (d) $Pd(OH)_2/C$, H_2, EtOH, 22 °C, 7 days, 100%; (e) 1,3-dichloro-4-fluorobenzene, *t*BuOK, NMP, 4 °C to 22 °C, 16 h, 81%; (f) L-DTTA, EtOH, EtOAc, 30 °C, 16 h, 29%.

The derivative **40** on diastereoselective hydrogenation in the presence of catalyst $(PPh_3)_3RuCl_2$ afforded derivative (±)-**41** as a solid compound. The lactam derivative **41** on reduction with Vitride (sodium bis(2-methoxyethoxy) aluminum hydride) furnished (±)-**42** as a crude oil, which on hydrogenation using $Pd(OH)_2/C$ in EtOH furnished (±)-**28** as a crude oil. The alcohol (±)-**28** on base catalyzed SNAr reaction with 1,3-dichloro-4-fluorobenzene furnished (±)-**30** as an oil, which on resolution using di-*p*-toluoyl-L-tartaric acid afforded diastereomeric salt in 29% yield and 92% *ee* from which SNRi **30** was recovered by recrystallization in >98% *ee*. On the other side, the synthesis of SNRi **29** commenced with pyrrolidine derivative **42** which on base catalyzed S_NAr reaction with 6-chloro-3-fluoro-2-methylpyridine afforded the derivative **43** in 65% yield (Scheme 7). The derivative **43** on treatment with KOMe/DMSO afforded the pyrrolidine moiety **44** which on hydrogenation using Pd/C in EtOH furnished the target compound **29** in 94% yield.



Scheme 7. *Reagents and conditions*: (a) 6-chloro-3-fluoro-2-methylpyridine, ^{t}BuOK, DMF, 19 ^{o}C, 40 h, 65%; (b) MeOK, DMSO, 100 ^{o}C, 1 h, 98%; (c) Pd/C, H_2, EtOH, 60 ^{o}C, 24 h, 94%.

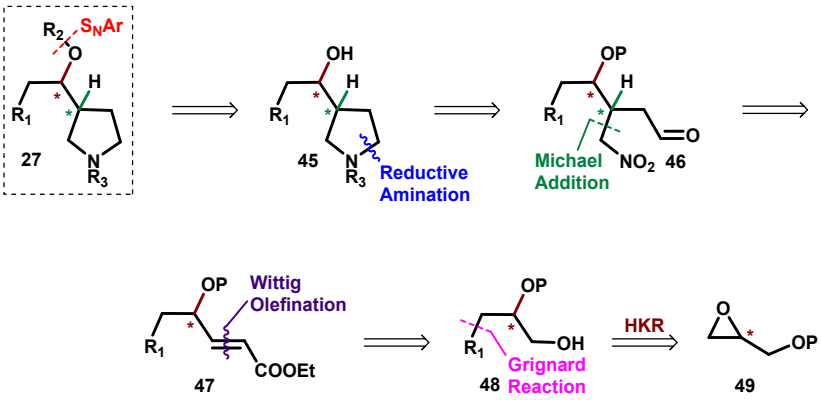
3.2.3 Present Work:

As part of our ongoing research programme towards the asymmetric syntheses of biologically active compounds, we became interested in developing a simple and flexible route to 3-substituted pyrrolidines **27** and its application to the asymmetric synthesis of SNRIs **29** and **30**. To the best of our knowledge, there is no any report documented in the literature to date for the enantioselective synthesis of 3-substituted pyrrolidines **27** employing Jacobsen's HKR and diphenylprolinol silyl ether mediated asymmetric Michael addition reactions as key steps.

3.2.4 Results and Discussion:

Our synthetic approach for the stereoselective synthesis of 3-substituted pyrrolidine skeleton **27** was envisioned *via* the retrosynthetic route as shown in Scheme 8. The

pyrrolidine core unit **45** was visualized as a synthetic intermediate from which 3-substituted pyrrolidine ethers **27**, SNRIs **29** and **30** could be synthesized *via* base catalyzed nucleophilic aromatic substitution reaction (S_NAr) with corresponding commercially available aromatic halides.



Scheme 8. Retrosynthesis of 3-substituted pyrrolidines

The pyrrolidinol derivative **45** in turn could be obtained from nitroaldehyde derivative **46** *via* intramolecular reductive amination. We envisaged that the nitroaldehyde **46** would serve as a key intermediate in this approach and could be prepared by means of diphenylprolinol silyl ether mediated asymmetric Michael addition of nitromethane to α,β-unsaturated aldehyde derived from the reduction of olefinic ester derivative **47**. The ester derivative **47** could be assembled from mono-protected terminal alcohol derivative **48** by oxidation followed by Wittig olefination. Enantiomerically pure alcohol derivative **48** could be easily accessed from the chiral glycidyl ether **49** prepared from racemic glycidyl ether *via* Jacobsen's HKR, subsequent treatment with suitable Grignard reagent followed by standard organic transformations. The configuration of 3-substituted pyrrolidine skeleton **27** could be manipulated by simply changing the (*S*)- and (*R*)-configuration of the readily available glycidyl ether using (*S*,*S*)-salen-Co-(OAc) and (*R*,*R*)-salen-Co-(OAc) in Jacobsen's HKR and/or by using L- and D-diphenylprolinol silyl ether catalyst during Michael addition step. Thus, in principle, all the four isomers of SNRIs **29** and **30** along with different substitutions at three different sites R_1, R_2 and R_3 could be accessed by this approach.

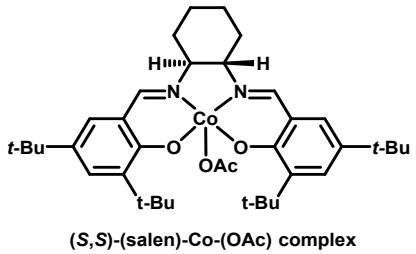
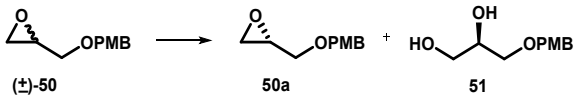


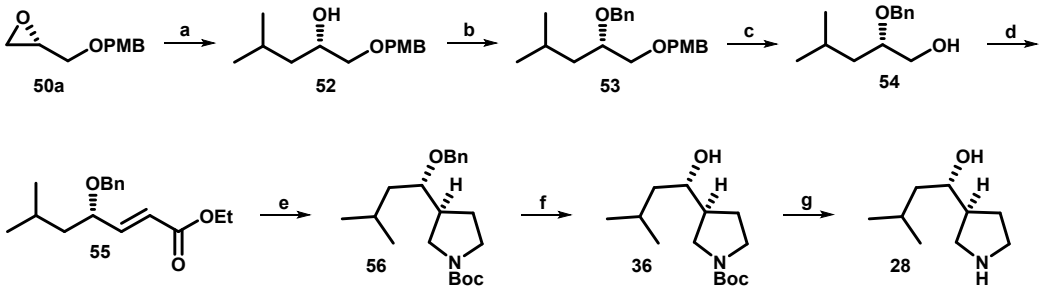
Figure 3. Structure of Jacobsen's HKR catalyst

As displayed in Scheme 9, the synthesis of pyrrolidine core **28** of SNRIs **29** and **30** commenced with readily available racemic PMB-protected glycidyl ether **50** which was subjected to Jacobsen's HKR[20a] conditions in the presence of catalytic amount of (*R*,*R*)-(salen)-Co-(OAc) complex (Figure 3) afforded (*S*)-PMB-protected glycidyl ether **50a** as a single enantiomer {$[\alpha]_D^{25}$ -2.7 (*c* 3, $CHCl_3$); {Lit.[20b] $[\alpha]_D^{24}$ -2.9 (*c* 3, $CHCl_3$)}, and (*R*)-PMB protected triol **51** (Scheme 9). The physical and spectroscopic data of (*S*)-PMB glycidyl ether **50a** were found to be in full agreement with those reported in the literature.[20b]



Scheme 9. *Reagents and conditions*: (a) (*R*,*R*)-(Salen-Co-(OAc) (0.5 mol%), dist. H_2O, THF, 0 ^oC to rt, 14 h, (47% for **50a**, 45% for **51**).

With enantiomerically pure (*S*)-PMB-protected glycidyl ether **50a** in hand, we then performed Cu(I)-catalyzed regioselective ring-opening with *iso*-propylmagnesium bromide at -20 ^oC which furnished the PMB protected alcohol (*S*)-**52** as the major product in 86% yield (Scheme 10). The IR spectrum of **52** showed hydroxyl absorption at 3459 cm^{-1}. Treatment of alcohol (*S*)-**52** with BnBr under the basic conditions successfully delivered the protected diol (*S*)-**53** in excellent yield. The selective deprotection of *O*-PMB ether group of (*S*)-**53** with DDQ furnished the terminal alcohol derivative (*S*)-**54** quantitatively. The IR spectrum of **54** showed hydroxyl absorption at 3351 cm^{-1}.



Scheme 10. *Reagents and conditions*: (a) $(CH_3)_2CHMgBr$, anhydrous THF, CuI, -20 ^oC, 6 h, 86%; (b) $PhCH_2Br$, NaH, DMF, 0 ^oC to rt, 3 h, 89%; (c) DDQ, CH_2Cl_2, rt, 8 h, 93%; (d) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h; ii) PPh_3=CHCOOEt, THF, rt, 24 h, 90% (over two steps); (e) i) DIBAL-H, CH_2Cl_2, -78 ^oC, 1 h; ii) (*R*)-diphenylprolinol silyl ether, CH_3NO_2, benzoic acid, MeOH, rt, 24 h; iii) Zn, CH_3COOH, H_2O, 0 ^oC to rt, 3 h; iv) $(Boc)_2O$, NaH, DMAP, DMF, 0 ^oC to rt, 10 h, 81% (over four steps); (f) H_2, Pd/C, MeOH, rt, 24 h, 87%; (g) TFA, CH_2Cl_2, rt, 5 h, 92%.

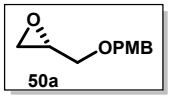
Oxidation of alcohol (*S*)-**54** under Swern conditions[21] and subsequent treatment of aldehyde with (ethoxycarbonylmethylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester (*S*)-**55** in 90% yield. The IR spectrum of **55** showed the ester carbonyl absorption at 1716 cm^{-1} and olefin C=C stretching at 1651 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 6.85 (doublet of doublet, one proton) with the coupling constant J = 4.0, 16.0 Hz and δ 6.01 (doublet, one proton) with the coupling constant J = 14.8 Hz indicating *trans*-olefin. Our next aim was to carry out the synthesis of 3-substituted pyrrolidine moiety. Towards this end, DIBAL-H reduction of ester (*S*)-**55** at -78 ^oC to α,β-unsaturated aldehyde and subsequent enantioselective conjugate addition[22] reaction of nitromethane in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether afforded the nitroaldehyde adduct which on spontaneous intramolecular reductive amination with Zn/CH_3COOH[23] followed by *N*-Boc protection under basic conditions furnished *N*-Boc-pyrrolidine skeleton **56** in 81% yield (single diastereomer). The pyrrolidine derivative **56** was then subjected to debenzylation under 1 atm H_2 pressure in the presence of a catalytic amount of Pd/C which afforded the alcohol **36** in 87% yield. The alcohol **36** upon S_NAr reaction with commercially 6-chloro-2-methylpyridine and subsequent *N*-Boc deprotection with TFA followed by methoxide moiety addition using the literature route[15] would furnish the SNRI **29**. Finally, the *N*-Boc deprotection of derivative **36** with TFA furnished the pyrrolidine core unit **28** in 92% yield $[\alpha]_D^{25}$ -25.6 (*c* 0.5, CH_3OH). On the other hand, pyrrolidine core unit **28** on S_NAr

reaction with commercially available 1,3-dichloro-4-fluorobenzene under basic conditions would furnish the pyrrolidine ether SNRIs **30** using the known procedure.[19]

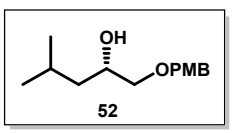
3.2.5 Conclusions:

In conclusion, we have described the first enantioselective approach for the synthesis of 3-substituted pyrrolidine skeleton **27** and its application to the asymmetric synthesis of pyrrolidine core unit **28** of SNRIs **29** and **30** from readily available chiral epoxides as starting material employed diphenylprolinol silyl ether mediated asymmetric Michael addition reactions as key step. The overall yield for the pyrrolidine core unit **28** was 42% after seven column chromatographic purification steps. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. Moreover, the synthetic strategy described has significant potential for variation of substituents at the 3-alkyl site, *O*-aryl and *N*-alkyl sites to synthesize various 3-substituted pyrrolidines with expected increase in antidepressant activities.

3.2.6 Experimental Section:



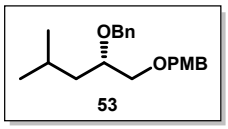
(*S*)-2-(((4-Methoxybenzyl)oxy)methyl)oxirane (50a): To a round bottom flask containing (*R*,*R*)-(salen)-Co(II) precatalyst (31 mg, 51.5 μmol, 0.5 mol%) was sequentially added (±)-PMB glycidyl ether **50** (2.0 g, 10.30 mmol) and AcOH (12 μL, 206 μmol). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 ^{o}C and then THF (100 μL) and H_2O (100 μL, 5.67 mmol) were added. The reaction was allowed to warm to rt over 2 h and stirred for an additional 12 h. The mixture was then purified by silica gel column chromatography (EtOAc/hexanes 1:9 v/v) to afford the desired (*S*)-PMB glycidyl ether **50a** as oil (940 mg, 47%).



(*S*)-1-((4-Methoxybenzyl)oxy)-4-methylpentan-2-ol (52): To a stirred solution of (*S*)-PMB-glycidyl ether **50a** (570 mg, 2.93 mmol) in dry THF (10 mL) and CuI (112 mg, 0.586 mmol) at -20 ^{o}C was added *iso*-propylmagnesiumbromide, freshly prepared from *iso*-propylbromide (720 mg, 550 μL, 5.86 mmol) and magnesium (210 mg, 8.79 mmol) in dry THF (10 mL). The reaction mixture was stirred for 6 h at the same temperature. The reaction was quenched with

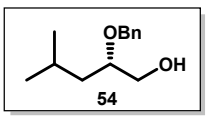
saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography (EtOAc/hexane 1:8 v/v) to afford the desired alcohol **52** (600 mg, 86%) as yellow oil. {$[\alpha]_D^{25}$ +7.8 (c 0.5, CH_3OH); IR (CH_2Cl_2) *v*; 3459, 1662, 1596, 1512, 1052, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.28-7.24 (m, 2H), 6.90-6.87 (m, 2H), 4.48 (s, 2H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 3.45 (m, 1H), 3.26 (m, 1H), 2.34 (d, 1H), 1.82-1.75 (m, 1H), 1.44-1.36 (m, 1H), 1.17-1.11 (m, 1H), 0.92-0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.2, 130.0, 129.3, 113.8, 74.7, 72.9, 68.5, 55.2, 41.9, 24.4, 23.3, 22.0; HRMS $(ESI)^+$ m/z calcd for $C_{14}H_{22}O_3Na^+$ $[M+Na^+]$ 261.1461; found 261.1459.

(*S*)-1-(((2-(Benzyloxy)-4-methylpentyl)oxy)methyl)-4-methoxybenzene (53):



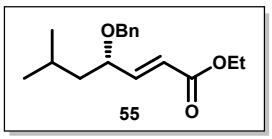
To a DMF solution (10 mL) of alcohol **52** (500 mg, 2.10 mmol) was added NaH (61 mg, 2.52 mmol) at 0 ^oC. After stirring the reaction mixture for 10 min, BnBr (542 mg, 3.15 mmol) was added and reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with cold water, extracted 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 1:19 v/v) to afford the derivative **53** (613 mg, 89%) as colourless oil. $[\alpha]_D^{25}$ +18.1 (*c* 0.7, CH_3OH); IR (CH_2Cl_2) *v*; 3435, 1623, 1562, 1512, 977 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.23 (m, 7H), 6.89-6.86 (m, 2H), 4.71 (d, J = 11.6 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 3.67-3.62 (m, 1H), 3.54-3.46 (m, 2H), 1.80-1.74 (m, 1H), 1.55-1.48 (m, 1H), 1.30-1.23 (m, 1H), 0.89 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.1, 138.9, 130.4, 129.1, 128.2, 127.8, 127.3, 113.7, 73.2, 72.9, 72.0, 55.2, 41.3, 24.4, 23.3, 22.1; HRMS $(ESI)^+$ m/z calcd for $C_{21}H_{28}O_3Na^+$ $[M+Na^+]$ 351.1930; found 351.1930.

(*S*)-2-(Benzyloxy)-4-methylpentan-1-ol (54): To a solution of compound **53** (550 mg, 1.67 mmol) in dry CH_2Cl_2 (10 mL) was added DDQ (456 mg, 2.01 mmol). After TLC indicated no remaining of compound **53**, aqueous saturated $NaHCO_3$ solution was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated



under reduced pressure. The residue obtained was purified by silica gel column chromatography (EtOAc/hexane 1:4 v/v) to afford the terminal alcohol **54** (320 mg, 93%) as a pale yellow oil. $[\alpha]_D^{25}$ -27.2 (*c* 0.76, CH_3OH); IR (CH_2Cl_2) *v*; 3351, 1761, 1575, 1506, 1151, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.37-7.25 (m, 5H), 4.58 (q, *J* = 12 Hz, 2H), 3.75-3.70 (m, 1H), 3.60-3.54 (m, 1H), 3.52-3.47 (m, 1H), 2.03 (t, *J* = 5.9 Hz, 1H), 1.77-1.67 (m, 1H), 1.61-1.54 (m, 1H), 1.32-1.25 (m, 1H), 0.92-0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 138.4, 128.4, 127.8, 127.7, 78.0, 71.4, 64.4, 40.1, 24.6, 22.9, 22.7; HRMS $(ESI)^+$ m/z calcd for $C_{13}H_{20}O_2Na^+$ $[M+Na^+]$ 231.1355; found 231.1352.

Ethyl-(*S*,*E*)-4-(benzyloxy)-6-methylhept-2-enoate (55): To a solution of oxalyl chloride (293 mg, 200 µL, 2.31 mmol) in dry CH_2Cl_2 (5 mL) at -78 °C was added dropwise DMSO (372 mg, 338 µL, 4.77 mmol) in CH_2Cl_2 (5 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of monobenzyl protected alcohol **54** (320 mg, 1.54 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -60°C and then Et_3N (685 mg, 950 µL, 6.77 mmol) was added dropwise and stirred for 30 min. The reaction mixture was poured into saturated solution of $NaHCO_3$ (50 mL) and the organic layer 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.

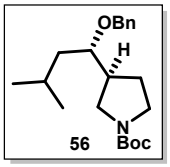


55

To a solution of (ethoxycarbonylmethylene)triphenylphosphorane (806 mg, 2.31 mmol) in THF (10 mL) was added a solution of the above aldehyde in THF (10 mL). The reaction mixture was stirred for 24 h at room temperature. It was then concentrated and purified by silica gel column chromatography by using EtOAc/hexane (1:19 v/v) as eluent to furnish the corresponding *α,β*-unsaturated ester **55** (380 mg, 90% over two steps) as a colorless liquid. $[\alpha]_D^{25}$ -45.6 (*c* 1, CH_3OH); IR (CH_2Cl_2) *v*; 2946, 2857, 1716, 1651, 1351, 1182 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 7.39-7.26 (m, 5H), 6.85 (dd, *J* = 4.0, 16.0 Hz, 1H), 6.01 (d, *J* = 14.8 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.21 (d, *J* = 7.2, 14.0 Hz, 2H) 4.02-3.96 (m, 1H), 1.84-1.74 (m, 1H), 1.65-1.56 (m, 1H), 1.35-1.25 (m, 4H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100

MHz) δ: 166.3, 148.7, 138.0, 128.3, 127.7, 127.6, 121.7, 71.0, 60.4, 44.1, 24.2, 23.0, 22.1, 14.2; HRMS (ESI)$^+$ m/z calcd for $C_{17}H_{25}O_3^+$ [M+H$^+$] 277.1798; found 277.1796.

***tert*-Butyl(*S*)-3-((*S*)-1-(benzyloxy)-3-methylbutyl)pyrrolidine-1-carboxylate (56):**



56

To a solution of ester **55** (380 mg, 1.38 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (0.87 mL, 1.52 mmol, 1.75 M in toluene) at -78 °C under argon atmosphere. The reaction was then stirred at this temperature for 45 min. Then a solution of tartaric acid (0.75 mL) was added. The resulting mixture was stirred for 15 min and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure to give α,β-unsaturated aldehyde as a colourless liquid, which was directly used in the next step without further purification.

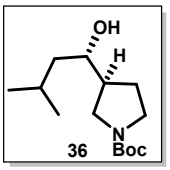
To a MeOH solution (3 mL) of catalyst (*R*)-diphenyltrimethylsiloxymethyl pyrrolidine (45 mg, 0.14 mmol, 10 mol%) was sequentially added above synthesized aldehyde, PhCOOH (17 mg, 0.14 mmol, 10 mol%) and nitromethane (253 mg, 225 μL, 4.14 mmol) at the room temperature. After stirring the reaction mixture at room temperature for 24 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was extracted with EtOAc and dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to afford nitroaldehyde derivative which was used as such for the next step without further purification.

To an AcOH (5.0 mL) and H_2O (5.0 mL) solution of above synthesized nitroaldehyde derivative was added Zn dust (2.15 g, 33.12 mmol) at 0 °C and stirred for 3 h at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ solution, extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to afford amine derivative which was used as such for the next step without further purification.

NaH (50 mg, 2.07 mmol) was added to the solution of above amine derivative in 5 mL of dry DMF at 0 °C. After the solution was stirred for 10 min, di-*tert*-butyl dicarbonate (450 mg, 2.07 mmol) and DMAP (85 mg, 0.69 mmol) were added at the same temperature. The reaction mixture was stirred at room temperature for 10 h. After completion of the reaction as monitored by TLC, the reaction was quenched with water and extracted with diethyl ether (3 x 20 mL). The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under

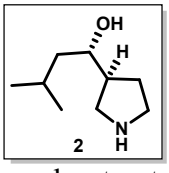
reduced pressure. Purification of the crude product by silica gel column chromatography (EtOAc/hexane 1:9 v/v) as eluent furnished the compound **56** (388 mg, 81%) as yellow oil. $[\alpha]_D^{25}$ -14.6 (*c* 1, CH_3OH); IR (CH_2Cl_2) *v*; 2955, 2847, 2262, 1888, 1611, 1582, 1468, 1375, 1259, 1106 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.34-7.24 (m, 5H), 4.56-4.46 (m, 2H), 3.52-3.33 (m, 3H), 3.26-3.15 (m, 1H), 3.01 (q, *J* = 10.4, 21.2 Hz, 1H), 2.42-2.26 (m, 1H), 2.04-1.96 (m, 1H), 1.79-1.67 (m, 2H), 1.59-1.49 (m, 1H), 1.45 (s, 9H), 1.29-1.19 (m, 1H), 0.93-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.5, 138.5, 128.3, 127.7, 127.5, 79.0, 78.8, 78.4, 71.9, 48.0, 45.9, 45.5, 43.4, 42.9, 42.4, 42.1, 28.5, 28.3, 27.2, 24.4, 23.5, 22.5, 22.3; HRMS $(ESI)^+$ m/z calcd for $C_{21}H_{33}NO_3Na^+$ $[M+Na^+]$ 370.2352; found 370.2352.

***tert*-Butyl(*S*)-3-((*S*)-1-hydroxy-3-methylbutyl)pyrrolidine-1-carboxylate (36):**



To a solution of **56** (300 mg, 0.86 mmol) in MeOH (10 mL) was added 10% Pd/C (50 mg, 5 mol%) and subjected to hydrogenation under 1 atm pressure for 24 h. After this time, reaction mixture was filtered through a pad of Celite, washed with additional MeOH (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography purification (EtOAc/hexanes 1:4 v/v) of the crude product furnished alcohol **36** (190 mg, 87 %) as a yellow oil. $[\alpha]_D^{25}$ -66.8 (*c* 1, CH_3OH); IR (CH_2Cl_2) *v*; 3396, 2962, 2911, 1588, 987 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.59-3.37 (m, 3H), 3.26-3.21 (m, 1H), 2.98 (q, *J* = 9.6 19.2 Hz, 1H), 2.16-2.02 (m, 2H), 1.79-1.61 (m, 4H), 1.45 (s, 9H), 1.29-1.14 (m, 1H), 0.94-0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.5, 79.1, 71.5, 71.0, 48.0, 47.9, 46.0, 45.7, 45.5, 45.4, 45.3, 44.9, 28.5, 28.0, 27.0, 24.3, 23.7, 21.5; HRMS $(ESI)^+$ m/z calcd for $C_{14}H_{27}NO_3Na^+$ $[M+Na^+]$ 280.1883; found 280.1879.

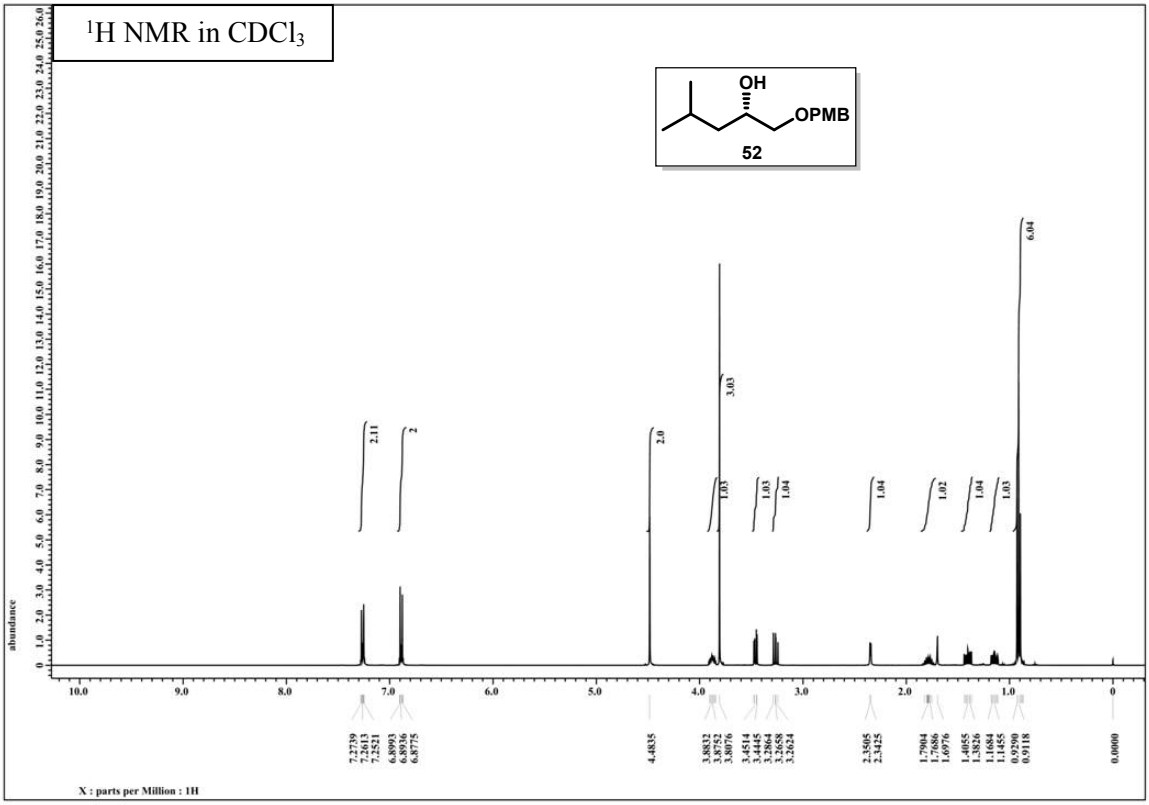
(*S*)-3-Methyl-1-((*S*)-pyrrolidin-3-yl)butan-1-ol (2): To a solution of *N*-Boc pyrrolidine **36** (100 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to near dryness. The crude product was purified by silica gel column chromatography using (CH_3OH/CH_2Cl_2 1:5 v/v) as eluent to give pyrrolidine core unit **28** (56 mg, 92%) as yellow oil. $[\alpha]_D^{25}$ -25.6 (*c* 0.5, CH_3OH); IR

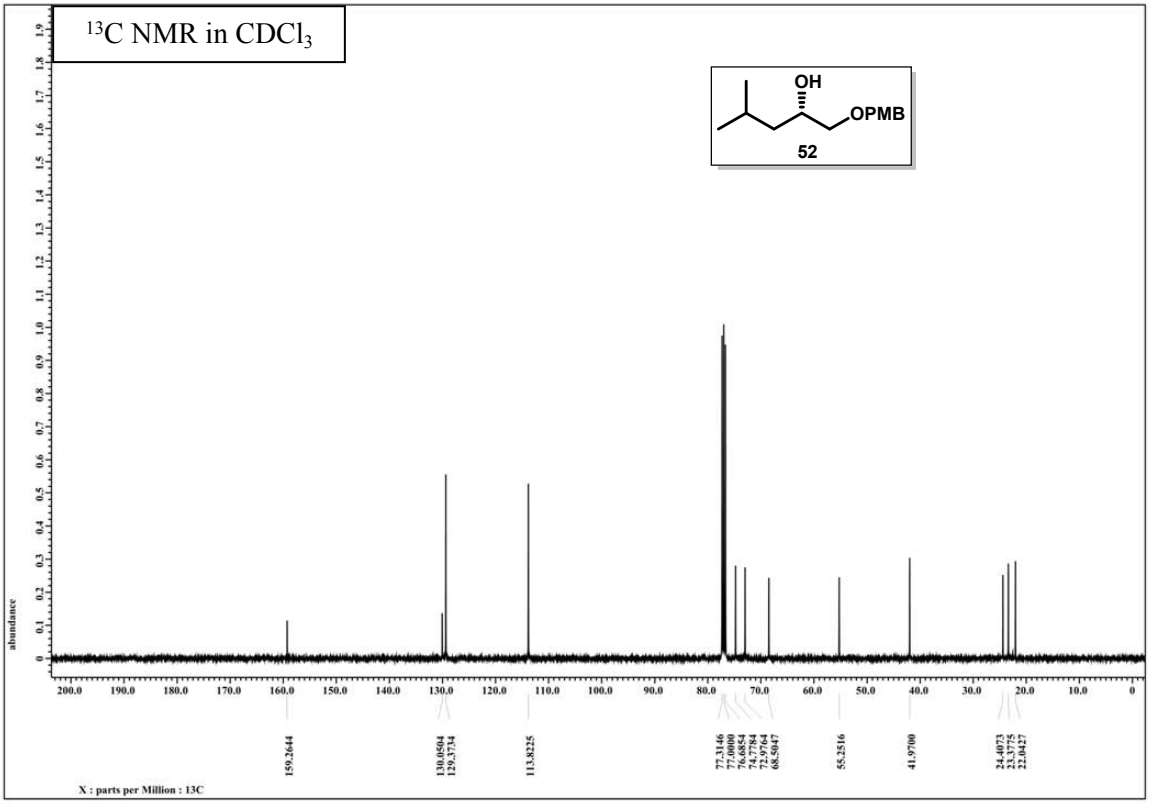


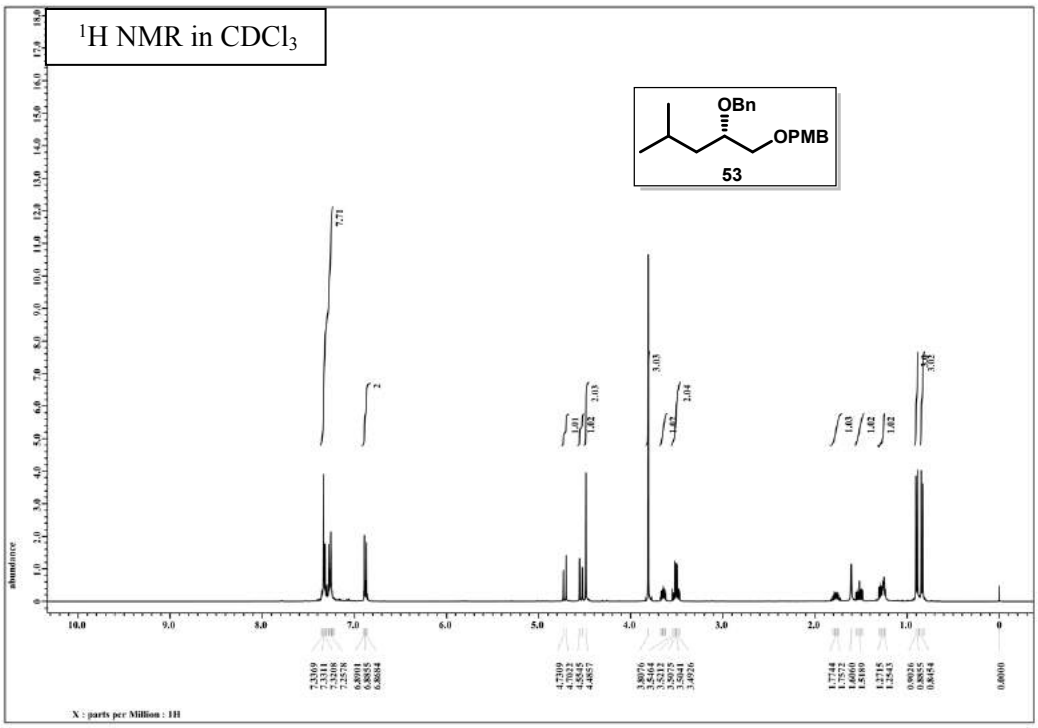
(MeOH) *v*; 3255, 3205, 3140, 2945, 2851, 1322, 1185, 978 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.57-3.52 (m, 1H), 3.31-3.11 (m, 3H), 2.95-2.90 (m, 1H), 2.28-2.19 (m, 1H), 2.00-1.77 (m, 3H), 1.40-1.28 (m, 1H), 1.14-1.07 (m, 1H), 0.95-0.89 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 67.6, 46.8, 45.1, 45.0, 44.0, 25.1, 24.1, 23.7, 21.8; HRMS $(ESI)^+$ m/z calcd for $C_9H_{20}NO^+$ $[M+H^+]$ 158.1540; found 158.1533.

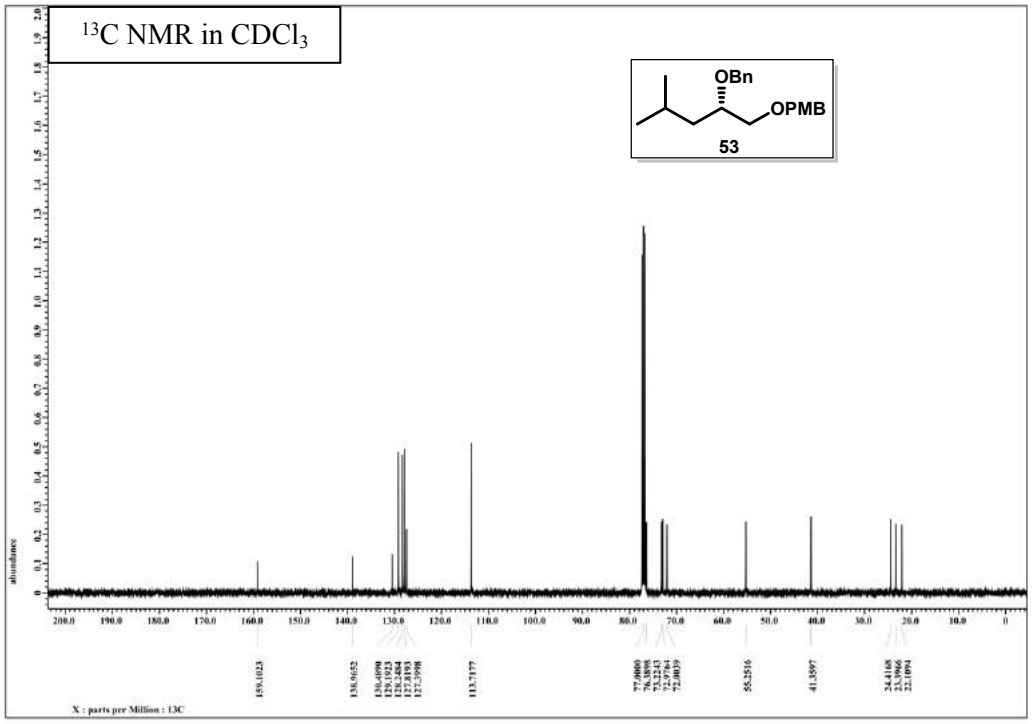
3.2.7 Spectra:

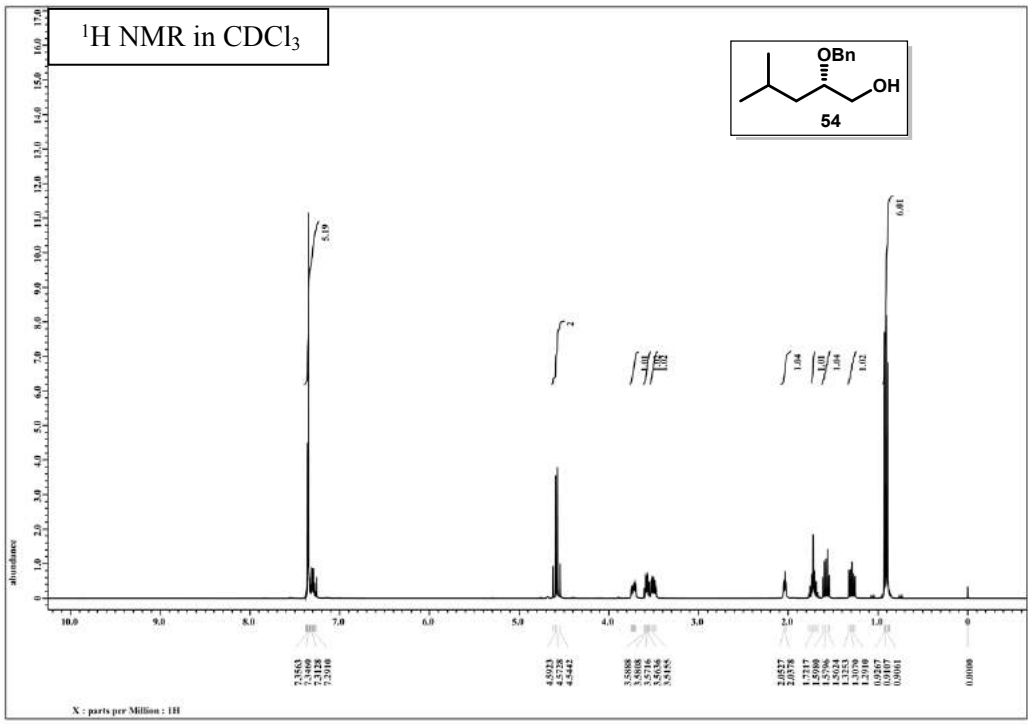
1. ^{1}H and ^{13}C NMR spectra of **52**
2. ^{1}H and ^{13}C NMR spectra of **53**
3. ^{1}H and ^{13}C NMR spectra of **54**
4. ^{1}H and ^{13}C NMR spectra of **55**
5. ^{1}H and ^{13}C NMR spectra of **56**
6. ^{1}H and ^{13}C NMR spectra of **36**
7. ^{1}H and ^{13}C NMR spectra of **28**
8. HPLC data of compound **56**

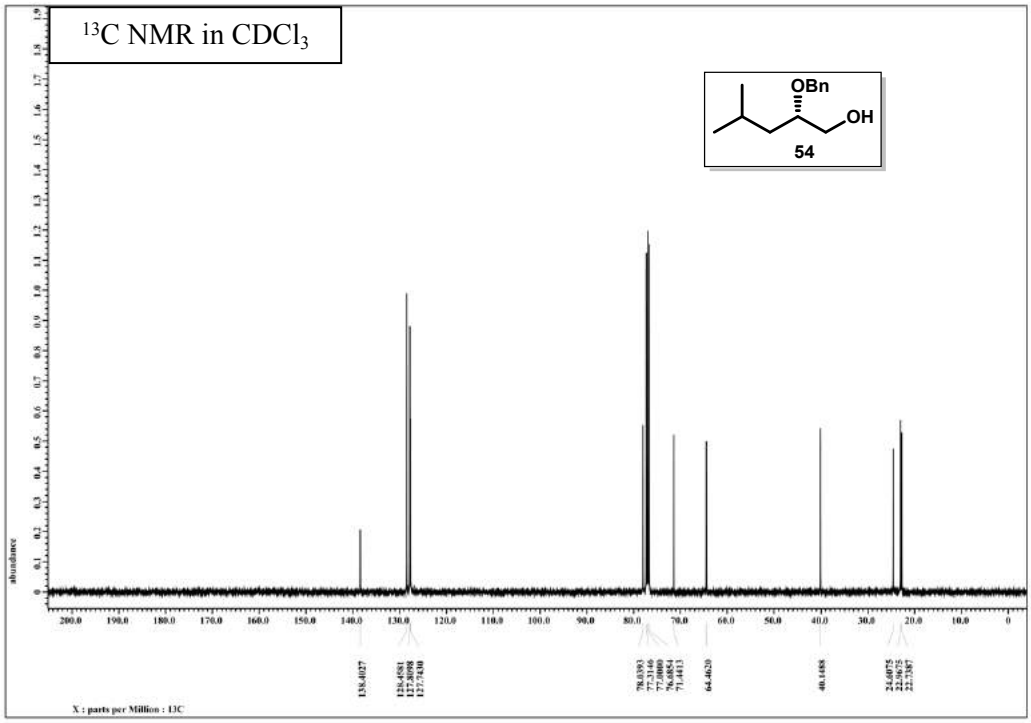

^{1}H NMR in $CDCl_3$
OH
OPMB
52
X : parts per Million : 1H

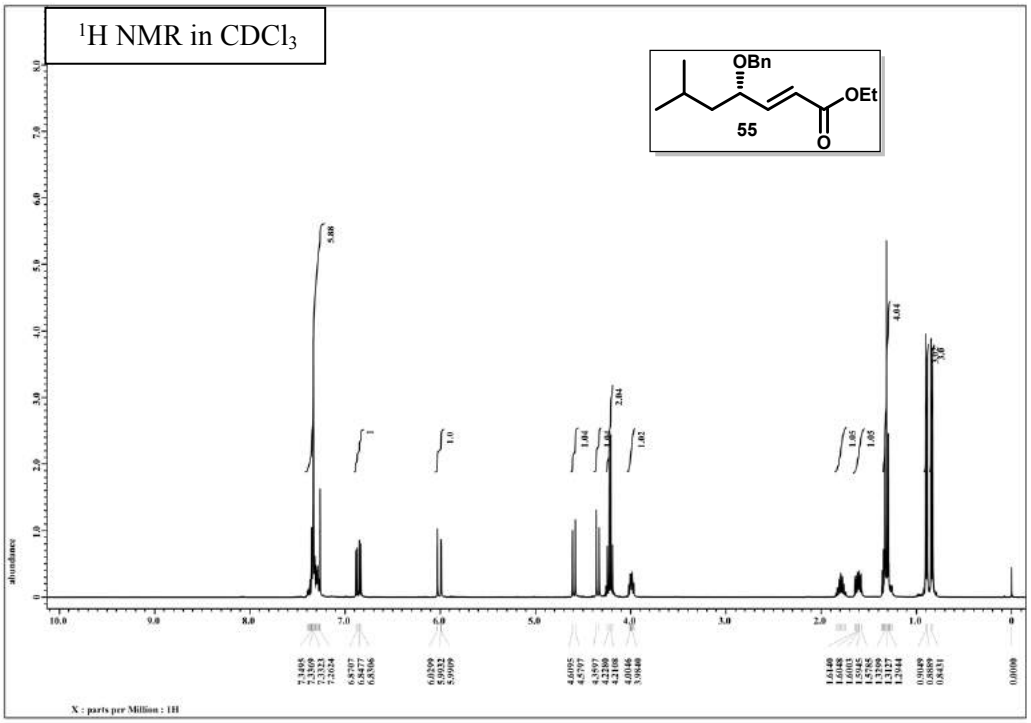

^{13}C NMR in $CDCl_3$
OH
OPMB
52
X : parts per Million : 13C

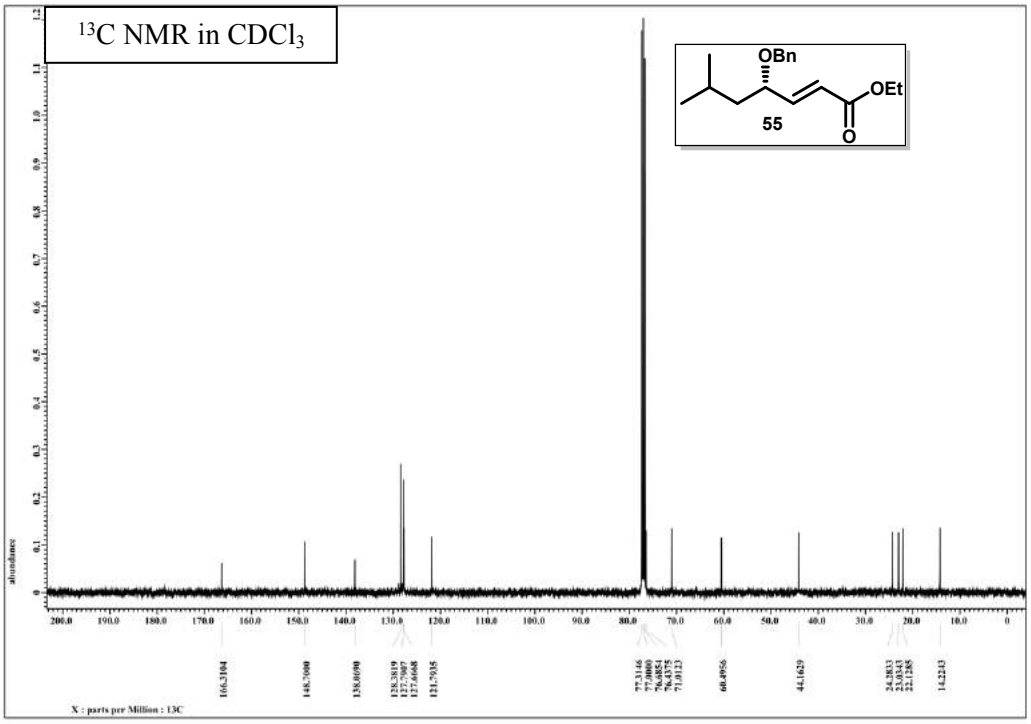

^{1}H NMR in $CDCl_3$
OBn
OPMB
53
X : parts per Million : 1H

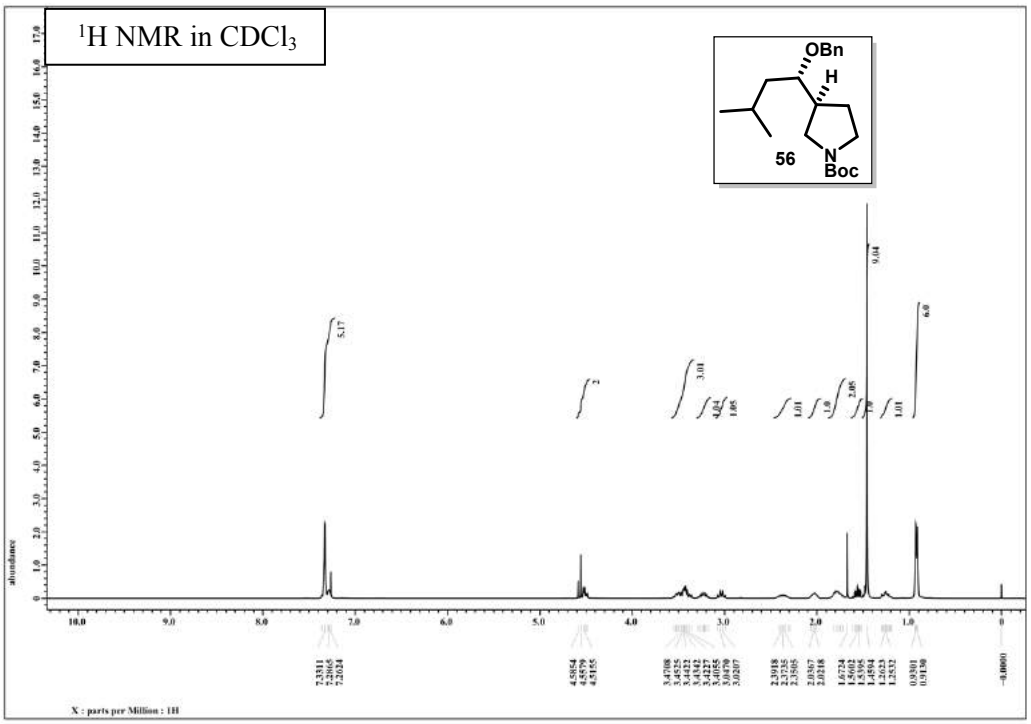

^{13}C NMR in $CDCl_3$
OBn
OPMB
53
X : parts per Million : 13C

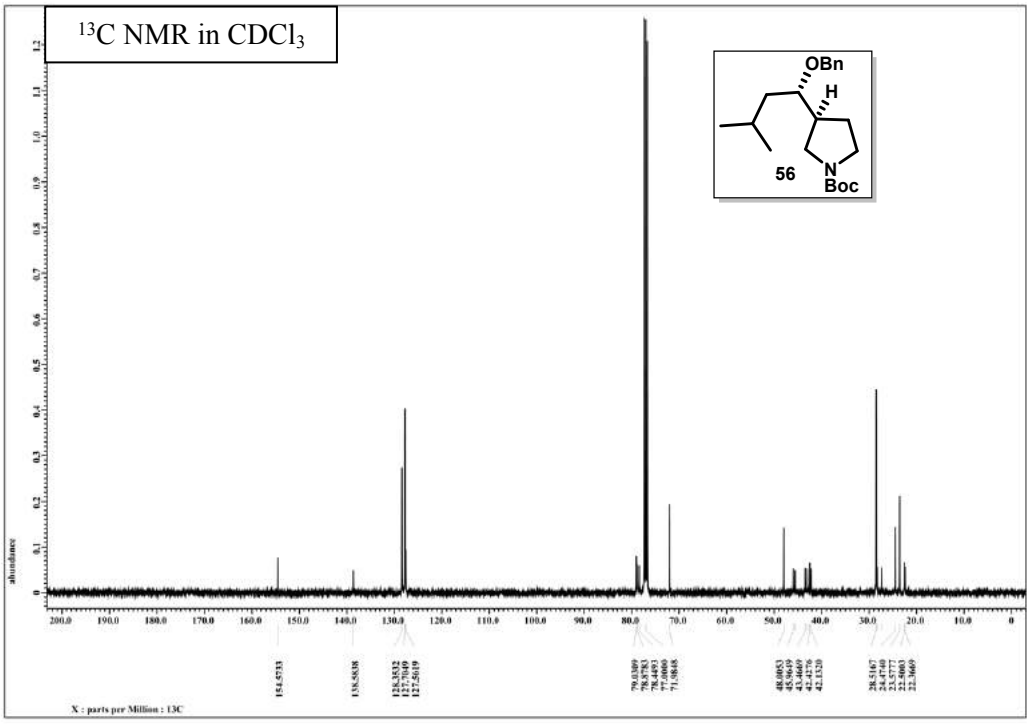

^{1}H NMR in $CDCl_3$
OBn
OH
54
X : parts per Million : 1H

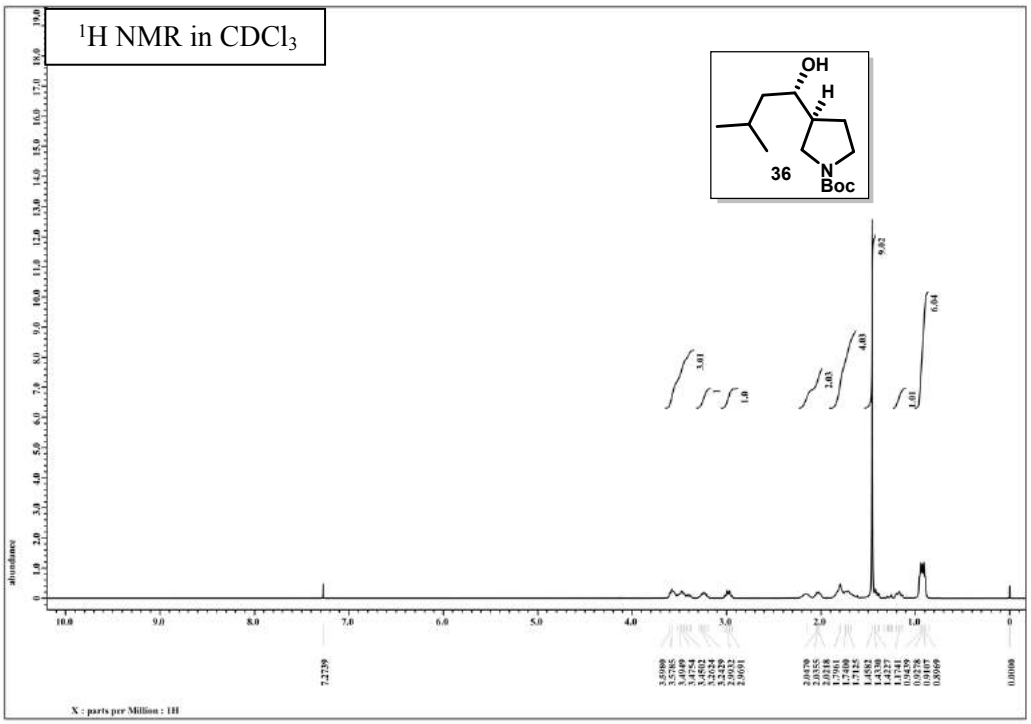

^{13}C NMR in $CDCl_3$
OBn
OH
54
X : parts per Million : 13C

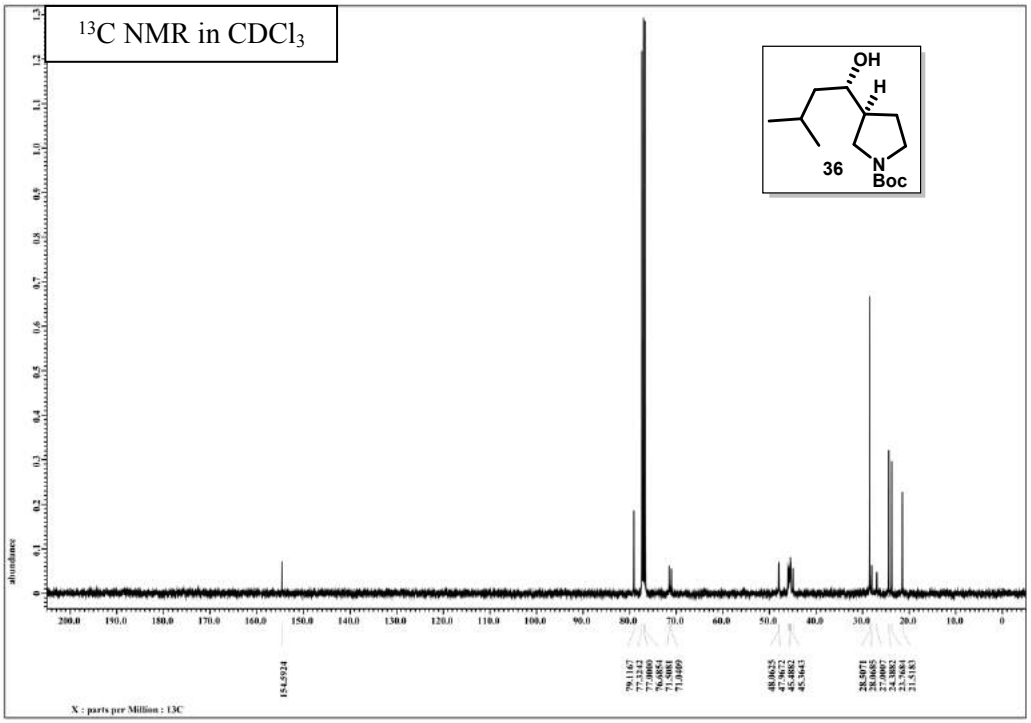

^{1}H NMR in $CDCl_3$
OBn
OEt
55
O


^{13}C NMR in $CDCl_3$
OBn
OEt
55
O


^{1}H NMR in $CDCl_3$
OBn
H
56
N
Boc
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OBn
H
56
N
Boc
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
H
36
N
Boc
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
H
36
N
Boc
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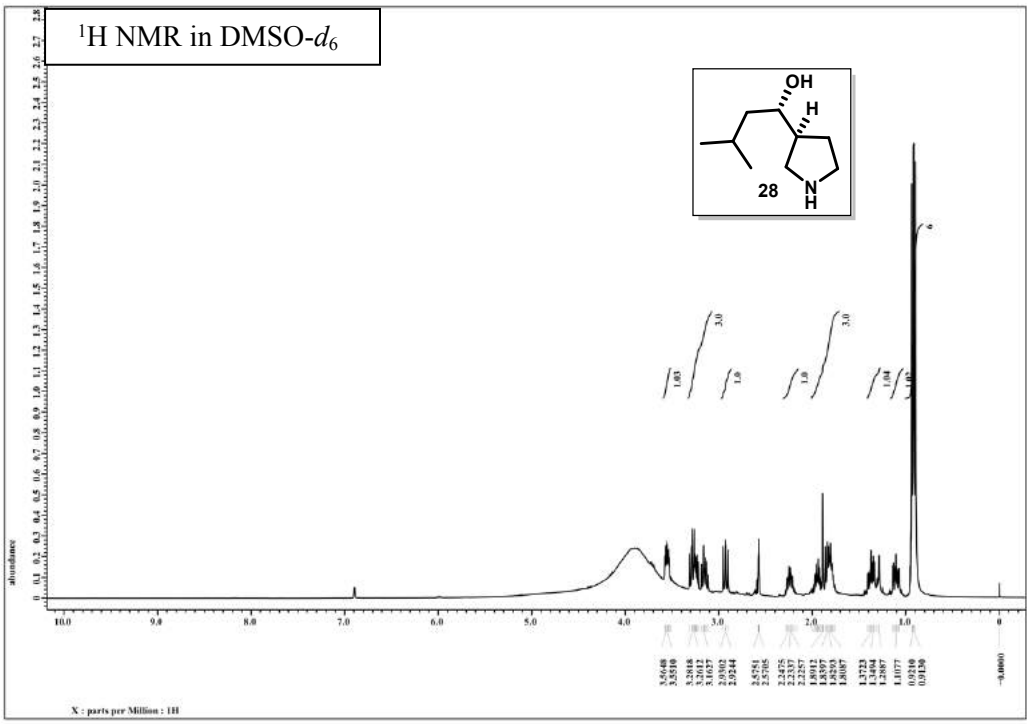
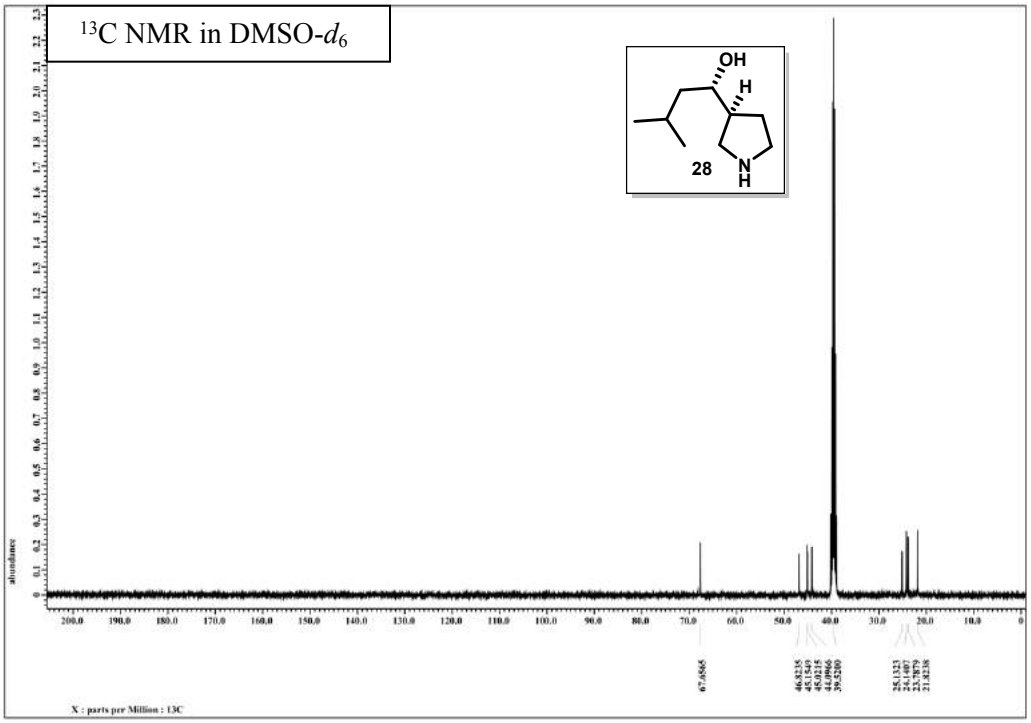

^{1}H NMR in DMSO-d_6
OH
H
28
N
H


^{13}C NMR in DMSO-d_6
OH
H
28
N
H

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CHAPTER 4

Development of stereocontrolled organocatalyzed tandem α-aminoxylation/Henry reactions approach towards the asymmetric synthesis of β,γ-dihydroxynitroalkanes from aldehydes and its application to the total synthesis of L-*threo*-sphinganine (safingol). This chapter is divided into two sections.

4.1 Section A

Stereocontrolled organocatalyzed tandem α-aminoxylation/Henry reactions approach for the asymmetric synthesis of β,γ-dihydroxynitroalkanes from aldehydes

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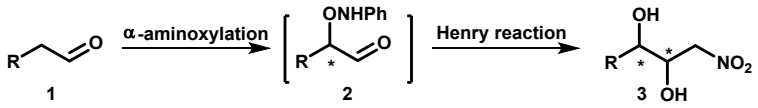
4.1.1 Introduction:

Enantiopure 1,2-diols are versatile chiral building blocks and have been used widely as starting material for the asymmetric synthesis of drugs and bioactive natural products. Various methods for the synthesis of 1,2-diols have been documented in the literature.[1,2] The Sharpless asymmetric dihydroxylation (AD) of *trans*-olefins[2] is one of the most efficient reaction leading to *syn*-1,2-diols in high enantiomeric excesses (*ee*'s) while *cis*-olefins giving rise to *anti*-1,2-diols show low enantioselectivity.[2b] Recent developments in asymmetric catalysis have included organocatalysis involving α-aminoxylation directed tandem reactions which demonstrate a rapid and atom-economical one pot catalytic process that provide enantiopure compounds.[3]

We envisioned that reactive α-aminoxy aldehyde intermediate **2** generated from the organocatalyzed α-aminoxylation of aldehydes **1** on *in situ* trapping with nitromethane under Henry reaction conditions[4] followed by cleavage of phenylamine moiety would provide β,γ-dihydroxy nitroalkane **3** (Scheme 1).



Scheme 1. An approach for α-aminoxylation-Henry reactions.

Enantiopure β,γ-dihydroxy nitroalkane **3** derivatives are valuable chiral building blocks and are potential precursor to the chiral 1-amino-2,3-diol **4**,[5a] α,β-dihydroxy acid **5**,[5e] α,β-dihydroxy aldehyde **6**,[5g] terminal triols **7** and α,β-dihydroxy ester derivatives **8**, which are the common structural features found in numerous biologically active compounds (Figure 1).[5]

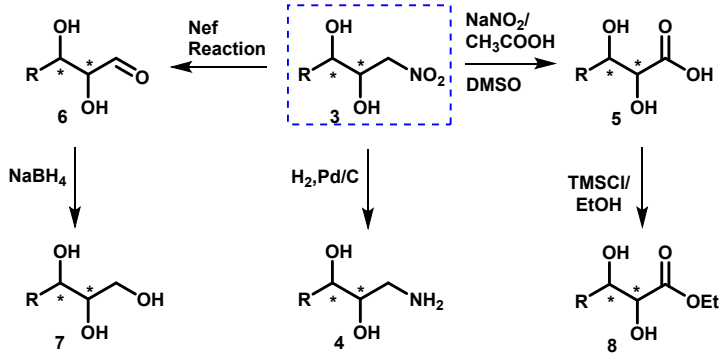


Figure 1. Selected synthetic transformations of chiral *β,γ*-dihydroxynitroalkane derivatives **3**.

The *β,γ*-dihydroxy nitroalkane fragments produced in tandem *α*-aminoxylation-Henry reactions are found in various drugs and bioactive natural products such as antineoplastic and antipsoriatic drug L-*threo*-sphinganine (safingol) **9**,[6a] antidepressant drug (*S*,*S*)-reboxetine **10**,[6c] potent inhibitor of the serine/threonine kinases protein kinase A, protein kinase C drug (*R*,*R*)-balanol **11**,[6b] hydroxylated piperdines with potent antimalarial drug febrifugine **12**,[6d] and antibiotic (-)-galantinic acid **13**[6e] (Figure 2).

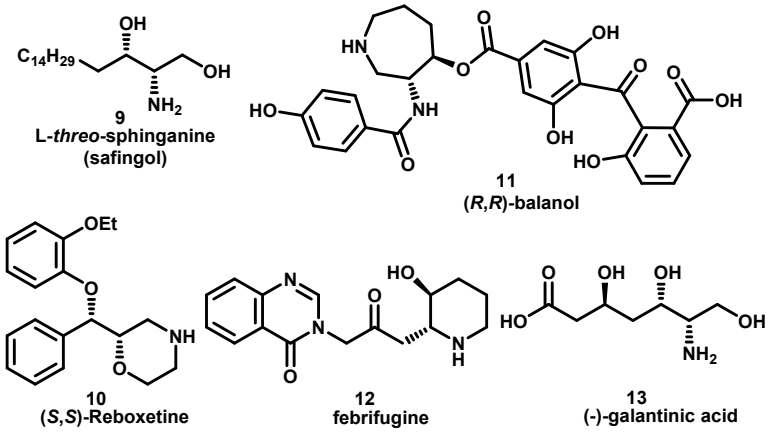


Figure 2. Some important biologically active compounds.

4.1.2 Review of Literature:

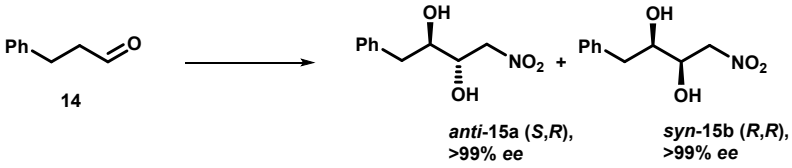
To the best of our knowledge, there is no any report documented in the literature for the asymmetric synthesis of *β,γ*-dihydroxy nitroalkane derivatives employing tandem *α*-aminoxylation-Henry reaction approach to date.

4.1.3 Present Work:

Herein, we describe a highly enantioselective one pot tandem approach to a non-terminal 1,2-diols unit β,γ-dihydroxy nitroalkanes involving the organocatalyzed α-aminoxylation of aldehydes followed by *in situ* Henry reaction.

4.1.4 Results and Discussions:

Our preliminary experiments were initiated by using 3-phenylpropionaldehyde **14** as the model substrate, nitrosobenzene, DMSO as the solvent and L-proline as the catalyst (Scheme 2).



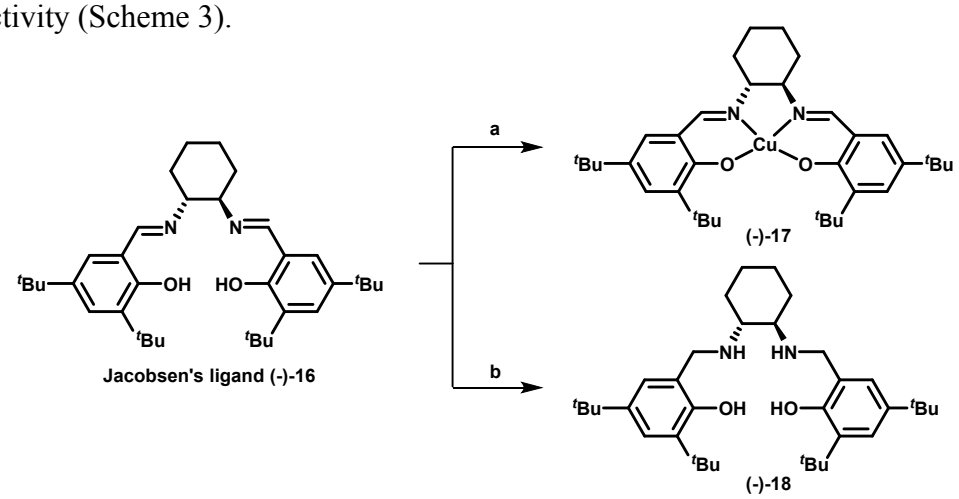
Scheme 2. *Reagents and conditions*: (a) i) Nitrosobenzene, L-proline, DMSO, rt, 30 min; ii) CH_3NO_2, DIPEA, rt, 12 h, 42%.

Nitromethane and base DIPEA were used in the second step and were added to α-aminooxylation reaction mixture until all the nitrosobenzene was consumed. Pleasingly, the tandem reaction proceeded smoothly with product *anti*-**15a** and *syn*-**15b** in 42% yield along with expected *O*-NHPh protected derivative of **15** in low yield (12%). It is also known that *in situ* partial N-O bond cleavage may occur during α-aminooxylation reaction.[1i] It is also worthy to mention that removal of *N*-phenylamino group could be achieved by either catalytic hydrogenation[1n] or by cleavage of N-O bond employing Cu(II) catalyzed reactions.[7] The separation of *anti*-**15a** and *syn*-**15b** on silica gel column chromatography indicated no diastereoselectivity in the second step (*anti*-**15a**/*syn*-**15b** 1:1), but excellent enantioselectivities were found (>99% *ee* for each of *anti*-**15a** and *syn*-**15b**) in one pot tandem α-aminooxylation-Henry reactions.

Guided by our favorable results, we then focused on using a chiral catalyst in the Henry reaction to improve the diastereoselectivity and chemical yield. After the first report of Shibasaki and co-workers,[4z] many efforts have been made continuously in the literature for asymmetric induction into the Henry reaction, using prochiral aldehydes and nitromethane in the presence of chiral metal complexes and organocatalysts.[4] Among them, Henry reaction catalyzed by the stable Cu(II)-salen complex has received more attention during the recent years.[4f-t] Towards this end, a

stable copper (II)-salen complex (-)-**17** was prepared by the treatment of commercially available (*R*,*R*)-Jacobsen's ligand[8] (-)-**16** with copper (II) acetate in methanol (Scheme 3) which was then used in tandem α-aminooxylation-Henry reactions. Initial result was not encouraging, as the tandem reaction proceeded with no improvement in *anti*-**15a**/*syn*-**15b** diastereomeric ratio even though with no loss in enantiomeric excess (*ee*'s).

We next envisioned that, due to the strong basicity and coordination capability of the secondary diamine ligands could affect the catalytic activity in the Cu catalyzed Henry reaction.[4f-i,m,o,v] Therefore, we have performed the reduction of ligand (-)-**16** with $NaBH_4$/acetic acid in DCE to diamine ligand (-)-**18** in excellent yield of 99% which was used further for controlling the stereoselectivity (Scheme 3).



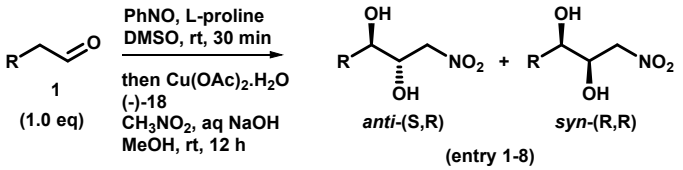
Scheme 3. *Reagents and conditions*: (a) $Cu(OAc)_2.H_2O$, MeOH, rt, 1 h; (b) $NaBH_4$, AcOH, DCE, 0 °C to rt, 2 h, 99%.

Serendipitously, ligand (-)-**18** on complexation with $Cu(OAc)_2.H_2O$ led to more promising outcome in the Henry reaction step to furnish relatively good yield of *anti*-**15a**/*syn*-**15b** in 52% without affecting the enantioselectivity. To further improve the diastereoselectivity and chemical yield, a series of other Cu (I) catalysts, such as CuI, CuBr, CuCl, CuCN, CuOAc and Cu (II) catalysts, such as $CuCl_2.2H_2O$, $Cu(OTf)_2$, $CuSO_4.5H_2O$ were surveyed in the presence of ligand (-)-**18**. Out of copper (I) and (II) catalysts, $Cu(OAc)_2.H_2O$ turned out to be the best choice for subsequent reactions which provided the highest *anti*/*syn* ratio.

After establishing the choice of catalyst, we moved further to screen the reaction solvents for tandem α-aminooxylation-Henry reactions. Previously, Guofu Zhong[1n] reported that DMSO acts as best solvent for α-aminooxylation in terms of yield and enantioselectivity. However, among

the solvents (DMSO, CH_3CN, MeOH, EtOH, DCM, IPA, DMF, Toluene, THF, 1,4-dioxane) screened for Henry reaction on α-aminooxylated aldehyde intermediates, polar protic solvent methanol was found to be best with respect to optical purity and chemical yield.

Table 1. Asymmetric synthesis of β,γ-dihydroxynitroalkane derivatives under optimized conditions



entry	Product	R	yield[a] (%)	dr[b] (*anti*/*syn*)	*ee*[c] (*anti*/*syn*,%)
1	**15**	Bn	67	1.37:1	99/92
2	**19**	*i*-Pr	64	1.35:1	>99/98
3	**20**	Me	67	1.75:1	98/94
4	**21**	C_4H_9	64	1.23:1	92/96
5	**22**	C_5H_{11}	62	6.34:1	98/82
6	**23**	C_7H_{15}	67	1.10:1	90/>99
7	**24**	$C_{10}H_{21}$	70	3.30:1	>99/98
8	**25**	$C_{15}H_{31}$	68	1.20:1	80/>99
9	**26**[d]	Bn	62	1.10:1	>99/96
10	**27**[d]	$C_{10}H_{21}$	65	1.10:1	70/96
11	**28**[d]	$C_{15}H_{31}$	67	1.64:1	86/97

[a]All were for isolated *anti*+*syn* products. [b]The *anti*/*syn* diastereomeric ratio was determined by chiral HPLC. All diastereomers were separable from the silica gel column chromatography. [c]The *ee*'s were determined by HPLC on Chiralpak IA, AD-H and Chiralcel OJ-H columns (see Supporting Information). [d]The α-aminooxylation reaction was performed *via* using D-proline as catalyst which furnished the *anti*-(*R*,*S*) and *syn*-(*S*,*S*) diastereomers (entry 9-11). The α-aminooxylated aldehydes are known to present in the form of oligomer in solution.[1m]

It is well known that a base could be employed in Henry reaction to generate the nitronate ion from nitromethane and to increase the reactivity of the catalyst.[4w] Among the screened bases (aq NaOH, aq KOH, K_2CO_3, K-O^{t}Bu, DIPEA, DMAP, NEt_3, NMM and DBU) for Henry reaction of nitromethane with α-aminooxylated aldehyde intermediates in methanol, aq NaOH was found to show the best reactivity for the *anti*-**15a**/*syn*-**15b**. With optimal reaction conditions in hand, we further explored the scope of this one-pot tandem approach to a variety of α-aminooxylated

aromatic and aliphatic aldehyde intermediates (Table 1). In every case, the tandem reaction worked successfully which furnished the adducts in good diastereoselectivities of *anti*/*syn* ratio (6.34:1), excellent enantioeselectivity (up to >99% *ee*'s) and good overall yields (up to 70%). The described tandem reaction does not require oxygen free or anhydrous conditions and was completed in 12 h at room temperature. The stereochemistry of this tandem transformation was assigned *via* ^{1}H-NMR determination of the *anti*- and *syn*-diastereomers which are in accordance with the previously established absolute configuration of the α-aminooxylated aldehyde.[11-n]

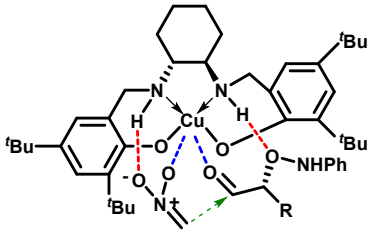


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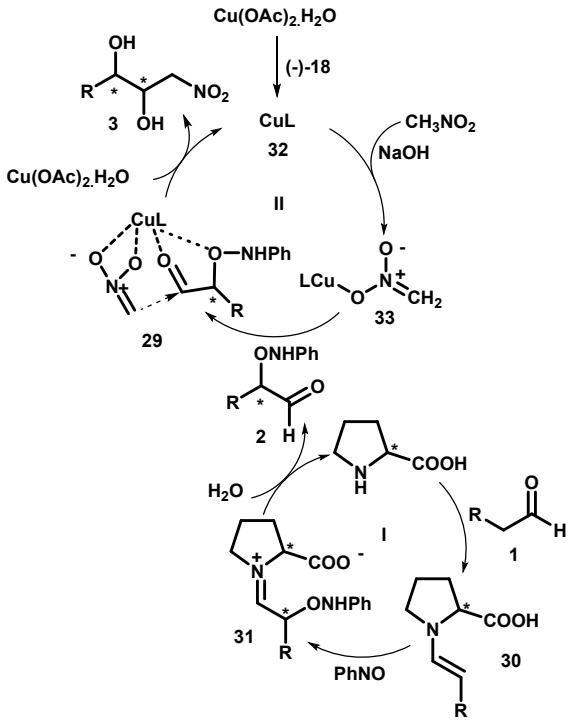
Figure 3. Plausible transition state for the tandem α-aminooxylation-Henry reactions.

As evident from Table 1 results that there is preference of (1*R*,2*R*)-ligand (-)-**18**/Cu(II) complex to give *anti*-β,γ-dihydroxynitroalkane derivatives during tandem α-aminooxylation-Henry reactions approach. This implies that nitronate ion attack at the *si* face of the α-aminooxylated aldehyde synthesized using the L-proline; to rationalize the outcome, a transition state **29** is proposed in Figure 3. In the proposed model, substrates are coordinated to (-)-**18**/Cu(II) complex under the bicyclic framework and C-C bond formation taking place from the less hindered side due to two simultaneously NH hydrogen bonding, one with *O*-NHPh of α-aminooxylated aldehyde and another with the nitronate ion. Since, in complex (-)-**17** this hydrogen bonding was absent leads to low or no diastereoselectivity.

As a probe to the mechanism, the α-aminooxylated aldehyde synthesized from D-proline was subjected to *in situ* treatment with nitromethane under the above optimized Henry reaction conditions which furnished the *anti*-selective diastereomer (*re* face attack) of β,γ-dihydroxynitroalkane in good yield and *anti*-**26a**/*syn*-**26b** 1.10:1 diastereomeric ratio (Table 1, **26**[d]). The results imply that the NH hydrogen bonding with *O*-NHPh of α-aminooxylated aldehyde furnished the more *anti*-selective diastereomeric ratio from both L- and D-proline. Based on our study and literature reports, a catalytic cycle that would incorporate a transition state **29** is proposed in Scheme 4.



Scheme 4. Proposed catalytic cycle for the synthesis of *β,γ*–dihydroxynitroalkane derivatives.

In the first cycle, the aldehyde **1** on *α*-aminooxylation would provide the enantiopure *α*-aminooxylated aldehyde intermediate **2** *via* reactive intermediates **30** and **31** which then undergo stereocontrolled Henry reaction. In the second cycle, ligand exchange of tetrahydrosalen (-)-**18** for acetic acid would afford complex **32**, which on further progress *via* Cu (II) complex **33** and transition state **29** complete the cycle while generating the *β,γ*-dihydroxynitroalkane derivative **3**.

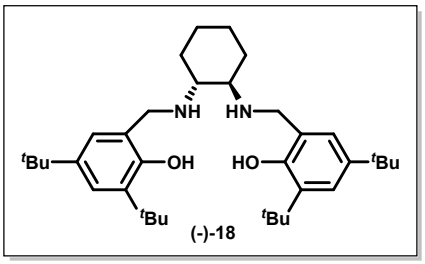
4.1.5 Conclusions:

In conclusion, we have developed a novel organocatalyzed tandem *α*-aminooxylation-Henry reactions approach for the asymmetric synthesis of *anti*- and *syn*-*β,γ*-dihydroxynitroalkane derivatives in good yield (up to 70%) with excellent enantio- (*ee*'s for *anti*- and *syn*up to >99%) and diastereselectivities (dr *anti*/*syn*, up to 6.34:1). The (*S*)- and (*R*)- configuration of *α*-aminooxylated aldehyde could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step and thus, in principle, all the four isomers of *β,γ*-dihydroxynitroalkane derivatives could be accessed from this developed tandem approach. This tandem strategy, which is amenable to both *anti*- and *syn*-1,2-diols, has significant potential for

its further extension to the asymmetric synthesis of a variety of natural- and natural-like bioactive compounds.

4.1.6 Experimental Section:

6,6'-((((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(azanediyl))bis(methylene))bis(2,4-di-*tert*-butyl phenol) (18): To a dichloroethane (20 mL) solution of (*R*,*R*)-Jacobsen's ligand (-)-**16** (2.0 g, 3.65 mmol) was added $NaBH_4$ (278 mg, 7.30 mmol) followed by acetic acid (2 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes 1:1 v/v) as eluent to afford the ligand (-)-**18** (1.99 g, 99%). $\{[\alpha]_D^{25}$ -14.0 (*c* 0.5, CH_3OH); IR (CH_2Cl_2) *v*: 3491, 3272, 2961, 2908, 2878, 1472, 1435, 1421, 1391, 1247, 991, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, *J* = 2.76 Hz, 2H), 6.86 (d, *J* = 2.28 Hz, 2H), 4.04 (d, *J* = 13.2 Hz, 2H), 3.90 (d, *J* = 13.2 Hz, 2H), 2.47-2.46 (m, 2H), 2.19-2.16 (m, 2H), 1.71-1.70 (m, 2H), 1.45-1.40 (m, 20H), 1.28-1.21 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 140.5, 135.9, 123.1, 122.9, 122.3, 59.8, 50.8, 34.8, 34.1, 31.6, 30.7, 29.5, 24.1. HRMS $(ESI)^+$ m/z calcd for $C_{36}H_{58}N_2O_2Na^+$ ($[M+Na]^+$) 573.4390; found 573.4391.



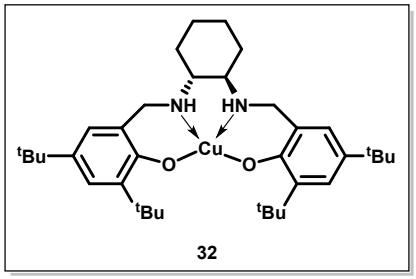
General Procedure for tandem α-aminooxylation-Henry reaction:

To a DMSO (1.5 mL) solution of aldehyde (1.0 mmol) and nitrosobenzene (1.0 mmol), L- or D-proline (30 mol %) was added and stirred for about 20-30 min at room temperature. The completion of the reaction was monitored by its colour change from green to orange or by TLC until all the nitrosobenzene was consumedand used as such for the next step without further purification.

The ligand (-)-**18** (0.055 mmol, 5.5 mol %) and $Cu(OAc)_2.H_2O$ (0.05 mmol, 5 mol %) were added to methanol (1.5 mL) and reaction mixture was stirred for 1 h at room temperature. To the resulting dark blue solution of the catalyst, solvent (1.5 mL), nitromethane (10.0 mmol), base (1.5 mmol), and above synthesized α-aminooxylatedaldehyde (1.0 mmol) were added. The reaction mixture was stirred for 30 min then $Cu(OAc)_2.H_2O$ (1.5 mmol) was added and further stirred for 12 h at room temperature. After completion of the reaction (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.

(-)-18/Cu(II) complex (32): To a MeOH (1.5 mL) solution of ligand (-)-**18** (30 mg, 0.055 mmol) was added $Cu(OAc)_2.H_2O$ (10 mg, 0.05 mmol) and stirred for 1 h at room temperature under air atmosphere. 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 using (EtOAc/hexane 1:4 v/v) as eluent to furnish the complex **32** (30 mg, 95% yield) as green solid. $\{[\alpha]_D^{25}$-558.4 (*c* 0.07, $CHCl_3$) [Lit.[4i] -558.8 (*c* 0.068, $CHCl_3$)]; IR (CH_2Cl_2) *v*: 3435, 3262, 3212, 2950, 2864, 2590, 2283, 1689, 1600, 1467, 1439, 1412, 1361, 1236, 1165, 1012, 926, 877, 827, 780, 738, 460 cm^{-1}; UV-vis (CH_2Cl_2) λ_{max}: 612, 410, 292, 248 nm [Lit.[4i] λ_{max}: 623, 423, 290, 246 nm]; HRMS $(ESI)^+$ m/z calcd for $C_{36}H_{57}N_2O_2Cu^+$ ($[M+H]^+$) 612.3711; found 612.3724.



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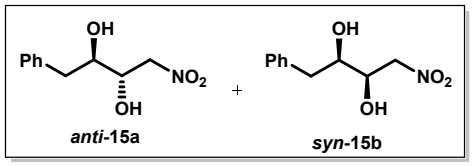
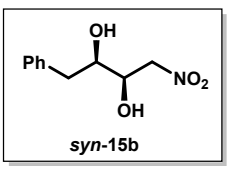
(*anti*/*syn*)-1-Nitro-4-phenylbutane-2,3-diol (15a and 15b): Following the general procedure for tandem α-aminooxylated-Henry reaction, the residue obtained was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**15a** and *syn*-**15b** diastereomers as white solid in 67% yield (142 mg, 0.67 mmol), (99% *ee* for *anti*-**15a**, 92% *ee* for *syn*-**15b**) and as 1.37:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3512, 3127, 2936, 1620, 1553, 1423, 1375, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.21 (m, 5H), 4.72-4.45 (m, 2H), 4.28-4.21 (m, 1H), 3.90-3.79 (m, 1H), 3.05-2.67 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.7, 136.6, 129.3, 129.2, 128.9, 127.0, 127.0, 78.6, 77.6, 73.2, 72.5, 71.2, 69.8, 39.9, 39.4. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 215 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 11.202 min, (*R*,*S*)-enantiomer: t_r = 12.012 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 8.866 min, (*S*,*S*)-enantiomer: t_r = 10.652 min.

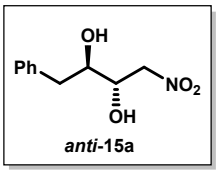


(2*R*,3*R*)-1-Nitro-4-phenylbutane-2,3-diol (15b): The above *anti*-/*syn*-diastereomers **15a** and **15b** (142 mg) were separated and purified by silica

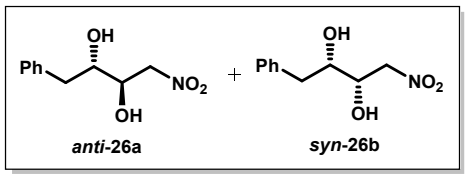


gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *syn*-**15b** diastereomer as white solid in 28% yield (57 mg, 0.28 mmol) with with 97% *ee*. $[\alpha]_D^{25}$ -25.4 (*c* 0.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.22 (m, 5H), 4.75-4.52 (m, 2H), 4.27-4.23 (m, 1H), 3.91-3.86 (m, 1H), 3.07-3.03 (m, 1H), 2.95-2.88 (m, 1H), 2.69-2.75 (m, 1H), 1.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.5, 129.3, 128.9, 127.1, 77.6, 73.1, 71.2, 39.5. HRMS $(ESI)^+$ m/z calcd for $C_{10}H_{13}NO_4Na^+$ ($[M+Na]^+$) 234.0737; found 234.0728. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 215 nm): (*R*,*R*)-enantiomer: t_r = 8.697 min, (*S*,*S*)-enantiomer: t_r = 10.580 min.

(2*S*,3*R*)-1-Nitro-4-phenylbutane-2,3-diol (15a): After separation of the *syn*-**15b** diastereomer, the *anti*-**15a** diastereomer was quickly eluted (EtOAc/hexane 1:4 v/v) as white solid in 39% yield (84 mg, 0.39 mmol) with >99% *ee*. $[\alpha]_D^{25}$ -8.2 (*c* 0.6, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.21 (m, 5H), 4.65-4.46 (m, 2H), 4.29-4.25 (m, 1H), 3.83-3.82 (m, 1H), 2.95-2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.7, 129.3, 129.2, 128.9, 127.0, 78.6, 72.5, 69.7, 39.9. HRMS $(ESI)^+$ m/z calcd for $C_{10}H_{13}NO_4Na^+$ ($[M+Na]^+$) 234.0737; found 234.0735. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 ^oC, UV detection at 215 nm): (*S*,*R*)-enantiomer: t_r = 11.108 min, (*R*,*S*)-enantiomer: t_r = 11.854 min.

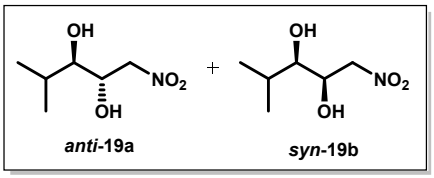


(*anti*/*syn*)-1-Nitro-4-phenylbutane-2,3-diol (26a and 26b): Following the general procedure for tandem α-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to afford the *anti*-**26a** and *syn*-**26b** diastereomers as white solid in 62% yield (131 mg, 0.62 mmol), (>99% *ee* for *anti*-**26a**, 96% *ee* for *syn*-**26b**) and as 1.1:1 *anti*:*syn* mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.15 (m, 5H), 4.69-4.42 (m, 2H), 4.26-4.21 (m, 1H), 3.89-3.77 (m, 1H), 3.01-2.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.8, 129.3, 129.3, 129.2, 128.8, 128.5, 126.9, 126.9, 78.6, 77.6, 73.3, 72.6, 71.3, 69.8, 39.8, 39.3. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis



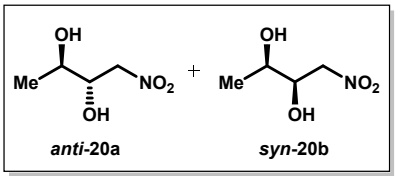
using a Chiralcel AD-H chiral column (4.6 x 250 mm) using mobile phase of (9:1 hexane/*i*-PrOH, flow rate of 1 mL/min at 25 °C, UV detection at 215 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 11.073 min, (*R*,*S*)-enantiomer: t_r = 11.738 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 8.353 min, (*S*,*S*)-enantiomer: t_r = 10.341 min.

(*anti*/*syn*)-4-Methyl-1-nitropentane-2,3-diol (19a and 19b):



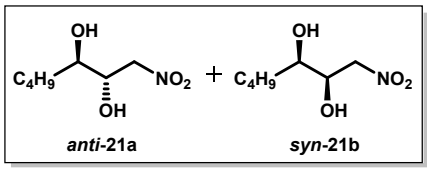
Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:6 v/v) as eluent to afford the *anti*-**19a** and *syn*-**19b** diastereomers as white solid in 64% yield (104 mg, 0.64 mmol), (>99% *ee* for *anti*, 98% *ee* for *syn*) and as 1.35:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3574, 3512, 2975, 2904, 2714, 1545, 1471, 1413, 1373, 1289, 1182, 1085, 1054, 931, 770 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.66-4.42 (m, 3H), 3.47-3.15 (m, 2H), 2.36 (br s, 1H), 1.91-1.76 (m, 1H), 1.03-0.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 79.2, 77.5, 77.5, 76.9, 69.6, 68.7, 30.7, 29.6, 18.9, 18.7, 18.2, 17.4. HRMS (ESI)$^-$ m/z calcd for $C_6H_{12}NO_4^-$ ($[M-H]^+$) 162.0772; found 162.0774. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chiracel OJ-H (4.6 x 250 mm) using mobile phase of (03:97 *i*-propanol/*n*-hexane, flow rate of 1.5 mL/min at 25 °C, UV detection at 220 nm): *anti* diastereomer (*R*,*S*)-enantiomer: t_r = 30.61 min, (*S*,*R*)-enantiomer: t_r = 28.97 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 21.40 min, (*S*,*S*)-enantiomer: t_r = 25.49 min.

(*anti*/*syn*)-1-Nitrobutane-2,3-diol (20a and 20b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:3 v/v) as eluent to furnish the *anti*-**20a** and *syn*-**20b** diastereomers as white solid in 67% yield (90 mg, 0.67 mmol), (98% *ee* for *anti*, 94% *ee* for *syn*) and as 1.75:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3589, 3532, 2978, 2925, 1742, 1653, 1561, 1539, 1458, 1378, 1061, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.64-4.49 (m, 2H), 4.24-4.16 (m, 1H), 3.97-3.76 (m, 1H), 2.98 (br s, 1H), 2.14 (br s, 1H), 1.32-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.3, 77.2, 72.3, 72.0, 68.6, 67.8, 19.5, 18.7. HRMS (ESI)$^-$ m/z calcd for $C_4H_8NO_4^-$ ($[M-H]^+$)134.0459; found

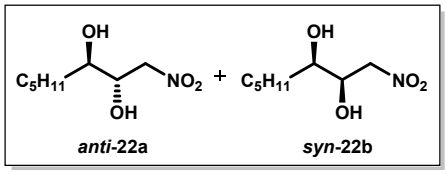


134.0489. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak AD-H (4.6 x 250 mm) using mobile phase of (05:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 41.52 min, (*R*,*S*)-enantiomer: t_r = 44.67 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 46.79 min, (*S*,*S*)-enantiomer: t_r = 56.15 min.

(*anti*/*syn*)-1-Nitroheptane-2,3-diol (21a and 21b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**21a** and *syn*-**21b** diastereomersas white solid in 64% yield (113 mg, 0.64 mmol), (92% *ee* for *anti*, 96% *ee* for *syn*) and as 1.23:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3531, 3133, 2937, 1586, 1572, 1522, 1472, 1381, 1282, 1224, 1118, 1110, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.27-4.22 (m, 1H), 3.77-3.54 (m, 1H), 2.65 (br s, 2H), 1.59-1.25 (m, 6H), 0.92 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.9, 71.8, 71.7, 70.9, 33.0, 32.2, 27.7, 27.5, 22.4, 13.9. HRMS (ESI)$^{-}$ m/z calcd for $C_7H_{14}NO_4^-$ ([M-H]$^{+}$) 176.0928; found 176.0942. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 150 mm) using mobile phase of (4:96:0.1 *i*-propanol:*n*-hexane:DEA, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 230 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.29 min, (*R*,*S*)-enantiomer: t_r = 15.38 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 18.53 min, (*S*,*S*)-enantiomer: t_r = 19.56 min.

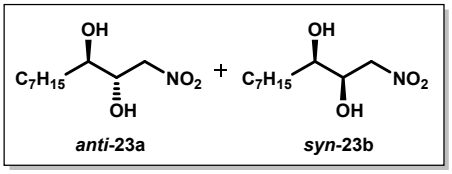


(*anti*/*syn*)-1-Nitrooctane-2,3-diol (22a and 22b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction,the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**22a** and *syn*-**22b** diastereomers as white solid in 62% yield (118 mg, 0.62 mmol), (98% *ee* for *anti*, 82% *ee* for *syn*) and as 6.34:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3364, 3211, 1715, 1682, 1665, 1579, 1512, 1366, 1344, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.27-4.21 (m, 1H), 3.77-3.54 (m, 1H), 2.83 (br s, 2H), 1.57-1.32 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7,

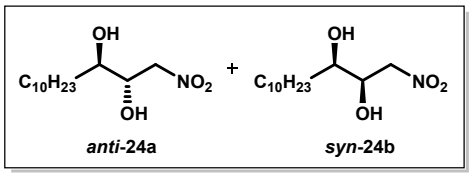


77.2, 72.8, 71.8, 71.7, 70.8, 33.3, 32.5, 31.5, 25.3, 25.1, 22.4, 13.9. HRMS (ESI)$^-$ m/z calcd for $C_8H_{16}NO_4^-$ ([M-H]$^+$) 190.1085; found 190.1095. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak AD-H (4.6 x 250 mm) using mobile phase of (5:95:0.1 *i*-propanol:*n*-hexane:DEA, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 230 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 18.11 min, (*R*,*S*)-enantiomer: t_r = 20.36 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 13.37 min, (*S*,*S*)-enantiomer: t_r = 14.41 min.

(*anti*/*syn*)-1-Nitrodecane-2,3-diol (23a and 23b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to furnish the *anti*-**23a** and *syn*-**23b** diastereomers as white solid in 67% yield (146 mg, 0.67 mmol), (90% *ee* for *anti*, >99% *ee* for *syn*) and as 1.1:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3459, 3122, 2962, 2877, 1732, 1652, 1591, 1561, 1466, 1371, 1265, 1092, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.62-4.48 (m, 2H), 4.26-4.22 (m, 1H), 3.77-3.54 (m, 1H), 2.44 (br s, 2H), 1.58-1.21 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 78.7, 77.2, 72.8, 71.8, 71.7, 70.8, 33.4, 32.6, 31.7, 29.3, 29.1, 25.6, 25.4, 22.5, 14.0. HRMS (ESI)$^-$ m/z calcd for $C_{10}H_{20}NO_4^-$ ([M-H]$^+$) 218.1398; found 218.1408. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (2:98 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 76.80 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 80.29 min, (*S*,*S*)-enantiomer: t_r = 86.91 min.

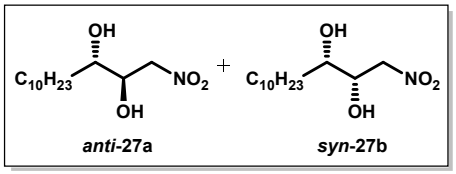


(*anti*/*syn*)-1-Nitrotridecane-2,3-diol (24a and 24b): Following the general procedure for tandem *α*-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**24a** and *syn*-**24b** diastereomers as white solid in 70% yield (182 mg, 0.70 mmol), (>99% *ee* for *anti*, 98% *ee* for *syn*) and as 3.3:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) *v*: 3520, 3123, 2933, 1596, 1582, 1562, 1518,

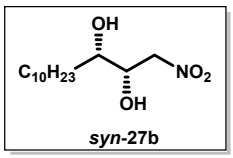


1472, 1379, 1279, 1232, 1115, 1072, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.62-4.48 (m, 2H), 4.28-4.21 (m, 1H), 3.79-3.54 (m, 1H), 3.18 (s, 1H), 2.32 (s, 1H), 1.59-1.26 (m, 18H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.7, 77.2, 72.8, 71.8, 71.6, 70.8, 33.4, 32.6, 31.8, 29.5, 29.4, 29.4, 29.4, 29.2, 25.6, 25.4, 22.6, 14.0. HRMS $(ESI)^-$ m/z calcd for $C_{13}H_{26}NO_4^-$ ($[M-H]^+$) 260.1867; found 260.1872. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (5:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^oC, UV detection at 210 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.51 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 22.03 min, (*S*,*S*)-enantiomer: t_r = 26.03 min.

(*anti*/*syn*)-1-Nitrotridecane-2,3-diol (27a and 27b): Following the general procedure for tandem α-aminoxylation-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**27a** and *syn*-**27b** diastereomers as off white solid in 65% yield (170 mg, 0.65 mmol) and as 1.1:1 *anti*:*syn* mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.63-4.49 (m, 2H), 4.29 (d, J = 5.04 Hz, 1H), 3.72-3.54 (m, 1H), 3.16 (br s, 1H), 1.58-1.24 (m, 18H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.7, 77.2, 72.8, 71.8, 71.6, 70.5, 33.4, 32.6, 31.8, 29.5, 29.5, 29.4, 29.4, 29.3, 25.6, 25.4, 22.6, 14.1. The above *anti*-/*syn*-diastereomers **27a** and **27b** were separated and purified by silica gel column chromatography to furnish the *anti*-**27a** (99% *ee*) and *syn*-**27b** (99% *ee*) diastereomers as white solid. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (5:95 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^oC, UV detection at 210 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 17.41 min, (*R*,*S*)-enantiomer: t_r = 19.40 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 22.18 min, (*S*,*S*)-enantiomer: t_r = 26.17 min.

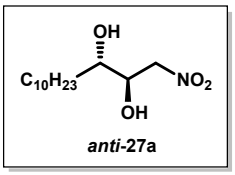


(2*S*,3*S*)-1-Nitrotridecane-2,3-diol (27b): The above *anti*-/*syn*-diastereomers **27a** and **27b** (170 mg) were separated and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *syn*-**27b** diastereomer as white solid in 29% yield (77 mg, 0.29 mmol). $[\alpha]_D^{25}$ +55.2 (*c* 0.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.63-4.49 (m, 2H), 4.27-4.18 (m, 1H), 3.75-3.72



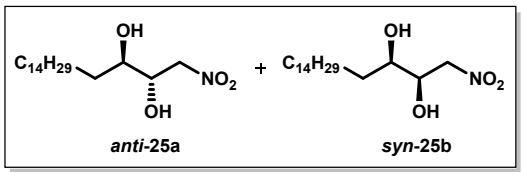
(m, 1H), 2.41 (br s, 2H), 1.56-1.20 (m, 18H), 0.86 (t, J = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.5, 73.1, 72.0, 33.0, 32.2, 29.9, 29.8, 29.7, 29.6, 25.9, 22.9, 14.4.

(2*R*,3*S*)-1-nitrotridecane-2,3-diol (27a): After separation of the *syn*-**27b** diastereomer, the *anti*-**27a** diastereomer was quickly eluted (EtOAc/hexane 1:5 v/v) as white solid in 36% yield (93 mg, 0.36 mmol). $[\alpha]_D^{25}$ +72.5 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62-4.48 (m, 2H), 4.25-4.21 (m, 1H), 3.59-3.51 (m, 1H), 1.61-1.20 (m, 18H), 0.86 (t, J = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.3, 71.4, 70.4, 33.2, 31.5, 29.3, 29.2, 29.1, 29.1, 29.0, 25.1, 22.3, 13.8.



anti-27a

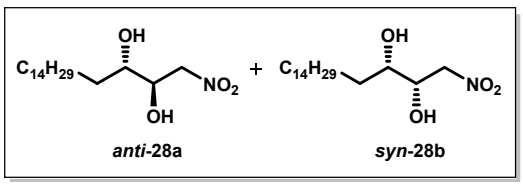
(*anti*/*syn*)-1-Nitrooctadecane-2,3-diol (25a and 25b):



anti-25a *syn*-25b

Following the general procedure for tandem α-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**25a** and *syn*-**25b** diastereomers as white solid in 68% yield (225 mg, 0.68 mmol), (80% *ee* for *anti*, >99% *ee* for *syn*) and as 1.2:1 *anti*:*syn* mixture of diastereomers. IR (CH_2Cl_2) ν: 3591, 3586, 2931, 1632, 1575, 1532, 1474, 1362, 1186, 1085, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62-4.48 (m, 2H), 4.26-4.23 (m, 1H), 3.78-3.55 (m, 1H), 2.96 (br s, 1H), 2.10 (br s, 1H), 1.60-1.25 (m, 28H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.6, 77.2, 72.8, 71.7, 71.6, 70.7, 33.5, 32.7, 31.9, 29.6, 29.6, 29.5, 29.4, 29.4, 29.3, 25.6, 25.4, 22.6, 14.1. HRMS (ESI)$^+$ m/z calcd for $C_{18}H_{38}NO_4^+$ ([M+H]$^+$) 332.2796; found 332.2798. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 37.04 min, (*R*,*S*)-enantiomer: t_r = 42.21 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 28.16 min, (*S*,*S*)-enantiomer: t_r = 32.99 min.

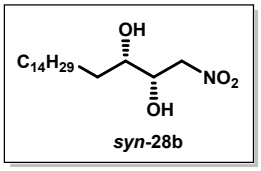
(*anti*/*syn*)-1-Nitrooctadecane-2,3-diol (28a and 28b): Following the general procedure for tandem α-aminooxylated-Henry reaction, the residue was purified by silica gel column chromatography using (EtOAc/hexane 1:5 v/v) as eluent to furnish the *anti*-**28a** and *syn*-**28b** diastereomers as off



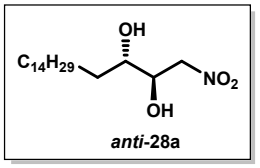
anti-28a *syn*-28b

white solid in 67% yield (220 mg, 0.67 mmol), (86% *ee* for *anti*, 97% *ee* for *syn*) and as 1.64:1 *anti*:*syn* mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.60-4.46 (m, 2H), 4.24-4.21 (m, 1H), 3.77-3.53 (m, 1H), 2.94 (br s, 1H), 1.58-1.23 (m, 28H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.3, 76.9, 72.4, 71.4, 71.3, 70.4, 33.2, 32.4, 31.5, 29.3, 29.3, 29.2, 29.1, 29.1, 29.0, 25.3, 25.1, 22.3, 13.8. The diastereomer ratio (dr) and enantiomeric purity (*ee*) were determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 220 nm): *anti* diastereomer (*S*,*R*)-enantiomer: t_r = 36.93 min, (*R*,*S*)-enantiomer: t_r = 42.07 min; *syn* diastereomer (*R*,*R*)-enantiomer: t_r = 28.04 min, (*S*,*S*)-enantiomer: t_r = 32.37 min.

(2*S*,3*S*)-1-Nitrooctadecane-2,3-diol (28b): The above *anti*-/*syn*-diastereomers **28a** and **28b** (220 mg) were separated and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the *syn*-**28b** diastereomer as white solid in 25% yield (84 mg, 0.25 mmol) with 98% *ee*. $[\alpha]_D^{25}$ +35.2 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.60-4.49 (m, 2H), 4.27-4.18 (m, 1H), 3.75-3.72 (m, 1H), 2.38 (br s, 2H), 1.59-1.40 (m, 2H), 1.37-1.20 (m, 26H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 77.2, 72.8, 71.7, 32.7, 31.9, 29.6, 29.5, 29.4, 29.3, 25.6, 22.6, 14.1. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-hexane, flow rate of 1 mL/min at 25 ^{o}C, UV detection at 220 nm): (*R*,*R*)-enantiomer: t_r = 29.88 min, (*S*,*S*)-enantiomer: t_r = 32.64 min.



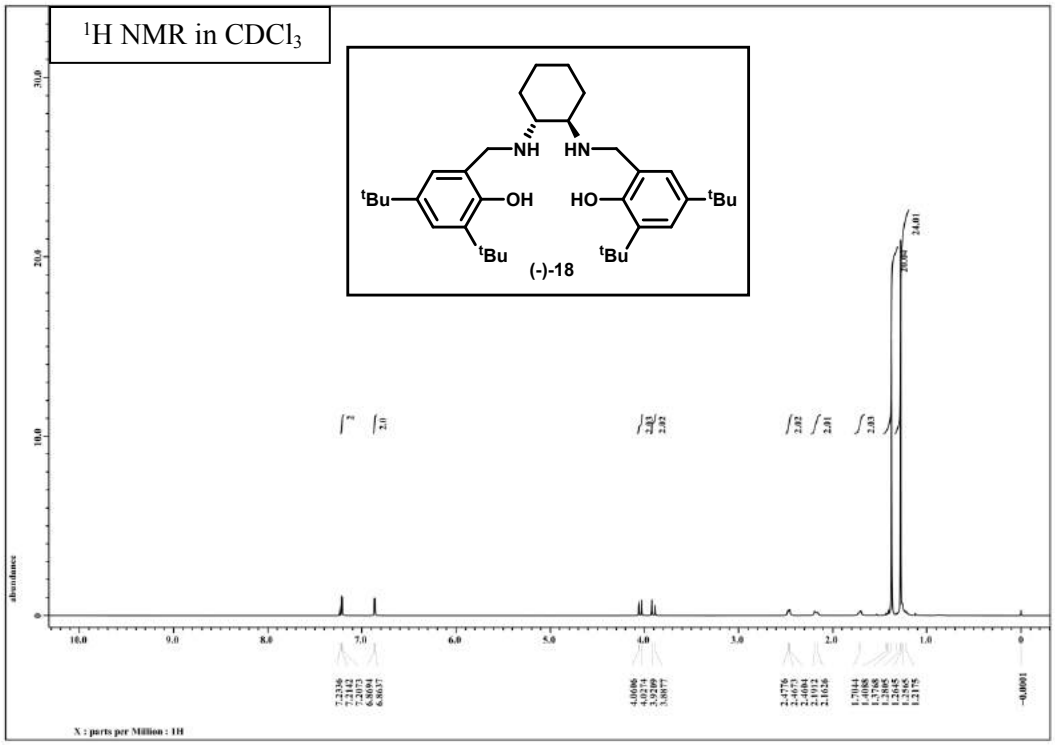
(2*R*,3*S*)-1-Nitrooctadecane-2,3-diol (28a): After separation of the *syn*-**28b** diastereomer, the *anti*-**28a** diastereomer was quickly eluted (EtOAc/hexane 1:5 v/v) as white solid in 42% yield (136 mg, 0.42 mmol) with 99% *ee*. $[\alpha]_D^{25}$ +48.7 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.63-4.48 (m, 2H), 4.26-4.22 (m, 1H), 3.59-3.55 (m, 1H), 1.64-1.48 (m, 2H), 1.42-1.21 (m, 26H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 78.6, 71.7, 70.7, 33.5, 31.9, 29.6, 29.5, 29.4, 29.4, 29.3, 25.4, 22.6, 14.1. The enantiomeric purity (*ee*) was determined by HPLC analysis using a Chirapak IA (4.6 x 250 mm) using mobile phase of (3:97 *i*-propanol:*n*-

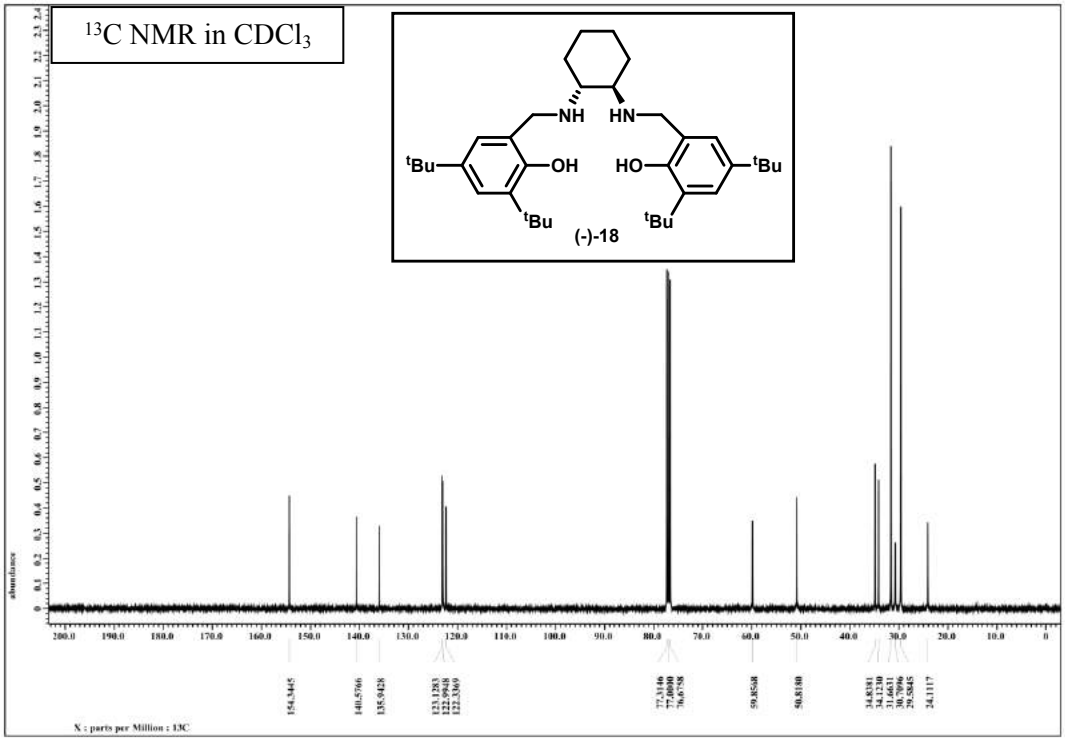


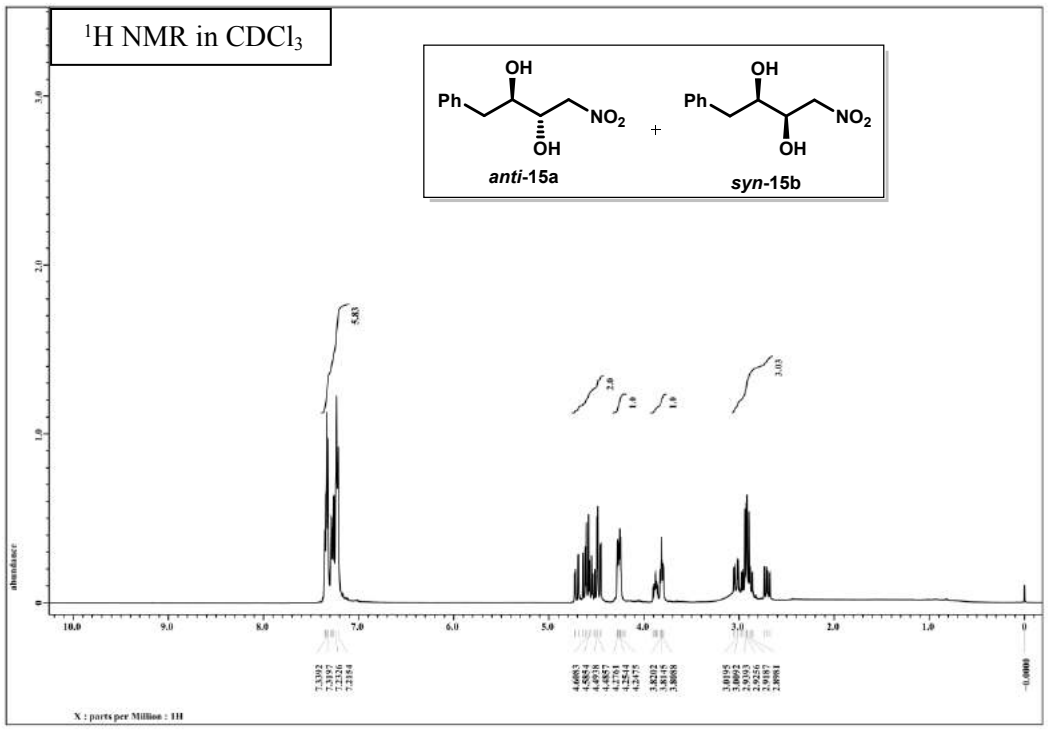
hexane, flow rate of 1 mL/min at 25 °C, UV detection at 220 nm): (*S*,*R*)-enantiomer: t_r = 38.68 min, (*R*,*S*)-enantiomer: t_r = 43.44 min.

4.1.7 Spectra:

1. ^{1}H and ^{13}C NMR spectra of **18**
2. ^{1}H and ^{13}C NMR spectra of **15**
3. ^{1}H and ^{13}C NMR spectra of **15b**
4. ^{1}H and ^{13}C NMR spectra of **15a**
5. ^{1}H and ^{13}C NMR spectra of **26**
6. ^{1}H and ^{13}C NMR spectra of **19**
7. ^{1}H and ^{13}C NMR spectra of **20**
8. ^{1}H and ^{13}C NMR spectra of **21**
9. ^{1}H and ^{13}C NMR spectra of **22**
10. ^{1}H and ^{13}C NMR spectra of **23**
11. ^{1}H and ^{13}C NMR spectra of **24**
12. ^{1}H and ^{13}C NMR spectra of **27**
13. ^{1}H and ^{13}C NMR spectra of **27b**
14. ^{1}H and ^{13}C NMR spectra of **27a**
15. ^{1}H and ^{13}C NMR spectra of **25**
16. ^{1}H and ^{13}C NMR spectra of **28**
17. ^{1}H and ^{13}C NMR spectra of **28b**
18. ^{1}H and ^{13}C NMR spectra of **28a**
19. HRMS of **15b** and **15a**
20. UV-vis spectrum of complex **32**
21. HPLC data


^{1}H NMR in $CDCl_3$
NH
HN
^{t}Bu
OH
HO
^{t}Bu
^{t}Bu
^{t}Bu
(-)-18


^{13}C NMR in $CDCl_3$
NH
HN
^{t}Bu
OH
HO
^{t}Bu
^{t}Bu
^{t}Bu
(-)-18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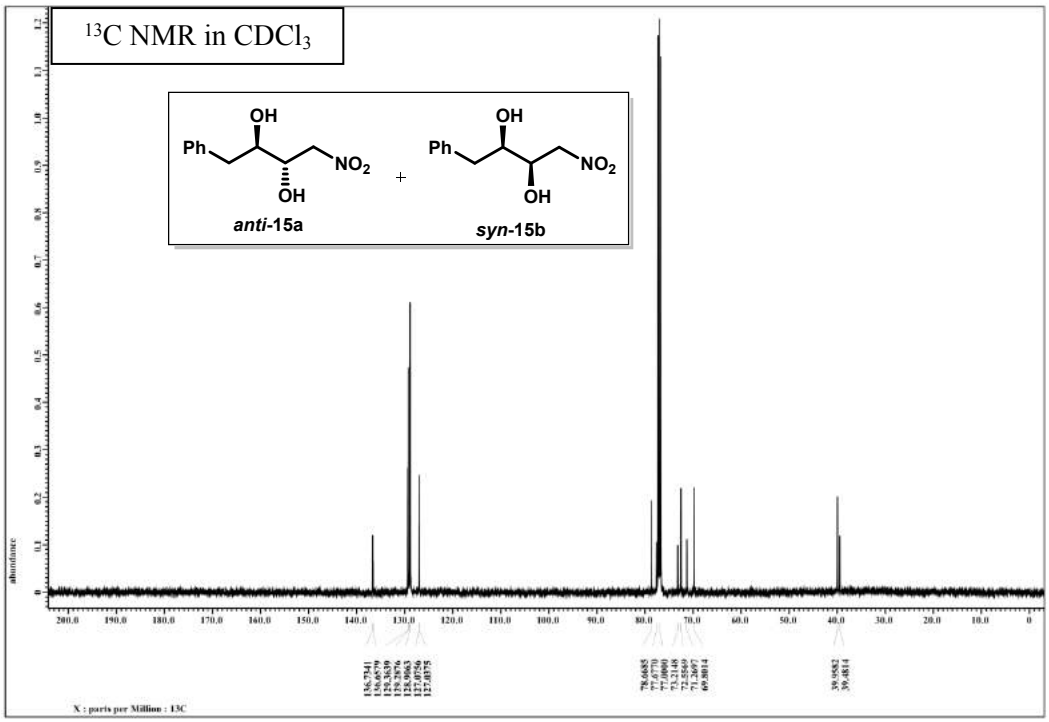
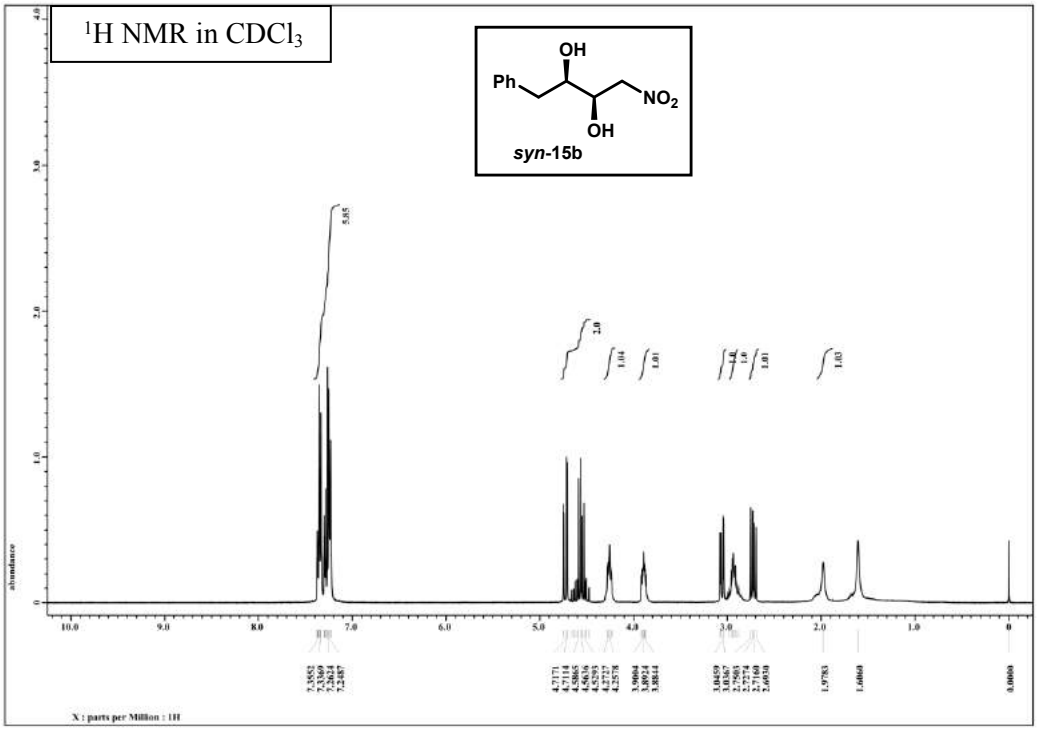
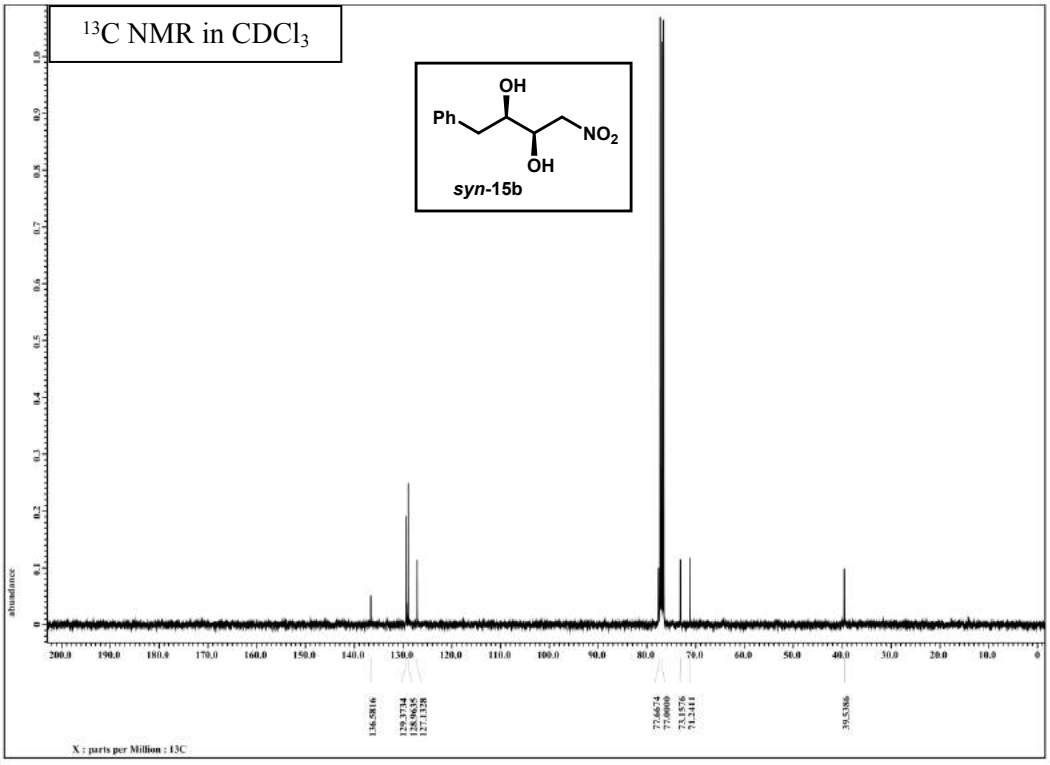
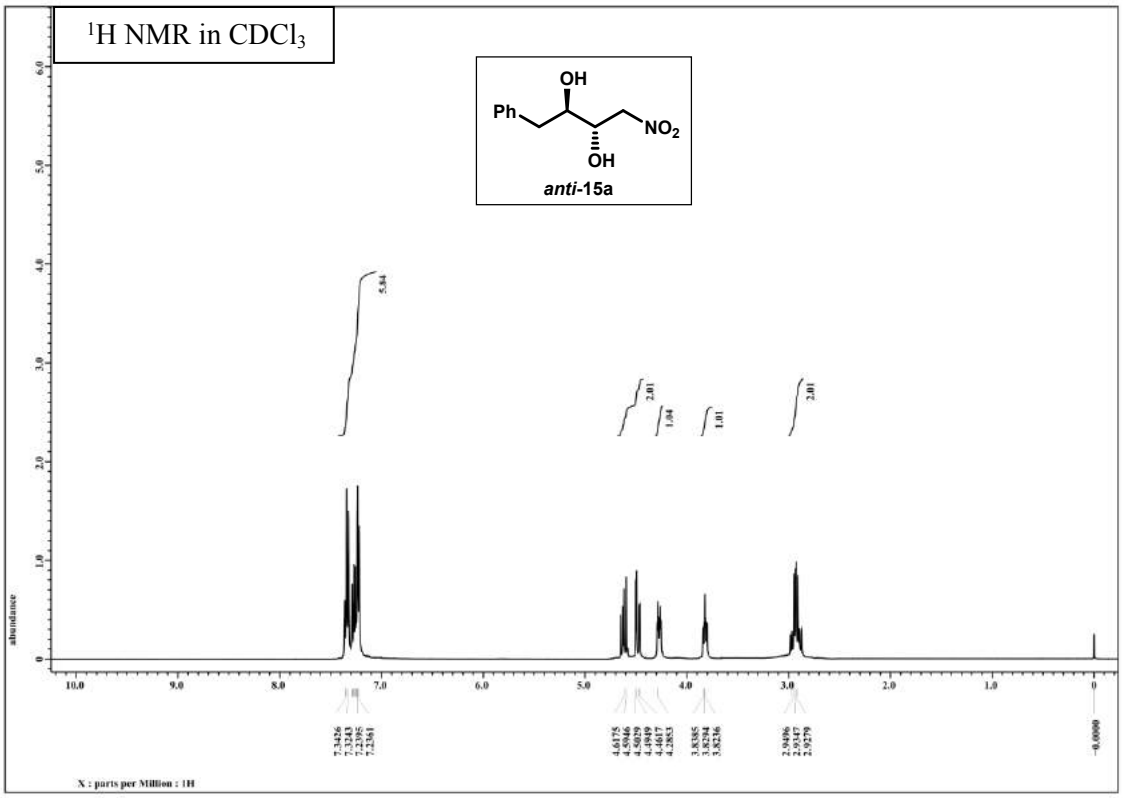
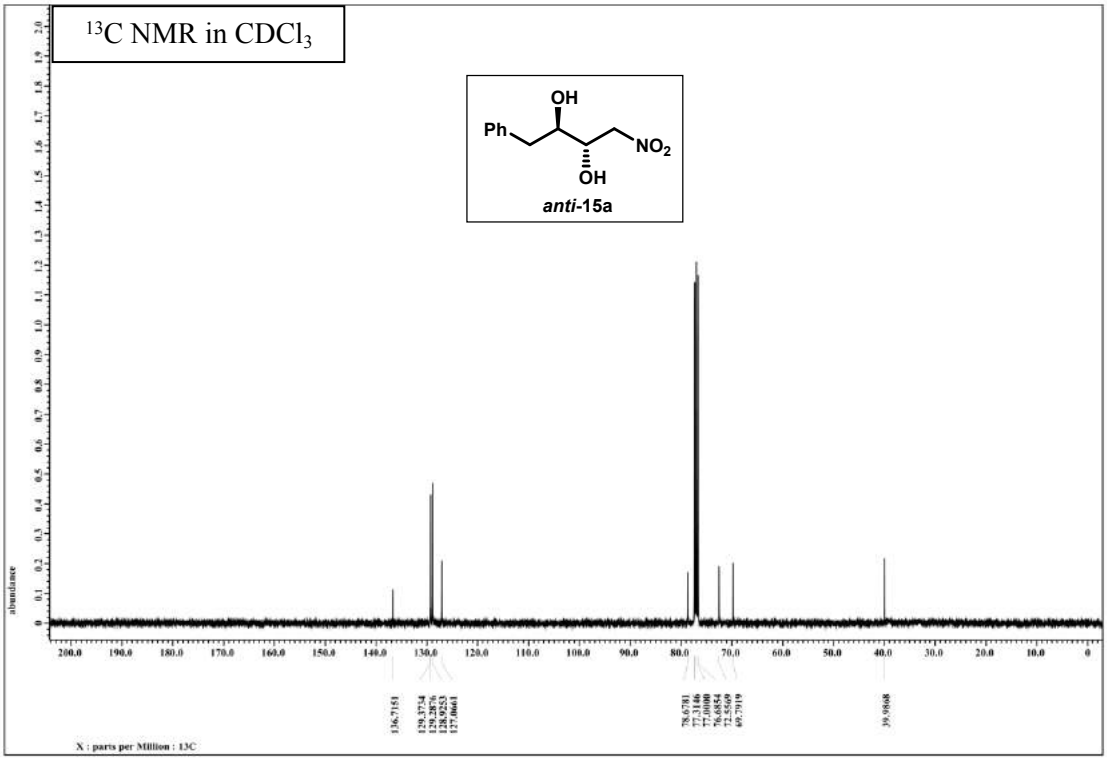
OH
Ph
NO_2
OH
anti-15a
+
OH
Ph
NO_2
OH
syn-15b

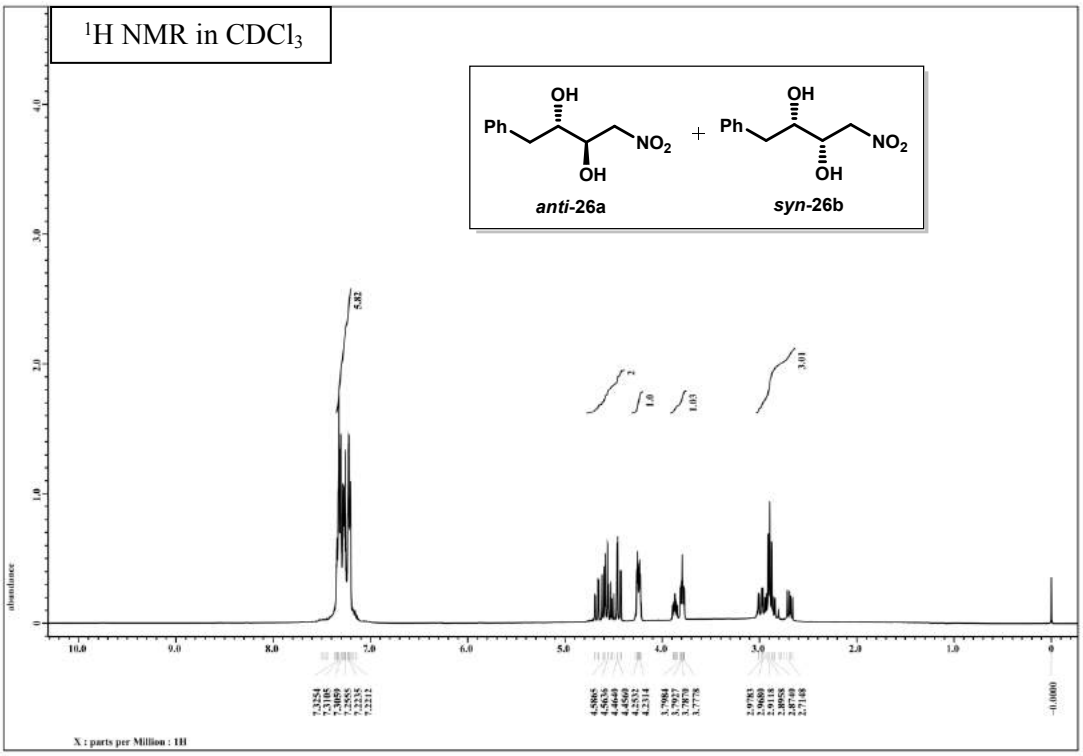

^{13}C NMR in $CDCl_3$
OH
Ph
NO_2
OH
anti-15a
+
OH
Ph
NO_2
OH
syn-15b

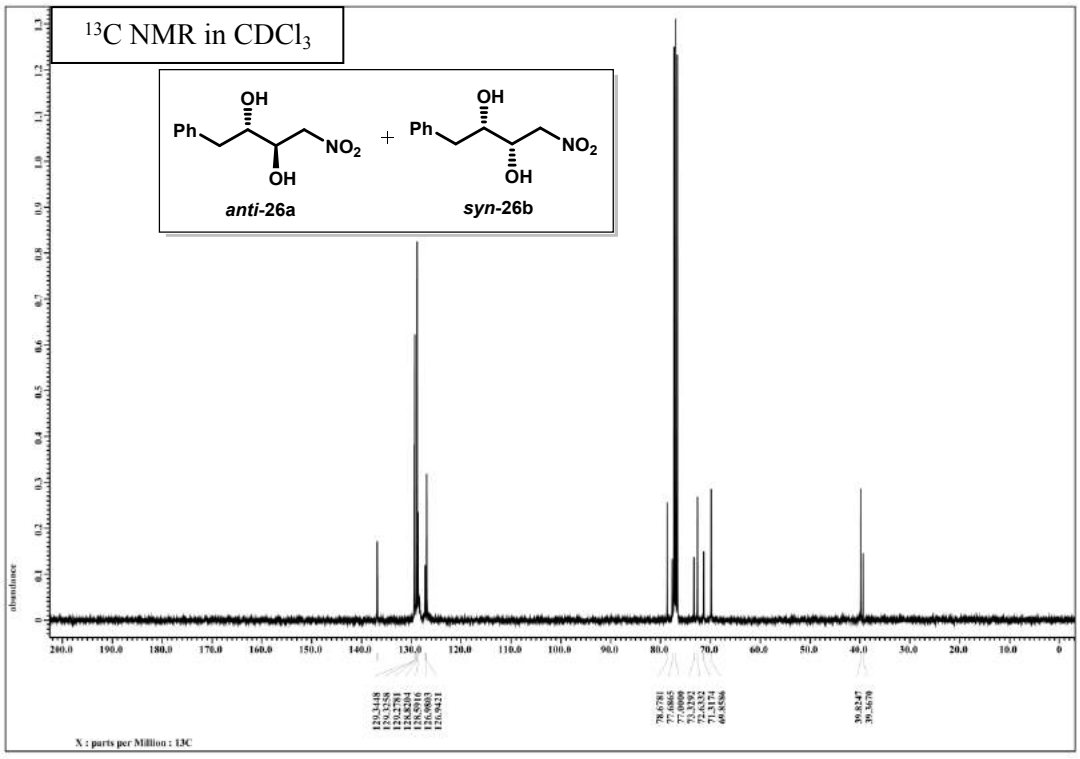

^{1}H NMR in $CDCl_3$
OH
Ph
NO_2
OH
syn-15b

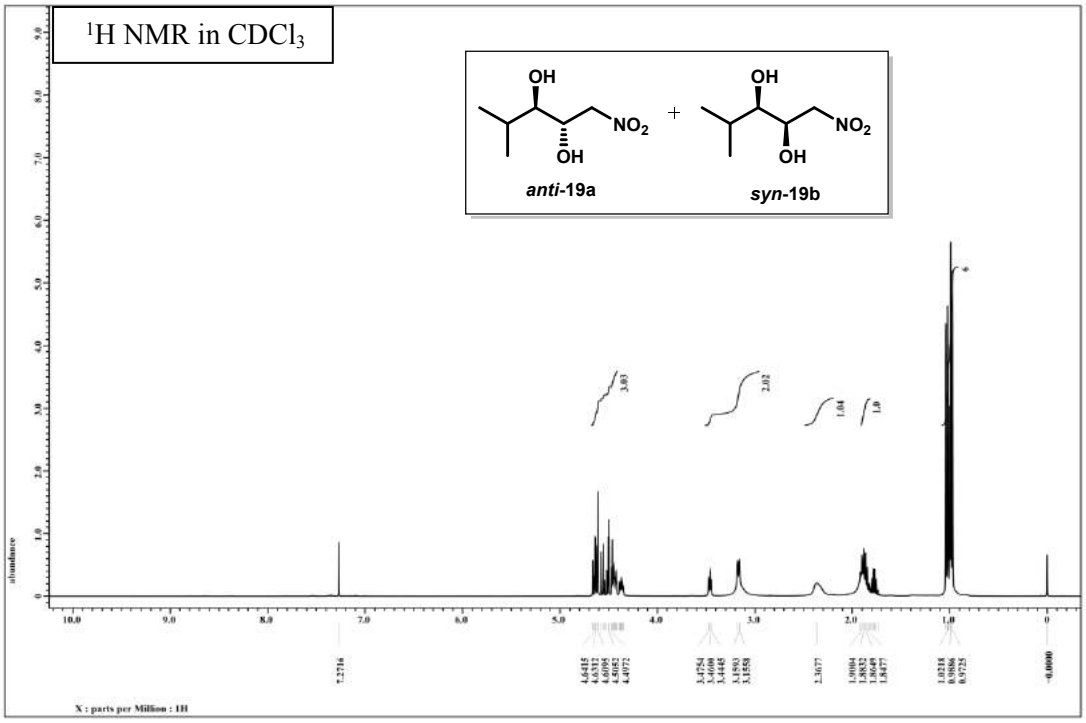

^{13}C NMR in $CDCl_3$
OH
Ph
NO_2
OH
syn-15b


^{1}H NMR in $CDCl_3$
OH
Ph
NO_2
OH
anti-15a
5.84
2.01
1.04
1.01
2.01
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
Ph
NO_2
OH
anti-15a
abundance
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
Ph
NO$_2$
OH
anti-26a
+
OH
Ph
NO$_2$
OH
syn-26b


^{13}C NMR in $CDCl_3$
OH
Ph
NO$_2$
OH
anti-26a
+
OH
Ph
NO$_2$
OH
syn-26b


^{1}H NMR in $CDCl_3$
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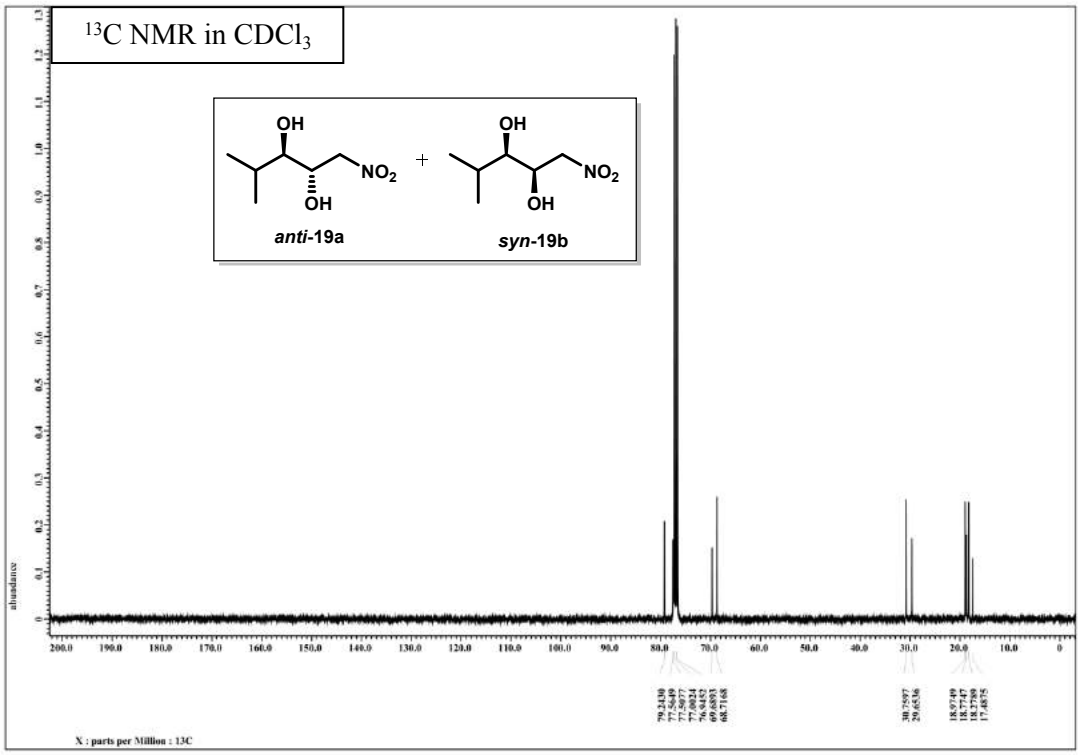
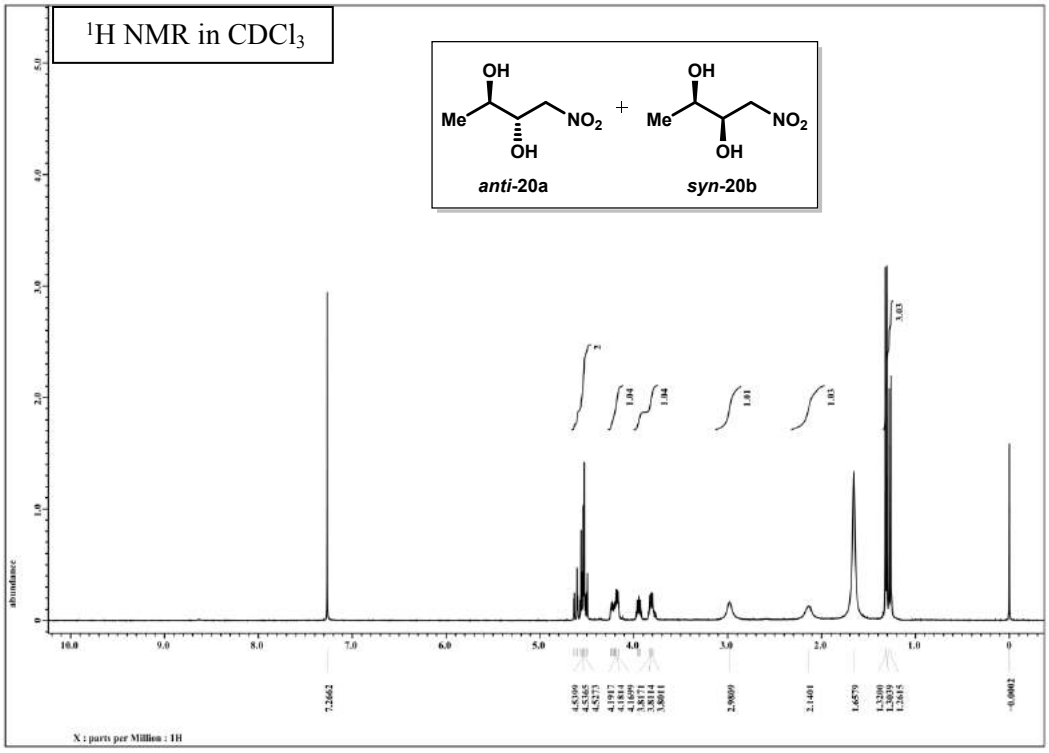
NO_2
OH
anti-19a
+
OH
NO_2
OH
syn-19b
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
NO_2
OH
anti-19a
+
OH
NO_2
OH
syn-19b
abundance
X : parts per Million : 13C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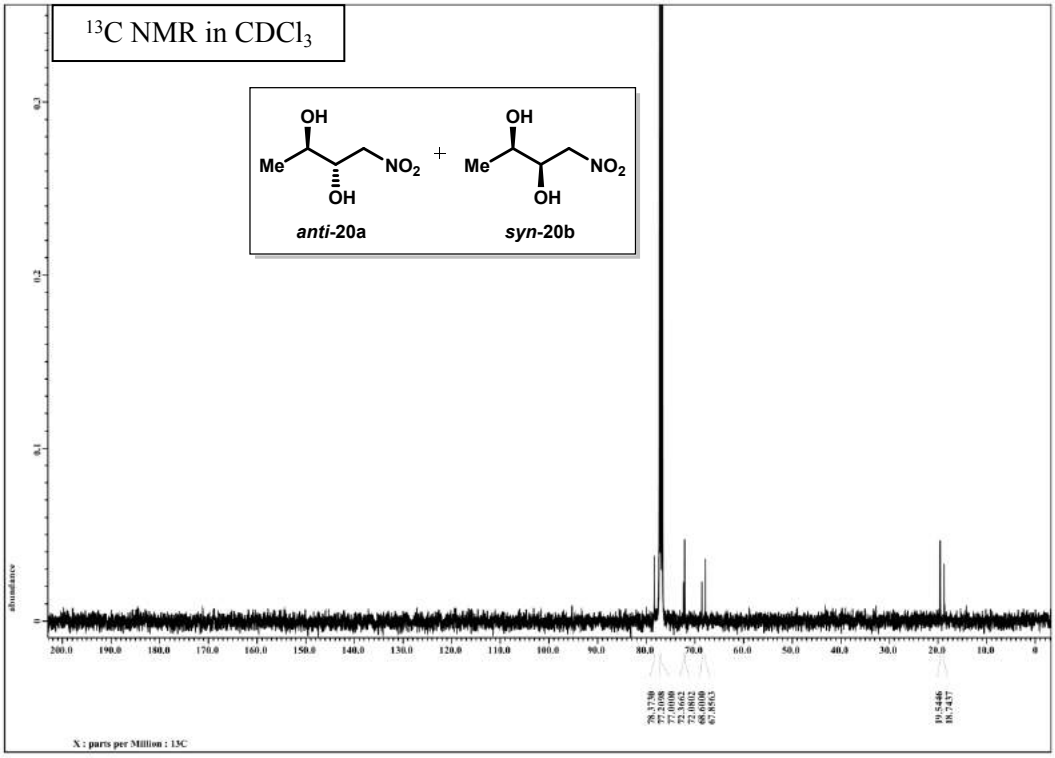
OH
Me
NO_2
OH
anti-20a
syn-20b
abundance
X : parts per Million : 1H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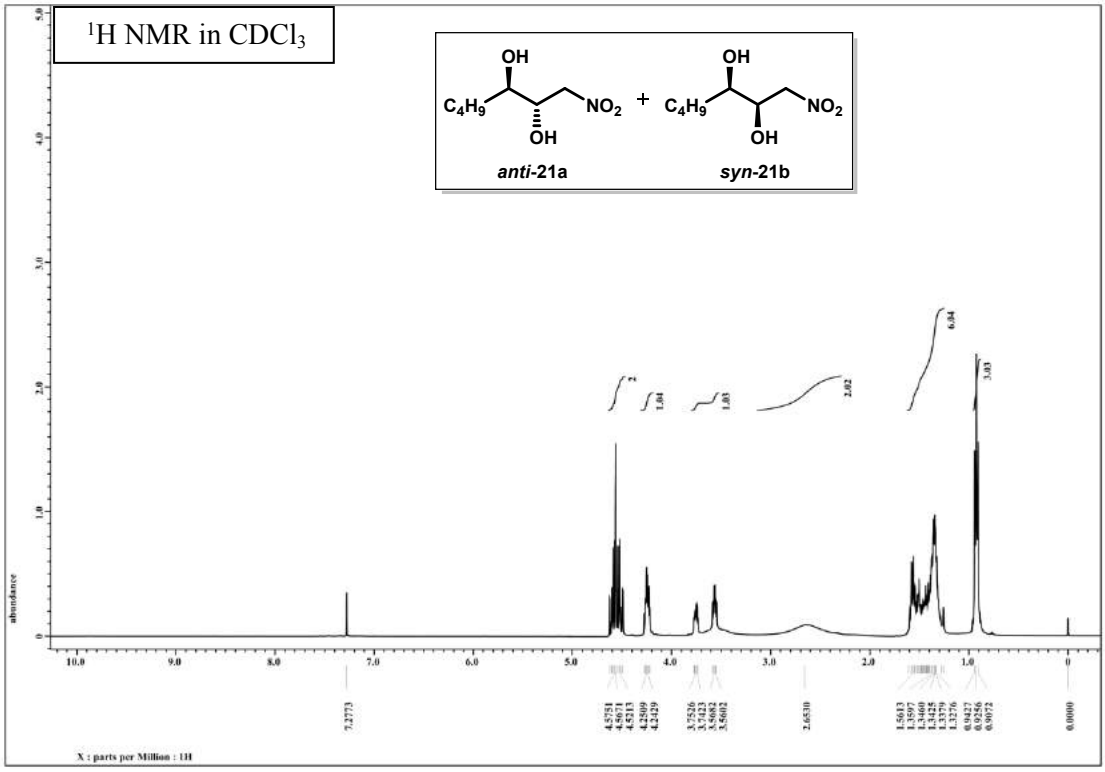
OH
Me
NO_2
OH
anti-20a
syn-20b
abundance
X : parts per Million : 13C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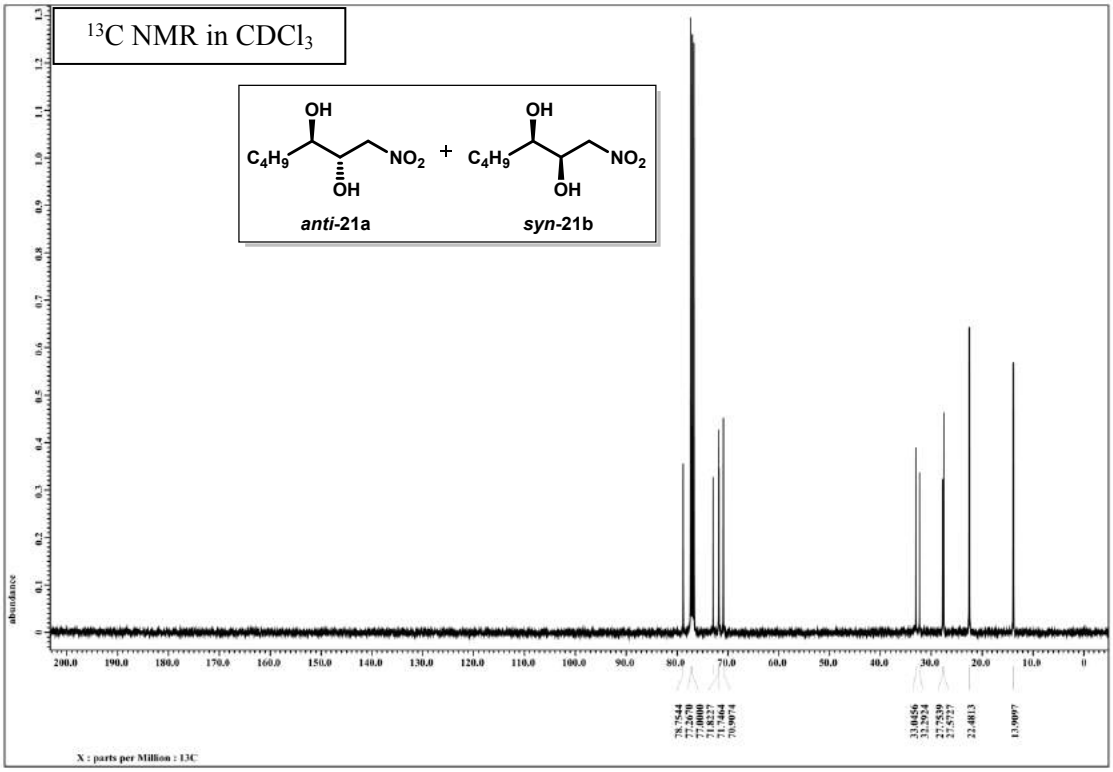
OH
C_4H_9
NO_2
OH
+
OH
C_4H_9
NO_2
OH
anti-21a
syn-21b
abundance
X : parts per Million : 1H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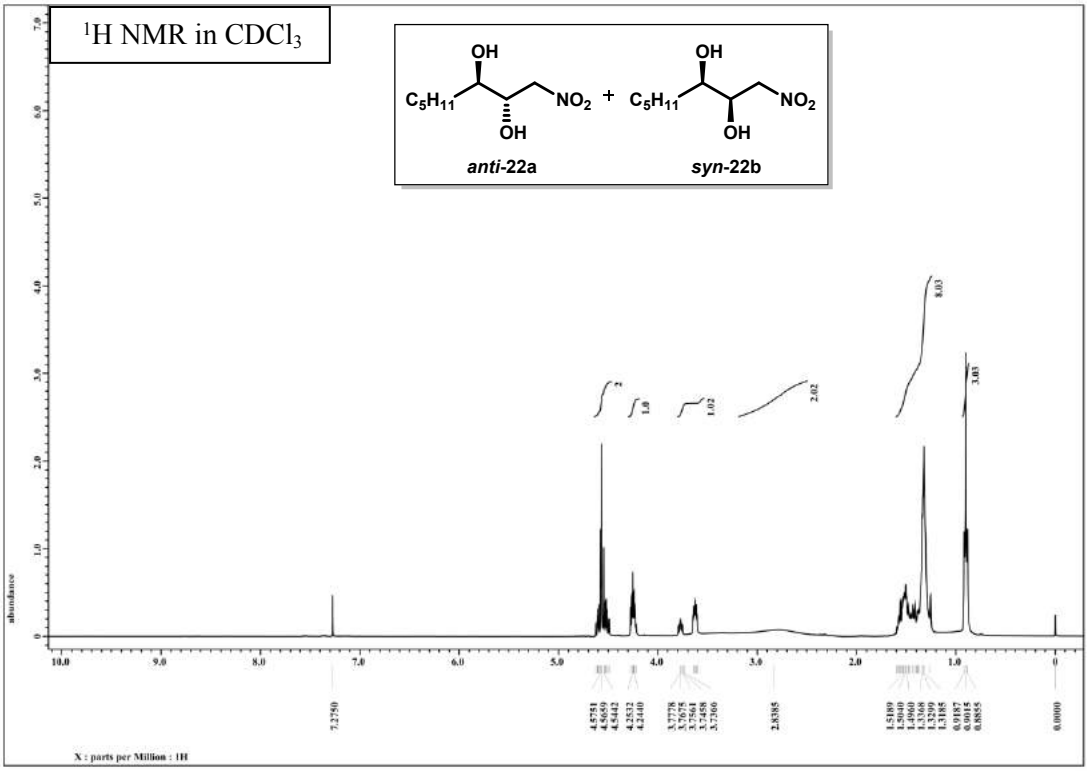
OH
C_4H_9
NO_2
OH
+
OH
C_4H_9
NO_2
OH
anti-21a
syn-21b
abundance
X : parts per Million : 13C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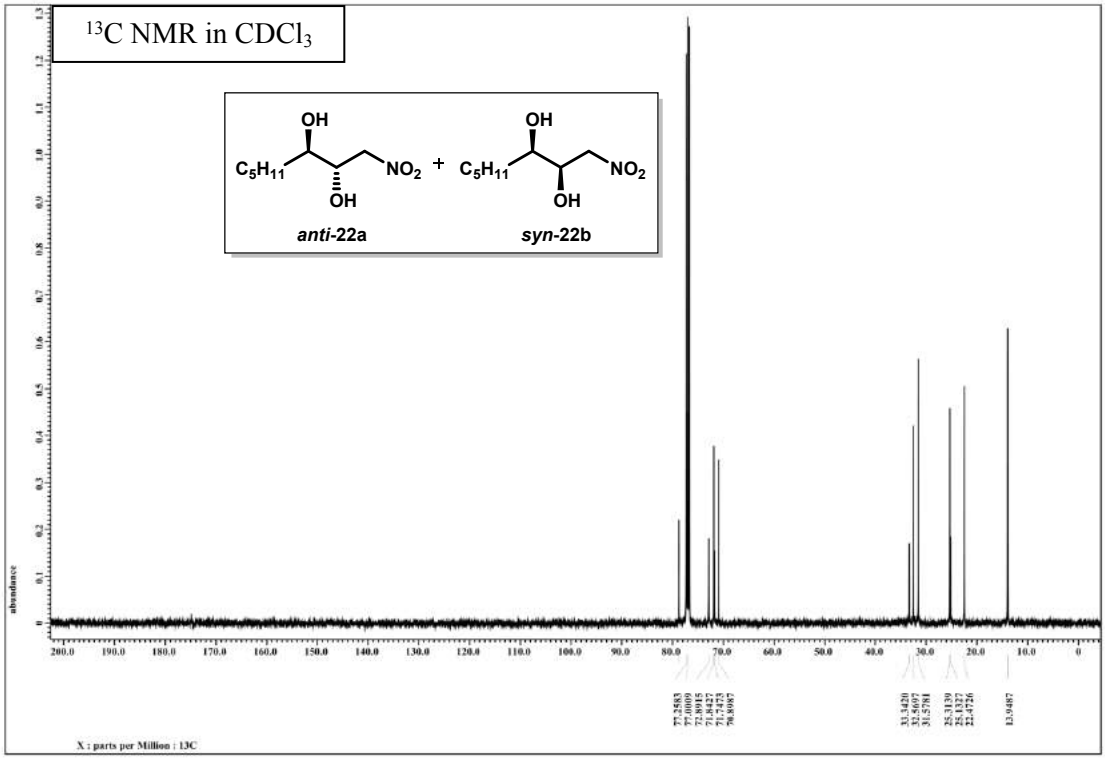
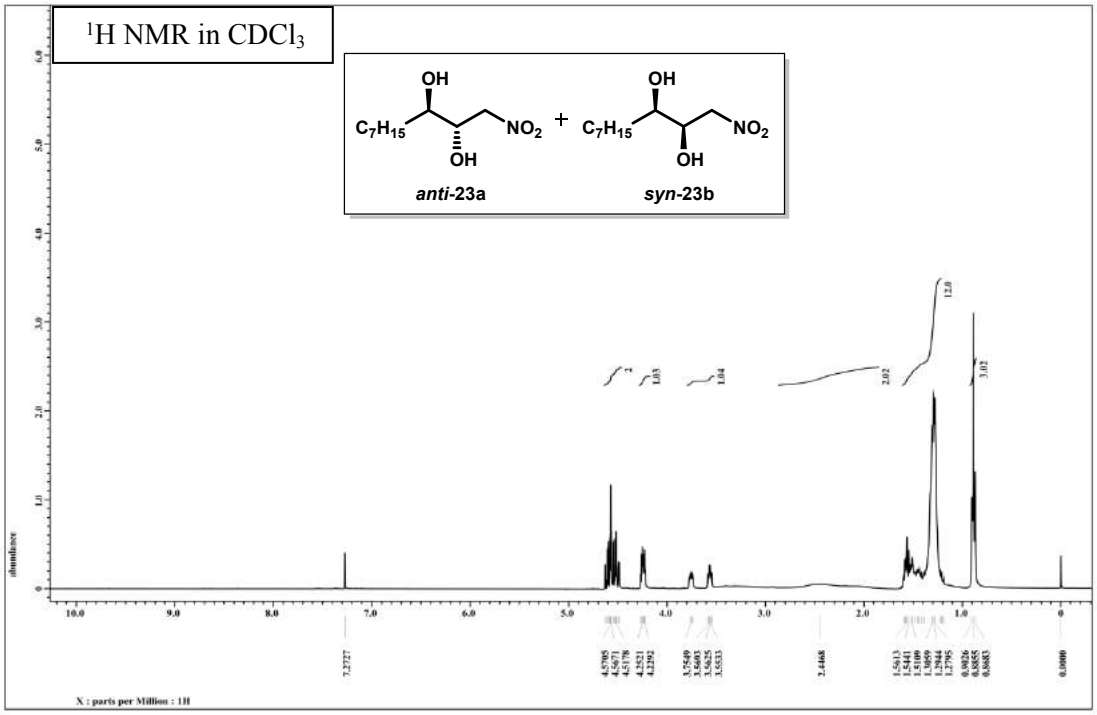
OH
C_5H_{11}
NO_2
OH
+
OH
C_5H_{11}
NO_2
OH
anti-22a
syn-22b
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
C_5H_{11}
NO_2
OH
+
OH
C_5H_{11}
NO_2
OH
anti-22a
syn-22b
abundance
X : parts per Million : 13C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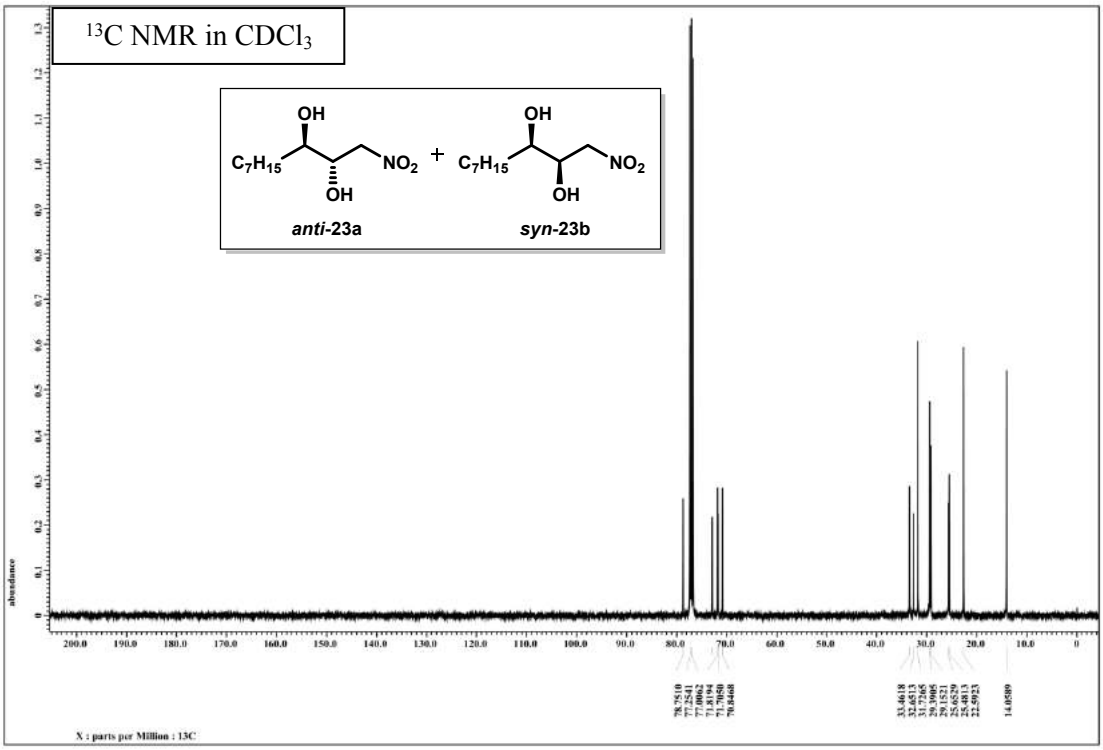
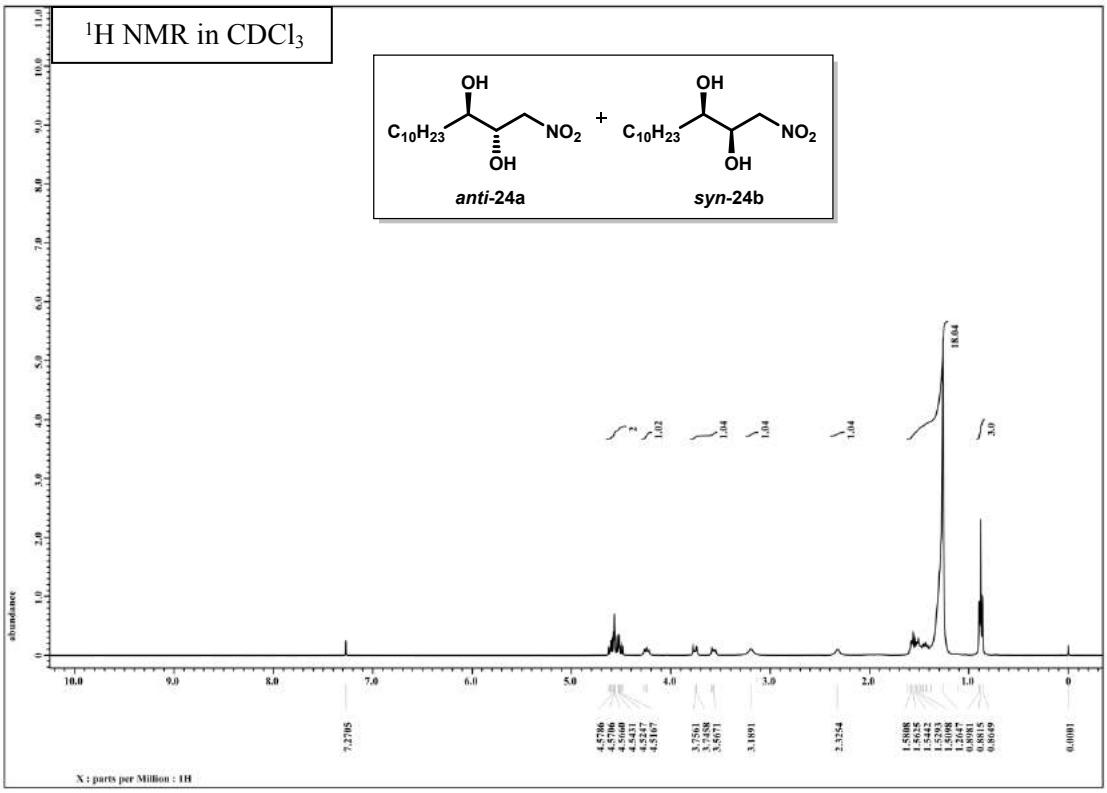
OH
C_7H_{15}
NO_2
OH
+
OH
C_7H_{15}
NO_2
OH
anti-23a
syn-23b
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
C_7H_{15}
NO_2
OH
+
OH
C_7H_{15}
NO_2
OH
anti-23a
syn-23b
abundance
X : parts per Million : 13C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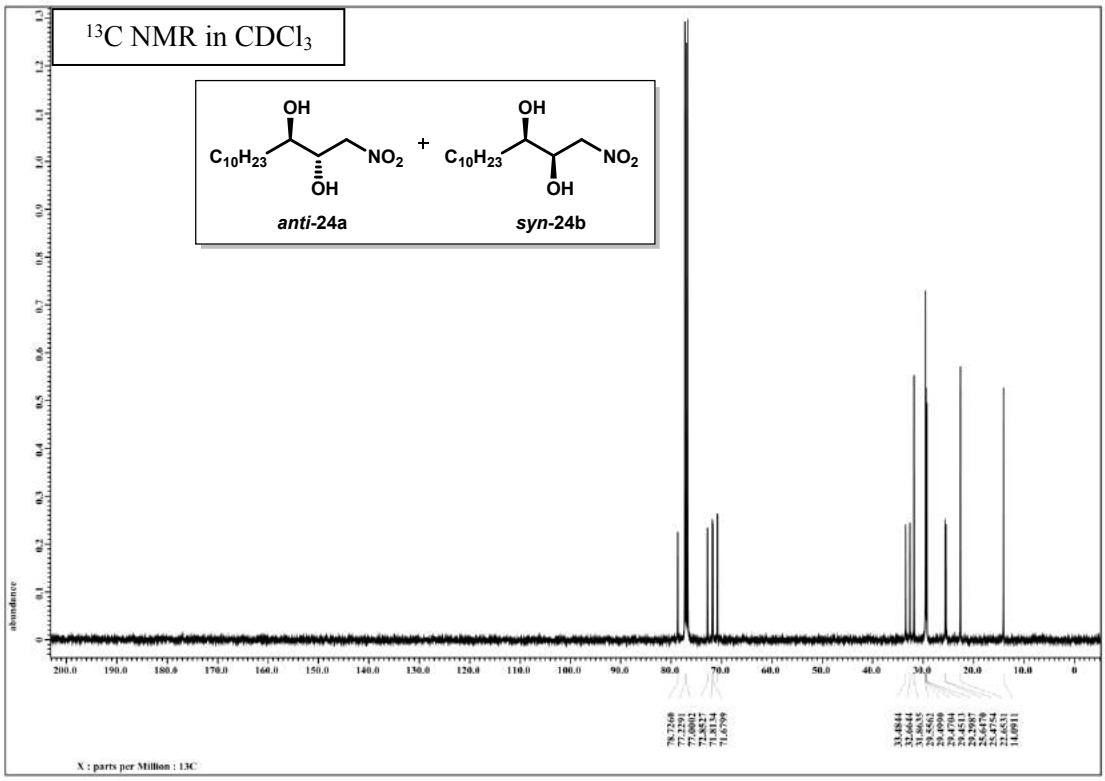
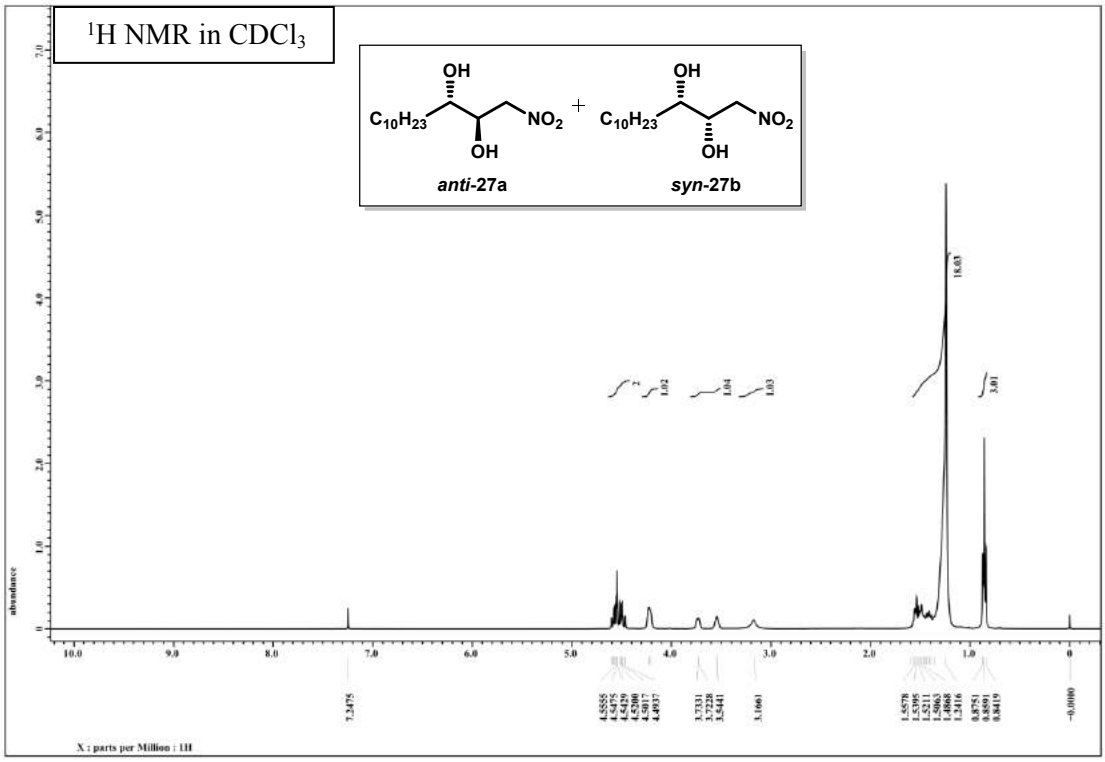
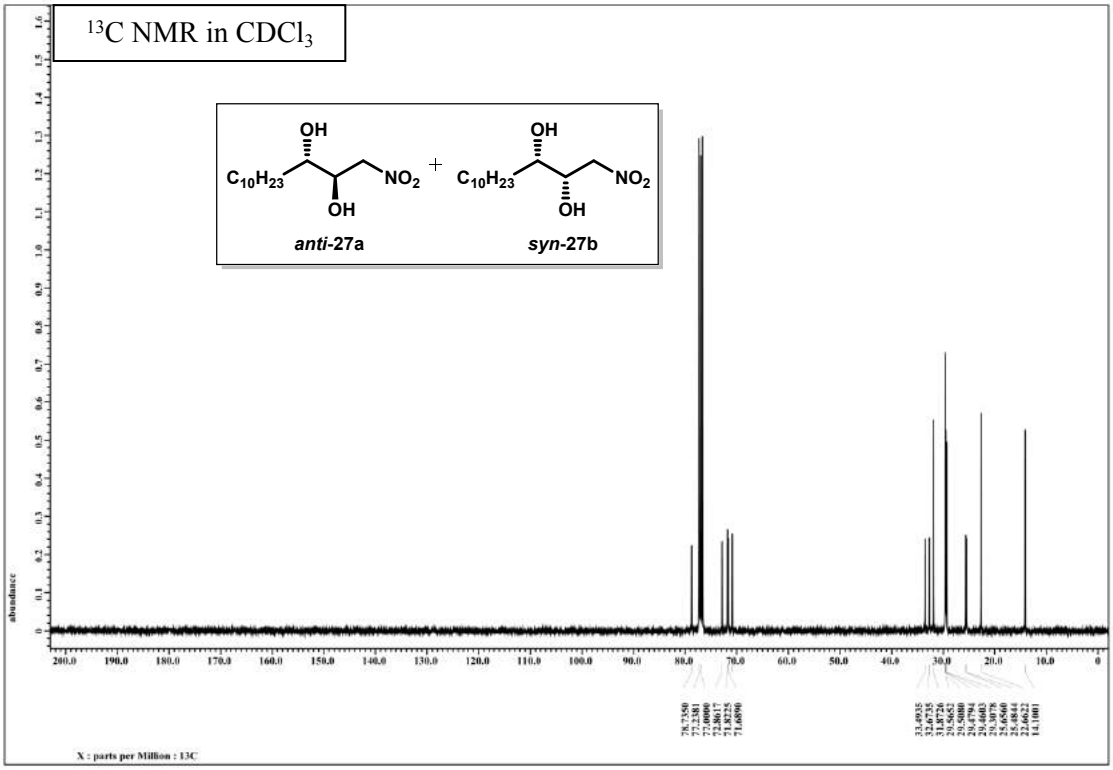
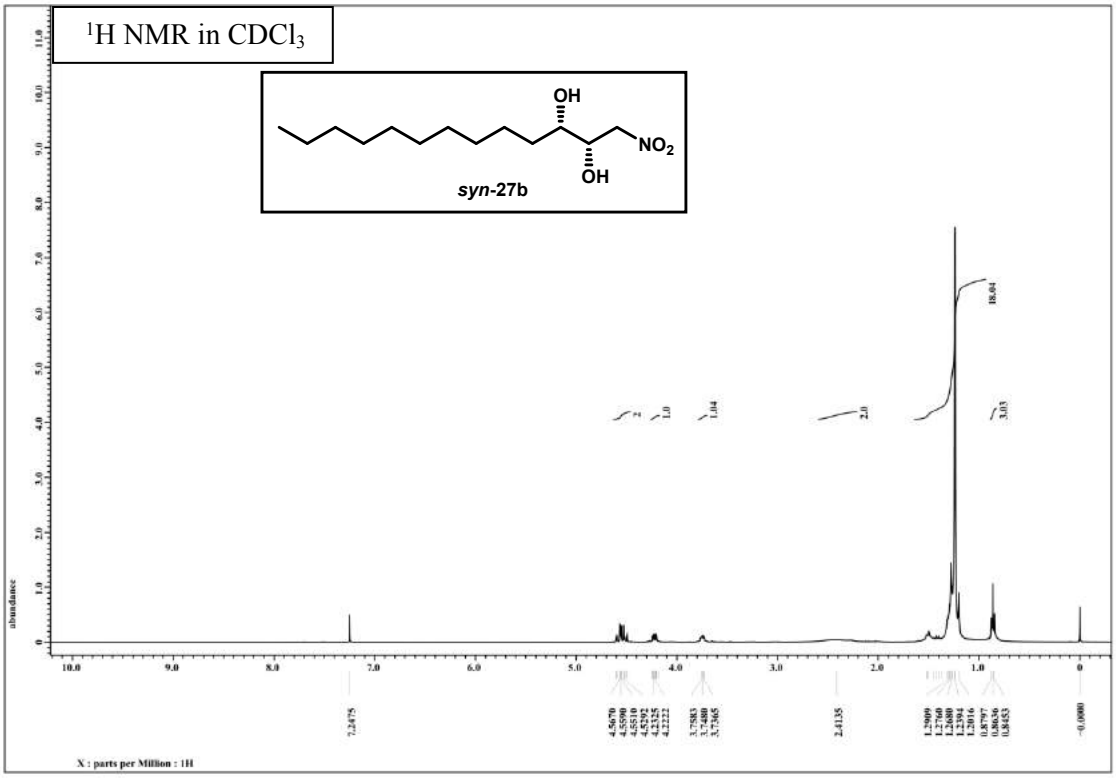
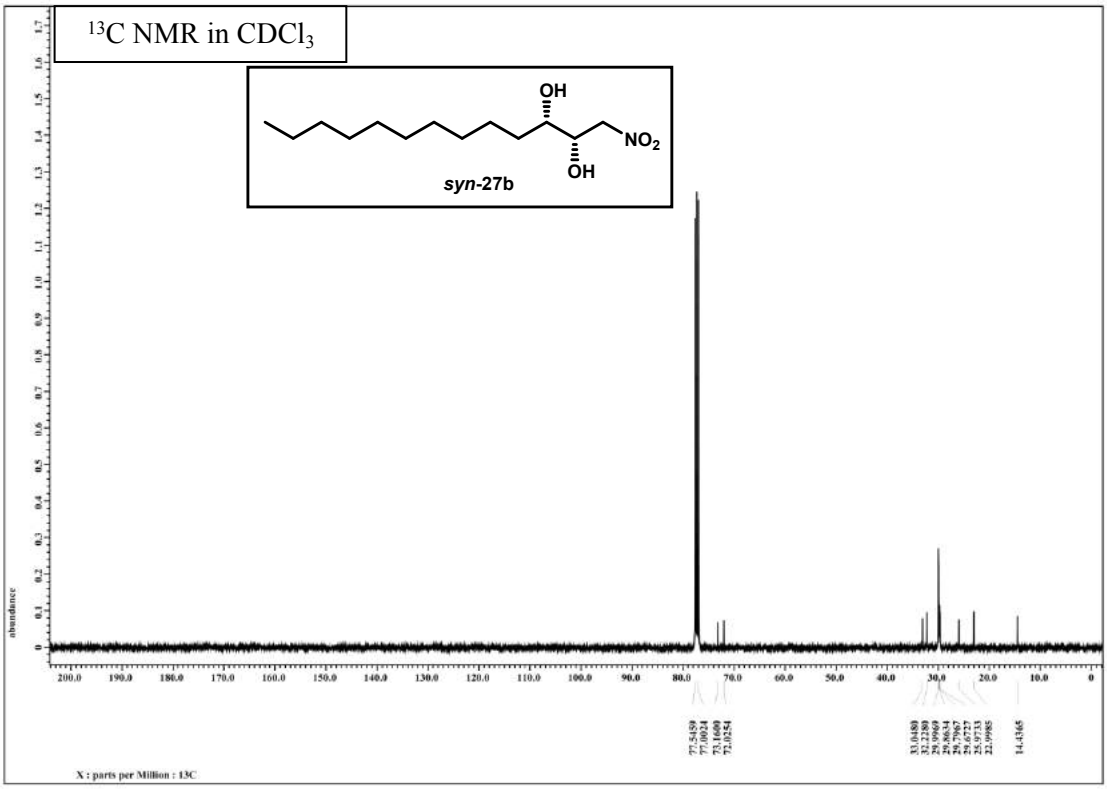
OH
$C_{10}H_{23}$
NO_2
OH
+
OH
$C_{10}H_{23}$
NO_2
OH
anti-24a
syn-24b
18.04
1.02
1.04
1.04
1.04
3.0
abundance
X : parts per Million : 1H

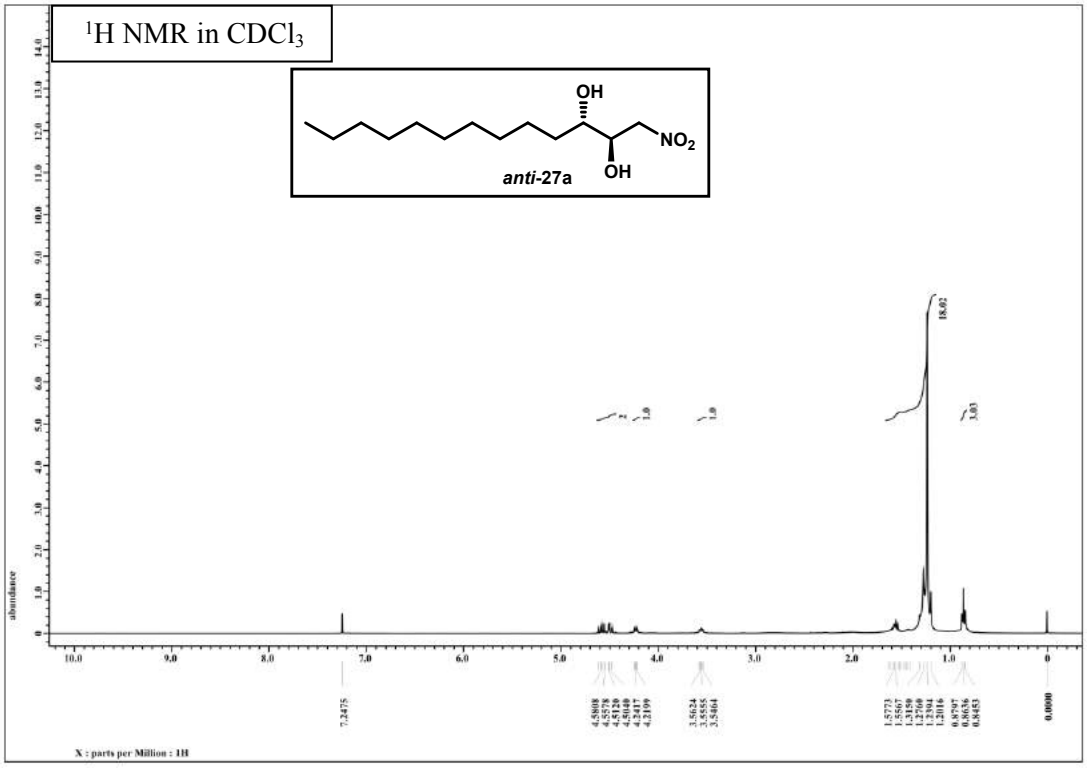

^{13}C NMR in $CDCl_3$
OH
$C_{10}H_{23}$
NO_2
OH
+
OH
$C_{10}H_{23}$
NO_2
OH
anti-24a
syn-24b
abundance
X : parts per Million : 13C

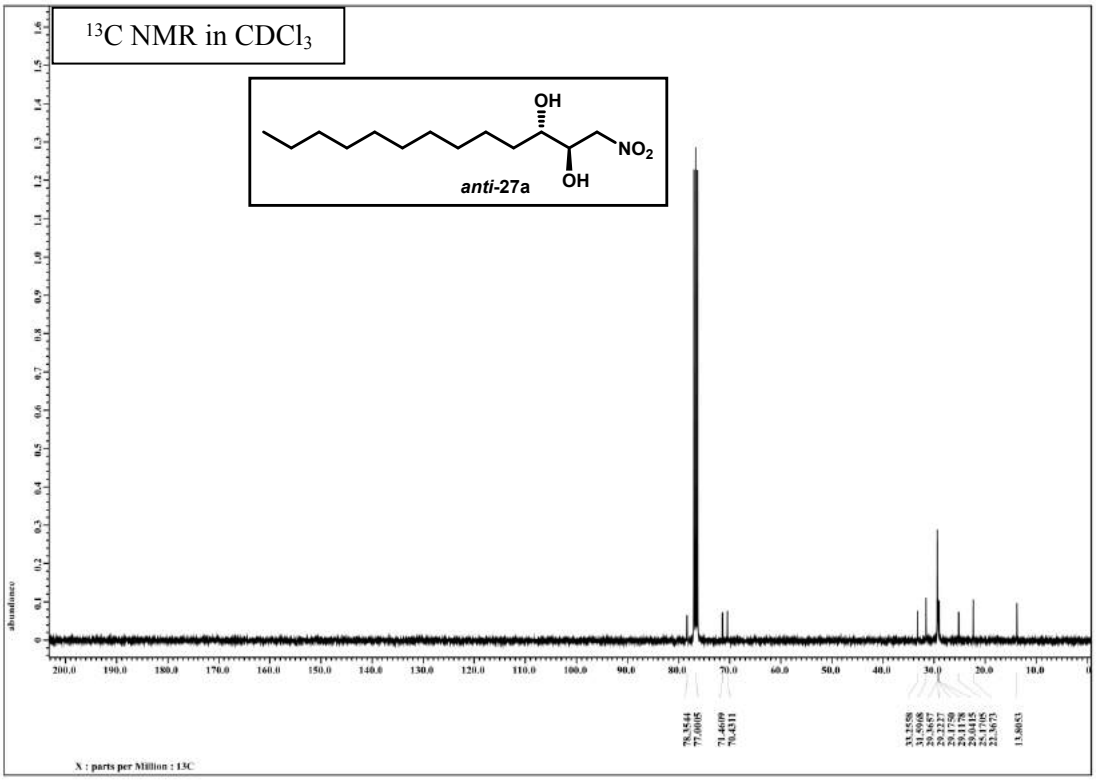

^{1}H NMR in $CDCl_3$
OH
$C_{10}H_{23}$
NO_2
OH
anti-27a
syn-27b
abundance
X : parts per Million : 1H

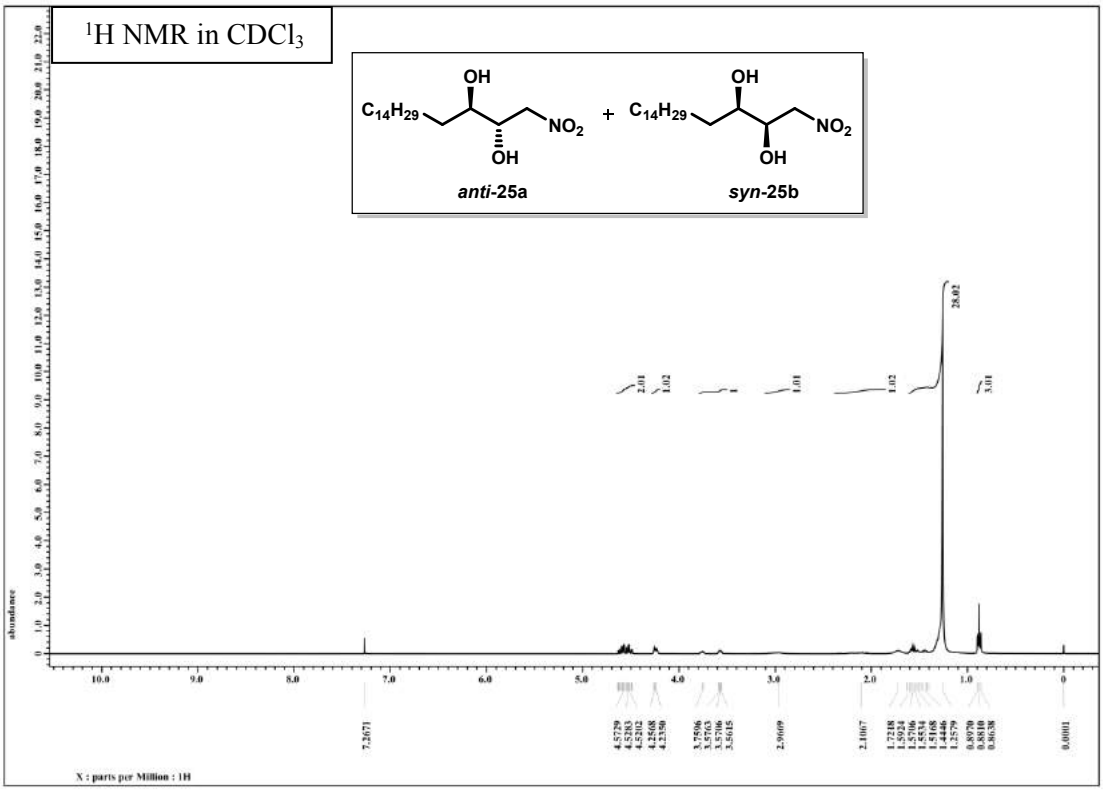

^{13}C NMR in $CDCl_3$
OH
$C_{10}H_{23}$
NO_2
OH
anti-27a
syn-27b
abundance
X : parts per Million : 13C

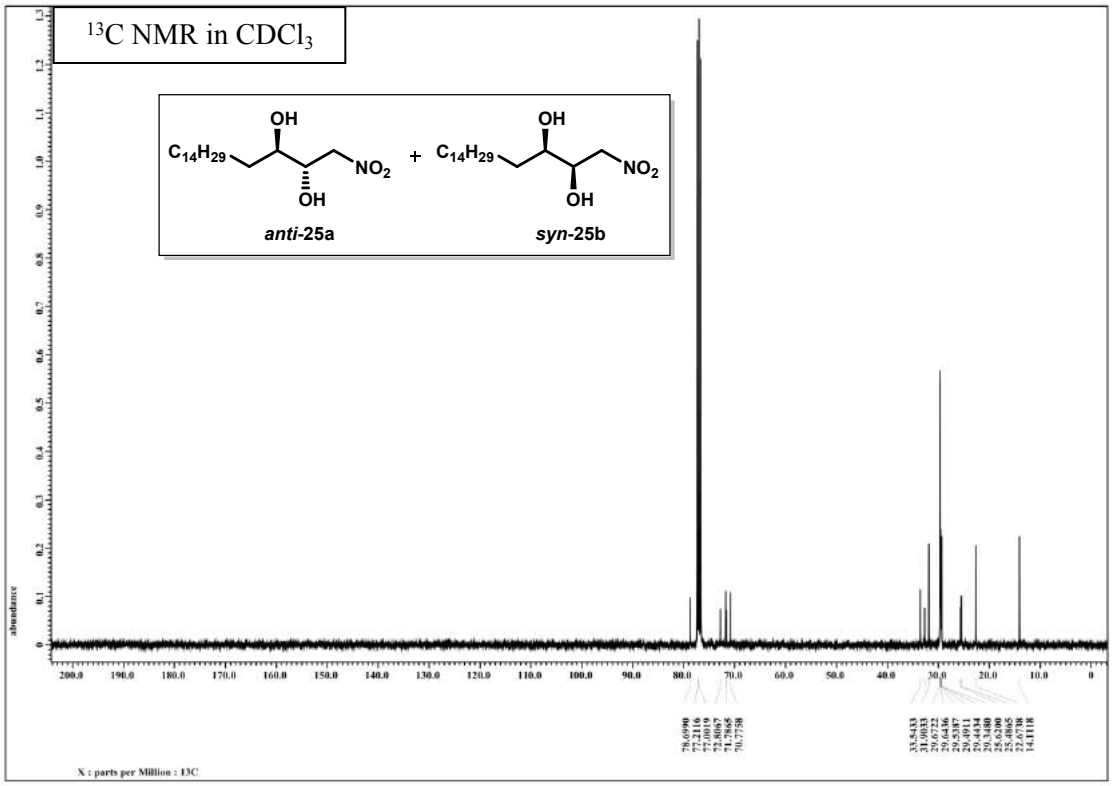

^{1}H NMR in $CDCl_3$
OH
NO_2
OH
syn-27b
abundance
X : parts per Million : 1H

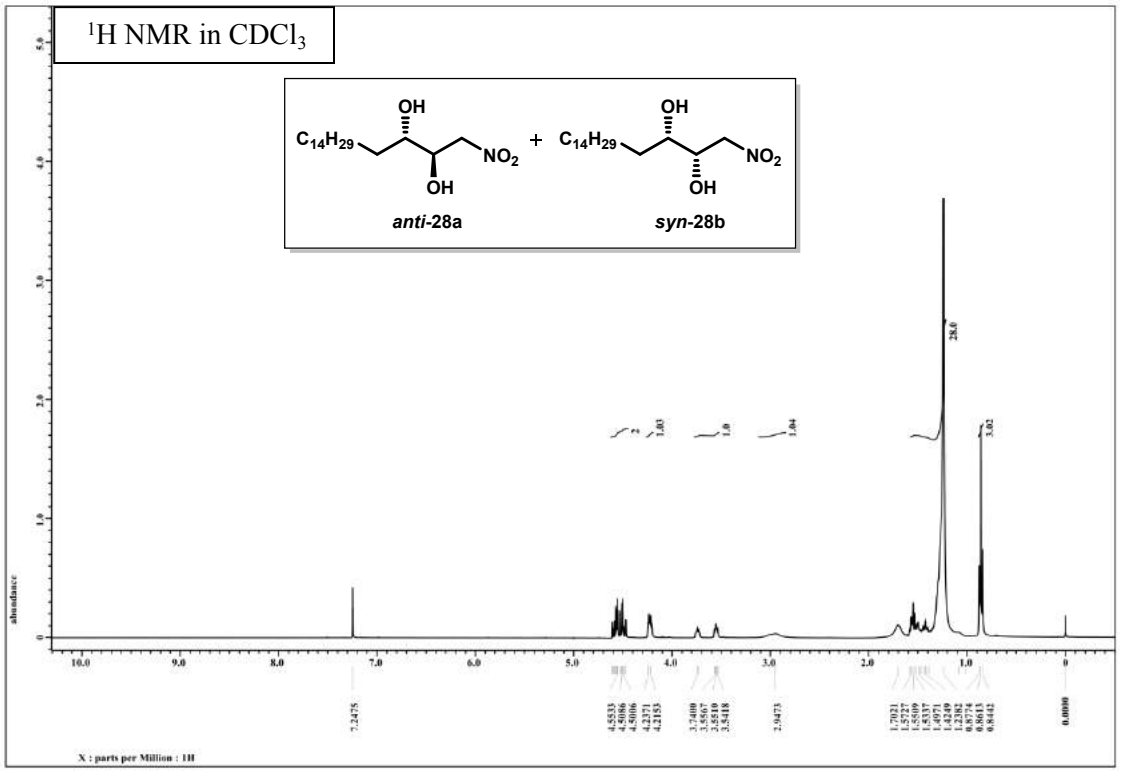

^{13}C NMR in $CDCl_3$
OH
NO_2
OH
syn-27b
abundance
X : parts per Million : 13C

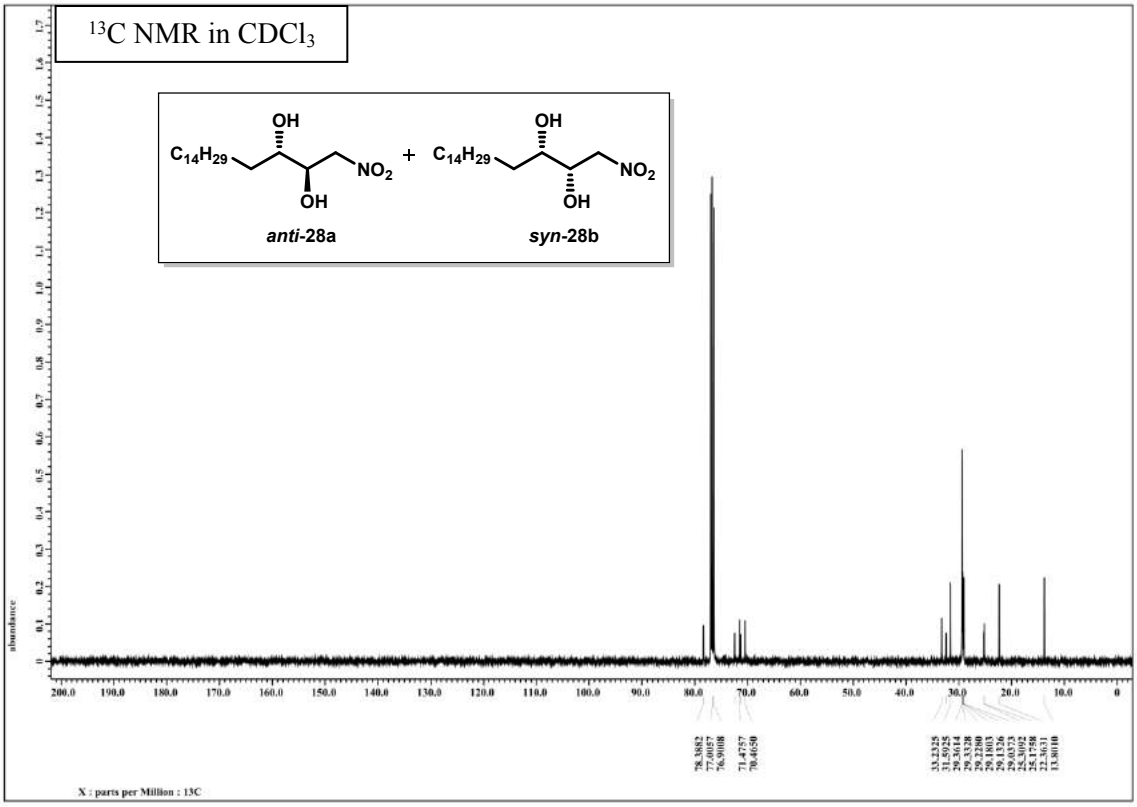

^{1}H NMR in $CDCl_3$
OH
NO_2
OH
anti-27a
18.02
1.0
1.0
3.03
abundance
X : parts per Million : 1H

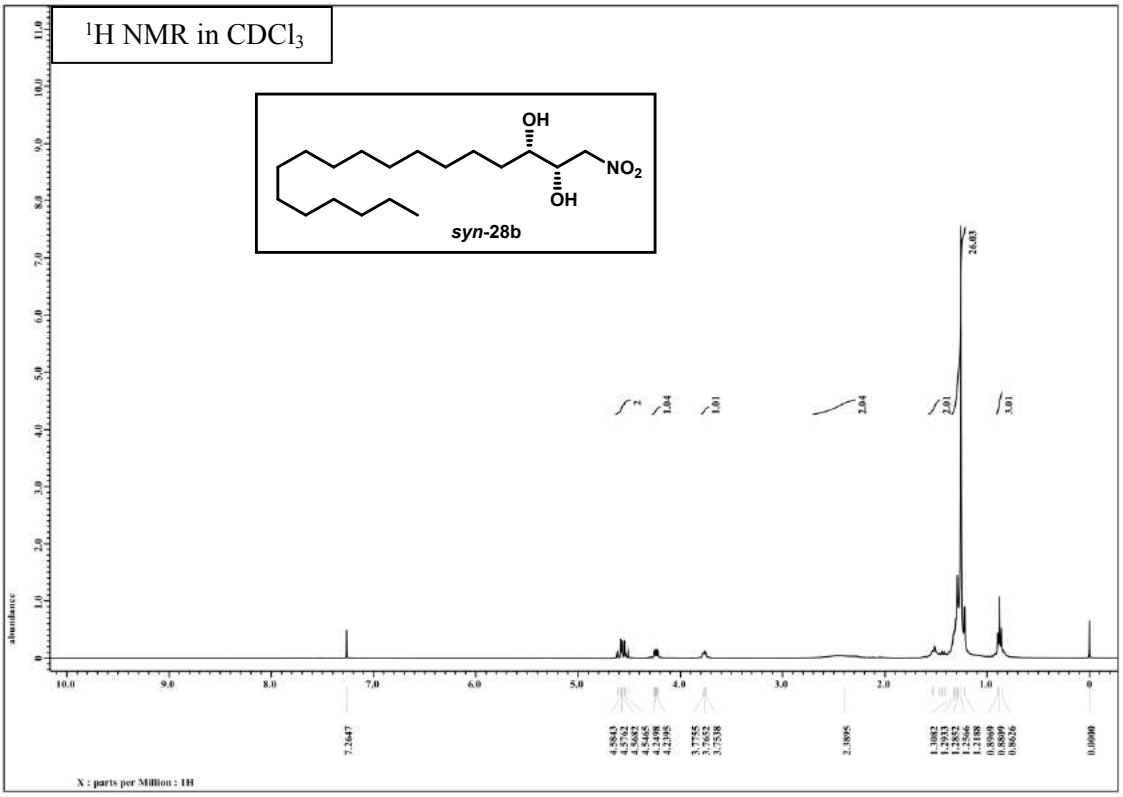

^{13}C NMR in $CDCl_3$
OH
NO_2
OH
anti-27a
abundance
X : parts per Million : 13C

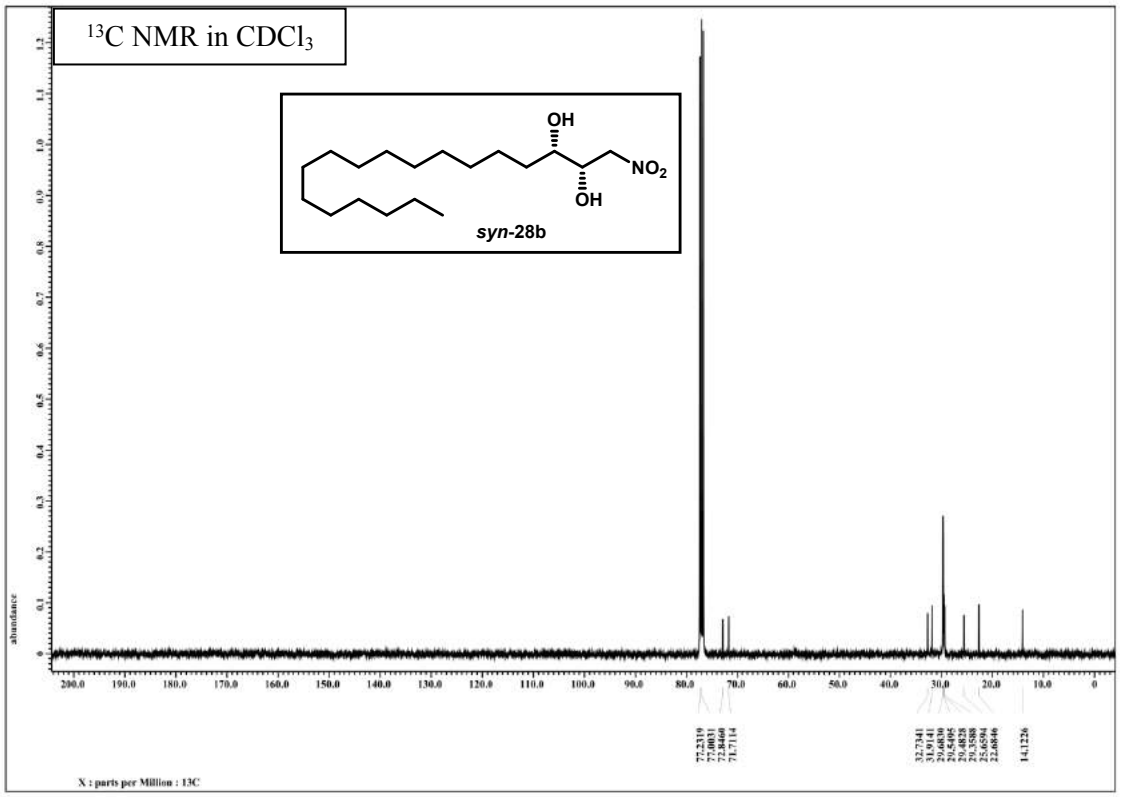

^{1}H NMR in $CDCl_3$
OH
$C_{14}H_{29}$
NO_2
OH
anti-25a
+
OH
$C_{14}H_{29}$
NO_2
OH
syn-25b
abundance
X : parts per Million : 1H

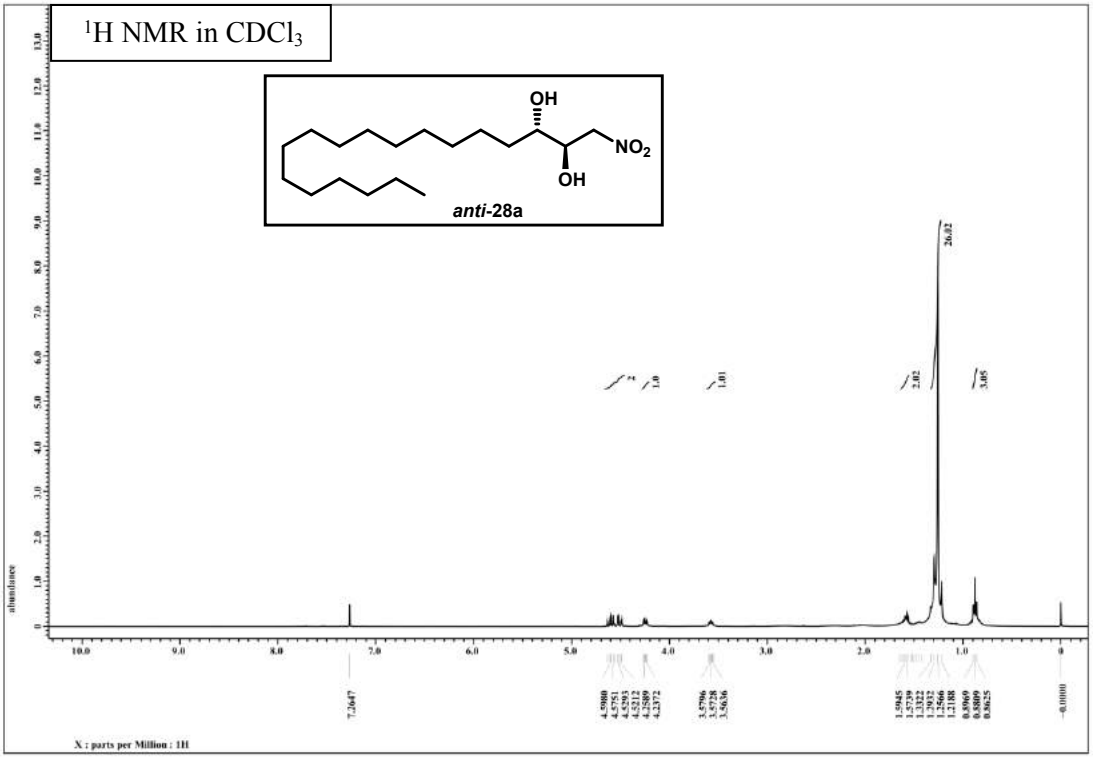

^{13}C NMR in $CDCl_3$
OH
$C_{14}H_{29}$
NO_2
OH
anti-25a
+
OH
$C_{14}H_{29}$
NO_2
OH
syn-25b
abundance
X : parts per Million : 13C

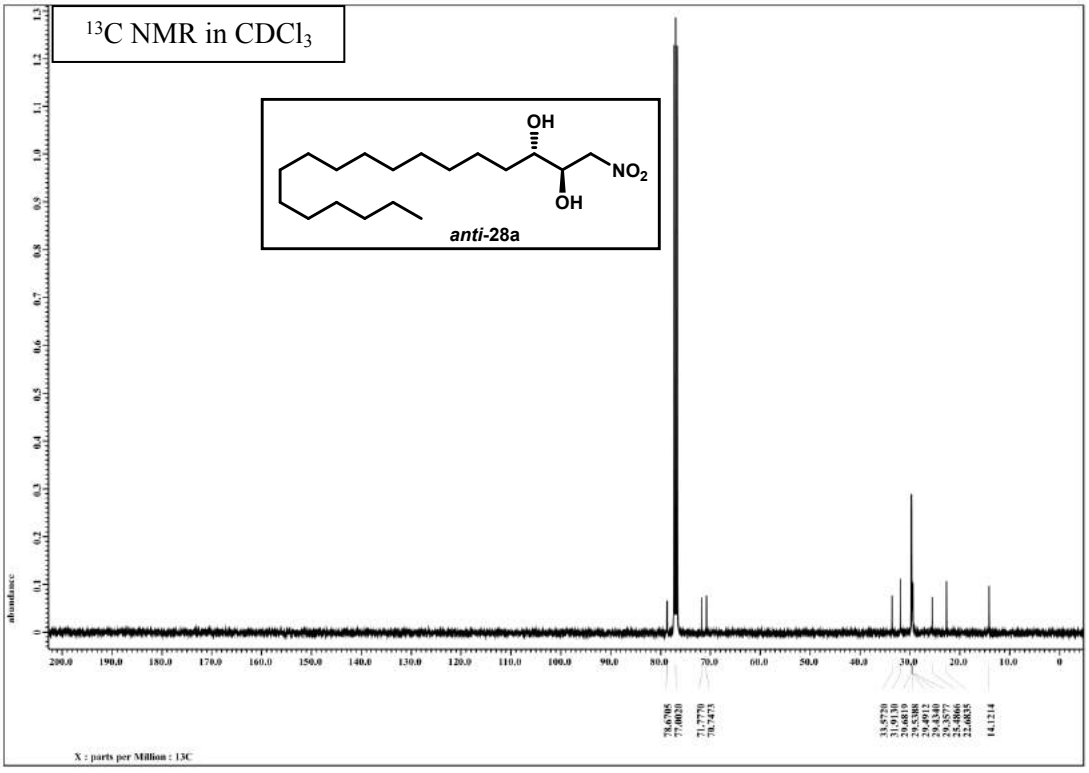

^{1}H NMR in $CDCl_3$
OH
$C_{14}H_{29}$
NO_2
OH
anti-28a
+
OH
$C_{14}H_{29}$
NO_2
OH
syn-28b
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
$C_{14}H_{29}$
NO_2
OH
anti-28a
+
OH
$C_{14}H_{29}$
NO_2
OH
syn-28b
abundance
X : parts per Million : 13C

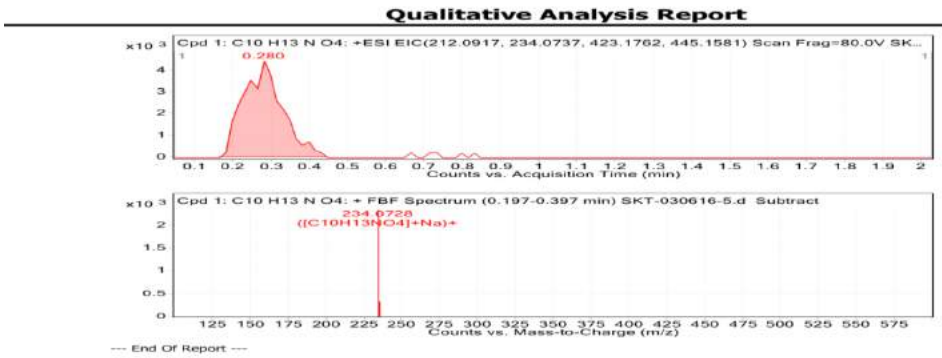

^{1}H NMR in $CDCl_3$
OH
NO2
OH
syn-28b
X : parts per Million : 1H

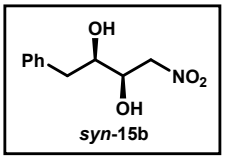

^{13}C NMR in $CDCl_3$
OH
NO2
OH
syn-28b
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
OH
NO_2
OH
anti-28a
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
NO_2
OH
anti-28a
X : parts per Million : 13C

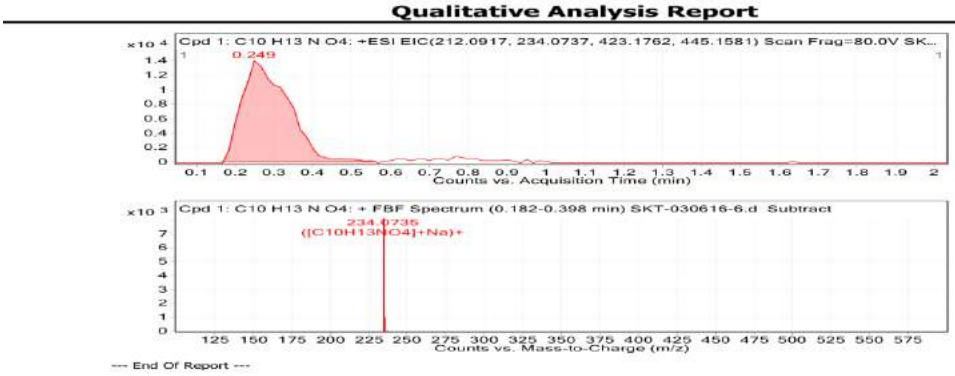
HRMS

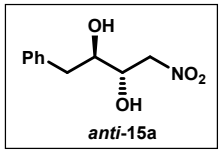




syn-15b

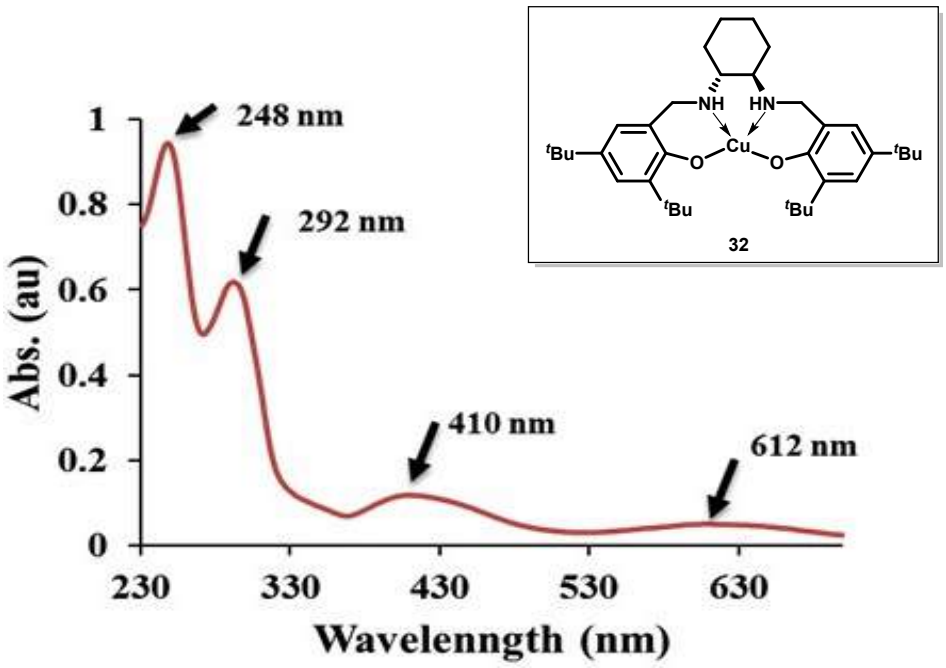
HRMS





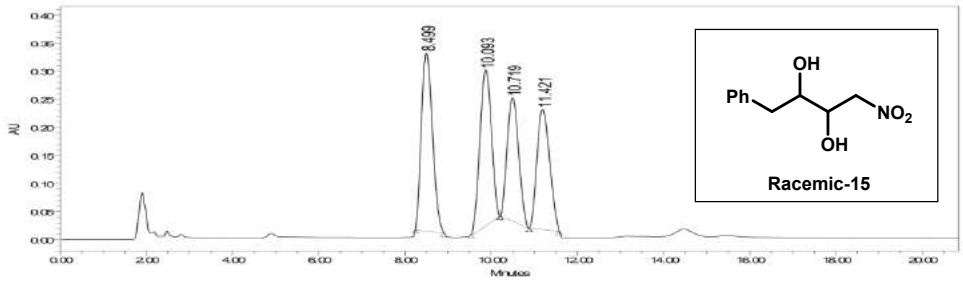
anti-15a

UV-vis spectrum of complex **32**



SAMPLE INFORMATION

Sample Name:	OL_14_7%_ADH	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	OL_14_2
Vial:	2:D1	Acq. Method Set:	YURAJ
Injection #:	1	Processing Method:	Default
Injection Volume:	10.00 ul	Channel Name:	215.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm(191-400)nm
Date Acquired:	30-04-2017 AM11:29:20 IST		
Date Processed:	01-05-2017 PM02:31:08 IST		



Racemic-15

	RT	Area	%Area	Height
1	8.499	5670436	29.07	317134
2	10.083	5308877	27.21	277781
3	10.719	4120816	21.13	219587
4	11.421	4405345	22.59	214094

Reported by User: System
Report Method: Default Individual Report
Report Method ID: 1008 1008
Page: 1 of 1

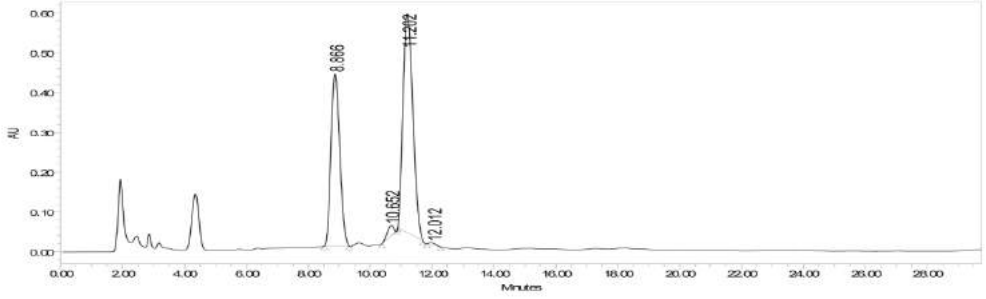
Project Name: Yura
Date Printed: 01-05-2017
02:31:36 PM Asia/Kolkata

Empower 3

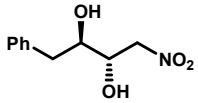
Default Individual Report

SAMPLE INFORMATION

Sample Name:	OL_07_0.6%_ADH	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	OL_07
Vial:	2:D6	Acq. Method Set:	YURAJ
Injection #:	1	Processing Method:	Default
Injection Volume:	10.00 ul	Channel Name:	215.0nm
Run Time:	120.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm(191-400)nm
Date Acquired:	01-05-2017 AM11:15:06 IST		
Date Processed:	05-05-2017 PM01:48:21 IST		

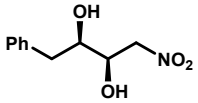


	RT	Area	%Area	Height
1	8.666	8449750	40.45	432108
2	10.652	371467	1.78	27019
3	11.202	11997161	57.43	549804
4	12.012	70801	0.34	4975



anti-15a

+



syn-15b

Reported by User: System
Report Method: Default Individual Report
Report Method ID: 1008 1008
Page: 1 of 1

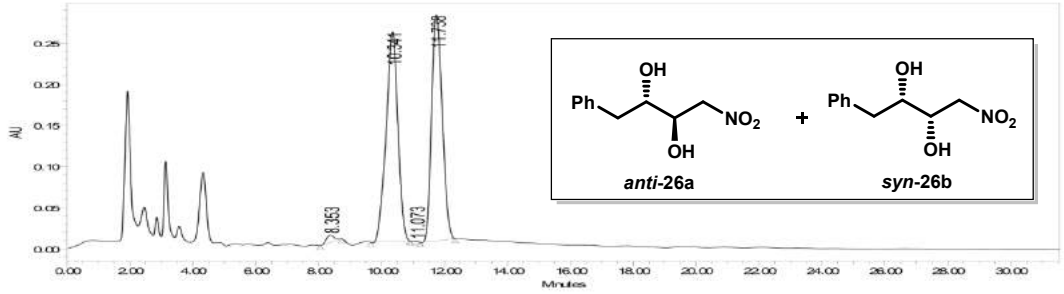
Project Name: Yura
Date Printed: 05-05-2017
04:48:41 PM Asia/Kolkata

Empower 3

Default Individual Report

SAMPLE INFORMATION

Sample Name:	OL_06_0.6%_ADH	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	OL_06
Vial:	2:D3	Acq. Method Set:	YURAJ
Injection #:	1	Processing Method:	Default
Injection Volume:	10.00 ul	Channel Name:	215.0nm
Run Time:	120.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm (191-400)nm
Date Acquired:	30-04-2017 PM10:03:30 IST		
Date Processed:	05-06-2017 PM04:42:35 IST		



anti-26a *syn*-26b

	RT	Area	%Area	Height
1	8.353	154152	1.17	8867
2	10.341	6665448	50.42	254863
3	11.073	8663	0.06	924
4	11.738	6391677	48.36	274715

Reported by User: System
Report Method: Default Individual Report
Report Method ID: 1008 1008
Page: 1 of 1

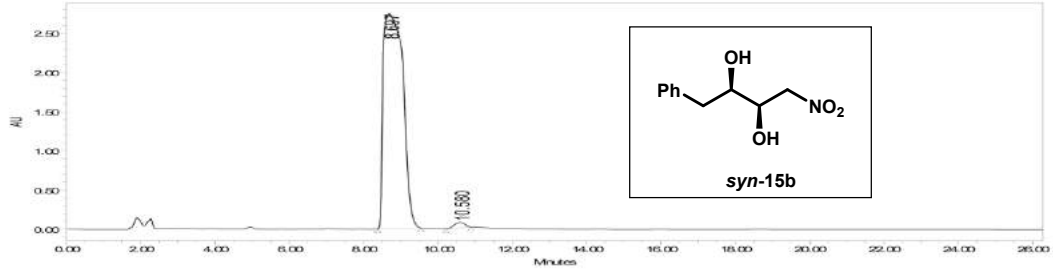
Project Name: Yura
Date Printed:
05-06-2017
04:43:28 PM Asia/Kolkata

Empower 3

Default Individual Report

SAMPLE INFORMATION

Sample Name:	OL_RJS_10%_ADH	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	OL_RJS_2
Vial:	2:D7	Acq. Method Set:	YURAJ
Injection #:	1	Processing Method:	Default
Injection Volume:	10.00 ul	Channel Name:	215.0nm
Run Time:	120.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm (191-400)nm
Date Acquired:	01-05-2017 PM12:16:16 IST		
Date Processed:	05-06-2017 PM04:51:27 IST		



syn-15b

	RT	Area	%Area	Height
1	8.697	10107734	98.71	2746194
2	10.580	1334717	1.29	69646

Reported by User: System
Report Method: Default Individual Report
Report Method ID: 1008 1008
Page: 1 of 1

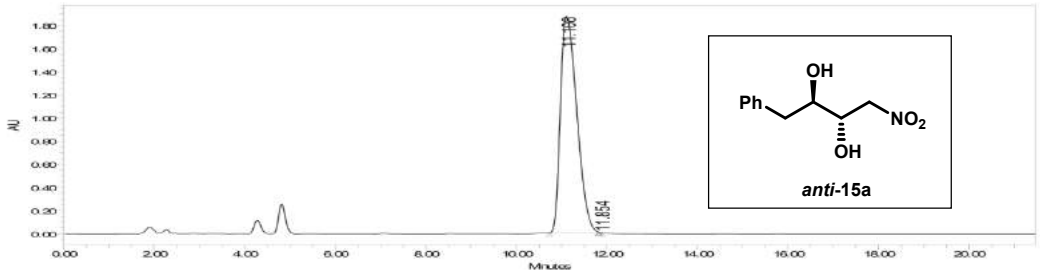
Project Name: Yura
Date Printed:
05-06-2017
04:51:43 PM Asia/Kolkata

Empower 3

Default Individual Report

SAMPLE INFORMATION

Sample Name:	OL_ELS_10%_ADH	Acquired By:	System
Sample Type:	Unknown	Sample Set Name:	OL_ELS
Vial:	2:D8	Acq. Method Set:	YURAJ
Injection #:	1	Processing Method:	Default
Injection Volume:	10.00 ul	Channel Name:	215.0nm
Run Time:	120.0 Minutes	Proc. Chnl. Descr.:	PDA 215.0 nm (191-400)nm
Date Acquired:	01-05-2017 PM02:39:08 IST		
Date Processed:	05-08-2017 PM04:50:13 IST		



anti-15a

	RT	Area	%Area	Height
1	11.10[illegible]	47230207	100.00	1868308
2	11.85[illegible]	1516	0.00	-612

Reported by User: System
Report Method: Default Individual Report
Report Method ID: 1008 1008
Page: 1 of 1

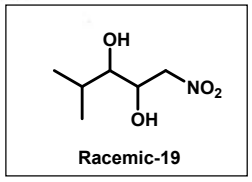
Project Name: Yura
Date Printed:
05-08-2017
04:50:34 PM Asia/Kolkata

D-7000 HPLC System Manager Report

Analyzed: 05/16/17 03:07 PM
Reported: 05/16/17 03:57 PM
Processed: 05/16/17 03:57 PM

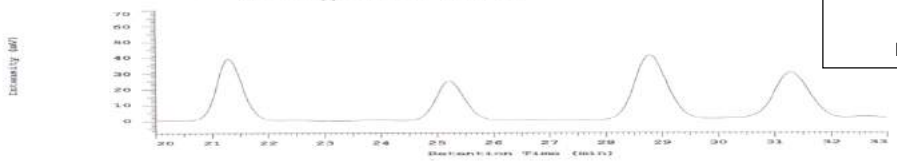
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9442\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: IV-1(Racemic)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

Series:9442
Volume: 10.0 ul



Racemic-19

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc I	BC
1	21.29	1223446	24.703	BB
2	25.22	854078	17.245	BB
3	28.77	1641137	33.137	BB
4	31.28	1233951	24.915	BB
		4952612	100.000	

Peak rejection level: 0

Project Leader: Dr.Tripathi P.K.
Column : Chiralcel OJ-H (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.5 ml/min.
Inject vol: 5ul

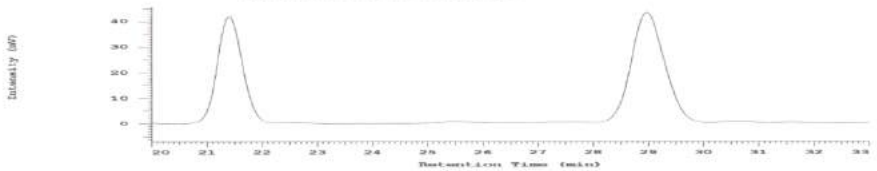
D-7000 HPLC System Manager Report

Analyzed: 05/16/17 03:44 PM
Reported: 05/16/17 04:27 PM
Processed: 05/16/17 04:27 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9443\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: IV-2 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

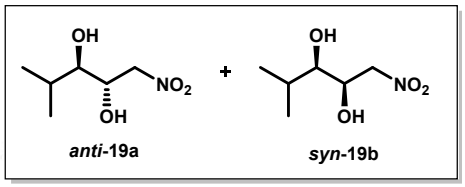
Series:9443
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	21.40	1314358	41.933	BB
2	25.49	14434	0.460	BB
3	28.97	1800400	57.439	BB
4	30.61	5254	0.168	BB
		3134446	100.000	

Peak rejection level: 0



anti-19a *syn*-19b

Project Leader: Dr.Tripathi P.K.
Column : Chiralcel OJ-H (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.5 ml/min.
Inject vol: 5ul

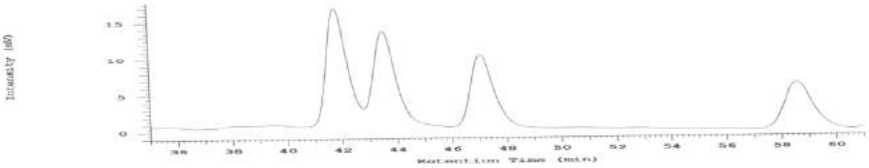
D-7000 HPLC System Manager Report

Analyzed: 05/23/17 02:59 PM
Reported: 05/23/17 04:09 PM
Processed: 05/23/17 04:08 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9481\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: PN-1 (Rac)
Injection from this vial: 1 of 1
Sample Description: IPA:n_Hexane(05:95)

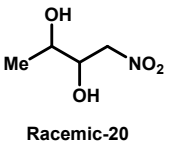
Series:9481
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	41.84	864572	32.271	BV
2	43.56	768431	28.682	VB
3	47.09	589183	21.992	BB
4	58.61	456922	17.055	BB
		2679108	100.000	

Peak rejection level: 0



Racemic-20

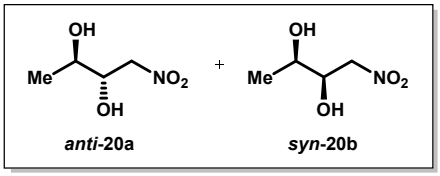
Project Leader: Dr.Tripathi P.K.
Column : Chiralpak AD-H (250 mmx4.6mm)
Mobile Ph : IPA:n-Hexane(05:95)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 2ul

D-7000 HPLC System Manager Report

Analyzed: 05/23/17 01:56 PM
Reported: 05/23/17 03:15 PM
Processed: 05/23/17 03:14 PM

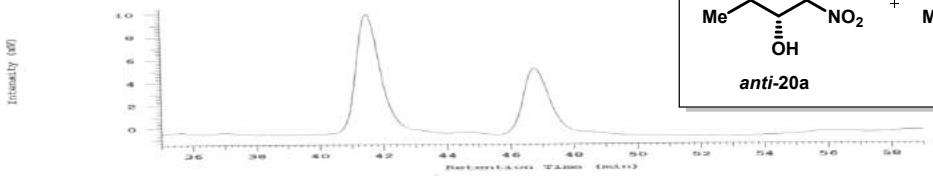
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9480\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: PN-2(Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(05:95)

Series:9480
Volume: 10.0 ul



anti-20a *syn*-20b

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	41.52	567432	63.251	BB
2	44.67	4303	0.480	BB
3	46.79	315319	35.148	BB
4	56.15	10054	1.121	BB
		897108	100.000	

Peak rejection level: 0

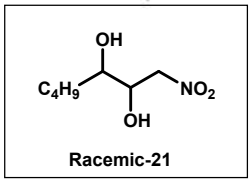
Project Leader: Dr.Tripathi P.K.
Column : Chiralpak AD-H (250 mmx4.6mm)
Mobile Ph : IPA:n-Hexane(05:95)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 2ul

D-7000 HPLC System Manager Report

Analyzed: 05/22/17 01:48 PM
Reported: 05/22/17 02:27 PM
Processed: 05/22/17 02:27 PM

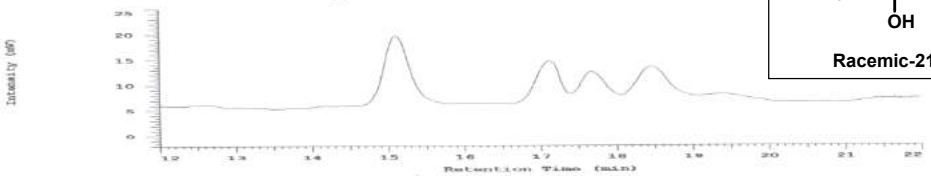
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9472\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: Hx-1 (Rac)
Injection from this vial: 1 of 1
Sample Description: IPA:n_Hexane:DEA(04:96:0.1)

Series:9472
Volume: 10.0 ul



Racemic-21

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	15.11	290727	36.278	BB
2	17.12	199039	24.837	BV
3	17.65	143436	17.898	VV
4	18.47	168191	20.987	VB
		801393	100.000	

Peak rejection level: 0

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (150 mmx4.6mm)
Mobile Ph : IPA:n-Hexane:DEA(04:98:0.1)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

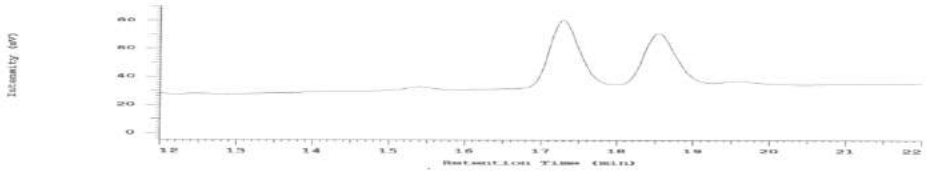
D-7000 HPLC System Manager Report

Analyzed: 05/22/17 01:23 PM
Reported: 05/22/17 02:24 PM
Processed: 05/22/17 02:24 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9471\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: Hx-2(chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane:DEA(04:96.0.1)

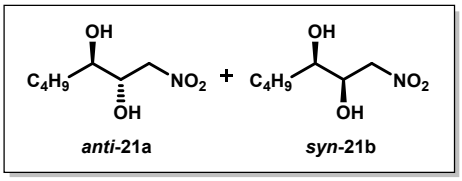
Series:9471
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	15.38	50224	2.044	BB
2	17.29	1305470	53.127	BV
3	18.53	1078960	43.909	VB
4	19.56	22625	0.921	BB
		2457279	100.000	

Peak rejection level: 0



anti-21a *syn*-21b

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (150 mmx4.6mm)
Mobile Ph : IPA:n-Hexane:DEA(04:98:0.1)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

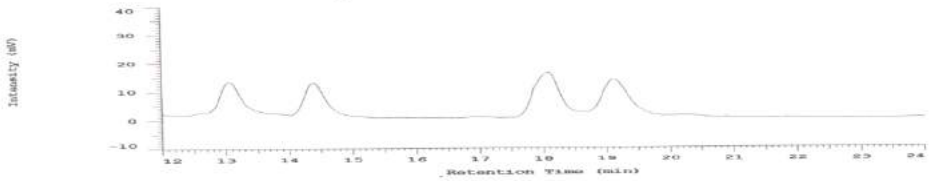
D-7000 HPLC System Manager Report

Analyzed: 05/22/17 03:00 PM
Reported: 05/22/17 04:14 PM
Processed: 05/22/17 04:14 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9473\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: HT-1(Rac)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane:DEA(05:95.0.1)

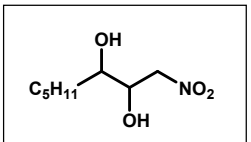
Series:9473
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	13.07	265340	15.156	BB
2	14.40	226110	12.915	BB
3	18.13	891088	50.898	BV
4	19.12	368208	21.031	VB
		1750746	100.000	

Peak rejection level: 0



Racemic-22

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak AD-H (250 mmx4.6mm)
Mobile Ph : IPA:n-Hexane:DEA(05:95:0.1)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

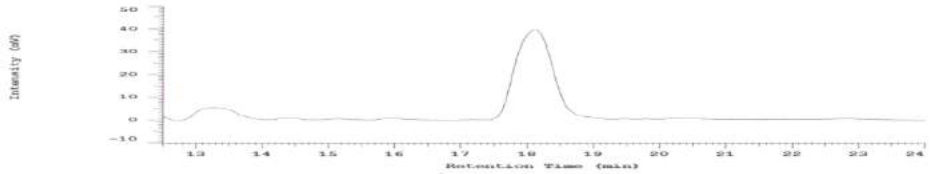
D-7000 HPLC System Manager Report

Analyzed: 05/22/17 03:31 PM
Reported: 05/22/17 04:16 PM
Processed: 05/22/17 04:15 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9474\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: HT-2 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n_Hexane:DEA(05:95:0.1)

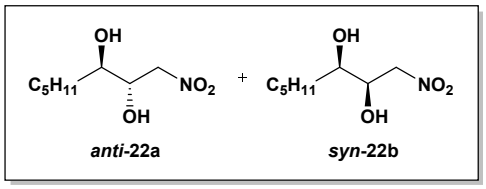
Series:9474
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	13.37	227193	12.449	BB
2	14.41	21311	1.168	BB
3	18.11	1561653	85.571	BB
4	20.36	14819	0.812	BB
		1824976	100.000	

Peak rejection level: 0



anti-22a *syn*-22b

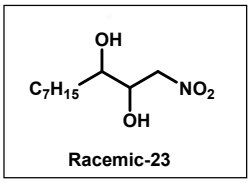
Project Leader: Dr.Tripathi P.K.
Column : Chiralpak AD-H (250 mmx4.6mm)
Mobile Ph : IPA:n-Hexane:DEA(05:95:0.1)
Wavelength : 230nm
Flow : 1.0 ml/min.
Inject vol: 5ul

D-7000 HPLC System Manager Report

Analyzed: 05/18/17 10:04 AM
Reported: 05/18/17 02:11 PM
Processed: 05/18/17 02:11 PM

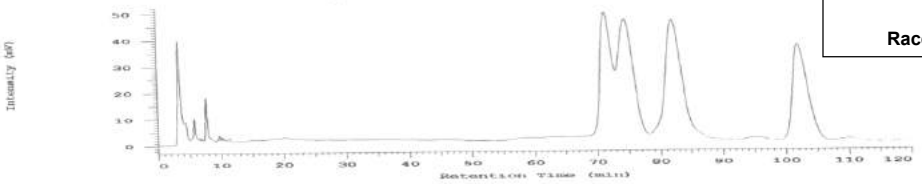
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9451\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: NO-1(Racemic)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(02:98)

Series:9451
Volume: 10.0 ul



Racemic-23

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	71.47	5908292	21.575	BV
2	74.64	7320626	26.733	VV
3	82.16	8171492	29.840	VB
4	102.16	5984176	21.852	BB
		27384586	100.000	

Peak rejection level: 0

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(02:98)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

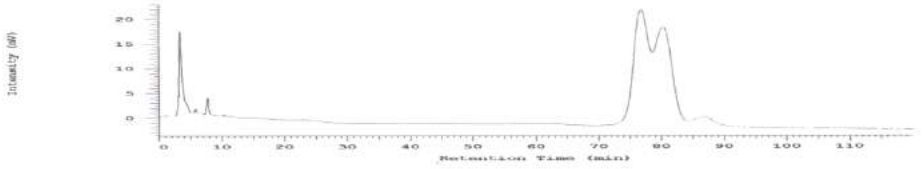
D-7000 HPLC System Manager Report

Analyzed: 05/18/17 12:16 PM
Reported: 05/18/17 02:23 PM
Processed: 05/18/17 02:23 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9452\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: NO-2 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(02:98)

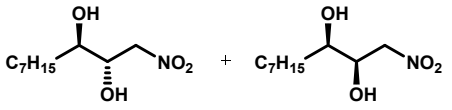
Series:9452
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	76.80	3909622	48.779	BV
2	80.29	3904620	48.716	VV
3	86.91	200796	2.505	TBB
		8015038	100.000	

Peak rejection level: 0



anti-23a *syn*-23b

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(02:98)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

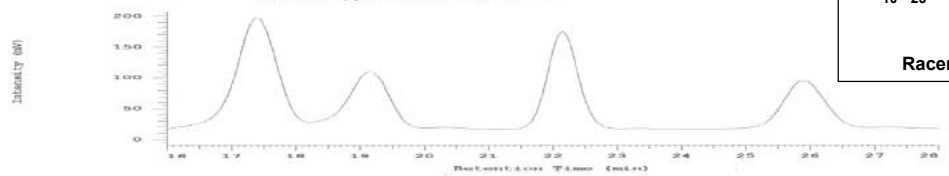
D-7000 HPLC System Manager Report

Analyzed: 05/16/17 10:25 AM
Reported: 05/16/17 11:14 AM
Processed: 05/16/17 11:14 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9436\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: DP-1(Racemic)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(05:95)

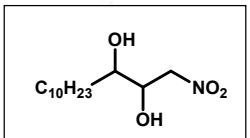
Series:9436
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	17.39	7036443	35.985	BV
2	19.15	3803165	19.450	VB
3	22.14	5282632	27.016	BB
4	25.89	3431513	17.549	BB
		19553753	100.000	

Peak rejection level: 0



Racemic-24

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(05:95)
Wavelength : 210nm
Flow : 1.0 ml/min.
Inject vol: 10ul

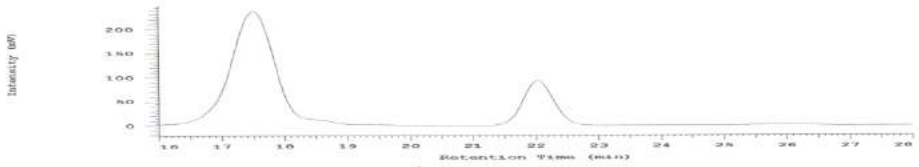
D-7000 HPLC System Manager Report

Analyzed: 05/16/17 11:00 AM
Reported: 05/16/17 11:41 AM
Processed: 05/16/17 11:41 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9437\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: DP-2D (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(05:95)

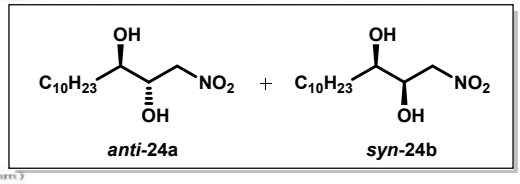
Series:9437
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	17.51	10579207	76.723	BB
2	22.03	3177970	23.048	BB
3	26.03	31595	0.229	BB
		13788772	100.000	

Peak rejection level: 0



anti-24a *syn*-24b

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(05:95)
Wavelength : 210nm
Flow : 1.0 ml/min.
Inject vol: 10ul

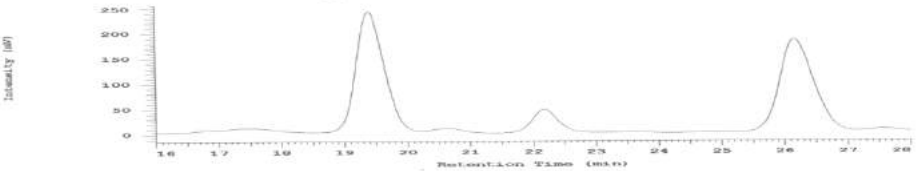
D-7000 HPLC System Manager Report

Analyzed: 05/16/17 11:32 AM
Reported: 05/16/17 12:17 PM
Processed: 05/16/17 12:16 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9438\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: DP-3 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(05:95)

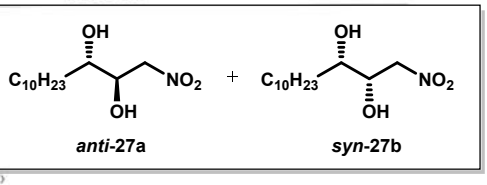
Series:9438
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	17.41	168355	1.087	BB
2	19.40	7287230	47.037	BB
3	22.18	1212096	7.824	BB
4	26.17	6824964	44.053	BB
		15492645	100.000	

Peak rejection level: 0



anti-27a *syn*-27b

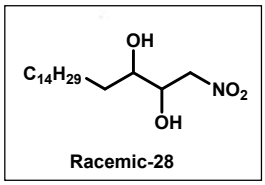
Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(05:95)
Wavelength : 210nm
Flow : 1.0 ml/min.
Inject vol: 10ul

D-7000 HPLC System Manager Report

Analyzed: 05/11/17 11:16 AM
Reported: 05/11/17 12:35 PM
Processed: 05/11/17 12:35 PM

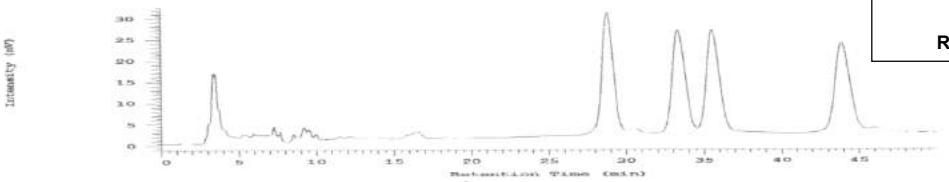
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9415\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: YP-1(Racemic)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

Series:9415
Volume: 10.0 ul



Racemic-28

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	28.81	1382109	25.246	BB
2	33.36	1366046	24.952	BV
3	35.59	1390622	25.401	VB
4	43.93	1335823	24.400	BB
		5474600	100.000	

Peak rejection level: 0

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

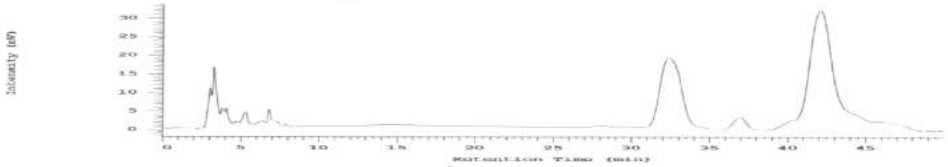
D-7000 HPLC System Manager Report

Analyzed: 05/11/17 12:59 PM
Reported: 05/11/17 01:56 PM
Processed: 05/11/17 01:56 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9417\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: YP-3 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

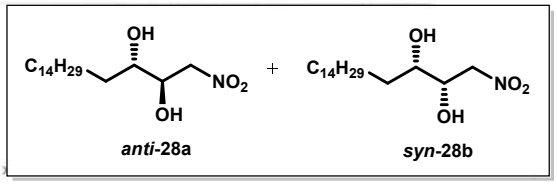
Series:9417
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	28.04	21938	0.508	BB
2	32.37	1613419	37.347	BB
3	36.93	181209	4.195	BB
4	42.07	2503302	57.950	BB
		4320068	100.000	

Peak rejection level: 0



anti-28a *syn*-28b

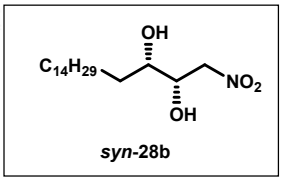
Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

D-7000 HPLC System Manager Report

Analyzed: 05/11/17 01:51 PM
Reported: 05/11/17 02:46 PM
Processed: 05/11/17 02:46 PM

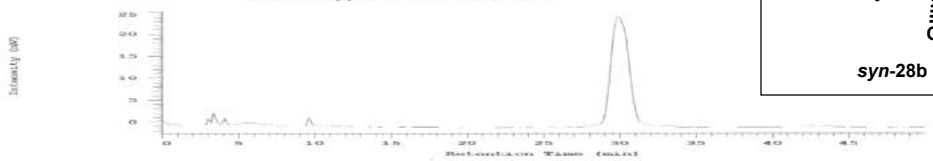
Data Path: C:\WIN32APP\HSM\HPLC\DATA\9418\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: YP-4 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

Series:9418
Volume: 10.0 ul



syn-28b

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	29.88	1959775	99.088	BB
2	32.64	18031	0.912	BB
		1977806	100.000	

Peak rejection level: 0

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

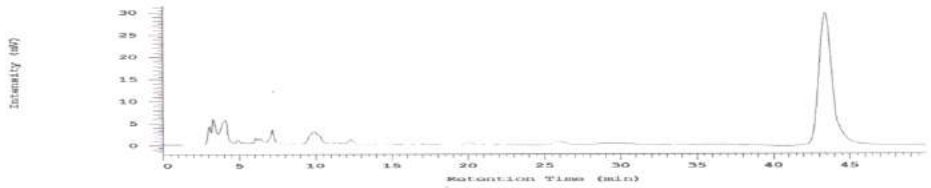
D-7000 HPLC System Manager Report

Analyzed: 05/11/17 02:41 PM
Reported: 05/11/17 03:47 PM
Processed: 05/11/17 03:47 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\9419\
Processing Method: cal
System(acquisition): Sys 1
Application: HPLC
Sample Name: YP-5 (Chiral)
Injection from this vial: 1 of 1
Sample Description: IPA:n-Hexane(03:97)

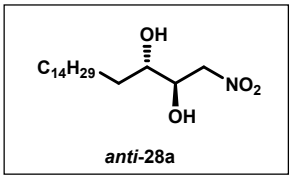
Series:9419
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Area	Conc 1	BC
1	38.68	9499	0.619	BB
2	43.44	1524678	99.381	BB
		1534177	100.000	

Peak rejection level: 0



anti-28a

Project Leader: Dr.Tripathi P.K.
Column : Chiralpak IA (250 mmx4.6mm)
Mobile Ph : IPA:n-HEXANE(03:97)
Wavelength : 220nm
Flow : 1.0 ml/min.
Inject vol: 5ul

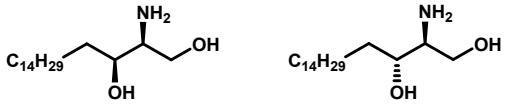
4.2 Section B

Enantioselective total synthesis of L-*threo*-sphinganine (safingol) *via* organocatalyzed tandem α-aminoxylation/Henry reactions

---

4.2.1 Introduction:

Sphingolipids were isolated from membranes of plants, mammals, yeast, fungi, viruses and some prokaryotic organisms.[9] Among the natural D-*erythro*-sphinganine **34** and three other unnatural isomers of sphingoid bases, L-*threo*-sphinganine (safingol) **9** illicit a myriad of biological activities that includes antineoplastic, antipsoriatic,[6a] inhibit protein kinase C[10] and acts as synergistic with anticancer drugs (Figure 4).[11b] The safingol **9** has been shown to elevate the cytotoxicity of the chemotherapeutic agent mitomycin C in gastric cancer cells by encoraging the drug induced apoptosis.[11a-c] Additionally, safingol **9** inhibits enzymatic activity by ^{3}H-phorbal dibutarate binding of purified rat brain PKC (IC_{50} = 37.5 μM, 31 μM, respectively) and also inhibits human PKCα, the major overexpressed isoenzyme in MCF-7 DOXR cells (IC_{50} = 40 μM).[11d]



L-*threo*-sphinganine 9 D-*erythro*-sphinganine 34

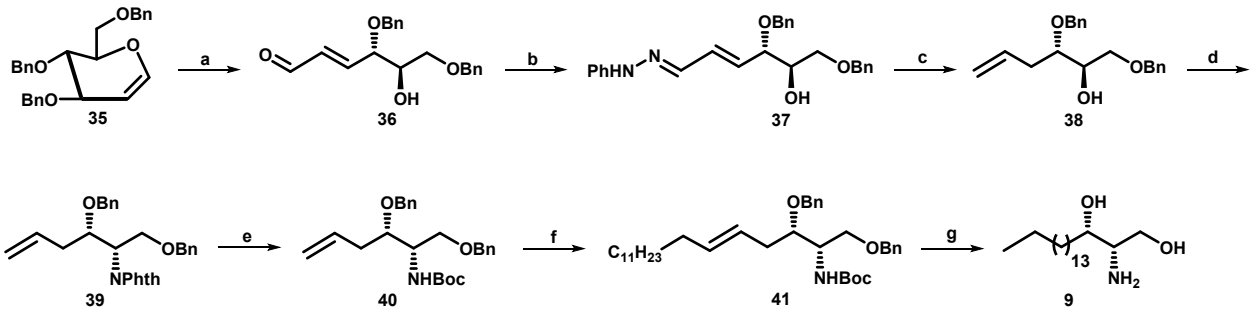
Figure 4. Structure of L-*threo*-sphinganine **9** and D-*erythro*-sphinganine **34**

4.2.2 Review of Literature:

Due to important biological activities L-*threo*-sphinganine **9**, various methods for the asymmetric synthesis have been documented in the literature.[12] Some of the recent syntheses of safingol **9** and its stereoisomers are described below.

Shaw, A. K. *et al*. (2016)[12a]

A. K. Shaw and co-workers reported the asymmetric synthesis of antineoplastic and antipsoriatic drug safingol **9** employing Mitsunobu reaction and olefin cross metathesis as key steps starting with chirons 3,4,6-tri-*O*-benzyl-D-galactal and 3,4,6-tri-*O*-benzyl-D-glucal (Scheme 5).

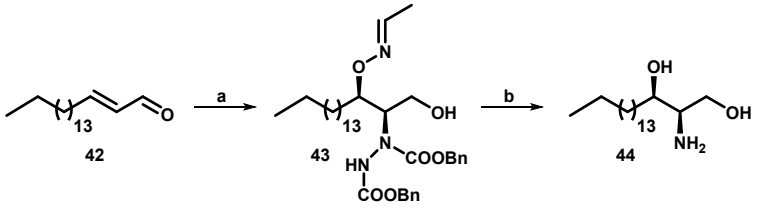


Scheme 5. *Reagents and conditions*: (a) ref 13; (b) $TsNHNH_2$, EtOH, 15min; (c) $NaBH_4$, AcOH, 70% (over two steps); (d) phthalimide, DIAD (Diisopropyl azodicarboxylate), THF, -20 °C, 83%; (e) i) $MeNH_2$ ii) $(Boc)_2O$, Et_3N, DCM, 96% (over two steps); (f) 1-tetradecene, Grubbs' second generation catalyst, DCM, 45 °C, 76%; (g) Pd/C, H_2, TFA, 92%.

The D-glucal **35** derived[13] *trans*-olefinic aldehyde **36** on reaction with tosylhydrazine reagent at room temperature furnished key intermediate olefinic-hydrazone **37** which on treatment with $NaBH_4$/AcOH synthesized the olefin **38** in quantitative yield. The alcohol derivative **38** on Mitsunobu reaction with phthalimide using DIAD furnished phthaloyl derivative **39** in 83% yield. The phthaloyl derivative **39** on phthalimide cleavage using $MeNH_2$ followed by *N*-Boc protection afforded olefinic derivative **40** in 96% yield. The olefin **40** on Grubbs' cross metathesis with 1-tetradecene furnished olefin **41** in 76% yield which on subsequent hydrogenation using Pd/C under acidic conditions furnished the final target safingol **9**.

Lu, G. *et al*. (2016)[12b]

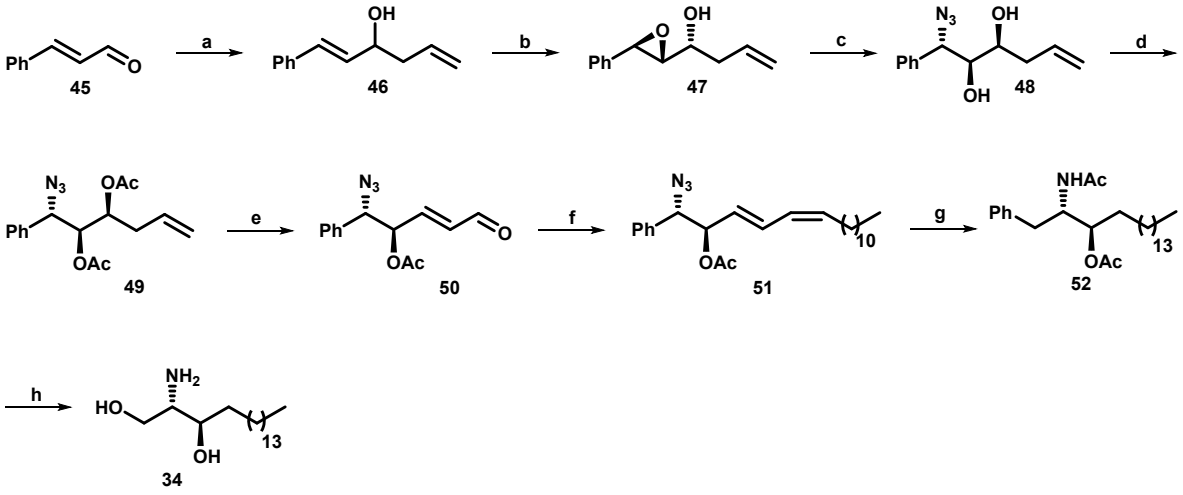
G. Lu and co-workers reported the asymmetric synthesis of (+)-safingol **44** employing secondary amine-catalyzed one-pot sequential oxa-Michael/α-amination reaction using *trans*-olefinic aldehyde **42** as starting material (Scheme 6). The aldehyde derivative **42** on asymmetric Michael addition reaction with (*E*)-benzaldoxime in the presence of catalyst (*S*)-diphenylprolinol silyl ether, subsequent α-amination reaction with dibenzyl azodicarboxylate (DBAD) followed by reduction with $NaBH_4$/MeOH furnished protected amino alcohol derivative **43** in 45% yield. Finally, derivative **43** on hydrogenation with $Pd(OH)_2/C$ furnished final target (+)-safingol **44** in 77% yield.



Scheme 6. *Reagents and conditions*: (a) i) (*S*)-diphenylprolinol silyl ether, PhCH=NOH, toluene, 0 °C, 12 h, ii) DBAD, THF, rt, 6 h, iii) $NaBH_4$, MeOH, 0 °C, 45%; (b) $Pd(OH)_2/C$, H_2, MeOH, rt, 18 h, 77%.

Barua, N. C. *et al*. (2013)[12c]

N. C. Barua and co-workers reported the asymmetric synthesis of sphinganine **34** employed Sharpless kinetic resolution, regioselective epoxide opening and Wittig olefination as key steps starting with commercially available *trans*-cinnamldehyde **45** (Scheme 7). The aldehyde **45** on Grignard reaction with allyl magnesium bromide furnished racemic alcohol derivative **46** which on subsequent treatment with Ti(*i*-PrO)$_4$/(-)-DET under Sharpless kinetic resolution conditions afforded epoxy alcohol derivative **47** in 47% yield. The epoxide **47** on regioselective nucleophilic opening with NaN_3 furnished azido alcohol derivative **48** which on subsequent *O*-acylation using Ac_2O/pyridine afforded acyl derivative **49** in 96% yield. The olefin **49** on oxidative cleavage using $OsO_4/NaIO_4$ furnished *trans*-olefinic aldehyde **50** which on further Wittig olefination under basic conditions afforded olefin **51** in 92% yield. The olefin derivative **51** on hydrogenation in the presence of catalytic amount of Pd/C followed by *N*- and *O*-acylation simultaneously furnished acylated derivative **52** in 91% yield. Finally, the derivative **52** on oxidative cleavage of phenyl ring using $NaIO_4/RuCl_3.H_2O$, subsequent *O*-Ac deprotection using NEt_3/MeOH followed by *N*-Ac deprotection under acidic conditions and reduction of acid using $BH_3.Me_2S$ furnished final target sphinganine **34** in 75% yield.

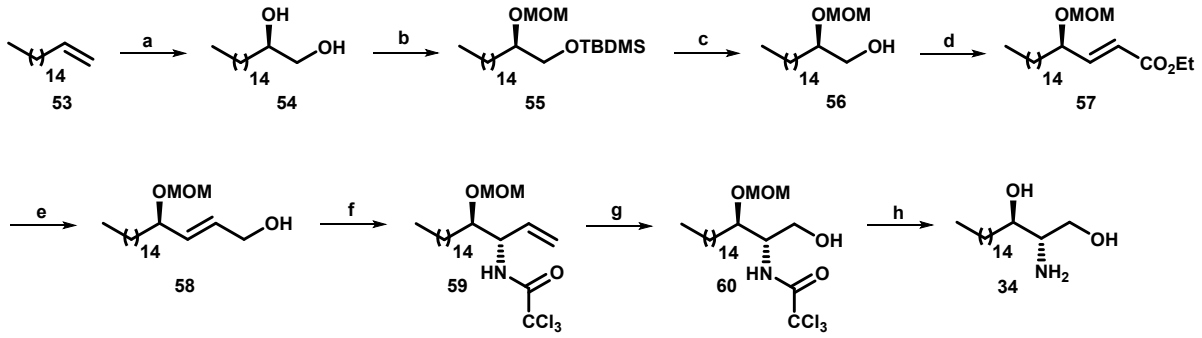


Scheme 7. *Reagents and conditions*: (a) allylmagnesium bromide, THF, 0 ^oC to rt, 2 h, 97%; (b) Ti(*i*-PrO)$_4$, (-)-DET, TBHP, DCM, -20 ^oC, 3 h, 47%; (c) NaN_3, CH_3CN, rt, 1.5 h, 89% yield,

99% *ee*; (d) Ac_2O, pyridine, DMAP, rt, 3 h, 96%; (e) OsO_4, 2,6-lutidine, dioxane/H_2O (3:1), $NaIO_4$, rt, 6 h, 68%; (f) $Br^-Ph_3P^+(CH_2)_{11}Me$, *n*-BuLi, THF, -15 °C to rt, 3 h, 92%; (g) (i) Pd/C, H_2, EtOAc, rt, 4 h; (ii) Ac_2O, pyridine, DCM, rt, 2 h, 91%; (h) (i) $NaIO_4$, $RuCl_3.H_2O$, $CCl_4/CH_3CN/H_2O$ (2:2:3), 0 °C to rt, overnight; (ii) Et_3N, MeOH, rt, 4 h; (iii) 6 N HCl, MeOH, reflux, 2.5 h; (iv) $BH_3.Me_2S$, THF, 0 °C to rt, 6 h, 75% yield (over four steps), 99% ee.

Sutherland, A. *et al*. (2013)[12d]

A. Sutherland and co-workers accomplished the multisteps asymmetric synthesis of D-*erythro*-sphinganine **34** employing palladium(II)-catalyzed MOM ether-directed rearrangement of an allylic trichloroacetimidate as key step starting from terminal alkene derivative **53** (Scheme 8). The olefin **53** on Sharpless asymmetric dihydroxylation (SAD) using AD-Mix-*β* afforded chiral diol **54** which on subsequent *O*-TBDPS and *O*-MOM protection furnished protected diol derivative **55**. The derivative **55** on *O*-TBDPS deprotection (**55→56**), and on oxidation under Swern conditions followed by 2C Wittig olefination furnished olefinic ester derivative **57**. The derivative **57** on DIBAL-H reduction afforded allylic alcohol **58** which on treatment with trichloroacetonitrile under basic conditions followed by Overman rearrangement using catalyst bis(acetonitrile)palladium(II) chloride and *p*-Benzoquinone furnished the terminal alkene derivative **59**. The derivative **59** on ozonolysis using O_3/MeOH followed by reduction with $NaBH_4$ furnished the terminal alcohol **60** in 78% yield. Finally, the derivative **60** on deprotection under acidic conditions afforded the final target D-*erythro*-sphinganine **34** in good yield.



Scheme 8. *Reagents and conditions*: (a) AD-Mix-*β*, *t*-BuOH/H_2O, rt, 40 h, 87%; (b) (i) TBDMSCl, imidazole, THF, 0 °C; (ii) MOMBr, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C, overnight, 100%; (c) TBAF, THF, 0 °C to rt, overnight, 91%; (d) (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C to rt, 3 h; (ii) Triethylphosphonoacetate, LiCl, DBU, MeCN, rt, overnight, 100%; (e) DIBAL-H, Et_2O, -78 °C to rt, 4 h, 86%; (f) Cl_3CCN, DBU, CH_2Cl_2, 0 °C to rt, 2 h; (ii) $PdCl_2(MeCN)_2$, *p*-

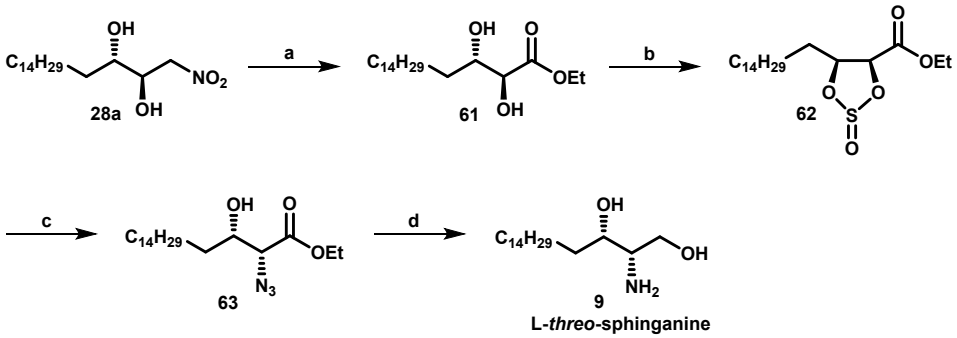
benzoquinone, toluene, 45 °C, 24 h, 78%; (g) O_3, MeOH, CH_2Cl_2, -78 °C; (ii) $NaBH_4$, 0 °C, 1.5 h, 78%; (h) 6M HCl, 60 °C, 24 h, 100%.

4.2.3 Present Work:

In continuation of our ongoing research programme towards the asymmetric syntheses of bioactive compounds, we demonstrated the synthetic application of our own previously developed tandem *α*-aminoxylation-Henry reactions towards the total synthesis of L-*threo*-sphinganine **9**. To the best of our knowledge, there is no any report documented in the literature to date for the enantioselective synthesis of L-*threo*-sphinganine **9** employing tandem *α*-aminoxylation-Henry reactions as key steps starting from commercially available aldehydes.

4.2.4 Results and Discussion:

With enantiomerically pure *anti*-**28a** (Table 1, **28**) diastereomer in hand, we then subjected it to $NaNO_2$/acetic acid mediated oxidation in DMSO to furnish acid[5b,e] which on spontaneous treatment with TMSCl/EtOH[14] afforded the *α,β*-dihydroxy ester **61** in 64% yield (Scheme 9). The diol **61** on treatment with thionyl chloride under basic conditions at 0 °C furnished the cyclic sulfite **62** in 95% yield. The regioselective nucleophilic opening of cyclic sulphite **62** at the *α*-carbon position with NaN_3/DMF at 80 °C afforded the *α*-azido-*β*-hydroxy ester **63** in 91% yield. Finally, concomitant reduction of ester and azide groups of derivative **63** with $LiAlH_4$ in THF at 70 °C afforded the target L-*threo*-sphinganine **9** in 81% yield. The physical and spectroscopic data were in full agreement with those documented in literature.[12]

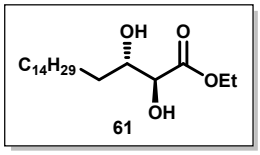


Scheme 9. *Reagents and conditions*: (a) i) $NaNO_2$, AcOH, DMSO, 35 °C, 24 h, ii) TMSCl, EtOH, rt, 12 h, 64% (over two steps); (b) $SOCl_2$, NEt_3, DCM, 0 °C, 1 h, 95%; (c) NaN_3, DMF, 80 °C, 12 h, 91%; (d) $LiAlH_4$, THF, reflux, 12 h, 81%.

4.2.5 Conclusions:

In conclusion, a practical and asymmetric synthesis of L-*threo*-sphinganine **9** has been achieved employing tandem α-aminoxylation-Henry reactions using commercially and readily available aldehydes. The overall yield for the L-*threo*-sphinganine **9** was 42% after five column chromatographic purification steps. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. The synthetic approach described has significant potential for further extension to other stereoisomers and related analogues of sphinganine.

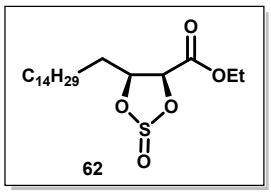
4.2.6 Experimental Section:



61

Ethyl (2*S*,3*S*)-2,3-dihydroxyoctadecanoate (61): A solution of *anti*-**28a** diastereomer (300 mg, 0.91 mmol), sodium nitrite (190 mg, 2.73 mmol), and acetic acid (0.54 mL, 9.1 mmol) in dimethyl sulfoxide (2 mL) was stirred at 35 °C for 24 h. The reaction mixture was then diluted with water, acidified with 10% aqueous solution of hydrochloric acid (10 mL), extracted with ether (3 x 50 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and used as such for the next step without further purification.

To an ethanolic (4.0 mL) solution of above crude was added chlorotrimethylsilane (230 µL, 1.82mmol) at room temperature and stirred for 12 h. The reaction mixture was then concentrated on a rotary evaporator and purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent to afford the diol ester **61** (200 mg, 64%) as white solid. $\{[\alpha]_D^{25}$ -13.8 (*c* 0.5, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3551, 3349, 1731, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.29 (q, *J* = 6.8, 14.2 Hz, 2H), 4.08 (d, *J* = 1.84 Hz, 1H), 3.90-3.86 (m, 1H), 1.63-1.58 (m, 2H), 1.49-1.25 (m, 29H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7, 72.9, 62.1, 72.5, 33.8, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 25.7, 22.6, 14.1; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{41}O_4^+$ ($[M+H]^+$) 345.3000; found 345.2998.

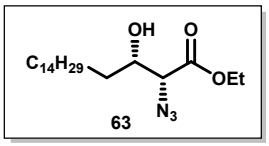


62

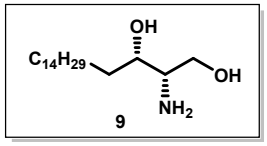
Ethyl (4*S*,5*S*)-5-pentadecyl-1,3,2-dioxathiolane-4-carboxylate 2-oxide (62): To a stirred solution of diol **61** (200 mg, 0.58 mmol) in dry CH_2Cl_2 (5 mL) were added Et_3N (160 µL, 1.16 mmol) and $SOCl_2$ (51 µL, 0.696 mmol) at 0 ^oC over a period of 10 min. The reaction mixture was then stirred for 1 h at 0 ^oC, quenched by adding water and extracted with CH_2Cl_2. The organic layer

was separated, washed with water followed by brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using (EtOAc/hexane 1:19 v/v) as eluent to afford the sulfite ester **62** (215 mg, 95%) as yellow oil. $\{[\alpha]_D^{25}$ -31.2 (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 1767, 1735, 1261, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.12-5.08 (m, 1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.34-4.27 (m, 2H), 1.57-1.22 (m, 31H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3, 82.6, 81.4, 62.5, 32.4, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.2, 22.6, 14.1, 14.0; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{39}O_5S^+$ ($[M+H]^+$) 391.2513; found 391.2511.

Ethyl (2*R*,3*S*)-2-azido-3-hydroxyoctadecanoate (63): To a solution of cyclic sulfite **62** (200 mg, 0.51 mmol) in dry DMF (5 mL) was added NaN_3 (100 mg, 1.53 mmol) under argon. The reaction mixture was stirred at 80 °C for 12 h under argon. The reaction mixture was diluted with water, extracted with ether (3 x 100 mL), dried over Na_2SO_4, concentrated and purified on a silica gel column chromatography using (EtOAc/hexane 1:40 v/v) as eluent to give azido ester **63** (166 mg, 91%) as white solid. $\{[\alpha]_D^{25}$ -43.1 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3621, 2108, 1733, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.32-4.26 (m, 2H), 3.95-3.90 (m, 2H), 1.58-1.50 (m, 2H), 1.37-1.21 (m, 29H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.9, 71.9, 66.1, 62.0, 33.0, 31.9, 29.6, 29.5, 29.5, 29.4, 29.3, 29.3, 25.3, 22.6, 14.1, 14.1; HRMS $(ESI)^+$ m/z calcd for $C_{20}H_{40}N_3O_3^+$ ($[M+H]^+$) 370.3064; found 370.3065.



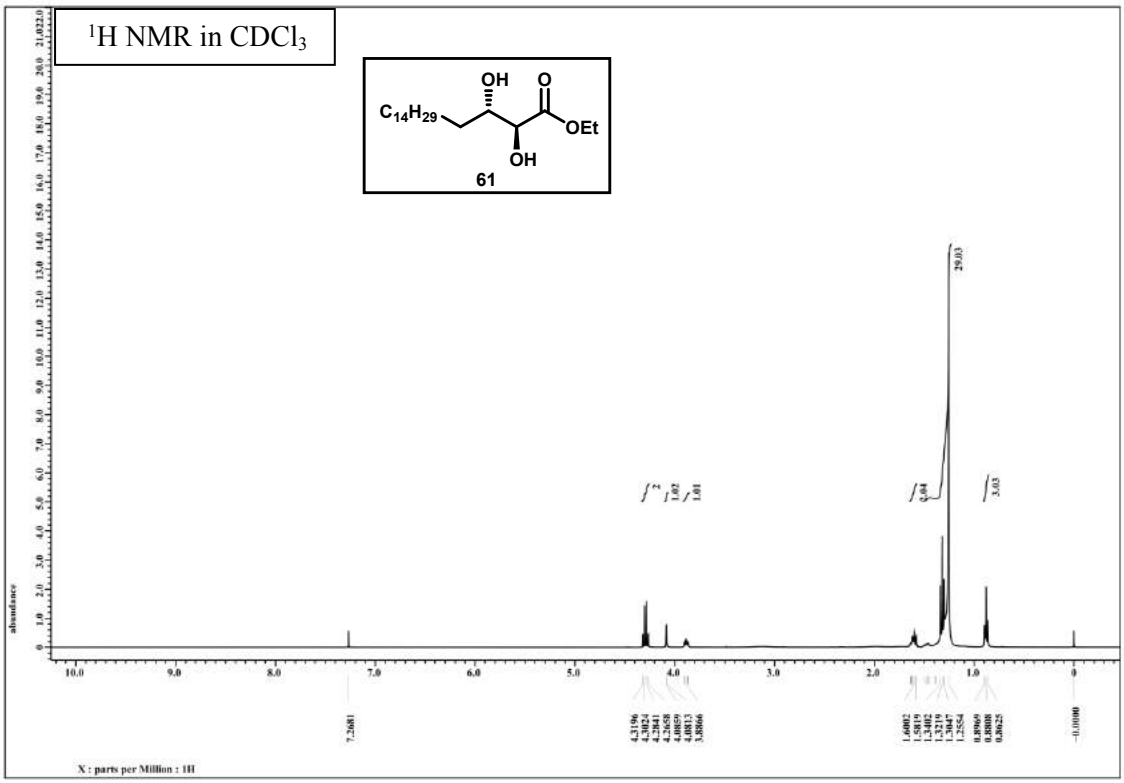
(-)-L-*threo*-sphinganine (Safingol) (9): To a freshly distilled THF (5 mL) solution of $LiAlH_4$ (70 mg, 1.8mmol) at 0 °C was added a solution of azido ester **63** (120 mg, 0.3 mmol) in 5 mL THF. After stirring the reaction mixture for 5 min, ice-cooled bath was removed and stirred the reaction mixture at 70 °C for 12 h until the full consumption of the azido ester (monitored by TLC). The reaction mixture was then diluted with 10 mL of dry THF and filtered through a pad of silica gel slurry in hexane in a sintered glass funnel to remove the impurities by gentle suction. The silica pad was washed with a mixture of $CHCl_3$/MeOH (1:4 v/v), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using ($CHCl_3$/MeOH/NH_4OH 32:6:1) as eluent to give the target L-*threo*-sphinganine (safingol) **9** (73 mg, 81%) as white solid. $\{[\alpha]_D^{25}$ -23.5 (*c* 0.5, $CHCl_3$/MeOH 3:1); IR (MeOH) *v*: 3623, 3425, 1565, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86-3.83 (m, 1H), 3.71-3.61 (m, 2H), 2.54 (bs s, 4H), 1.46-1.12 (m, 28H), 0.88 (t, *J* = 6.4 Hz,



3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.2, 62.6, 61.9, 34.1, 31.8, 30.2, 29.8, 29.6, 29.3, 29.2, 22.6, 14.0. HRMS $(ESI)^+$ m/z calcd for $C_{18}H_{40}NO_2^+$ ($[M+H]^+$) 302.3054; found 302.3035.

4.2.7 Spectra:

1. ^1H and ^{13}C NMR spectra of **61**
2. ^1H and ^{13}C NMR spectra of **62**
3. ^1H and ^{13}C NMR spectra of **63**
4. ^1H and ^{13}C NMR spectra of **9**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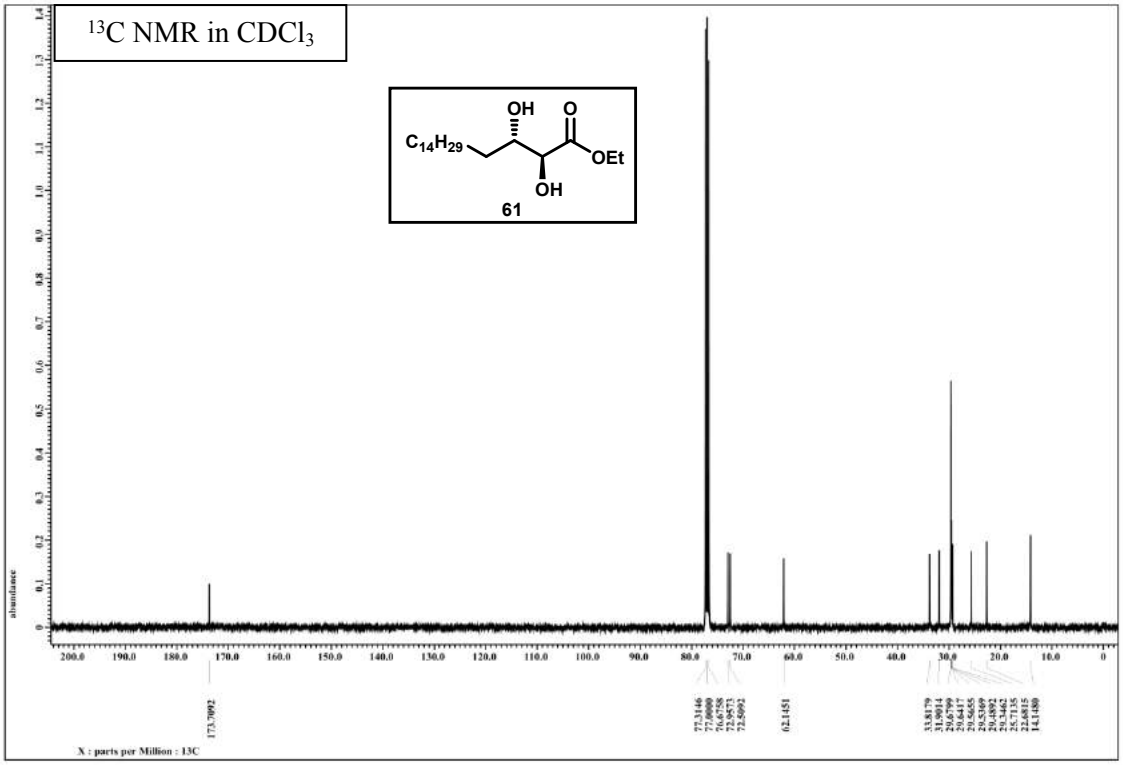
OH
O
$C_{14}H_{29}$
OEt
OH
61
X : parts per Million : 1H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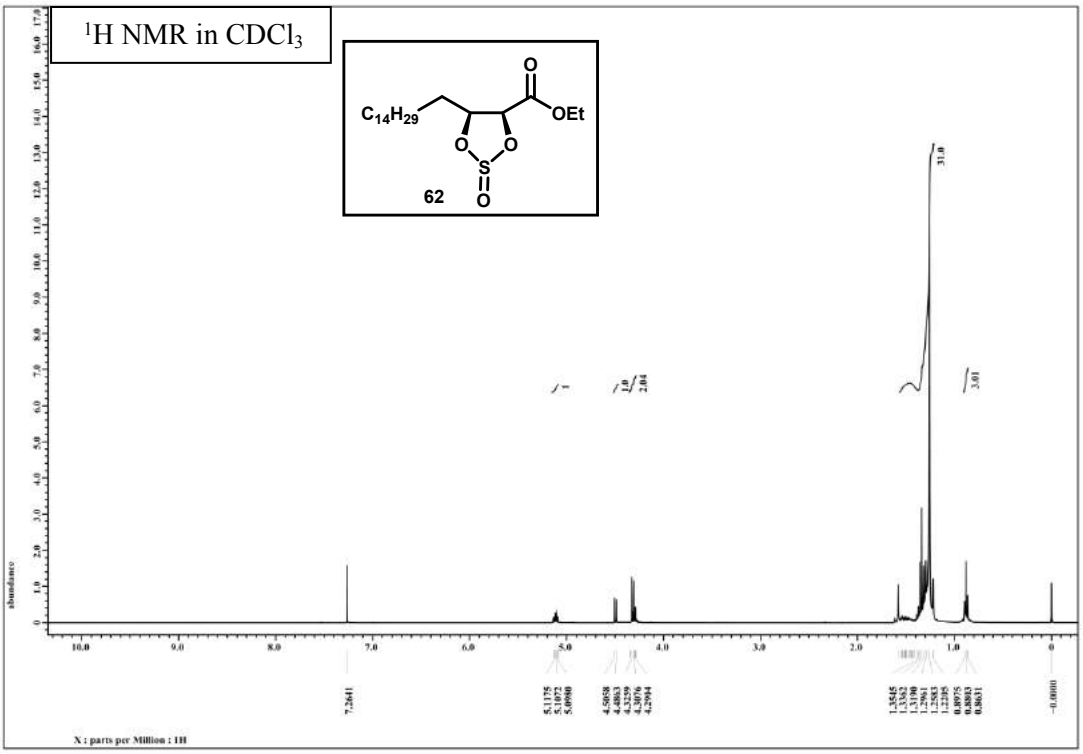
O
$C_{14}H_{29}$
OEt
OH
61
X : parts per Million : 13C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$C_{14}H_{29}$
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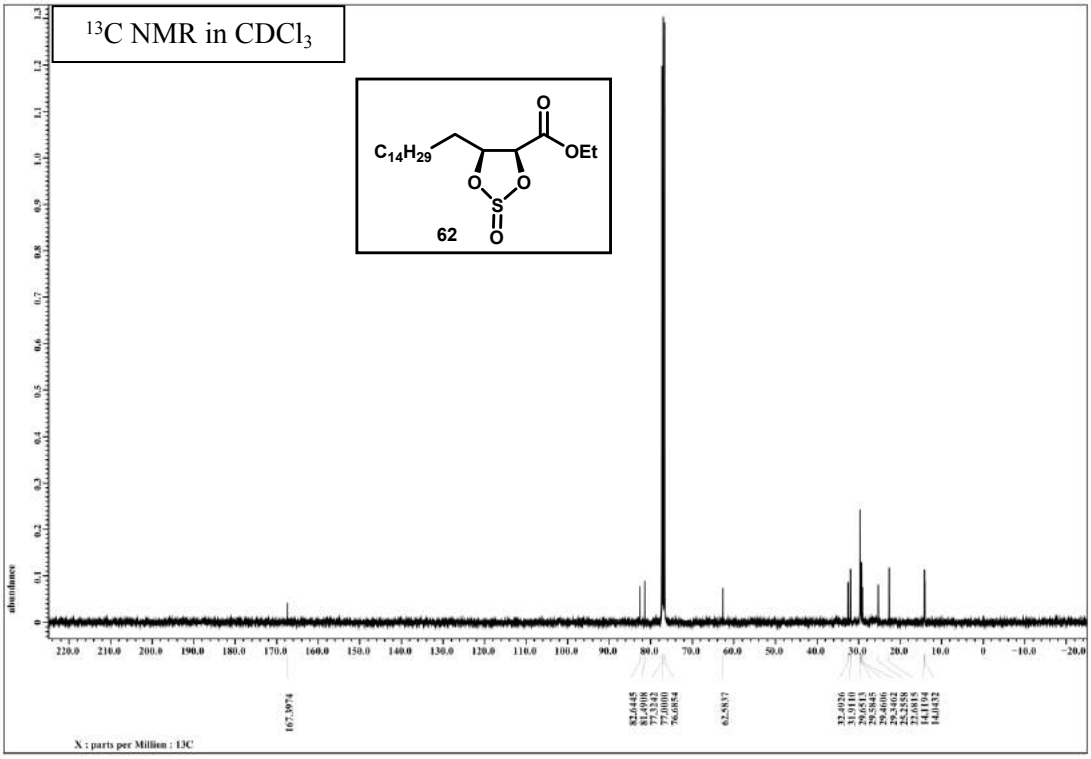
62
X : parts per Million : 1H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$C_{14}H_{29}$
OEt
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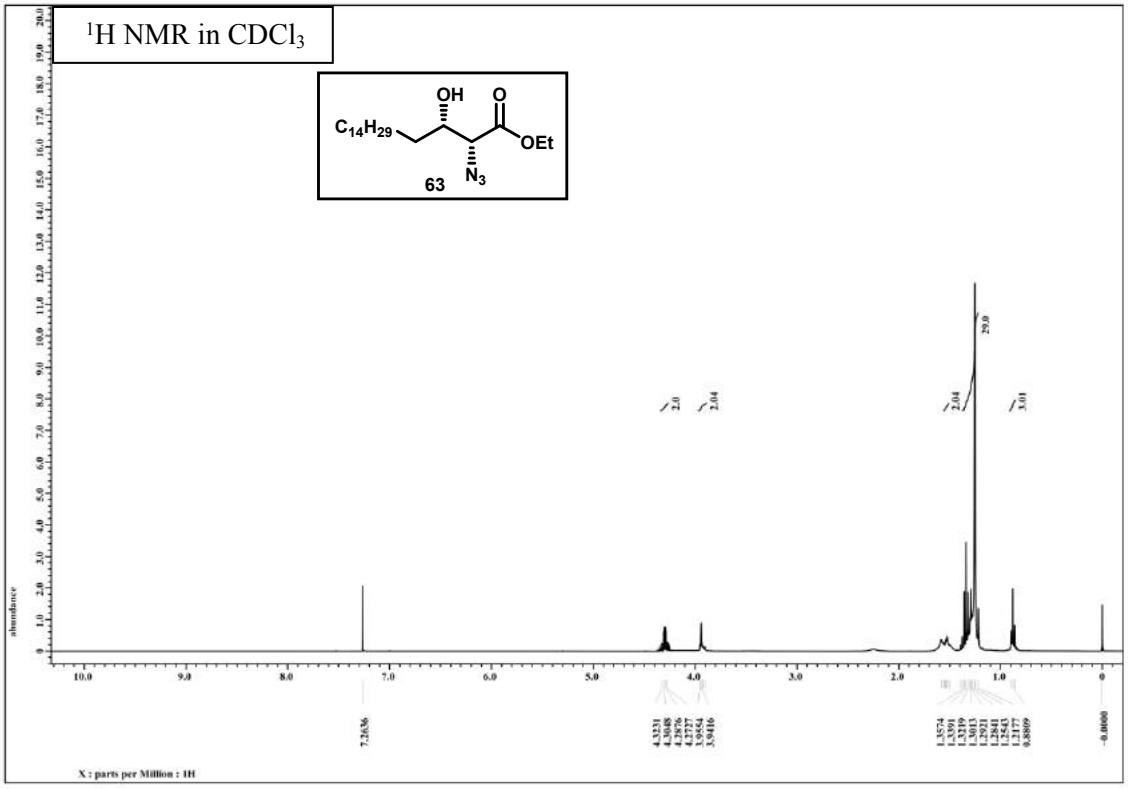
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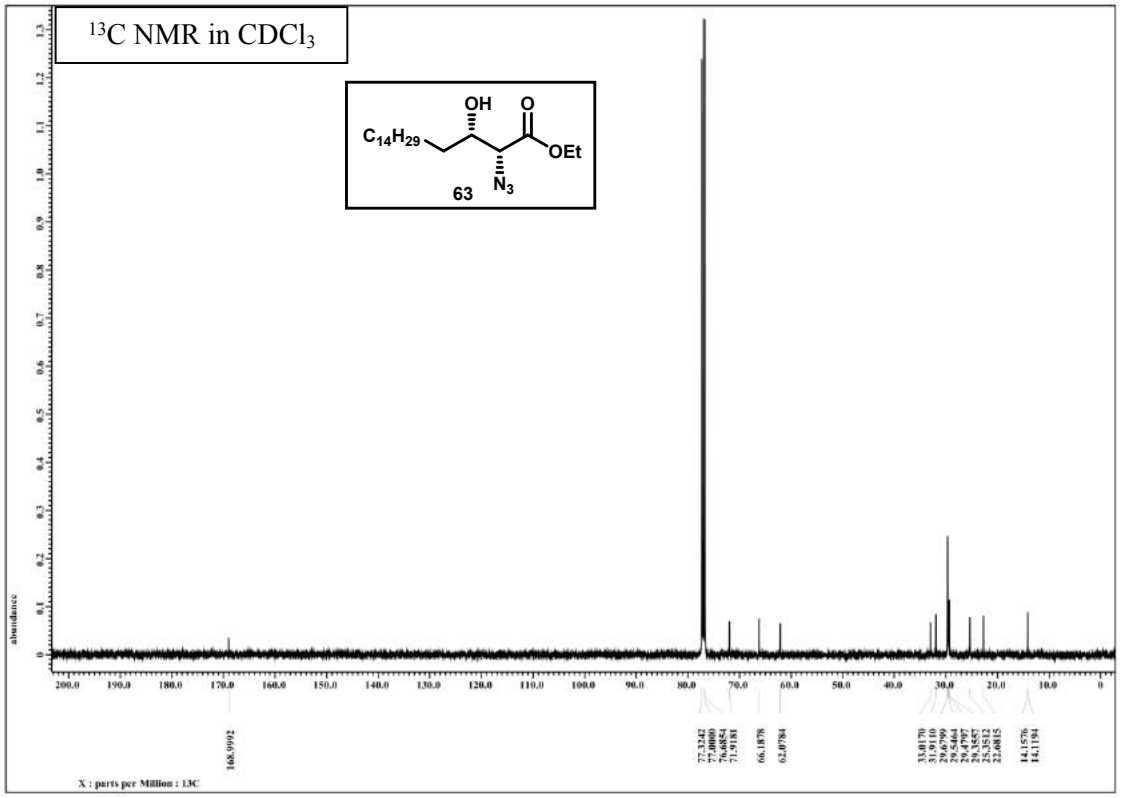
OH
O
$C_{14}H_{29}$
OEt
N_3
63
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
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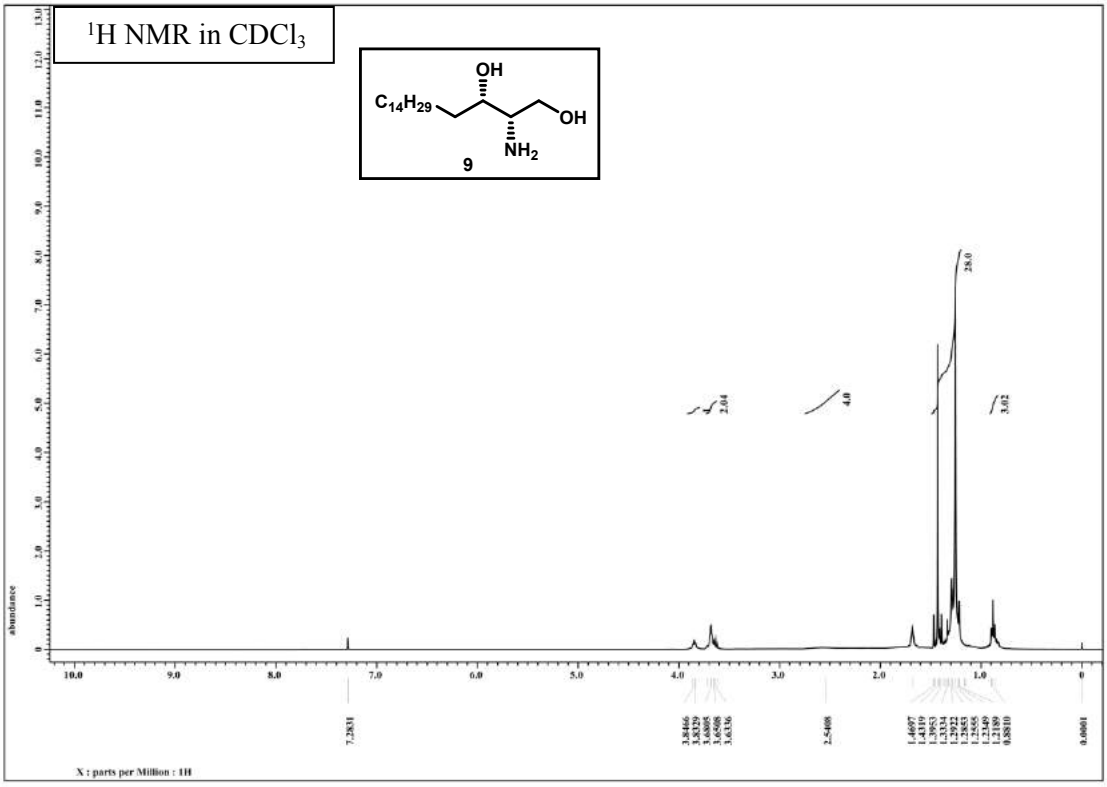
O
$C_{14}H_{29}$
OEt
N_3
63
X : parts per Million : 13C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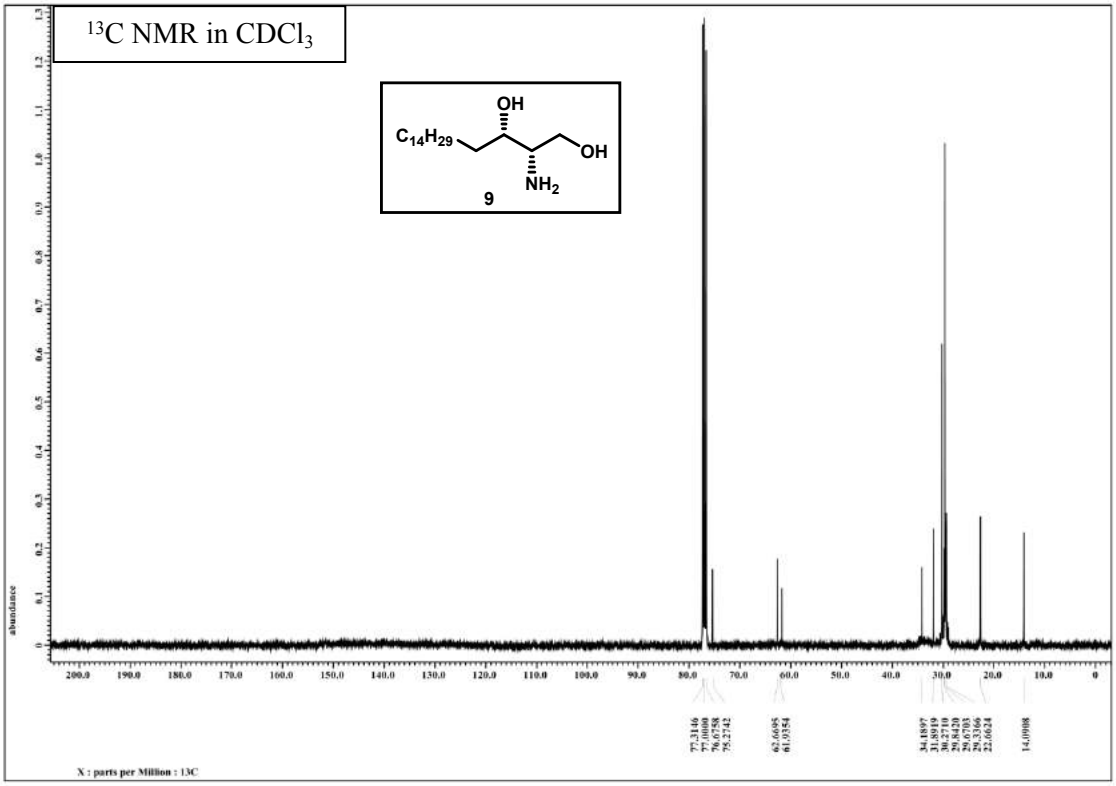
$C_{14}H_{29}$
OH
NH_2
9
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
$C_{14}H_{29}$
OH
NH_2
9
X : parts per Million : 13C

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CHAPTER 5

Two different enantioselective approaches for the total synthesis of (+)-disparlure, a lepidopteran sex pheromone. This chapter is divided into two sections.

5.1 Section A

Enantioselective synthesis of (+)-disparlure *via* organocatalyzed tandem α-aminoxylation/Henry reactions.

5.1.1 Introduction:

The novel straight chain lepidopteran sex pheromone *cis*-(+)-disparlure **1a** was isolated from the female gypsy moth, *Porthetria disar L*., a widespread pest causing damage to wild ecosystem (Figure 1).[1] *cis*-(+)-Disparlure **1a** is a sex attractant pheromone required for the upwind flight of male moths to the pheromone releasing females binds selectively to PBP1 protein, while the *cis*-(-)-disparlure **1b** cancels the upwind flight behavior in the males binds selectively to PBP2 protein of gypsy moth.[2] Over the decades, *cis*-(+)-disparlure **1a** has been used worldwide as a pesticide against this gypsy moth by confusing and preventing the male moths from locating and mating with females or leading them into traps for the protection of forests. *cis*-(+)-Disparlure **1a** and analogues (**1b-d**) have been synthetic targets of considerable interest for academia and agroindustries due to their astonishing biologically properties combined with attractive structural features with an array of functionalities.

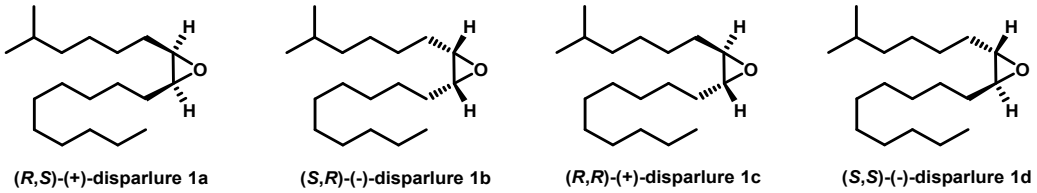


Figure 1. Structure of isomers of disparlure

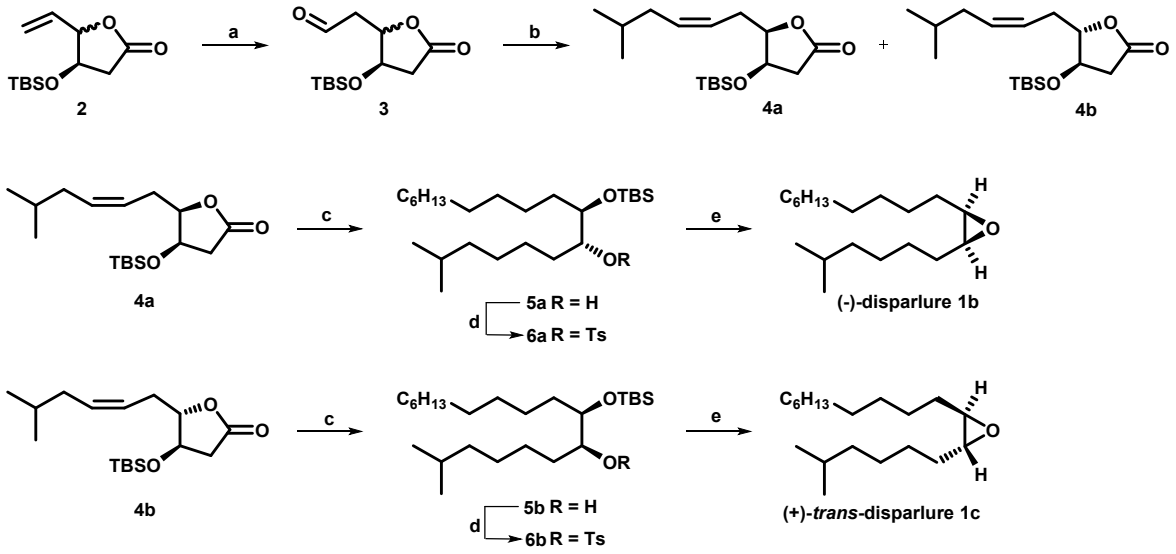
5.1.2 Review of Literature:

Various methods for the synthesis of *cis*-(+)-disparlure **1a** and its analogues (**1b-d**) mainly based on chiral auxillary and chiral pool approaches have been documented in the literature.[3] Some of the recent syntheses of *cis*-(+)-disparlure **1a** and its analogues (**1b-d**) are described below.

Fernandes, R. A. *et al*. (2014)[3a]

R. A. Fernandes and co-workers reported the enantioselective total synthesis of (-)-**1b** and (+)-disparlure **1c** employing domino palladium-catalyzed recombinant γ-isomerization and reverse Wacker oxidation of γ-vinyl-γ-butyrolactone in 19.3% and 20.7% overall yield respectively,

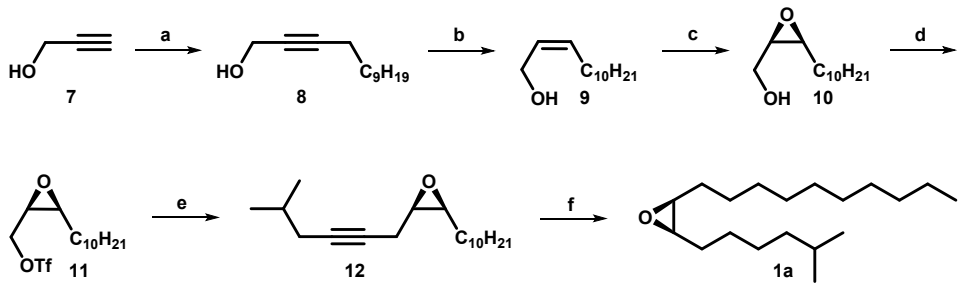
starting from lactone **2** which was synthesized from D-glucono-*δ*-lactone by known method (Scheme 1). The alkene **2** on heteroatom directed reverse Wacker oxidation using $PdCl_2$/CuCl under O_2 gas atmosphere furnished aldehyde derivative **3** which on subsequent Wittig olefination under basic conditions afforded alkene derivative *syn*-**4a** and *anti*-**4b** in 1:4 diastereomeric ratio with 80% overall yield. The *syn*-lactone **4a** on DIBAL-H reduction and subsequent Wittig olefination followed by hydrogenation using $Pd(OH)_2$/C furnished alcohol **5a** in 83% yield. Finally, the alcohol **5a** on *O*-tosylation using TsCl/DMAP, subsequent *O*-TBS deprotection using TBAF and *in situ* replacement of *O*-Ts with alcohol in S_N2 fashion furnished target compound (-)-diaparlure **1b** in 91% yield. On the other side, *anti*-lactone **4b** on reduction using DIBAL-H and subsequent Wittig olefination followed by hydrogenation using $Pd(OH)_2$/C afforded alcohol derivative **5b** in 83% yield. Finally, the alcohol derivative **5b** on *O*-tosylation followed by *O*-TBS deprotection furnished the target (+)-disparlure **1c** in 88% yield.



Scheme 1. *Reagents and conditions*: (a) (i) CuCl, DMF/H_2O (7:1), O_2, rt, 20 min; (ii) $PdCl_2$, rt, 6 h; (b) (*iso*-pentyl)triphenylphosphonium bromide, LiHMDS, THF, 0 °C, 45 min, -20 °C, **3**, 8 h, 80%; (c) (i) DIBAL-H, Et_2O, -78 °C, 1 h; (ii) $Ph_3P^+CH_2(CH_2)_6CH_3Br^-$, THF, *n*-BuLi, 0 °C, 1 h, lactol, 0 °C to rt, 8 h; (iii) H_2, $Pd(OH)_2$/C, *i*PrOH, rt, 3 h, 86% for **5a** and 83% for **5b** (over three steps); (d) 4-Dimethylaminopyridine, TsCl, CH_2Cl_2, 0 °C to rt, 24 h, **6a** (quant), **6b** (94%); (e) TBAF, THF, 0 °C to rt, 5 h, (-)-**1b** (91%), (+)-**1c** (88%).

Jianfeng, Z. *et al*. (2012)[3b]

Z. Jianfeng and co-workers reported the asymmetric synthesis of (+)-disparlure **1a** *via* Zhou's modified Sharpless asymmetric epoxidation starting from commercially available propargyl alcohol **7** in six steps with 29% yield (Scheme 2). The terminal alkyne **7** on treatment with 1-bromodecane using *n*-BuLi/HMPA furnished non terminal alkyne derivative **8** in 84% yield. The alkyne **8** on partial hydrogenation over Lindlar's catalyst (5% $Pd/CaCO_3$) poisoned with 3.5% Pb furnished *cis*-olefinic allylic alcohol **9** which on Sharpless asymmetric epoxidation using Ti(*i*-PrO)$_4$/(-)-DIPT afforded epoxide **10** in 60% yield. The alcohol **10** on *O*-Tf using Tf_2O under basic conditions furnished epoxy derivative **11** which on subsequent treatment with lithium acetylide of the 4-methylpent-1-yne using *n*-BuLi/HMPA afforded alkyne derivative **12** in 85% yield. Finally, alkyne derivative **12** on hydrogenation using Pd/C furnished the final target (+)-disparlure **1a** in 81% yield.

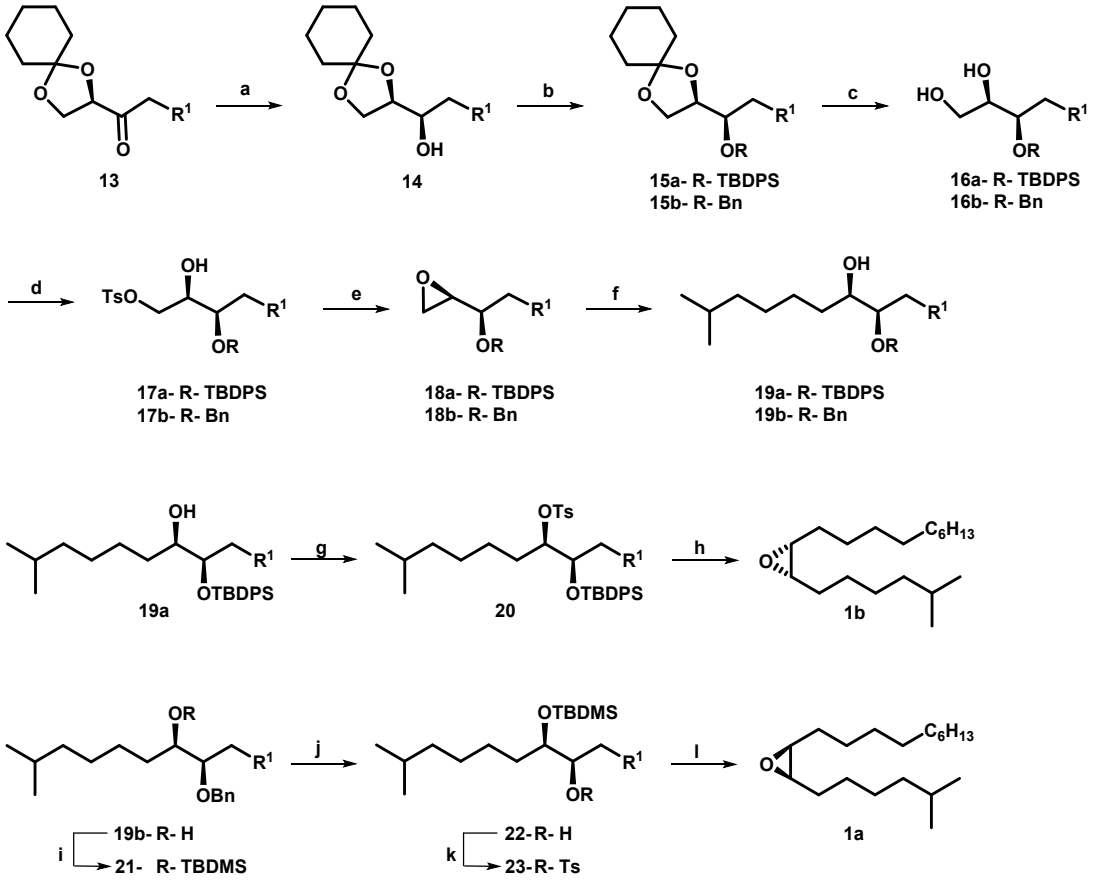


Scheme 2. *Reagents and conditions*: (a) *n*-BuLi, HMPA, *n*-$C_{10}H_{21}Br$, THF, -78 ^oC, 5 h, 84%; (b) H_2, *n*-hexane, $Pd/CaCO_3$, 0 ^oC, 2 h, 94%; (c) Ti(*i*-PrO)$_4$, D-(-)-DIPT, *t*-BuOOH, CaH_2, SiO_2, CH_2Cl_2, -25 ^oC, 72 h, 60%; (d) Tf_2O, NEt_3, CH_2Cl_2, -78 ^oC to -60 ^oC, 30 min, 85%; (e) 4-methylpent-1-yne, *n*-BuLi, HMPA, Et_2O, -78 ^oC, 1 h, 85%; (f) Pd/C, H_2, *n*-hexane, rt, 2 h, 81%.

Chattopadhyay, A. *et al*. (2011)[3c]

A. Chattopadhyay and co-worker reported the asymmetric synthesis of disparlure **1a** and **1b** *via* asymmetric ketone reduction in 10.75 % and 13.97%, respectively, starting from chiral compound **13** which was synthesized from (*R*)-2,3-cyclohexylideneglyceraldehyde using known methods (Scheme 3). The ketone derivative **13** on reduction with $LiAlH_4$ afforded alcohol **14** which on further *O*-TBDPS protection with TBDPS-Cl under basic conditions furnished protected derivative **15a** in 95% yield. The derivative **15a** on dekatalisation under acidic conditions furnished terminal diol derivative **16a** which on subsequent *O*-tosylation afforded alcohol derivative **17a** in quantitative yield. The derivative **17a** on epoxide formation under basic conditions furnished epoxy derivative **18a** which on copper catalyzed regioselective nucleophilic

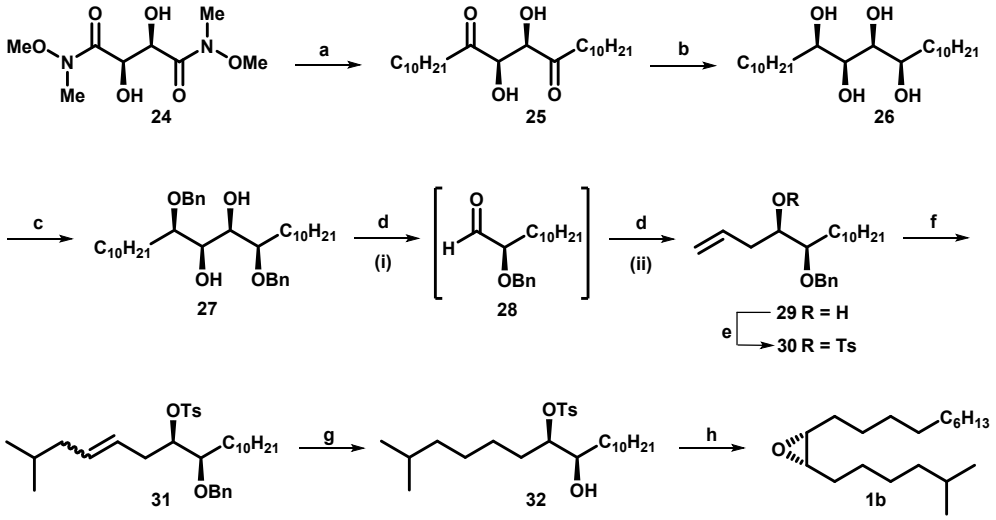
ring opening with Grignard reagent *iso*-hexylmagnesium bromide afforded alcohol derivative **19a** in 70% yield. The alcohol derivative **19a** on *O*-tosylation gave tosylated derivative **23** which on subsequent *O*-TBDPS deprotection using TBAF followed by *in situ* replacement of *O*-Ts with alcohol furnished epoxide **1b** in 75% yield. On the other side, the alcohol derivative **19b** was converted to disparlure **1a** following an analogue series of reactions as those in the synthesis of **1b**.



Scheme 3. *Reagents and conditions*: (a) $LiAlH_4$, dry THF, 0 °C, 2.5 h, 59.7%; (b) (i) TBDPSCl, imidazole, DMAP, dry CH_2Cl_2, rt, 10 h, 95%; (ii) $PhCH_2Br$, NaH, dry THF, 60 °C, 1 h, 90%; (c) aq. TFA (80%), CH_2Cl_2, 0 °C, 2.5 h, 80%; (d) TsCl, pyridine, DMAP, 0 °C, 4 h, quantitatively; (e) K_2CO_3, CH_3OH, rt, 3 h, 85%; (f) $(CH_3)_2CH(CH_2)_2CH_2MgBr$, CuBr, dry THF, -50 °C to rt, overnight, 70%; (g) TsCl, pyridine, DMAP, 0 °C, 9 h, quantitatively; (h) TBAF, dry THF, 0 °C to rt, 4 h, 75%; (i) TBDMS-Cl, imidazole, DMAP, dry CH_2Cl_2, rt, 10 h, 90%; (j) Pd/C, H_2, C_2H_5OH, rt, 3 h, 85%; (k) TsCl, pyridine, DMAP, 0 °C, 6 h, quantitatively; (l) TBAF, dry THF, 0 °C to rt, 6 h, 75%.

Prasad, K. R. *et al*. (2007)[3h]

K. R. Prasad and co-workers accomplished the asymmetric synthesis of (-)-disparlure **1b** *via* the cross metathesis of a chiral homoallylic alcohol starting from Weinreb amide derivative of L-(+)-tartaric acid in eight steps (Scheme 4). The amide **24** on Grignard reaction with *n*-decylmagnesium bromide furnished diketone derivative **25** which on further reduction using *K*-selectride afforded tetrahydroxy derivative **26** in 93% yield. The alcohol **26** on *O*-benzylation using BnBr/NaH afforded benzylated derivative **27** which on subsequent oxidative cleavage of diol using $Pd(OAc)_4/MgBr_2.OEt_2$ furnished α-*O*-Bn aldehyde derivative **28**. The aldehyde derivative **28** on allylation using allyltributyltin under Keck conditions furnished the allylic alcohol **29** which on further *O*-tosylation afforded alkene derivative **33** in 87% yield. The alkene **30** on Grubbs cross metathesis with 4-methylpent-1-ene using Ru-catalyst afforded alkene derivative **31** which on further hydrogenation using Pd/C furnished alcohol derivative **35** in 90% yield. Finally, the alcohol derivative **32** on replacement of *O*-Ts under basic conditions furnished final target (-)-disparlure **1b** in 89% yield.



Scheme 4. *Reagents and conditions*: (a) $C_{10}H_{21}MgBr$, THF, 0 ^oC, 2.5 h, 92%; (b) *K*-selectride, THF, -78 ^oC, 2.5 h, 93%; (c) (i) NaH, BnBr, DMF, 0 ^oC, 3 h; (ii) $FeCl_3.6H_2O$, DCM, rt, 3 h, 89% (over two steps); (d) (i) $Pd(OAc)_4$, benzene, rt, 1.5 h; (ii) $MgBr_2.OEt_2$, DCM, -78 ^oC, 3 h, 79% (over two steps); (e) TsCl, DMAP, DCM, rt, 5 h, 87%; (f) $(CH_3)_2CHCH_2CH=CH_2$, Grubbs 2nd gen. catalyst (5 mol%), DCM, reflux, 6 h, 92%; (g) H_2, Pd/C, MeOH, rt, 3 h, 90%; (h) K_2CO_3, MeOH, rt, 1 h, 89%.

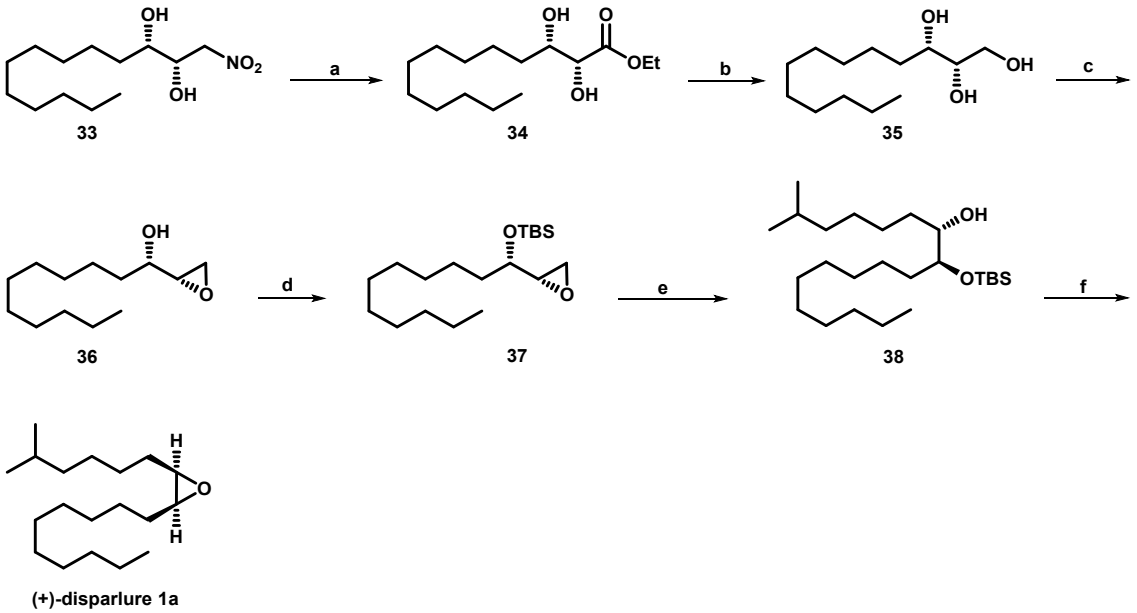
5.1.3 Present Work:

As part of our research programme aimed at developing enatioselective synthesis of naturally occurring compounds, we demonstrated the synthetic application of our own previously developed tandem α-aminoxylation-Henry reactions approach towards the total synthesis of *cis*-(+)-disparlure **1a** and its analogues (**1b-d**).

5.1.4 Results and Discussion:

As illustrated in Scheme 5, synthesis of (+)-disparlure **1a** commenced with *syn* diastereomer **33** (**27**, Table 4, Chapter 4) which was synthesized employing our previously developed tandem α-aminoxylation-Henry reactions approach using a commercially available aldehyde. The *syn*-β,γ-dihydroxy nitrotridecane **33** on $NaNO_2$/AcOH mediated oxidation in DMSO to acid[4] and subsequent treatment with TMSCl/EtOH[5] afforded the ester derivative **34** in 61% yield. The reduction of dihydroxy ester **34** to corresponding triol **35** was achieved with DIBAL-H at 0 ^oC to rt in quantitative yield. The selective primary alcohol tosylation of triol derivative **35** was accomplished *via* using TsCl/NEt_3 in the presence of catalytic amount of dibutyltin oxide and subsequently converted to terminal epoxide **36** under basic conditions in excellent yield.

Our next aim was to synthesize the non-terminal 1,2-diols from terminal epoxide **36**. To this side, treatment of free hydroxyl group of epoxide **36** was protected with TBSCl using the basic conditions of imidazole/DMAP to afford epoxide derivative **37** which on CuI catalysed regioselective ring-opening of epoxide at terminal end with *i*-hexylmagnesium bromide at -60 ^oC afforded the TBS protected diol derivative **38** in 76% yield. Finally, the alcohol **38** was treated with tosyl chloride under basic conditions of DMAP to afford *O*-tosylated diol and *in situ* replacement with alcohol synthesized by *O*-TBS deprotection using TBAF furnished the sex pheromone (+)-disparlure **1a** in 87% yield. The physical and spectroscopic data of (+)-disparlure **1a** were found to be in full agreement with those reported in the literature.[1,3]

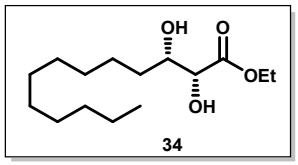


Scheme 5. *Reagents and conditions*: (a) i) $NaNO_2$, acetic acid, DMSO, 35 ^oC, 24 h, ii) TMSCl, EtOH, rt, 12 h, 61% (over two steps); (b) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 3 h, 82%; (c) i) TsCl, NEt_3, Bu_2SnO (10 mol%), dry CH_2Cl_2, 0 ^oC to rt, 2 h, ii) KOH, Et_2O, rt, 12 h, 74% (over two steps); (d) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 14 h, 91%; (e) $Me_2CH(CH_2)_3MgBr$, anhydrous THF, CuI, -60 ^oC, 6 h, 76%; (f) i) TsCl, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 24 h, ii) TBAF, THF, rt, 6 h, 87% (over two steps).

5.1.5 Conclusions:

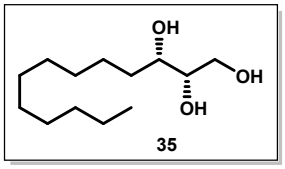
In conclusion, a concise and efficient syntheses of (+)-disparlure **1a** was accomplished using asymmetric organocatalytic tandem α-aminoxylation/stereocontrolled Henry reactions of the commercially available dodecanal, which was shown to be a highly effective route for preparing optically active diols. The overall yield for the (+)-disparlure **1a** was 14% after seven column chromatographic purification steps. Further extension of this versatile strategy to biologically active molecules of more structural complexity and diversity is possible from the developed α-aminoxylation/ Henry reactions.

5.1.6 Experimental Section:



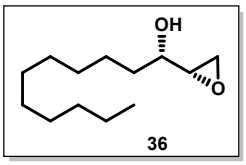
Ethyl (2*R*,3*S*)-2,3-dihydroxytridecanoate (34): A solution of *syn*-diastereomer **33** (600 mg, 2.3 mmol), sodium nitrite (476 mg, 6.9 mmol), and acetic acid (1.36 mL, 23 mmol) in dimethyl sulfoxide (5 mL) was stirred at 35 °C for 24 h. The reaction mixture was then diluted with water, acidified with 10% aqueous solution of hydrochloric acid (25 mL), extracted with ether (3 x 50 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and used as such for the next step without further purification.

To an ethanolic (10 mL) solution of above crude was added chlorotrimethylsilane (580 µL, 4.6 mmol) at room temperature for 12 h. The reaction mixture was then concentrated on a rotary evaporator and purified by silica gel column chromatography (EtOAc/hexanes 2:8 v/v) as eluent to afford the diol ester **34** (385 mg, 61%) as white solid. $\{[\alpha]_D^{25}$ -63.4 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) *v*: 3549, 3362, 1729, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.29 (q, *J* = 7.32, 14.2 Hz, 2H), 4.09-4.07 (m, 1H), 3.92-3.86 (m, 1H), 3.05 (d, *J* = 5.2 Hz, 1H), 1.92-1.86 (m, 1H), 1.34-1.26 (m, 21H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.6, 72.9, 72.5, 62.1, 33.8, 31.8, 29.5, 29.3, 25.7, 22.6, 14.1; HRMS $(ESI)^+$ m/z calcd for $C_{15}H_{31}O_4^+$ ($[M+H]^+$) 275.2217; found 275.2219.



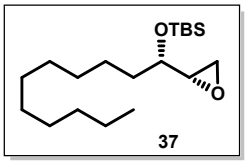
(2*S*,3*S*)-Tridecane-1,2,3-triol (35): To a solution of **34** (370 mg, 1.35 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added dropwise DIBAL-H (1.15 mL, 2.02 mmol, 1.75 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 3 h, then re-cooled to 0 °C and treated with saturated solution of sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography purification (EtOAc/hexanes 4:1 v/v) of the crude product furnished triol **35** (255 mg, 82%) as a white solid. $[\alpha]_D^{25}$ -56.2 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*; 3467, 3232, 2958, 2854, 1478, 1389, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.85-3.54 (m, 4H), 2.80 (br s, 1H), 2.33 (br s, 2H), 1.55-1.27 (m, 18H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.1, 65.3, 63.4, 34.0, 33.3, 32.2, 29.8, 29.6, 26.2, 25.8, 22.9, 14.4. HRMS $(ESI)^+$ m/z calcd for $C_{13}H_{28}O_3Na^+$ [$M+Na^+$] 255.1930; found 255.1929.

(*S*)-1-((*S*)-Oxiran-2-yl)undecan-1-ol (36): To a CH_2Cl_2 (10 mL) solution of triol **35** (250 mg, 1.08 mmol) were added NEt_3 (150 µL, 1.08 mmol), *p*-TsCl (207 mg, 1.08 mmol) and catalytic amount of dibutyltin oxide (27 mg, 0.108 mmol, 10 mol%) sequentially at 0 °C. The reaction mixture was stirred till completion (2 h) of the starting material, diluted with water and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated to near dryness. The crude product was as such for the next step without further purification.



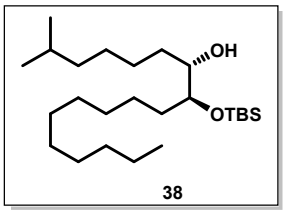
To an Et_2O (10 mL) solution of above tosylated crude was added finely powdered KOH (182 mg, 3.24 mmol) and stirred vigorously for 12 h at room temperature. The reaction mixture was then poured into 20 mL water, extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (EtOAc/hexanes 1:4 v/v) of the crude product furnished epoxide **36** (172 mg, 74%) as a yellow oil. $[\alpha]_D^{25}$ -83.9 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*; 3325, 2931, 2978, 2856, 1489, 1379, 1051, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 3.49-3.41 (m, 2H), 3.00-2.97 (m, 1H), 2.84-2.82 (m, 1H), 2.73-2.71 (m, 1H), 1.84-1.82 (m, 1H), 1.60-1.20 (m, 17H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 71.6, 55.3, 45.2, 34.4, 31.8, 29.5, 29.5, 29.3, 25.2, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{13}H_{27}O_2^+$ $[M+H^+]$ 215.2006; found 215.2026.

***tert*-Butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)undecyl)oxy)silane (37):** To a solution of alcohol **36** (160 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was added imidazole (102 mg, 1.5 mmol), DMAP (46 mg, 0.375 mmol) followed by *tert*-butyldimethylsilyl chloride (150 mg, 0.97 mmol) at 0 °C. The reaction was then stirred under N_2 for 14 h, after which it was quenched by adding aqueous saturated NH_4Cl (10 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:19 v/v) as eluent furnished **37** (225 mg, 91%) as pale yellow oil. $[\alpha]_D^{25}$ -41.4 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*: 2956, 2914, 2858, 1459, 1377, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 3.52-3.48 (m, 1H), 2.83-2.80 (m, 1H), 2.67-2.64 (m, 1H), 2.61-2.60 (m, 1H), 1.52-1.21 (m, 18H), 0.86-0.81 (m, 12H), -0.004 (d, *J* = 1.36 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 71.6, 55.0, 45.1, 35.5,



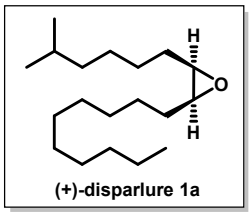
32.2, 30.0, 29.9, 29.8, 29.6, 26.1, 25.1, 23.0, 18.4, 14.4, -4.06, -4.5. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{40}O_2SiNa^+$ $[M+Na^+]$ 351.2690; found 351.2688.

(7*S*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-methyloctadecan-7-ol (38): To a stirred solution of TBS-protected epoxide **37** (200 mg, 0.61 mmol) in dry THF (5 mL) and CuI (12 mg, 0.061 mmol) at -60 °C was added *i*-hexylmagnesiumbromide, freshly prepared from *i*-hexylbromide (200 mg, 176 µL, 1.22 mmol) and magnesium (44 mg, 1.83 mmol) in dry THF (10 mL). The reaction mixture was then stirred for 6 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purification by silica gel column chromatography (EtOAc/hexane 1:19 v/v) as eluent furnished **38** (190 mg, 76%) as pale yellow oil. [Lit.[3a] -5.6 (*c* 0.16, $CHCl_3$)]}; IR (CH_2Cl_2) *v*: 3435, 2967, 2912, 2856, 1456, 1378, 1333, 1278, 1125, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.71-3.44 (m, 2H), 2.15 (s, 1H), 1.51-1.19 (m, 27H), 0.91-0.77 (m, 18H), 0.082 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.2, 74.6, 38.9, 34.1, 33.8, 31.8, 29.8, 29.8, 29.5, 29.3, 27.8, 27.4, 26.4, 26.1, 25.8, 25.7, 22.6, 22.6, 18.0, 14.1, -4.4, -4.6. HRMS $(ESI)^+$ m/z calcd for $C_{25}H_{55}O_2Si^+$ $[M+H^+]$ 415.3966; found 415.3969.



38

(+)-Disparlure (1a): To a CH_2Cl_2 (5 mL) solution of alcohol **38** (120 mg, 0.29 mmol) was added 4-(dimethylamino)pyridine DMAP (142 mg, 1.16 mmol) and *p*-toluenesulfonyl chloride (222 mg, 1.16 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was used as such for the next step without further purification.



(+)-disparlure 1a

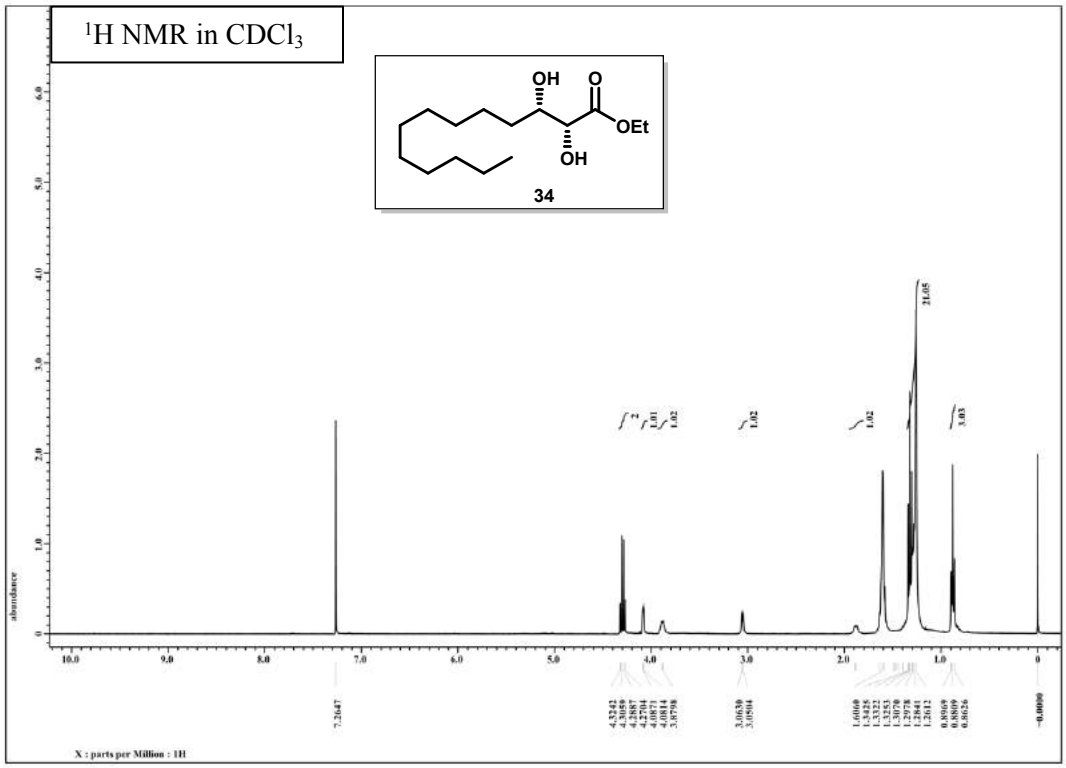
To a stirred solution of above tosylated crude in dry THF (10 mL) was added TBAF (1.0 M in THF, 1.45 mL, 1.45 mmol) at 0 °C under an N_2 atmosphere. The reaction mixture was slowly warmed to room temperature and stirred for 6 h. It was then quenched with water and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane

1:40 v/v) as eluent furnished **1a** (71 mg, 87%) as oil. {$[\alpha]_D^{25}$ +1.2 (*c* 1.1, CCl_4) [Lit.[3a] +1.6 (*c* 1.1, CCl_4)]}; IR (CH_2Cl_2) *v*: 2975, 2945, 2844, 1474, 1362, 1314, 1245, 1171, 1051, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.92-2.88 (m, 1H), 2.66-2.63 (m, 1H), 1.57-1.12 (m, 27H), 0.89-0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 57.2, 38.8, 31.8, 29.5, 29.3, 27.8, 27.8, 27.8, 27.3, 26.8, 26.5, 26.0, 22.6, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{39}O^+$ $[M+H^+]$ 283.2996; found 283.2994.

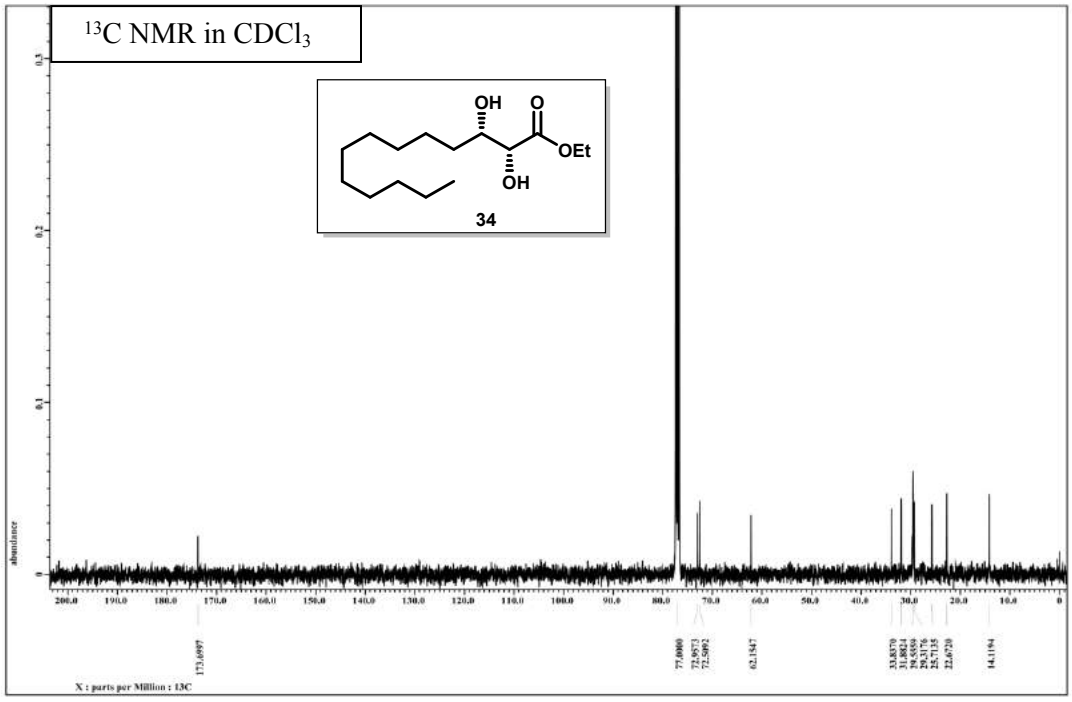
5.1.7 Spectra:

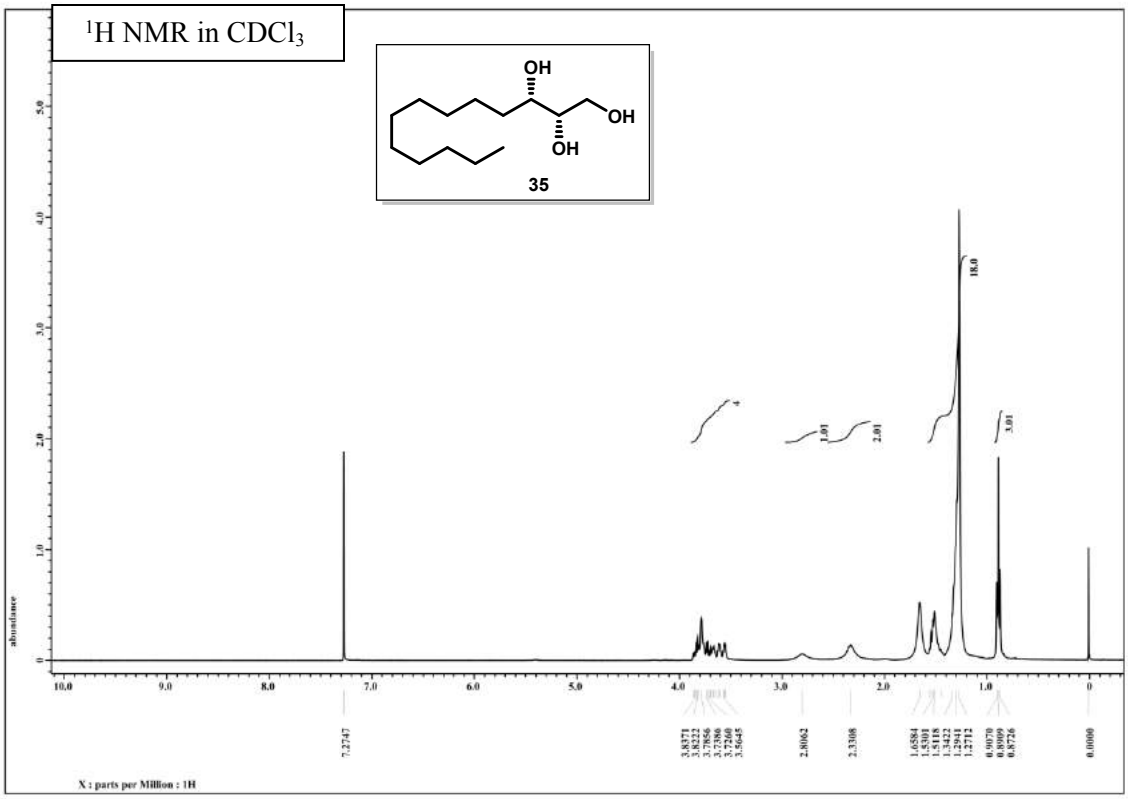
1. ^1H and ^{13}C NMR spectra of **34**
2. ^1H and ^{13}C NMR spectra of **35**
3. ^1H and ^{13}C NMR spectra of **36**
4. ^1H and ^{13}C NMR spectra of **37**
5. ^1H and ^{13}C NMR spectra of **38**
6. ^1H and ^{13}C NMR spectra of **1a**

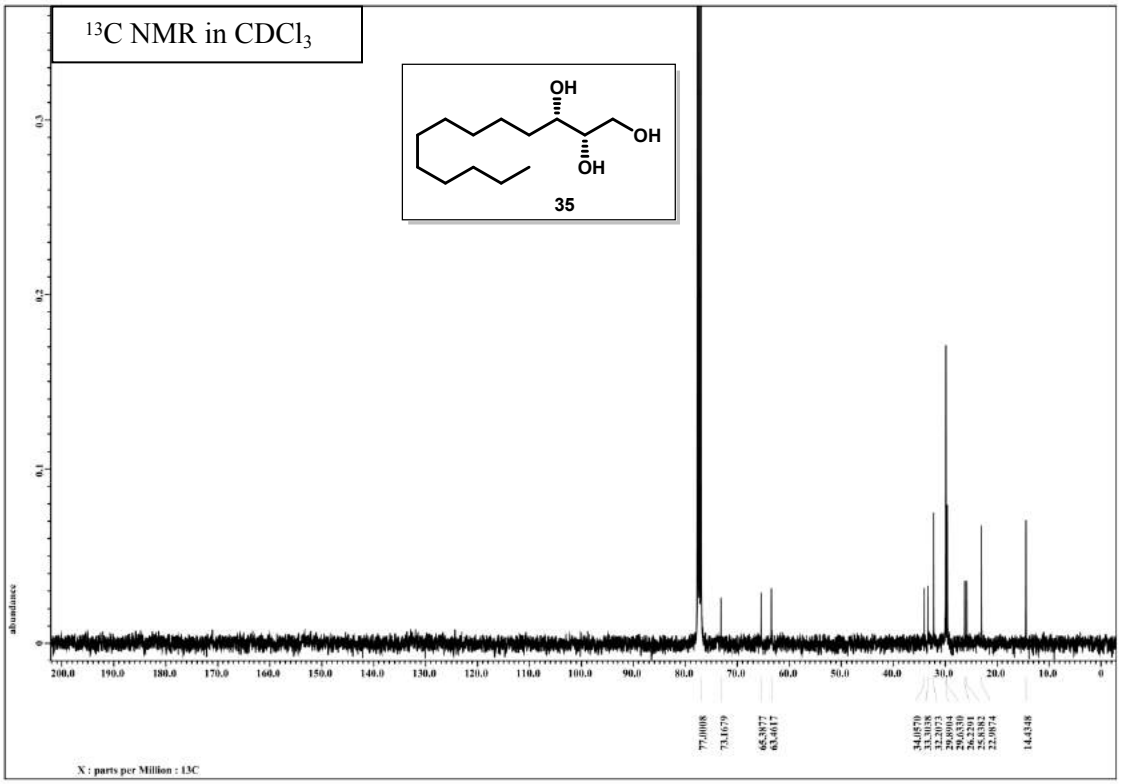
^{1}H NMR in $CDCl_3$



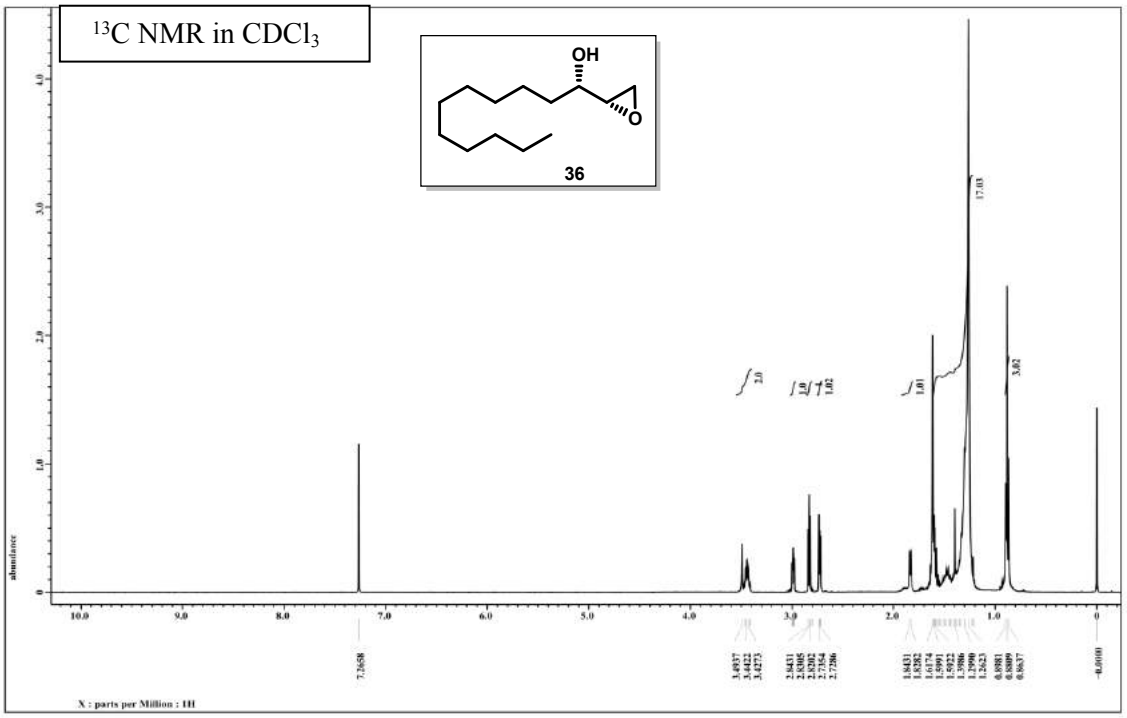
^{13}C NMR in $CDCl_3$

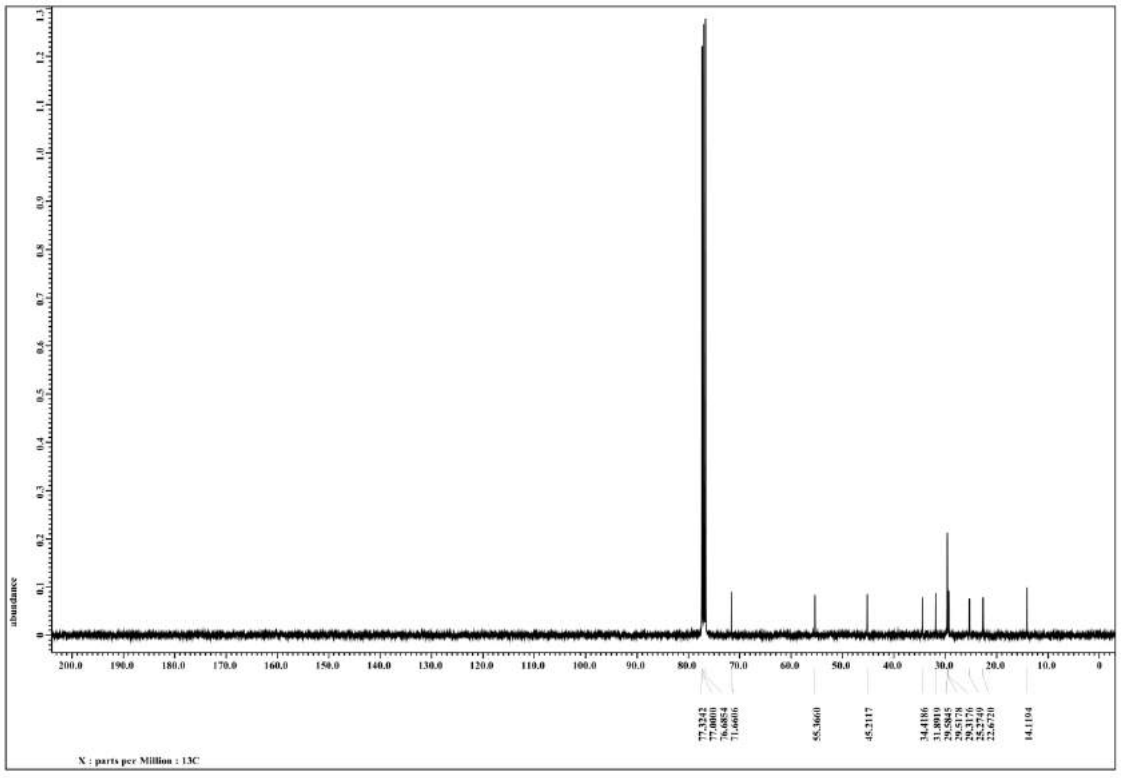



^{1}H NMR in $CDCl_3$
OH
OH
OH
35
abundance
X : parts per Million : 1H

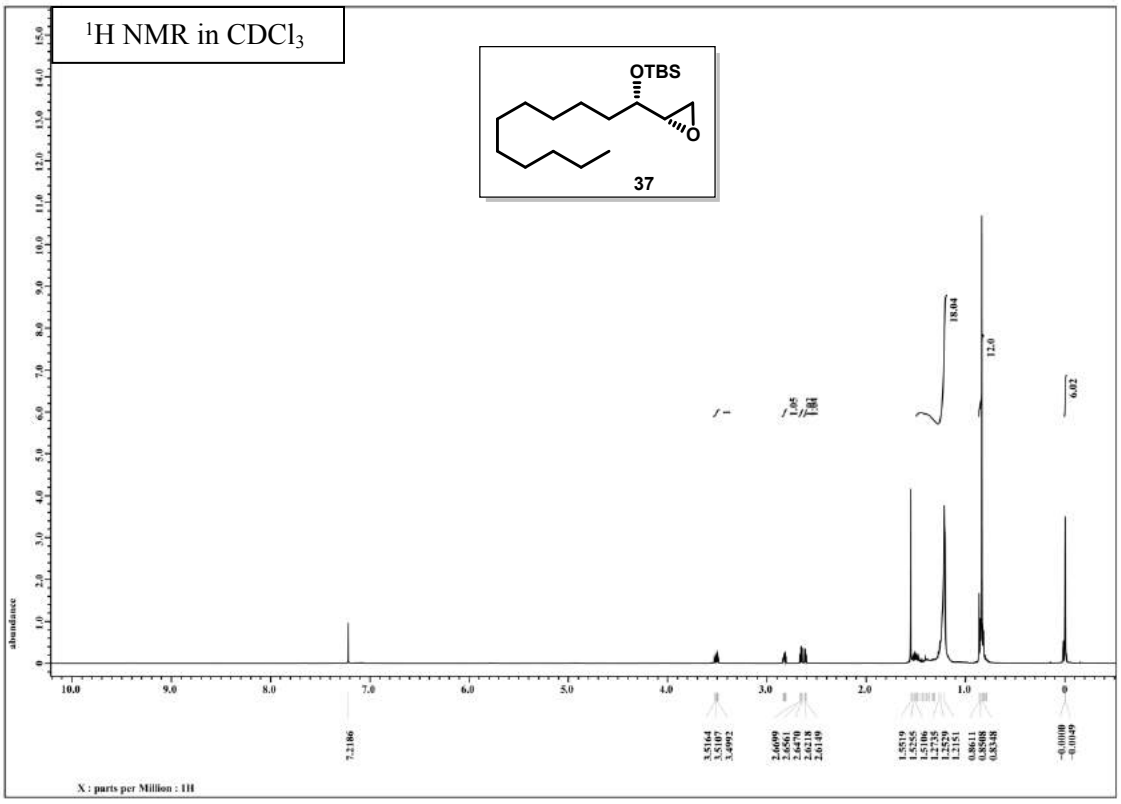

^{13}C NMR in $CDCl_3$
OH
OH
OH
35
abundance
X : parts per Million : 13C

^{13}C NMR in $CDCl_3$

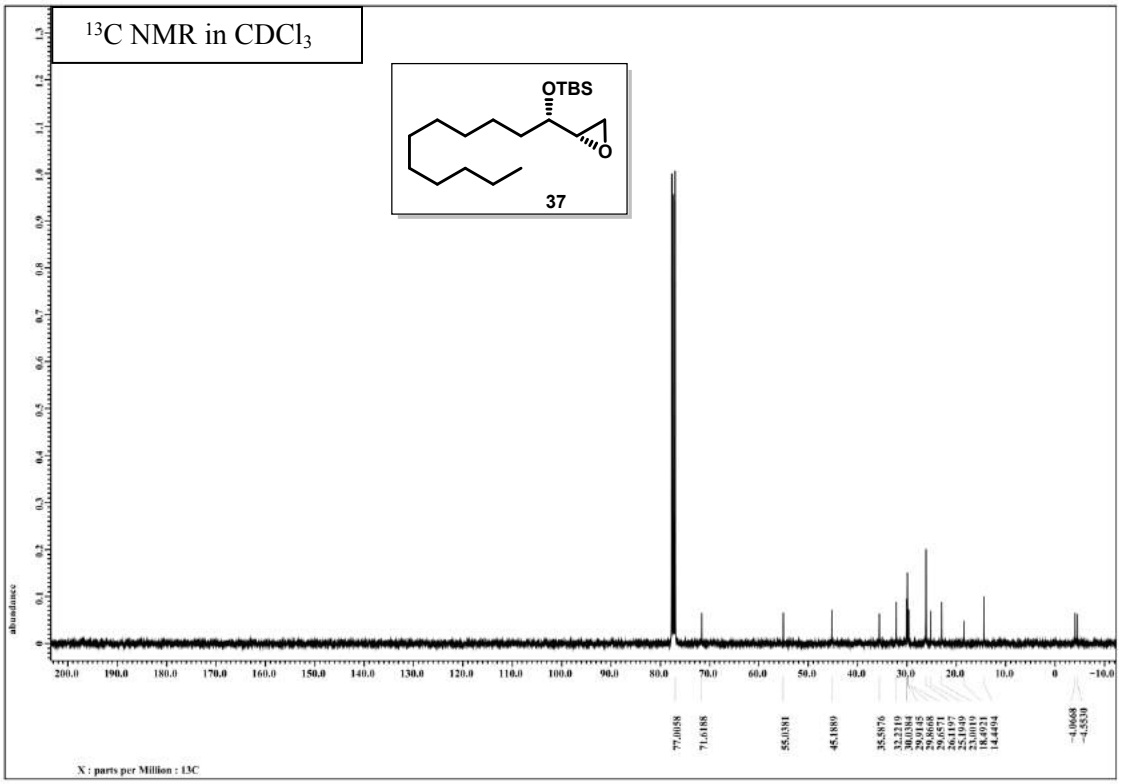


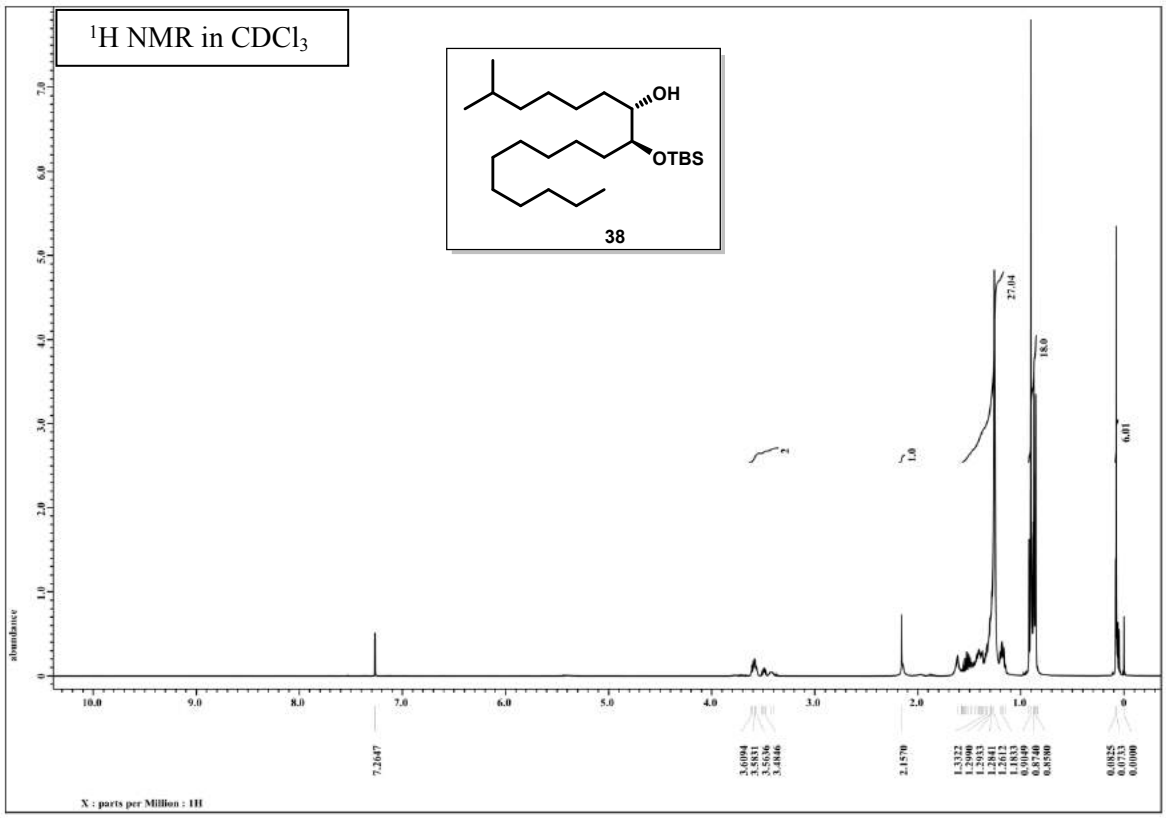


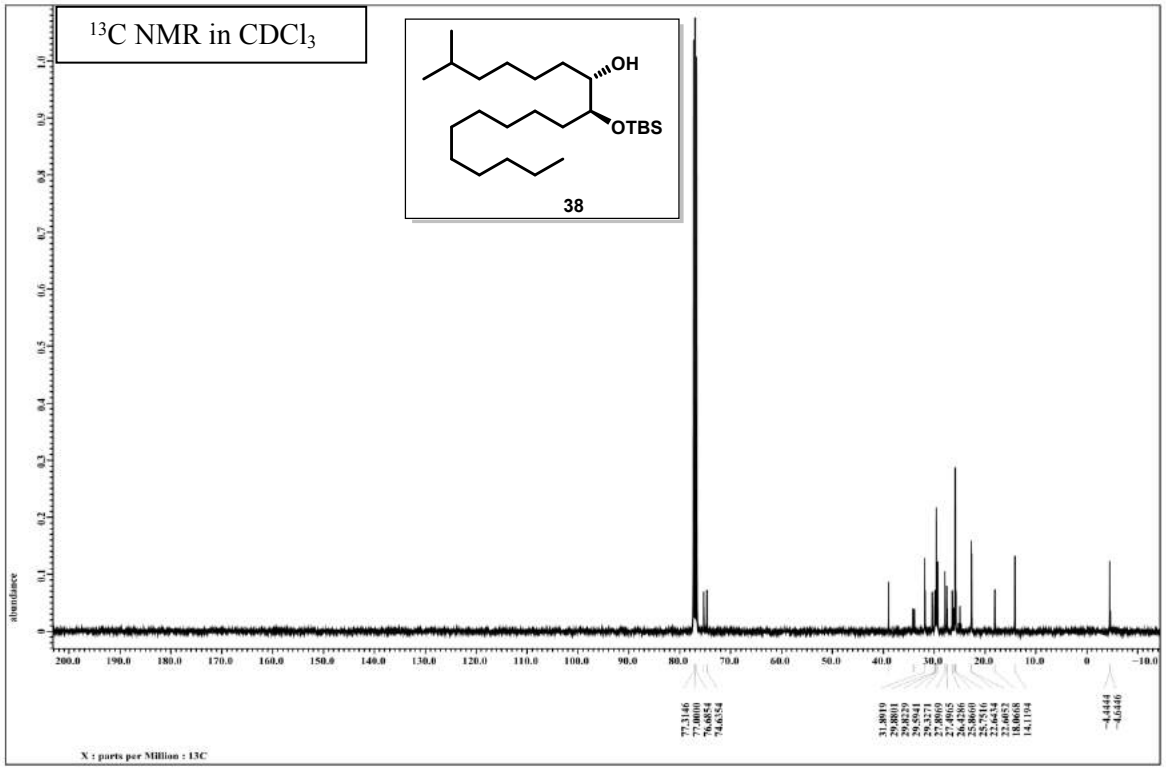
^{1}H NMR in $CDCl_3$

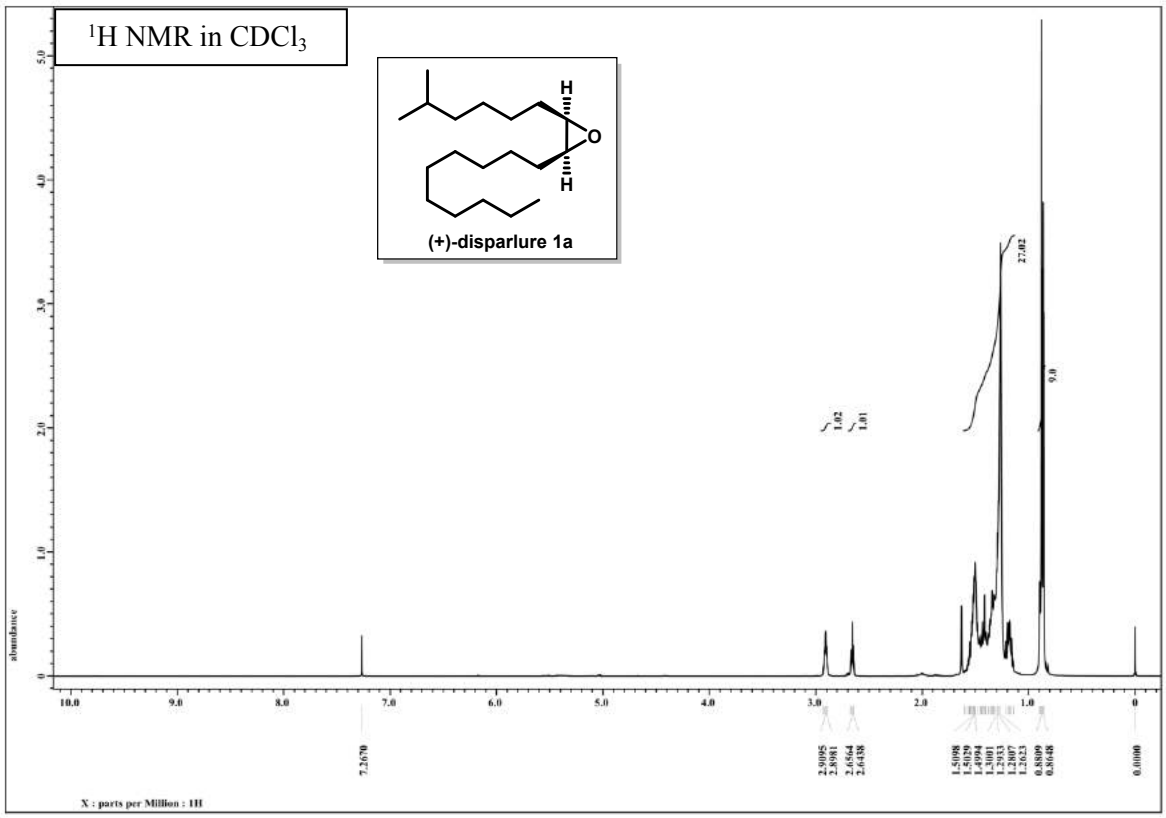


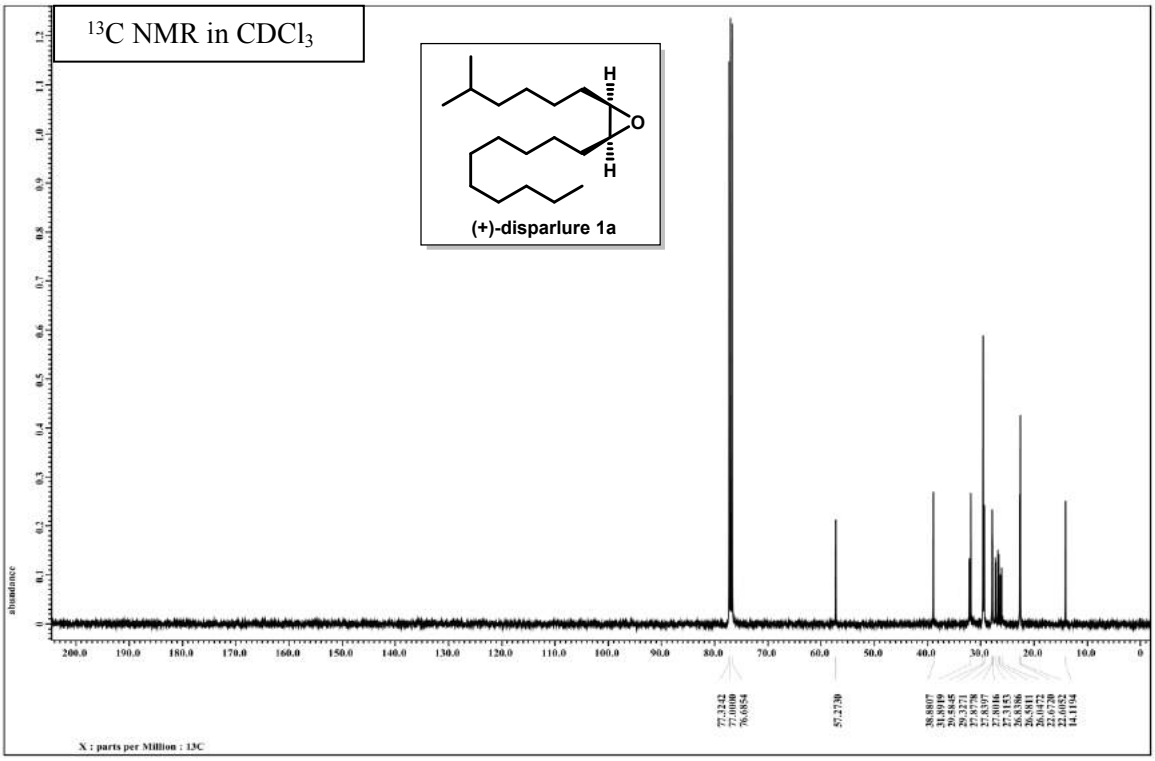
^{13}C NMR in $CDCl_3$




^{1}H NMR in $CDCl_3$
OH
OTBS
38
27.04
18.0
6.01
2
1.0
abundance
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.2647
3.6094
3.5831
3.5636
3.4446
2.1570
1.3322
1.2990
1.2933
1.2841
1.2612
1.1833
0.9049
0.8740
0.8580
0.0825
0.0753
0.0000
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OH
OTBS
38
abundance
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
−10.0
77.5146
77.0000
76.4854
74.6254
31.8919
29.8801
29.6229
29.3641
29.3271
27.8969
27.4965
26.4286
25.8060
25.7516
22.6634
22.6052
18.0668
14.1194
−4.4444
−4.6346
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
(+)-disparlure 1a
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
(+)-disparlure 1a
abundance
X : parts per Million : 13C

5.2 Section B

Enantioselective synthesis of (+)-disparlure *via* asymmetric organocatalysis.

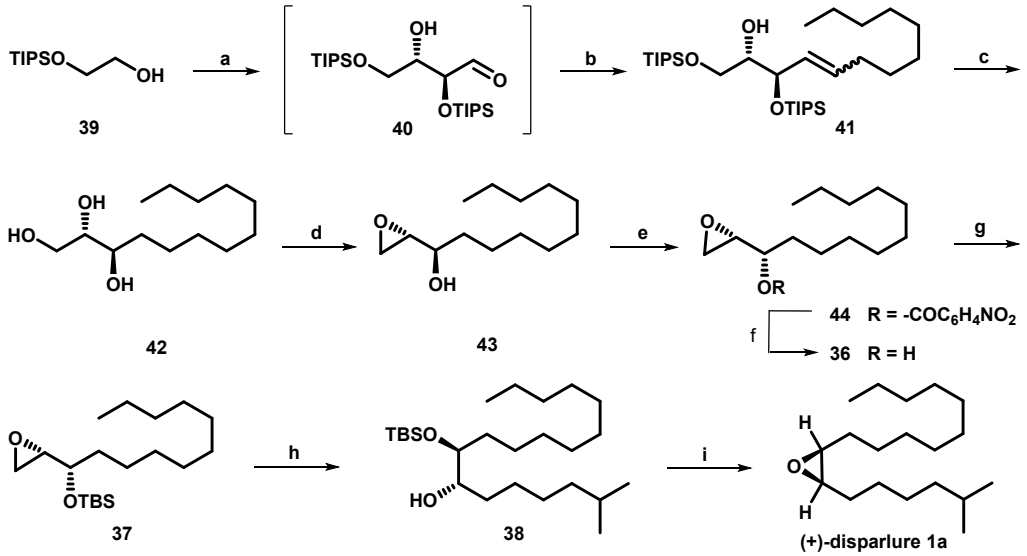
5.2.1 Present Work:

As part of our research programme aimed at developing enatioselective synthesis of naturally occurring compounds, we report herein an another novel approach for asymmetric synthesis of (+)-disparlure **1c** and **1c** by employing Macmillan's self aldol, Wittig olefination and regioselective opening reaction of an epoxide as key steps. All the stereoisomers of disparlure (**1a-d**) could be synthesized by using this approach by simply changing the D-proline and L-proline, respectively, during organocatalytic Macmillan's self aldol reaction and/or by Mitsunobu inversion.

5.2.2 Results and Discussion:

As outlined in Scheme 6, the synthesis of (+)-disparlure **1a** commenced with readily available monosilylated ethylene glycol **39**, which can be easily synthesized from base catalyzed selective protection of ethylene glycol with TIPS-Cl.[6] Oxidation of monosilylated alcohol **39** under Swern conditions,[7] subsequent asymmetric Macmillan's self aldol reaction[8] of aldehyde in the presence of catalytic amount of L-proline afforded the *anti*-diastereomer **40** as the major product along with its column separable *syn*-diastereomer in 4:1 ratio and 90% combined isolated yield, following the known literature procedure.[8] With enantiomerically pure *anti*-diastereomer **40** in hand, it was then subjected to Wittig olefination with (nonyl)triphenylphosphonium bromide using KHMDS to furnish the olefin **41** in 65% yield. Since the incipient olefin would be eventually hydrogenated for the synthesis of the target compound, we did not analyse the olefin geometry of **41**. The cleavage of silyl ether in compound **41** with TBAF and subsequent hydrogenation under 1 atm pressure in the presence of a catalytic amount of Pd/C furnished the triol derivative **42** in 90% yield. Our next aim was to carry out epoxide formation using terminal diols. Towards this end, triol **42** on base catalyzed selective monotosylation with tosyl chloride (TsCl) in the presence of catalytic amount of

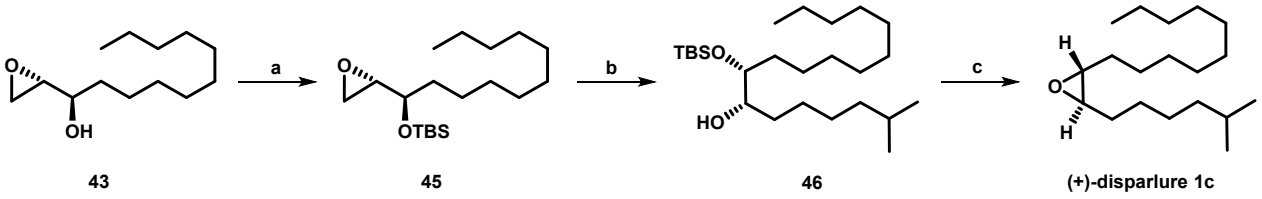
dibutyltin oxide followed by base treatment delivered the epoxide **43** in 76% yield. The free hydroxyl group of compound **43** on treatment with *p*-nitrobenzoic acid (PNBA) and diisopropyl azodicarboxylate (DIAD) under the Mitsunobu esterification conditions successfully furnished the ester **44**, which on basic hydrolysis synthesized the inverted alcohol **36** in 95% yield.



Scheme 6. *Reagents and conditions*: (a) i) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 ^oC, 2 h, ii) L-proline (10 mol%), DMF, rt, 24 h, 72%; (b) KHMDS, $C_9H_{19}PPh_3Br$, THF, -78 ^oC to rt, 4 h, 65% (c) i) TBAF, THF, rt, 12 h; ii) H_2, Pd/C, EtOAc, rt, 8 h, 90% (over two steps); (d) i) TsCl, NEt_3, Bu_2SnO (10 mol%), dry CH_2Cl_2, 0 ^oC to rt, 2 h, ii) KOH, Et_2O, rt, 12 h, 76% (over two steps); (e) PPh_3, PNBA, DIAD, toluene, 0 ^oC to rt, 2 h, 97%; (f) $LiOH.H_2O$, THF:MeOH:H_2O (3:2:1), rt, 1 h, 95%; (g) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 14 h, 89%; (h) *iso*-hexylMgBr, dry THF, CuI, -60 ^oC, 6 h, 81%; (i) i) TsCl, DMAP, dry CH_2Cl_2, 0 ^oC to rt, 24 h, ii) TBAF, THF, rt, 6 h, 85% (over two steps).

Treatment of alcohol **36** with TBSCl using the basic conditions of imidazole/DMAP synthesized the protected derivative **37** in 89% yield. The epoxide **37** on Cu(I)-catalyzed regioselective ring opening with *iso*-hexylMgBr at -60 ^oC, furnished the alcohol **38** in 81% yield. Finally, the free hydroxyl group of compound **38** was subjected to *O*-tosylation using TsCl/DMAP and subsequent silyl ether cleavage using TBAF delivered the sex pheromone *cis*-(+)-disparlure **1a** in 85% yield $\{[\alpha]_D^{25}$ +1.2 (*c* 1.1, CCl_4) [Lit.[3a]

+1.6 (*c* 1.1, CCl_4)]}. The spectroscopic and physical data of *cis*-(+)-disparlure **1a** were found to be in full accordance with those documented in the literature.[3]



Scheme 7. *Reagents and conditions*: (a) TBSCl, imidazole, DMAP, dry CH_2Cl_2, 0 °C to rt, 14 h, 87%; (b) *iso*-hexylMgBr, dry THF, CuI, -60 °C, 6 h, 85%; (c) i) TsCl, DMAP, dry CH_2Cl_2, 0 °C to rt, 24 h, ii) TBAF, THF, rt, 6 h, 84% (over two steps).

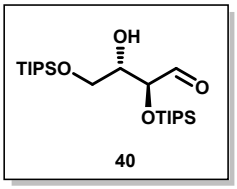
For synthesis of *trans*-(+)-disparlure **1c**, the free hydroxyl group of compound **43** on treatment with TBSCl under the basic conditions of imidazole/DMAP furnished the silyl ether derivative **45** in 87% yield (Scheme 7). The *trans*-(+)-disparlure **1c** was synthesized from compound **45** following an analogous series of reactions as shown in Scheme 6. The spectroscopic and physical data of *trans*-(+)-disparlure **1c** were found to be in full accordance with the literature data.[3]

5.2.3 Conclusions:

In conclusion, a practical and enantioselective synthesis of (+)-disparlure **1a** and **1c** have been achieved from readily available starting materials employing Macmillan's self aldol, Wittig olefination and regioselective opening reaction of an epoxide as key steps. The overall yield for the (+)-disparlure **1a** was 18% after seven column chromatographic purification steps. The merits of this synthesis are high enantio- and diastereoselectivity with high yielding reaction steps. Moreover, the synthetic strategy described has significant potential for stereochemical variation and further extension to synthesize other stereoisomers and analogues of disparlure (**1a-d**).

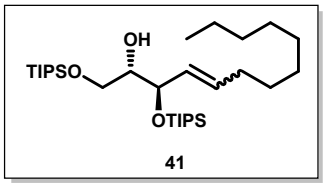
5.2.4 Experimental Section:

(2*S*,3*S*)-3-hydroxy-2,4-bis(triisopropylsilyloxy)butanal (40): To a solution of oxalyl chloride (635 mg, 435 µL, 5.0 mmol) in dry CH_2Cl_2 (10 mL) at -78 °C was added dropwise DMSO (800 mg, 735 µL, 10.3 mmol) in CH_2Cl_2 (10 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of monosilylated ethylene glycol **39** (720 mg, 3.3 mmol)



in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -60°C and then Et_3N (1.37 g, 1.9 mL, 13.6 mmol) was added dropwise and stirred for 30 min. The reaction mixture was diluted with water and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 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 a DMF (20 mL) solution of above synthesized aldehyde was added L-proline (38 mg, 0.33 mmol, 10 mol%) and stirred for 24 h at room temperature. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed successively with water (15 mL) and brine (15 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to furnish the *anti-/syn*-diastereomeric mixture as yellow oil. The *anti-/syn*-diastereomers were then separated and purified by silica gel column chromatography using (EtOAc/hexane 1:99 v/v) as eluent to furnish the *syn*-diastereomer (130 mg, 18%) and the more quickly eluted *anti*-diastereomer **40** (520 g, 72%) as yellow oil.

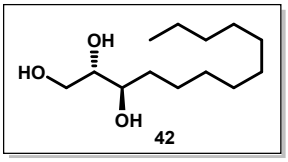


41

(5*R*,6*S*)-5-(dec-1-enyl)-3,3,9,9-tetraisopropyl-2,10-dimethyl-4,8-dioxa-3,9-disilaundecan-6-ol (41): PPh_3 (875 mg, 3.3 mmol) was added to a stirred solution of 1-bromononane (690 mg, 3.3 mmol) in MeCN (10 mL) and the resultant mixture was heated at reflux for 48 h before being concentrated *in vacuo* to give (nonyl)triphenylphosphonium bromide (1.56 g) as yellow viscous oil.

KHMDS (3.3 mL, 3.3 mmol, 1 M in THF) was added dropwise to a solution of (nonyl)triphenylphosphonium bromide (1.56 g) in THF (20 mL) at -78 °C and the reaction mixture was left to warm to rt over 1 h before being cooled to -78 °C and a solution of above synthesized aldehyde **40** (1.0 g, 2.31 mmol) in THF (10 mL) was added dropwise. After 5 min, the cooling bath was removed and the reaction mixture was left to warm to rt over 3 h before the addition of H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were then dried over Na_2SO_4, concentrated *in vacuo* and purified *via* silica gel column chromatography (EtOAc/hexane 1:30 v/v) as eluent furnished the compound **41** (815 mg, 65%) as yellow oil.

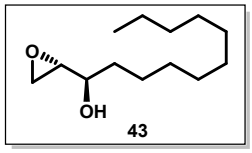
(2*S*,3*R*)-Tridecane-1,2,3-triol (42): To a solution of compound **41** (400 mg, 0.742 mmol) in THF (10 mL) was added TBAF solution (2.3 mL, 1.0 M in THF, 2.3 mmol) drop wise *via* syringe. The mixture was stirred for 12 h at room temperature and then the mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, concentrated under reduced pressure and used as such for the next step without further purification.



42

To an EtOAc (10 mL) solution of above crude was added 10% Pd/C (40 mg) and subjected to hydrogenation under 1 atmosphere H_2 pressure for 8 h. After this time, reaction mixture was filtered through a pad of Celite, washed with additional MeOH (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography purification (EtOAc/hexanes 4:1 v/v) of the crude product furnished triol **42** (155 mg, 90%) as a white solid. $[\alpha]_D^{25}$ -71.2 (*c* 0.5, CH_3OH); IR (CH_2Cl_2) *v*; 3472, 3249, 2968, 2861, 1475, 1361, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.86-3.55 (m, 4H), 2.79 (br s, 1H), 2.32 (br s, 2H), 1.55-1.27 (m, 18H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.9, 65.0, 63.1, 33.7, 32.9, 31.8, 29.5, 29.3, 25.9, 25.5, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{13}H_{28}O_3Na^+$ $[M+Na^+]$ 255.1930; found 255.1929.

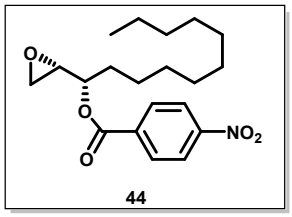
(*R*)-1-((*S*)-Oxiran-2-yl)undecan-1-ol (43): To a CH_2Cl_2 (10 mL) solution of triol **42** (130 mg, 0.56 mmol) were added NEt_3 (77 µL, 0.56 mmol), *p*-TsCl (107 mg, 0.56 mmol) and catalytic amount of dibutyltin oxide (14 mg, 0.056 mmol, 10 mol%) sequentially at 0 ^oC. The reaction mixture was stirred till completion (2 h) of the starting material, diluted with water and extracted with dichloromethane (3 x 15 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated to near dryness. The crude product was as such for the next step without further purification.



43

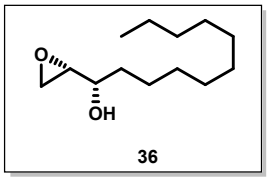
To an Et_2O (10 mL) solution of above tosylated crude was added finely powdered KOH (94 mg, 1.68 mmol) and stirred vigorously for 12 h. The reaction mixture was then poured into 20 mL water, extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (EtOAc/hexanes 1:4 v/v) of the crude product furnished epoxide **43** (90 mg, 76%) as a yellow oil. $[\alpha]_D^{25}$ -47.5 (*c* 0.6, CH_3OH); IR (CH_2Cl_2) *v*; 3305, 2963, 2927, 2834, 1477, 1357, 1077, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.84-

3.83 (m, 1H), 3.04-3.02 (m, 1H), 2.82-2.79 (m, 1H), 2.73-2.72 (m, 1H), 1.86-1.83 (m, 1H), 1.66-1.64 (m, 2H), 1.61-1.26 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.3, 54.5, 43.3, 33.4, 31.8, 29.6, 29.5, 29.5, 29.3, 25.2, 22.6, 14.1. HRMS (ESI)$^+$ m/z calcd for $C_{13}H_{27}O_2^+$ [M+H$^+$] 215.2006; found 215.2012.



44

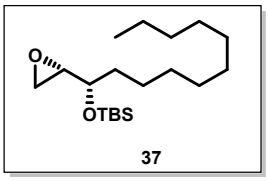
(*S*)-1-((*S*)-Oxiran-2-yl)undecyl-4-nitrobenzoate (44): To a toluene (15 mL) solution of alcohol **43** (80 g, 0.37 mmol) were added PPh_3 (393 mg, 1.5 mmol), *p*-nitrobenzoic acid (PNBA) (310 mg, 1.85 mmol) and diisopropylazodicarboxylate (DIAD) (0.3 ml, 1.5 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 2 h. The reaction mixture was then concentrated and purified by silica gel column chromatography using (EtOAc/hexane 1:9 v/v) as eluent to furnish the ester **44** (130 mg, 97%) as oil. {$[\alpha]_D^{25}$ +58.1 (*c* 0.5, $CHCl_3$); IR (CH_2Cl_2) *v*: 3064, 3017, 2957, 2861, 1723, 1636, 1623, 1529, 1455, 1341, 1272 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31-8.22 (m, 4H), 4.98-4.94 (m, 1H), 3.24-3.21 (m, 1H), 2.91-2.89 (m, 1H), 2.72-2.71 (m, 1H), 1.86-1.79 (m, 2H), 1.44-1.21 (m, 16H), 0.87 (t, J = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 150.5, 135.4, 130.8, 123.5, 76.1, 52.9, 45.0, 31.8, 31.4, 29.5, 29.4, 29.4, 29.3, 29.2, 25.1, 22.6, 14.1. HRMS (ESI)$^+$ m/z calcd for $C_{20}H_{30}NO_5$ [M+H$^+$] 364.2119; found 364.2131.



36

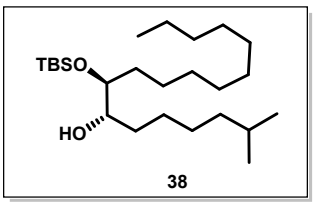
(*S*)-1-((*S*)-Oxiran-2-yl)undecan-1-ol (36): To a THF:MeOH:H_2O (3:2:1, 3 mL) solution of *p*-nitro benzoate ester **44** (120 mg, 0.33 mmol) was added LiOH.H_2O (21 mg, 0.5 mmol) at room temperature and stirred for 1 h. The reaction was then quenched with water, extracted with EtOAc (3 x 10 ml), washed with brine, dried over Na_2SO_4, concentrated and purified by silica gel column chromatography using (EtOAc/hexane 1:4 v/v) as eluent furnished the alcohol **36** (67 mg, 95%) as oil. $[\alpha]_D^{25}$ -83.9 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*; 3325, 2931, 2978, 2856, 1489, 1379, 1051, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.49-3.41 (m, 2H), 3.00-2.97 (m, 1H), 2.84-2.82 (m, 1H), 2.73-2.71 (m, 1H), 1.84-1.82 (m, 1H), 1.60-1.20 (m, 17H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.6, 55.3, 45.2, 34.4, 31.8, 29.5, 29.5, 29.3, 25.2, 22.6, 14.1. HRMS (ESI)$^+$ m/z calcd for $C_{13}H_{27}O_2^+$ [M+H$^+$] 215.2006; found 215.2026.

***tert*-Butyldimethyl(((*S*)-1-((*S*)-oxiran-2-yl)undecyl)oxy)silane (37):** To a solution of alcohol **36** (60 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was added imidazole (38 mg, 0.56 mmol), 4-dimethylaminopyridine DMAP (17 mg, 0.14 mmol) followed by *tert*-butyldimethylsilyl chloride (56 mg, 0.36 mmol) at 0 ^oC. The reaction was then stirred under N_2 for 14 h, after which it was quenched by adding aqueous saturated NH_4Cl (10 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (EtOAc/hexane 1:19 v/v) as eluent furnished **37** (82 mg, 89%) as pale yellow oil. $[\alpha]_D^{25}$ -41.4 (*c* 1.0, CH_3OH); IR (CH_2Cl_2) *v*: 2956, 2914, 2858, 1459, 1377, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 3.52-3.48 (m, 1H), 2.83-2.80 (m, 1H), 2.67-2.64 (m, 1H), 2.61-2.60 (m, 1H), 1.52-1.21 (m, 18H), 0.86-0.81 (m, 12H), -0.004 (d, *J* = 1.36 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 71.6, 55.0, 45.1, 35.5, 32.2, 30.0, 29.9, 29.8, 29.6, 26.1, 25.1, 23.0, 18.4, 14.4, -4.06, -4.5. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{41}O_2Si^+$ $[M+H^+]$ 329.2871; found 329.2862.



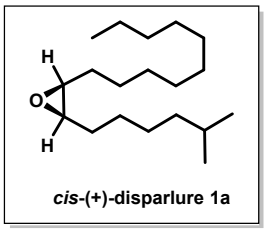
37

(7*S*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-methyloctadecan-7-ol (38): To a stirred solution of TBS-protected epoxide **37** (75 mg, 0.23 mmol) in dry THF (5 mL) and CuI (66 mg, 0.35 mmol) at -60 ^oC was added *i*-hexylmagnesiumbromide (1 M in THF), freshly prepared from *i*-hexylbromide (112 mg, 100 µL, 0.68 mmol) and magnesium (20 mg, 0.81 mmol) in dry THF. The reaction mixture was then stirred for 6 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by silica gel column chromatography using (EtOAc/hexane 1:19 v/v) as eluent to furnish the alcohol **38** (77 mg, 81%) as pale yellow oil. {$[\alpha]_D^{25}$ -5.1 (*c* 0.16, $CHCl_3$) [Lit.[3a] -5.6 (*c* 0.16, $CHCl_3$)]}; IR (CH_2Cl_2) *v*: 3435, 2967, 2912, 2856, 1456, 1378, 1333, 1278, 1125, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 3.71-3.44 (m, 2H), 2.15 (s, 1H), 1.51-1.19 (m, 27H), 0.91-0.77 (m, 18H), 0.082 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 75.2, 74.6, 38.9, 34.1, 33.8, 31.8, 29.8, 29.8, 29.5, 29.3, 27.8, 27.4, 26.4, 26.1, 25.8, 25.7, 22.6, 22.6, 18.0, 14.1, -4.4, -4.6. HRMS $(ESI)^+$ m/z calcd for $C_{25}H_{55}O_2Si^+$ $[M+H^+]$ 415.3966; found 415.3969.



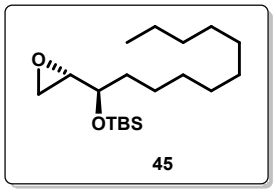
38

***cis*-(+)-Disparlure (1a):** To a CH_2Cl_2 (5 mL) solution of alcohol **38** (70 mg, 0.17 mmol) was added 4-(dimethylamino)pyridine DMAP (82 mg, 0.68 mmol) and *p*-toluenesulfonyl chloride (39 mg, 0.20 mmol) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was used as such for the next step without further purification.

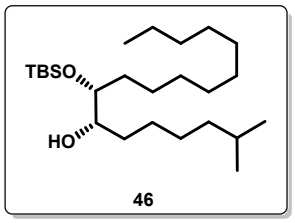


To a stirred solution of above tosylated crude in dry THF (10 mL) was added TBAF (1.0 M in THF, 0.85 mL, 0.85 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was slowly warmed to room temperature and stirred for 6 h. It was then quenched with water and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/hexane 1:40 v/v) as eluent furnished the sex pheromone **1a** (40 mg, 85%) as oil. {$[\alpha]_D^{25}$ +1.2 (*c* 1.1, CCl_4) [Lit.[3a] +1.6 (*c* 1.1, CCl_4)]}; IR (CH_2Cl_2) *v*: 2975, 2945, 2844, 1474, 1362, 1314, 1245, 1171, 1051, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.92-2.88 (m, 1H), 2.66-2.63 (m, 1H), 1.57-1.12 (m, 27H), 0.89-0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 57.2, 38.8, 31.8, 29.5, 29.3, 27.8, 27.8, 27.8, 27.3, 26.8, 26.5, 26.0, 22.6, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{39}O^+$ $[M+H^+]$ 283.2996; found 283.2994.

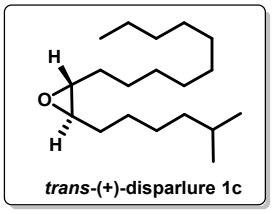
***tert*-Butyldimethyl(((*R*)-1-((*S*)-oxiran-2-yl)undecyl)oxy)silane (45):** This compound was prepared from **43** (60 mg, 0.28 mmol) by a similar procedure as described for the synthesis of **37**, to give **45** (84 mg, 87%) as a yellow oil. $[\alpha]_D^{25}$ -66.2 (*c* 0.5, CH_3OH); IR (CH_2Cl_2) *v*: 2952, 2911, 2857, 1457, 1371, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.51-3.50 (m, 1H), 2.82-2.79 (m, 1H), 2.67-2.65 (m, 1H), 2.64-2.60 (m, 1H), 1.27-1.21 (m, 18H), 0.87-0.83 (m, 12H), -0.003 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 71.2, 54.7, 44.8, 35.2, 31.9, 29.7, 29.5, 29.5, 29.3, 25.7, 24.8, 22.6, 18.1, 14.1, -4.38, -4.87. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{40}O_2SiNa^+$ $[M+Na^+]$ 351.2690; found 351.2688.



(7*S*,8*R*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-methyloctadecan-7-ol (46): This compound was prepared from **45** (75 mg, 0.23 mmol) by a similar procedure as described for the synthesis of **38**, to give **46** (81 mg, 85%) as a yellow oil. $\{[\alpha]_D^{25}$ -1.3 (*c* 0.8, $CHCl_3$) [Lit.[3a] -1.1 (*c* 0.8, $CHCl_3$)]}; IR (CH_2Cl_2) *v*: 3432, 2962, 2908, 2865, 1461, 1357, 1321, 1269, 1113, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.73-3.57 (m, 2H), 1.55-1.17 (m, 27H), 0.86-0.78 (m, 18H), 0.01 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.4, 73.3, 36.8, 32.4, 31.8, 29.8, 29.5, 29.3, 25.8, 24.4, 22.6, 18.0, 14.1, -4.4, -4.5. HRMS $(ESI)^+$ m/z calcd for $C_{25}H_{55}O_2Si^+$ $[M+H^+]$ 415.3966; found 415.3956.

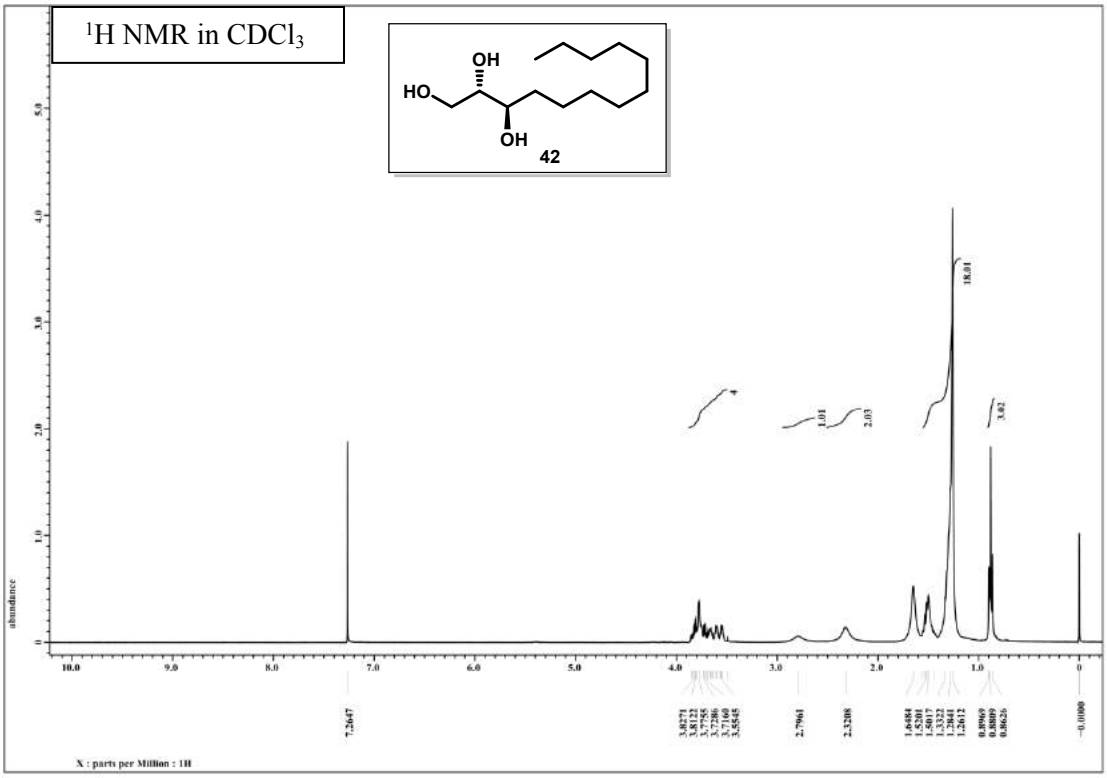


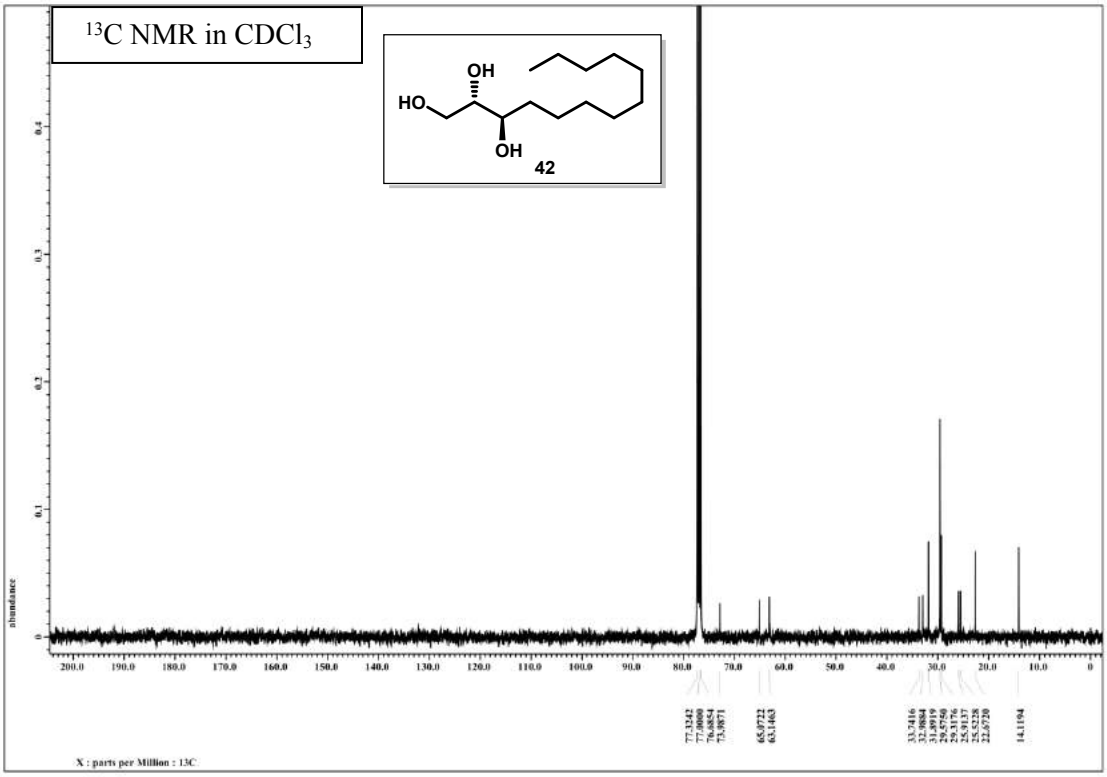
***trans*-(+)-Disparlure (1c):** This compound was prepared from **46** (70 mg, 0.17 mmol) by a similar procedure as described for the synthesis of **1a**, to give **1c** (38 mg, 84%) as a yellow oil. $\{[\alpha]_D^{25}$ +27.8 (*c* 0.5, CCl_4); IR (CH_2Cl_2) *v*: 2958, 2908, 2866, 1472, 1372, 1357, 1231, 1151, 1031, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.68-2.63 (m, 2H), 1.60-1.12 (m, 27H), 0.88-0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.8, 38.8, 32.3, 32.1, 31.8, 29.5, 29.5, 29.4, 29.2, 27.8, 27.1, 26.2, 26.0, 22.6, 14.1. HRMS $(ESI)^+$ m/z calcd for $C_{19}H_{39}O^+$ $[M+H^+]$ 283.2996; found 283.2990.

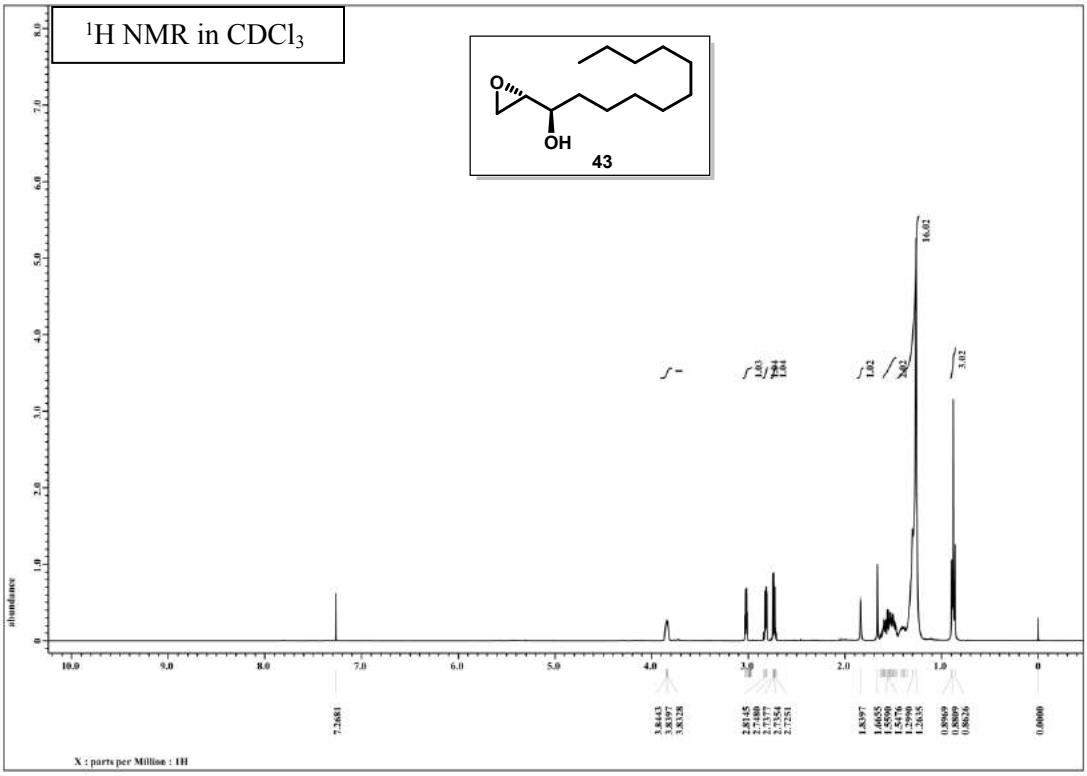


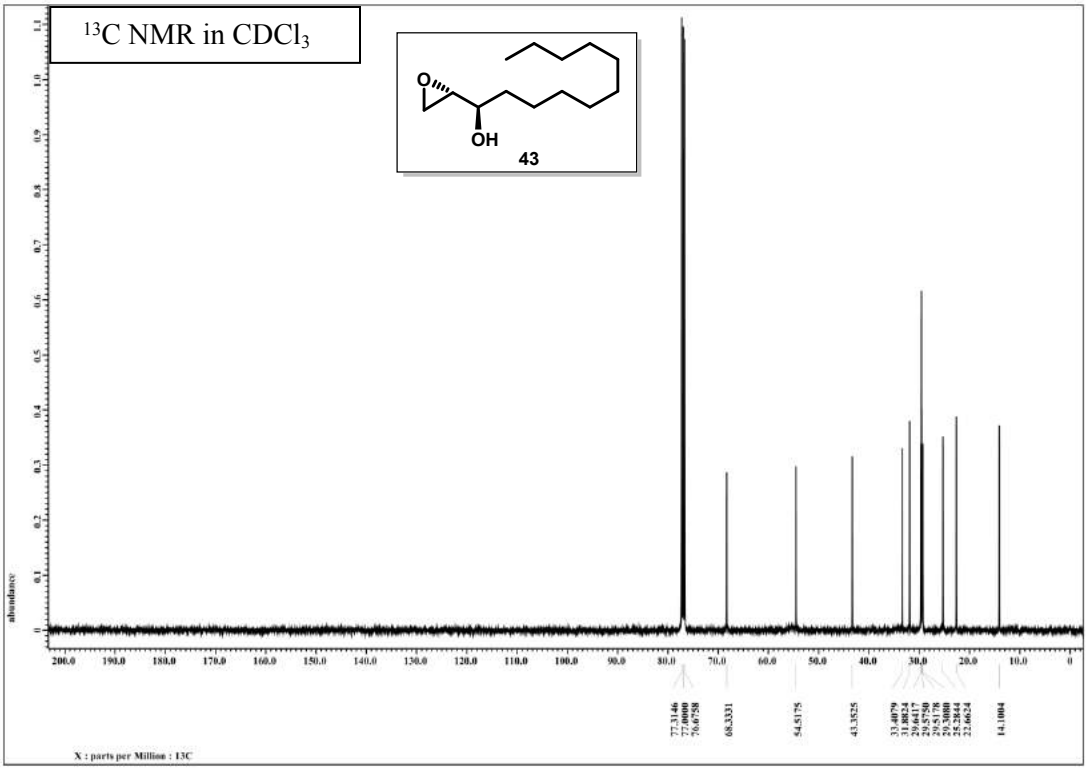
5.2.5 Spectra:

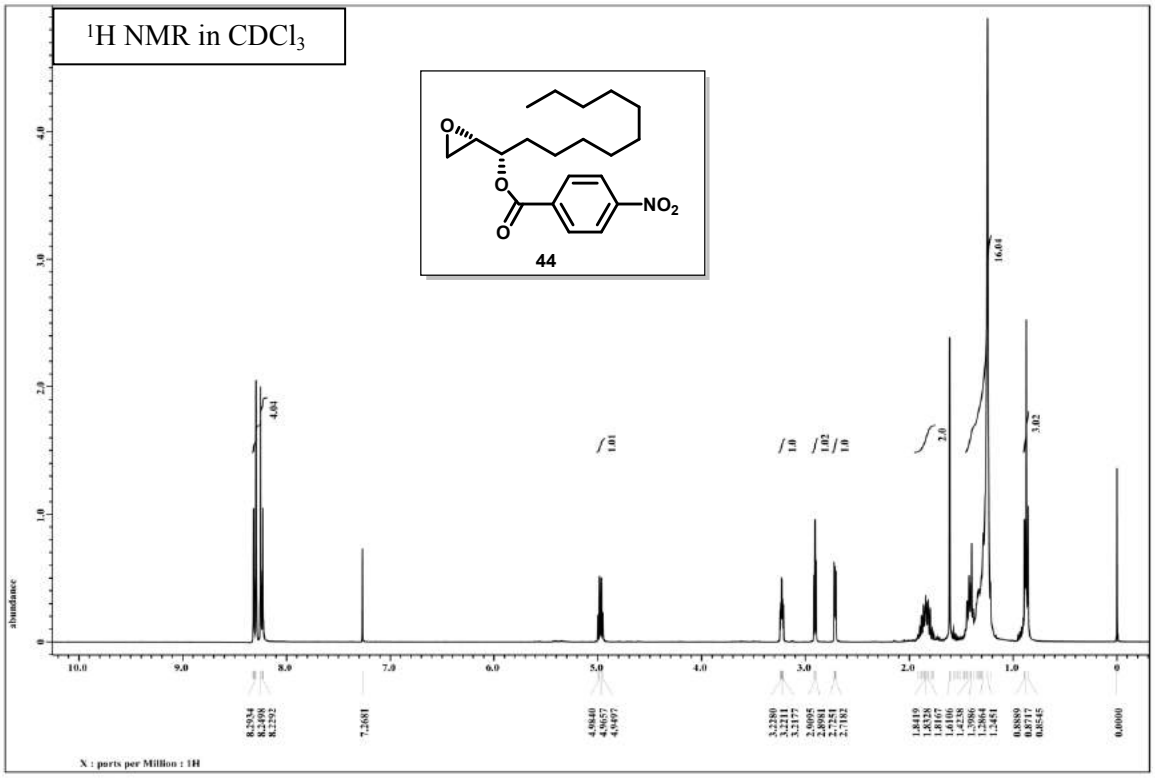
1. ^1H and ^{13}C NMR spectra of **42**
2. ^1H and ^{13}C NMR spectra of **43**
3. ^1H and ^{13}C NMR spectra of **44**
4. ^1H and ^{13}C NMR spectra of **45**
5. ^1H and ^{13}C NMR spectra of **46**
6. ^1H and ^{13}C NMR spectra of **1c**

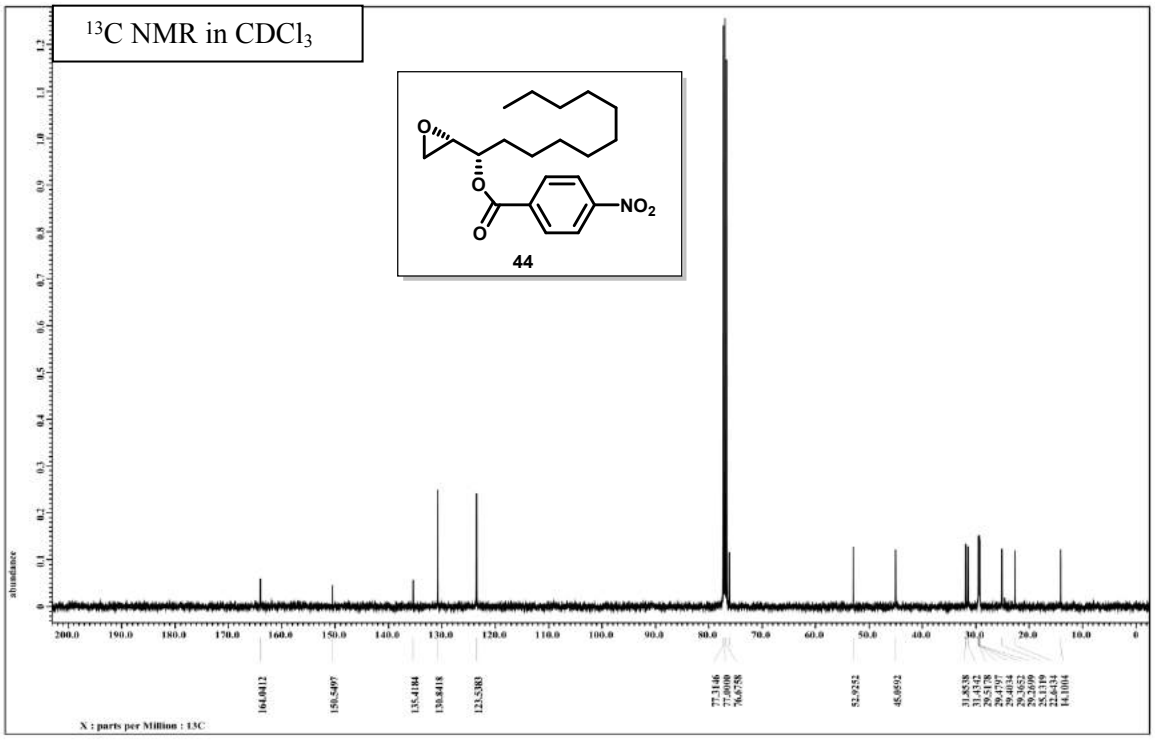

^{1}H NMR in $CDCl_3$
OH
HO
OH
42
abundance
X : parts per Million : 1H

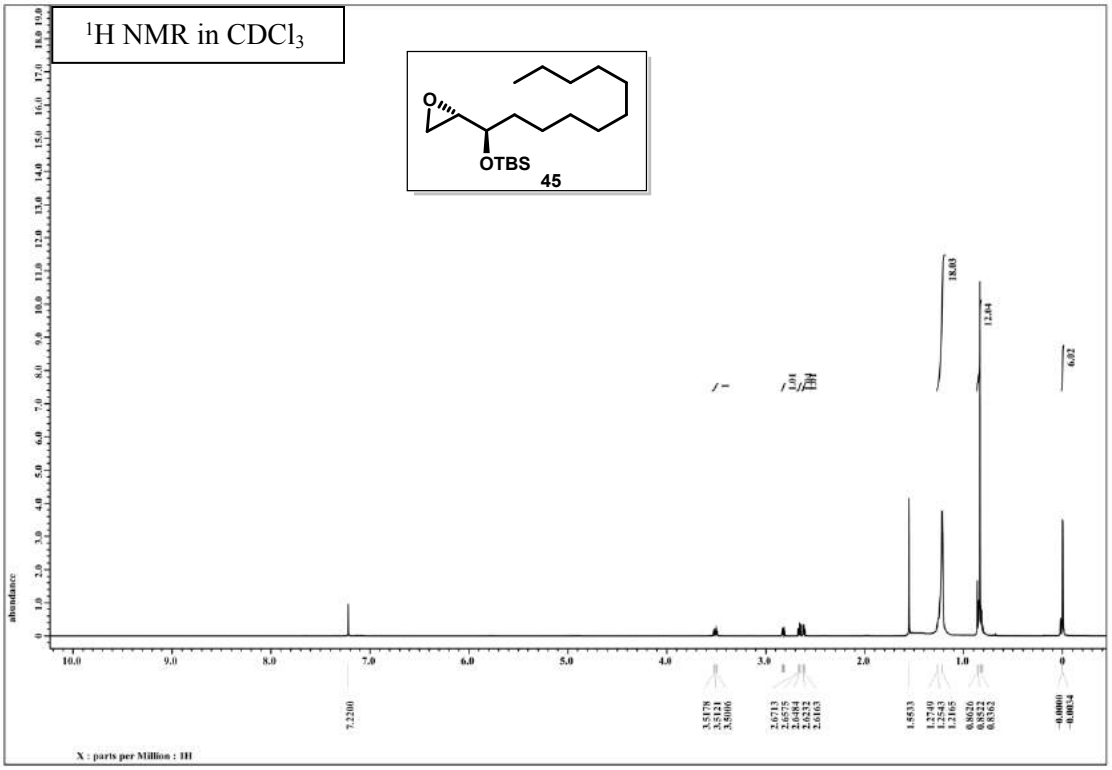

^{13}C NMR in $CDCl_3$
OH
HO
OH
42
abundance
X : parts per Million : 13C

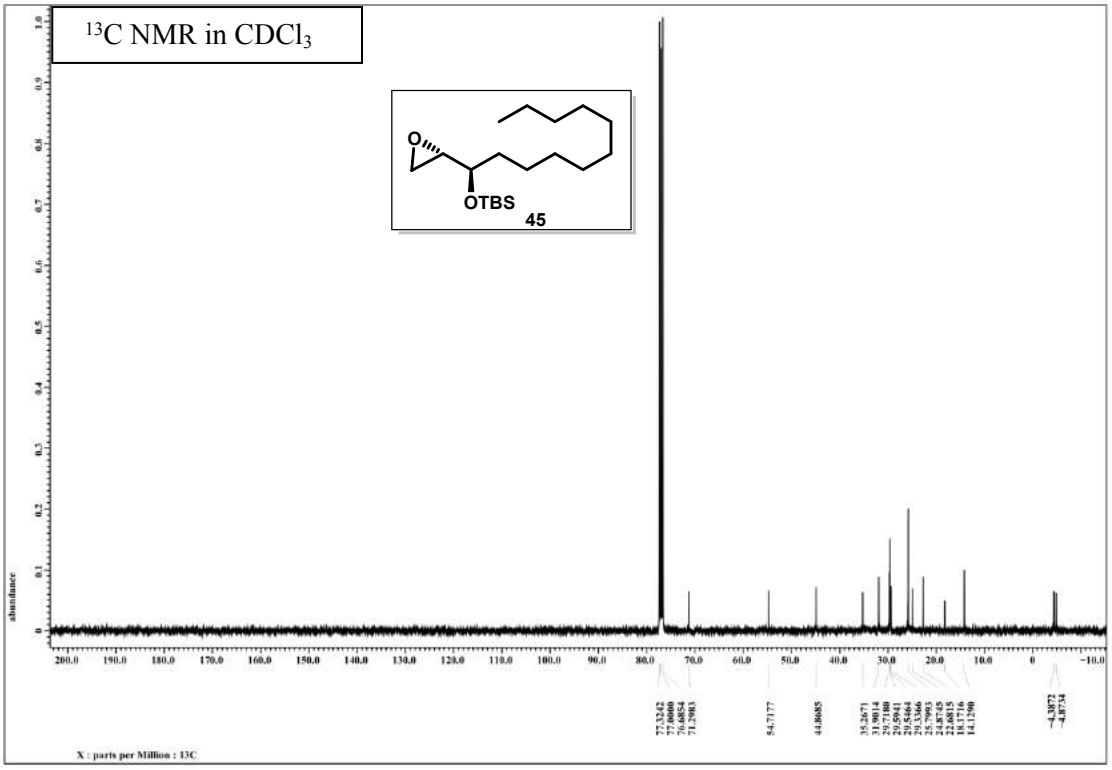

^{1}H NMR in $CDCl_3$
O
OH
43
16.02
3.02
abundance
X : parts per Million : 1H

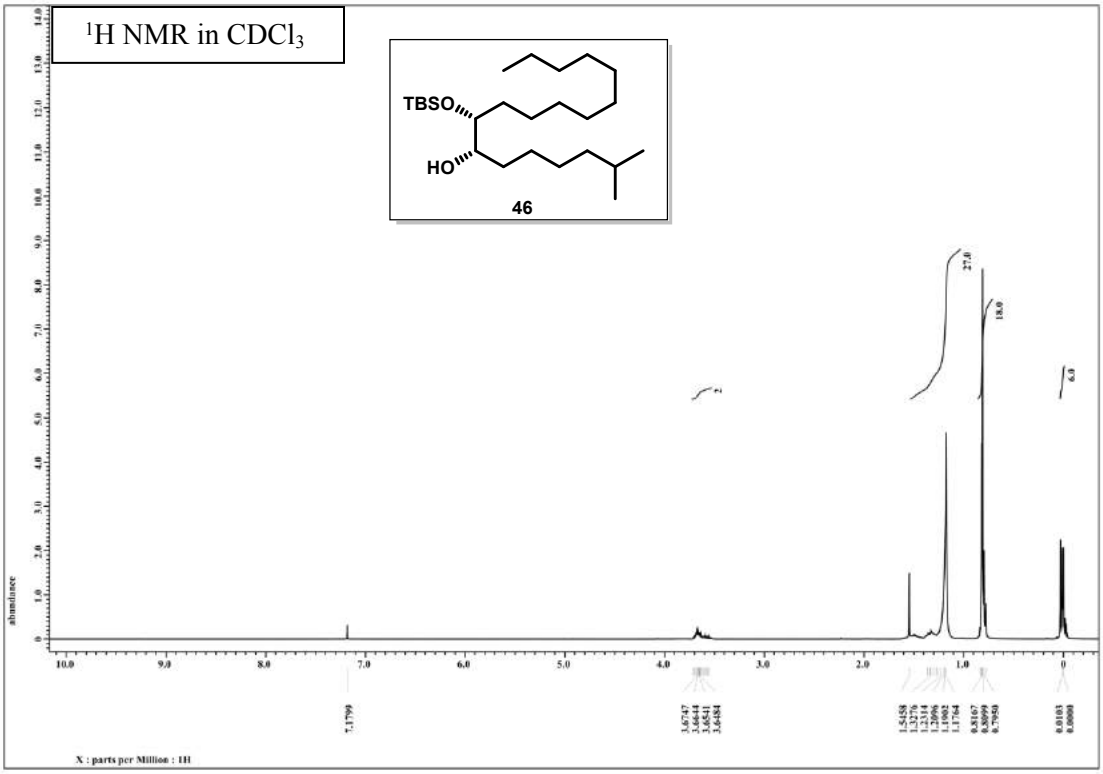

^{13}C NMR in $CDCl_3$
O
OH
43
abundance
X : parts per Million : 13C

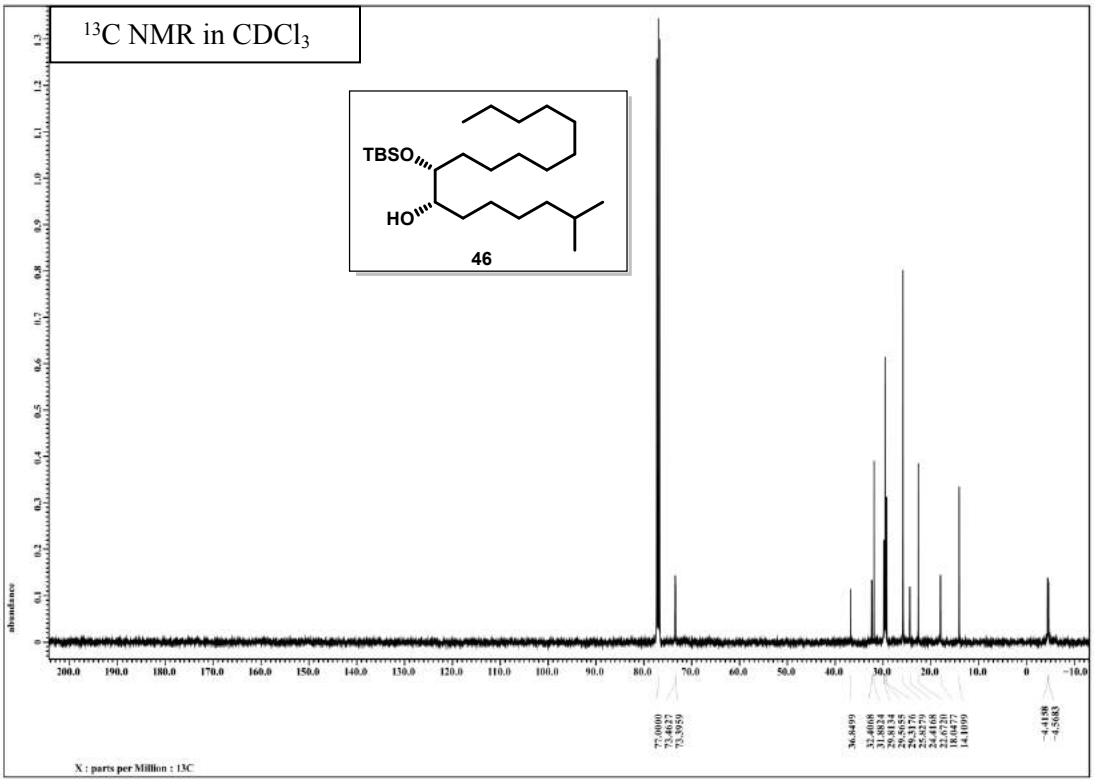

^{1}H NMR in $CDCl_3$
44
NO_2
X : parts per Million : 1H

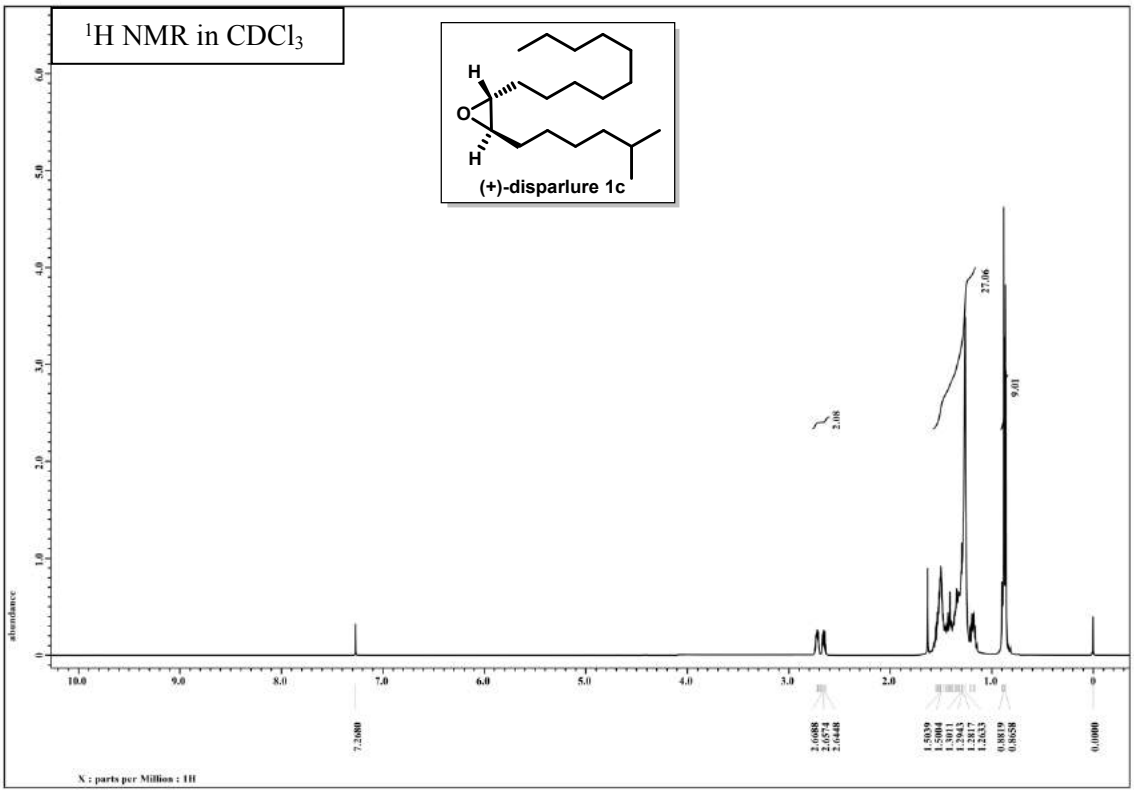

^{13}C NMR in $CDCl_3$
44
NO_2
X : parts per Million : 13C

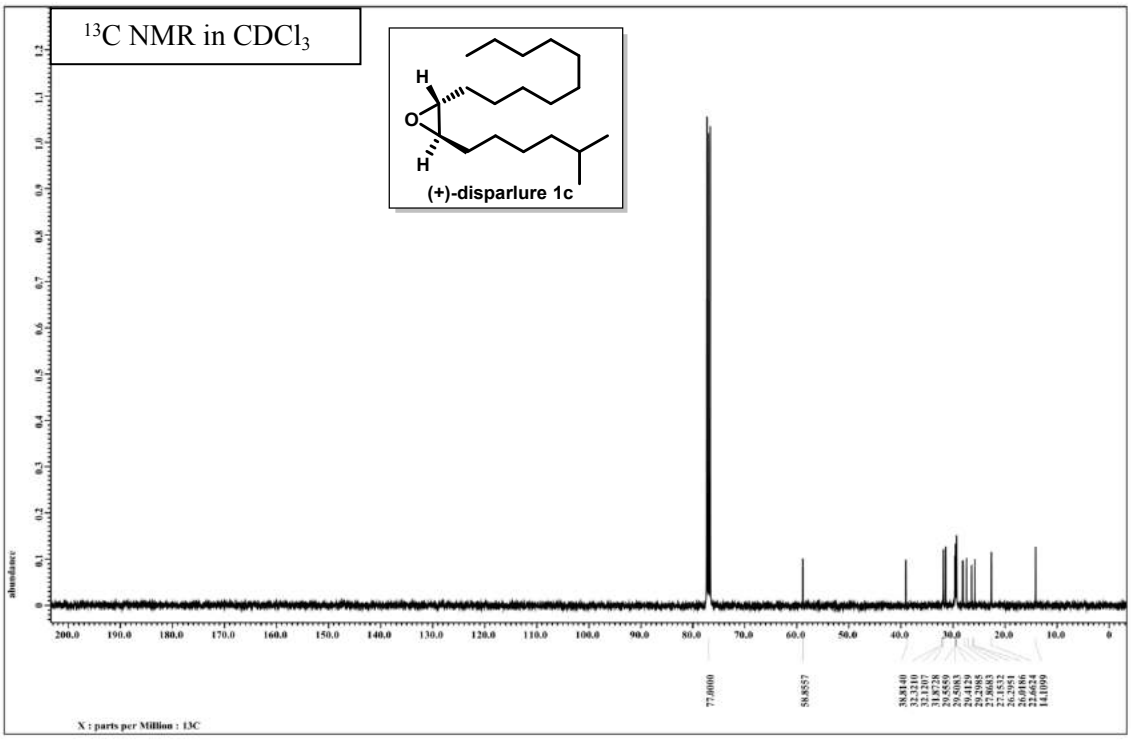

^{1}H NMR in $CDCl_3$
OTBS
45
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
OTBS
45
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
TBSO
HO
46
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
TBSO
HO
46
X : parts per Million : 13C


^{1}H NMR in $CDCl_3$
(+)-disparlure 1c
abundance
X : parts per Million : 1H


^{13}C NMR in $CDCl_3$
(+)-disparlure 1c
abundance
X : parts per Million : 13C

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An Enantioselective Approach to Functionalized Amino Acids: Total Synthesis of Antiepileptic Drug (*R*)-Lacosamide

Yuvraj Garg and Satyendra Kumar Pandey*

School of Chemistry and Biochemistry, Thapar University, Patiala 147001, India

Supporting Information

ABSTRACT: A short and highly efficient synthetic approach to enantiopure functionalized amino acids (FAAs) **1** skeleton from racemic butadiene monoepoxide as a starting material and its application to the total synthesis of an antiepileptic drug (*R*)-lacosamide **2** are described. The synthesis utilizes the palladium catalyzed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) as key step.

Functionalized amino acids (FAAs) **1** are advanced novel class of anticonvulsant agents, from which (*R*)-lacosamide **2** emerged as a best antiepileptic drug (AED) and has been suggested for the treatment of partial-onset seizures in patients with epilepsy and as add-on treatment in brain tumor patients (Figure 1).[1] Currently, (*R*)-Lacosamide **2** (Vimpat) is marketed in U.S. and Europe, and its worldwide expected sale in 2015−2020 is € 1.2 billion (UCB pharma). Epilepsy is a chronic neurological disorder that arises from dysregulations and hypersynchronous neuronal firing, which affects almost over 10 million people in India and 50 million people worldwide.[2] The precise mechanism of action of (*R*)-lacosamide **2** in humans has not yet been fully elucidated, but it enhances the slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.[3] Additionally, (*R*)-lacosamide **2** is also under clinical trials for the treatment of neuropathic pains.[4]

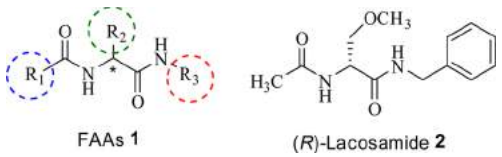

Figure 1. Structures of FAAs **1** and (*R*)-lacosamide **2**.

(*R*)-Lacosamide **2** has been a synthetic target of considerable interest due to its anticonvulsant activity with an array of functionalities. Various methods for the synthesis of (*R*)-lacosamide **2** have been documented in the literature from pharmaceutical industries and academia.[5,6] Most of the synthesis described employed chiral pool approach and started from unnatural amino acid D-serine and derivatives. The synthetic approaches of (*R*)-lacosamide **2** from D-serine mainly involve acylation, amidation, Kuhn's methylation, protection and deprotection strategies. The Kuhn *O*-methylation occurs in the presence of Ag_2O and MeI, which is commercially not viable due to its high cost, nonregenerability of catalyst and longer reaction time (3−5 days).[7] Very recently, Sebastian Stecko reported the total synthesis of **2** employing stereospecific allylcyanate-to-isocyanate rearrangement, which proceeds with chirality transfer starting from ethyl L-lactate.[5h] Herein, we wish to report a new, general and highly efficient synthetic approach for FAAs **1** and its application to the total synthesis of (*R*)-lacosamide **2** employing Trost's DYKAT as a key step.[8]

Our synthetic approach for the synthesis of (*R*)-lacosamide **2** was envisioned via the retrosynthetic route as shown in Scheme 1. The phthalimide derivative **3** was visualized as a synthetic intermediate from which FAAs **1** and (*R*)-lacosamide **2** could be synthesized via phthalimide cleavage and acylation. The phthalimide derivative **3** in turn could be obtained from the phthaloyl alcohol derivative **4** through base catalyzed alkylation. The terminal double bond of derivative **4** could be available for the functional group manipulation via standard organic transformations. Enantiopure phthaloyl alcohol derivative **4** could be easily prepared from the racemic butadiene monoepoxide **5** by means of Trost's DYKAT. The (*S*)- and (*R*)- configuration of the derivative **4** could be manipulated by simply changing chiral ligands (*R,R*)-DACH and (*S,S*)-DACH (Figure 2), respectively, in the Trost's DYKAT step.

The synthesis of (*R*)-lacosamide **2** started from the commercially available racemic butadiene monoepoxide **5**, which can easily be synthesized from silver-catalyzed oxidation of 1,3-butadiene (Scheme 2).[9] Deracemisation of butadiene monoepoxide **5** with palladium catalyzed Trost's DYKAT in the presence of 1.2 mol % (*R,R*)-DACH and 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, phthalimide and base Na_2CO_3 afforded asymmetric allylic alkylation (AAA) product phthaloyl alcohol **6** as a single enantiomer in 98% yield with ≥99% ee {$[\alpha]^{25}_D$ −72.2 (*c* 2.02, CH_2Cl_2) [Lit.[8] −72.2 (*c* 2.02, CH_2Cl_2)]}.

With enantiomerically pure alcohol **6** in hand, we then subjected it to O-methylation with MeI in the presence of NaH

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An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine†

Yuvraj Garg, Suraksha Gahalawat and Satyendra Kumar Pandey*

A simple and highly efficient synthetic approach to enantiopure 2-alkyl substituted tetrahydroquinoline **1** skeleton from aldehydes as starting materials and its application to the total synthesis of (+)-angustureine **2** is described. Key transformations include proline catalyzed aminoxylation, Corey–Fuchs protocol, Sonogashira coupling and intramolecular Mitsunobu reactions.

Introduction

Quinoline and tetrahydroquinoline alkaloids are found abundantly in nature and most of them exhibit interesting biological activity.[1] Enantiomerically pure 2-alkyl substituted tetrahydroquinoline alkaloids **1** from which angustureine **2**, galipeine **3**, cuspareine **4**, and galipinine **5** were first extracted from the bark of the *Galipea officinalis* Hancock shrub tree found in the mountains of Venezuela (Fig. 1).[2]

These alkaloids exhibits anti-malarial, anti-tuberculous, cytotoxic, and antiplasmodial activities.[3] *Galipea* species have also been used in folk medicine for the treatment of dysentery, dyspepsia, chronic diarrhea, spinal motor nerve problems and fevers.[4] Enantiomerically pure 2-alkyl substituted tetrahydroquinoline alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities. Various methods for the synthesis of (+)-angustureine **2** and others **3–5** have been documented in the literature.[5] Very recently, M. Yus and co-workers reported the synthesis of the (+)-angustureine **2** using diastereoselective addition of an allylic indium intermediate to chiral *O*-bromophenyl *N*-*tert*-butylsulfinyl aldimines.[5v] Herein, we wish to report a new, general and highly efficient synthetic approach for enantiopure 2-alkyl substituted tetrahydroquinolines **1** and its application to the total synthesis of (+)-angustureine **2** employing proline catalyzed asymmetric aminoxylation, Corey–Fuchs protocol, palladium catalyzed Sonogashira coupling, and Mitsunobu reaction as key steps.

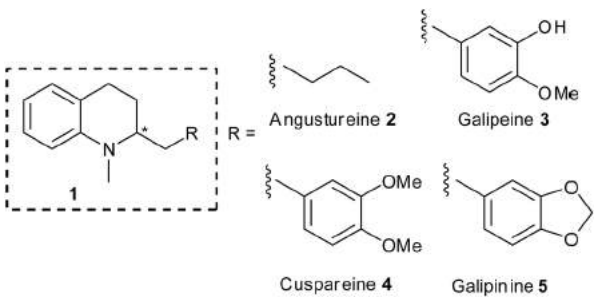

Fig. 1 Some naturally occurring 2-alkyl substituted tetrahydroquinoline alkaloids.

Results and discussion

Our retrosynthetic approach for the synthesis of 2-alkyl substituted tetrahydroquinolines **1** including (+)-angustureine **2** is outlined in Scheme 1. We envisioned that the aryl nitro-alkyne derivative **6** from which 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2** could be synthesized *via* hydrogenation, Mitsunobu intramolecular ring closer in S_N2 fashion followed by alkylation. The aryl nitro-alkyne derivative **6** could be obtained from the monoprotected alkyne derivative **7** through palladium catalyzed Sonogashira coupling reaction with suitable aromatic nitro-halides. The alkyne derivative **7** in turn could be obtained by means of Corey–Fuchs protocol from the aldehyde synthesized from oxidation of monoprotected alcohol **8**. Enantiomerically pure monoprotected alcohol **8** could be obtained from the commercially available aldehydes **9** *via* proline catalyzed aminoxylation followed by standard organic transformation. The (*S*)- and (*R*)-configuration of the 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2** could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step.

School of Chemistry and Biochemistry, Thapar University, Patiala 147001, India. E-mail: skpandey@thapar.edu; Fax: +91-175-236-4498; Tel: +91-175-239-3832

† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **2** and **11–16**. See DOI: 10.1039/c5ra05987a

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ASIAN JOURNAL OF ORGANIC CHEMISTRY Communication

Total synthesis (+)-Petromyroxol

Total Synthesis of (+)-Petromyroxol, a Marine Natural Product

Suraksha Gahalawat, Yuvraj Garg, and Satyendra Kumar Pandey*[a]

Dedicated to Professor Ganesh Pandey in recognition of his seminal contributions to so many aspects of organic chemistry.

Abstract: An efficient total synthesis of (+)-petromyroxol, a marine natural product, is described. The synthesis utilizes the Sharpless asymmetric dihydroxylation (AD), intramolecular S_N2 cyclization and stereoselective Grignard reaction as key steps.

The 2,5-disubstituted-3-oxygenated THF motif is found abundantly in biologically active natural products.[1] Petromyroxol (**1**), *iso*-petromyroxol (**2**),[2] *trans*-(−)-kumausyne (**3**), *trans*-(+)-deacetylkumausyne (**4**),[3] and anthelmintic oxylipid (**5**),[4] marine natural products, are few examples of dihydroxytetrahydrofurans from the acetogenin family[5] (Figure 1).

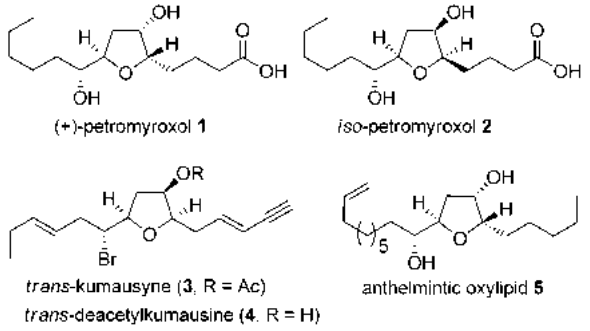
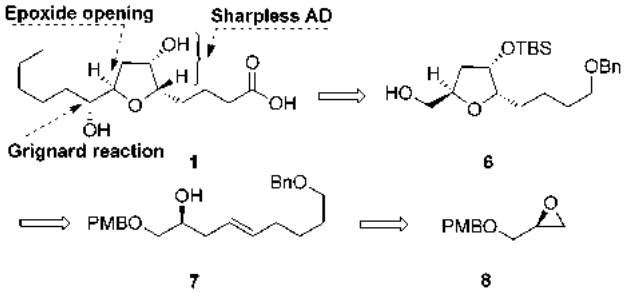


Figure 1. Some structures of the acetogenin family natural products.

The dihydroxylated THF enantiomers (+)-petromyroxol[2a] and *iso*-petromyroxol[2b] were recently isolated by Li and co-workers from water conditioned with larvae of the sea lamprey, *Petromyzon marinus* L., which is the first example of dihydroxylated THF-containing metabolites isolated from a vertebrate.[2] The sea lamprey is an aggressive predator of trout populations, and is found in the northern Atlantic Ocean along shores of North America and Europe, on the shores of the Great Lakes, and in the western Mediterranean Sea.[6] Thus, there has been an extensive investigation on various aquatic pest-control and aquatic pheromones, which is ongoing.[7] (+)-Petromyroxol has been a synthetic target of considerable interest due to its potent olfactory activity in the concentration range of 0.01–1 μM and its array of functionalities. The absolute configuration of the four stereogenic centers of (+)-petromyroxol and *iso*-petromyroxol were determined by Li and co-workers with the help of 2D NMR studies, compared with known substituted THFs, and Mosher ester analysis. To the best of our knowledge, until now only two syntheses of (+)-petromyroxol have been documented in the literature.[8] The first, reported by Boyer, involved the construction of the THF motif via diastereoselective, rhodium-catalyzed denitrogenation and rearrangement of the 1-sulfonyl-1,2,3-triazole into a *trans*-2,5-disubstituted dihydrofuran-3-one as key steps.[8a] More recently, Mullapudi and Ramana disclosed the multistep synthesis of **1** from a chiral pool building block.[8b] Therefore, it is highly desirable to develop a general and enantiopure synthetic route that provides a common pivotal intermediate from which 2,5-disubstituted-3-oxygenated THF motifs with desired stereochemical variations can be synthesized. Herein, we report a synthetic approach for the total synthesis of (+)-petromyroxol employing Sharpless asymmetric dihydroxylation (AD), intramolecular S_N2 cyclization, and stereoselective Grignard reaction as the key steps.

Our synthetic approach for the synthesis of (+)-petromyroxol was envisioned via the retrosynthetic route as shown in Scheme 1. The 2,5-disubstituted-3-oxygenated THF derivative **6** was visualized as a synthetic intermediate from which (+)-petromyroxol could be synthesized via oxidation of the free alcohol followed by stereoselective Grignard reaction and standard organic transformations. The THF derivative **6** in turn could be



Scheme 1. Retrosynthetic approach for (+)-petromyroxol (**1**). Bn = benzyl. TBS = *tert*-butyldimethylsilyl.

[a] S. Gahalawat, Y. Garg, S. K. Pandey
School of Chemistry and Biochemistry
Thapar University
Patiala-147001 (India)
E-mail: skpandey@thapar.edu

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COMMUNICATION

Enantioselective total synthesis of (*S*)-nakinadine B†‡

Yuvraj Garg and Satyendra Kumar Pandey*

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A novel approach for the synthesis of α-phenyl-β^2-amino acid core unit **1** and its application to the total synthesis of (*S*)-nakinadine B **3**, a marine natural product, is described. The synthesis utilizes the optimized combination of diphenylprolinol silyl ether mediated asymmetric Michael addition and a proline catalyzed aminoxylation reactions as key steps.

Introduction

During recent years, marine sponges have been recognized as a rich source of bioactive natural products with fascinating chemical structures. The nakinadine A–F (**3–8**) alkaloids were recently isolated from an Okinawan marine sponge *Amphimedon* sp. (SS-1059) (Fig. 1).[1] Metabolites from the Okinawan marine sponge family illicit a myriad of biological activities that includes antimicrobial, cardiotonic, cytotoxic and antitumor activities.[2] The nakinadine alkaloids possess an α-phenyl-β-amino acid moiety with a long chain *N*-alkyl substituent capped by a terminal 3-pyridyl moiety. The nakinadine B **3** and C **4** possess an α-phenyl-β^2-amino acid core unit **1** which is different from the nakinadines A **5** and D–F (**6–8**) having an α-phenyl-β^{2,3}-amino acid core unit **2**. The nakinadine A–C (**3–5**) alkaloids have been shown to possess significant cytotoxicity against a variety of tumour cell lines including L1210 murine leukaemia and KB human epidermoid carcinoma cells.[1]

The absolute configuration of (*S*)-nakinadine B **3** was determined by Kobayashi and co-workers with the help of 2D NMR spectroscopic studies. The paucity of the material in isolation has hampered further studies of the biochemistry of nakinadine A–F (**3–8**).[1] Therefore, in order to achieve nakinadine alkaloids in larger quantities for further biological evaluation, it is highly desirable to develop a general, convergent and enantiopure synthetic approach which involves stable intermediates. The nakinadine A–F (**3–8**) have been synthetic targets of considerable interest due to its high cytotoxic activity and with an array of functionalities.[3] More recently, Davies and co-workers reported the first asymmetric synthesis of the (*S*)-nakinadine B **3** in nine steps employing conjugate addition of lithium dibenzylamide to an *N*-α-phenylacryloyl SuperQuat derivative with *in situ* diastereoselective enolate protonation as the key step.[3b] As part of our research on the asymmetric synthesis of bioactive compounds,[4] we wish to report herein, a new, general and highly efficient synthetic approach for enantiopure α-phenyl-β^2-amino acid core unit **1** and its application to the total synthesis of (*S*)-nakinadine B **3** employing diphenylprolinol silyl ether mediated asymmetric Michael addition and proline catalyzed aminoxylation reactions as key steps.

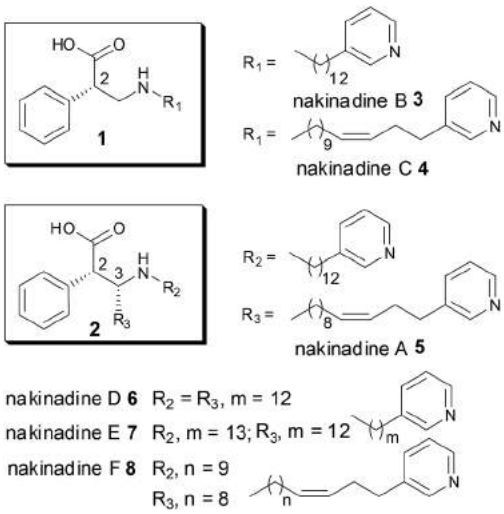

Fig. 1 Structures of nakinadine A–F alkaloids.

Results and discussion

Our synthetic approach for the synthesis of α-phenyl-β^2-amino acid core unit **1** and (*S*)-nakinadine B **3** was envisioned *via* the

School of Chemistry and Biochemistry, Thapar University, Patiala 147001, India. E-mail: skpandey@thapar.edu; Fax: +91-175-236-4498; Tel: +91-175-239-3832

† Dedicated to Prof. Bhisma K. Patel in recognition of his seminal contributions to so many aspects of organic chemistry.

‡ Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **3**, **11** and **13–17**. See DOI: 10.1039/c6ra03915d

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Chemistry SELECT Full Papers

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.

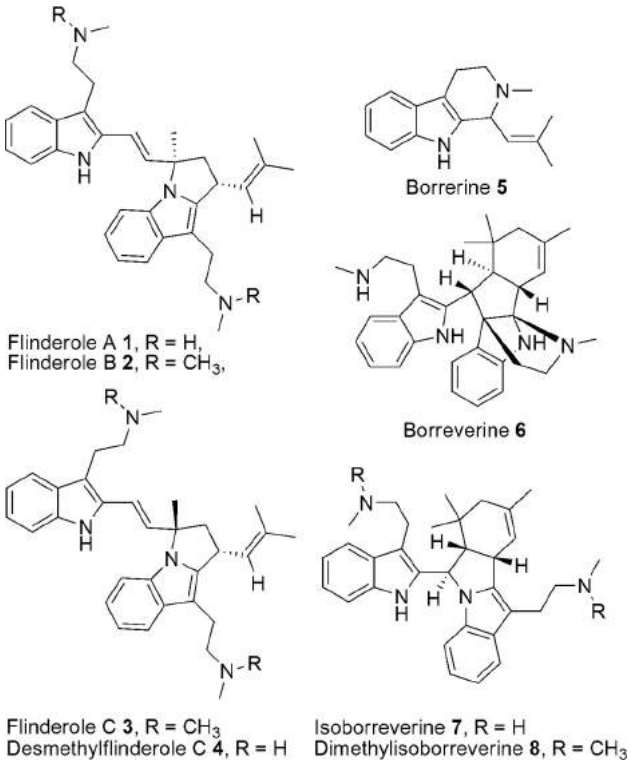

Figure 1. Structures of borreverine and flinderole alkaloids.

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).

[a] *R. Kaur, Y. Garg, Dr. S. K. Pandey*
School of Chemistry and Biochemistry
Thapar University
Patiala, 147001, India
E-mail: skpandey@thapar.edu

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(12) **United States Patent**
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(54) **PROCESS FOR THE PREPARATION OF(R)-LACOSAMIDE**

(71) Applicants: **Satyendra Kumar Pandey**, Patiala (IN); **Yuvraj Garg**, Patiala (IN)

(72) Inventors: **Satyendra Kumar Pandey**, Patiala (IN); **Yuvraj Garg**, Patiala (IN)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by **0** days.

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See application file for complete search history.

(56) **References Cited**

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Primary Examiner Shailendra Kumar

(57) **ABSTRACT**

The present invention is directed towards an improved, five step method for the preparation of the anti-epileptic drug (R)-lacosamide, as illustrated in FIG. 2. The active form of the drug is (R)-enantiomer and the present method gives high yields of (R)-enantiomer of lacosamide. The method does not involve use of any unnatural amino acids as starting material or use of protection/deprotection strategies, strong acids or hydrogenation. Instead, the method uses a cheap and easily available racemic butadiene monoepoxide as the starting material.

16 Claims, 2 Drawing Sheets

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(72) Inventor; and
(71) Applicant : **PANDEY, Satyendra Kumar** [IN/IN]; School of Chemistry and Biochemistry, Thapar University, Patiala 147001 (IN).

(72) Inventor: **GARG, Yuvraj**; School of Chemistry and Biochemistry, Thapar University, Patiala 147001 (IN).

(74) Agent: **BANSAL, Kompal**; For Corporate Consultants, # 5568, Sector 38 West, Chandigarh 160014 (IN).

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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF (R)-LACOSAMIDE

(57) Abstract: The present invention is directed towards an improved, five step method for the preparation of the anti-epileptic drug (R)-Lacosamide, as illustrated in Fig. 2. The active form of the drug is (R)-enantiomer and the present method gives high yields of (R)-enantiomer of lacosamide. The method does not involve use of any unnatural amino acids as starting material or use of protection/deprotection strategies, strong acids or hydrogenation. Instead, the method uses a cheap and easily available racemic butadiene monoepoxide as the starting material.

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Enantioselective total synthesis of *cis*-(+)- and *trans*-(+)-disparlure

Yuvraj Garg, Anand Kumar Tiwari, Satyendra Kumar Pandey *

School of Chemistry and Biochemistry, Thapar University, Patiala 147001, India

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Sex-attractant pheromone
Disparlure
MacMillan's self aldol reaction
Wittig olefination
Mitsunobu esterification

ABSTRACT

An expedient enantioselective synthetic approach for the gypsy moth sex-attractant pheromone *cis*-(+)-**1** and *trans*-(+)-disparlure **2** is described employing the optimized combination of organocatalytic MacMillan's self aldol reaction, Wittig olefination, regioselective ring opening of an epoxide and Mitsunobu esterification reactions as key steps.

Introduction

Over the last decades, *cis*-(+)-disparlure **1** has been used worldwide as a pesticide against the gypsy moth, *Lymantria disar L.*, a widespread pest causing damage to the wild ecosystem of Europe, Africa, and North America (Fig. 1).[1] The straight chain lepidopteran sex pheromone *cis*-(+)-disparlure **1** was isolated by Bierl and co-workers from the *Porthetria disar L.*, female gypsy moths.[2] Iwaki and co-workers established the absolute configuration of *cis*-(+)-disparlure **1** *via* its synthesis from (*S*)-glutamic acid.[3] The *cis*-(+)-disparlure **1** is required for the upwind flight of male moths to the pheromone releasing females and binds selectively to PBP1 protein, while the *cis*-(−)-disparlure **3** cancels the upwind flight behavior in the males which binds selectively to PBP2 protein of gypsy moth.[4]

Therefore, *cis*-(+)-disparlure **1** has been used to confuse and preventing male moths from locating and mating with females or leading male moths into traps for the protection of forests.[5] The *cis*-(+)-disparlure **1** and its analogues (**2**–**4**) have been synthetic targets of considerable interest for academia and agriculture due to their astonishing biological properties combined with attractive structural features. Various elegant syntheses of *cis*-(+)-disparlure **1** and its analogues (**2**–**4**) mainly based on chiral pool approaches have been documented in the literature.[6] Very recently, Fernandes and co-workers reported the stereoselective synthesis of *cis*-(+)-disparlure **1** and its analogues (**2**–**3**) using a domino Pd-catalyzed recombinant γ-isomerization/Wacker oxidation reactions of γ-vinyl-γ-butyrolactone as key steps.[6a] As part of our research program towards the asymmetric synthesis of bioactive compounds,[7] we report herein, a novel synthesis of *cis*-(+)-**1** and *trans*-(+)-disparlure **2** employing the MacMillan's self aldol reaction, Wittig olefination, regioselective ring opening of an epoxide and Mitsunobu esterification reactions as key steps.

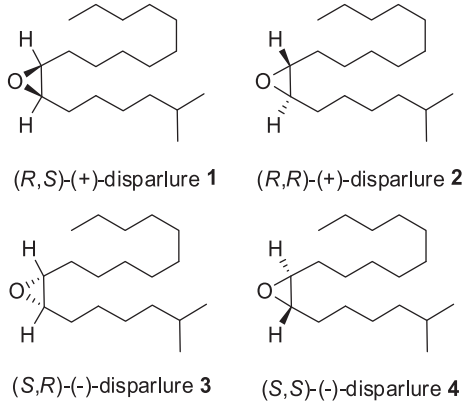

Fig. 1. Structures of stereoisomers of disparlures (**1**–**4**).

* Corresponding author.
E-mail address: skpandey@thapar.edu (S. Kumar Pandey).

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An enantioselective approach to 3-substituted pyrrolidines: Asymmetric synthesis for pyrrolidine core of serotonin norepinephrine reuptake inhibitors (SNRIs)

Yuvraj Garg, Pooja Sharma, Satyendra Kumar Pandey *

School of Chemistry and Biochemistry, Thapar University, Patiala 147001, India

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PMB glycidyl ether
Michael addition

ABSTRACT

A novel and efficient synthetic approach to enantiopure 3-substituted pyrrolidine skeleton from readily available (*S*)-PMB glycidyl ether as a starting material and its application to the asymmetric synthesis of pyrrolidine core **1** of serotonin norepinephrine reuptake inhibitors (SNRIs) **2** and **3** are described. The synthesis utilizes the organocatalyzed asymmetric Michael addition reaction as key step.

Introduction

Pyrrolidines and their substituted derivatives are among the most bioactive *N*-heterocyclic compounds in organic chemistry due to prevalence of these structural motifs either as itself or as a part of a more complex structural moiety in a large number of biologically active molecules and natural products.[1] Among them, enantiomerically pure 3-substituted pyrrolidine **1** and their derivatives are important subclass of compounds possessing interesting pharmacological activities.[2] Serotonin norepinephrine reuptake inhibitors (SNRIs) are advanced novel class of antidepressant drugs which have been suggested for the treatment of several central nervous disorders including chronic painful conditions such as fibromyalgia and diabetic peripheral neuropathic pain.[3] The precise mechanism of action of SNRIs has not yet been fully elucidated, but it is believed to be mainly caused by decreasing the levels of serotonin and norepinephrine in the synaptic cleft, resulting erratic signalling.[4] Currently, several SNRIs marketed worldwide have proven to be effective and safe drugs in chronic painful conditions and mood disorders but the search for new SNRIs has always been of greater significance upon past drugs in regards to efficacy, tolerability and fewer side effects. In 2013, Johansson and co-workers[5] reported the discovery of novel 3-substituted pyrrolidine ether SNRI **2**, which is the first example showing improved norepinephrine transporter activity, acceptable metabolic stability and exhibiting minimal drug to drug interaction. Stangeland and co-workers have also reported previously the discovery of an another novel 3-substituted pyrrolidine ether SNRI **3** which showed inhibition of the serotonin and/or norepinephrine transporter, for the treatment of neuropathic pain with reduced side effects such as nausea (Fig. 1).[6]

The SNRIs **2** and **3** have been synthetic targets of considerable interest for pharmaceutical industries due to their utility in treatment of central nervous disorders with an array of functionalities.[5–7] More recently, Magnus and co-workers reported the

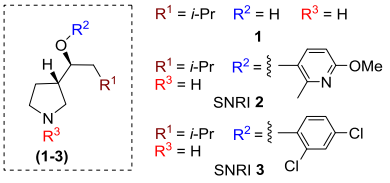

Fig. 1. Structures of 3-substituted pyrrolidines **1**–**3**.

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

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