SYNTHETIC STUDIES TOWARDS BIOLOGICALLY ACTIVE COMPOUNDS CONTAINING INDOLIZIDINE, PYRROLIZIDINE QUINOLIZIDINE AND LACTONE MOIETIES EMPLOYING ASYMMETRIC DIHYDROXYLATION AND PROLINE CATALYZED ORGANIC TRANSFORMATIONS

A THESIS SUBMITTED TO THE
SAVITRIBAI PHULE PUNE UNIVERSITY

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

BY
SHRUTI VANDANA KAULOORKAR

UNDER THE GUIDANCE OF
DR. PRADEEP KUMAR

DIVISION OF ORGANIC CHEMISTRY
CSIR-NATIONAL CHEMICAL LABORATORY
PUNE-411008, INDIA

SEPTEMBER 2016

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE-411 008, INDIA.

हीरक जयन्ती वर्ष 2009-10

Dr. Pradeep Kumar, FNA
Chief Scientist & Head
Organic Chemistry Division
Pune-411008

Telephone: + 91-20-25902760
Fax:+ 91-20-25902629
E-mail: pk.tripathi@ncl.res.in
Website: http://www.ncl-india.org

CERTIFICATE

This is to certify that the research work presented in the thesis entitled "**Synthetic studies towards biologically active compounds containing indolizidine, pyrrolizidine, quinolizidine and lactone moieties employing asymmetric dihydroxylation and proline catalyzed organic transformations**" has been carried out under my supervision and is a bonafide work **Ms. Shruti Vandana Kauloorkar**. This work is original and has not been submitted for any other degree or diploma of this or to any other University.

(Dr. Pradeep Kumar)
Research Guide

September 2016

Blank CD

Savitribai Phule Pune University

(formerly University of Pune)

Declaration of Result of the Doctor of Philosophy (Ph. D.)

Shrutivandana Kauloorkar (श्रृतीवंदना कौलूरकर)

Mother's Name : Shaila (शैला)

University has accepted thesis submitted by the above-mentioned candidate for award of Ph.D., as per reports of referees and examiners of open defence of the thesis. Accordingly, it is hereby notified that, the above-mentioned candidate is declared to have passed the examination of Ph. D. and has become eligible for the award of Ph. D. Degree.

RELEVANT DETAILS ARE AS UNDER :

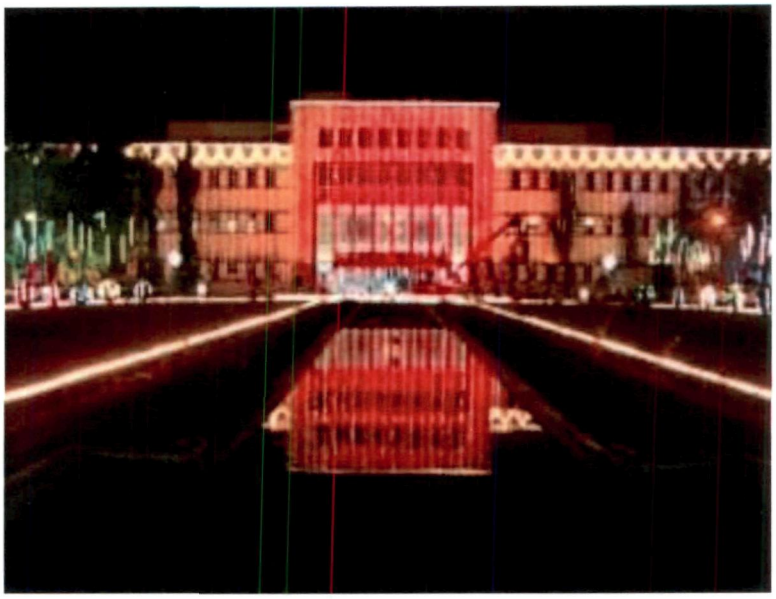
1.	Faculty	:	Science
2.	Subject	:	Chemistry
3.	Title of the Thesis	:	"Synthetic studies towards biologically active compounds containing indolizidine, pyrrolizidine, quinolizidine and lactone moieties employing asymmetric dihydroxylation and proline catalyzed organic transformations."
4.	Place of Research	:	Department of Chemistry, CSIR-National Chemical Laboratory Pashan Road, Pune- 411008.
5.	Name and Address of the Guide	:	Pradeep Kumar CSIR-National Chemical Laboratory Pashan Road, Pune- 411008.
6.	Date of Registration	:	18th June, 2012
7.	Date of Declaration of Result	:	13th August, 2018

SAVITRIBAI PHULE PUNE UNIVERSITY Admission Section PUNE-7.

Ganeshkhind, Pune 411007.
Ref. No. PGS/Ph.D. / 464
Date : 16 AUG 2018

16/8/2018.
For Director
Board of Examinations and Evaluation

P.U.P—2000-3-2015(1052)[2]



CANDIDATE'S DECLARATION

I hereby declare that the thesis entitled "**Synthetic studies towards biologically active compounds containing indolizidine, pyrrolizidine, quinolizidine and lactone moieties employing asymmetric dihydroxylation and proline catalyzed organic transformations**" submitted for the degree of Doctor of Philosophy in Chemistry to the Savitribai Phule Pune University has not been submitted by me to any other university or Institution. This work was carried out at CSIR-National Chemical Laboratory, Pune, India.

Shruti Vandana Kauloorkar
Senior Research Fellow
Division of Organic Chemistry
CSIR- National Chemical Laboratory
Pune-411008, INDIA

September 2016

Acknowledgement

It gives me immense pleasure to express my deep sense of gratitude to my research supervisor ***Dr. Pradeep Kumar*** *for his advice, guidance, support and motivation during every stage of my research work. His optimism and passion for work are invaluable sources of inspiration for me. I sincerely thank him for instilling excellent work ethic in me. I wish to emulate the decency and dignity with which he lives.*

I am very thankful to Dr. S. P. Chavan, Dr. M. S. Shashidhar and Dr. Dhavale for their help and support during the course of my research work.

I would take this occasion to thank Dr. P. R. Rajmohanan and NMR group (Kavya, Dinesh, Srikant and others) for their time, effort and co-operation. I am grateful to Ms. Sunita Kunte for her help in HPLC analysis, Dr. Senthil Kumar for help in LCMS and Dr. Santakumari for her help in HRMS analysis. Support from OCD office staff Ms. C. Raphel, Fernandes and Thangaraj is also acknowledged.

I would like to express my genuine gratitude to my seniors Dr. Satyendra Pandey, Dr. Nagendra Kondekar, Dr. Mandar Bodas, Dr. Puspesh, Dr. Abhishek Dubey, Dr. Namrata Dwivedi, Dr. Priti Gupta, Dr. Divya Tripathi, Dr. Shijo, Dr. Krishanu Show, Dr. Menaka Pandey, Dr. Anand Saxena, Dr. Ankush Bhise, Dr. Partha Chowdhary, Dr. Ruchi Jain, Dr. Eshwarbegari and Dr. Sandeep Shinde for their scientific suggestions, support and help during my Ph.D. tenure. I would like to thank Arun, Kiran, Poonam, Jignesh, Arjun, Amruta, Brijesh, Nookaraju, Shrikant, Jayant and Chandani for maintaining a warm and cheerful atmosphere in the lab. It was fun working with them and I cherish every moment spent in that lab. I would also like to thank my other colleagues for a pleasurable work atmosphere.

I would like to thank all my seniors and friends Richa, Gowri, Sutar, Saikat, Pankaj, Jyoti, Mujahid, Mr. Ganesh Jogdand for their cheerful company during my Ph.D. life. Priya, Krithika , Ketki, Tanaya, Manjushree, Reema, Rohini, Harshali and others for all the funtime during cricket practice and matches. Special thanks to Shyam da and Sujit da for their valuble time to coach us win those lovely medals. My roomies Anjali, Ruby, Nisha, Preeti, Gayatri for making my stay in SA memorable. Prajitha and Tusshara for sumptuous south Indian meals.

Life in Strasbourg has a special place in my heart, Thank you Somuda, Ananya bhabhi, Mimi, Jagadeesh, Shanti, Deekshu, Manik, Pradeepa, Ithi, Rajendra, Senthil, Poorni, Vijetha, Hemanth, Koteshwari, Ashok, Mehboob, Sushmita, Leema, Sudha for a pleasurable time in Europe.

I would like to thank Dr.Sourav Pal, Dr.Guruswamy, Dr.Magesh Nandagopal and Bhakti, for a wonderful time during INSPIRE workshops.

Special thanks to my M.Sc Professor Dr. Vijayaragahvan, Prof .Vijayakumar B.Sc. teacher Mr. Khan and my school teachers Sheelu aunty, Sheela aunty, Sulabha aunty, Anand sir, Sagar uncle, Padma aunty, Madhuri aunty for their support. I would also like to thank my close friends Niharika, Ravi, Namrata, Prathika, Sohini, Raghu, Sujitha, Sudhan, Shaifali, Sana, Saika, Vamsi, Asha who gave me the best memories.

It is impossible to express my sense of gratitude to Ayi and baba in mere words. I owe all my achievements to their unconditional support, constant encouragement, commitment to my ambition and endless sacrifices. I am equally indebted to Dinesh mama, Rekha aunty, Tai, Jyotsna maushi, Suhas maushi and Udaykaka for their unconditional love and support, for tremendous support and encouragement this day would not have been possible without you all. Words fall short to thank Chetana and Vikrant for all their sacrifices and unconditional love because of which I am today.

Heartfelt thanks to my in laws Maa and papa for their constant support. Their blessings have definitely given me immense strength to balance both professionl and personal life. I indeed owe a lot to Manik bhaiyya, Sujata bhabhi, Shweta di, Ashish ji, Abhigyan and Atulya for their love and encouragement.

Special thanks goes out to Rahul-A friend, philosopher and guide at every stage of my life. His constant support and motivation has helped me throughout my course of research.

I thank Director, CSIR-National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to UGC, New Delhi for the financial assistance in the form of fellowship. At last but not the least, I thank whole heartedly, the almighty God for giving me the patience, determination and strength that has helped me throughout the course of my research work.

Shruti

Contents

Chapter 1

Sharpless asymmetric dihydroxylation and proline catalyzed reactions

Chapter 2

Asymmetric synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems using proline catalyzed α-amination reaction

Chapter 3

Synthesis of dihydroxylated and monohydroxylated izidines using proline catalyzed a-amination followed by Sharpless asymmetric dihydroxylation

3.1 Section A: Stereoselective approach to Indolizidine and Pyrrolizidine Alkaloids: Total synthesis of (-)-Lentiginosine, (-)-*epi*-Lentiginosine and (-)-Dihydroxypyrrolizidine

3.2 Section B: Stereoselective approach to the synthesis of 1-hydroxyindolizidines and pyrrolizidines

Chapter 4

An organocatalytic approach to asymmetric synthesis of Hagen's gland lactones and (-)-Colletallol

4.1 Section A: A stereocontrolled synthesis of Hagen's gland lactones via iterative proline catalyzed α-aminoxylation and oxa-Michael addition reactions

Ac	-	Acetyl
AcOH	-	Acetic acid
Ac_2O	-	Acetic anhydride
ACN	-	Acetonitrile
Bn	-	Benzyl
BnBr	-	Benzyl bromide
Boc	-	*tert*-Butoxy carbonyl
$(Boc)_2O$	-	Di-*tert*-butyl dicarbonate
BuLi	-	Butyl lithium
Cat.	-	Catalytic
$CDCl_3$	-	Deuterated chloroform
Cbz	-	Benzyloxy carbonyl
DBAD	-	Dibenzyl azadicarboxylate
DBU	-	1,8-Diazabicyclo[5.4.0]undecene-7
DCM	-	Dichloromethane
$(DHQ)_2PHAL$	-	1,4-Bis(dihydroquinin-9-*O*-yl)phthalazine
$(DHQD)_2PHAL$	-	1,4-Bis(dihydroquinindin-9-*O*-l)phthalazine
DIBAL-H	-	Diisobutylaluminiumhydride
DMP	-	Dess-Martin periodinane
DMF	-	*N, N'*-Dimethylformamide
DMAP	-	*N,N'*-Dimethylaminopyridine
DMSO	-	Dimethyl sulfoxide
ee	-	Enantiomeric excess
equiv.	-	Equivalents
EtOH	-	Ethanol
Et	-	Ethyl
Et_2O	-	Diethyl ether
EtOAc	-	Ethyl acetate
Et_3N	-	Triethylamine
Hz	-	Hertz
HPLC	-	High pressure liquid chromatography

IBX	-	Iodoxybenzoic Acid
Im	-	Imidazole
Me	-	Methyl
MeOH	-	Methanol
mg	-	Milligram
min	-	Minutes
mL	-	Millilitre
mmol	-	Millimole
M. P.	-	Melting point
Ms	-	Methanesulfonyl
Me	-	Methyl
MeI	-	Methyl iodide
$NaBH_4$	-	Sodiumborohydride
NaH	-	Sodium hydride
Ph	-	Phenyl
Py	-	Pyridine
PMB	-	*para*-Methoxy benzyl
p-TSA	-	*para*-Toluenesulfonic acid
TBAI	-	Tetra-*n*-butylammonium iodide
TBAF	-	Tetra-*n*-butylammonium fluoride
TBDMS	-	*tert*-Butyldimethyl silyl
TBSCl	-	*tert*-Butyldimethyl silyl chloride
TFA	-	Trifluoroacetic acid
THF	-	Tetrahydrofuran
TPP	-	Triphenylphosphine
p-TSA	-	*p*-Toluenesulphonic acid
TsCl	-	*p*-Toluenesulphonyl chloride

- ^{1}H NMR spectra were recorded on AC-200 MHz, AC-400 MHz, Jeol-400 MHz and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, AC-100 MHz, Jeol-100 MHz and DRX-125 MHz spectrometer.
- EI Mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 eV using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- 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 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 Buchi rotary evaporator below 40 °C.
- Silica gel (60–120) used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.
- All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
- The compounds, scheme and reference numbers given in each section of chapter refers to that particular section of the chapter only.

Abstract

The thesis entitled "**Synthetic studies towards biologically active compounds containing indolizidine, pyrrolizidine, quinolizidine and lactone moieties employing asymmetric dihydroxylation and proline catalyzed organic trasformations**" has been divided into four chapters.

Chapter 1: Sharpless asymmetric dihydroxylation (AD) and proline catalyzed reactions

Chapter 2: Asymmetric synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems using proline catalyzed α- amination reaction

Chapter 3: Synthesis of dihydroxylated and monohydroxylated izidines using proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation

Chapter 4: An organocatalytic approach to asymmetric synthesis of Hagen's gland lactones and (-)-Colletallol

---

Chapter 1: Sharpless asymmetric dihydroxylation (AD) and proline catalyzed reactions

This chapter gives a brief introduction to proline-catalyzed organic transformations and Sharpless asymmetric dihydroxylation (AD).

In recent years, area of organocatalysis has emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis, thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[1] Proline has been defined as a "universal catalyst" because of its high utility in a variety of asymmetric organic transformations. Proline is the only natural amino acid with a secondary amine functionality, which raises the pKa value and better nucleophilicity as compared to other amino acids. It can act as a nucleophile to carbonyl groups (iminium intermediate) or Michael acceptors (enamines). It can be regarded as a bifunctional catalyst as the secondary amine acts as Lewis base and the acid group as Brönsted acid.[2]

Over two decades the Sharpless Asymmetric Dihydroxylation (AD)[3] has emerged as one of the most powerful synthetic method to convert prochiral olefins into diols. Several modifications and optimization in terms of ligands and yields have been achieved. Today AD has been successfully employed in the synthesis of complex natural products, many a time as the key chirality introduction step. The diol obtained has been modified in several ways to obtain either an alcohol, amino alcohol, halo alcohol, diamines, β-hydroxy acids/lactones, epoxides, α-hydroxy ketones and so on.

Having employed the AD reaction as a key chirality-inducing step, diol can be converted through synthetic manipulations into various biologically active compounds.

Chapter 2: Asymmetric synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems using proline catalyzed α- amination reaction

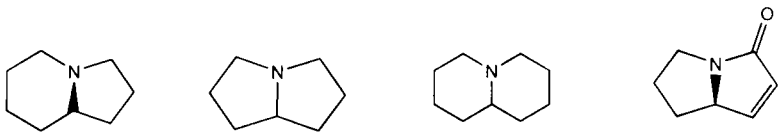
Section A : Synthesis of indolizidine, pyrrolizidine ring systems by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde

Indolizidine **1** and pyrrolizidine **2** (Figure 1) skeletons are frequently found as a key structural component in numerous alkaloids, which display a wide range of biological and pharmacological activity.[4] Considering their potent biological activity and less abundance,

these azabicyclic ring systems always remain an area of considerable synthetic effort, resulting in a wide range of different strategies toward the synthesis of a variety of izidines (pyrrolizidines, indolizidines, quinolizidines). However, a diverse and efficient synthetic route for the synthesis of this class of compounds is still desirable.

Proline in the recent past has been defined as 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom economical access to enantiomerically pure products.[5]List *et al.* have developed a proline-catalyzed direct α-amination of aldehyde protocol for the synthesis of α-amino aldehydes from readily available achiral aldehyde.[2a] We envisioned that the proline-catalyzed α-amination could be utilized to incorporate amine functionality and this sequential reaction followed by further manipulations of the olefin could easily give us a synthetic access to azabicyclic ring systems.

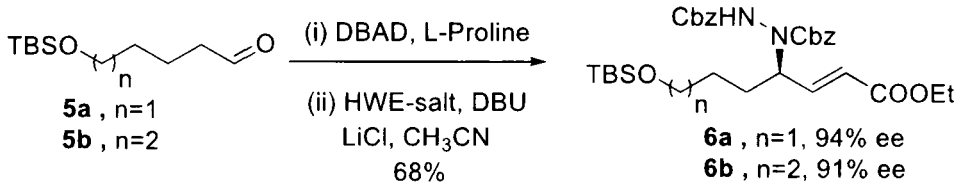
Figure 1. Aza bicyclic ring systems



1 Indolizidine | 2 Pyrrolizidine | 3 Quinolizidine | 4 Pyrrolam A

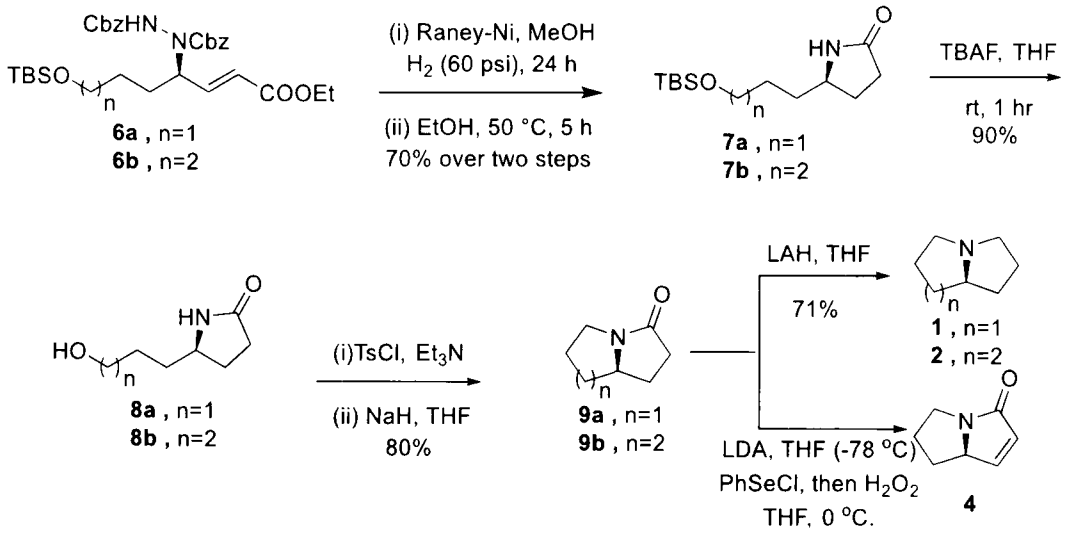
Toward the synthesis of azabicyclic ring systems, our first goal was to synthesize various γ-hydrazino-α,β-unsaturated esters by the protocol developed recently by us. Our synthesis commenced with aldehyde **5a**, which on sequential α-amination using commercially available dibenzylazodicarboxylate (DBAD) as the nitrogen source, L-proline as a catalyst and subsequent HWE olefination using triethylphosphonoacetate furnished the γ-amino-α,β-unsaturated ester **6a** in 68% yield and 94% enantioselectivity as determined using HPLC.

Scheme 1. Synthesis of γ-hydrazino esters



The γ-hydrazino α ,β-unsaturated esters were then subjected to reductive hydrogenation conditions using Raney-Ni to furnish the free amine which was converted to lactam **7a** on heating with EtOH at 50 °C. Subsequent treatment with TBAF afforded the free hydroxyl compound **8a** in 90% yield, which was converted to its toluenesulfonyl ester followed by base treatment using sodium hydride to yield the fused lactam **9a** in 80 % yield. LAH reduction of the fused lactam then gave the target compound **1** in 71% yield. Interestingly fused lactam **9a** can be converted to pyrrolam **4** using known procedure.[6]Using the same reaction sequence as mentioned above, fused lactam **9b** was readily assembled from the hydroxyl compound **8b**, via lactam **7b**. The lactam **7b** was prepared from γ-amino-α,β-unsaturated ester **6b** which in turn was synthesized from aldehyde **5b** in 68% yield and 91% enantioselectivity. (determined using HPLC.)

Scheme 2. Synthesis of indolizidine and pyrrolizidine ring systems.



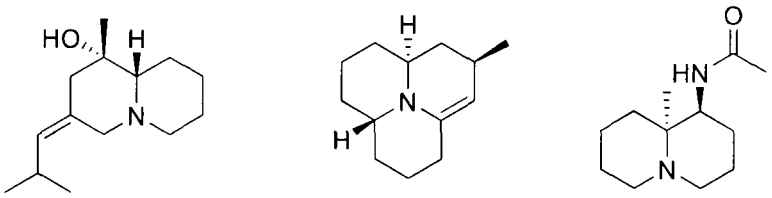
In conclusion, we have developed a new protocol employing proline-catalyzed sequential α-amination and Horner–Wadsworth–Emmons olefination approach to the synthesis of pyrrolizidine **1** and indolizidine **2** ring systems. The present method is easily amenable for the synthesis of a variety of alkaloids containing these ring system.

Section B: Synthesis of quinolizidine ring system by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde

Quinolizidine alkaloids are important as potential sources of medicine. They have a broad range of pharmacological properties, including cytotoxic, oxytocic, antipyretic, antibacterial, antiviral, and hypoglycemic activities, as determined by *in vivo* pharmacological screening.[7]Some quinolizidine alkaloids containing plants, for example *Sophoraflavescens,* have been used as

sources of crude drugs in Chinese–Japanese medicine.[8]

Figure 1. Quinolizidine alkaloids

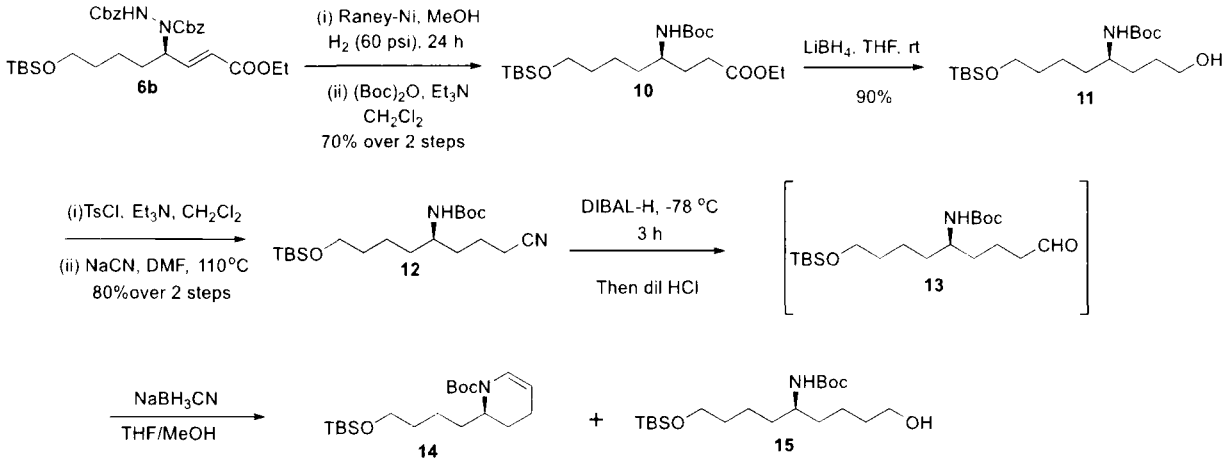


Homopumillitoxin Alkaloid 191B Epiquinamide

As an extension of above methodology for the synthesis of quinolizidine **3**, γ-amino-α,β-unsaturated ester **6b** was employed as the starting material. This was first subjected to N-N bond cleavage using Raney-Ni to furnish the free amine that was subsequently protected as its Boc derivative **10** in 70% yield. Ester group of Boc-derivative **10** was reduced using $LiBH_4$ to give the alcohol **11** in 90% yield which was converted into its toluenesulfonate derivative. Subsequent treatment with NaCN in dry DMF at 110 °C furnished the cyano compound **12** which on treatment with DIBAL-H at -78 °C followed by acid hydrolysis gave the aldehyde **13**.

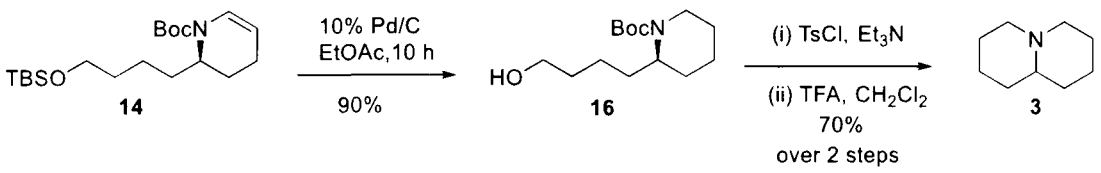
Compound **13** was subjected to $NaBH_4$ reduction to get the alcohol **15**, but to our surprise it led to the formation of compound **14** as a major product **(Scheme 1)**.

Scheme 1: Synthesis of quinolizidine



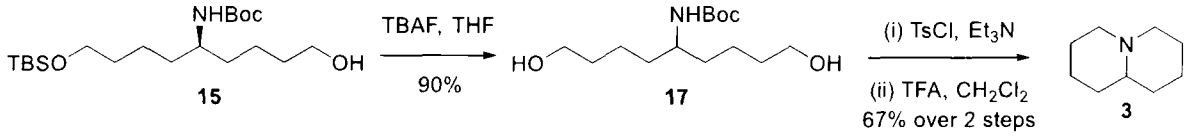
We then proceeded optimizing the reaction conditions to obtain the required product in substantial amount. It was observed during optimization that the formation of cyclized product **14** depends on the equivalents of $NaBH_4$ used in the reaction. When 2 eq. of $NaBH_4$ was used in the reaction, both the compounds **14** and **15** were formed in equal ratio (1:1), on increasing the equivalent of $NaBH_4$ to 4 eq. marginal improvement in the ratio of **14**:**15** (6:4) was observed. Further increase to 10 eq. led to the considerable enhancement in the ratio of **14**:**15** (9:1). We then used $LiBH_4$ (5 eq.) and found the ratio of **14**:**15** was same as that in the case of $NaBH_4$. Finally, when $NaBH_3CN$ was used we got **14** as the major product with trace amounts of **15**.This led to a conclusion that under every reaction condition employed, compound **14** was the only major product. Compound **14** was then subjected to the double bond reduction ensuing TBS deprotection under hydrogenation conditions in one step using 10% Pd-C in EtOAc to give the alcohol **16**. Finally alcohol **16** was converted to its toluenesulfonylester, concomitant cleavage of the Boc group with TFA followed by nucleophilic displacement of the tosyl with resultant amine in the presence of diisopropylethyl amine led to the formation of quinolizidine ring system **3**[8] (Scheme 2).

Scheme 2: Synthesis of quinolizidine



We then further considered converting even compound **15**, obtained as a minor product to the target quinolizidine **3** as illustrated in scheme **3**. Towards this end, the TBS group of alcohol **15** was cleaved using TBAF to give the diol **17**. Subsequent treatment with toluenesulfonyl chloride and triethylamine and concomitant cleavage of the Boc group with TFA followed by nucleophilic displacement of the tosyl with the resultant amine in the presence of diisopropylethyl amine afforded the quinolizidine **3** in 67% yield.

Scheme 3: Synthesis of quinolizidine



In conclusion, we have developed a practical, efficient and organocatalytic approach to the synthesis of quinolizidine ring system using proline catalyzed sequential α-amination reaction and HWE olefination reaction of an aldehyde as the key step. The synthetic strategy described here is easily amenable for the synthesis of a variety of alkaloids containing quinolizidine ring system.

Chapter 3: Synthesis of hydroxylated pyrrolizidine and indolizidine using proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation and is further divided into two sections.

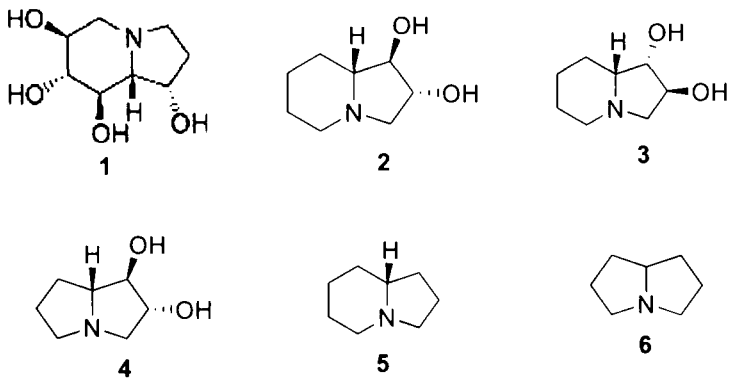
Section A : Total synthesis of (-)-lentiginosine,(-)-epi-lentiginosine and (-)-dihydroxy pyrrolizidine

The synthesis of enantiopure therapeutics with a high medicinal value has always been a prime concern among synthetic chemists. Among them, azasugars have gained much attention in recent years as they mimic carbohydrates. These "izidines" show different patterns of oxygenation, for instance, the highly oxygenated castanospermine **1,** its less hydroxylated congeners such as lentiginosine **2,** *epi*-lentiginosine **3**, and dihydroxypyrrolizidine **4** or the non oxygenated ring systems such as coniceine **5** and pyrrolizidine **6** *etc.* are widespread in plants and microorganisms[9](Figure 1).

Lentiginosine was isolated in 1990 by Elbein and co-workers from the source *Astralagus*

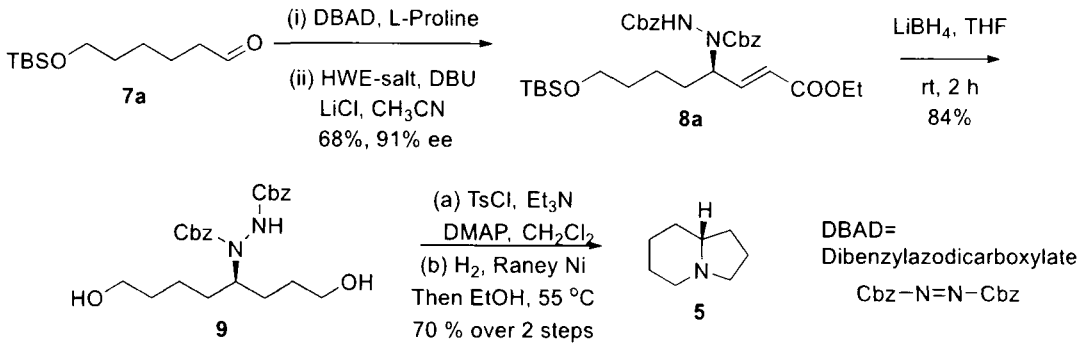
Lentiginosus.[10]It is known to exhibit excellent anti-HIV, anti-tumour and immunomodulating activities apart from being a significant inhibitor of amyloglycosidases with IC_{50}=5μg/mL. Interestingly, its pyrrolizidine analogue was also found to belong to an important class of alkaloids that display a wide range of biological activities mainly due to their action as specific glycosidase inhibitors. Both the hydroxylated indolizidine and pyrrolizidine derivatives have gained considerable interest as antiviral and anticancer agents. Since the biological activity varies substantially with the number, position and the stereochemistry of the hydroxyl groups on the aza bicyclic skeleton, the synthesis of both naturally occurring compounds and their stereoisomers and analogues have been very interesting targets.

Figure 1. Some indolizidine and pyrrolizidine alkaloids



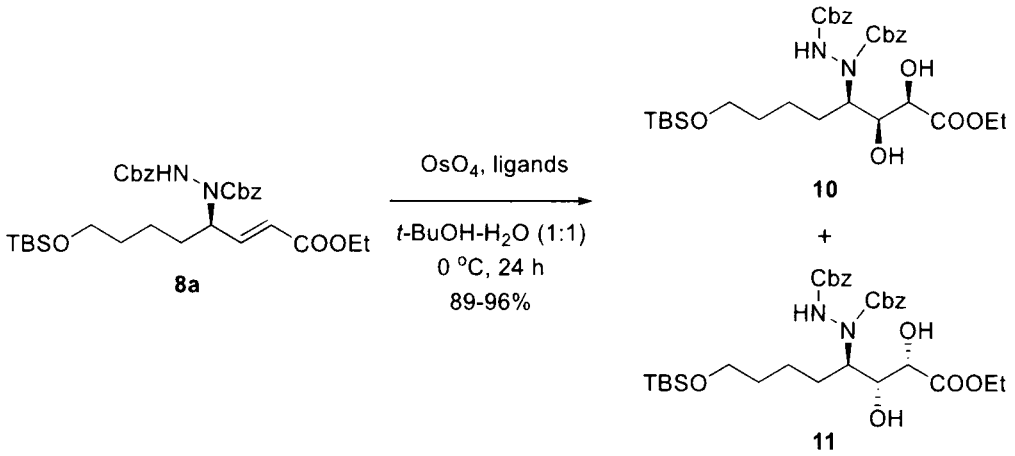
Before embarking on the synthesis of the target molecules, we considered exploring a model synthesis to test the devised strategy (**Scheme 1**), in particular, the concomitant cleavage of the N-N bond and nucleophilic displacement under hydrogenation conditions. Thus, previously synthesized γ-amino-α, β-unsaturated ester **8a** was subjected to ester reduction ensuing double bond reduction and TBS deprotection in one step using $LiBH_4$ in THF to provide the diol **9**.[11] Compound **9** on treatment with toluenesulfonyl chloride and triethylamine resulted in the formation of di-tosylate which was subjected to hydrogenation conditions for the cleavage of N-N bond using Raney-Ni to give the free amine which on nucleophilic displacement of di-tosylate led to the formation of indolizidine alkaloid (*R*)-coniceine **5** (Scheme 1). The extrapolation of this strategy allowed the successful completion of the synthesis of all the three target molecules in a very short and efficient manner.

Scheme 1: Synthesis of (*R*)-coniceine



The synthesis of the target molecules (-)-lentiginosine and its 1,2-epimer commenced with γ-amino-α,β-unsaturated ester **8a**. At this stage we investigated the use of the Sharpless asymmetric dihydroxylation reaction used for the embedding two hydroxy groups in the substrate containing a pre-existing chiral centre with a bulky substituent at the allylic nitrogen.

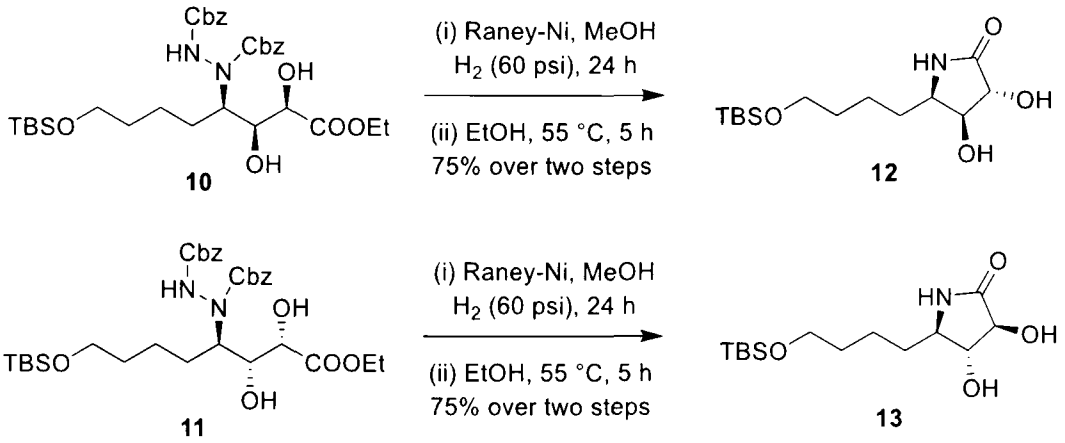
Scheme 2: Optimization of dihydroxylation reaction



The use of cinchona alkaloid ligand variants to achieve the two requisite stereocentres provided a general synthetic pathway to the family of hydroxylated azasugars in a highly diastereoselective manner. Dihydroxylation of **8a** under Sharpless conditions in the absence of a chiral ligand interestingly gave "*syn* facial selectivity" (*syn*-**10**/*anti*-**11**:83/17) where both products were easily separable by silica gel column chromatography. Extensive

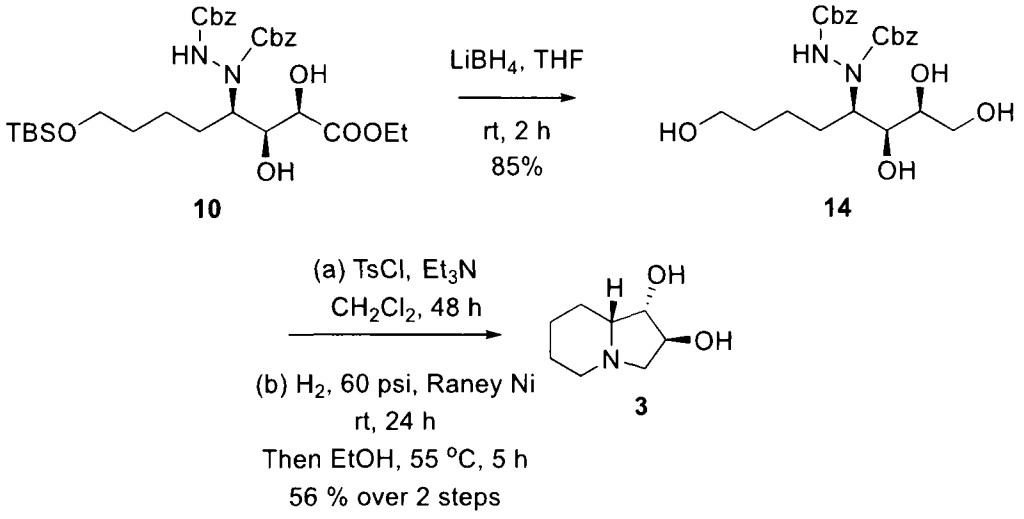
NMR studies were carried out on compounds **12** and **13** to determine the relative stereochemistry.

Scheme 3: Preparation of cyclic derivatives



After determining the relative stereochemistry of compounds **12** and **13**, we proceeded to the synthesis of target molecules. For the synthesis of (-)-1,2-*epi*-lentiginosine **3**, diol **10** was subjected to $LiBH_4$ reduction to give tetrol **14**. Compound **14** was subjected to selective primary tosylation using TsCl and Et_3N to give the di-tosyl, which was subjected to hydrogenation conditions using freshly prepared Raney-Ni to deliver the free amine which on nucleophilic displacement of di-tosylate led to the formation of the desired (-)-1,2-*epi*-lentiginosine **3** (Scheme 4).

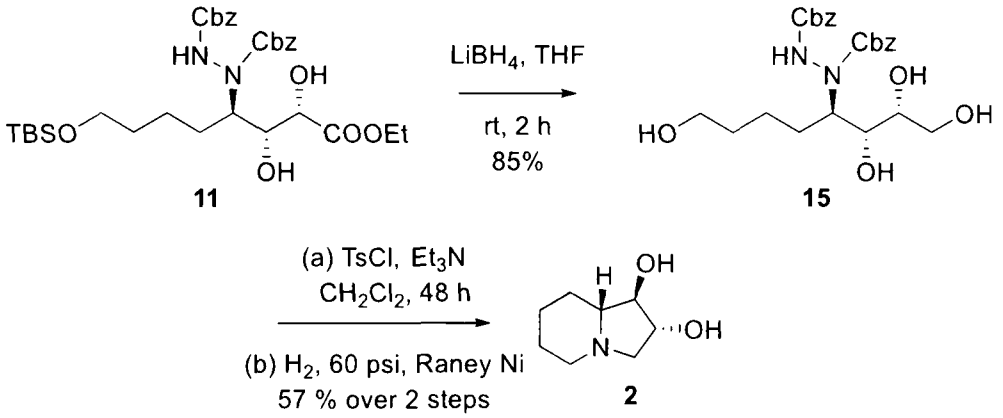
Scheme 4. Synthesis of 1,2-*epi*-lentiginosine



In a similar way, as illustrated in Scheme 5, (-)-lentiginosine **2** was synthesized from diol **11** by an analogous series of reactions to those shown in Scheme 4. The strategy can also

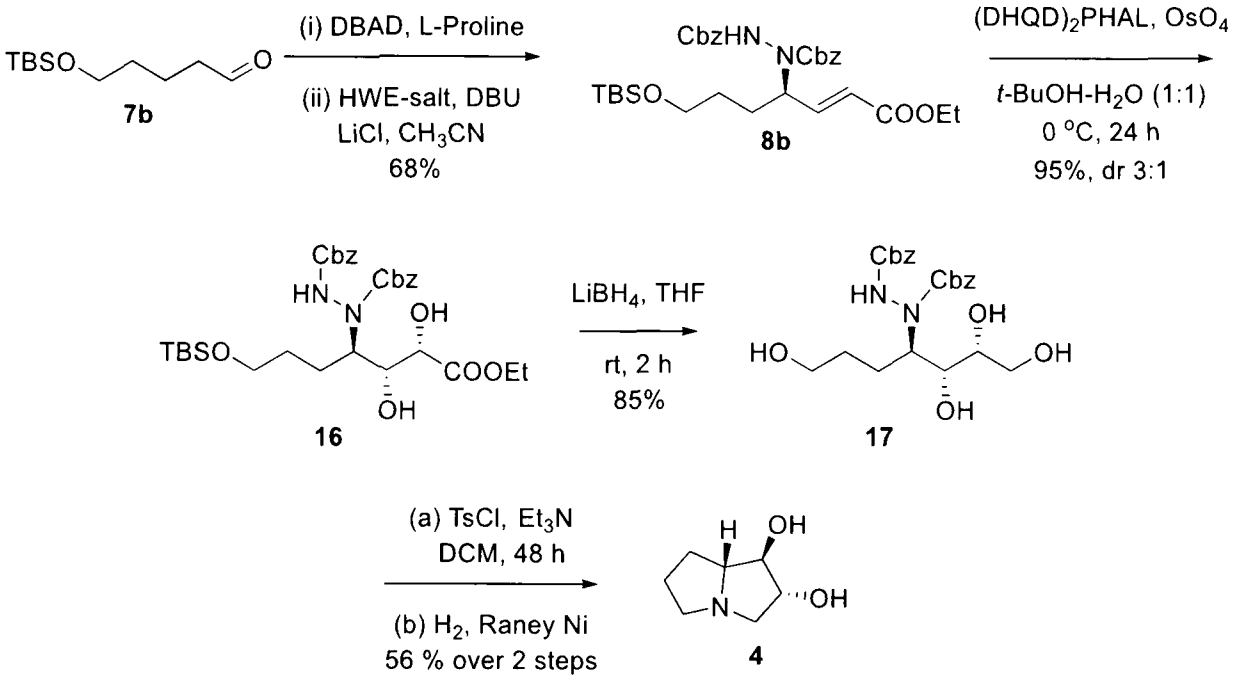
be extended to the synthesis of the natural enantiomer and other stereoisomers by simply using the other enantiomer of proline for the α-amination and different ligands for dihydroxylation.

Scheme 5. Synthesis of (-)-lentiginosine



After the successful completion of the synthesis of (-)-lentiginosine and its 1,2-epimer we thought to extrapolate our strategy to other analogues such as dihydroxypyrrolizidine **4** by simply altering the chain length. As illustrated in Scheme 6, the synthesis started with the aldehyde **7b**, which on sequential α-amination followed by HWE olefination furnished the γ-amino-α, β-unsaturated ester **8b** in 68% yield and 94%ee as determined by HPLC. The olefinic compound **8b** was subjected to Sharpless asymmetric dihydroxylation using $(DHQD)_2PHAL$ as the ligand to give the diol **16** in diastereomeric ratio of 3:1. The desired diastereomer was separated by silicagel column chromatography and was subjected to same set of reactions as described in Schemes 5 and 6.

Scheme 6. Synthesis of (-)-dihydroxypyrrolizidine



In conclusion, we have developed a new, highly efficient and concise protocol to dihydroxylated indolizidine and pyrrolizidine alkaloids using a proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation reaction as the key steps. Its utility was illustrated by the total synthesis of (-)-lentiginosine, (-)-*epi*-lentiginosine and (-)-dihydroxypyrrolizidine. The synthetic strategy allows implementation of the desirable stereocenters at C-1, C-2 and C-8a and can be extended to the synthesis of other stereoisomers and analogues with variable ring size and different degrees of hydroxylation.

Our synthetic approach afforded the target compound **3** in a linear sequence of 4 steps with an overall yield of 31%, target compound **2** with an overall yield of 23% and target compound **4** with an overall yield of 23%.This strategy is the shortest synthesis reported so far from easily available starting materials with high yields.

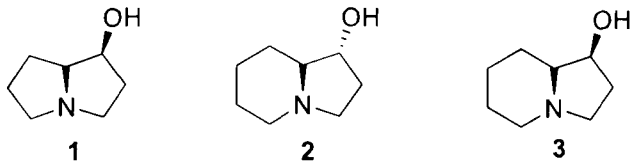
Section B: Stereoselective approach to the synthesis of 1-hydroxyindolizidines and pyrrolizidines

Biosynthesis of many hydroxylated indolizidine and pyrrolizidine alkaloids reveal the formation of useful intermediates such as D and L-1-hydroxy indolizidines other than amino acids such as pipecolinic acid. These compounds were found to be useful precursors for the synthesis of toxic indolizidine and pyrrolizidine alkaloids such as salframine and

swainsonine.[12]A close study of both the isomers of hydroxyl indolizidines revealed an insight to the biosynthesis of swainsonine. Cytotoxicity and other biological properties have attracted many chemists to take up hydroxyl indolizidines and pyrrolizidines as target compound for synthesis.

Both indolizidines and pyrrolizidines have been molecules of great interest as evident from our earlier communications. We have used tools like HKR, proline catalyzed α-aminoxylation in our previous strategies for the synthesis of molecules like swainsonine, conine and conicine. We then devised a short and an efficient strategy using proline catalyzed α-amination and Sharpless asymmetric dihydroxylation to achieve the synthesis of lentiginosine and analogues in high enantio and diasteroeselectivity.

Figure 1. Some mono hydroxylated indolizidine and pyrrolizidine alkaloids

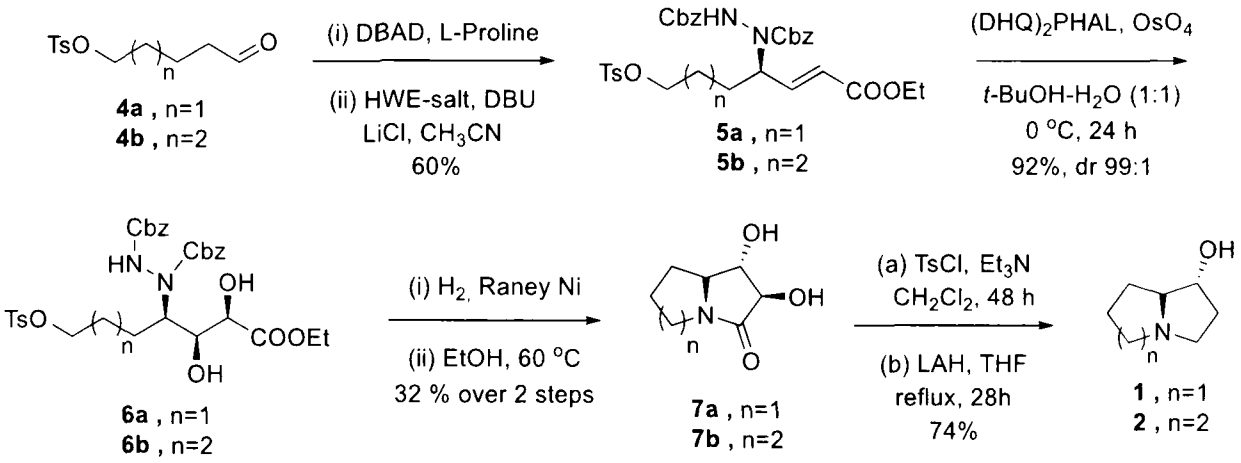


1 2 3

Our synthesis started from mono tosylated 1,6-hexane diol **4**. Selective mono tosylation was found to be an alternative to our previously reported silyl ethers in order to avoid protection and deprotection steps. Oxidation of the primary alcohol using IBX in ethyl acetate gave aldehyde **4** which was subjected to α-amination reaction using DBAD as a nitrogen source and L-proline as a catalyst followed by HWE olefination reaction to get α, β-unsaturated hydrazino ester **5a** in 60 % yield and 92% ee using HPLC. The product **5a** was then treated with OsO_4 in the presence of suitable cinchona alkaloid ligand and other additives to give syn diastereomer **6a** as the major product. In the dihydroxylation step, it was seen that no much difference was observed in the present case although the protecting group (TBS) was changed.[13] This was first observed on TLC that the ratio of diastereomers remained same which was further confirmed using HPLC where we observed similar results as in our previous case. With the desired diol **6a** in hand we proceeded to the cyclization step where compound **6a** was treated with freshly prepared Raney Ni in methanol with few drops of glacial acetic acid to simultaneously cleave N-N bond and cyclisation to give the aza bicyclic lactam **7a** in only 32% yield. Further efforts to increase

the yield of cyclization step were futile. The α-hydroxy group of **7a** was then selectively tosylated followed by reduction with $LiAlH_4$ to give target compound **1** in 74% yield. In a similar way, as illustrated in Scheme 1, compound **2** was synthesized from diol **6b** by an analogous series of reactions to those shown in Scheme 1. The strategy can also be extended to the synthesis of the natural enantiomer and other stereoisomers by simply using the other enantiomer of proline for the α-amination and different ligands for dihydroxylation.

Scheme 1. Synthesis of (-)-monohydroxyizidines



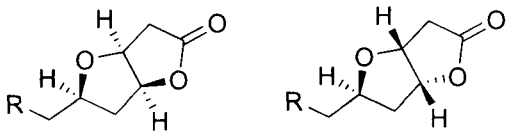
<u>Chapter 4:</u> An organocatalytic approach to asymmetric synthesis of Hagens gland lactones and (-)- colletallol is divided into two sections.

<u>Section A</u>: A stereocontrolled synthesis of Hagen's gland lactones via iterative proline catalyzed α-aminoxylation and oxa-Michael addition reactions

Hagen's glands (Fig. 1) earlier known as pygidialglands (located near the abdominal tips) of the braconid wasps, *D. Longicaudata* (Ashmead), D. Tryoni (Cameron) and *Fopius* (Biosteres) arisanus, are found to contain fragrance rich lactones.[14] This was first observed by Hagen (1953) and Buckingham (1975) who also put in efforts to study the significance of these secretions in the pest management of fruitfly population control in Hawaii and eastern queensland, especially against the queensland fruitfly Bactroceratryoni which is known to be an aggressive pest with a wide host range.[15] Williams *et al.* suggested the presence of two bicyclic lactones and experimentally characterized these bicyclic lactones

by NMR studies using Karplus based calculations. Kitching *et al.* have determined the absolute stereochemistry of these lactones through synthesis which employs an interesting route that uses 1,3-diol approach followed by $PdCl_2$-catalyzed oxycarbonylation-lactonization reaction.[16]

Figure 1. Hagen's gland lactones and their epimers



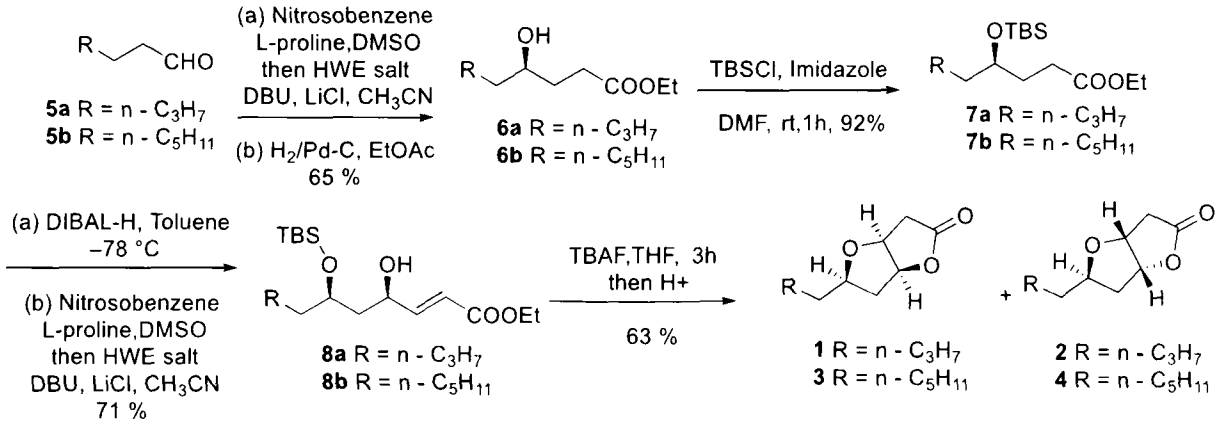
1 R = n - C_3H_7 **2** R = n - C_3H_7
3 R = n - C_5H_{11} **4** R = n - C_5H_{11}

Proline in the recent past has been defined as 'universal catalyst' because of its utility in different reactions providing rapid, catalytic, atom economical access to enantiomerically pure products. Recently, we reported a concise synthesis of γ-hydroxy ester by proline catalyzed sequential α-aminoxylation and HWE olefination of an aldehyde and successfully used this reaction in iterative fashion for the enantiopure synthesis of *syn-/anti*-1,3-polyols.[17]We now report the application of this methodology along with a highly diastereoselective oxa-Michael addition reaction in the concise synthesis of substituted tetrahydrofuro[3,2-b]furan-2(3*H*)-one derivatives.

Thus commercially available aldehyde **5a** on sequential α-aminoxylation using nitroso benzene as oxygen source and L-proline as catalyst and subsequent Horner-Wadsworth-Emmons (HWE) olefination using ylide generated from triethylphosphonoacetate followed by hydrogenation using catalytic amount of H_2-Pd/C furnished the γ-hydroxy ester **6a** in 65% yield and 94% ee (determined using HPLC). The free hydroxy group of γ-hydroxy ester **6a** was protected as TBS ether using TBSCl to furnish compound **7a** in excellent yield (Scheme 1).The TBS protected hydroxyester **7a** was then reduced using DIBAL-H in toluene at -78 °C to furnish an aldehyde. Crude aldehyde was further subjected to α-aminoxylation reaction using L-proline as a catalyst followed by HWE-olefination to yield compound **8a** in good diastereomeric excess (dr ratio 95:5)as measured by HPLC. With *syn*-1,3-diol **8a** in hand we proceeded to the synthesis of Hagen's gland lactone using oxa-Michael addition which was triggered through the fluoride-mediated cleavage of a silyl protecting group using TBAF in THF followed by lactonization with catalytic amount of

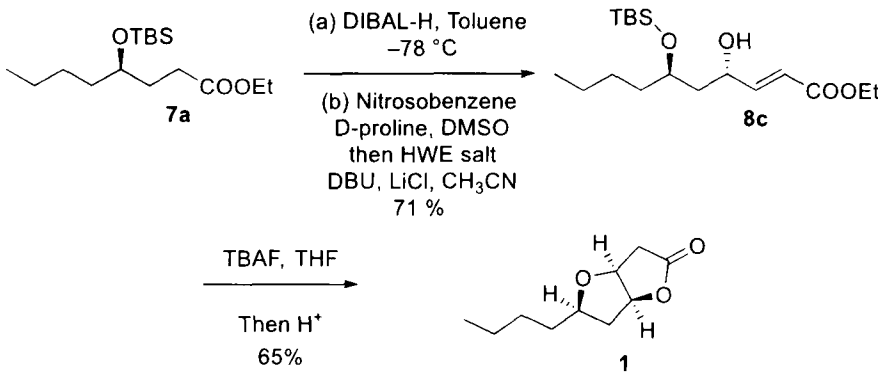
HCl (pH~3 in toluene). At this stage we could observe the formation of two products **1&2**. In order to rationalise our findings, we planned to test the devised strategy by synthesizing 1,3-anti diol as an intermediate (Scheme 2). For this purpose, we started with previously synthesized protected γ-hydroxy ester **7a** which was reduced using DIBAL-H in toluene at -78 °C to furnish corresponding aldehyde. Crude aldehyde was further subjected to α-aminoxylation/HWE olefination reaction using D-proline as a catalyst to obtain 1,3-anti diol **8c**

Scheme 1. Synthesis of Hagen's gland Lactones



with an excellent dr ratio (97:3) determined using HPLC. To test the formation of diastereomeric mixture one-pot oxa-Michael/ lactonisation was performed on the diol **8c**. In this case we observed the formation of only one product (**1**) as characterised by the ^{13}C NMR which was an entirely different result when compared to the *syn*-diol product (Scheme 2).

Scheme 2. Synthesis of epi-Hagen's gland Lactones



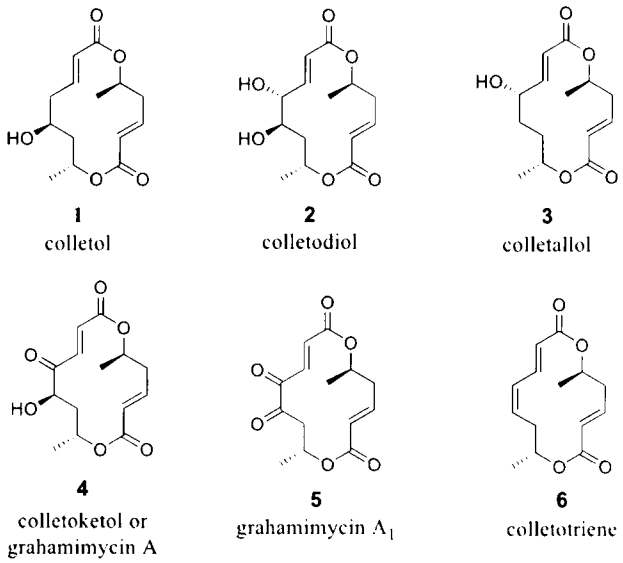
To check the reproducibility and improve the confidence in the stereochemical outcome by the above methods, we thought of extrapolating the strategy to the synthesis of **3** and **4** isolated from *D.krausii*. Both the compounds could easily be synthesized to obtain a separable mixture of cis and trans isomers from the corresponding aldehyde octanal **5b** by subjecting it to similar set of reaction conditions as described in scheme 1.

In conclusion, we have developed a new, efficient and organocatalytic protocol to Hagens gland lactones using a proline catalyzed α-aminoxylation and consequent oxa-Michael reaction. Desirable stereocenters can be obtained by using the suitable catalyst and this approach could further be extended to the synthesis of other stereoisomers and synthetic analogues.

Section B: Total synthesis of (–)-(6*R*,11*R*,14*S*)-colletallol via proline catalyzed α-aminoxylation and Yamaguchi macrolactonization

(-)-Colletallol **3,** a 14-membered unsymmetrical bis-macrolactone, was isolated from the plant pathogen *Collectotrichumcapsici* along with structurally related macrolides colletol **1,** colletodiol **2** and colletoketol **4** (Fig. 1).[18]Recently, two structurally isomeric 14-membered bis-lactones, grahamimycin A **4** and grahamimycin A_1**5** were isolated from the aerobic fermentation of cultures of *Cytosporasp.* ATCC 20502.[19] It was later realized that the structures of colletoketol and grahamimycin A were identical.[20]These macrolactones can result from a biosynthesis *via* the macrodiolide colletotriene **6.**[21]

Figure 1: Some 14 membered macrolides



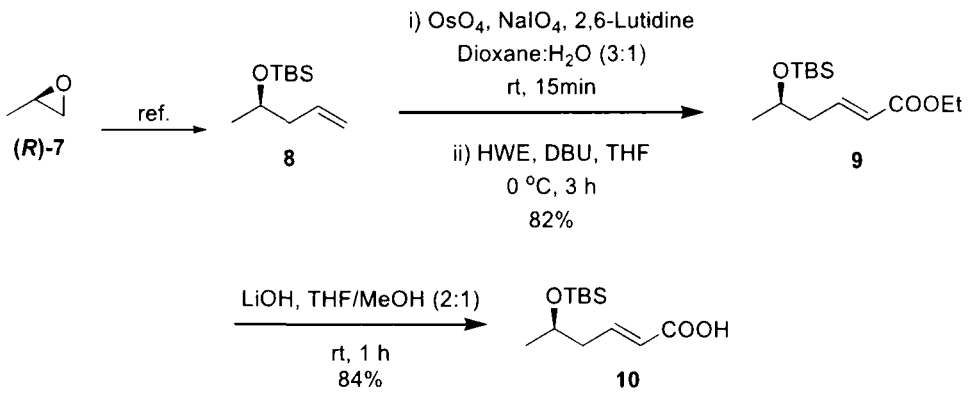
The promising biological activity and the unique structure of the 14-membered unsymmetrical diolides make them attractive synthetic target and so far three syntheses of colletallol **3** including a racemic synthesis have been reported in the literature. However, the natural (6*R*,11*R*,14*R*) colletalol was found to be inactive, its 14-epimer was found to be a useful target for structure activity studies.[22]

Colletallol could be synthesized from the alcohol fragment 14 and acid fragment **10**. Both the acid and alcohol fragment could be accessed independently from commercially available chiral propylene oxide.

Synthesis of acid fragment

Synthesis of acid fragment started with (*R*)-propylene oxide **7**, which was converted to TBS protected homoallylic alcohol **8** using literature procedure.[23] The olefin of TBS protected homoallylic alcohol **8** was subjected to oxidative cleavage in the presence of OsO_4 and $NaIO_4$ and the aldehyde obtained was proceeded without further purification to HWE olefination with triethylphosphonoacetate in dry THF at 0°C to furnish the *trans*-olefin **9** in 82% (two steps, E/Z 99:1) yield. The ester group of *trans*-olefin **9** was hydrolyzed with LiOH to afford the corresponding acid **10** in 84% yield (Scheme 2).

Scheme 2. Synthesis of acid fragment

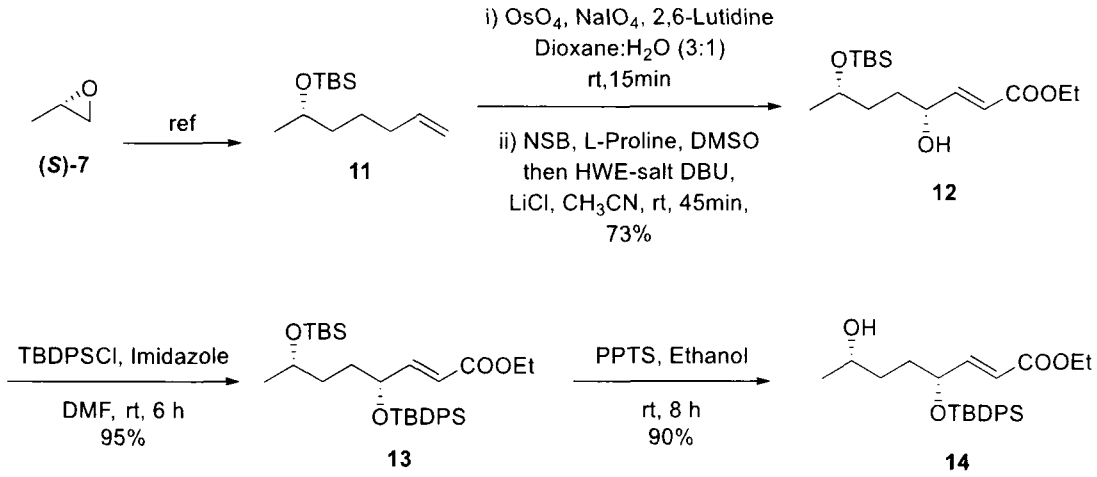


Synthesis of alcohol fragment

Synthesis of alcohol fragment started with same (*S*)-propylene oxide **7** which was converted to TBS protected alkenol **11** by literature procedure.[24]The olefin of TBS

protected alkenol **11** was oxidized to aldehyde in the presence of OsO_4 and $NaIO_4$ and the aldehyde was subjected to α-aminoxylation reaction using L-proline as a catalyst followed by HWE-olefination to yield compound **12** in 73% (two steps) yield and good diastereomeric excess (dr ratio 98:2). Protection of the free hydroxyl group as its TBDPS ether gave **13** in 95% yield. The TBS group was deprotected using PPTS in ethanol for 8 h to give alcohol fragment **14** in 90% yield (Scheme 2).

Scheme 3. Synthesis of alcohol fragment



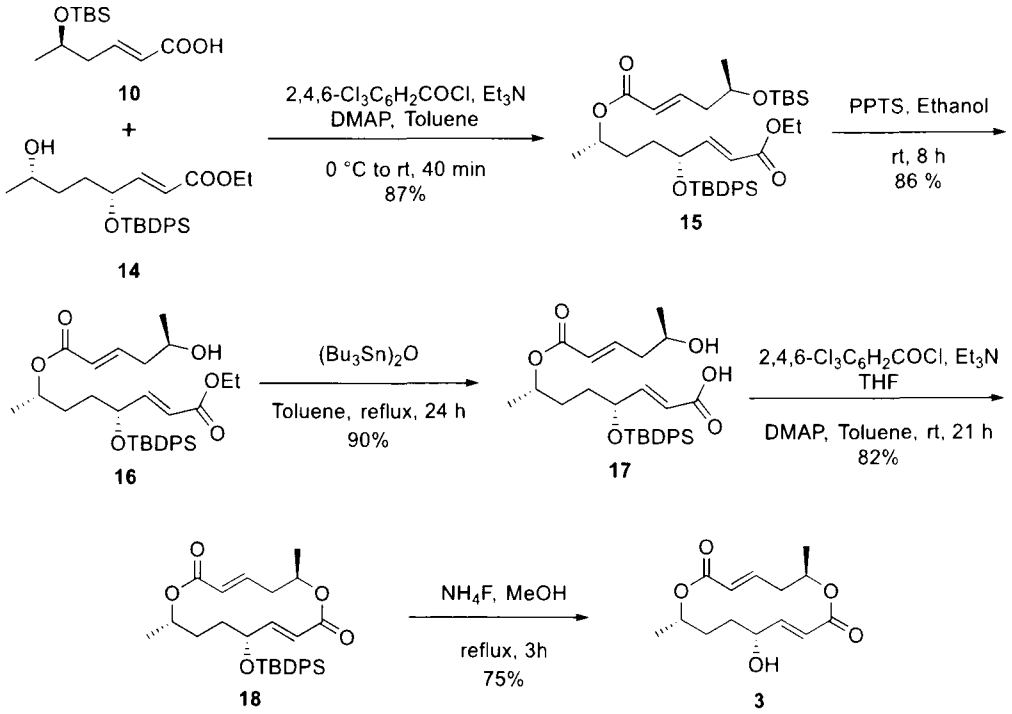
Completion of synthesis

Having obtained both the fragments alcohol **14** and acid **10** in substantial amount we required to couple them and achieve the synthesis of target molecule by synthetic manipulations. Thus, both the fragments were subjected to esterification under different conditions. Our first few attempts using Steglich condition, Shiina condition and Mitsonobu procedures were unsuccessful. We then proceeded with Yamaguchi protocol where after a few optimizations, we could observe the formation of **15** within 40 minutes (87% yield) when the reaction was performed at 0°C (scheme 4). The TBS ether of **15** was cleaved using PPTS in EtOH to afford alcohol **16** in 86% yield.

Hydrolysis of ethyl ester **16** to seco acid **17** using LiOH however failed inspite of several attempts with different solvent combinations, temperature and equivalents, instead we ended up hydrolyzing the ester and acid fragment **(Table 1)**. Use of DBU in benzene gave

only a complex reaction mixture. Since basic conditions were not found suitable to our substrate, therefore we

Scheme 4: Completion of synthesis of colletallol



considered changing the conditions to neutral medium. Finally the desired seco acid **17** was obtained in 90% yield using bis(tributyltin) oxide[25](5 equiv.) in toluene under reflux conditions. Macrolactonization of seco acid **17** was achieved using Yamaguchi coupling conditions to give the corresponding macrocyclic lactone **18**. From our previous experiences we thought that prolonged reaction times using PPTS would cleave TBDPS but attempts under varied temperature and reaction conditions were unsucessful. We then chose ammonium fluoride in methanol under reflux conditions which afforded the target molecule **3** in 75% yield.

In conclusion, a new and efficient total synthesis of (-)-colletallol with high diastereoselectivity has been developed using proline catalyzed α-aminoxylation and Yamaguchi macrolactonization reactions. The synthetic strategy described here has significant potential as we have achieved overall yield of 22% in 11 linear steps and also a flexible approach for further extension to the synthesis of all the isomers of (-)-colletallol and other 14-membered unsymmetrical bis-macrolactones.

Chapter 1

Sharpless asymmetric dihydroxylation (AD) and proline-catalyzed reactions

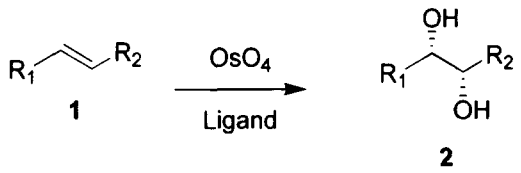
1.1. SHARPLESS ASYMMETRIC DIHYDROXYLATION (AD)

1.1.1. Introduction

Preparation of enantiomerically pure compounds active as drug scaffolds requires a variety of chiral molecules that can be used to construct complex targets. Such chirons are mostly known to exist naturally as a source from either marine organisms, plants or animals. However, the availability of such molecules in nature is rather low meaning they may either be available as the other isomer or may lack a particular type of starting material or the intermediate.

In recent times, several strategies and powerful methods have appeared in the literature for synthesizing pharmacologically useful compounds in a highly enantio and diastereo selective manner. Several methods such as use of auxialiaries, easily available chiral catalysts and reagents are known. The use of "chiral catalyst" approach is of a particular interest in the scientific community because by using a small amount of chiral catalyst a large amount of required material can be synthesized. Such strategies become useful techniques and prove to be beneficial for reasons that the chiral inducing agents are used economically.[1] Use of transition metal mediated reactions such as epoxidation,[2] aminohydroxylation,[3] dihydroxylation[4] have evolved as a fruitful result of tremendous interest in the oxidative addition of heteroatoms to olefins. The incidence of " ligand acceleration" is identified to be a familiar feature in these methods[7] wherein a metal catalyzed process turns over faster in the presence of a coordinating ligand.

The osmium catalyzed bis hydroxylation better known as Sharpless asymmetric dihydroxylation (AD) reaction, introducing two hydroxyl groups to an olefin is known to be the most dependable and selective transformations in organic synthesis.

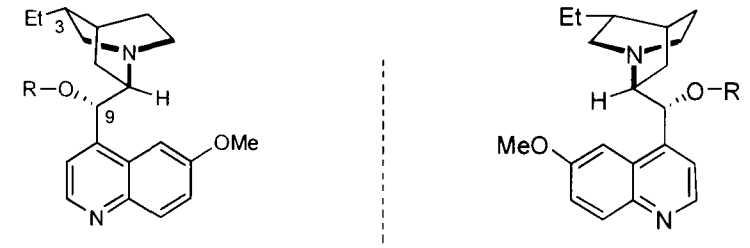


Scheme 1: Dihydroxylation reaction of olefin

Initially, during studies on the stoichiometric oxidative reaction of osmium tetroxide with olefins it was studied that pyridine was known to accelerate the reaction

significantly. When it was found that this reaction was not cost effective , efforts were made to study the reaction to address the issue.[8] Relatively inexpensive reagents were then used mainly for reoxidation of the osmium (VI) glycolate esters, boosting its synthetic utility.[5b] *N*-Methylmorpholine *N*-oxide (NMO) was found to show better results.[9a,b] Tsuji *et al.* then showed that $K_3Fe(CN)_6$ and a base K_2CO_3 gave excellent results where osmium could be used in catalytic amount for the dihydroxylation reaction.[9c]

Later enantioselective induction in the osmylation reaction was studied. Chiral pyridine derivatives by Sharpless and Hentges failed because of its low affinity for OsO_4.[10] Pyridine derivatives were then replaced by quinuclidines to show moderate to good enantiomeric excess when acetate esters of cinchona alkaloids (Figure **1**) were used in stoichiometric amount as chiral ligands. Marko and Sharpless later improvised the method by making it catalytic by simply adding NMO as a co-oxidant.[11] The enantiomeric excess was found to be low when compared to the *stoichiometric* reaction.

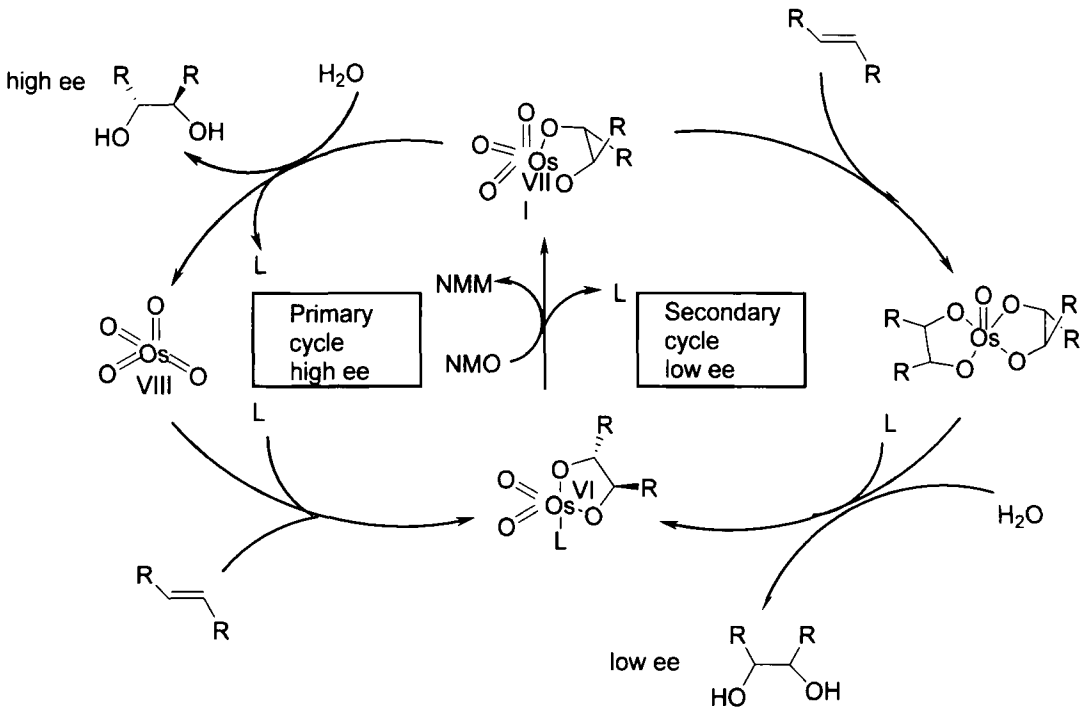


Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

Figure 1. Cinchona alkaloid ligands for AD under catalytic conditions.[22,25]

This was due to the presence of a second catalytic cycle, [12] (Scheme **2**) which exhibited only low or no enantioselectivity. Kwong performed the reaction under a biphasic medium which showed that the participation of the second catalytic cycle can be eliminated using $K_3Fe(CN)_6$ as the stoichiometric re-oxidant.[13] Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions. **(Scheme 3)**

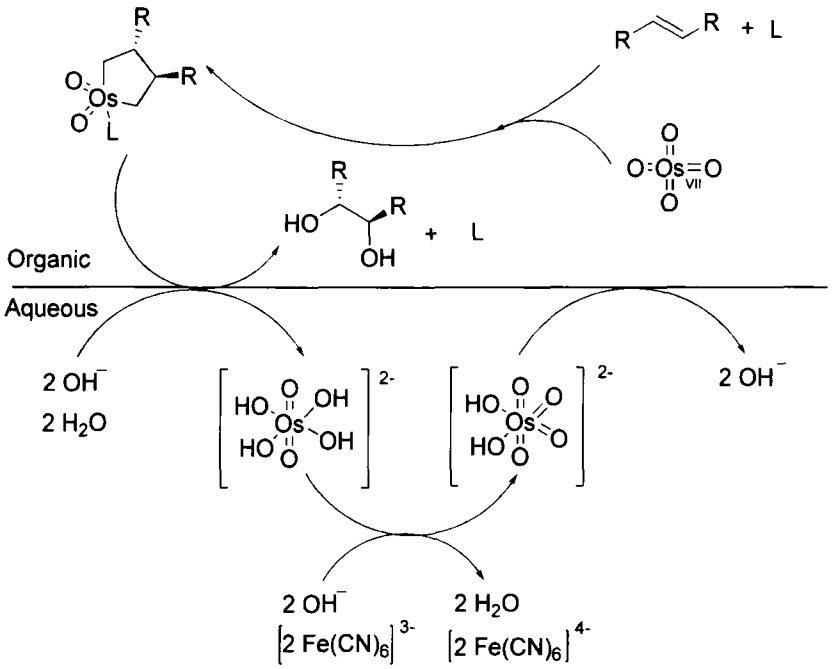


Scheme 2. Two catalytic cycle for the AD reaction using NMO as the Co-oxidant

$MeSO_2NH_2$ another additive was then introduced by Sharpless *et al.*[14] for the hydrolysis of the osmium (VI) glycolate ester. This was particularly effective even in the presence of sterically encumbered substrates, and tetra substituted olefins. Due to this "sulfonamide effect", most of dihydroxylation reactions run smoothly at 0°C rather than at room temperature, that may influence the stereoselectivity.[15]

Cinchona alkaloids were then discovered by Hartung[14] (phthalazine core) and Crispino[16] (diphenylpyrimidine core) attached to a heterocyclic spacer which has led to a substantial enhancement in both selectivity and the scope of the bis-hydroxylation (Figure **2**).

Figure 2. The latest generation of "dimeric" PHAL and PYR ligands



Scheme 3. Biphasic medium of AD reaction with $K_3Fe(CN)_6$ as the Co-oxidant

1.1.2. Empirical rules for predicting the face selectivity

Sharpless has proposed a 'mnemonic device' in which the plane of the olefin is divided into the four quadrants. The SE becomes sterically unapproachable therefore only hydrogen can be placed here. The NW quadrant is slightly more approachable and the NE quadrant appears to be quite open. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[17c] An olefin which is placed according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives (Figure 2).

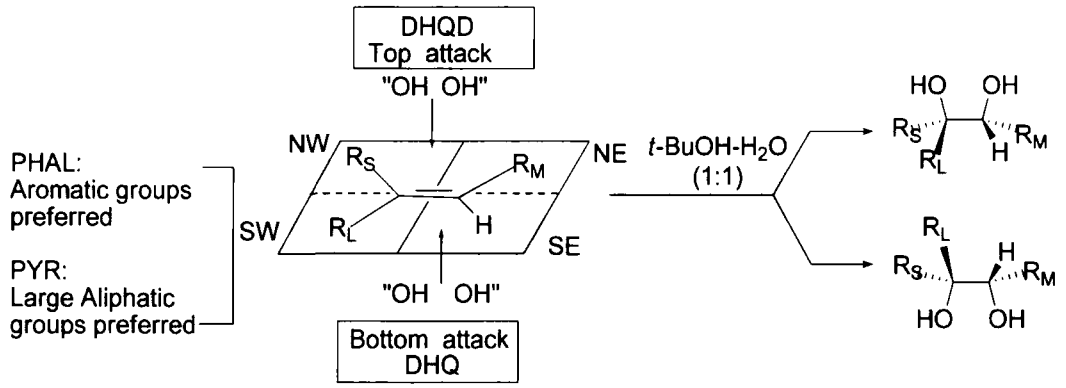


Figure 2. The mnemonic device for predicting the face selectivity

1.1.3. Reaction Conditions

A general procedure of the reaction is to perform the reaction in 1:1 mixture of water and *t*-BuOH keeping the olefin concentration to 0.1 M.[18] Stoichiometric amounts of $K_3Fe(CN)_6$ is used in 3 equivalents as the re-oxidant, osmium generally as a solution in toluene or tertiary butanol is used in 0.2-0.4 mol%, 1 mol% of the cinchona alkaloid ligand, 3 equivalents of K_2CO_3 and 1 equivalent of $CH_3SO_2NH_2$. A major feature of the reaction is that the ligand can be recovered especially when large scale reactions are performed. Work up procedures are generally easy, In case of second generation ligands, acidic work up with 3% aq. H_2SO_4 satuarated with K_2SO_4 (ca. 40 mL/1g of ligand). The ligand enters the aqueous layer as its hydrogen sulphate salt and the solution can be reused directly for the subsequent AD reaction without further purification. However, the amount of K_2CO_3 may be increased when reused to neutralize excess acid and to release the salt as its free base.

1.1.4. The cinchona alkaloid ligands and their substrate preferences

Phthalazine (PHAL) ligands

The most widely used class of ligands especially in the presence of aromatic groups, for instance in *trans*-stilbene where the enantioselectivity is as high as 99.8%.[21] However, PHAL ligands give mediocre results with aliphatic olefins, especially if they are substituted with smaller groups.

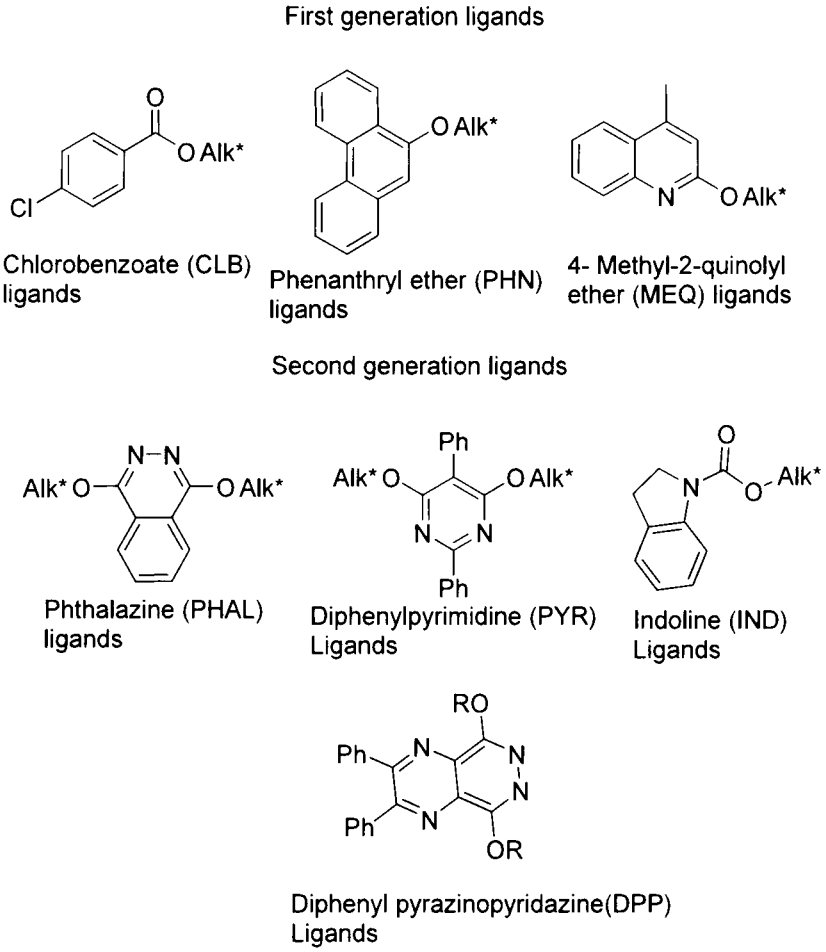


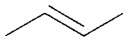
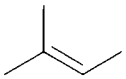
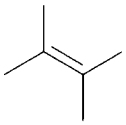
Figure 3. Dihydroxylation ligands

Anthraquinone (AQN) ligands

In the presence of aliphatic substituents, AQN proves to be very useful. Other suitable substrates are allyl halides or allylic alcohols that show satisfactory results, however are generalized to show poor selectivity for olefins with aromatic or sterically demanding substituents.[26]

Pyrimidine (PYR) ligands

The pyrimidine ligands are the ligands of choice for olefins with sterically demanding substituents.[23]

Olefin						
Choice of ligand	PYR PHAL	PHAL	IND	PHAL	PHAL	PYR PHAL
ee%	30-97%	70-97%	20-80%	90-99.8%	90-99%	20-97%

Diphenyl pyrazinopyridazine (DPP) and diphenyl phthalazine (DP-PHAL) ligands

These class of ligands are found to be a little superior over PHAL class. Not very effective with the olefins that are suitable to AQN ligands. These are also known to give good results with cis 1,2-disubstituted olefins.[24]

Indoline (IND) ligands

Mostly a choice for cis 1,2-disubstituted olefins.

1.2 PROLINE-CATALYZED ASYMMETRIC ORGANIC TRANSFORMATIONS

1.2.1. Introduction to organocatalysis

Organocatalysis has been a very interesting field of research for the synthesis of very important pharmaceuticals. Organocatalysis involves the use of small organic molecules for many organic transformations, known to be fairly new and popular field within the domain of chiral molecule (or enantioselective) synthesis. Although chemical transformations using organic molecules were known over a period of time for instance Stork enamine reaction was one such reaction that uses secondary amines for simple conversions.[27] Of late the use of such molecules have been evident for inducing chirality. α -Functionalisation reaction has seen a rapid growth since 1970's first publication by Hajos and Wiechert on highly enantioselective catalytic aldol reactions using small amino acid catalyst ie., proline.

Rediscovery of such processes has led to tremendous growth in both industry and in academics. With the advent of use of organic molecules as catalyst, the process has attracted not only academic researchers but has also fascinated many industries. This is mainly due to being cost effective, easy experimental procedures, and diminution in toxic industrial waste, that presents a huge advantage for production of intermediates when compared with traditional metal catalysts. Organic can act as very efficient catalysts and infact contribute to green processes. Efforts will however continue towards the design of variety of catalysts with better efficacy and reactivities.

1.2.2. Proline as a Universal catalyst

Proline has been defined as a "universal catalyst" in the recent past as it was found to be a very useful tool in a variety of organic transformations, the only existing naturally occurring amino acid having a secondary amine functionality. In comparison to other amino acids it is known to raise the pKa value and show a better nucleophilicity. It can undergo both iminium mode of catalysis (nucleophile) as well as enamine catalysis (acts as good Michael acceptors).[28] It can also act as a bifunctional catalyst as it has both acidic and basic handle (Figure **4**). Proline-catalyzed reactions are found to be extremely stereoselective probably due to the formation of structured transition states with many

hydrogen bonding skeletons. Although several derivatives of proline are known , proline by itself is found to be an ideal catalyst.

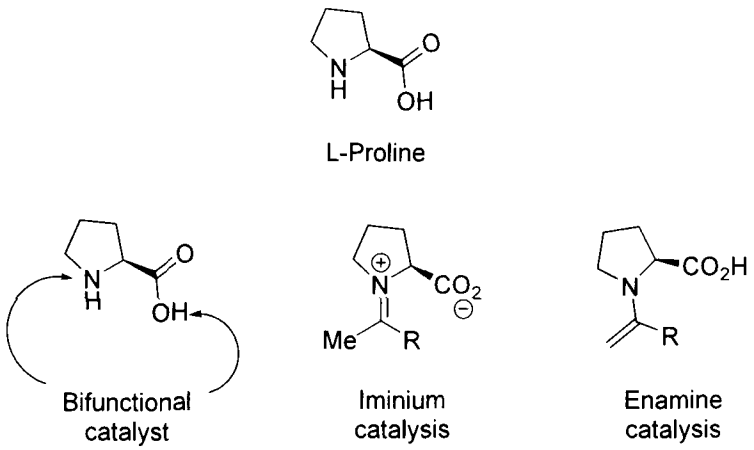


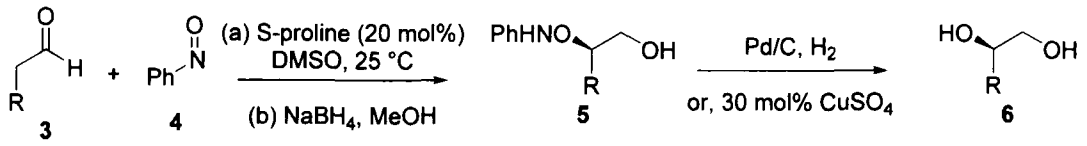
Figure 4. Modes of proline catalysis

Several reactions like aldol. [29] Diels-Alder. [30] and α-functionalization[32] especially in the carbonyl functionalities are known to be catalyzed using proline of which particularly proline-catalyzed α-aminoxylation[34] and α-amination[35] reactions have emerged to be powerful methods for the synthesis of pharmacologically important moieties.

1.3 PROLINE-CATALYZED ASYMMETRIC α-AMINOXYLATION

1.3.1. Proline-catalyzed α-aminoxylation

Carbonyl compounds are found to be very useful handles in organic synthesis. α–Functionalisation of carbonyl compounds has recently become a major area of research useful for development of powerful and efficient methodologies. Thus, for the preparation of α-oxygenated carbonyls well-established methods are reported including the use of Davis oxaziridine,[36a] Sharpless dihydroxylation,[36b] and epoxidations.[36c,d] These methods suffer in the fact that they are neither catalytic nor direct. Zhong *et al.* have proposed an α-aminoxylation[34b] rection where an aldehyde **3** without substitution is reacted with L-proline as a catalyst, nitrosobenzene as an electrophile and DMSO as a solvent at an ambient temperature, aminoxylation of the aldehyde takes place at the α-position. Prone to racemization this aldehyde can be trapped by reducing *in situ* with sodium borohydride and the aminoxyl moiety undergoes hydrogenolysis with Pd/C, H_2 or any of the copper salts such as copper acetate to give the corresponding diols that mimic the dihydroxylation products by forming vicinal diol **6** in very high enantioselectivities (Scheme **4**).



R = Ph, *i*-Pr, *n*-Bu, CH_2Ph etc. > 99% ee

Scheme 4. Proline-catalyzed α-aminoxylation

Other means of trapping the aldehyde is possible by using any of the sequential reactions, for instance Horner Wordsworth Emmons olefination reaction.

1.3.2. Mechanism of proline-catalyzed α-aminoxylation

The mechanism initially proposed for α-aminoxylation reaction is depicted in figure **5**. The enantioselectivitiy of the reaction can be explained by the fact that the proton of the acid shows a hydrogen bonding with the nitrogen of the electrophile forming a chair like transition state where the *Si* face of the anti-enamine is proximal to the oxygen atom of nitrosobenzene to afford an α-aminoxylated aldehyde having *R* configuration.

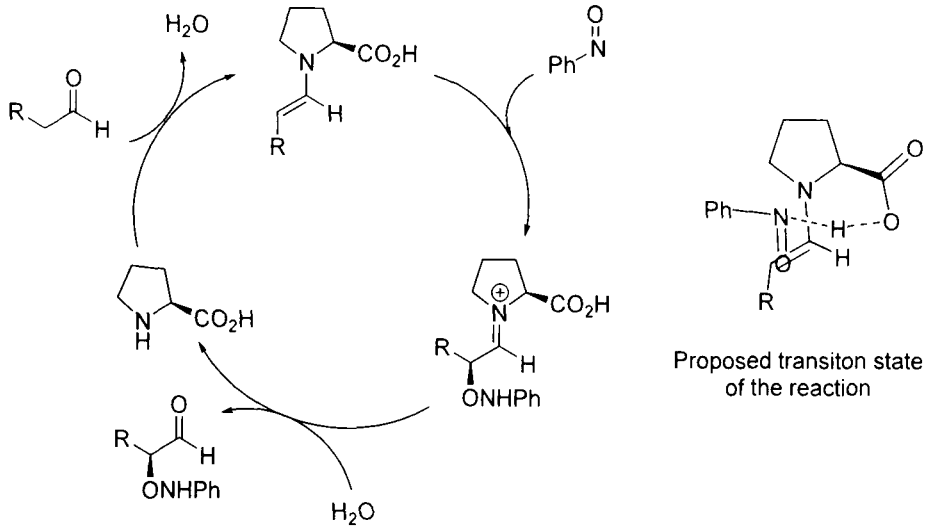


Figure 5. Proposed mechanism of the α-aminoxylation reaction

An autoinductive approach was proposed by Blackmond for α-aminoxylation of aldehydes. A detailed study of the reaction kinetics of proline-catalyzed aminoxylation of aldehydes by the Blackmond group revealed that the reaction is autocatalytic. In addition to the rate enhancement, the enantiomeric excess gets improved during the course of the reaction. A catalytic cycle involving an adduct of proline with the reaction product was proposed to account for this unusual reaction kinetics not observed in other proline-catalyzed reactions except for α-amination.[37]

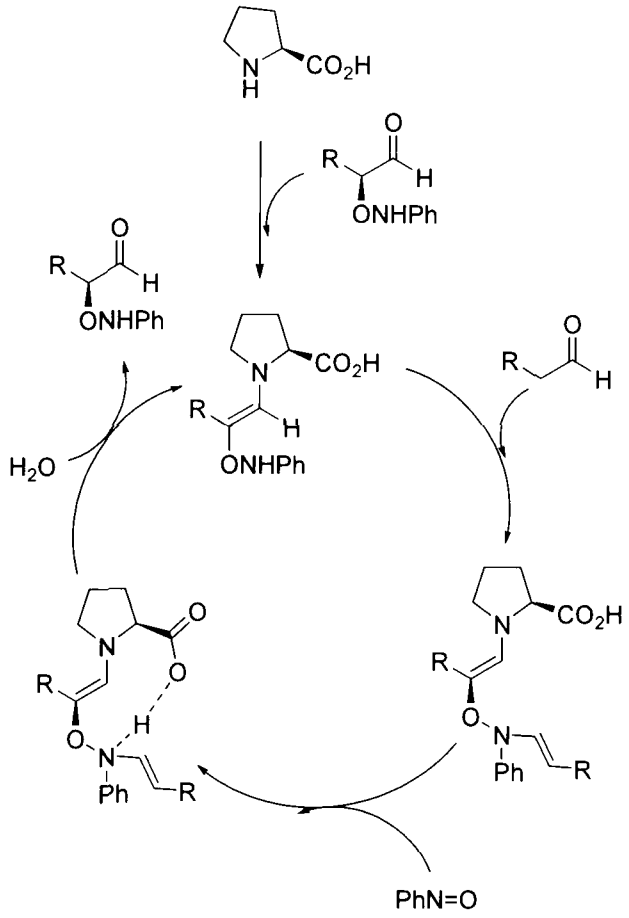
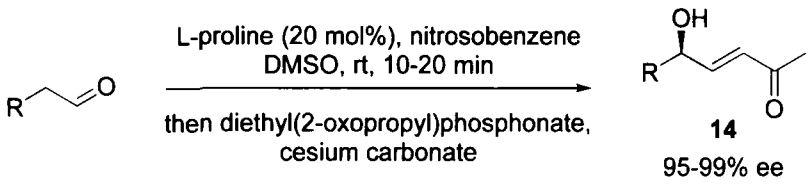


Figure 6. Autocatalytic mechanism proposed by Blackmond and coworkers

1.3.3. Proline-catalyzed sequential transformations

1.3.3.1. Sequential aminoxylation-olefination[38a]

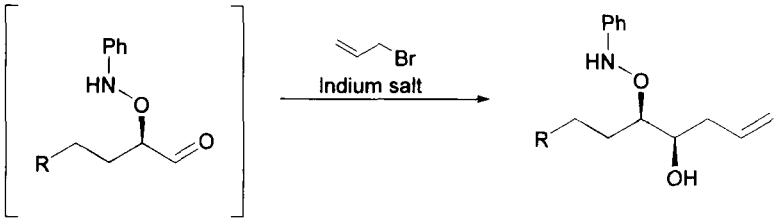
The product of α-aminoxylation reaction gave an α- functionalized aldehyde which was found to be a useful handle for further organic transformations, one of the best method was reported by Zhong and co workers who have reported Horner-Wadsworth-Emmons olefination to trap the corresponding aldehyde to give active allylic alcohols **14** in good ee with cesium carbonate. (Scheme **5**).



Scheme 5: Sequential aminoxylation-olefination

1.3.3.2. Sequential aminoxylation-allylation[38b]

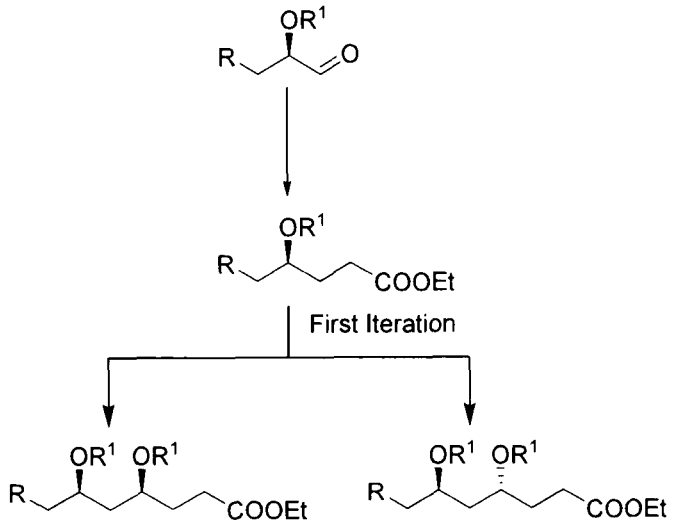
Zhong and coworkers have developed a methodology for the synthesis of 1,2-diols. The product *syn* and *anti* diols were isolated in good yields with the dr 4 : 1 (*syn/anti*) and syn as a major product, obtained in the one-pot tandem aminoxylation - allylation reaction.



Scheme 6: Sequential aminoxylation-allylation

1.3.3.3. Iterative proline catalyzed α-aminoxylation[38c]

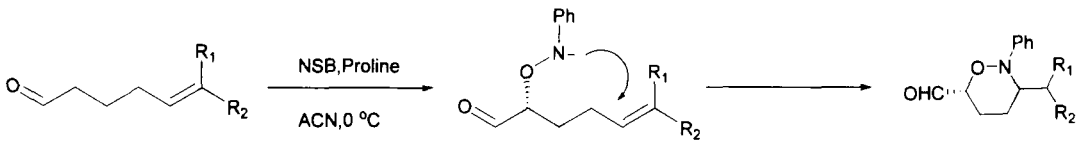
1,3-Polyols are very important motifs in many biologically important molecules. Many methods have been developed to synthesize *syn /anti* 1,3-diols. Kumar and coworkers have devised a feasible and a versatile method for the synthesis of 1,3,5- polyols using proline catalyzed α-aminoxylation reaction in a highly iterative fashion. The desired stereocenter could be obtained by simply changing the proline catalyst.



Scheme 7: Iterative proline catalyzed α-aminoxylation

1.3.3.4. Sequential aminoxylation - Michael reaction[38d,e]

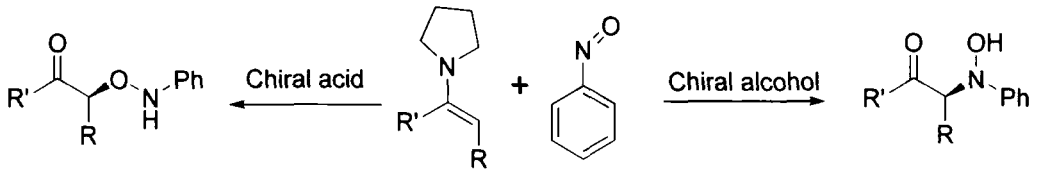
In the presence of unsaturated aldehydes, the aminoxylation reaction was known to be followed by a tandem oxa-Michael reaction by Zhong and coworkers.



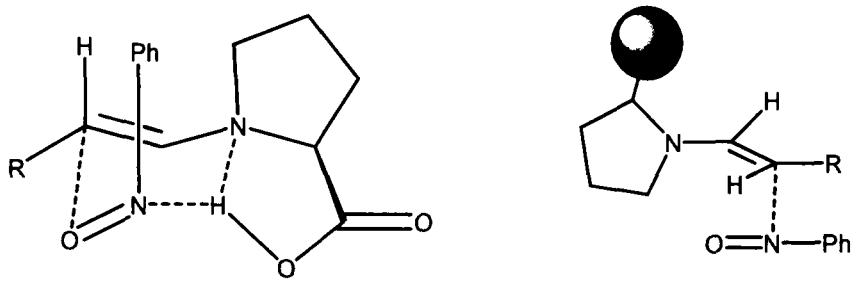
Scheme 8: Sequential aminoxylation - Michael reaction

1.3.4. Oxyaldol v/s aminoaldol[39]

Selective attack of oxygen over nitrogen as an electrophile is observed when proline is used as a catalyst. In such cases preferential formation of oxy products is observed.



This may be explained due to the fact that the nitrogen atom is protonated by the acidic proton forming a hydrogen bonding to give a six membered transition state. When proline derivatives especially sterically hindered aromatic substituents were used, it was observed that predominantly nitrosoaldol products were formed. This observation could be rationalized by the fact that the steric bulk of the substituents directs the incoming electrophile in a way that it facilitates the attack of nitrogen to give N-selectivity.



Oxy-aldol
95-99% ee
O:N>99:1

Amino-aldol
80-90% ee
O:N>1:9

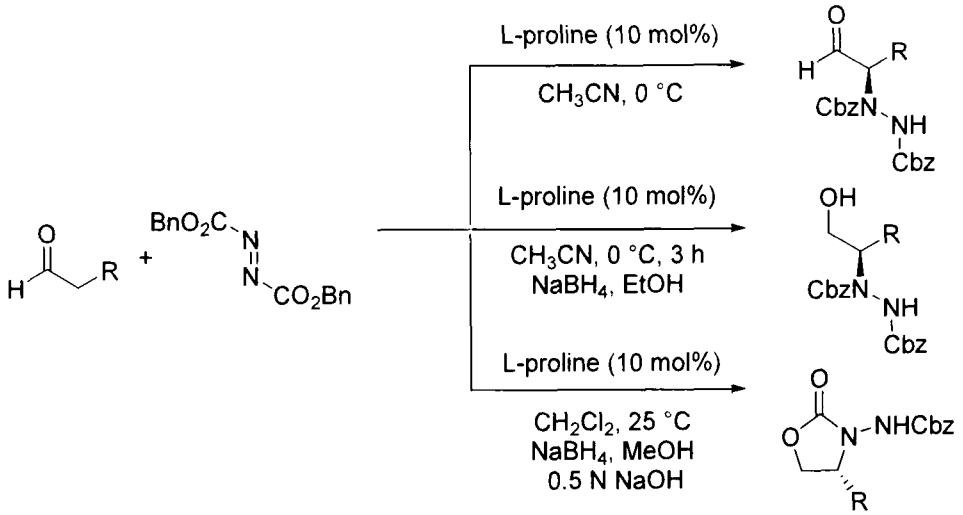
Figure 7: Transition state models for oxy aldol and amino aldol

1.4 PROLINE-CATALYZED ASYMMETRIC α-AMINATION

1.4.1. Proline-catalyzed α-amination

The significance of α-amino compounds has been of special interest among synthetic chemists as their preparation in an highly stereoselective manner becomes a major concern. Several approaches have been designed for the introduction of amine functionality in the molecule. Chiral pool approach using α-amino acids have been quiet useful but lack in the fact they have limited functionalities. SAR studies have showed the use of varied skeletons for bioactivity.

List[35a] and Jørgensen[35b] have independently approached asymmetric α-amination[35] reaction using proline as a catalyst. Synthesis of α- hydrazino aldehydes in good yields and excellent enantio selectivities has been a significant contribution to the field of organocatalysis.



Scheme 9. Proline-catalyzed α-amination

When an aldehyde is reacted with azodicarboxylate as an electrophile/nitrogen source with proline as a catalyst and acetonitrile as a solvent at ambient temperature, α-hydrazino aldehydes are obtained in excellent ee and very good yields. The resulting functionalized aldehyde may then be reduced using sodium borohydride to give amino alcohol or may further be treated with sodium hydroxide to give *N*-amino oxazolidinone.

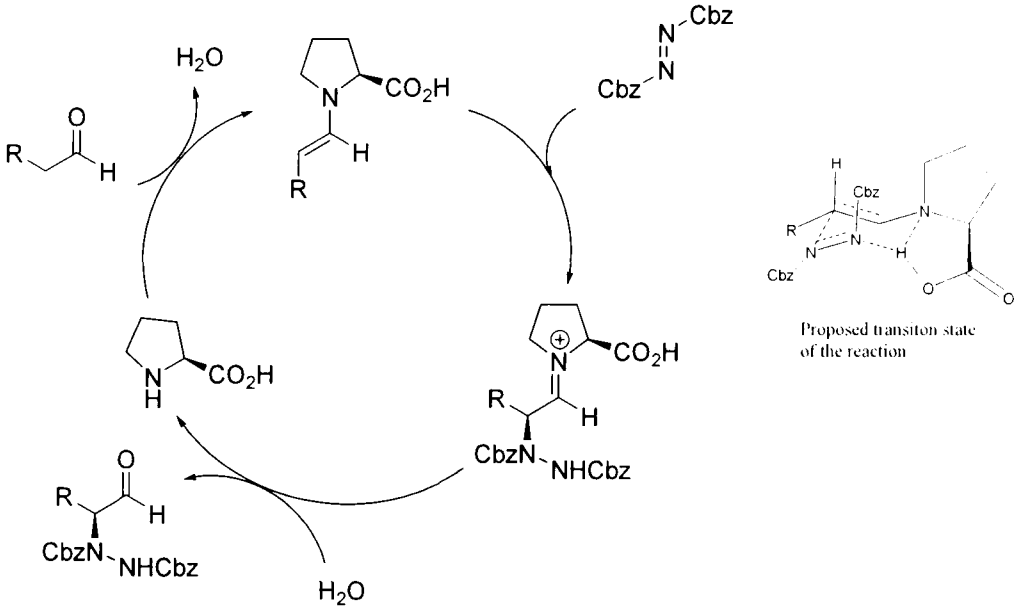


Figure 8: Mechanism for amination reaction

While the six-membered transition state similar to that in case of aminoxylation directed by the hydrogen bonding should be favored. An autocatalysis reaction was proposed by Blackmond *et al.* as in the case of aminoxylation reaction. Jorgenson *et al.* had questioned the effect of hydrogen bonding on the ee and so developed a silyloxy catalyst that did not participate in any kind of hydrogen bonding. In this case it was observed that the selectivity was defined on the basis of stereochemistry of the enamine and the steric bulk of the substituent. This was further confirmed using DFT calculations.

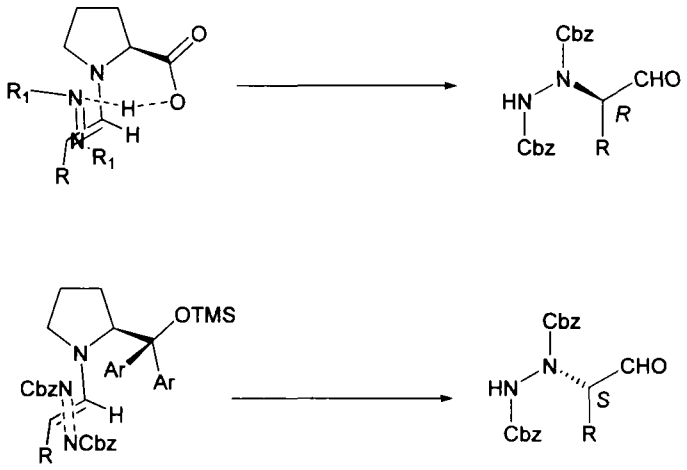


Figure 9. Transition states for amination reaction

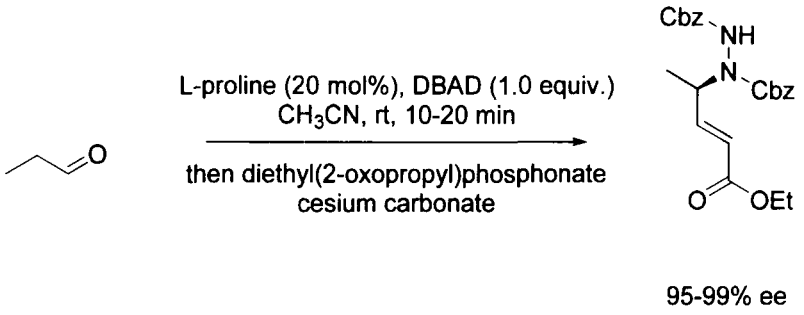
It was observed that when an *anti-E-enamine* was approached from a *Re* face via a possible bonding it gave an *R* product whereas in the presence of a sterically hindered substituent the approach of the electrophile takes place from the *Re* face therefore directing it for a *Si* face attack giving an *S* product.

1.4.2. Proline catalyzed sequential transformations

Proline-catalyzed amination reaction,[40] is a recently developed area in the field of organic synthesis. As a result, many one-pot procedures were developed by various groups over a period of time. Some selective sequential reactions are discussed below.

1.4.2.1. Sequential α-amination-olefination[40a]

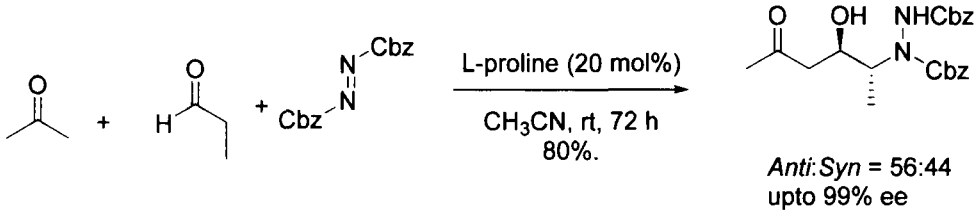
The proline catalyzed α-amination reaction was extended by Sudalai *et al.* They have reported a one-pot procedure for asymmetric α-amination/HWE olefination reaction of aldehydes in good enantioselectivities and high yields on variety of substrates (Scheme **10**).



Scheme 10. Sequential α-amination-olefination

1.4.2.2. Sequential amination-aldol[40b]

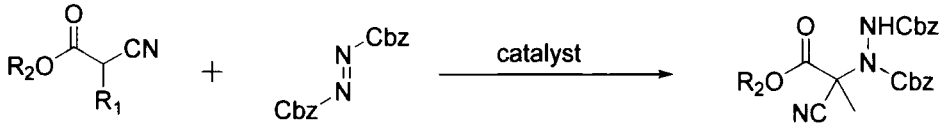
One-pot procedure for the synthesis of functionalized β-amino alcohols was developed by Barbas III *et al.* from aldehydes, ketones and azodicarboxylates (Scheme **11**).



Scheme 11. Sequential amination-aldol

1.4.2.3. α-Amination of cyano acetates[40c]

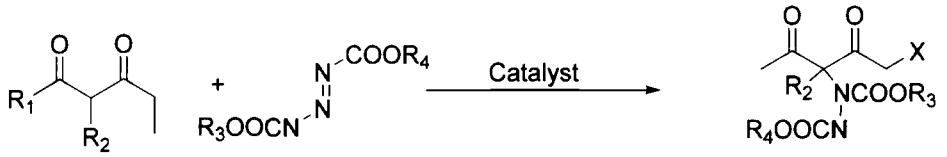
A variety of compounds were found to be useful substrates for α-amination reaction, for example cyano esters were found to be very useful substrates.



Scheme 12. α-Amination of cyano acetates

1.4.2.4. α-Amination on 1, 3-dicarbonyl compounds[40d]

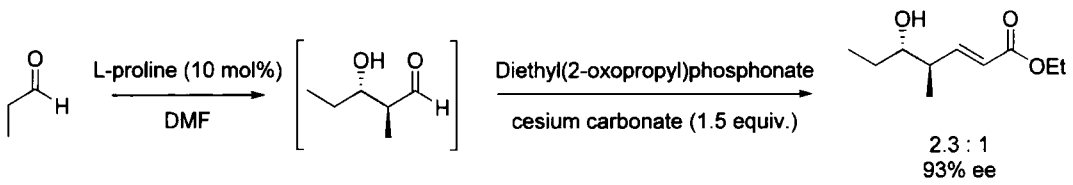
1,3-Dicarbonyls were found to be suitable substrates that gave very high ee and overall yields.



Scheme 13. α-Amination of 1,3-dicarbonyl compounds

1.4.2.5. Sequential aldol-olefination[40e]

Cordova *et al.* have reported one-pot organocatalytic asymmetric aldol-Horner-Wittig-Emmons olefination (Scheme **14**).



Scheme 14. Sequential aldol-olefination

1.5 References:

2. For reviews, see; I. Ojima, : *Catalytic Asymmetric Synthesis*. Ed.; VCH Publishers: New York, **1993**.
3. (a) T. Katsuki, V. S. Martin, *Org. React.* **1996**, *48*, 1; (b) T. J. Katsuki, *Mol. Catal. A: Chem.* **1996**, *113*, 87. For a review, see: R. A. Johnson, K. B. Sharpless, *Catalytic Asymmetric Synthesis* . I. Ojima, Ed.; VCH Publishers: New York, **1993**. pp. 101.
4. (a) F. E. McDonald, T. B. Towne, *J. Org. Chem.* **1995**, *60*, 5750; (b) R. M. Kennedy, S. Tang *Tetrahedron Lett.* **1992**, *33*, 3729; (c) S. Tang, Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299; (d) Tang, S., Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303; (e) R. S. Boyce, R. M. Kennedy, *Tetrahedron Lett.* **1994**, *35*, 5133.
5. K. B. Sharpless, A. Y. Teranishi, J. E. Backvall, *J. Am. Chem. Soc.* **1977**, *99*, 3120.
6. (a) H. C. Kolb, M.S. VanNieuwenhze, K. B. Sharpless , *Chem. Rev.* **1994**, *94*, 2483; (b) M. Schroder, *Chem. Rev.* **1980**, *80*, 187.
7. (a) G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem., Int. Ed.* **1996**, *35*, 451; (b) G. Li, K. B. Sharpless, *Acta Chem. Scand.* **1996**, *50*, 649; (c) J. Rudolph, P. C. Sennhenn, C. P. Vlaar, K. B. Sharpless, *Angew. Chem., Int. Ed.* **1996**, *35*, 2810; (d) G. Li, H. H. Angert, Sharpless, K. B. *Angew. Chem.*, Int. *Ed.* **1996**, *35*, 2813; (e) R. Angelaud, Y. Landais, K. Schenk, *Tetrahedron Lett.* **1997**, *38*, 1407.
8. D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.
9. (a) R. Criegee, *Justus Liebigs Ann. Chem.* **1936**, *522*, 75; (b) R. Criegee, *Angew. Chem.* **1937**, *50*, 153; (c) R. Criegee, *Angew. Chem.* **1938**, *51*, 519; (d) R. Criegee, B. Marchand, H. Wannowias, *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.
10. (a) W. P. Schneider, A. V. McIntosh, US Patent 2, 769, 824 Nov. 6, 1956; (b) V. VanRheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, 1973; (c) M. Minato, K. Yamamoto, J. Tsuji, *J. Org. Chem.* **1990**, *55*, 766.
11. (a) S. G. Hentges, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 4263
12. E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968.
13. J. S. M. Wai, I. Marko, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123.
14. H. L. Kwong, C. Sorato, Y. Ogino, H. Chen, K. B. Sharpless, *Tetrahedron Lett.* **1990**, *31*, 2999.

15. K. B. Sharpless, W. Amberg, Y. L .Bennani, G. A. Crispino, J. Hartung, K. S .Jeong, H. L .Kwong, K. Morikawa, Z. M. Wang, D. Xu, Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

16. Gobel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1993**, *32*, 1329.

17. G. A. Crispino, K.S. Jeong, H. C. Kolb, Z.M. Wang, D. Xu, K. B. Sharpless, *J. Org. Chem.* **1993**, *58*, 3785.

18. (a) H. C. Kolb, P. G.Andersson, K. B. Sharpless, *J. Am. Chem. Soc.* **1994**, *116*, 1278; (b) K. B. Sharpless, W.Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu , X. L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768; (c) K. P. M. Vanhessche, K. B. Sharpless, *J. Org. Chem.* **1996**, *61*, 7978.

19. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong , H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu, ; X. L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768.

20. H. C. Kolb, P. G. Andersson, Y. L. Bennani, G. A. Crispino, K. S. Jeong, H. L. Kwong, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 12226.

21. H. Becker, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1996**, *35*, 448.

22. G. A. Crispino, K. S. Jeong, H. C. Kolb, Z. M. Wang, D. Xu, K . B. Sharpless, *J. Org. Chem.* **1993**, *58*, 3785.

23. H. Becker, S. B. King, M. Taniguchi, K. P. M. VanHessche, K. B. Sharpless, *J. Org. Chem.* **1995**, *60*, 3940.

24. L. Wang, K. B. Sharpless , *J. Am. Chem. Soc.* **1992**, *114*, 7568.

25. Z. M. Wang, K. Kakiuchi, K. B. Sharpless, *J. Org. Chem.* **1994**, *59*, 6895.

26. (a) W. Baker, F. B. Field, *J. Chem. Soc.* **1932**, 86 ; (b) W. W. Catlson, L. H. Cretcher, *J. Am. Chem. Soc.* **1947**, *69*, 1952.

27. Y.Gao , K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538.

28. D. W. C. MacMillian, *Nature* **2008**, *455*, 304.

29. J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719.

30. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

31. (a) G. Sabitha, N. Fatima, E. V. Reddy, J. S. Yadav, *Adv. Synth. Catal.* **2005**, *347*, 1353; (b) D. B. Ramachary, N. S. Chowdari C. F. Barbas III, *Synlett* **2003**, 1910.

32. M. T. Hechavarria Fonseca, B. List, *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.

33. For α-functionalization reviews: (a) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjarsgaard, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; (b) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465.

34. For a review of proline-catalyzed asymmetric reactions see: List, B. *Tetrahedron* **2002**, *58*, 5573.

35. (a) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293; (b) G. Zhong, *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) A. Cordova, H. Sunden, A. Bogevig, M. Johansson, F. Himo, *Chem. A-Eur. J.* **2004**, *10*, 3673.

36. (a) B. List, *J. Am. Chem. Soc.* **2002**, *125*, 5656; (b) A. Bogevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jorgensen, *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; (c) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bogevig, K. A. Jorgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254; (d) H. Vogt, S. Vanderheiden, S. Brase, *Chem. Commun.* **2003**, 2448; (e) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770.

37. (a) F. A. Davis, C. Bang-Chi *Chem. Rev.* **1992**, *92*, 919; (b) K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama, K. B. Sharpless, *J. Am. Chem. Soc.* **1993**, *115*, 8463; (c) W. Adam, R. T. Fell , V. R.Stegmann, C. R. Saha-Moller, *J. Am. Chem. Soc.* **1996**, *118*, 708; (d) Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 7819

38. (a) S. P. Mathew, H. Iwamura, D. G. Blackmond, *Angew. Chem. Int. Ed.* **2004**, *43*, 3317. (b) P. Merino, T. Tejero, *Angew. Chem., Int. Ed.* **2004**, *43*, 2995.

38. (a) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637;(b) G. Zhong, *Chem. Commun.* **2004**, 606. (c) N. B. Kondekar, P. Kumar, *Org. Lett.* **2009**, *11*, 2611. (d) D. Zhu, M. Lu, P. J. Chua, B. Tan, F. Wang, X. Yang , G. Zhong, *Org.Lett.* **2008**, *10*, 4585; (e) M. Lu, D. Zhu, Y. Lu, Y. Hou, B.Tan, G. Zhong, *Angew. Chem. Int. Ed.* **2008**, *47*,10187.

39. (a) P. H.-Y. Cheong, K.N. Houk , *J.Am. Chem. Soc.* **2004**, *126*, 13912; (b) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Gong, A.-Q. Mi,; Y.-Z. Jiang, *Chem.Commun.* **2006**, 429; (c) C. Palomo, S. Vera, I. Velilla, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem. Int. Ed.* **2007**, *46*, 8054.

40. (a) S. P. Kotkar, V. B. Chavan , A. Sudalai *Org.Lett.* **2007**, *9*, 1001 (b) N. S. Chowdari, D. B. Ramachary, C. F. Barbas, III *Org. Lett.* **2003**, *5*, 1685; (b) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637;(c) S. M. Kim, J. H. Lee, D. Y. Kim, *Synlett* **2008**, 2659; (d) S. Saaby, M. Bella, K.A. Jorgensen, *J. Am. Chem. Soc* **2004**, *126*, 8120;(e) W. –W. Liao, A.I. Ibrahem, A. Cordova *Chem.Commun.* **2006**, 674.

Chapter 2

Asymmetric synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems using proline catalyzed α- amination reaction

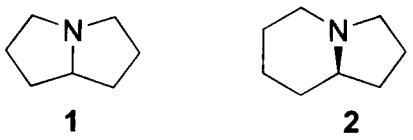
2.1. SECTION A

Synthesis of indolizidine, pyrrolizidine ring systems by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde

2.1.1 Introduction

Alkaloids are naturally occurring compounds having a basic often cyclic, nitrogen-containing functional group. They are primarily found in the plant kingdom, a few examples of alkaloids being nicotine (tobacco), quinine (malaria), morphine (poppy). Other alkaloids include strychnine and coniine, coniine was derived from hemlock and known for its toxicity; cocaine and heroin belonging to the narcotic class. The bitter taste of most alkaloids makes them very good antifeedant. Synthetic organic chemists have been involved in the synthesis of alkaloids with the hopes of finding alkaloids for use in pharmacology and medicine. Earlier it was believed that alkaloids were only found in plants. However it is now well known that alkaloids occur in microbes like fungi, bacteria, plants, invertebrates and vertebrates; in terrestrial as well as marine sources.

Pyrrolizidine **1**, indolizidine **2** cyclic systems **(Figure 1)** found as a key skeletons component in several alkaloids, display a wide range of biological and pharmaceutical activity.[1,2] Considering their potent biological activity and low abundance, they always remain an area of synthetic effort, resulting in a wide range of different strategies toward the synthesis of izidines namely (pyrrolizidines, indolizidines).[3,4] Considerable effort is being invested in the design of innovative methods for preparing the parent bicyclic systems and, more especially, for the stereocontrolled inclusion of a substituent.



1 Pyrrolizidine 2 Indolizidine

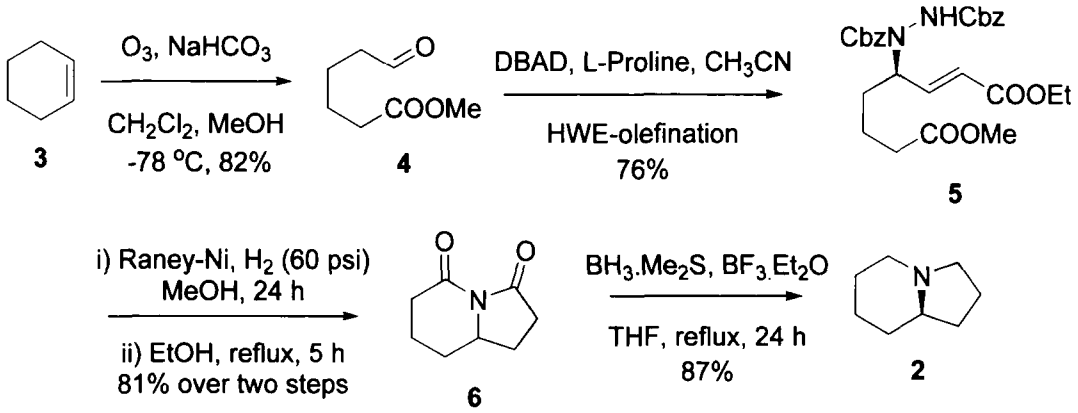
Figure 1: Structures of various azabicyclic ring system.

2.1.2. Review of Literature

There are several reports on the synthesis of indolizidine, pyrrolizidine ring systems in the literature.[3,4,5] A detailed report of recent syntheses is described below.

Kalkote *et al.* (2010)[4a]

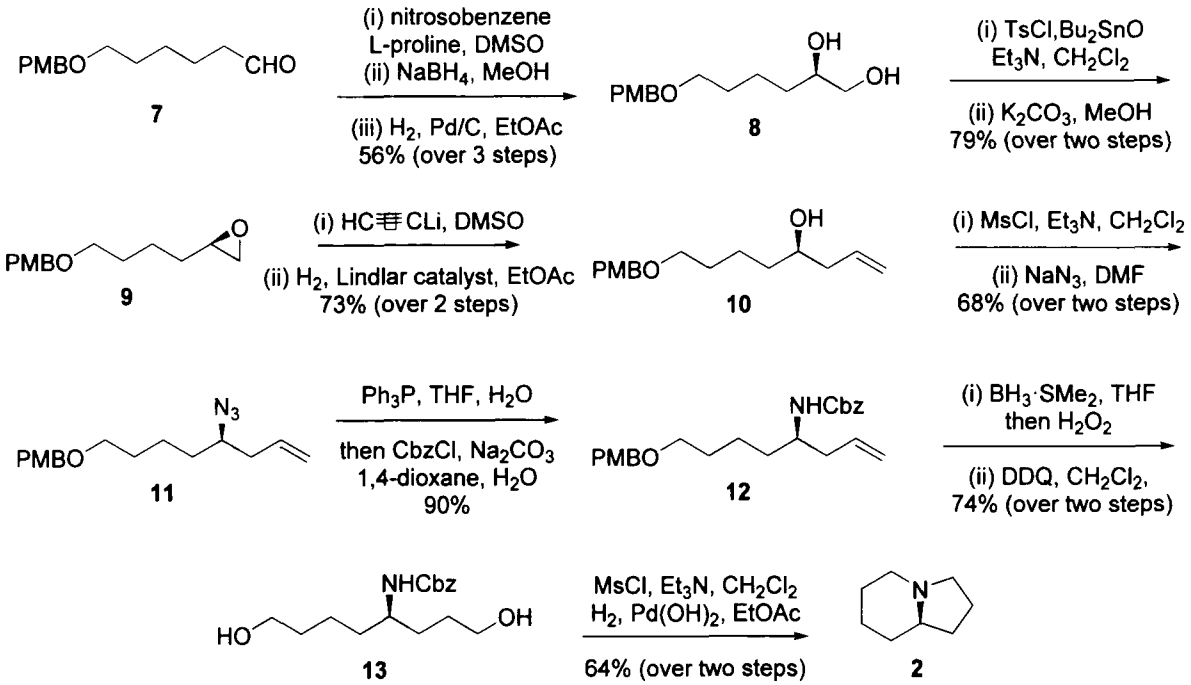
Kalkote and coworkers synthesized the indolizidine bicyclic core conicine **2** starting from cyclohexene **3**. Ozonolysis in the presence of sodium bicarbonate followed by treatment with acetic anhydride gave the functionalised aldehyde **4**. The aldehyde **4** was then subjected to sequential α-amination reaction and Horner Wadsworth Emmons reaction to give exclusively the *trans* γ-amino α,β-unsaturaed ester **5**. Raney Ni catalyzed hydrogenation of ester **5** followed by cyclization gave the bicyclic lactam **6** in 81% yield. Reduction of the bicyclic lactam **6** using Borane dimethyl sulfide with $BF_3.OEt_2$ afforded the target compound **2** (**Scheme 1**).



Scheme 1 : Synthesis of indolizidine ring system (Kalkote's method)

Kumar *et al.* (2010)[4h]

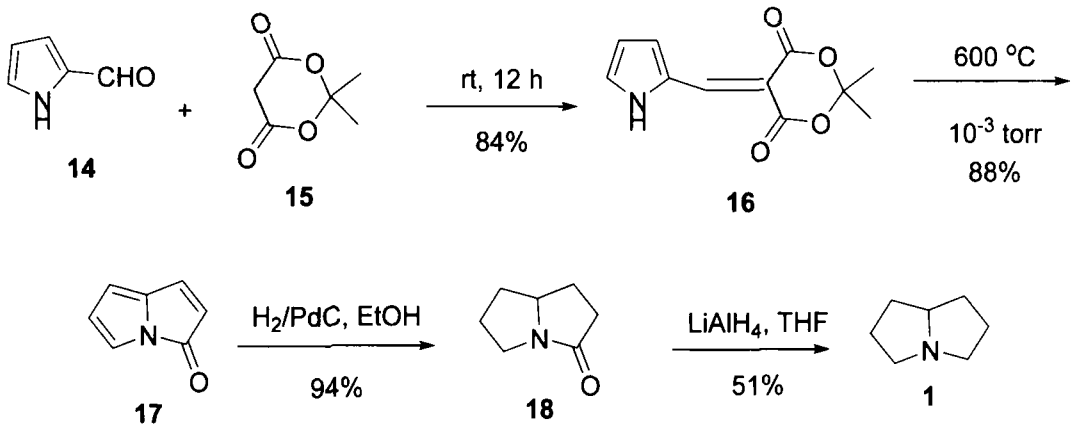
Our own group synthesized the indolizidine core conicine **2** using organocatalytic α-aminoxylation starting from aldehyde **7**. Aldehyde **7** on proline catalyzed α–aminoxylation followed by reduction gave diol **8** which on treatment with TsCl followed by base treatment gave epoxide **9**. Epoxide opening of **9** in a highly regioselective manner with lithium acetylide followed by reduction with Lindlar catalyst gave the alcohol **10**. The free hydroxy was then transformed into an azido functionality, following a two-step process of mesylation and subsequent sodium azide treatment, to afford the azide **11**. Azide of **11** along with in situ protection of free NH_2 group with Cbz gave protected homoallylic amine **12**. Hydroboration–oxidation reaction of the homoallylic amine **12** afforded the corresponding alcohol which on deprotection of PMB group using DDQ, gave the diol **13**. Mesylation of both hydroxyl groups followed by NCbz deprotection and tandem cyclization under hydrogenation conditions furnished (*S*)-coinicine **2** (**Scheme 2**).



Scheme 2 : Synthesis of indolizidine ring system (Kumar's method)

McNab *et al.* (2009)[5a]

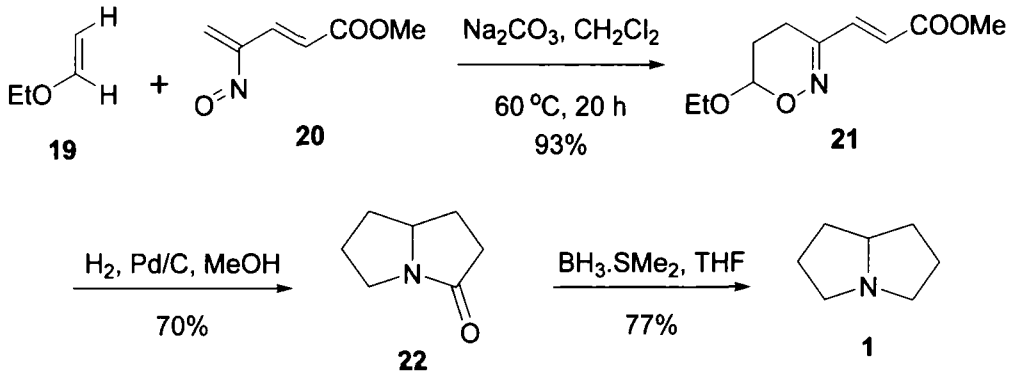
McNab and coworkers used pyrrole carboxaldehyde **14** for the construction of pyrrolizidine skeleton. **14** on treatment with Meldrum's acid **15** gave pure adduct **16** which on flash vacuum pyrolysis at 600° C furnished pyrrolizine-3-one **17**. **17** on subsequent hydrogenation followed by lithium aluminium hydride reduction gave the pyrrolizidine skeleton **1** (**Scheme 3**).



Scheme 3 : Synthesis of pyrrolizidine ring system (McNab's method)

Reissig *et al.* (2008)[5b]

Reissig and coworkers synthesized the pyrrolizidine ring using ring contraction method. Electron-rich olefin **19** on Diels–Alder reaction with nitrosoalkene **20**, gave 1,2-oxazine **21** which on hydrogenolysis furnished pyrrolizidinone **22** via ring contraction method. **22** on treatment with borane-dimethyl sulfide complex in tetrahydrofuran gave pyrrolizidine ring **1** (**Scheme 4**).



Scheme 4 : Synthesis of pyrrolizidine ring system (Reissig's method)

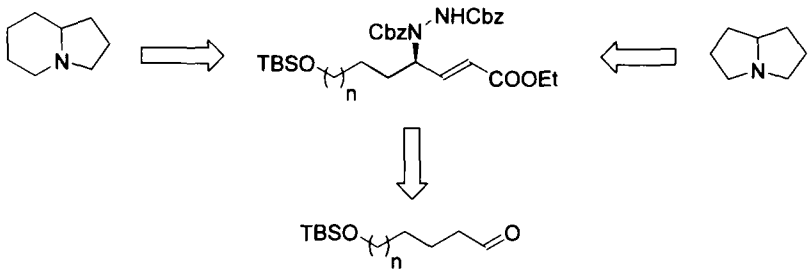
2.1.3. Present work

Objective

During the recent past, use of organocatalyzed transformations has persistently gained momentum and has been a promising strategy as an alternative to protein catalysis and toxic metal catalysis that are known to be rather expensive.[6,7] Similarly, organocatalytic processes are providing efficient means to construct complex target molecules in an rapid way from simple and readily available precursors in an environmentally friendly manner, minimizing yield, time and energy losses.[8] In continuation of our interest in organocatalysis and asymmetric synthesis of alkaloids,[9] we considered developing a route using α-amination and Horner–Wadsworth–Emmons (HWE) olefination approach,[10] for the synthesis of azabicyclic ring system such as pyrrolizidine **1** and indolizidine **2**.

2.1.4 Results and discussion

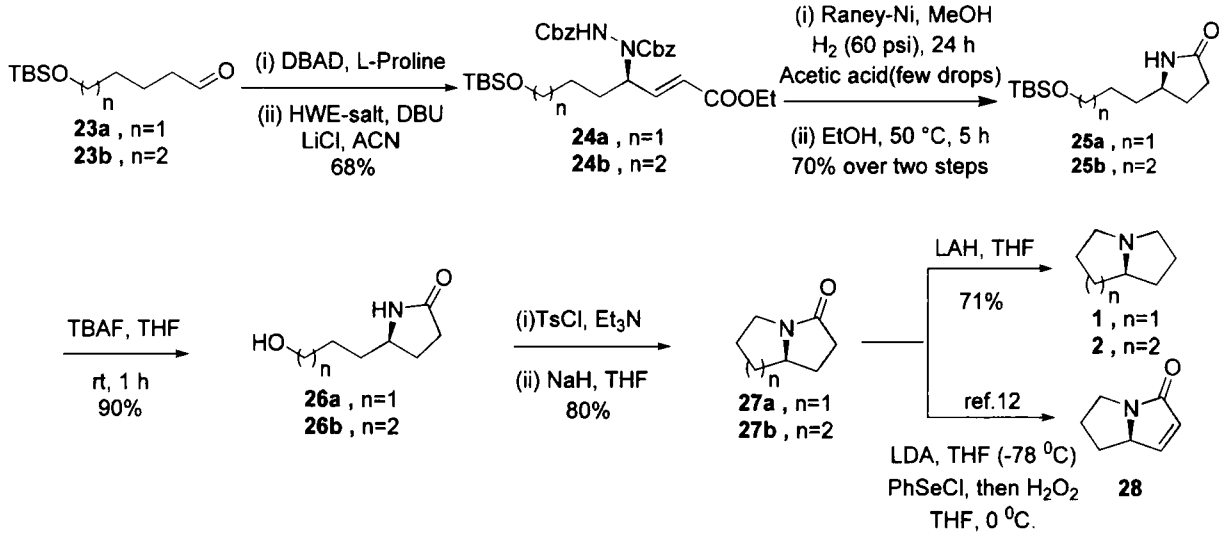
Our synthetic journey for the construction of target azabicycles via α-amination was envisioned through the retrosynthetic analysis as shown in **Scheme 5**. γ-Hydrazino-α,β-unsaturated ester was visualized as an useful intermediate for developing the alkaloid bicyclic system which was found to be the product of α-amination of the corresponding aldehyde, followed by HWE olefination as depicted in **scheme 5**.



Scheme 5: Retrosynthetic analysis of azabicyclic ring system.

Our journey started with an aldehyde **23a**,[11] which on sequential α-amination using commercially available dibenzyl azodicarboxylate (DBAD) as an electrophile, L-proline as a catalyst and later trapping the γ - hydrazino aldehyde using a subsequent HWE olefination

using triethylphosphonoacetate furnished the γ-hydrazino-α,β-unsaturated ester **24a** in good yields and enantioselectivity (94%)[12] (**Scheme 6**). Compound **24a** was then subjected to N-N bond cleavage under using Raney-Ni conditions to furnish the free amine which underwent cyclization on heating with EtOH at 50 °C to give **25a**. Disappearance of the Cbz proton peaks in the aromatic region ranging from δ7.27-7.39 confirmed the formation of product. Formation of Product was also confirmed using the IR spectroscopy where the ester peak at 1735 cm^{-1} was not observed, instead a new peak at 1700 was seen that corresponds to a 5 membered lactam. Subsequent treatment of lactam **25a** in presence of a fluoride source (TBAF) afforded the free hydroxyl compound **26a** in 90% yield. Compound **26a** was then converted to its toluenesulfonyl ester followed by treatment with sodium hydride to yield the fused lactam **27a** via a nucleophilic substitution reaction in 80% yield. Disappearance of peak at δ6.94 (brs, 1H) confirmed the formation of product. Compound **27a** on subsequent reduction with lithium aluminium hydride gave the pyrrolizidine ring system **1**. Interestingly pyrrolam can be converted from the fused lactam **27a** to **28** using a reported protocol.[12]



Scheme 6: Synthesis of indolizidine and pyrrolizidine

As depicted in **Scheme 6**, compound **27b** was subjected to similar reaction conditions and reaction sequence as mentioned above, indolizidine system **2** was synthesized from fused lactam **27b** which was readily assembled from the hydroxyl compound **26b**, via lactam **25b**.

The lactam **25b** was prepared from γ-amino-α,β-unsaturated ester **24b** which in turn was synthesized from aldehyde **23b** in 68% yield and excellent enantioselectivity (91%).[12]

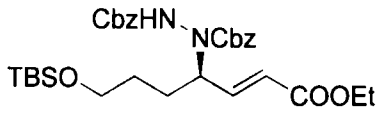
2.1.5 Conclusion

In conclusion, a new protocol has been developed using proline-catalyzed α-amination and Horner–Wadsworth–Emmons olefination approach to the synthesis of pyrrolizidine **1** and indolizidine **2** ring systems. The present method is easily amenable for the synthesis of different alkaloids containing variable ring system.

2.1.6. Experimental Section

Compound 23a was prepared using a reported protocol.[11]

(*R*,*E*)-Dibenzyl 1-(7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24a):



General procedure for sequential α-amination/ Horner-Wadsworth-Emmons olefination:

To a cooled solution of dibenzylazodicarboxylate (DBAD) (0.54 g, 1.81 mmol) and L-proline (0.02 g, 8 mol%) in ACN (34 mL) at 0 °C was added compound **23a** (0.5 g, 2.17 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C.[9] This was followed by addition of lithium chloride (0.11 g, 2.7 mmol), HWE salt (0.54 mL, 2.71 mmol) and DBU (0.27 mL, 1.81 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave **24a** as a colorless syrupy liquid.

Yield: 0.84 g, yield 68%

Mol. Formula: $C_{31}H_{44}O_7N_2Si$

$[\alpha]_D^{25}$: + 4.73 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3296, 2995, 2857,1720,1657, 1258, 1097

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.87 (s, 9H), 1.29 (t, J = 7Hz, 3H), 1.43-1.58 (m, 2H), 4.70-4.88 (m, 1H), 5.03-5.22 (m, 4H), 5.94 (d, J = 15.2 Hz, 1H), 6.57 (brs, 1H), 6.86 (dd, J = 15.2 Hz, 6.6 Hz, 1H), 7.27-7.39 (m, 10H) ppm

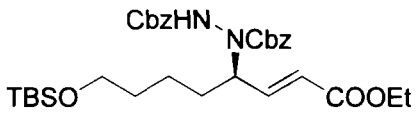
^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, 14.1, 18.3, 25.9, 27.1, 28.9, 58.7, 60.5, 62.4, 67.7, 68.3, 122.9, 126.9, 127.4, 127.8, 128.1, 128.4, 135.6, 144.8, 155.6, 156.4, 166.1 ppm

MS(ESI) : m/z 607.29 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{44}O_7N_2Si$ 607.2810; Found 607.2819

HPLC: Kromasil 5 –Amycoat (250 X 4.6mm) (2-propanol: pet ether = 10:90, flow rate 0.5ml/min, λ = 254 nm). Retention time (min):13.458 (major) and 18.067 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 94%.

Dibenzyl (*R,E*)-1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (24b):



Yield: 0.84 g, yield 68%

Mol. Formula: $C_{31}H_{44}O_7N_2Si$

$[\alpha]_D^{25}$: + 2.67 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3297, 1716, 1044, 695

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.03 (s , 6H) , 0.88 (s , 9H), 1.28 (t, J = 7 Hz, 3H), 1.37-1.59 (m, 4H), 1.59-1.76 (m, 2H), 3.50-3.65 (m, 2H), 4.18 (q, J = 7 Hz, 2H) 4.64-4.89 (m, 1H) 5.02-5.14 (m, 4H), 5.92 (d, J =15.4 Hz, 1H), 6.62 (brs, 1H), 6.87 (dd, J = 7.2 Hz, 15.4 Hz, 1H), 7.27-7.32 (m, 10H) ppm

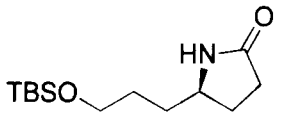
^{13}C NMR (50 MHz, $CDCl_3$): -5.4, 14.1, 18.2, 22.0, 25.8, 30.4, 32.1, 58.8, 60.4, 62.6, 67.7, 68.2, 122.9, 127.8, 128.1, 128.2, 128.4, 135.6, 144.8, 155.5, 156.5, 166.1 ppm

MS(ESI) : m/z 621.24 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{44}O_7N_2Si$ 607.2810; Found 607.2819

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : Petroleum ether = 10:90, flow rate 0.5ml/min, (λ = 230 nm). Retention time (min):13.300 (major) and 16.225 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 91%.

(*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (25a):



General procedure of N-N bond cleavage using Raney-Ni:

The solution of **24a** (0.5 g, 0.83 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with freshly prepared Raney nickel (1.0 g, excess) under H_2 (65 psig) atmosphere for 24 h. The reaction mixture was then filtered over a thick pad of celite and concentrated in vacuo to give crude compound of free amine which was subjected to cyclisation in EtOH at 50 ^{0}C for 5 h. The reaction mixture was then concentrated to give a crude mixture. Silica gel column chromatography (petroleum ether: ethyl acetate: 40:60) of the crude product gave lactam **25a** as a syrupy liquid.

Yield: 0.16 g, yield 70%

Mol. Formula: $C_{13}H_{27}O_2NSi$

$[\alpha]_D^{25}$: + 37.76 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2857, 1694, 1651, 1255, 1099

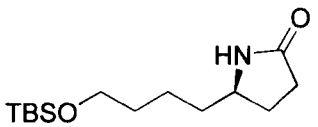
^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.46-1.62 (m, 4H), 1.67-1.76 (m, 1H), 2.17-2.39 (m, 3H), 6.55 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.4, 18.2, 25.9, 27.2, 29.1, 30.2, 33.4, 54.5, 62.7, 178.5 ppm.

MS(ESI) : m/z 280.12 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{13}H_{27}O_2NSiNa$ 280.1703; Found 280.2639

(*R*)-5-(4-((tert-Butyldimethylsilyl)oxy)butyl)pyrrolidin-2-one (25b):



Yield: 0.16 g, yield 70%

Mol. Formula: $C_{14}H_{29}O_2NSi$

$[\alpha]_D^{25}$: + 35.52 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2858, 1712, 1255, 1099

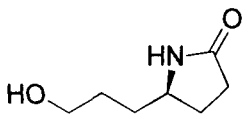
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.33-1.42 (m, 2H), 1.46-1.60 (m, 4H), 1.68-1.74 (m, 1H), 2.20-2.38 (m, 3H), 3.58-3.67 (m, 3H), 6.14 (brs, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): -5.4, 18.3, 22.1, 25.9, 27.2, 30.2, 32.5, 36.4, 54.6, 62.8, 178.5 ppm.

MS(ESI) : m/z 294.13 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{30}O_2NSi$ 272.20403; Found 272.20402

(*R*)-5-(3-Hydroxypropyl)pyrrolidin-2-one (26a):



General procedure for TBS deprotection:

The solution of the silylated lactam **25a** (0.25 g, 0.92 mmol) in THF (3 mL) at 0 ^oC was treated with tetra butylammonium fluoride (0.5 mL, 1.8 mmol) in THF (1N). The reaction mixture was left to stir under rt for 1 h and was later quenched using a sat.solution of ammonium chloride (1 mL). The layer was then extracted using ethyl acetate (3 × 30 mL). The combined organic layers were washed with a saturated solution of brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure followed by silica gel column chromatography (CH_2Cl_2: MeOH: 95:5) of the crude to afford **26a** as a syrupy liquid.

Yield: 0.13 g, 90%

Mol. Formula: $C_7H_{13}O_2N$

$[\alpha]_D^{25}$: - 27.50 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$,cm^{-1}): ν^{max} 3412, 2953, 2857, 1694, 1096

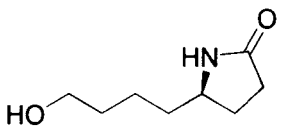
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.59-1.65 (m, 3H), 1.66-1.76 (m, 1H), 2.18-2.25 (m, 3H), 2.28-2.39 (m, 2H), 3.59-3.79 (m, 3H), 6.94 (brs, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 27.3, 28.9, 30.4, 33.4, 54.7, 62.0, 178.7 ppm.

MS(ESI) : m/z 144.09 $(M+H)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_7H_{14}O_2N$ 144.1019; Found 144.1015

***(R)*-5-(4-Hydroxybutyl)pyrrolidin-2-one (26b):**



Yield: 0.13 g, 90%

Mol. Formula: $C_8H_{15}O_2N$

$[\alpha]_D^{25}$: - 23.94 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3435, 2928, 1668, 1101

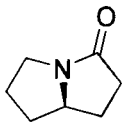
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42-1.49 (m, 2H), 1.50-1.60 (m, 2H), 1.70-1.84 (m, 4H), 2.21-2.41 (m, 3H), 3.61-3.69 (m, 3H), 6.55 (brs, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): 22.1, 27.2, 30.4, 32.1, 36.3, 54.7, 61.9, 179.15 ppm.

MS(ESI) : m/z 180 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_7H_{14}O_2N$ 158.1176: Found 158.1176

Tetrahydro-1H-pyrrolizin-3(2H)-one (27a):



General procedure for cyclisation:

To a stirred solution of **26a** (0.05g, 0.31 mmol) at 0°C and TEA (0.08 mL, 0.63 mmol) in dry DCM (2 mL) was added toluenesulfonyl chloride (0.07 g, 0.34 mmol) over 20 min. The resulting mixture was allowed to warm up to room temperature and left to stir for 8 h. After diluting with 8 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude tosylated product which was subjected to next step without further purification.

To a solution of tosylated compound in THF cooled to 0 °C was added NaH (0.019 g, 60% dispersion in oil). On completion of reaction as indicated by TLC (8h) the reaction mixture

was cooled to 0 °C, quenched by addition of ice pieces, and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with water, brine, and dried (Na_2SO_4). Silica gel column chromatography in EtOAc furnished **27a** as a colorless liquid.

Yield: 0.035 g, 80%

Mol. Formula: $C_7H_{11}ON$

$[\alpha]_D^{25}$: - 18.68 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2972, 2876, 1645

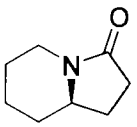
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.25-1.37 (m, 1H), 1.66-1.79 (m, 1H), 1.97-2.14 (m, 3H) , 2.25-2.34 (m, 1H), 2.39-2.52 (m, 1H), 3.0-3.12 (m, 1H), 3.48-3.57(m, 1H), 3.82-3.97 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$) : 26.9, 27.1, 32.2, 35.4, 40.9, 62.1, 174.8 ppm

MS(ESI) : m/z 126.13 $(M+H)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_7H_{11}ON$ 126.0914; Found 126.0914

***(R)*-Hexahydroindolizin-3(2H)-one (27b):**



Yield: 0.035 g, 80%

Mol. Formula: $C_8H_{13}ON$

$[\alpha]_D^{25}$: - 32.14 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2933, 1663, 1570.

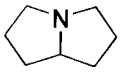
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13 - 1.26 (m, 1H), 1.34-1.46 (m, 2H), 1.52-1.68 (m, 2H), 1.83-1.93 (m, 2H), 2.12- 2.26 (m, 1H), 2.32-2.40 (m, 2H), 2.55-2.69 (m, 1H), 3.33-3.48 (m, 1H), 4.08-4.17 (m, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): 23.7, 24.4, 25.3, 30.3, 38.6, 40.2, 57.3, 178.7 ppm.

MS (ESI): m/z 140.12 $(M+H)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_7H_{11}ON$ 140.1070; Found 140.1070

Hexahydro-1H-pyrrolizine (1):



General procedure for amide reduction:

To a stirred suspension of $LiAlH_4$ (0.015 g, 0.39 mmol) in dry THF (1 mL) was added a solution of **27a** (0.025 g, 0.39 mmol) in THF (1 mL), and the mixture was refluxed for 6 h. After being cooled to ambient temperature, the mixture was treated with a saturated aqueous solution of sodium sulfate (2 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (MeOH: CH_2Cl_2: 2:8) of the crude product gave **1** as a colorless liquid.

Yield: 0.008 g, 71%

Mol. Formula: $C_7H_{13}N$

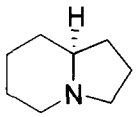
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26-1.72 (m, 8H), 2.06-2.86 (m, 4H), 3.67-3.73 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): 27.4, 33.5, 54.5, 62.4 ppm

(ESI): m/z 112.09 $(M+H)^+$

HRMS (ESI) *m/z*: 112.1123 $(M+H)^+$ Calcd.112.1121

(*R*)-Octahydroindolizine (2):



Yield: 0.007 g, 71%

Mol. Formula: $C_8H_{15}N$

$[\alpha]_D^{25}$: - 9.8 (*c* 1.1, EtOH), {Lit[13] $\{[\alpha]_D^{25}$: -10.2 (*c* 1.76, EtOH)}

IR ($CHCl_3$, cm^{-1}): ν^{max} 2952, 2920, 1461, 1454, 1320,1255, 1096

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.12-1.85 (m, 10 H), 2.27-2.50 (m, 3H), 3.48-3.61 (m, 2H) ppm

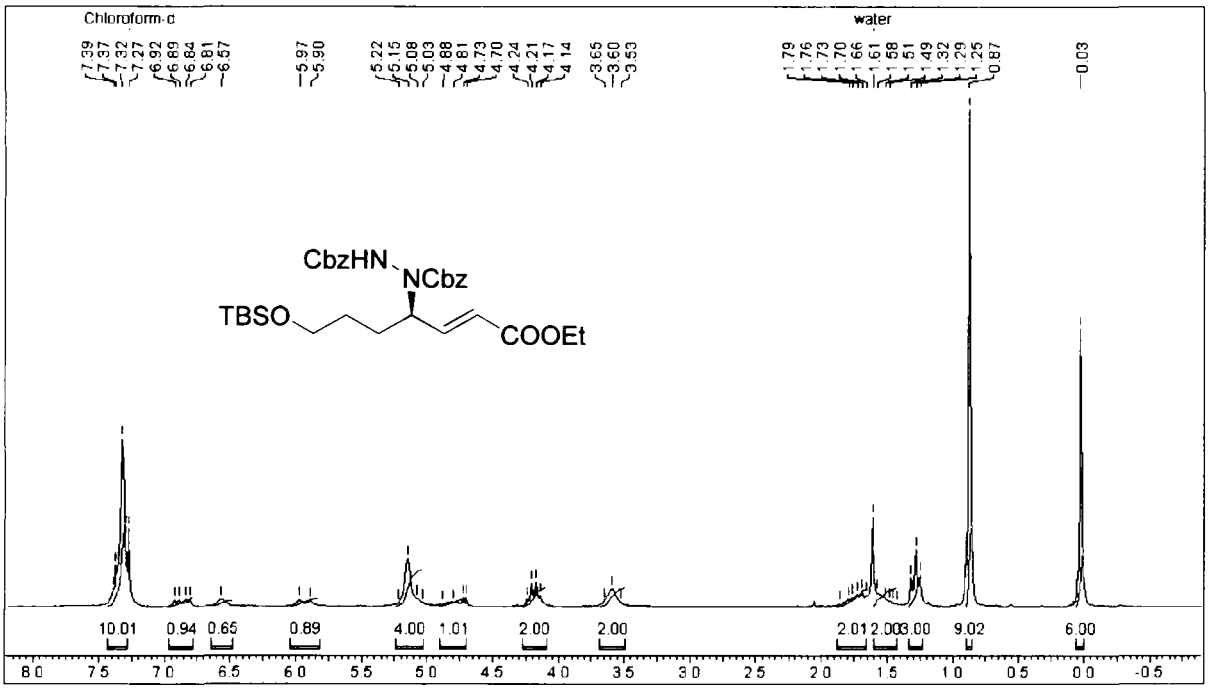
^{13}C NMR (50 MHz, $CDCl_3$): 23.0, 27.1, 29.6, 30.2, 32.2, 44.6, 54.5, 64.7 ppm

MS (ESI): m/z 126.19$(M+H)^+$

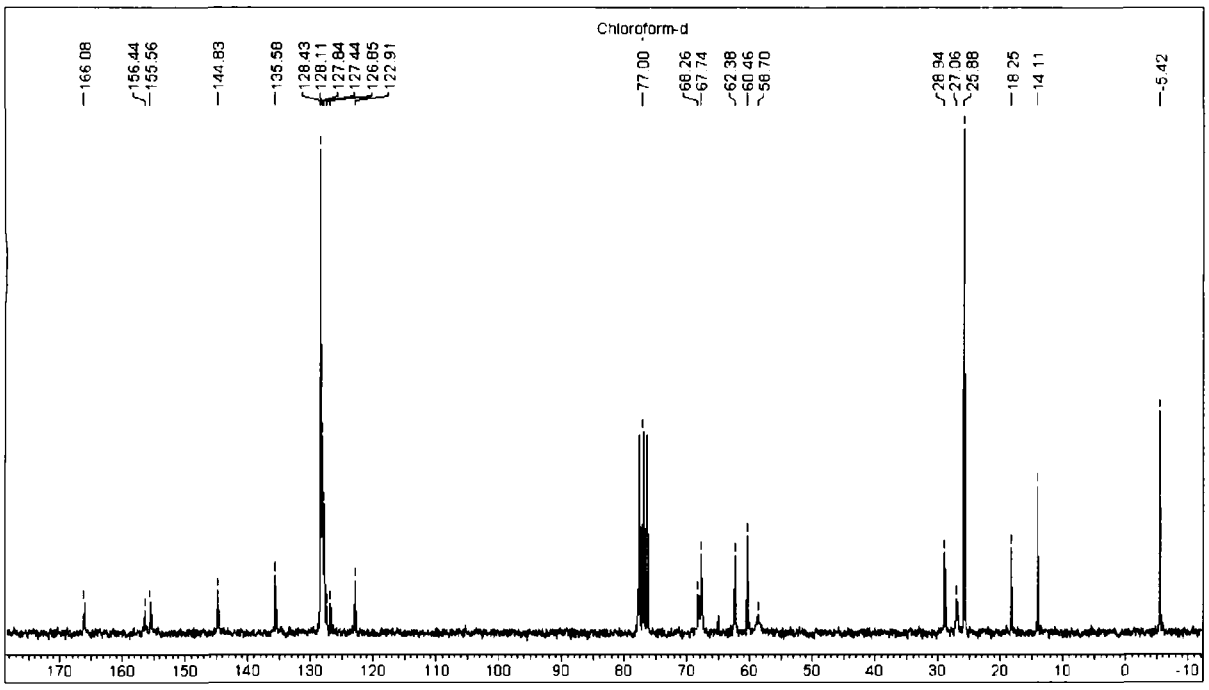
HRMS (ESI) ***m/z*:** 126.1278 $(M+H)^+$ Calcd.126.1277

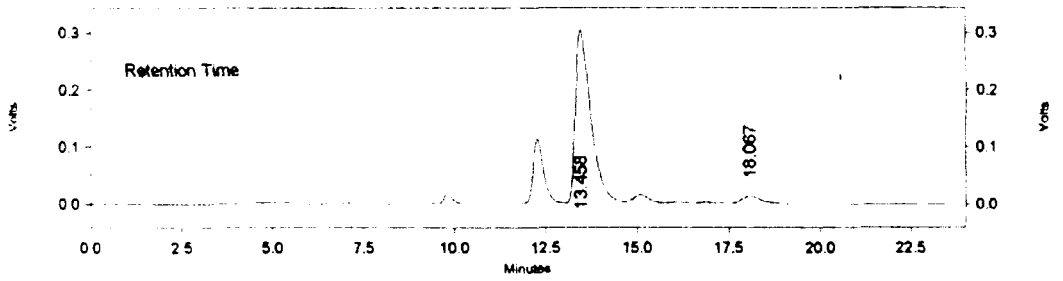
2.1.7. Spectra

^{1}H NMR ($CDCl_3$, 200MHz) of (*R,E*)-Dibenzyl 1-(7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en- -yl)hydrazine-1,2-dicarboxylate (24a):



^{13}C NMR ($CDCl_3$, 50MHz) of (*R,E*)-Dibenzyl 1-(7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxohept-2-en-4-yl)hydrazine-1,2-dicarboxylate (24a):

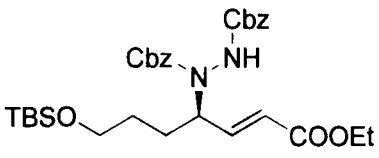


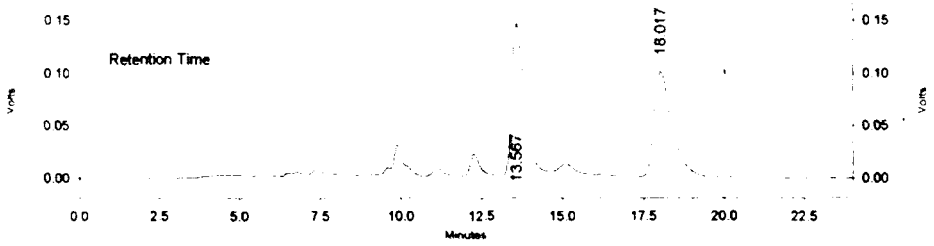


Detector A - 1 (254nm)

Retention Time	C Area	Area %
13.458	8409897	96.917
18.067	267556	3.083
Totals	8677453	100.000

Project Leader : Dr.P.K.TRIPATHI
Column :Kromasil 5-AmyCoat (250x4.6 mm)
Mobile Phase :IPA: Pet Ether (10:90)
Wavelength :254nm
Flow Rate :0.5ml/min(29Kgf)
conc. : 1mg/1.0 mL
Inj vol- .5 ul

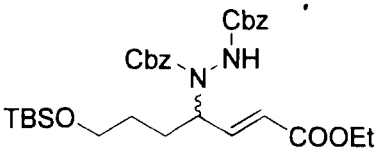




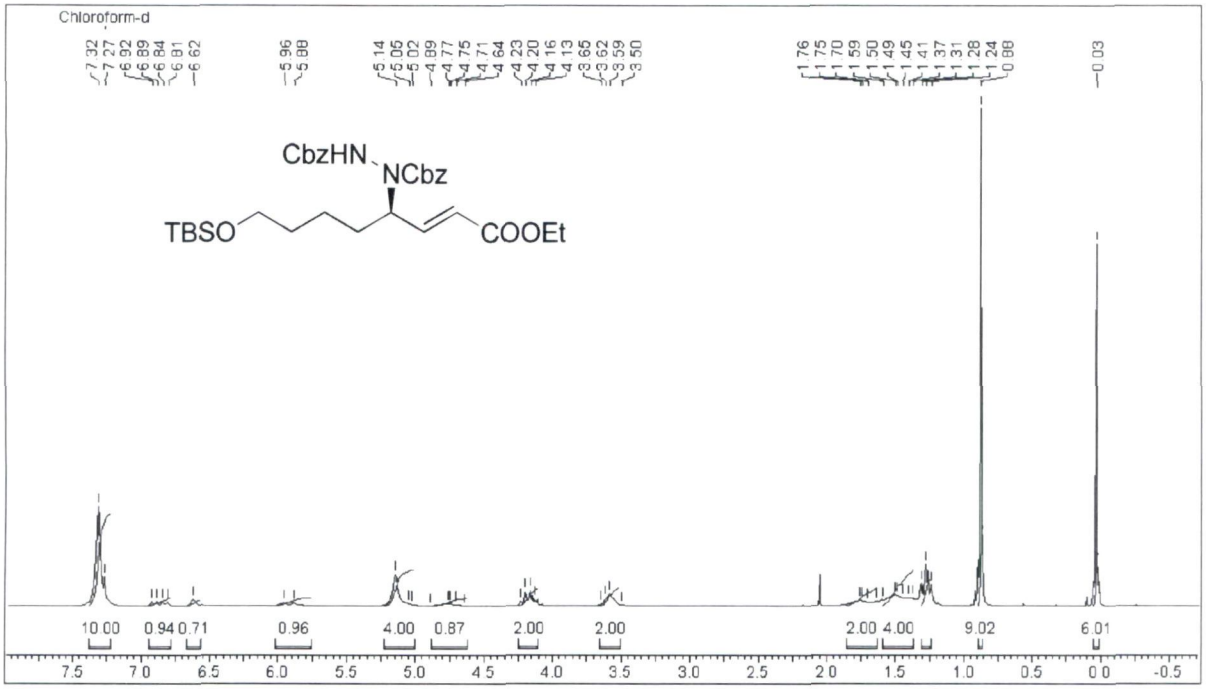
Detector A - 1 (254nm)

Retention Time	C Area	Area %
13.567	3832587	50.664
18.017	3732153	49.336
Totals	7564740	100.000

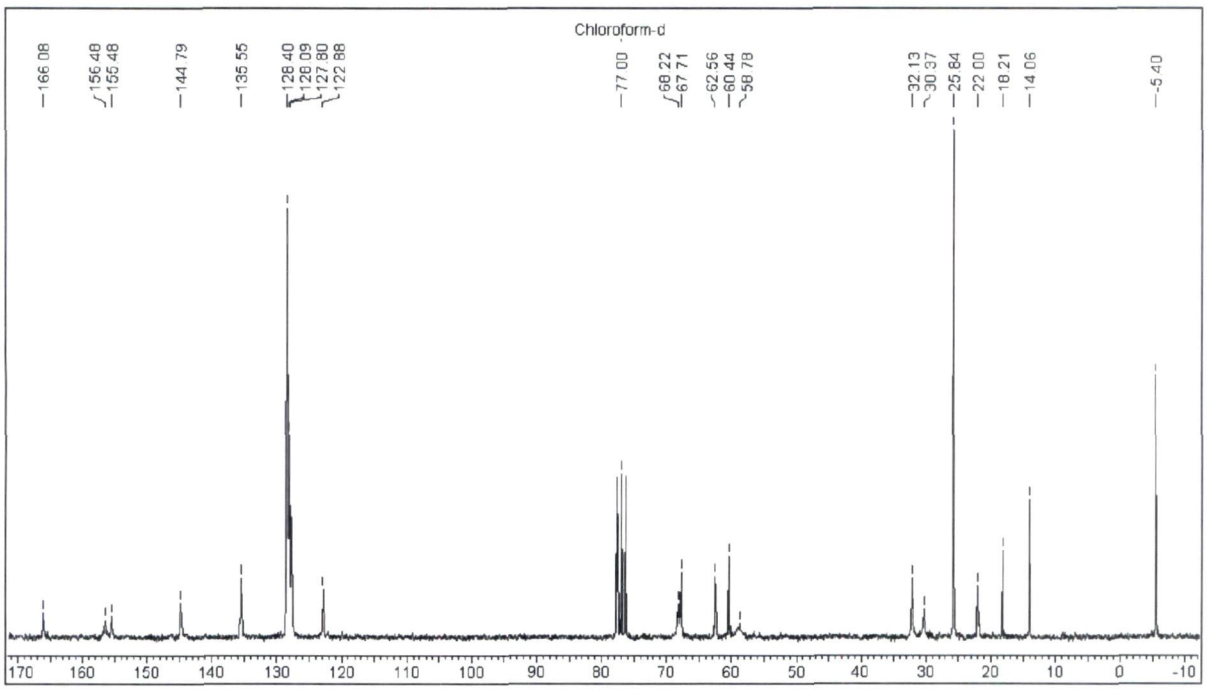
Project Leader : Dr.P.K.TRIPATHI
Column :Kromasil 5-AmyCoat (250x4.6 mm)
Mobile Phase :IPA: Pet Ether (10:90)
Wavelength :254nm
Flow Rate :0.5ml/min(29Kgf)
conc : 1mg/1.0 mL
Inj vol- :5 ul



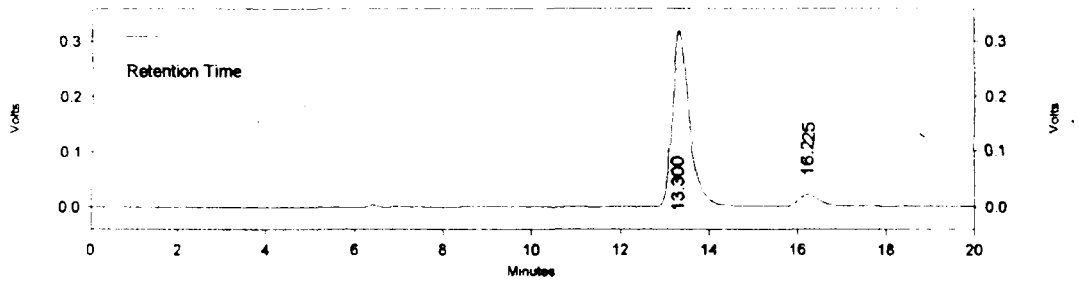
^{1}H NMR ($CDCl_3$, 200MHz) of (*R,E*)-Dibenzyl1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (24b):



^{13}C NMR ($CDCl_3$, 50MHz) of (*R,E*)-Dibenzyl1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate (24b):



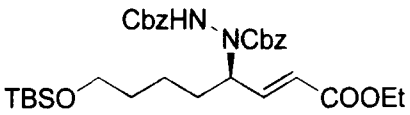
Th-14679

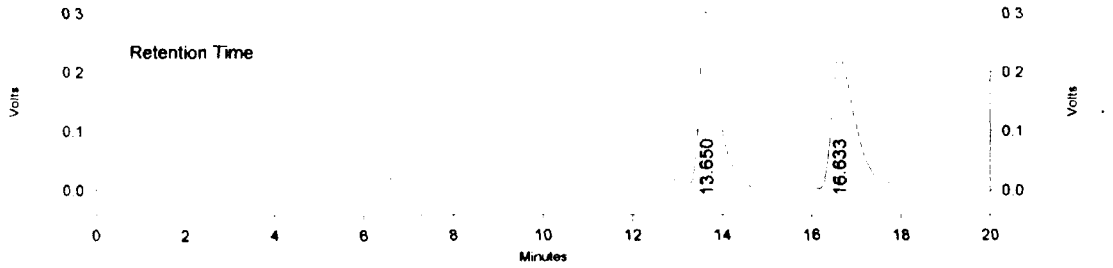


Detector A - 1 (230nm)

Retention Time	C Area	Area %
13.300	8015760	95.313
16.225	394165	4.687
Totals	**8409925**	100.000

Project Leader : Dr. Pradeep kumar
Column : Kromasil 5-AmyCoat(250x4.6 mm)
Mobile Phase : IPA: Pet ether (10:90)
Wavelength :230nm
Flow Rate :0.5ml/min(396psi)
conc. : 1mg/1.0 mL
Inj vol- :5ul

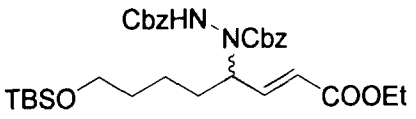




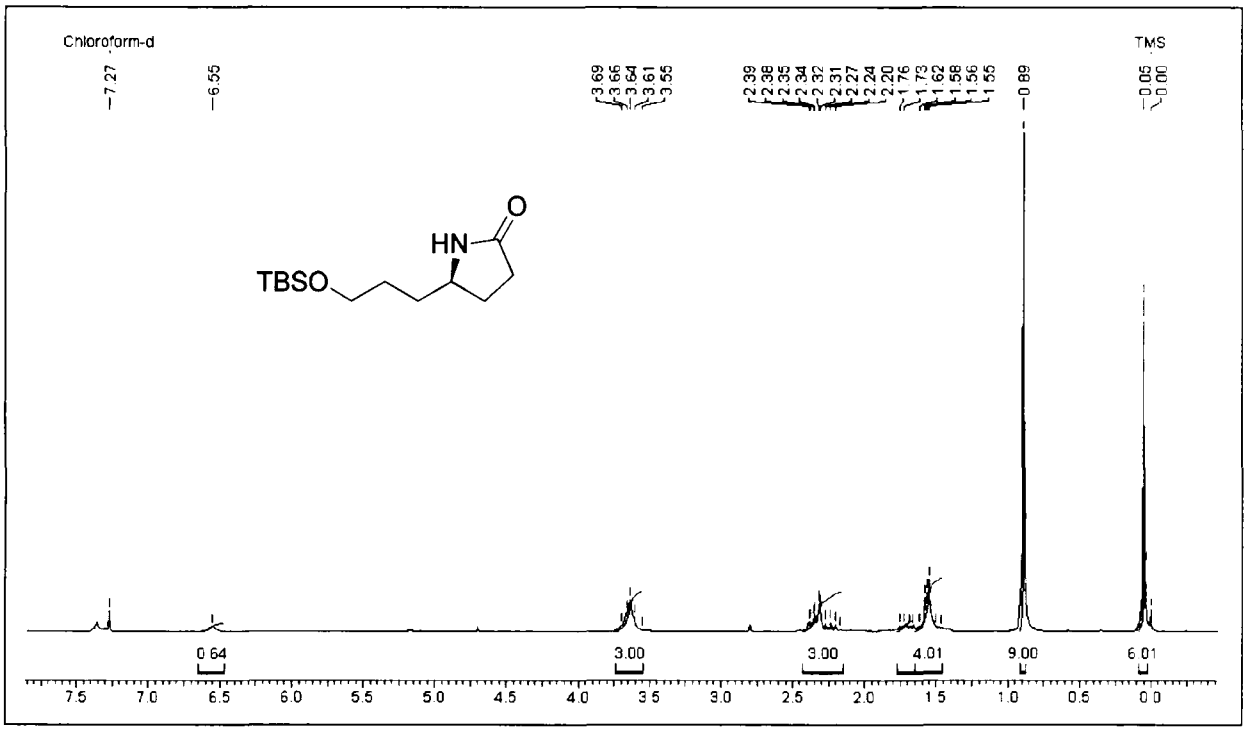
Detector A - 1 (254nm)

Retention Time	C Area	Area %
13.650	8063940	51.217
16.633	7680650	48.783
Totals	15744590	100.000

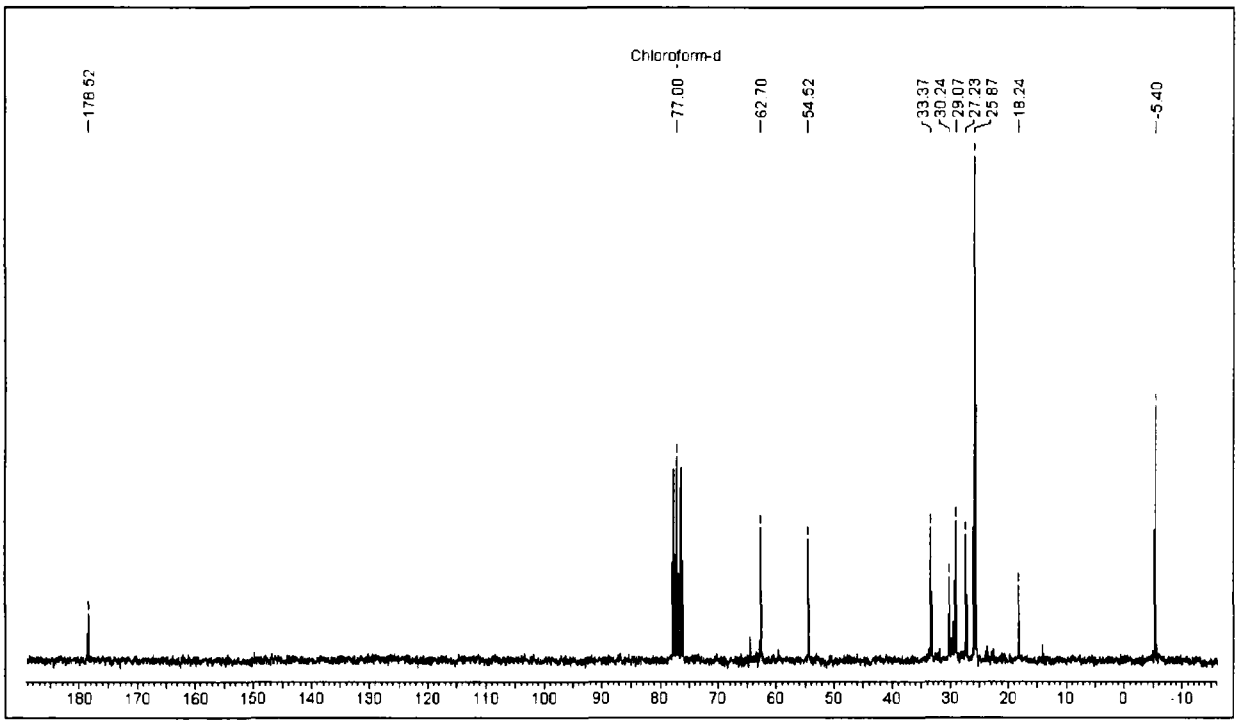
Project Leader : Dr.P.K.TRIPATHI
Column :Kromasil 5-AmyCoat (250x4.6 mm)
Mobile Phase :IPA: Pet Ether (10:90)
Wavelength :254nm
Flow Rate :0.5ml/min(29Kgf)
conc. : 1mg/1.0 mL
Inj vol- :5 ul



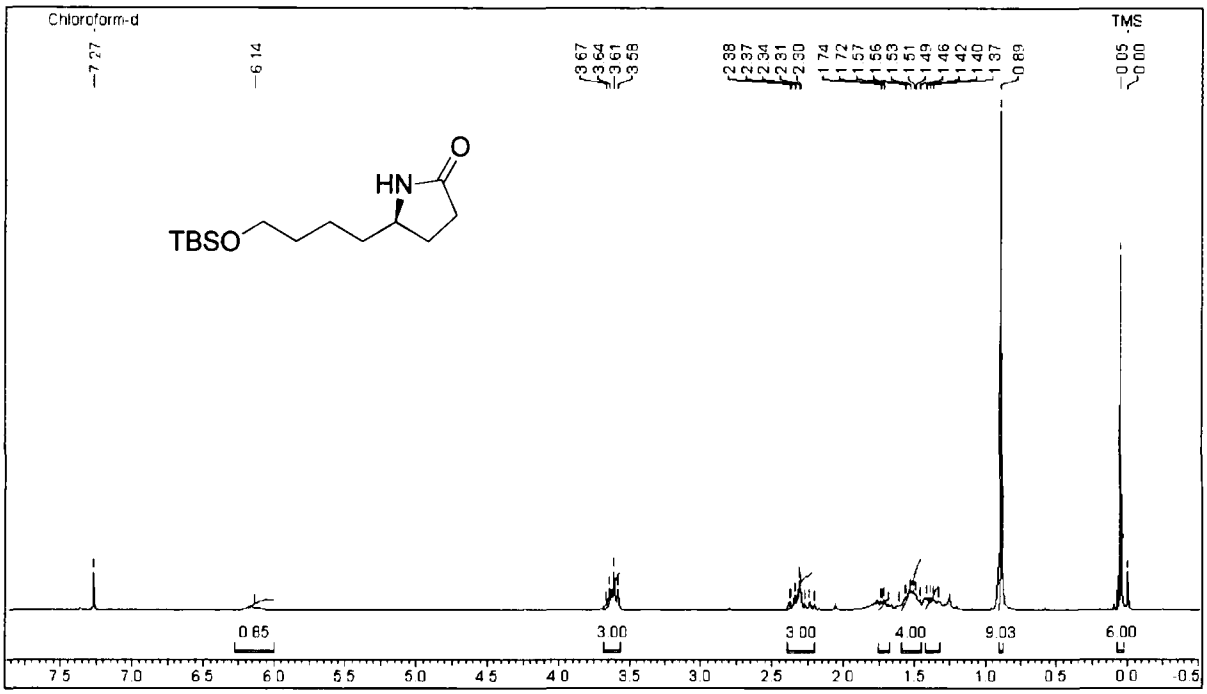
^{1}H NMR ($CDCl_3$,200MHz) of (*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (25a):



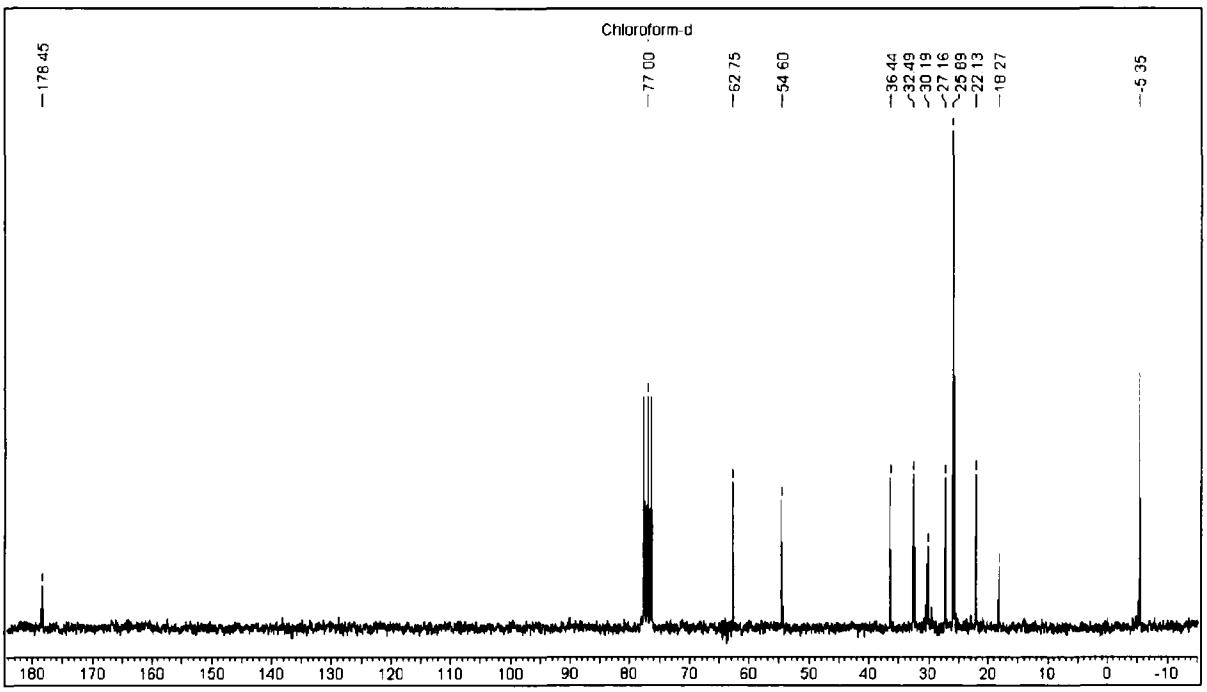
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (25a):



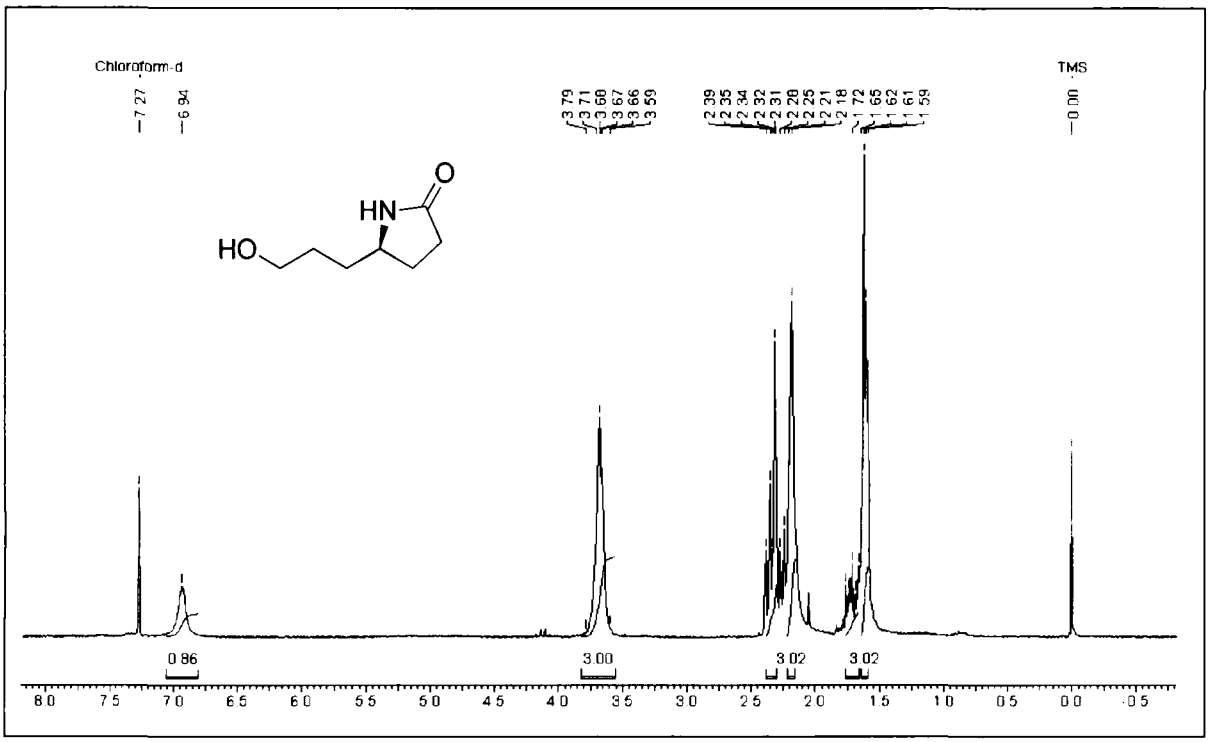
^{1}H NMR ($CDCl_3$,200MHz) of (*R*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)pyrrolidin-2-one (25b):



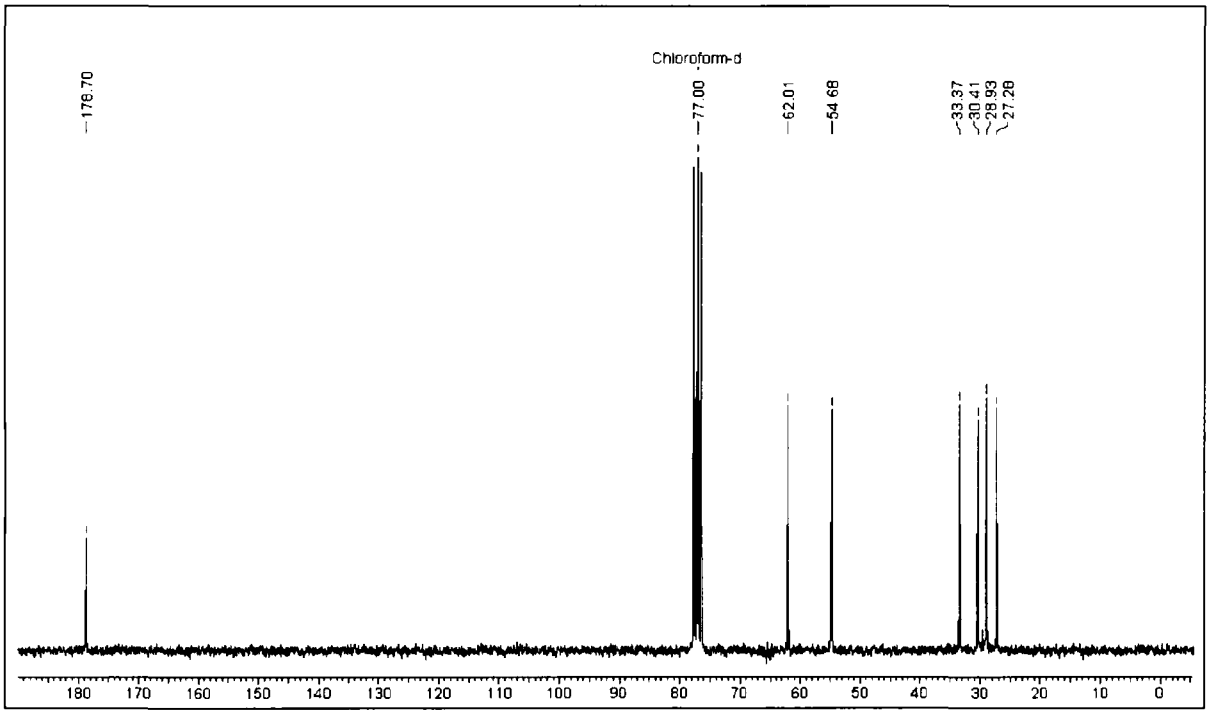
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-5-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)pyrrolidin-2-one (25b):



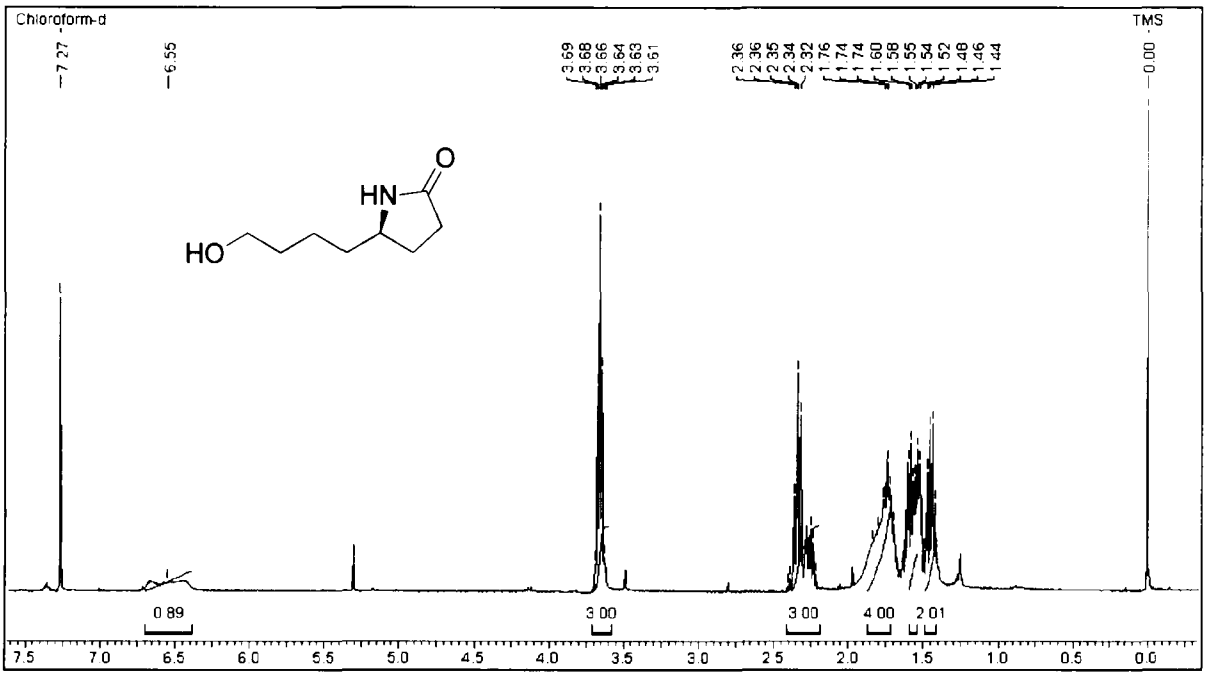
^{1}H NMR ($CDCl_3$,200MHz) of (*R*)-5-(3-Hydroxypropyl)pyrrolidin-2-one (26a):



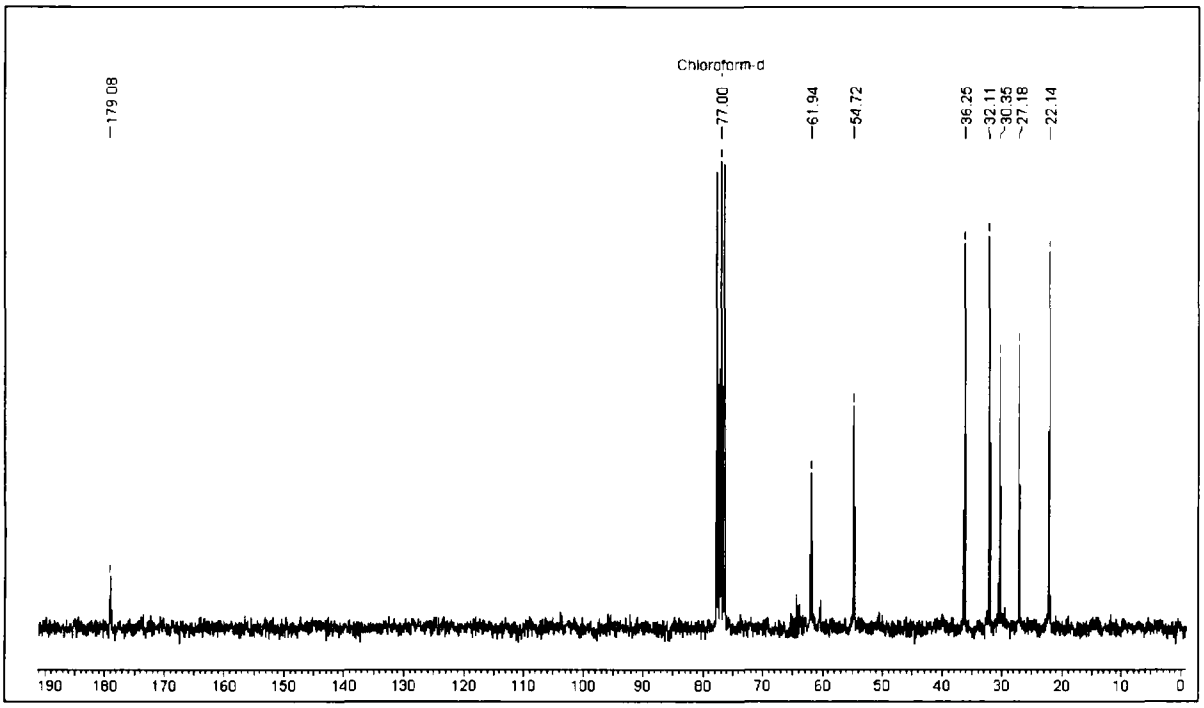
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-5-(3-Hydroxypropyl)pyrrolidin-2-one (26a):



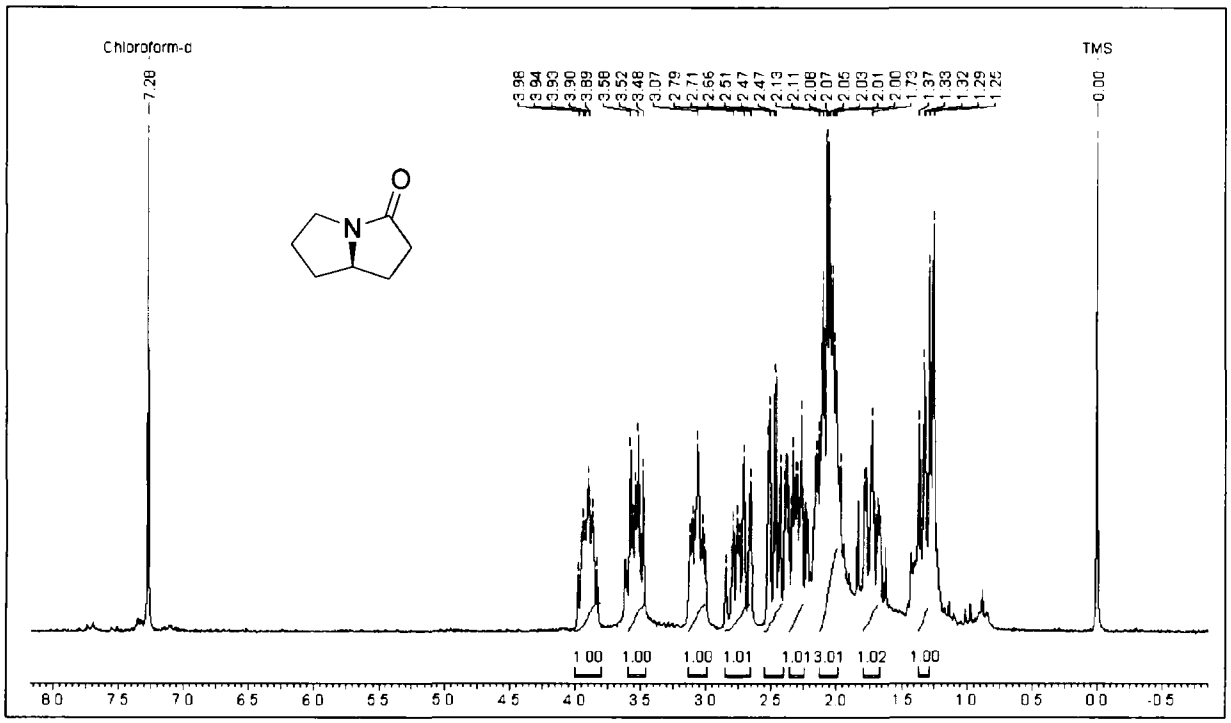
^{1}H NMR ($CDCl_3$,200MHz) of (*R*)-5-(4-Hydroxybutyl)pyrrolidin-2-one (26b):



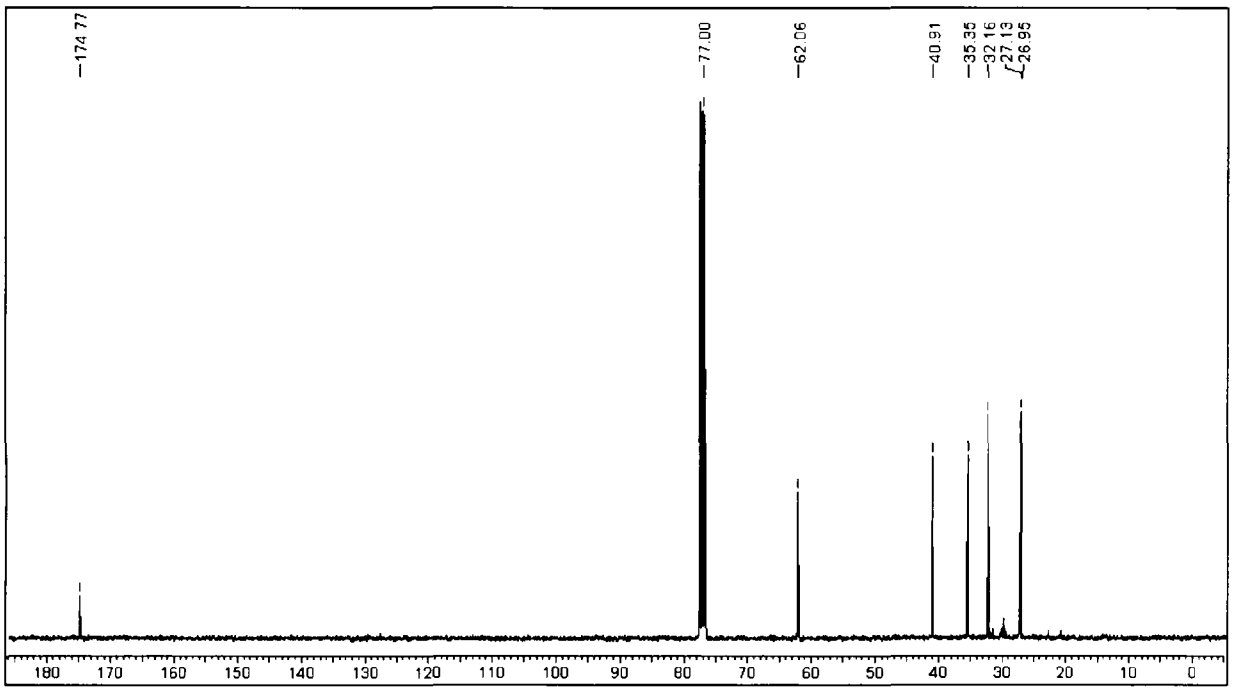
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-5-(4-Hydroxybutyl)pyrrolidin-2-one (26b):



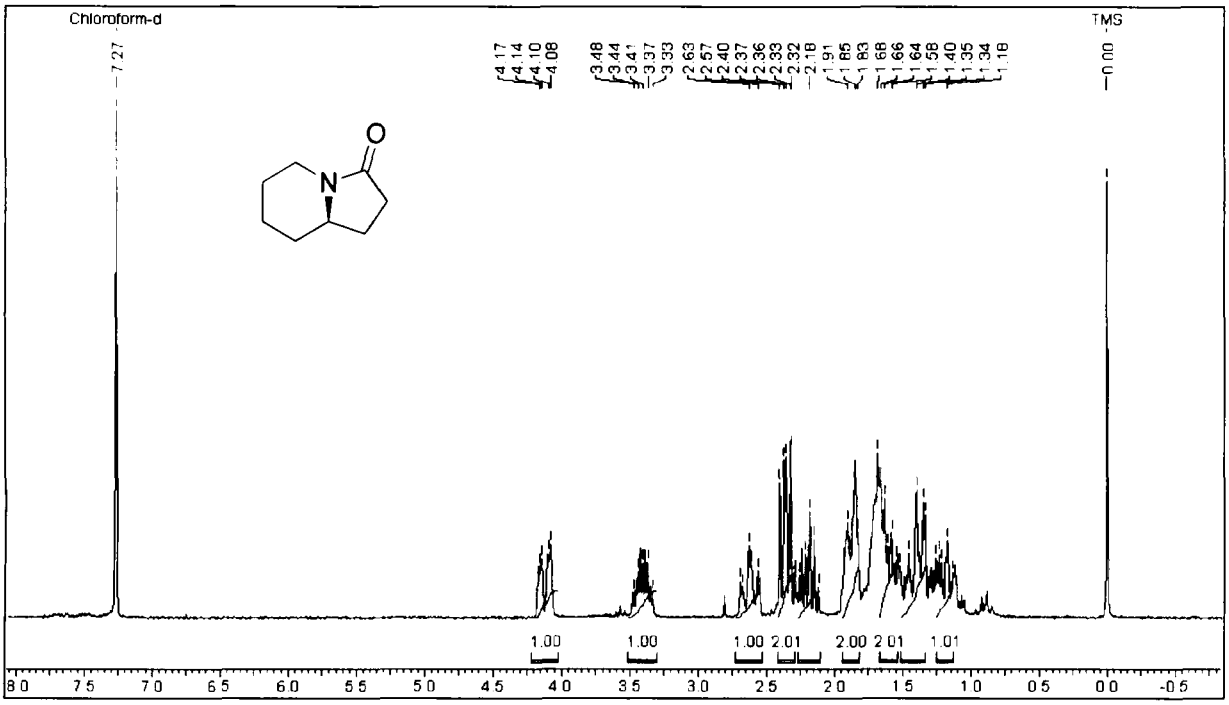
^{1}H NMR ($CDCl_3$,200MHz) of (*R*)-Tetrahydro-1H-pyrrolizin-3(2H)-one (27a):



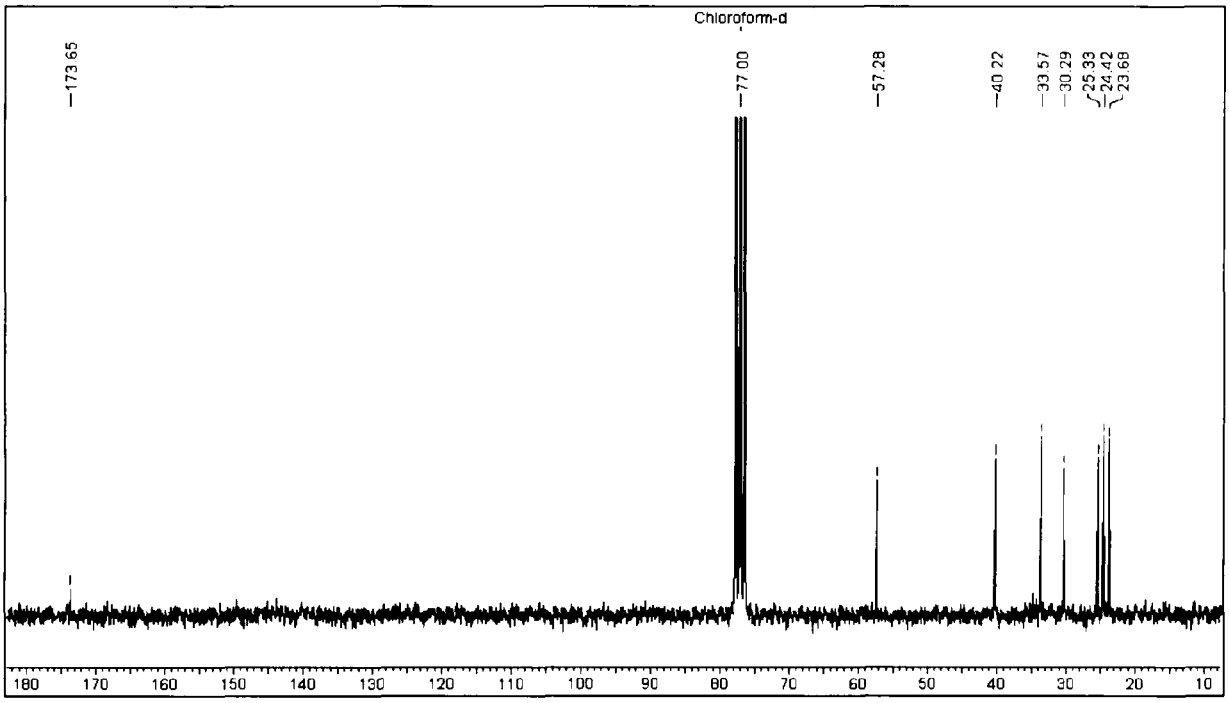
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-Tetrahydro-1H-pyrrolizin-3(2H)-one (27a):



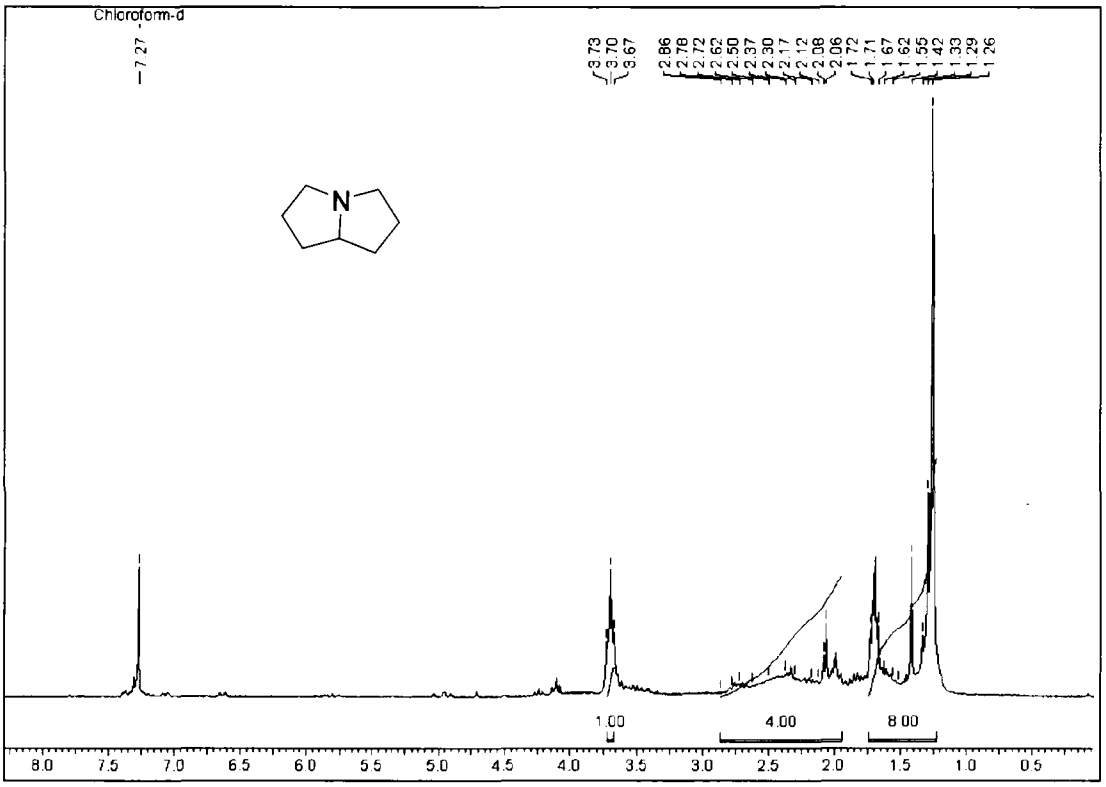
^{1}H NMR ($CDCl_3$, 200MHz) of (*R*)-Hexahydroindolizin-3(2H)-one (27b):



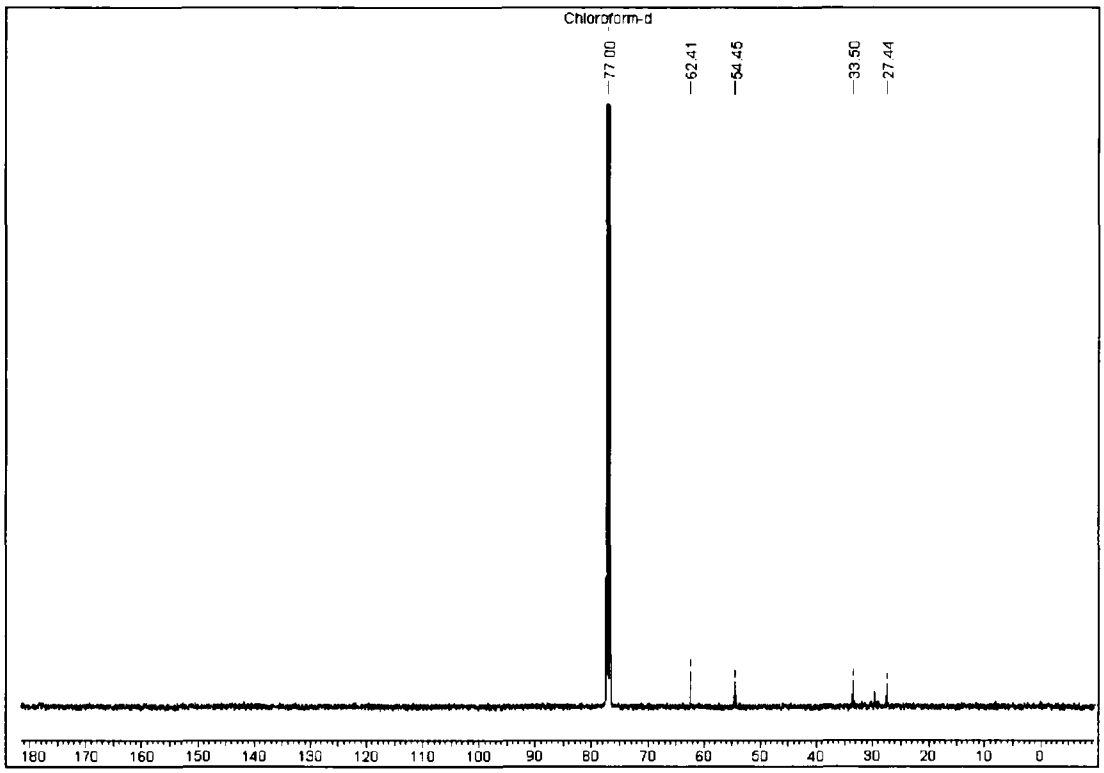
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-Tetrahydro-1H-pyrrolizin-3(2H)-one (27b):



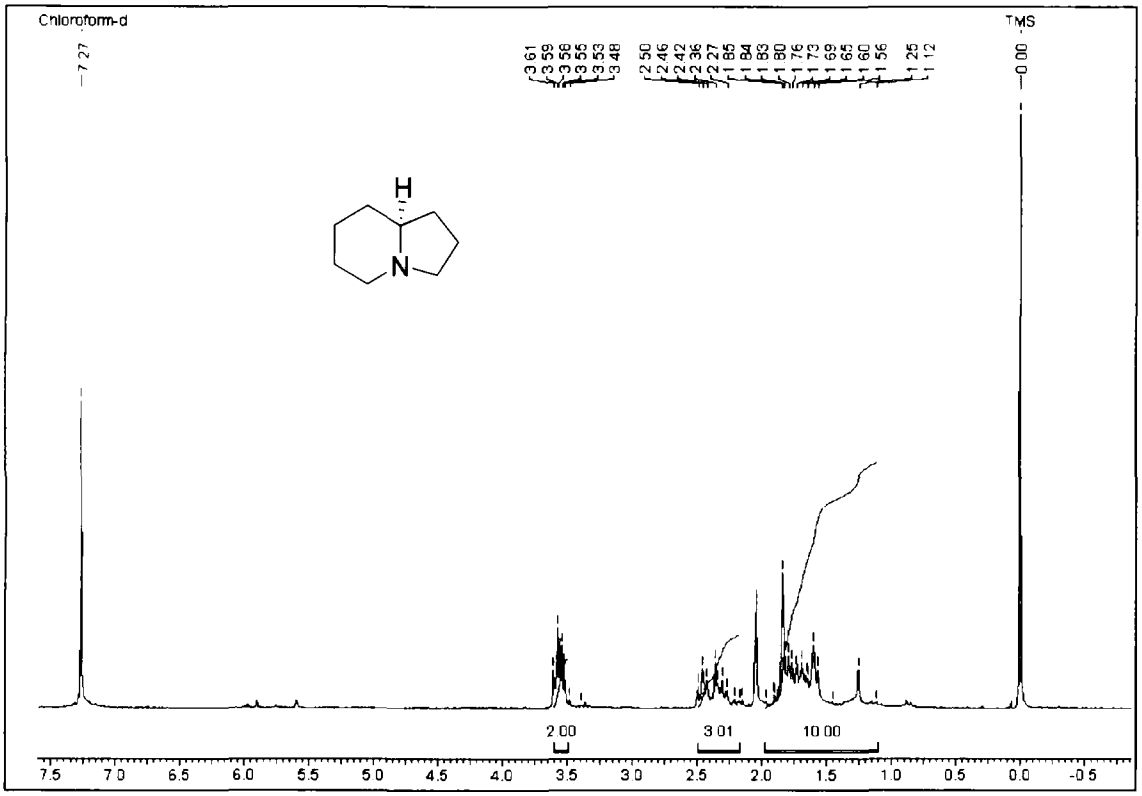
^{1}H NMR ($CDCl_3$, 200MHz) of Hexahydro-1H-pyrrolizine (1):



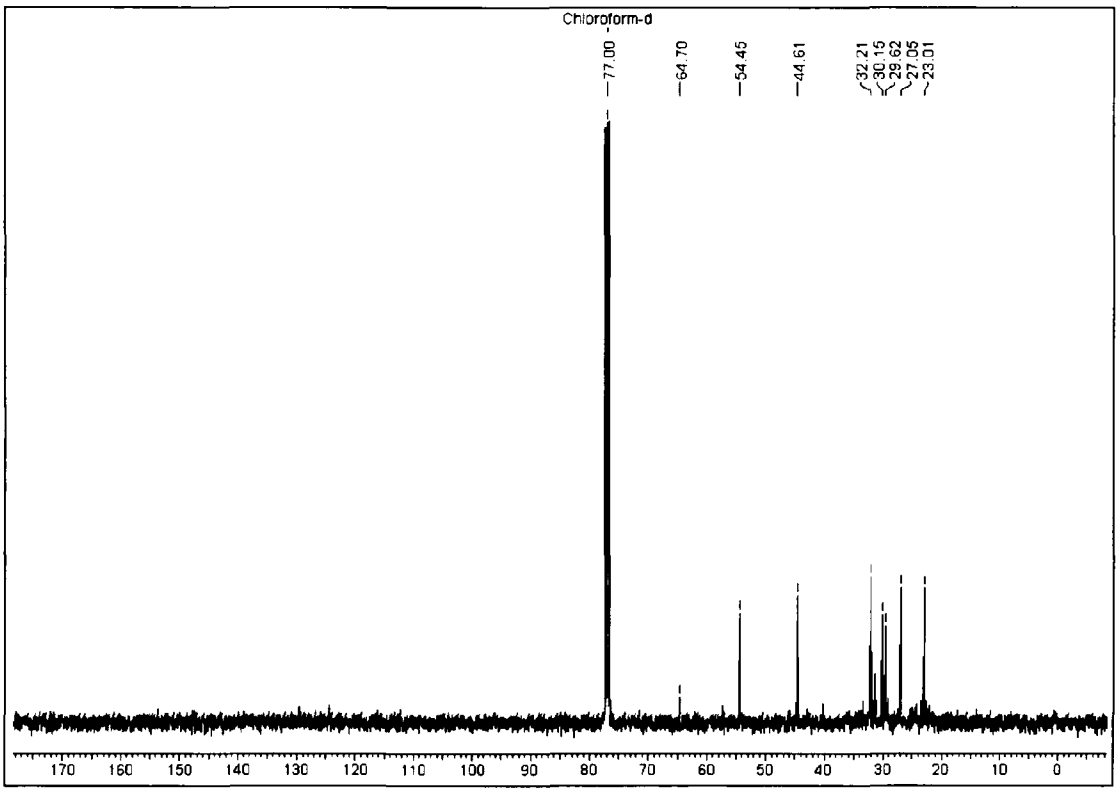
^{13}C NMR ($CDCl_3$, 50MHz) of Hexahydro-1H-pyrrolizine (1):



^{1}H NMR ($CDCl_3$, 200MHz) of (*R*)-Octahydroindolizine (2):



^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-Octahydroindolizine (2):



2.1.8. References:

1. (a) R. A. Pilli, G. B. Rosso, M. D. C. F. De Oliveira, *Nat. Prod. Rep.* **2010**, *27*, 1908; (b) H. Greger, J. Schinnerl, S. Vajrodaya, L. Brecker, O. Hofer, *J. Nat. Prod.* **2009**, *72*, 1708; (c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 603; (d) C. Seger, K. Mereiter, E. Kaltenegger, T. Pacher, H. Greger, O. Hofer, *Chem. Biodiversity* **2004**, *1*, 265; (e) A. Mitchenson, A. Nadin, *J. Chem. Soc. Perkin Trans.* 1 2000, 2862; (f) R. A. Pilli, G. B. Rosso, M. D. C. F. De Oliveira, *Nat. Prod. Rep.* **2000**, *17*, 117; (g) D. O. Hagan, *Nat. Prod. Rep.* 1997, **14**, 637; (h) H. Shinozaki, M. Ishida, *Brain Res.* **1985**, *334*, 33; (i) K. Sakata, K. A. Oki, C.-F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem.* **1978**, *42*, 457.
2. (a) D. R. Williams, K. Shamim, R. Khalida, J. Reddy, G. S. Amato, S. M. Shaw, *Org. Lett.* **2003**, *5*, 3361; (b) H. Morita, M. Arisaka, J. Kobayashi, *J. Org. Chem.* **2000**, *65*, 6241; (c) C. Zou, J. Li, H. Lei, H. Fu, W. Lin, *J. Chin. Pharm. Sci.* **2000**, *9*, 113; (d) W. Lin, R. Xu, Q. Zhong, *HuaxueXuebao* **1991**, *38*, 927; (e) F. G. Fang, G. B. Feigelson, S. J. Danishefsky, *Tetrahedron Lett.* **1989**, *30*, 2743; (f) E. Valencia, V. Fajardo, A. J. Freyer, M. Shamma, *Tetrahedron Lett.* **1985**, *26*, 993; (g) S. R. Johns, J. A. Lamberton, A. A. Sioumis, *Aust. J. Chem.* **1969**, *22*, 793; (h) S. R. Johns, J. A. Lamberton,c A. A. Sioumis, *Chem. Commun.* **1968**, *21*, 1324.
3. (a) S. H. Park, H. J. Kang, S. Ko, S. Park, S. Chang, *Tetrahedron: Asymmetry* **2001**, *12*, 2621; (b) A. Costa, C. Nájera, J. M. Sansano, *Tetrahedron: Asymmetry* **2001**, *12*, 2205; (c) H.Yoda, H. Katoh, Y. Ujihara, K. Takabe, *Tetrahedron Lett.* **2001**, *42*, 2509; (d) M. Arisawa, M. Takahashi, E. Takezawa, T. Yamaguchi, Y. Torisawa, A. Nishida, M. Nakagawa, *Chem. Pharm. Bull.* **2000**, *48*, 1593; (e) D. Michael, M. D. Groaning, A. I. Meyers, *Chem. Commun.* **2000**, 1027; (f) S. B. Davies, M. A. McKervey, *Tetrahedron Lett.* **1999**, *40*, 1229; (g) F.Sánchez-Sancho, B. Herradón, *Tetrahedron: Asymmetry* **1998**, *9*, 1951; (h) Y. Sato, S. Nukui, M. Sodeoka, M. Shibasaki, *Tetrahedron* **1994**, *50*, 371; (i) S. Nukui, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 4965; (j) H. Waldmann, M. Braun, *J. Org. Chem.* **1992**, *57*, 4444; (k) D. H. Hua, S. N. Bharathi, J. A. K. Panangadan, A. Tsujimoto, *J. Org. Chem.* **1991**, *56*, 6998; (l) Y. Arai, T. Kontani, T. Koizumi, *Chem. Lett.* 1991, 2135; (m) D. H. Hua, S.

N. Bharathi, F. Takusagawa, T. Tsujimoto, J. A. K. Panangadan, M. H. Hung, A. A. Bravo, A. M. Erpelding, *J. Org. Chem.* **1989**, *54*, 5659.

4. (a) S. P. Panchgalle, H. B. Bidwai, S. P. Chavan, U. R. Kalkote, *Tetrahedron: Asymmetry* **2010**, *21*, 2399. (b) N. B. Kondekar, P. Kumar *Synthesis* **2010**, *18*, 3105; (c) D. L. J. Clive, Z. Li, M. Yu *J. Org. Chem.* **2007**, *72*, 5608; (d) T Hjelmgaard, D. Gardette, D. Tanner, D. J. Aitken, *Tetrahedron: Asymmetry* **2007**, *18*, 671; (e) R. K. Dieter, N. Chen, R. T. Watson, *Tetrahedron* **2005**, *61*, 3221; (f) P. Panchaud, C. Ollivier, P. Renaud, S. Zigmantas, *J. Org. Chem.* **2004**, *69*, 2755; (g) J. M. Andrés, I. Herráiz-Sierra, R. Pedrosa, A. Pérez-Encabo, *Eur. J. Org. Chem.* **2000**, 1719; (h) M. P. Sibi, J. W. Christensen, *J. Org. Chem.* **1999**, *64*, 6434; (i) H. Takahata, M. Kubota, S. Takahashi, T. Momose, *Tetrahedron: Asymmetry* **1996**, *7*, 3047; (j) J. Michael, M. J. Munchhof, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 7084.

5. (a) X. L. M. Despinoy, H. McNab, *Org. Biomol. Chem.* 2009, **7**, 4502; (b) R. Zimmer, M. Collas, R. Czerwonka, U. H. Reissig, *Synthesis* **2008**, *2*, 237.

6. (a) A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; (b) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH: Weinheim, **2007**.

7. D. W. C. MacMillian, *Nature (London)* **2008**, *455*, 304

8. For reviews on organocatalytic tandem reactions, see: (a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; (b) X. Yu,; W. Wang, *Org. Biomol. Chem.* **2008**, ***6***, 2037; (c) A. M. Walji, D. W. C. MacMillan, *Synlett* **2007**, 1477.

9. (a) V. Jha , P. Kumar, *RSC Adv.*, **2014**, *4*, 3238; (b) V. Jha , P. Kumar, *Synlett* **2014**, *25*, 1089; (c) S. V Kauloorkar, V. Jha , P. Kumar, *RSC Adv.* **2013**, *3*, 18288;

10. S. P. Kotkar, V. B. Chavan, A. Sudalai, *Org. Lett.* **2007**, *9*, 1001.

11. (a) D. M. Evans, P. J. Murphy, *Chem. Comm.* **2011**, *47*, 3225; (b) F. Kaiser, L. Schwink, J.Velder, H. Schmalz, *J. Org. Chem.* **2002**, *67*, 9248.

12. The enantiomeric excess was determined using chiral HPLC (see experimental section pg. 30 & 31).

13. Majik, J. Shet, S. G. Tilve, P. S. Parameswaranb, *Synthesis* **2007**, 663.

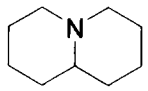
2.2. SECTION B

Synthesis of quinolizidine ring system by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde

2.2.1 Introduction

Quinolizidine skeleton **(Figure 1)** constitutes about 2% of more than 7000 alkaloids from plants.[1] They can also be classified into various alkaloid groups. Quinolizidine alkaloids are secondary metabolites found in seeds of many species of plants, possibly protecting them against pathogens and seed predators.[2] Quinolizidine alkaloids were isolated from Ormosia arborea seeds and bioassayed against red-rumped agoutis (Dasyprocta leporina, Rodentia: Caviomorpha) to verify if they inhibit seed predation and food hoarding (seed dispersal).[3] Three treatments were used: (1) seeds of O. arborea, (2) palatable seeds of Mimusops coriacea (Sapotaceae) treated with MeOH, and (3) seeds of M. coriacea treated with QAs dissolved in MeOH in similar concentration to that present in O.arborea. Palatable seeds were significantly more preyed upon than seeds treated with QAs and Ormosia seeds, but QAs did not influence hoarding behavior. QAs in O. arborea may have a strong effect in avoiding seed predation by rodents, without reducing dispersal.

Quinolizidine alkaloids are important as potential sources of medicine. They have a broad range of pharmacological properties, including cytotoxic, oxytocic, antipyretic, antibacterial, antiviral, and hypoglycemic activities, as determined by *in vivo* pharmacological screening.[4] Some quinolizidine alkaloids containing plants, for example *Sophora flavescens*, have been used as sources of crude drugs in Chinese–Japanese medicine.[5] Considering their potent biological activity and less abundance, these quinolizidine ring systems always remain an area of considerable synthetic effort. Many innovative synthetic as well as biosynthetic methods for preparing quinolizidine ring system has been reported in the literature.[6]



1
quinolizidine

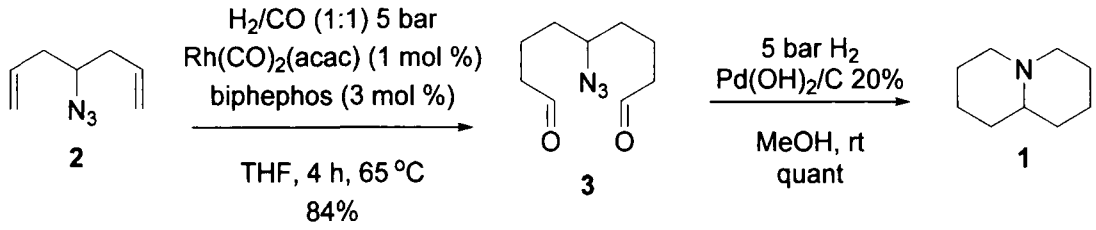
Figure 1: Structure of quinolizidine ring system

2.2.2. Review of Literature

There are several reports on the synthesis of quinolizidine ring system in the literature.[6] A detailed report of recent syntheses is described below.

Mann *et al.* (2010)[6a]

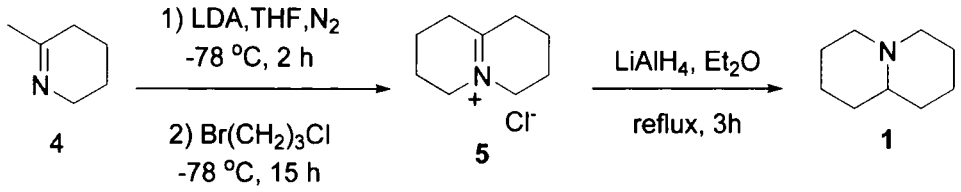
Mann and coworkers synthesized the quinolizidine bicyclic core starting from bis-homoallylic azide **2**. Bis-homoallylic azide **2** was subjected to regioselective hydroformylation condition employing the biphephos/rhodium (I) catalyst to get bisaldehyde **3** (**Scheme 1**). The bisaldehyde **3** on catalytic hydrogenation employing Pearlman's catalyst gave quinolizidine **1**.



Scheme 1 : Synthesis of quinolizidine ring system (Mann's method)

De Kimpe *et al.* (2003)[6b]

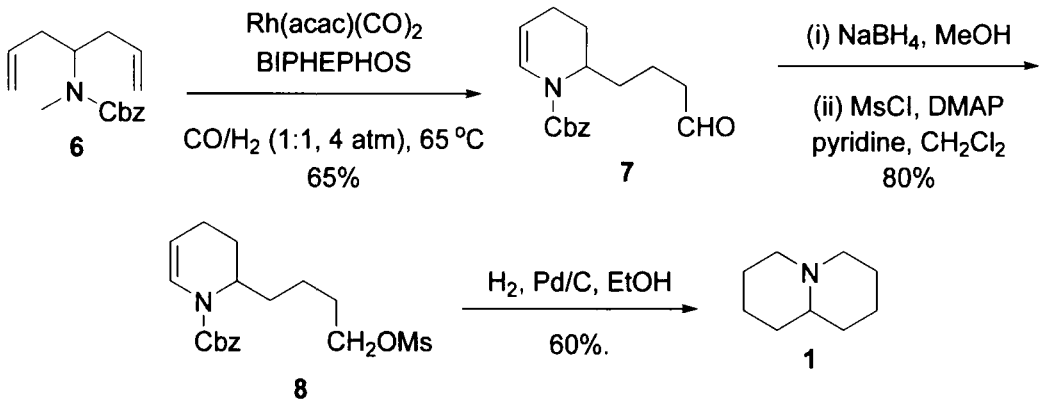
De Kimpe and coworkers synthesized the quinolizidine bicyclic starting from tetrahydropyridine **4**. Alkylation of tetrahydropyridine **4** with 1-bromo-3-chloropropane gave salt **5**, which on $LiAlH_4$ reduction in diethylether gave quinolizidine **1** (**Scheme 2**).



Scheme 2 : Synthesis of quinolizidine ring system (De Kimpe's method)

Ojima *et al.* (1998)[6c]

Ojima and coworkers synthesized the quinolizidine bicyclic starting from 4-amido-1,6-heptadiene **6** which on cyclohydrocarbonylation catalyzed by Rh catalyst piperidine gave compound **7**. The aldehyde functionality of piperidine **7** was reduced and furthur mesylated to get compound **8** which on catalytic hydrogenation gave quinolizidine **1** (**Scheme 3**).



Scheme 3 : Synthesis of quinolizidine ring system (Ojima's method)

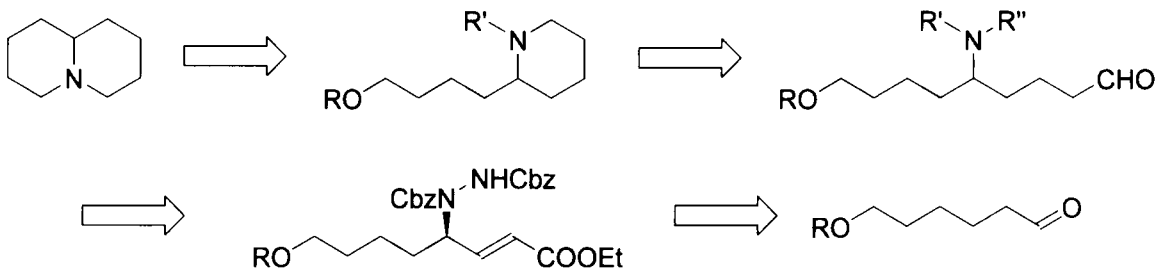
2.2.3. Present work

Objective

Recently, we reported an iterative approach to enantiopure synthesis of *syn/anti*-1,3-aminoalcohols *via* proline catalyzed sequential α-aminoxylation/α-amination and HWE olefination of aldehydes.[7] As a part of our research interest on developing new methodologies[8] and their subsequent application to bioactive compounds,[9] we envisioned that the proline catalyzed α-amination[10] could easily give us synthetic access to quinolizidine ring system. Since the α-amino aldehydes are prone to recemization, they

have been sucessesfully trapped *in situ* by HWE salt to furnish γ-amino-α,β-unsaturated ester using a mild procedure developed by Sudalai *et al.*[11] It is noteworthy that γ-amino-α,β-unsaturated ester, an allylic amines serve as useful building blocks and can further be elaborated to the synthesis of variety of compounds of biological importance.

Our strategy for the synthesis of quinolizidine is outlined in **Scheme 4**.



Scheme 4: Retro synthetic analysis of quinolizidine ring system.

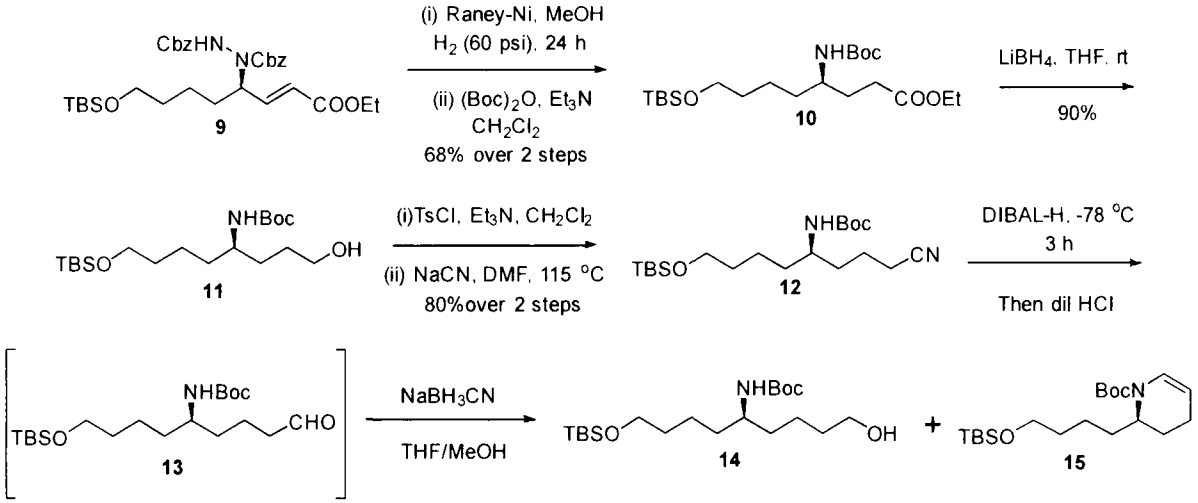
Our synthetic approach for the synthesis of target quinolizidine via α-amination was envisioned through the retro synthetic route shown in **Scheme 4**. Quinolizidine **1** was thought to be synthesized from hydroxyl piperidine, which in turn can be synthesized from γ-amino-α,β-unsaturated ester. This γ-amino-α,β-unsaturated ester could easily be obtained by α-amination of the corresponding aldehyde.

2.2.4 Results and discussion

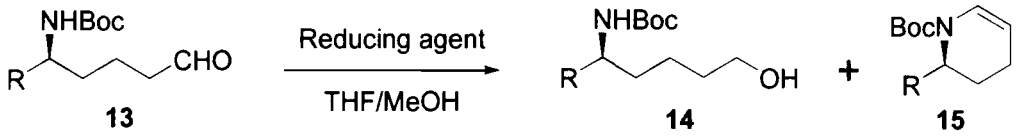
Thus synthesis of quinolizidine **1** started with synthesized γ-amino-α,β-unsaturated ester **9** (procedure as reported in the chapter 2, section A page 29) , which was first subjected to hydrogenation conditions using freshly prepared Raney-Ni at 60 psi for N-N bond cleavage to furnish the free amine that was subsequently protected as its Boc derivative **10** in 68% yield. Disappearance of the Cbz proton peaks in the aromatic region ranging from δ 7.27-7.39 confirmed the formation of product. Ester group of Boc-derivative **10** was reduced using $LiBH_4$ to give the alcohol **11** in 90% yield as determined from the proton NMR where we observed the disappearance of ester peak in the range of δ 4.12 as quartet and 1.25 as triplet. Alcohol **11** was converted into its toluenesulfonate derivative, on which one carbon homologation was performed via a nucleophilic substitution with

NaCN in dry DMF at 115 °C to furnish the cyano compound **12**. Disappearance of peak at 3365 cm-1 and appearance of peak at 2247 cm^{-1} in IR spectrum confirmed the formation of cyano compound. Cyano compound **12** on treatment with DIBAL-H at -78 °C followed by acid hydrolysis gave the aldehyde **13** which was then subjected to $NaBH_4$ reduction to get the alcohol **14**, but to our surprise it led to the formation of compound **15** as a major product **(Scheme 5)** along with the formation of alcohol **14** as a minor product. We then proceeded optimizing the reaction conditions to obtain the required product in substantial amount.

Scheme 5: Synthetic route to quinolizidine



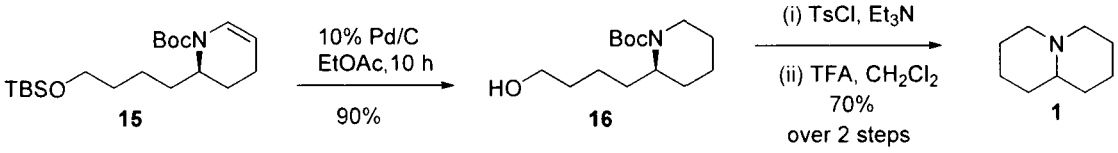
It was observed during optimization that the formation of cyclized product **15** depends on the equivalents of $NaBH_4$ used in the reaction. When 2 eq. of $NaBH_4$ was used in the reaction, both the compounds **14** and **15** were formed in equal ratio (1:1), on increasing the equivalent of $NaBH_4$ to 4 eq. marginal improvement in the ratio of **14:15** (4:6) was observed. Further increase to 10 eq. led to the considerable enhancement in the ratio of **14:15** (1:9). We then used $LiBH_4$ (5 eq.) and found the ratio of **14:15** was same as that in the case of $NaBH_4$. Finally, when $NaBH_3CN$ was used we got **15** as the sole product with trace amounts of **14** (**Table 1**).



Equiv. Of Reagent Used	14	15
2	1	1
4	2	3
5	3	7
10	1	9
5($LiBH_4$)	3	7
5($NaBH_3CN$)	Trace	>9.7

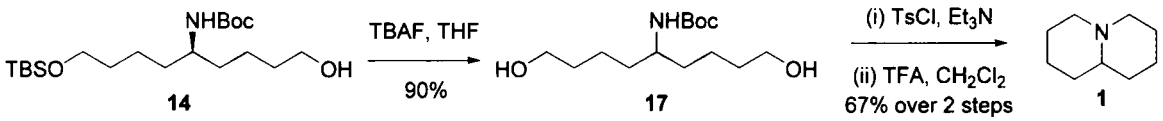
Table 1: Optimization of reductive cyclization reaction.

We used both the compounds **14** and **15** for the synthesis of target compound **1**. First compound **15** was subjected to the double bond reduction ensuing TBS deprotection under hydrogenation conditions in one step using 10% Pd-C in EtOAc to give the alcohol **16**. The disappearance of olefinic protons in the range of δ 4.77-4.87 as multiplet and 6.64-6.82 again as multiplet in ^1H NMR spectrum confirmed the formation of compound **16**. Finally alcohol **16** was converted to its toluenesulfonyl ester, concomitant cleavage of the Boc group with TFA followed by nucleophilic displacement of the tosyl with resultant amine in the presence of diisopropylethyl amine led to the formation of quinolizidine ring system **1**[12] (**Scheme 6**).



Scheme 6: Synthesis of quinolizidine

We then further considered converting compound **14**, obtained as a minor product to the target quinolizidine **1**. Towards this end, the TBS group of alcohol **14** was cleaved using TBAF to give the diol **17**. Subsequent treatment with toluenesulfonyl chloride and triethylamine and concomitant cleavage of the Boc group with TFA followed by nucleophilic displacement of the tosyl with the resultant amine in the presence of diisopropylethyl amine afforded the quinolizidine **1** in 67% yield **(Scheme 7)**.



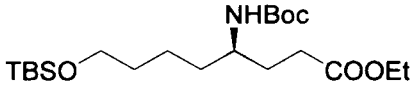
Scheme 7: Alternate synthesis of quinolizidine

2.2.5 Conclusion

In conclusion, we have developed a practical, efficient and organocatalytic approach to the synthesis of quinolizidine ring system using proline catalyzed sequential α-aminoxylation/α-amination reaction and HWE olefination reaction of an aldehyde as the key step. The synthetic strategy described here is easily amenable for the synthesis of a variety of alkaloids containing quinolizidine ring system. Currently, studies are in progress in this direction.

2.2.6. Experimental Section

Ethyl-(*R*)-4-((*tert*-butoxycarbonyl)amino)-8-((*tert*-butyldimethylsilyl)oxy)octanoate (10):



The solution of dibenzyl (*R,E*)-1-(8-((tert-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate **9** (2.0 g, 3.3 mmol) in MeOH (12 mL) and acetic acid (8 drops) was treated with Raney nickel (4.0 g, excess) under H_2 (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free amino alcohol which was further treated with triethylamine (0.93 mL, 6.7 mmol), Boc anhydride (1.2 mL, 5.1 mmol) and cat. DMAP in dry DCM (4 ml) for 2 h. Ice pieces were added to the reaction mixture and organic layer was separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude *N*-Boc derivative. Silica gel column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave **10** as a viscous liquid (0.98 g, 68%).

Yield: 0.84 g, yield 68%

Mol. Formula: $C_{21}H_{43}O_5NSi$

$[\alpha]_D^{25}$: + 0.23 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3366, 2862, 1699

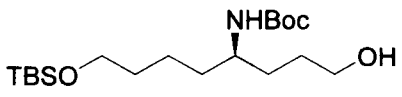
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.25 (t, *J* = 7.2Hz, 2H), 1.31-1.38 (m, 2H), 1.43 (s, 9H), 1.48-1.61 (m, 3H), 1.62-1.93 (m, 3H), 2.36 (t, *J* = 7.4Hz, 2H), 3.51-3.67 (m, 3H), 4.13 (q, *J* = 7.2Hz, 2H), 4.26-4.31 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 14.2, 18.3, 22.2, 25.9, 28.3, 30.5, 31.1, 32.6, 35.5, 50.3, 60.4, 62.9, 78.9, 155.6, 173.6 ppm

MS (ESI): m/z 440.26 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{44}O_7N_2Si$ 440.2803; Found 440.2812

***tert*-Butyl (*R*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11):**



To a stirred suspension of $LiBH_4$ (0.60 g, 2.2 mmol) in dry THF (1 mL) was added a solution of **10** (0.60 g, 1.4 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at

room temperature for 3 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (petroleum ether: ethyl acetate: 65:35) of the crude product gave **11** as a colorless liquid.

Yield: 0.48 g, 90%

Mol. Formula: $C_{19}H_{41}O_4NSi$

$[\alpha]_D^{25}$: + 0.82 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3368, 2930, 1688, 1098

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.26 - 1.38 (m, 4H), 1.44 (s, 9H), 1.49 - 1.58 (m, 3H), 1.61 - 1.64 (m, 3H), 3.52 - 3.69 (m, 5H), 4.33 (brs, 1H) ppm

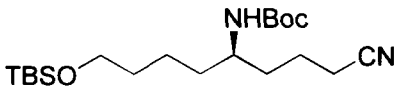
^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 18.3, 22.2, 25.9, 28.4, 28.9, 32.1, 32.6, 35.4, 50.4, 62.6, 62.9, 78.9, 155.9 ppm

MS (ESI): m/z 398.18 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{41}O_4NSiNa$ 398.2697; Found 398.2703

$[M+H]^+$ Calcd for $C_{19}H_{42}O_4NSi$ 376.2878; Found 376.2882

***tert*-Butyl (*S*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-cyanooctan-4-yl)carbamate (12):**



To an ice-cold stirred solution of **11** (0.50 g, 1.33 mmol) and triethylamine (0.27 mL, 1.99 mmol) in anhydrous CH_2Cl_2 (8 mL) was added toluenesulfonyl chloride (0.5 g, 2.66 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 6 h. After diluting with 10 mL CH_2Cl_2, the solution was washed with (3 x 15 mL) brine, dried over Na_2SO_4 and concentrated to give the crude tosylated product which was subjected to next reaction without purification.

To a solution of tosyl ester in DMF was added NaCN (0.13 g, 2.66 mmol) and was stirred at 115 °C for 10 h. After the consumption of starting material the reaction mixture was poured into H_2O and extracted with ether (25 mL). The organic phase was washed with H_2O and brine (15 mL) dried (Na_2SO_4) and concentrated in vacuo. Silica gel column chromatography of the crude product (petroleum ether: ethyl acetate 90:10) gave **12** as yellow syrupy liquid.

Yield: 0.41 g, 80%

Mol. Formula: $C_{20}H_{40}O_3N_2Si$

$[\alpha]_D^{25}$: - 2.62 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$,cm^{-1}): ν^{max} 3360, 2936, 2247, 1688, 1170

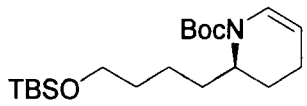
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 1.26-1.38 (m, 2H), 1.44 (s, 9H), 1.49-1.58 (m, 4H), 1.61-1.76 (m, 4H), 2.40 (t, *J* = 6.8Hz, 2H), 3.52-3.67 (m, 3H), 4.27 (brs, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 16.9, 18.3, 22, 22.2, 25.9, 28.3, 32.5, 34.8, 35.5, 49.7, 62.9, 79.2, 119.5, 155.8 ppm

MS(ESI): m/z 407.21 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{40}O_3N_2SiNa$ 407.2700; Found 407.2700

***tert*-Butyl 2-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydropyridine-1(2H) carboxylate (15):**



To a solution of **12** (0.25 g, 0.65 mmol) in CH_2Cl_2 (10 mL), was added DIBAL-H (0.715 mL 1M solution in toluene, 0.71 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 2 h. Then, saturated solution of ammonium chloride (0.8 mL) was added. The resulting mixture was warmed to ambient temperature and was then diluted with 0.2 M aqueous HCl (0.67mL) followed by EtOAc and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde **13** as a colorless liquid, which was directly used in the next step without further purification.

To the cooled solution of anhydrous THF was added a solution of $NaBH_3CN$ (0.164 g, 2.6 mmol) in absolute methanol in one portion with stirring for 20 min followed by addition of aldehyde **13**. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After being cooled to ambient temperature, the mixture was quenched with ice pieces and extracted with EtOAc (3 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give pale yellow oil. The crude product was then purified by using silica gel flash column chromatography (petroleum ether:EtOAc 90:10) gave **15** as a pale yellow oil. Continuation of the column chromatography by increasing the polarity (petroleum ether: EtOAc 75:25) eluted **14** as a colorless oil.

Yield: 0.30 g, 70%

Mol. Formula: $C_{20}H_{39}O_3NSi$

$[\alpha]_D^{25}$: - 56.17 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2929, 2857, 1720, 1649, 1360

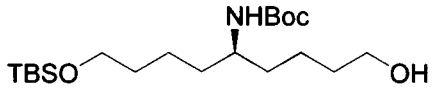
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.80 (s, 9H), 1.26-1.44 (m, 4H), 1.49 (s, 9H), 1.54-1.61(m, 3H), 1.64-1.80 (m, 2H), 1.94-2.01 (m, 1H), 3.61 (t, J = 6.3Hz, 2H), 4.13-4.29 (m, 1H), 4.77-4.87 (m, 1H), 6.64-6.82 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): as a rotameric mixture (2:1) δ -5.3, 17.5, 18.3, 25.9, 28.3, 30.2, 30.8, 32.7, 49.5, 50.6, 63.0, 80.2, 104.6, 105.1, 123.9, 124.2, 152.2, 152.6 ppm

MS(ESI): m/z 392.15 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{40}O_3NSi$ 370.2772; Found 370.2771

***tert*-Butyl (*S*)-(1-((*tert*-butyldimethylsilyl)oxy)-9-hydroxynonan-5-yl)carbamate (14):**



Yield: 0.090 g, 30%

Mol. Formula: $C_{20}H_{43}O_4NSi$

$[\alpha]_D^{25}$: - 2.10 (*c* 0.6 $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3365, 2929, 2857, 1691

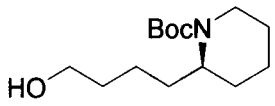
^{1}H NMR (200 MHz, CDCl3): δ 0.04 (s, 6H), 0.89 (s, 9H),1.25-1.40 (m, 4H), 1.44 (s, 9H), 1.48-1.61 (m, 5H), 1.69-1.76 (m, 1H), 2.68-2.82 (m, 1H), 3.65 (t, J = 6.5Hz, 2H), 3.90-4.02(m, 1H), 4.16-4.28 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 21.9, 22.2, 24.1, 25.9, 28.4, 29.7, 32.5, 32.6, 35.4, 50.4, 62.7, 63.0, 79.4, 155.8 ppm

MS(ESI): m/z 412.16 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{43}O_4NSi$ 390.3034; Found 390.3032

***tert*-Butyl *(S)*-2-(4-hydroxybutyl)piperidine-1-carboxylate (16):**



To the solution of **15** (0.1 g, 0.27 mmol) in ethyl acetate was added Pd-C (10%) under hydrogenation conditions. The reaction mixture was allowed to stir overnight. On completion of reaction (until ^{1}H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give **16** as a colorless liquid.

Yield: 0.062 g, 90%

Mol. Formula: $C_{14}H_{27}O_3N$

$[\alpha]_D^{25}$: - 24.26 (*c* 0.8 $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3436, 2933, 2862, 1688, 1668

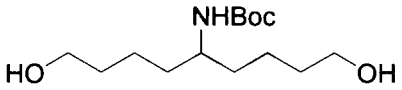
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.26-1.42 (m, 5H), 1.45 (s, 9H), 1.49-1.59 (m, 6H), 1.69-1.76 (m, 1H), 2.68 -2.82 (m, 1H), 3.65 (t, J = 6.5Hz, 2H), 3.90-4.02 (m, 1H), 4.16-4.28 (m, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): as a rotameric mixture (2:1): δ 18.9, 22.3, 25.6, 28.4, 29.3, 29.6, 32.4, 38.7, 50.5, 62.6, 79.1, 155.2 ppm

MS(ESI): m/z 280.09 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{27}O_3N$ 280.1883; Found 280.1878

tert-Butyl (1,9-dihydroxynonan-5-yl)carbamate (17):



The solution of **14** (0.1g, 0.25 mmol) in THF (3mL) was treated with TBAF (0.15 mL, 0.51 mmol) at 0 °C. The reaction mixture was stirred for 2 h and quenched with H_2O (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Silica gel column chromatography (Petether: EtOAc 35: 65) of the crude product afforded **17** as a syrupy liquid.

Yield: 0.63 g, 90 %

Mol. Formula: $C_{14}H_{29}O_4N$

IR ($CHCl_3$, cm^{-1}): ν^{max} 3347, 2935, 2864, 1688, 1172

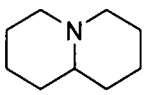
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25-1.40 (m, 4H), 1.44 (s, 9H), 1.51-1.62 (m, 4H),1.83-2.10 (m, 4H), 2.49-3.72 (m, 5H), 4.38 (brs, 1H) ppm

^{13}C NMR (50 MHz, $CDCl_3$): δ 21.9, 28.4, 32.4, 35.4, 50.3, 60.6, 79.1, 156.0 ppm

MS(ESI): m/z 298.05 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{27}O_3N$ 298.1989; Found 298.1985

Octahydro-2H-quinolizine (1):



To an ice-cold stirred solution of **16** (0.05g, 0.19 mmol) and triethylamine (0.08 mL, 0.58mmol) in anhydrous CH_2Cl_2 (2 mL) was added toluenesulfonyl chloride (0.08 g, 0.38mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 8 h. After diluting with 5 mL CH_2Cl_2, the solution was washed with water (3 x 10 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude tosylated product which was subjected to next step without further purification.

To the solution of tosylated product in dry CH_2Cl_2 (1 mL) was added TFA (0.075 mL, 0.76 mmol) at 0 °C and reaction mixture was allowed to stir at rt for 2 h. Then solvent was evaporated and neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give crude product. Silica gel column chromatography in EtOAc furnished **1** as a colorless liquid.

Yield: 0.019 g, 67%

Mol. Formula: $C_9H_{17}N$

IR ($CHCl_3$, cm^{-1}): ν^{max} 3367, 3020, 2400, 1215

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.13-1.44 (m, 6H), 1.45 (s, 9H), 1.48-1.60 (m, 5H), 1.73-2.06 (m, 4H), 2.31 -2.65 (m, 2H)ppm

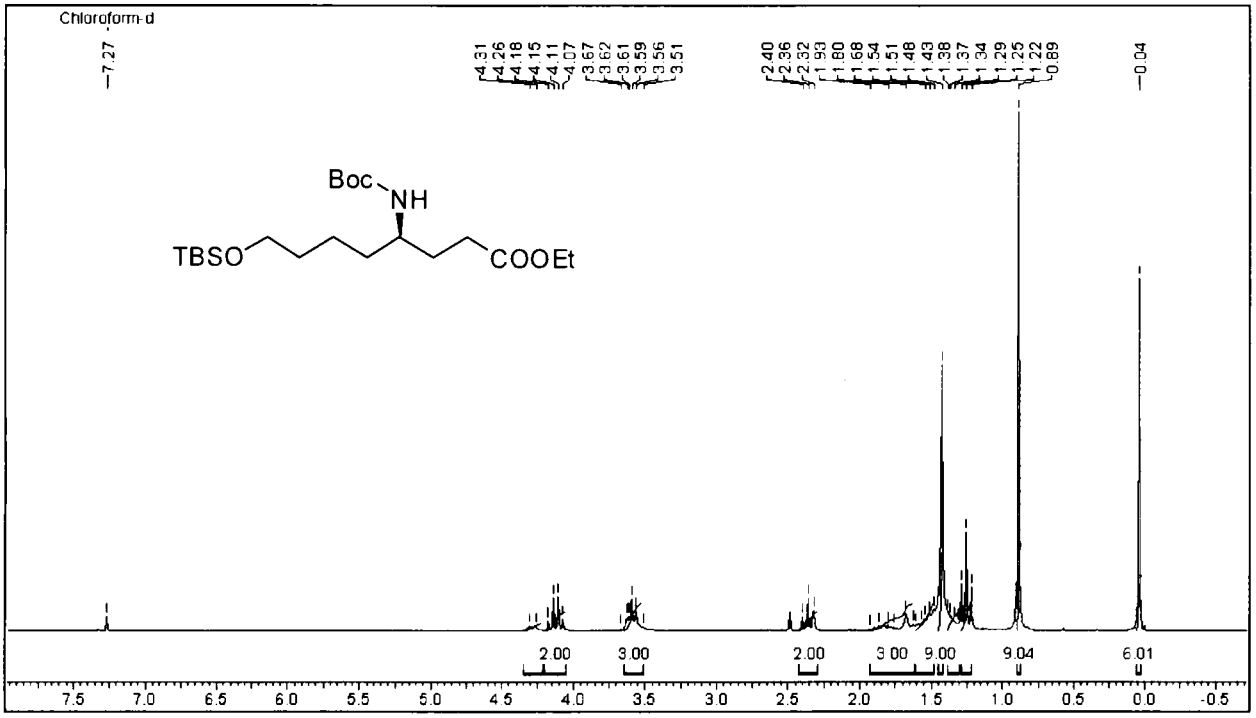
^{13}C NMR (50 MHz, $CDCl_3$): δ 22.8, 29.6, 30.0, 55.6, 64.9 ppm

MS(ESI): m/z 140.21 $(M+H)^+$

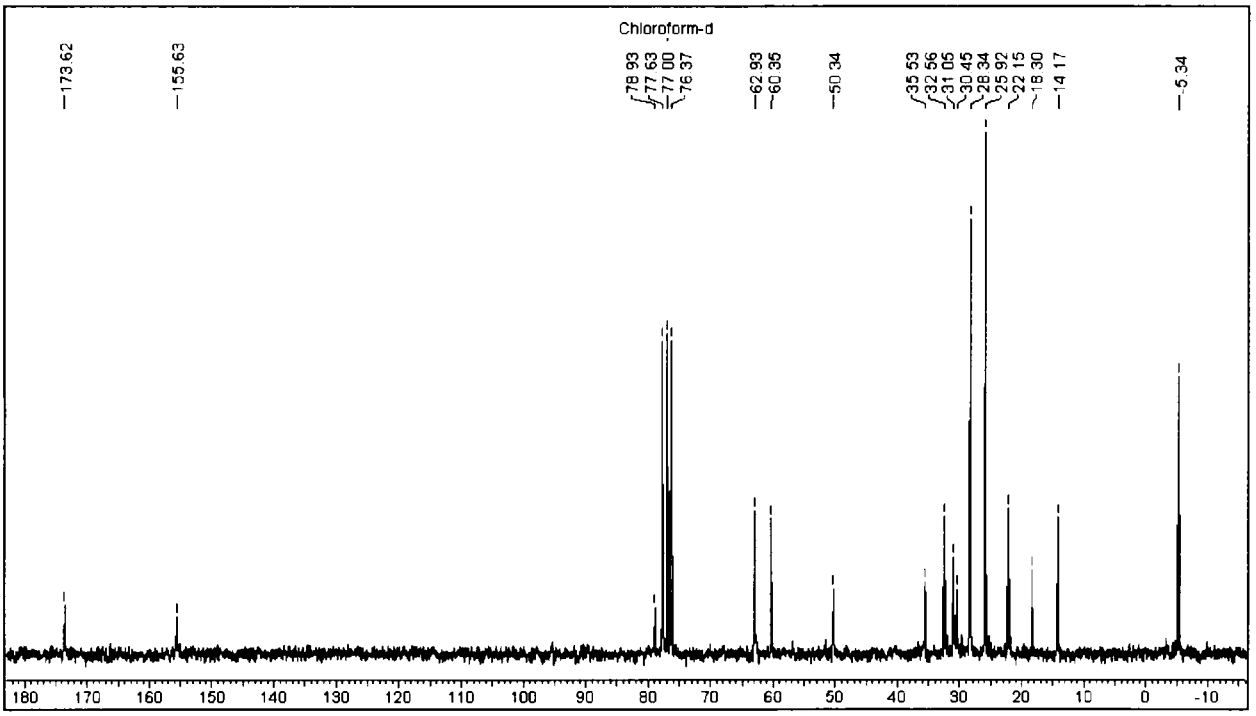
HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_9H_{17}N$ 140.1434; Found 140.1434

2.2.7. Spectra

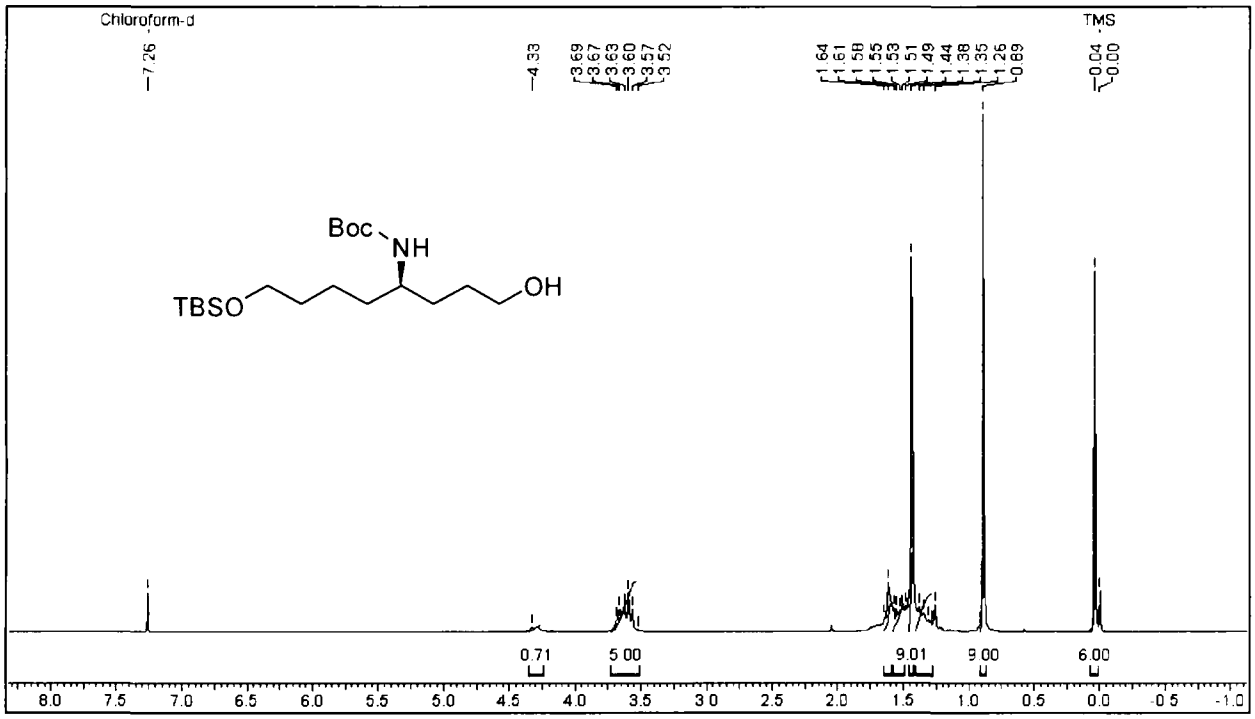
^{1}H NMR ($CDCl_3$, 200MHz) of (*R*)-Ethyl 4-((*tert*-butoxycarbonyl)amino)-8-((*tert* butyldimethylsilyl)oxy)octanoate (10):



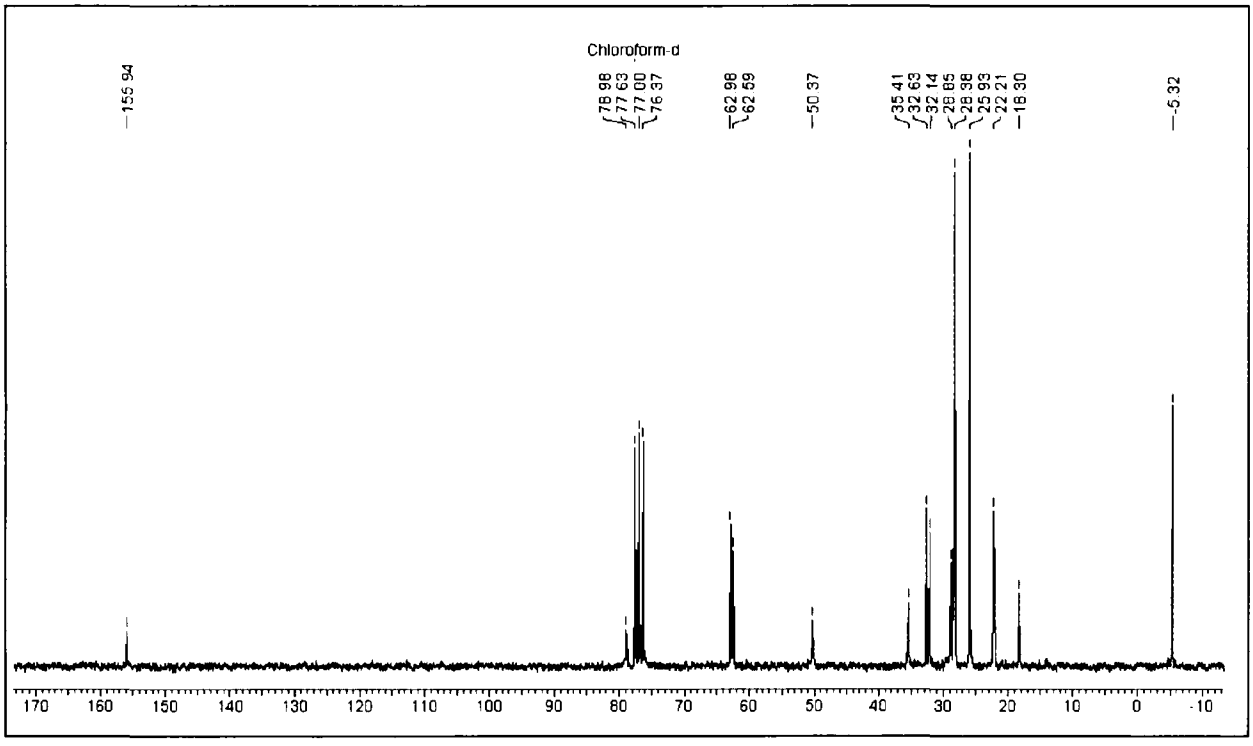
^{13}C NMR ($CDCl_3$, 50MHz) of (*R*)-Ethyl 4-((*tert*-butoxycarbonyl)amino)-8-((*tert* butyldimethylsilyl)oxy)octanoate (10):



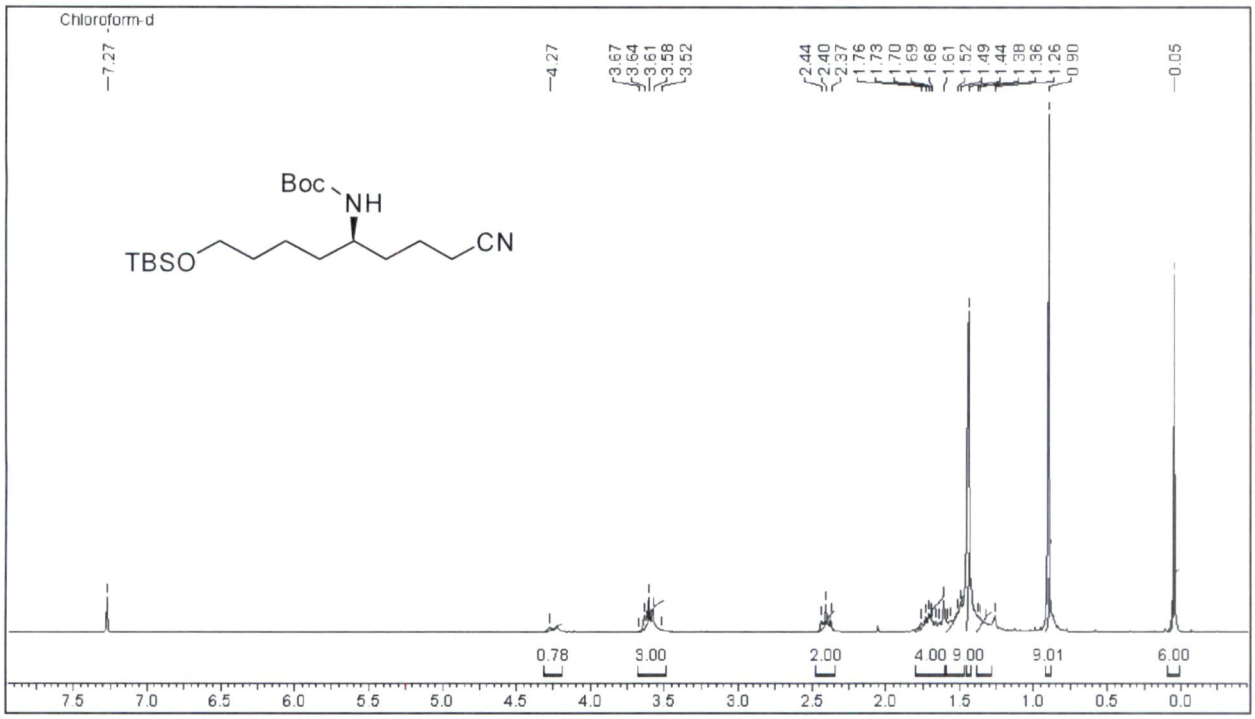
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl(*R*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11):



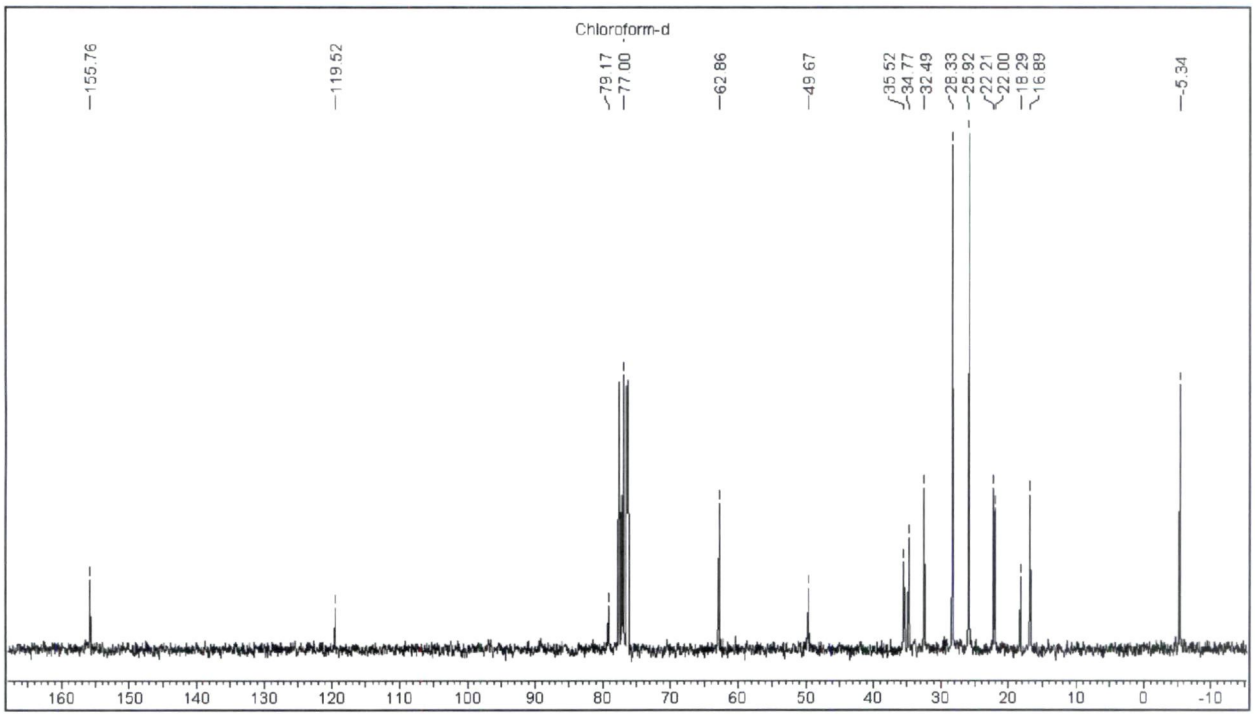
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl(*R*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctan-4-yl)carbamate (11):



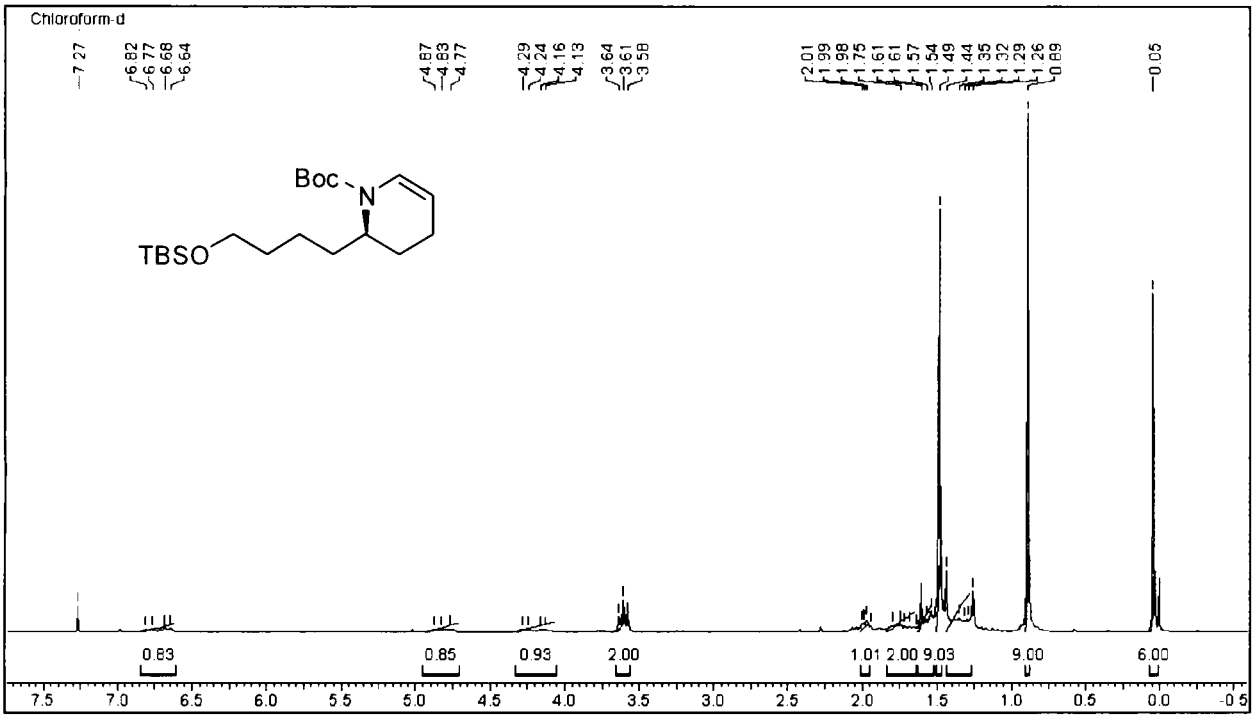
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl(*S*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-cyanooctan-4-yl)carbamate (12):



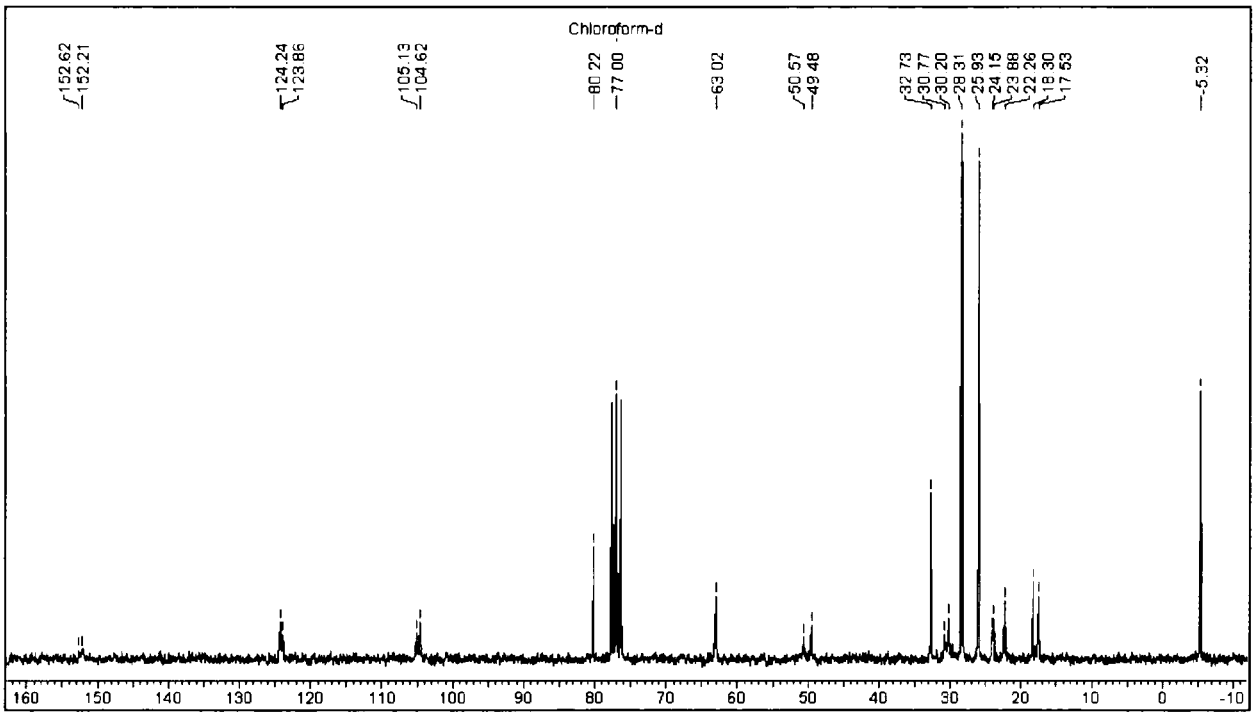
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl(*S*)-(8-((*tert*-butyldimethylsilyl)oxy)-1-cyanooctan-4-yl)carbamate (12):



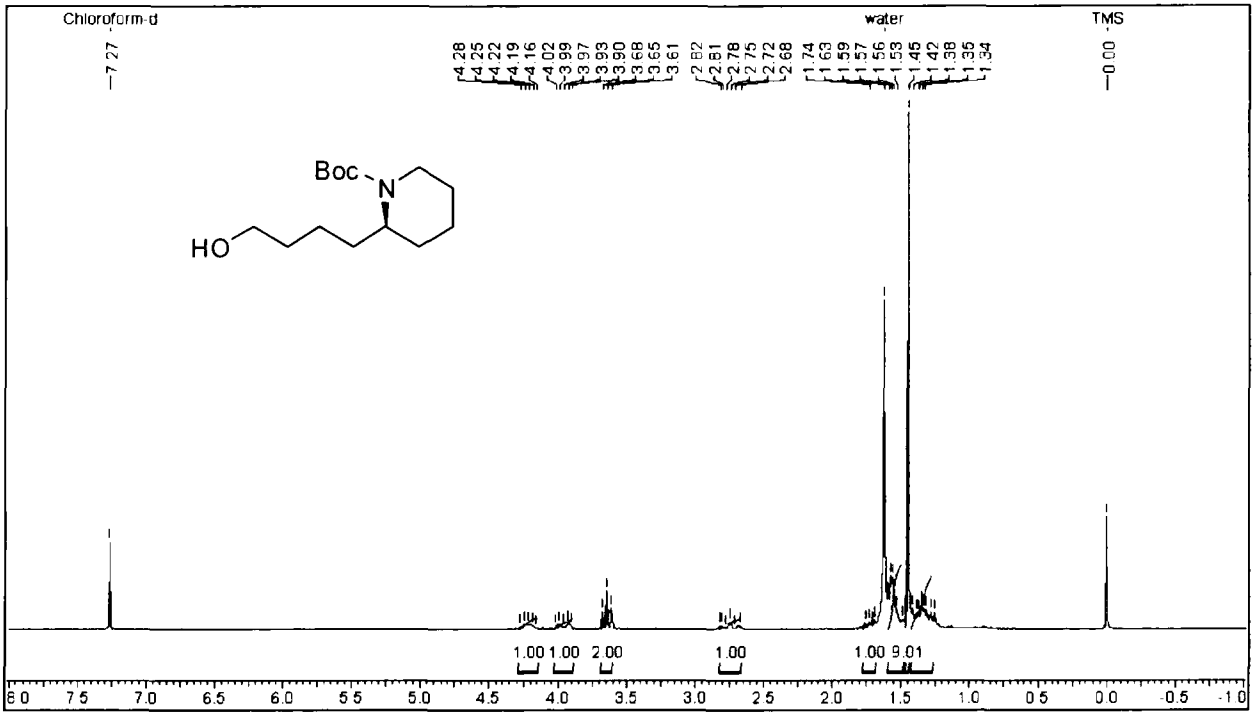
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl(*R*)-2-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydropyridine-1(2H)-carboxylate (15):



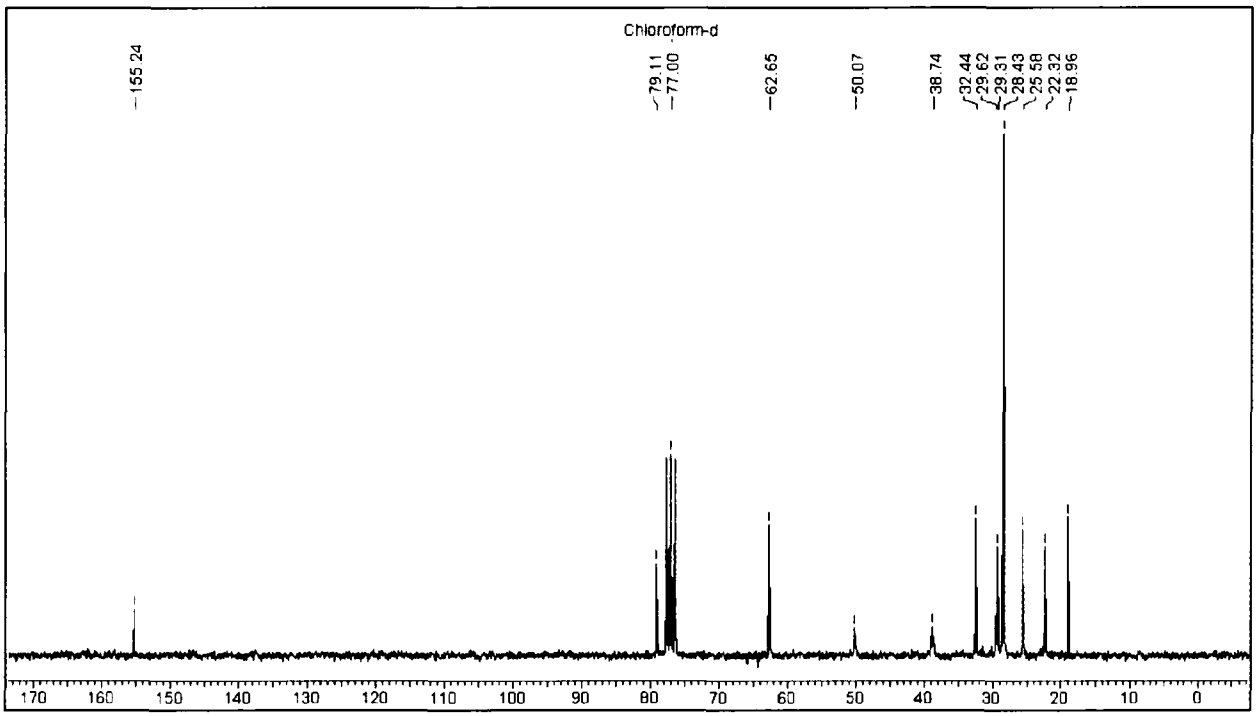
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl(*R*)-2-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydropyridine-1(2H)-carboxylate (15):



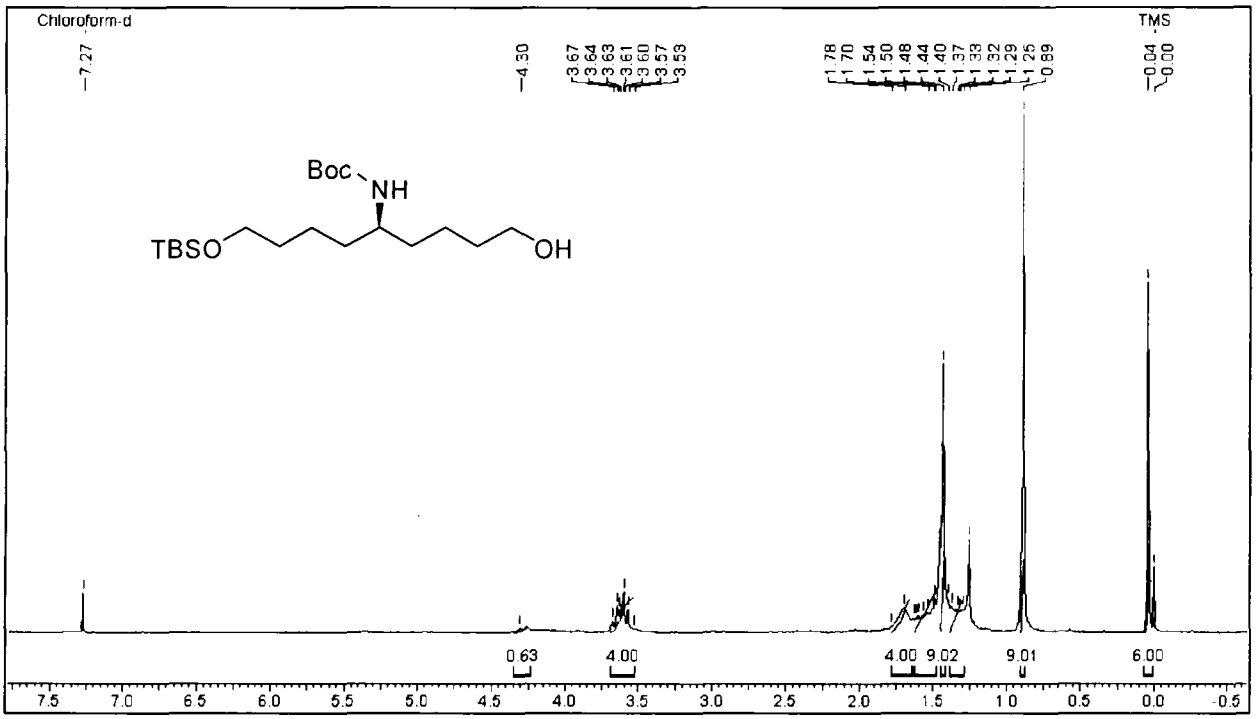
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl(*S*)-2-(4-hydroxybutyl)piperidine-1-carboxylate (16):



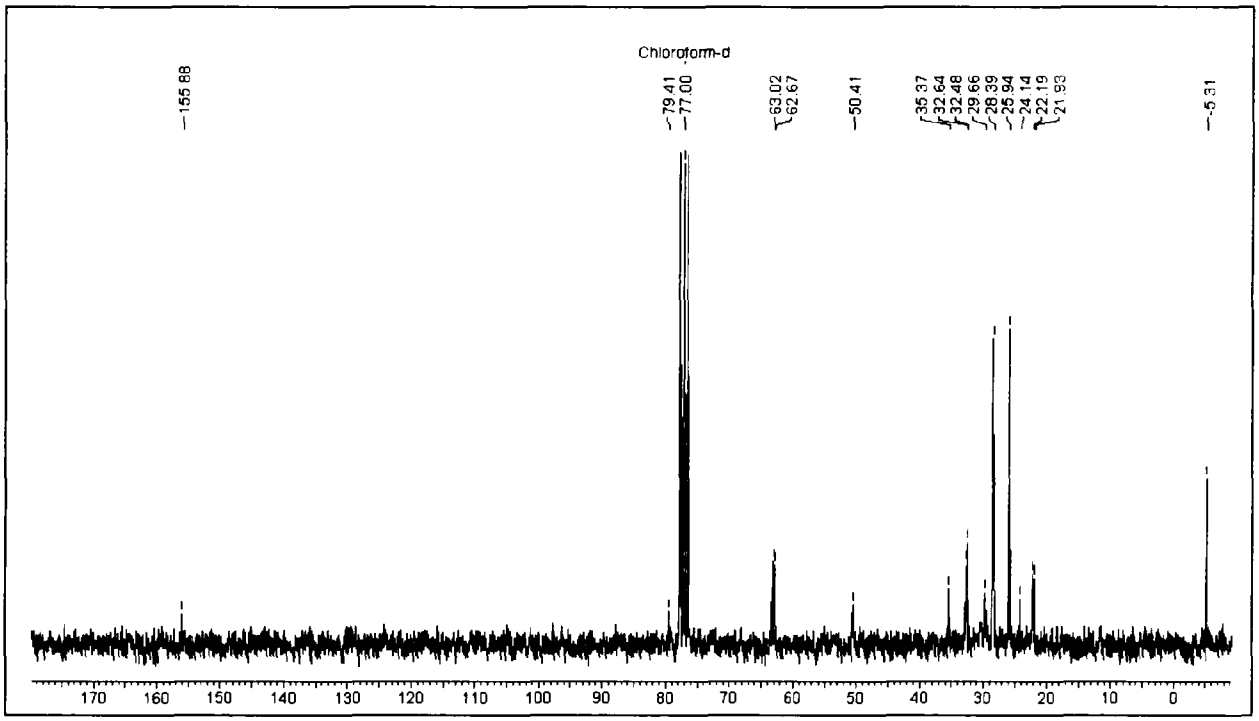
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl(*S*)-2-(4-hydroxybutyl)piperidine-1-carboxylate (16):



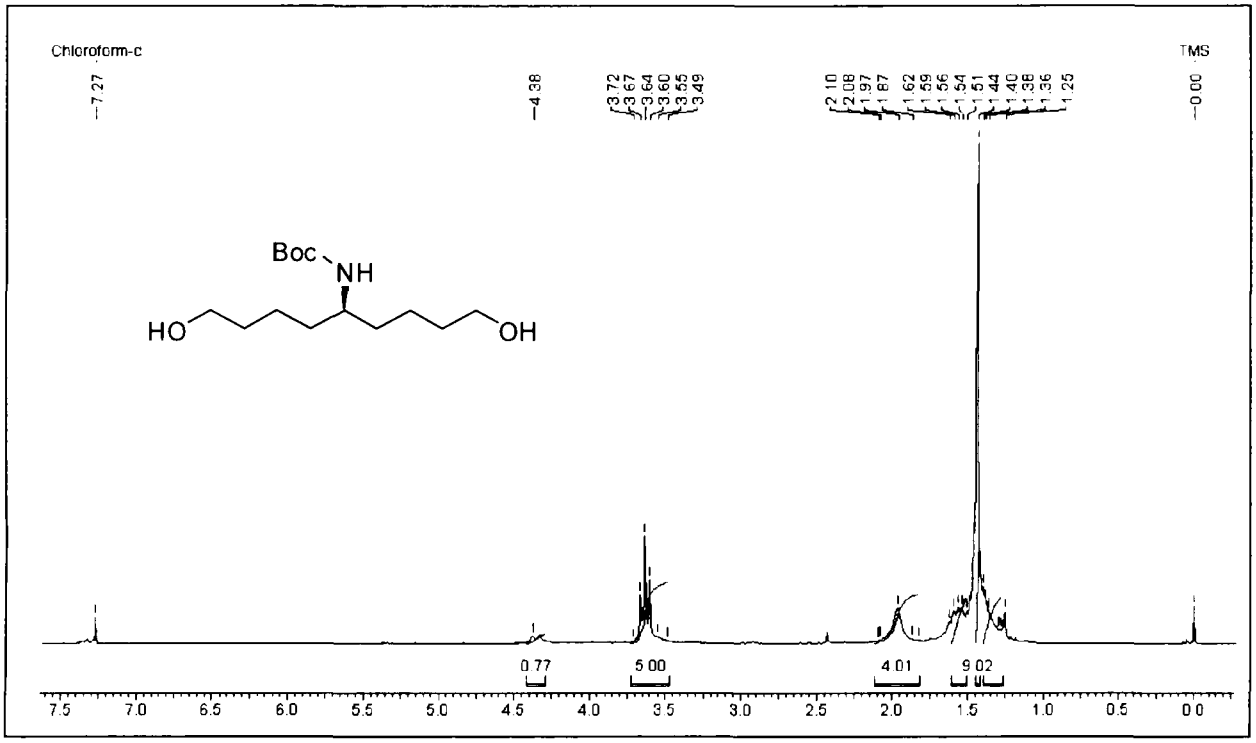
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl(*S*)-(1-((tert-butyldimethylsilyl)oxy)-9-hydroxynonan-5-yl)carbamate (14):



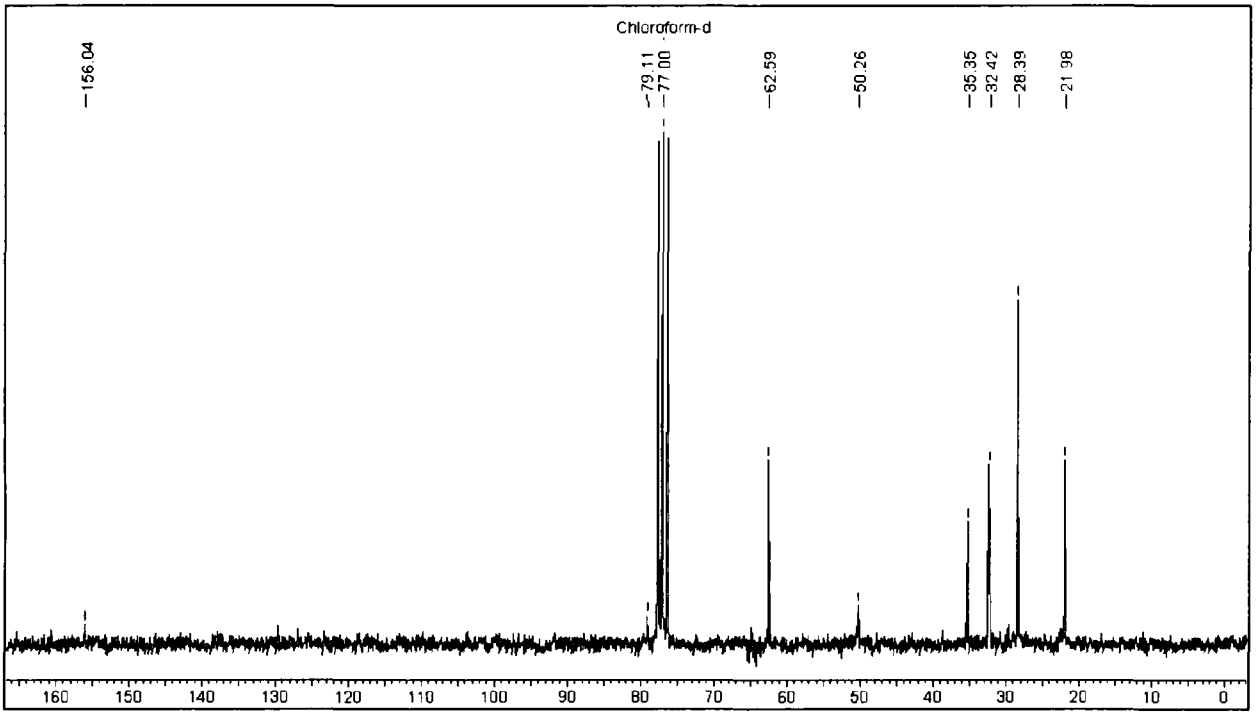
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl(*S*)-(1-((tert-butyldimethylsilyl)oxy)-9-hydroxynonan-5-yl)carbamate (14):



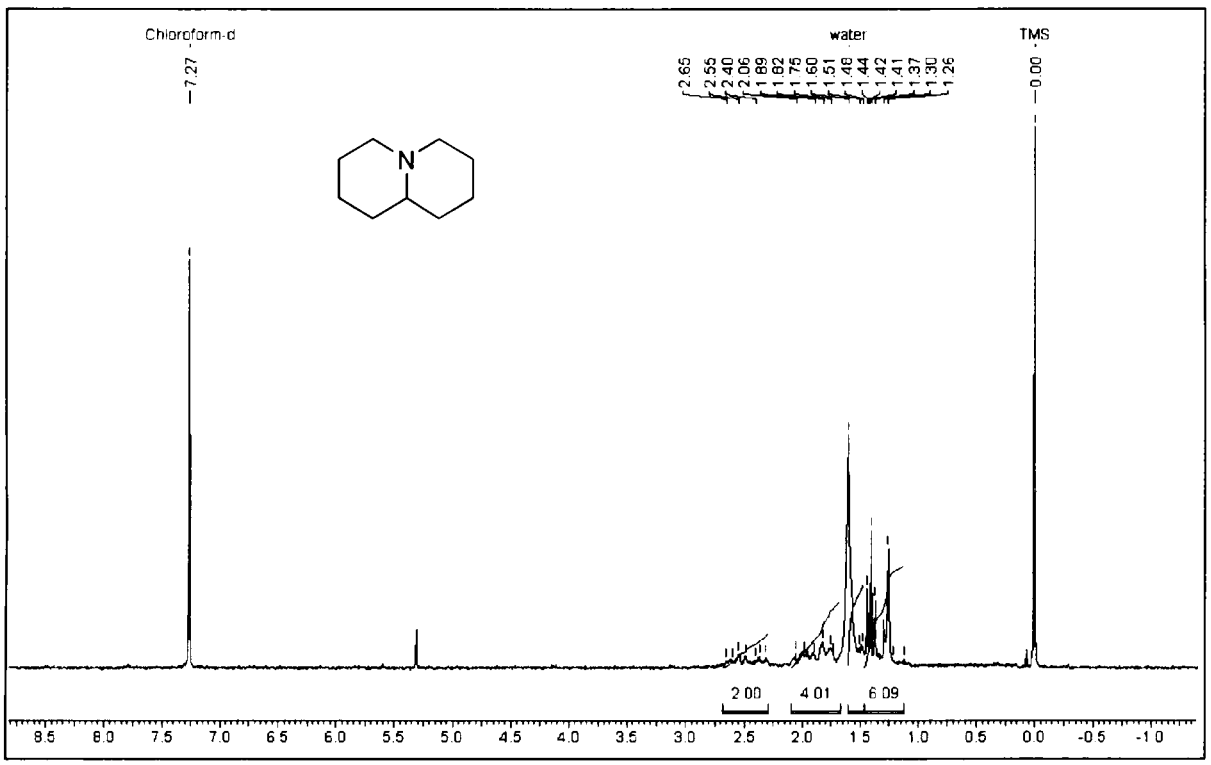
^{1}H NMR ($CDCl_3$, 200MHz) of *tert*-Butyl (1,9-dihydroxynonan-5-yl)carbamate (17):



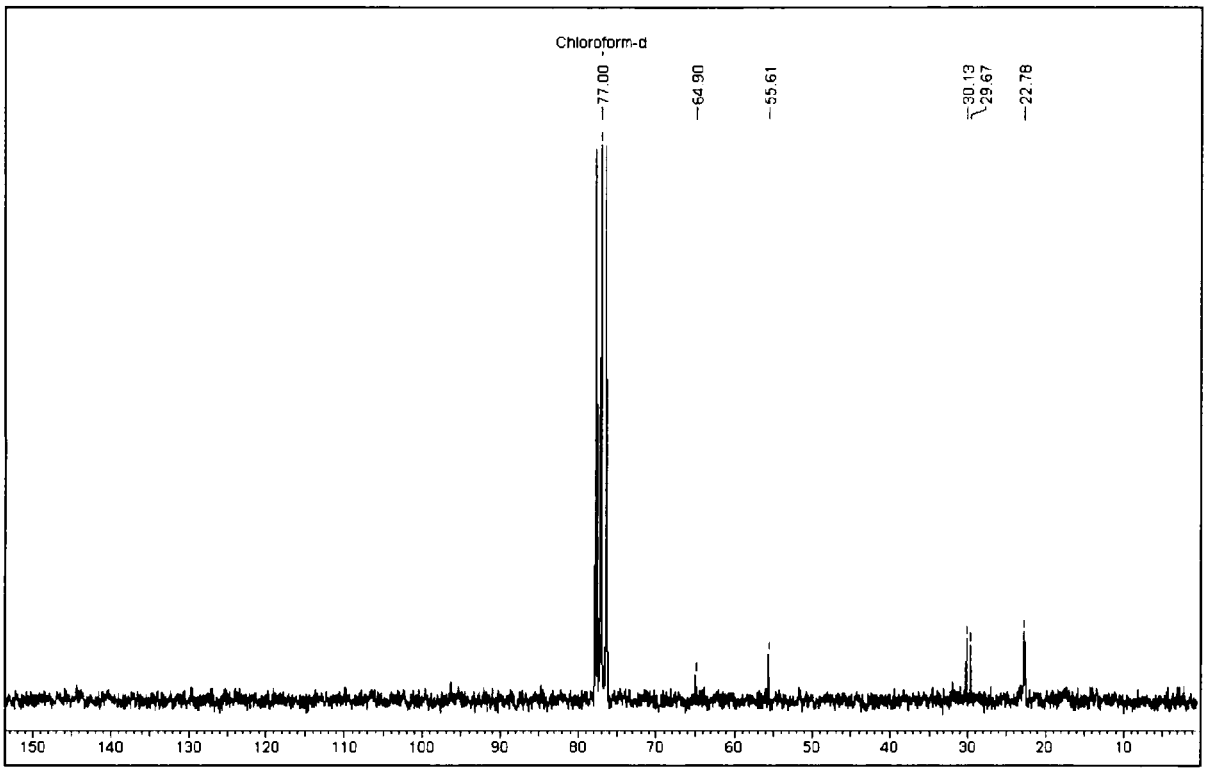
^{13}C NMR ($CDCl_3$, 50MHz) of *tert*-Butyl (1,9-dihydroxynonan-5-yl)carbamate (17):



^{1}H NMR ($CDCl_3$, 200MHz) of Octahydro-2H-quinolizine (1):



^{13}C NMR ($CDCl_3$, 50MHz) of Octahydro-2H-quinolizine (1):



2.2.8 References:

1. (a) M. F. Grundon, *Natural Product Report* **1989**, *6*, 523; (b) M. F. Grundon, *Natural Product Report* **1987**, *4*, 415; (c) M. Wink, *Planta Medica* **1987**, 509; (d) A. D. Kinghorn, M. F. Balandrin, In Alkaloids: Chemical and biological perspectives, (ed. W. S. Pelletier), **1984**, p. 105, Wiley, New York; (e) J. E. Saxton, M. F. Grundon, (1971-1983) The Alkaloids (London), vol. 1-13.
2. (a) G. R. Waller, E. Nowacki, Alkaloid biology and metabolism in plants, Plenum Press, **1978**, New York, London; (b) M. Wink in: Proc. 3. Int. lupin Conf., **1984**, p. 325, ILA, La Rochelle; (c) M. Wink, *Z. Naturforsch* **1984**, *39c*, 548.
3. (a) S. Ohmiya, K. Saito, I. Murakoshi, In *The Alkaloids: Chemistry and Pharmacology*, **1995**, Vol. 47, (ed. G. A. Cordell), London: Academic Press, 1–114; (b) M. Wink, C. Meißner, L. Witte, *Phytochemistry* **1995**, *38*, 139.
4. (a) K. Saito, I. Murakoshi, *Natural Products Chemistry*, **1995**, Vol. 15, *Structure and Chemistry (Part C)*, ed. A. U. Rahman, (Amsterdam: Elsevier), 519–550; (b) A. Sparataro, M. Veronese, F. Sparataro, *Farmaco, Edizione Scientifica* **1987**, *42*, 159.
5. W. Tang, G. Eisenbrand, **1992**, *Chinesedrugsofplantorigin: Chemistry, Pharmacology, and Use in Traditional and ModernMedicine*, Berlin: Springer. (c)
6. (a) E. Airiau, T. Spangenberg, N. Girard, B. Breit, A. Mann, *Org Lett.* **2009**, *12*, 528; (b) K. A. Tehrani, M. D'hooghe, N. De Kimpe, *Tetrahedron* **2003**, 59, 3099; (c) I. Ojima, D. M. Iula, M. Tzamafioudaki, *Tetrahedron Lett.* **1998**, *39*, 4599; (d) D. L. Comins, S. O'Connor, *Tetrahedron Lett.* **1987**, *28*, 1843; (e) P. D. Edwards, A. I. Meyers, *Tetrahedron Lett.* **1984**, *25*, 939.
7. V. Jha, N. B. Kondekar, P. Kumar, *Org. Lett.* **2010**, *12*, 2762.
8. (a) P. Kumar, V. Jha, R. G. Gonnade, *J. Org. Chem.* **2013**, *78*, 11756; (b) P. Kumar, N. Dwivedi, *Acc. Chem. Res.* **2013**, *46*, 289; (c) N. B. Kondekar, P. Kumar, *Org. Lett.* **2009**, *11*, 2611.
9. (a) V. Jha, P. Kumar, *RSC Adv.* **2014**, *4*, 3238; (b) V. Jha, P. Kumar, *Synlett* **2014**, *25*, 1089; (c) S. V. Kauloorkar, V. Jha, G. Jogdand, P. Kumar, *Org. Biomol.*

Chem. **2014**, *12*, 4454; (d) V. Jha, S. V. Kauloorkar, P. Kumar, *Eur. J. Org. Chem.* **2014**, 4897.

10. B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.
11. S. P. Kotkar, V. B. Chavan, A. Sudalai, *Org. Lett.* **2007**, *9*, 1001.
12. R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata, M. Kawanisi, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 215.

Chapter 3

Synthesis of dihydroxylated and monohydroxylated izidines using proline catalyzed α- amination followed by Sharpless asymmetric dihydroxylation

3.1. SECTION A

Stereoselective Approach to Indolizidine and Pyrrolizidine Alkaloids: Total Synthesis of (-)-Lentiginosine, (-)-*epi*-Lentiginosine and (-)-Dihydroxypyrrolizidine

3.1.1 Introduction

The synthesis of enantiopure therapeutics with a high medicinal value has always been a prime concern among synthetic chemists. Among them, azasugars have gained much attention in recent years as they mimic carbohydrates. Structurally, they are known to contain fused bicyclic systems with nitrogen at the bridge head and variable ring size based on which they may be classified as indolizidines[1] and pyrrolizidines.[2] These "izidines" show different patterns of oxygenation, for instance, the highly oxygenated castanospermine **1,** its less hydroxylated congeners such as lentiginosine **2,** 8a-*epi*-lentiginosine **3**, and dihydroxypyrrolizidine **4** or the non oxygenated ring systems such as coniceine **5** and pyrrolizidine **6** *etc.* are widespread in plants and microorganisms[3] (**Figure 1**).

Lentiginosine was isolated in 1990 by Elbein and co-workers from the source *Astralagus Lentiginosus.*[4] It is known to exhibit excellent anti-HIV, anti-tumour and immunomodulating activities apart from being a significant inhibitor of amyloglycosidases (lowering the absorption of carbohydrates in the GI tract) with IC_{50}=5μg/mL. Lentiginosine is an interesting compound from a biochemical standpoint. It was found to be the first glycosidase inhibitor with only two hydroxyl groups. All the other reported glycosidase inhibitors have three or more hydroxyl functions. The fact that a pyrrolizidine alkaloid can also inhibit these glycosidases indicates that a six-membered ring is not essential for inhibitory activity. It seems likely that the nitrogen in the ring is an essential requirement. The mechanism of action is related to inhibition of the biosynthesis of glycoproteins which are responsible for recognition and adhesion of exogenous agents.[5] Effective inhibitors are known to mimic the terminal unit of oligosaccharides competing the natural substrate for occupying the enzyme active site.

Interestingly, its pyrrolizidines analogue was also found to belong to an important class of alkaloids that display a wide range of biological activities mainly due to their action as specific glycosidase inhibitors. Both the hydroxylated indolizidine and pyrrolizidine derivatives have gained considerable interest as antiviral and anticancer agents. Since the biological activity varies substantially with the number, the position and the stereochemistry of the hydroxyl groups on the aza bicyclic skeleton, the synthesis of both naturally occurring compounds and their stereoisomers and analogues have been very interesting targets.

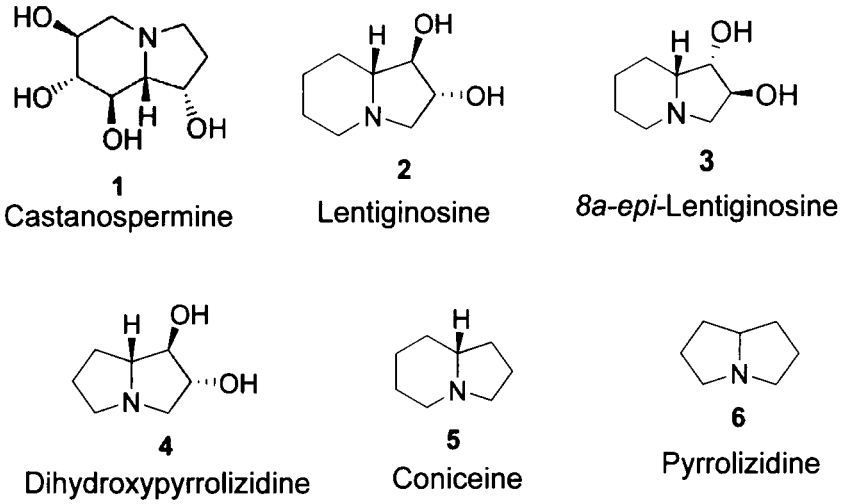


Figure 1. Some indolizidine and pyrrolizidine alkaloids

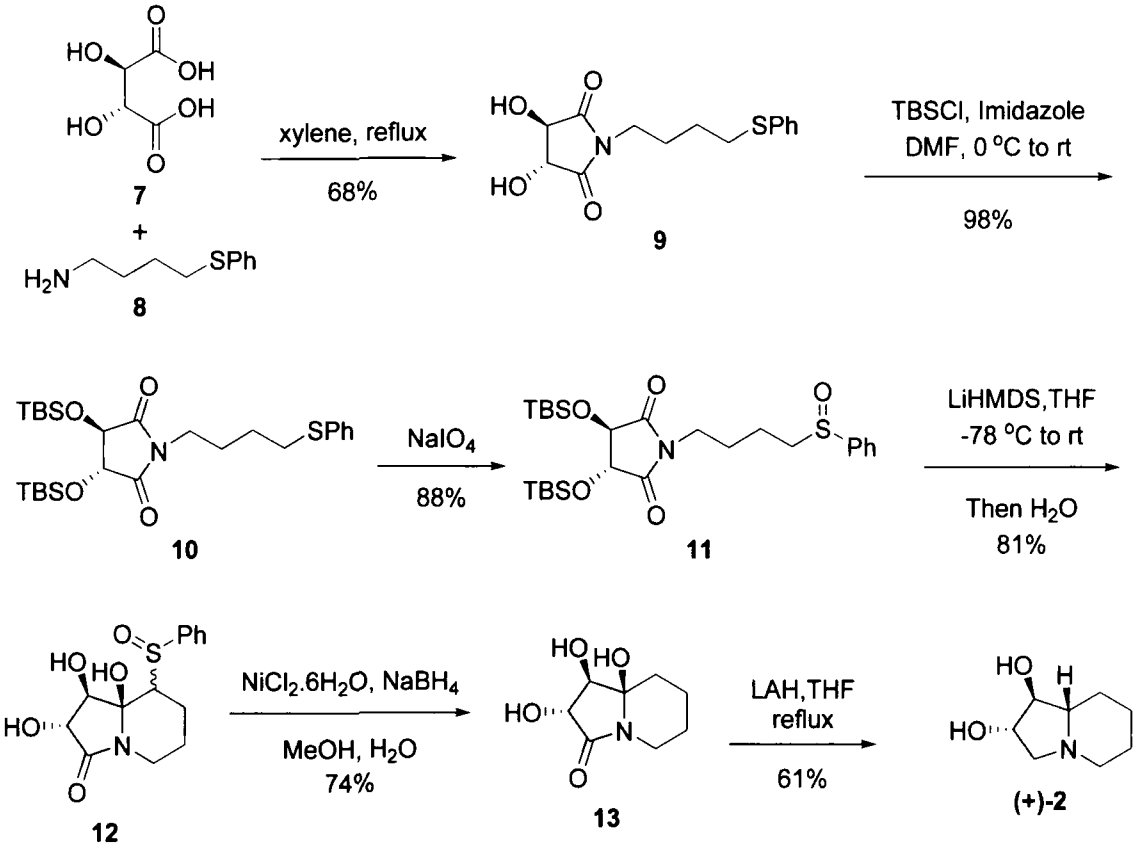
3.1.2. Review of Literature

Owing to its potent biological activity, lentiginosine and its analogues have aroused a great deal of interest among synthetic organic chemists, resulting in a number of syntheses.[6-10] Majority of the syntheses reported employ chiral pool starting materials such as sugars and amino acids and involve many steps. A detailed report of recent syntheses is described below.

Pohmakotr *et al.* (2014)[6h]

Pohmakotr and coworkers have synthesized (+)-lentiginosine using chiral pool starting material (+)-tartaric acid **7**. Aminosulfide **8** and (+)-tartaric acid **7** was refluxed in xylene to afford the corresponding chiral hydroxyimides **9**. Protection of both the hydroxyl groups as

their silyl ethers using TBSCl gave compound **10** which on oxidation with $NaIO_4$ in aqueous methanol at 0 °C furnished the required sulfinylimides **11**. Sulfinylimides **11** on treatment with LiHMDS gave α-sulfinyl carbanions which undergo intramolecular cyclization reaction to give the dihydroxylated 1-azabicyclic compound **12** as a diastereomeric mixture. Reductive cleavage of the phenylsulfinyl group of compound **12** was accomplished by using a combination of $NiCl_2 \cdot 6H_2O/NaBH_4$ in aqueous methanol to get corresponding indolizidinone **13** as a single isomer. Subsequently, reduction of indolizidinone **13** with $LiAlH_4$ in THF furnished (+)-lentiginosine **2**.

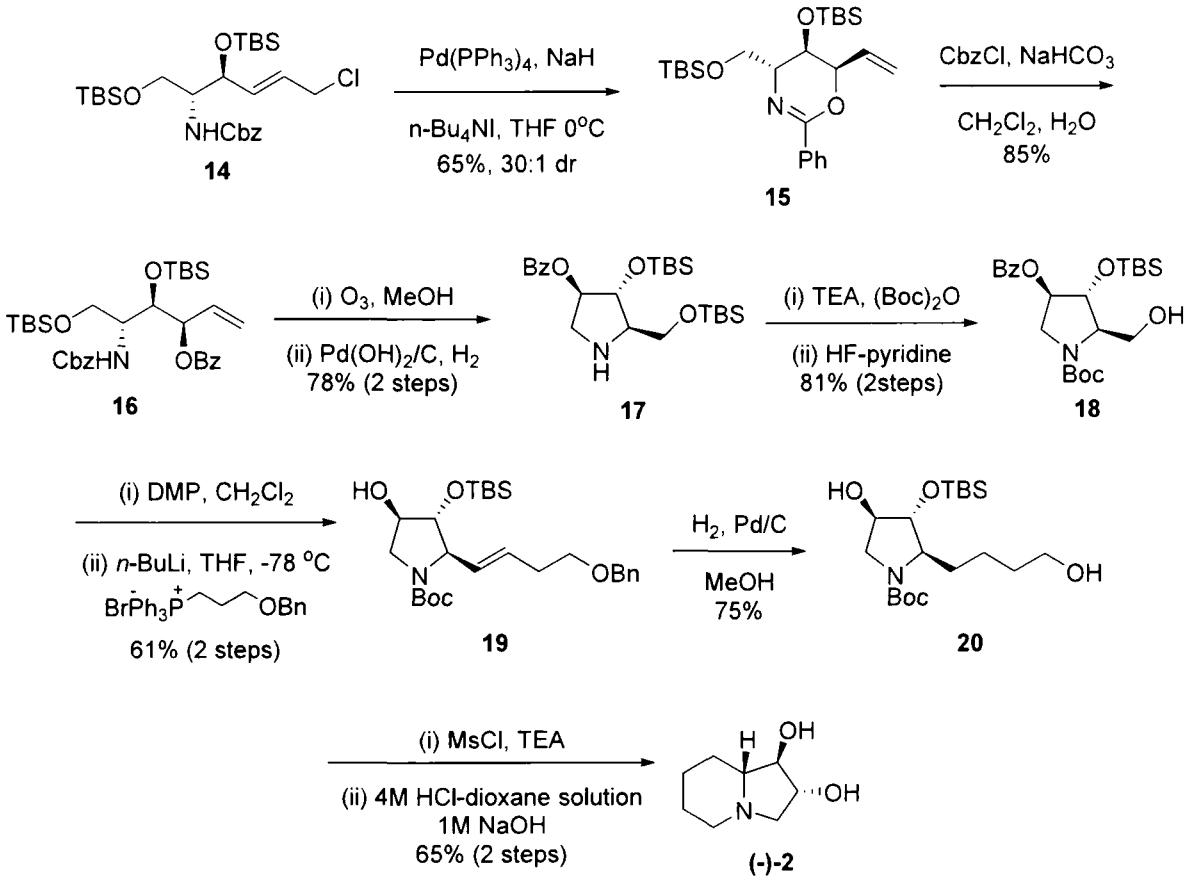


Scheme1. Synthesis of (+)-lentiginosine (Pohmakotr's method)

Ham *et al.* (2014)[10h]

Ham and coworkers successfully synthesized (-)-lentiginosine starting from γ-allyl benzamide **14** which in the presence of $Pd(PPh_3)_4$, NaH and n-Bu_4NI gave anti, syn-oxazine **15** with high stereoselectivity. The bulk of the protecting group on the secondary alcohol is responsible for controlling the diastereoselectivity of oxazine ring formation. Anti,syn-

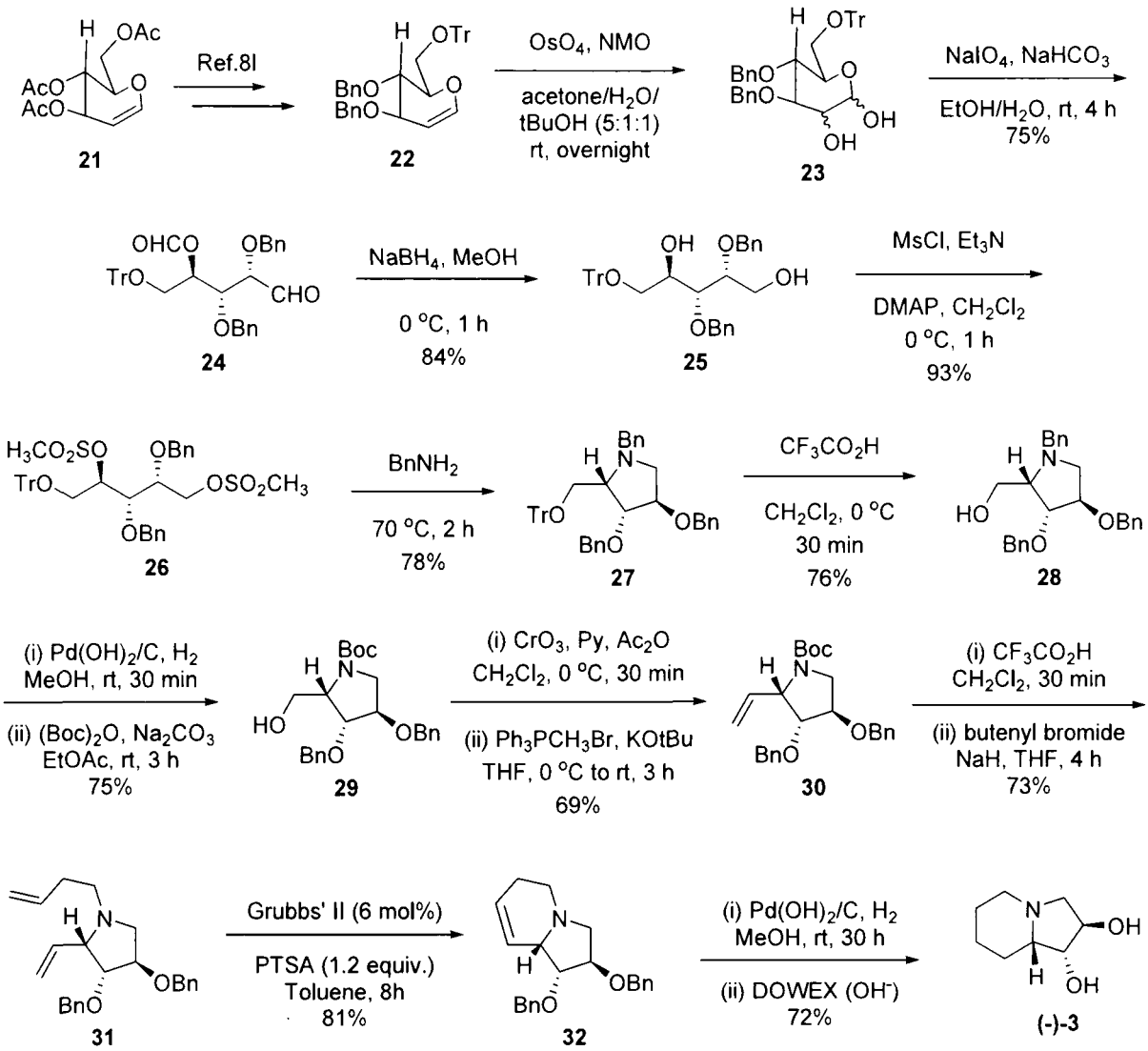
oxazine **15** under Schotten–Baumann conditions afforded the carbamate product **16**. Ozonolysis of the terminal olefin of carbamate **16** gave the corresponding aldehyde which on hydrogenolysis gave aminoaldehyde intermediate which undergoes cyclization to get pyrrolidine ring **17**. The pyrrolidine ring **17** was protected with Boc_2O and N-Boc compound was reacted with HF–pyridine to afford the selectively deprotected free primary alcohol **18**. Oxidation of the primary hydroxyl group of compound **18** with Dess–Martin periodinane produced the corresponding aldehyde, which was subsequently reacted with (3-benzyloxypropyl)triphenylphosphonium bromide in the presence of *n*-BuLi to give the debenzoylated olefin **19**. Catalytic hydrogenation of **19** with Pd/C produced by simultaneous deprotection of the benzyl group and reduction of the internal olefin to get compound **20**. Mesylation of the primary alcohol of compound **20** gave the mesylate compound which on removal of the Boc and TBS groups with 4 M HCl–dioxane solution resulted into cyclization to afford (-)-lentiginosine **2**.



Scheme 2. Synthesis of (-)-lentiginosine (Ham's method)

Vankar *et al.* (2014)[8k]

Vankar and coworkers successfully synthesized 8a-epi-(-)-lentiginosine starting from sugar derivative. 3,4,6-Tri-O-acetyl-D-glycals **21** which was converted to its corresponding 6-O-trityl-3,4-dibenzyl-D-glycals **22**, following a literature procedure.[8l] Glucal **22** was subjected to dihydroxylation reaction using a catalytic amount of OsO_4 to obtain a 2.2:1 mixture of diols **23** which were not separated at this stage. Subsequent oxidative cleavage of the diol **23** gave dicarbonyl compound **24** which on further reduction furnished the diol **25**.

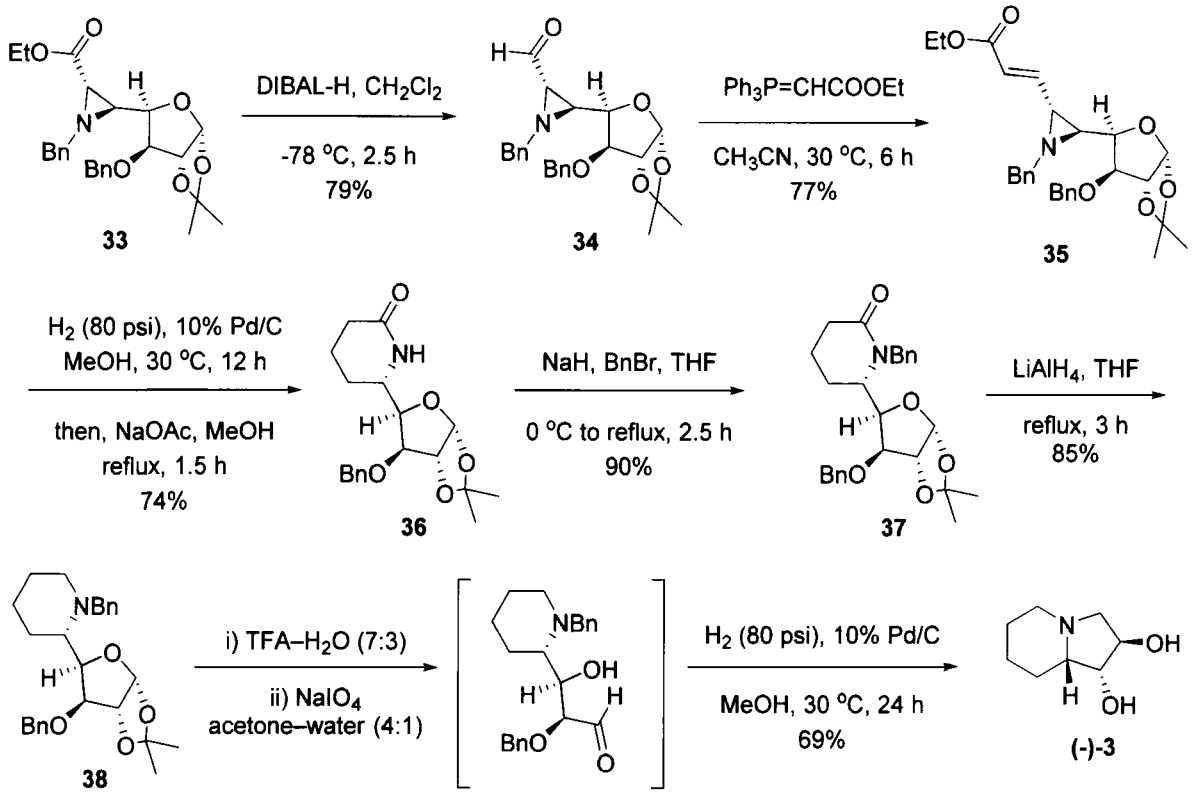


Scheme 3. Synthesis of 8a-*epi*-(-)-lentiginosine (Vankar's method)

Mesylation of diol **25** was carried out using mesyl chloride to get dimesyl compound **26** which on treatment with benzylamine undergoes double nucleophilic displacement reaction to obtain pyrrolidine **27**. The trityl protection on pyrrolidine **27** was removed to yield compound **28**. Benzyl group protection on the amine of compound **28** was replaced with tert-butylcarbamate to get compound **29**. Primary alcohol present in compound **29** was oxidized using Cornforth conditions to obtain aldehyde in a facile manner and the crude aldehyde was directly subjected to Wittig olefination using methyltriphenylphosphonium bromide to furnish alkene **30**. Subsequently, the carbamate group of compound **30** was deprotected and the crude amine was treated with butenyl bromide to furnish diene **31**. Ring closing metathesis of diene **31** gave cyclized product **32** which was subjected to hydrogenolysis to get 8a-*epi*-(-)-lentiginosine **3**.

Dhavale *et al.* (2007)[8j]

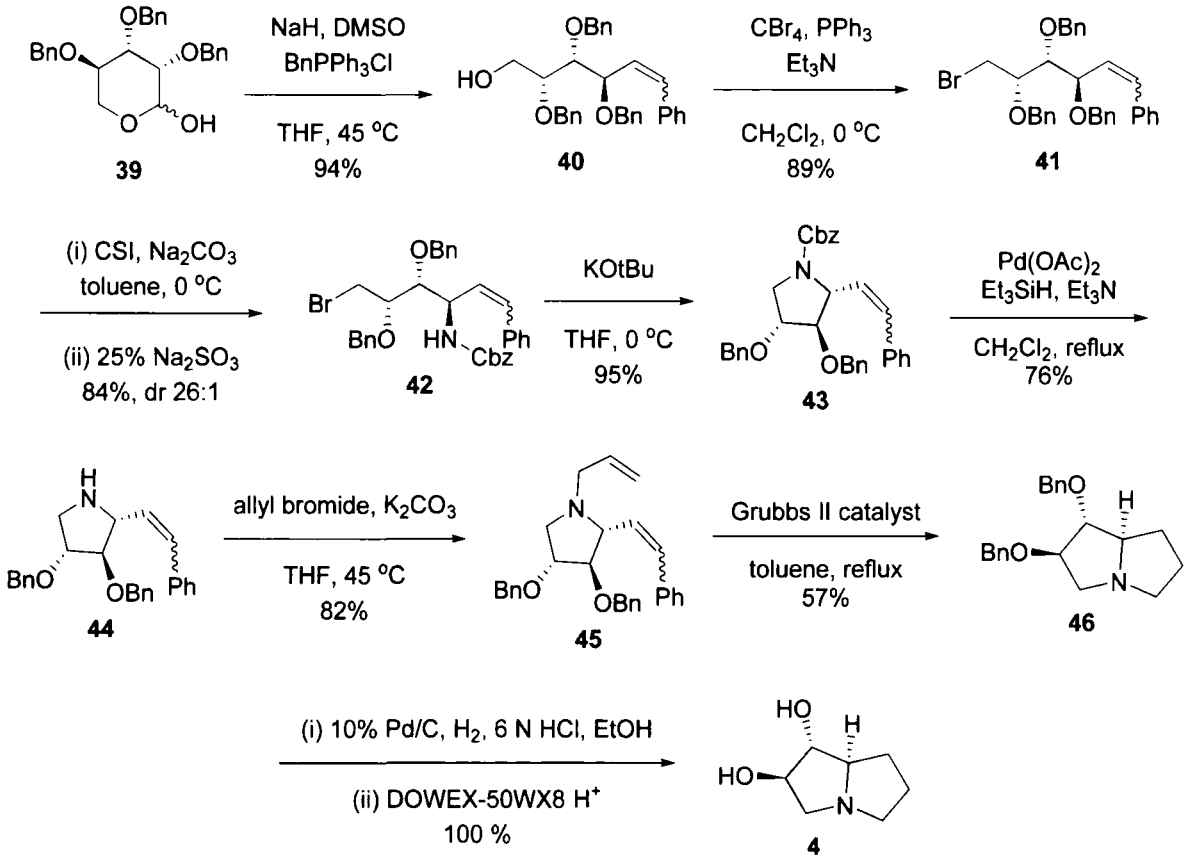
Dhavale and coworkers successfully synthesized 8a-epi-(-)-lentiginosine starting from D-glucose-derived aziridine carboxylate. Aziridine carboxylate **33** on DIBAL-H reduction at -78 ^{o}C gave aldehyde **34** which on 2-C Wittig olefination reaction gave compound **35**. Compound **35** on reductive aziridine ring opening furnished δ-lactam **36** which was subjected to benzyl protection to get compound **37**. δ-Lactam **36** was reduced to piperidine **38**, which on acetonide deprotection, oxidation and hydrogenation gave 8a-*epi*-(-)-lentiginosine **3.**



Scheme 4. Synthesis of 8a-*epi*-(-)-lentiginosine (Dhavale's method)

Jung *et al.* (2010)[8i]

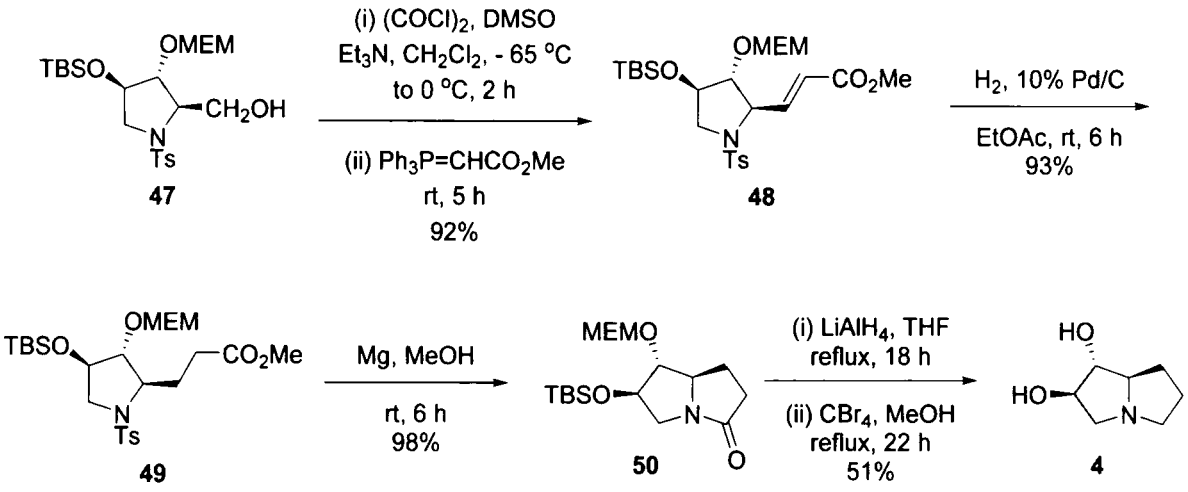
Jung and coworkers successfully synthesized dihydroxypyrrolizidine using chiral pool approach. Their synthesis started with benzylated pyranose **39** which on Wittig reaction gave compound **40**. The hydroxy moiety of compound **40** was then converted into the bromide **41** which on treatment with chlorosulfonyl isocyanate afforded the *anti*-3,4-amino alcohol **42**. The intramolecular cyclization of compound **42** provided the corresponding pyrrolidine **43**, which on removal of the Cbz moiety afforded pyrrolidine **44**. Allylation of the pyrrolidine **44** gave diene **45** which on ring closing metathesis afforded the pyrrolizidine core **46**. Finally, catalytic hydrogenation of **46** provided the 1,2-dihydroxypyrrolizidine **4**.



Scheme 5. Synthesis of dihydroxypyrrolizidine (Jung's method)

Angle *et al.* (2007)[8f]

Angle and coworkers successfully synthesized dihydroxypyrrolizidine starting from prolinol derivative derived from D-mannitol. Prolinol **47** on Swern oxidation followed by Wittig olefination gave α,β-unsaturated ester **48**. The olefin moiety of compound **48** was reduced to get compound **49**, which on deprotection of Ts group afforded lactam **50**. Reduction of the lactam and cleavage of the protecting groups of **50** gave 1.2-dihydroxypyrrolizidine **4**.



Scheme 6. Synthesis of dihydroxypyrrolizidine (Angle's method)

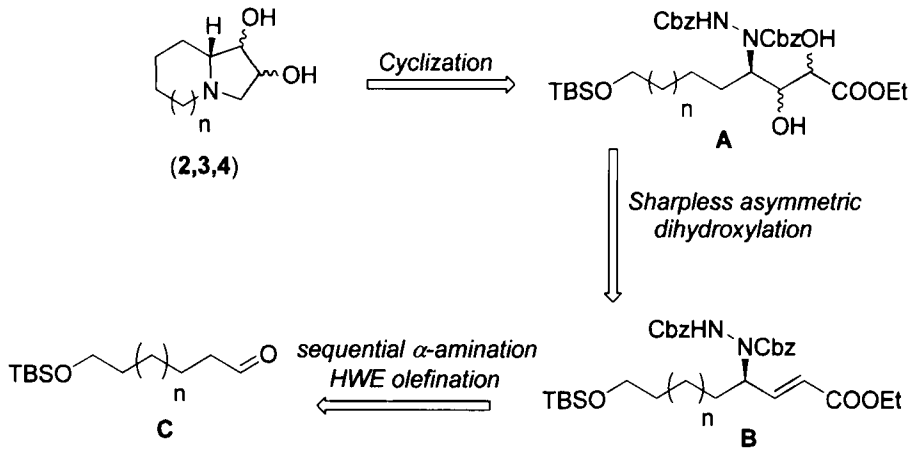
3.1.3. Present work

Objective

Although the majority of the literature reports have used a chiral pool approach, they prove to be useful protocols for only a limited number of molecules and also involve a large number of synthetic steps. Therefore, a general enantioselective synthetic approach to several azasugars and their unnatural analogues that are amenable to implementation of requisite stereochemical variations and different forms of substitution has become essential. As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds,[11] we envisioned that the proline-catalyzed α-amination[12] of aldehydes could easily give us stereocontrolled synthetic access to indolizidine and pyrrolizidine. Since the α-amino aldehydes are prone to recemization, they have been sucessesfully trapped *in situ* by various methods to furnish 1,2-amino alcohol, γ-amino-α,β-unsaturated ester, β-amino alcohol etc. We chose to trap them by HWE olefination to furnish γ-amino-α,β-unsaturated ester using a mild procedure developed by Sudalai *et al.*[13] It is noteworthy that γ-amino-α,β-unsaturated ester, an allylic amines serve as useful building blocks and can further be elaborated to the synthesis of a variety of compounds of biological importance.

3.1.4. Results and Discussion

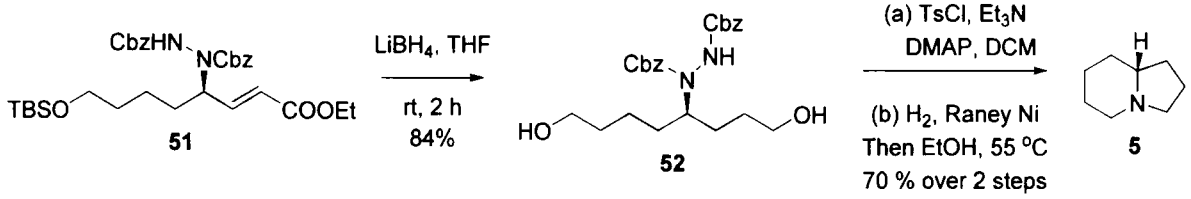
Our synthetic approach for the synthesis of target aza sugars was envisioned through the retrosynthetic route shown in **Scheme 7**. We were interested in a versatile approach using Sharpless asymmetric dihydroxylation reaction for introducing the hydroxyl groups, while a proline catalysed α-amination reaction was utilised to stereoselectively introduce the amine functionality. Lentiginosine **2**, *epi*-lentiginosine **3** and dihydroxy pyrrolizidine **4** could be obtained by cyclization of **A**. Compound **A** could be synthesized by Sharpless asymmetric dihydroxylation[14] of the α,β-unsaturated ester **B** for the introduction of the two hydroxy groups adjacent to the amine functionality which in turn could be synthesized from aldehyde **C** via a proline catalyzed α-amination reaction.



Scheme 7. Retrosynthetic analysis of of lentiginosine and its analogue.

Before embarking on the synthesis of the target molecules, we considered exploring a model synthesis to test the devised strategy (**Scheme 8**), in particular, by the concomitant cleavage of the N-N bond and nucleophilic displacement under hydrogenation conditions. Thus previously synthesized γ-amino-α, β-unsaturated ester **51** was subjected to ester reduction ensuing double bond reduction[15] and TBS deprotection in one step using $LiBH_4$ in THF to provide the diol **52**. The disappearance of ester and olefinic protons in the range of δ 1.28 as triplet, 4.18 as quartet, 5.92 as doublet and 6.87 as dd in ^1H NMR spectrum confirmed the formation of the product. Compound **52** on treatment with toluenesulfonyl chloride and triethylamine resulted in the formation of di-tosylate which was subjected to hydrogenation

conditions for the cleavage of N-N bond using Raney-Ni to give the free amine which on nucleophilic displacement of di-tosylate led to the formation of indolizidine alkaloid (*R*)-coniceine **5**. The extrapolation of this strategy allowed the successful completion of the synthesis of all the three target molecules in a very short and efficient manner.

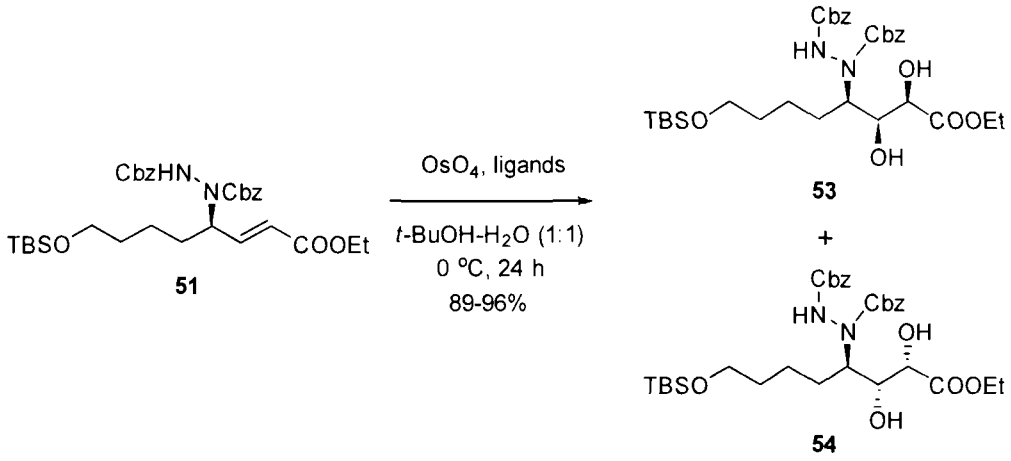


Scheme 8. Synthesis of indolizidine alkaloid coniceine

The synthesis of the target molecules (-)-lentiginosine and its 1,2-epimer commenced with γ-amino-α,β-unsaturated ester **51**. At this stage we investigated the use of the Sharpless asymmetric dihydroxylation reaction used for the embedding two hydroxy groups in the substrate containing a pre-existing chiral centre with a bulky substituent at the allylic nitrogen. The use of cinchona alkaloid ligand variants to achieve the two requisite stereocentres provided a general synthetic pathway to the family of hydroxylated azasugars in a highly diastereo selective manner.

In general, Kishi's empirical rule is used to determine the stereochemical outcome of the osmylation products. The presence of a bulky substituent at the allylic position generally determines the formation of dihydroxylation product. This rule is however seen to be generalised in case of carbohydrates. In the present method, dihydroxylation of **51** under Sharpless conditions in the absence of a chiral ligand interestingly gave "*syn* facial selectivity" (*syn*-**53**/*anti*-**54**:83/17)[16] where the diastereomers were easily separable by silica gel column chromatography. The disappearance of olefinic protons in the ^{1}H NMR confirmed the formation of the dihydroxylated product which was further confirmed by IR spectroscopy which showed strong absorption at 3748 and 3421cm^{-1}. This result showed that the bulk of the allylic NCbz substituent had little impact on the stereodifferentiation of the two π faces and did not follow the Kishi empirical rule. The probable explanation for this diastereofacial bias could be attributed to the presence of H-bonding between the OsO_4 and NCbz-NHCbz group that facilitates the formation of *syn* -diastereomer **53** as a major product (**Figure 2**).[17] We then examined the efficacy of various cinchona alkaloid containing ligands

and the results are summarized in **Table 1**. To achieve the "*anti* facial selectivity" (based on the Sharpless mnemonic device) we used $(DHQD)_2$ PHAL, surprisingly the diastereomeric outcome (*anti*-**54**/*syn*-**53**) was found to be 3/2. Switching the ligand to $(DHQD)_2$ PYR gave a similar result (*anti*-**54**/*syn*-**53**-10:3/2). Finally, $(DHQD)_2$AQN was found to be a better ligand as the dr for the *anti* compound **54** increased to 3/1. To favour the "*syn* antipode" both $(DHQ)_2$PHAL and $(DHQ)_2$AQN were found to be useful ligands. In these case, the reaction progressed with high diastereoselectivity and we obtained *syn*-**53** essentially as a single diastereomer (**Table 1**, entries 3,6). In all the cases, however the yield remained almost the same.



Entry	Ligands*	yield (%)	Ratio (53:54)
1	no ligand	94	83:17
2	$(DHQD)_2$PHAL (5 mol %)	95	2:3
3	$(DHQ)_2$PHAL (5 mol %)	93	99:1
4	$(DHQD)_2$PYR (5 mol %)	89	2:3
5	$(DHQD)_2$AQN (5 mol %)	96	1:3
6	$(DHQ)_2$AQN (5 mol %)	96	99.8:0.2

Table 1. Optimization of Sharpless asymmetric dihydroxylation reaction conditions

*Reactions were carried out in the presence of 1 mol% of OsO_4 and 3 eq of K_2CO_3 and K_3FeCN_6

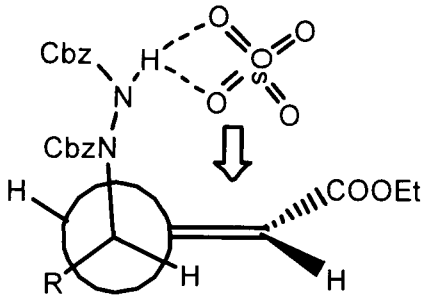
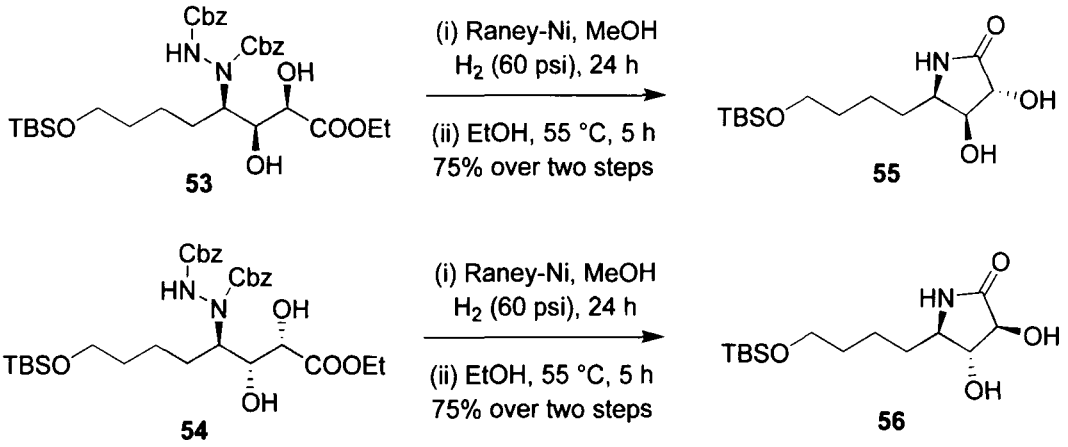


Figure 2. Proposed transition state for *syn* selectivity

The relative stereochemistry of the three stereocenters generated were unambiguously determined using 2D NMR spectroscopy. For this purpose, diols **53** and **54** were subjected to hydrogenation conditions using Raney-Ni to cleave N-N bond to get free amine which subsequently undergoes cyclization to give cyclic derivatives **55** and **56**, respectively. Extensive NMR studies were carried out on compounds **55** and **56** to determine the relative stereochemistry (**Scheme 9**).



Scheme 9. Preparation of cyclic derivatives

The two cyclic isomers **55** and **56** were subjected to 2D NMR spectroscopy after carefully studying their peak patterns in 1D NMR. ^{1}H, ^{13}C and DEPT NMR spectra of the cyclized compounds were determined in $CDCl_3$ initially, it was found that the compound **56** showed resolved peaks for the methine protons α, β and γ whereas this was not the case for compound **55**. Acetone-d_6 proved to be a more suitable solvent for a better quality NMR spectra. The compounds **55** and **56** were then characterized using the 1D NMR experiments

(^{1}H, ^{13}C DEPT) as well as 2D homonuclear (COSY, and NOESY) and heteronuclear (HSQC and HMBC) NMR spectroscopy.

For compound **55**, the α, β, γ protons resonated at δ 4.04, 4.22 and 3.55 ppm respectively. The α proton shows the distinct doublet at 4.04 ppm having a coupling constant of 6.63 Hz which indicated the *trans* stereochemistry between the α and β-methine protons. The β and γ- protons showed multiplet like pattern which prohibited extraction of the coupling constants from 1D spectrum. Therefore the 2D NOESY spectrum was used to determine the relative stereochemistry at the β and γ-position. The NOESY spectra of compound **55** shows cross peak between the β and γ proton which confirmed their *syn* relationship between the β and γ methine protons, the α and β protons did not show NOESY correlation which indicated their *trans* relationship as shown in the **Fig. 3**.

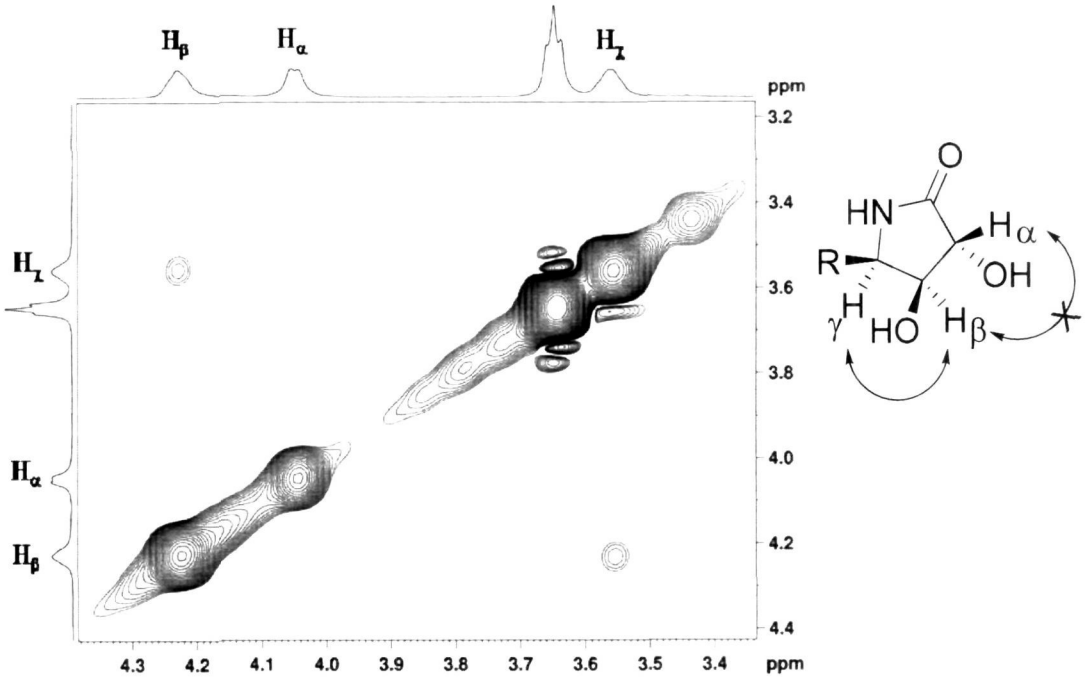


Figure 3: NOESY spectrum of compound **55**

For compound **56**, the α, β, γ protons resonated at δ 4.06, 3.77 and 3.28 respectively. The α proton showed as a distinct doublet at 4.06 ppm having coupling constant of 7.3 Hz which indicated the *trans* stereochemistry between α and β methine protons. The β and γ protons showed multiplet like patterns which prohibited extraction of their coupling constants.

Therefore the 2D NOESY spectrum was used to find out the relative stereochemistry at the β and γ positions. The NOESY spectra of compound **56** did not show a correlation between the β and γ protons which confirmed their *anti* stereochemistry. The α and β protons did not show NOESY correlation which indicated the *trans* relationship between them as shown in the **Fig. 4**.

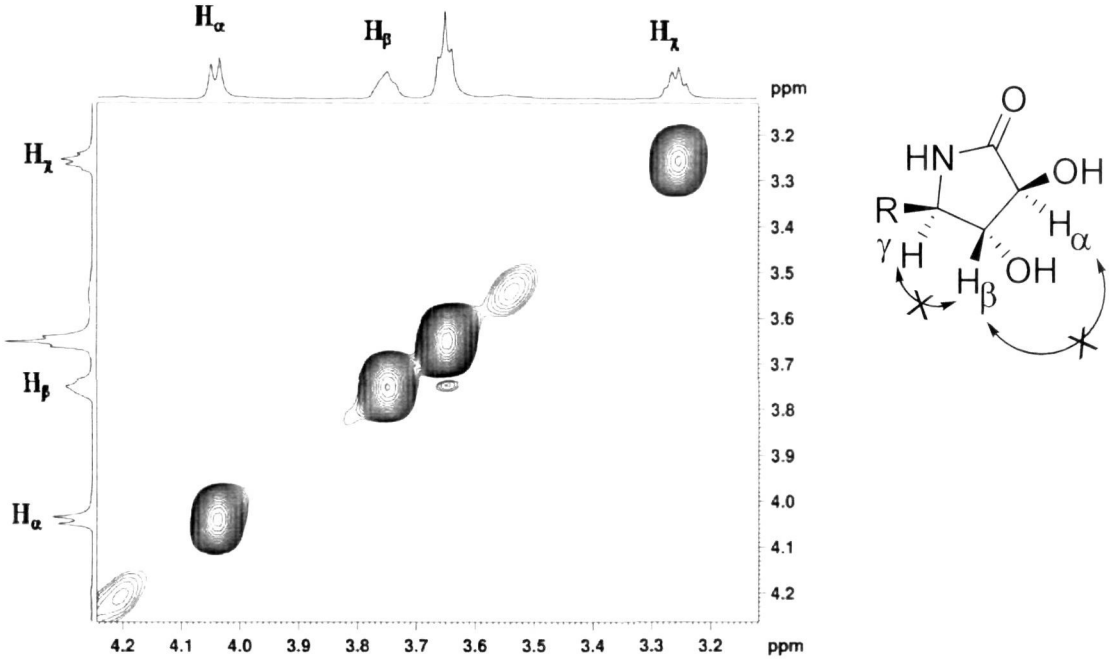
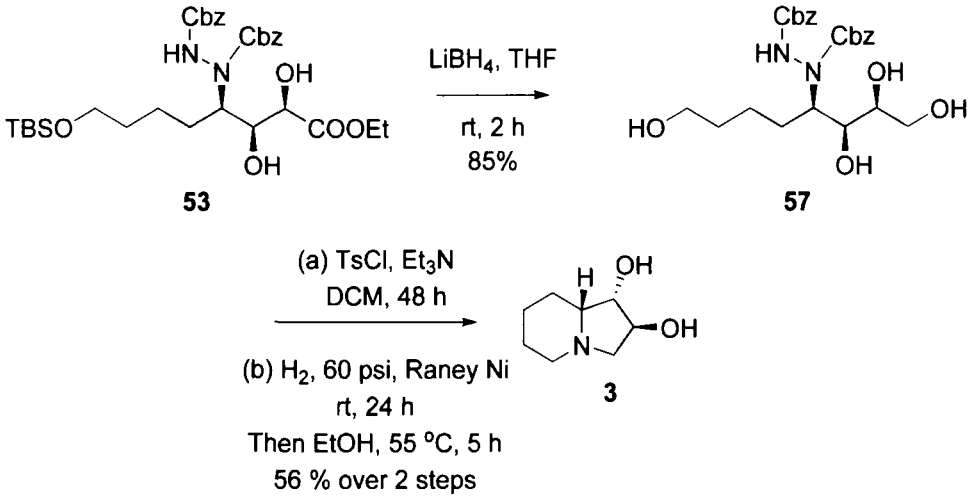


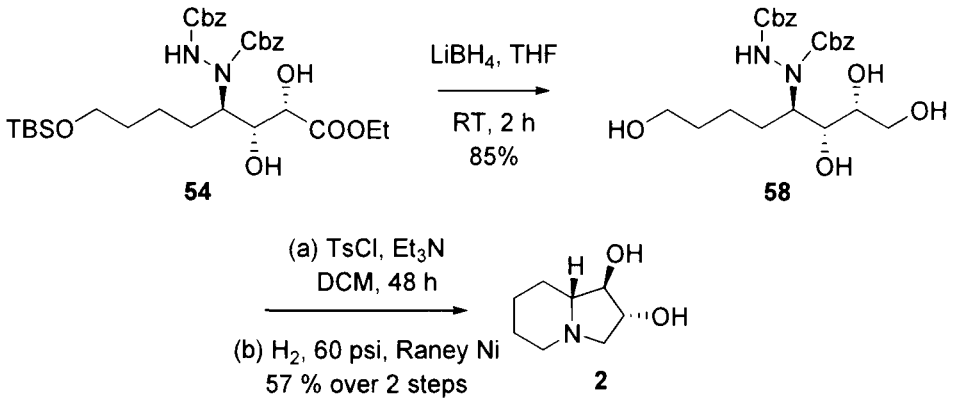
Figure 4: NOESY spectrum of compound **56**

After determining the relative stereochemistry of compounds **53** and **54**, we proceeded to the synthesis of target molecules. For the synthesis of 8a-*epi*-(-)-lentiginosine **3**, diol **53** was subjected to $LiBH_4$ reduction to give tetrol **57**. The disappearance of ester and olefinic protons in the range of δ 1.28 as triplet, 4.18 as quartet, 5.92 as doublet and 6.87 as dd in ^1H NMR spectrum confirmed the formation of the product. Compound **57** was then subjected to selective primary tosylation using TsCl and Et_3N to give the di-tosyl intermediate, which was subjected to hydrogenation conditions using freshly prepared Raney-Ni to deliver a free amine which on nucleophilic displacement of di-tosylate led to the formation of the desired 8a-*epi*-(-)-lentiginosine **3** (**Scheme 10**). The characterisation of **3** was in good agreement with the reported literature.



Scheme 10: Synthesis of 8a-*epi*-lentiginosine

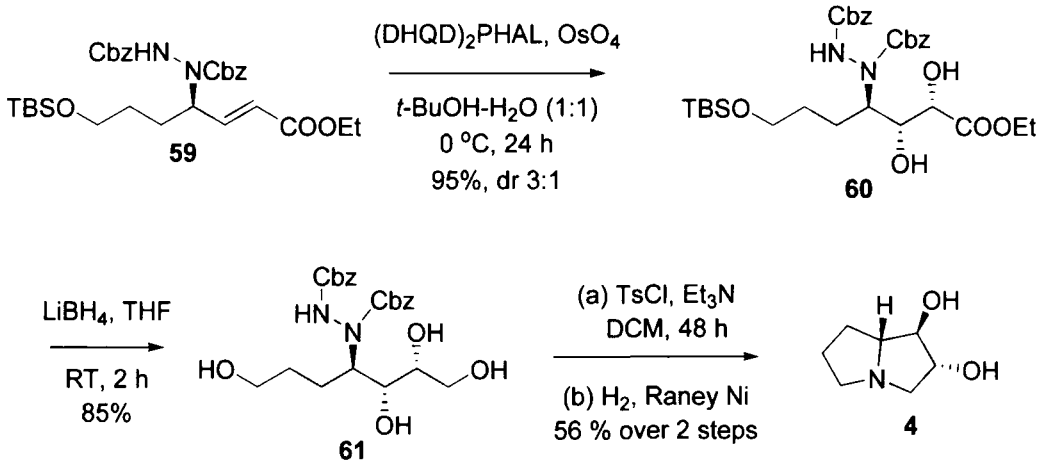
In a similar way, as illustrated in **Scheme 11**, (-)-lentiginosine **2** was synthesized from diol **54** by an analogous series of reactions to those shown in **Scheme 10**. The strategy can also be extended to the synthesis of the natural enantiomer and other stereoisomers by simply using the other enantiomer of proline for the α-amination and different ligands for dihydroxylation.



Scheme 11: Synthesis of (-)-lentiginosine.

After the successful completion of the synthesis of lentiginosine and its 8a-epimer we thought to extrapolate our strategy to other analogues. Thus, by simply altering the chain length to C5 aldehyde, the synthesis of dihydroxy pyrrolizidine **4** was achieved. As illustrated in **Scheme 12**, the synthesis started with previously synthesized γ-amino-α,β-unsaturated ester **59**. The olefinic compound **59** was subjected to Sharpless asymmetric

dihydroxylation using $(DHQD)_2AQN$ as the ligand to give the diol **60**. Diol **60** was converted to give the target compound **4** using same set of reactions as described in **Scheme 11**.



Scheme 12: Synthesis of dihydroxy pyrrolizidine **4**

Our synthetic approach afforded the target compound **3** in a linear sequence of 4 steps with an overall yield of 31%, target compound **2** with an overall yield of 23% and target compound **4** with an overall yield of 23%.This strategy is the shortest synthesis reported so far from easily available starting materials with high yields.

3.1.5. Conclusions

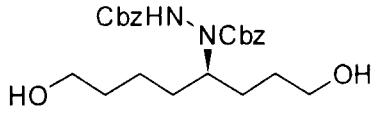
In conclusion, we have developed a new, highly efficient and concise protocol to dihydroxylated indolizidine and pyrrolizidine alkaloids using a proline catalyzed α-amination followed by Sharpless asymmetric dihydroxylation reaction as the key steps. Its utility was illustrated by the total synthesis of (-)-lentiginosine, (-)-*epi*-lentiginosine and (-)-dihydroxypyrrolizidine. The synthetic strategy allows implementation of the desirable stereocenters at C-1, C-2 and C-8a and can be extended to the synthesis of other stereoisomers and analogues with variable ring size and different degrees of hydroxylation.

3.1.6. Experimental section

Dibenzyl (*R*,*E*)-1-(8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-1-oxooct-2-en-4-yl)hydrazine-1,2-dicarboxylate(51):

The spectral data for compound **51** have been reported in chapter 2A.

Dibenzyl (R)-1-(1,8-dihydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (52):



To a solution of ethyl ester **51** (0.5 g, 0.80 mmol) in THF (7 mL), was added $LiBH_4$ (0.035 g, 1.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. It was then quenched with ice cold aq. HCl (1N) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Silica gel column chromatography of the crude product using ethyl acetate as eluent gave **52** as a waxy solid.

Yield: 0.312 g, 84%

Mol. Formula: $C_{24}H_{32}O_6N_2$

$[\alpha]_D^{25}$: + 0.32 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3289, 2292, 1709, 1662, 1218

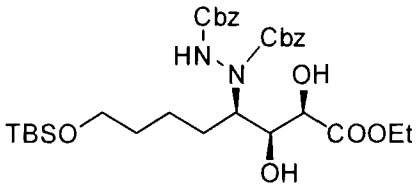
^1H NMR (200 MHz, $CDCl_3$): δ 1.26-1.60 (m, 10H), 1.96 (brs, 2H), 3.47-3.67 (m, 4H), 4.02-4.29 (m, 1H), 4.96-5.26 (m, 4H), 7.04 (brs, 1H), 7.31-7.35 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$): as a rotameric mixture δ 22.1, 25.5, 28.7, 29.3, 29.7, 31.9, 32.6, 61.8, 62.2, 62.3, 62.8, 67.7, 67.8, 67.9, 68.3, 127.6, 128.0, 128.2, 128.3, 128.4, 128.5, 135.5, 135.8, 136.0, 156.4, 156.8, 156.9,157.3

MS (ESI) : *m/z* 467.15 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{33}O_6N_2$ 445.2333; Found 445.2328

Dibenzyl 1-((2*R*,3*S*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (53):



General procedure for Sharpless asymmetric dihydroxylation: To a mixture of $K_3Fe(CN)_6$ (0.825 g, 2.50 mmol), K_2CO_3 (0.345 g, 2.50 mmol), $(DHQ)_2AQN$ (6.5mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 10 mL) at 0 °C was added osmium tetroxide (0.32 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methane sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the olefin **51** (0.500 g, 0.83 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (0.5 g). Stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (R_f = 0.40, EtOAc /petroleum ether, 3:7) of the crude product gave **53** as a white waxy solid.

Yield: 0.507 g , 96%

Mol. Formula: $C_{32}H_{48}O_9N_2Si$

$[\alpha]_D^{25}$: + 0.22 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 3474, 3250, 3036, 2925, 2855, 1718, 1682, 1462

^1H NMR (200 MHz, $CDCl_3$) : δ -0.01 (m, 6H), 0.85 (m, 9H), 1.21-1.32 (m, 6H), 1.39-1.53 (m, 3H), 3-3.29 (m, 1H), 3.45-3.82 (m, 3H), 4.02-4.17 (m, 1H), 4.27 (q, J = 7 Hz, 2H), 5.04-5.34 (m, 4H), 6.68 -7.02 (m, 1H), 7.14-7.37 (m, 10H)

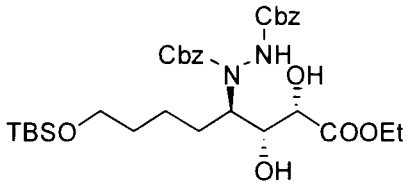
^{13}C NMR (50 MHz, $CDCl_3$) : δ -5.3, -5.4, 14.1, 18.3, 21.7, 25.9, 31.8, 61.8, 62.2, 68.5, 71.1, 71.3, 71.9, 72.1, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6, 134.9, 135.7, 156.0, 157.1, 172.7

MS (ESI) : *m/z* 655.29 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{48}O_9N_2SiNa$ 655.3021; Found 655.3018

HPLC: Kromasil RP-18 (150 X 4.6mm) (methanol : H_2O = 85:15, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.42 and 7.43

Dibenzyl 1-((2*S*,3*R*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (54) :



Product **54** was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from γ-amino-α,β-unsaturated ester **51** and using $(DHQD)_2AQN$ as a ligand.

Yield: 0.380 g, 96%

Mol. Formula: $C_{32}H_{48}O_9N_2Si$

$[\alpha]_D^{25}$: + 8.04 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3748, 3421, 3019, 1734,1541

^1H NMR (200 MHz, $CDCl_3$) : δ 0.00 (m , 6H) , 0.82-0.91 (m , 9H), 1.22-1.54 (m, 8H), 1.78-1.98 (m, 1H), 3.55-3.64 (m, 2H), 3.90-4.09 (m, 1H), 4.14-4.38 (m, 3H), 4.90-5.34 (m, 4H) , 6.68-6.84 (m,1H), 7.26-7.45 (m, 10H)

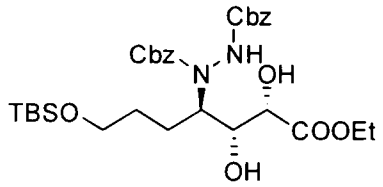
^{13}C NMR (50 MHz, $CDCl_3$) : -5.3, 14.1, 18.3, 25.9, 25.8, 31.4, 32.3, 61.8, 62.4, 67.8, 68.5, 70.3, 70.4, 72.9, 127.8, 128.0, 128.2, 128.3, 128.5, 135.5, 156.6, 156.9, 172.8

MS (ESI) : *m/z* 655.29 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{48}O_9N_2SiNa$ 655.3021; Found 655.3018

HPLC: Kromasil RP-18(150 X 4.6mm) (methanol : H_2O = 85:15, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 7.33 and 8.23

Dibenzyl 1-((2*S*,3*R*,4*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (60):



Product **60** was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from γ-amino-α,β-unsaturated ester **51** and using $(DHQD)_2AQN$ as a ligand.

Yield: 0.378 g, 95%

Mol. Formula: $C_{31}H_{46}O_9N_2Si$

$[\alpha]_D^{25}$: + 10.96 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 3456, 2956, 2857,1731, 1416

^1H NMR (200 MHz, $CDCl_3$) : δ -0.02 (m, 6H), 0.80 (m, 9H), 1.17-1.31 (m, 3H), 1.38-1.68 (m, 3H), 1.87-2.03 (m, 1H), 3.28-3.68 (m, 3H), 3.85-3.99 (m,1H), 4.16-4.30 (m, 3H), 4.86-5.27(m, 4H), 7.26(m, 10H), 7.48-7.70 (m,1H)

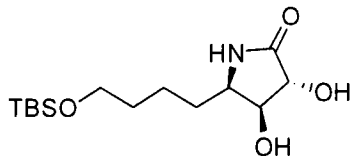
^{13}C NMR (50 MHz, $CDCl_3$) : δ -5.6, 13.9, 18.2, 25.8, 28.7, 60.2, 61.6, 62.2, 68.0, 68.3, 70.9, 71.8, 126.8, 127.5, 127.7, 128.0, 128.3, 128.4, 135.0, 135.7, 156.1, 156.9, 172.7

MS (ESI) : *m/z* 641.31$(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{46}O_9N_2SiNa$ 641.2868; Found 641.2869

HPLC: Kromasil RP-18 (150 X 4.6mm) (methanol : H_2O = 85:15), flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.18 and 7.28

(3*R*,4*S*,5*R*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55): General procedure for cyclization:



Determination of relative configuration:

A solution of compound **53** in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel (1g, excess) under a H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give the crude free amine which was further subjected to cyclisation by stirring in EtOH at 55 ^oC for 5 h. The reaction mixture was concentrated in vacuo to give the crude product. Silica gel column chromatography (ethyl acetate: petroleum ether/ 6:4) of the crude product gave **55** as a syrupy liquid.

Yield: 0.359 g, 75%

Mol. Formula: $C_{31}H_{46}O_9N_2Si$

$[\alpha]_D^{25}$: +31.25 (*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3285, 2930, 2858, 1712, 1255

^1H NMR (200 MHz, $CDCl_3$) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.29-1.56 (m, 5H), 1.71-1.89 (m, 1H), 3.60- 3.66 (m, 3H), 4.24-4.45 (m, 2H), 6.29 (brs,1H)

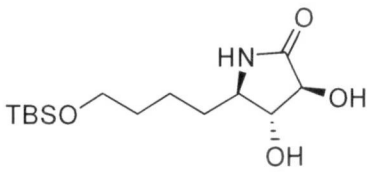
^1H NMR (500 MHz, Acetone-d_6) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.40 (m, 2H), 1.56 (m, 3H), 1.81 (m, 1H), 2.92 (brs, 2H), 3.58 (m, 1H), 3.67 (t, J = 5.72 Hz, 2H), 4.06 (d, J = 5.35 Hz, 1H), 4.25 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ -5.3, 18.4, 22.5, 25.9, 29.7, 32.5, 55.1, 62.9, 74.1, 74.9, 175.4.

MS (ESI) : *m/z* 326.18 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{29}O_4NSiNa$ 326.1758; Found 326.1764

(3*S*,4*R*,5*R*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):



Lactam **56** was prepared using the procedure described for compound **55** and starting from diol **54**.

Yield: 0.180 g, 75%

Mol. Formula: $C_{14}H_{29}O_4NSi$

$[\alpha]_D^{25}$: + 3.77(*c* 0.5, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3354, 2922, 1711, 1463, 1377

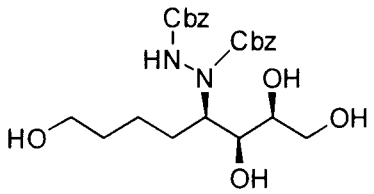
^1H NMR (200 MHz, $CDCl_3$) : δ 0.05 (s, 6H), 0.89 (s, 9H), 1.50-1.53 (m, 4H), 1.73-2.12 (m, 2H), 3.31- 3.42 (m, 1H), 3.63 (t, J = 5.9 Hz, 2H), 3.87-3.94 (m, 1H), 4.29-4.32 (m, 1H), 6.67 (brs,1H) ^1H NMR (500 MHz, Acetone-d_6) : δ 0.07 (s, 6H), 0.91 (s, 9H), 1.51-1.58 (m, 5H), 1.75 (m, 1H), 2.94 (brs, 2H), 3.26-3.30 (m, 1H), 3.67 (t, J = 6.10 Hz, 2H), 3.77(m, 1H), 4.06 (d, J = 7.3 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.3, 22.1, 25.9, 32.5, 33.3, 56.8, 62.9, 76.3, 79.8, 175.3.

MS (ESI) : m/z 326.15 $(M+Na)^+$

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{29}O_4NSiNa$ 326.1758; Found 326.1764

Dibenzyl1-((2*S*,3*S*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (57):



General procedure for $LiBH_4$ reduction:

To a solution of ethyl ester **53** (0.5 g, 0.79 mmol) in THF (7 ml), was added $LiBH_4$ (0.05 g, 0.24 mmol) at 0 °C. The reaction was mixture was stirred at rt for 2 h. It was then quenched with aq. HCl (1N) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give the crude product. Silica gel column chromatography (methanol: CH_2Cl_2: 1:20) of the crude product gave **57** as a white solid.

Yield: 0.32 g, 85%

Mol. Formula: $C_{24}H_{32}O_8N_2$

M.P. : 123-125 °C

$[\alpha]_D^{25}$: +0.13 (*c* 0.3, CH_3OH)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215

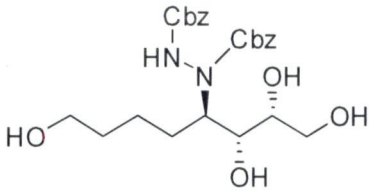
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32-1.58 (m, 6H), 3.45-3.68 (m, 6H), 4.5-4.59 (m, 1H), 5.02-5.24 (m, 4H), 7.24-7.44 (m, 10H)

^{13}C NMR (50 MHz, $CDCl_3$): as a rotameric mixture 23.4, 30.5, 30.8, 33.1, 33.3, 62.8, 65.0, 69.1, 69.2, 69.4, 71.7, 71.8, 72.2, 72.5, 128.7, 129.1, 129.3, 129.4, 129.7, 137.4, 137.7, 158.6, 158.7, 158.9

MS (ESI) : *m/z* 499.17 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{32}O_8N_2Na$ 499.2051; Found 499.2047

Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):



Tetrol **58** was prepared using general procedure for $LiBH_4$ reduction and starting from diol **54**.

Yield: 0.32 g, 85%

Mol. Formula: $C_{24}H_{32}O_8N_2$

M.P: 116-118 °C

$[\alpha]_D^{25}$: +0. 34 (*c* 0.85, CH_3OH)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3384, 3282, 3019, 2926, 1749, 1720, 1646, 1215, 760

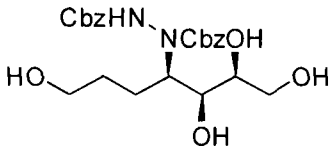
^1H NMR (200 MHz, $CDCl_3$): δ 1.36-1.41 (m, 1H), 1.49-1.66 (m, 5H), 3.48 -3.69 (m, 6H), 4.16-4.36 (m, 1H), 5.02-5.24 (m, 4H), 7.29-7.47 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$): as a rotameric mixture δ 27.1, 30.5, 31.1, 33.8, 33.9, 63.0, 63.2, 63.3, 68.7, 69.4, 69.7, 71.8, 72.2, 72.4, 128.9, 129.3, 129.4, 129.5, 129.6, 129.7, 129.9, 137.9, 138.0, 158.5, 158.9, 159.1

MS (ESI) : *m/z* 499.22$(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{32}O_8N_2Na$ 499.2051; Found 499.2047

Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (61):



Tetrol **61** was prepared using general procedure for $LiBH_4$ reduction and starting from diol **60**.

Yield: 0.32 g, 85%

Mol. Formula: $C_{23}H_{30}O_8N_2$

M.P : 125-127 °C

$[\alpha]_D^{25}$: -0.19 (*c* 0.55, CH_3OH)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3376, 3280, 3022, 2929, 1716, 1638, 1190

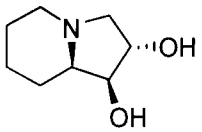
^1H NMR (200 MHz, $CDCl_3$) : δ 1.27-1.44 (m, 2H), 1.70-1.90 (m, 2H), 3.54-3.66 (m, 5H), 3.83-4.05 (m, 1H), 4.15-4.40 (m, 1H), 5.05-5.15 (m, 4H), 7.10-7.36 (m, 10H)

^{13}C NMR (125 MHz, $CDCl_3$): as a rotameric mixture δ 23.3, 33.5, 34.1, 63, 64.6, 68.5, 69.3, 72.7, 75.6, 77.5, 80.2, 128.0, 128.7, 129.1, 129.2, 129.4, 129.5, 129.6, 129.7, 137.5, 137.7, 143.5, 157.7, 158.8

MS (ESI) : *m/z* 485.22 $(M+Na)^+$

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{30}O_8N_2Na$ 485.1894; Found 485.1891

(1*S*,2*S*,8a*R*)- Octahydroindolizine-1,2-diol (3):



General procedure for cyclization:

To an ice-cold stirred solution of **57** (0.25g, 0.5 mmol) and triethylamine (0.22 mL, 1.5mmol) in anhydrous CH_2Cl_2 6mL) was added toluenesulfonyl chloride (0.20 g, 1.0 mmol) over 15 min. The resulting mixture was allowed to warm up to room temperature and stirred for 48 h. After diluting with 6 mL CH_2Cl_2, the solution was washed with water (3 x 15 mL), brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude di-tosylated product which was subjected to next step without further purification.

A solution of crude tosylated compound in MeOH (10 mL) and acetic acid (5 drops) was treated with Raney nickel 1 g, excess) under H_2 (60 psi) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude free amine which was further subjected to cyclization by stirring in EtOH at 55 °C for 20 h. The reaction mixture was concentrated in vacuo to give crude product. Silica gel (neutralized) column chromatography (methanol: CH_2Cl_2: 1:15) of the crude product gave **3** as a white solid.

Yield: 0.046 g, 56%

Mol. Formula: $C_8H_{15}O_2N$

M.P: 134-136 °C [lit.[6c]: 137-138]

$[\alpha]_D^{25}$: - 6.48 (*c* 1, CH_3OH). [lit.[6c]: $[\alpha]_D^{25}$: - 5.3 (*c* 0.3, CH_3OH)]

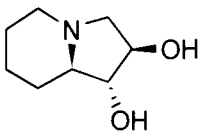
^{1}H NMR (200 MHz, D_2O) : δ 1.34-1.55 (m, 3H), 1.67-1.88 (m, 3H), 2.16-2.34 (m, 2H) , 2.42-2.49 (m, 1H), 3.15 (d, J =11.2 Hz, 1H), 3.52 (dd, J = 7Hz, 11.2 Hz, 1H), 3.98 (d, J = 4.1 Hz, 1H), 4.08 – 4.15 (m, 1H)

^{13}C NMR (50 MHz, D_2O) : 25.0, 25.9, 26.0, 55.1, 62.1, 69.6, 77.9, 80.6

MS (ESI) : *m/z* 158.11$(M+H)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}O_2N$ 158.1176; Found 158.1175

(1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol (2):



(-)-Lentiginosine **2** was prepared using general procedure for cyclization reaction and starting from tetrol **58**.

Yield: 0.047 g, 57%

Mol. Formula: $C_8H_{15}O_2N$

M.P: 106-108 °C [lit.[5a]: 106-107];

$[\alpha]_D^{25}$: - 2.92 (*c* 0.5, CH_3OH), [lit.[5a]: $[\alpha]_D^{23}$ −1.6 (*c* 0.24, CH_3OH), lit.[7c] $[\alpha]_D$ −3.05 (*c* 1.0, CH_3OH)].

^{1}H NMR (200 MHz, D_2O): δ 1.28 -1.34 (m, 2H), 1.47-1.53 (m, 1H), 1.68-1.70 (m, 1H), 1.82-1.86 (m, 1H), 1.94-1.98 (m, 1H), 2.13-2.27 (m, 2H), 2.81 (dd, J = 7.59, 11.3 Hz , 1H),

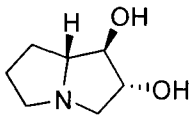
2.94 (d, *J*=11.3 Hz, 1H), 3.06 (d, *J* = 11.7 Hz, 1H), 3.70 (dd, *J* = 3.4, 9.1Hz, 1H) 4.10- 4.13 (m, 1H)

^{13}C NMR (50 MHz, D_2O): 25.5, 26.4, 29.9, 55.4, 62.7, 71.4, 78.1, 85.1

MS (ESI) : *m/z* 158.11 $(M+H)^+$

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}O_2N$ 158.1176; Found 158.1174

(1*R*,2*R*,7a*R*)-Hexahydro-1H-pyrrolizine-1,2-diol (4):



Dihydroxypyrrolizidine **4** was prepared using general procedure for cyclization reaction and starting from tetrol **61**.

Yield: 0.047 g, 56%

Mol. Formula: $C_7H_{13}O_2N$

M.P: 138-140 °C [lit.[8f]: 141-143]

$[\alpha]_D^{25}$: - 6.67 (*c* 1.3, CH_3OH), [lit.[8f]: $[\alpha]^{24}_D$ – 6.4 (*c* 1, CH_3OH), lit.[10e] $[\alpha]_D$ + 7.6 (c 1.3, CH_3OH)]

^{1}H NMR (200 MHz, CD_3OD) : δ 1.63-1.80 (m, 2H), 1.84-1.99 (m, 2H), 2.50 (dd, *J* = 7 Hz , 10.7 Hz ,1H), 2.63-2.74 (m, 1H), 2.84-2.92 (m, 1H), 3.14-3.19 (m, 1H), 3.23-3.26 (m,1H), 3.60 (t, *J* = 5.6 Hz, 1H), 3.94- 4.05 (m,1H).

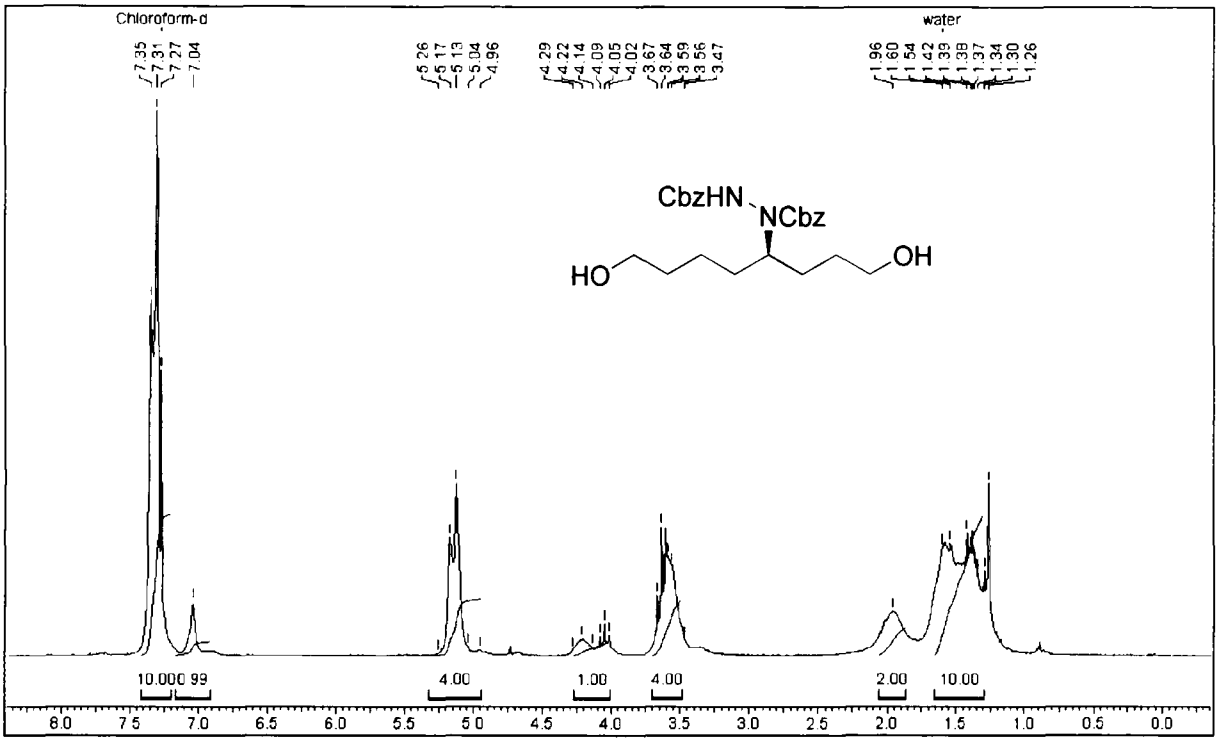
^{13}C NMR (50 MHz, CD_3OD): 26.4, 31.5, 56.8, 59.7, 71.0, 78.8, 82.9

MS (ESI) : *m/z* 144.12 $(M+H)^+$

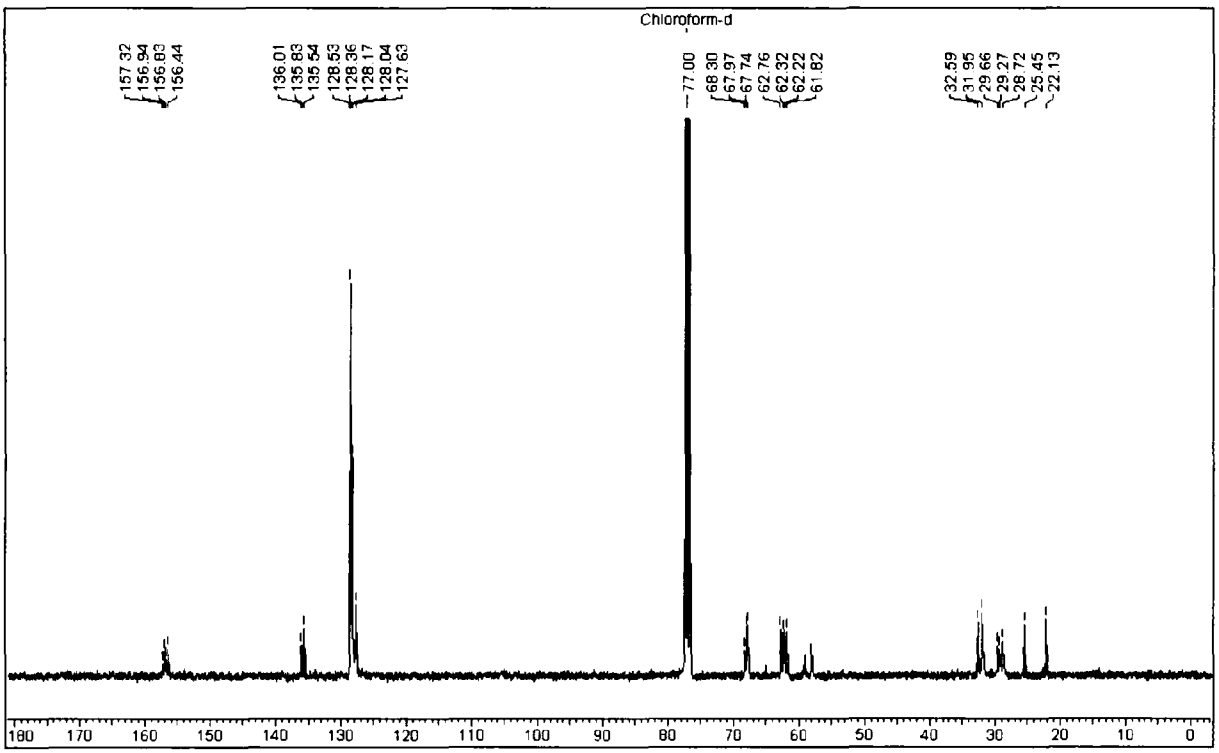
HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_7H_{14}O_2N$ 144.1019; Found 144.1020

3.1.7. Spectra

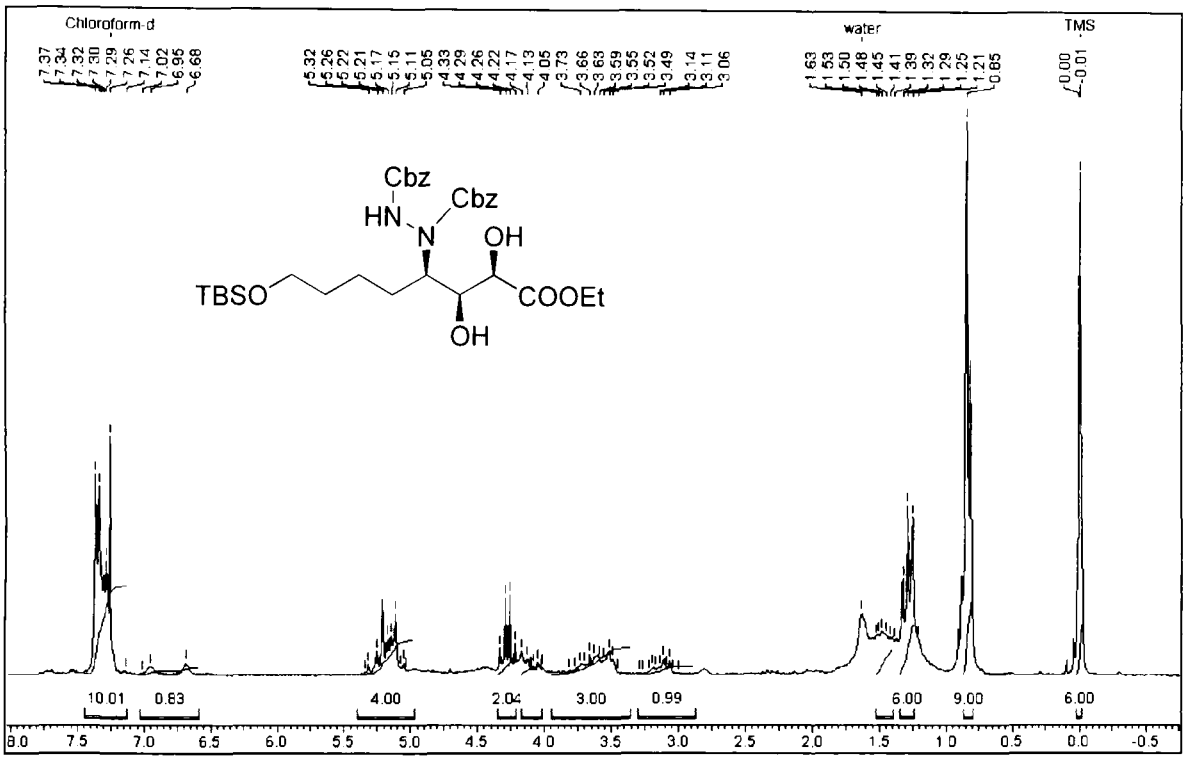
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl (*R*)-1-(1,8-dihydroxyoctan-4-yl) hydrazine-1,2 dicarboxylate (52):



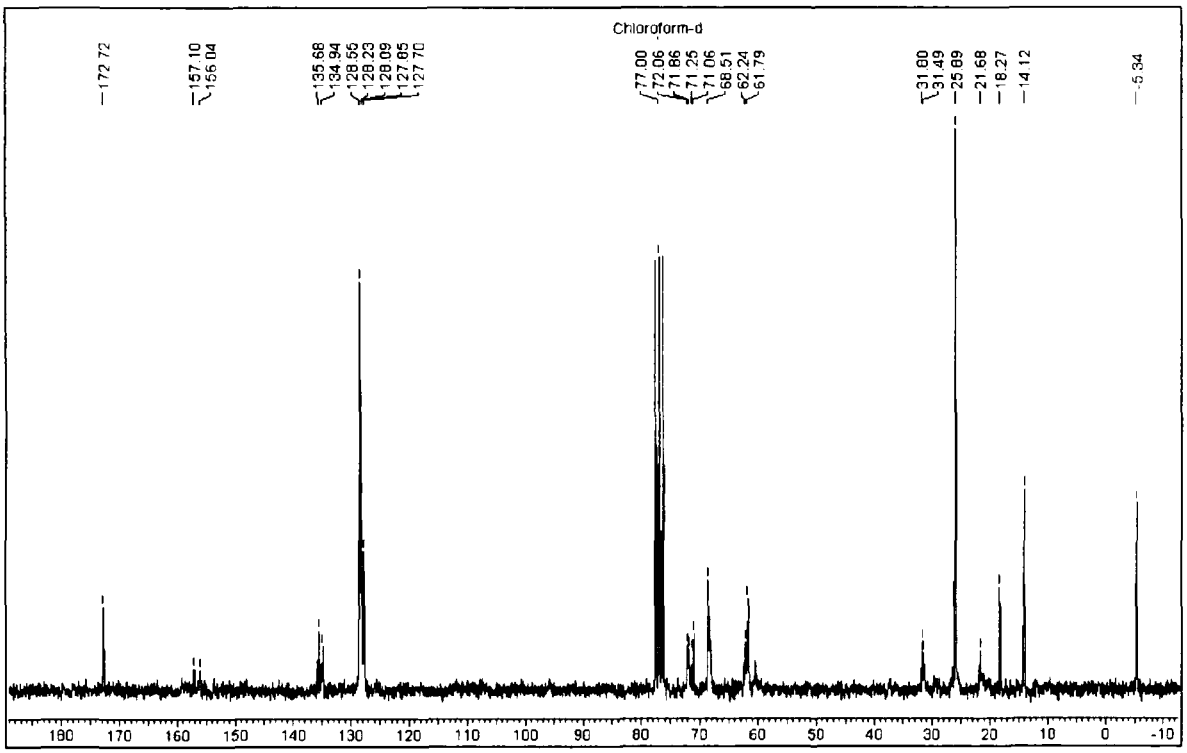
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl (*R*)-1-(1,8-dihydroxyoctan-4-yl) hydrazine-1,2-dicarboxylate (52):



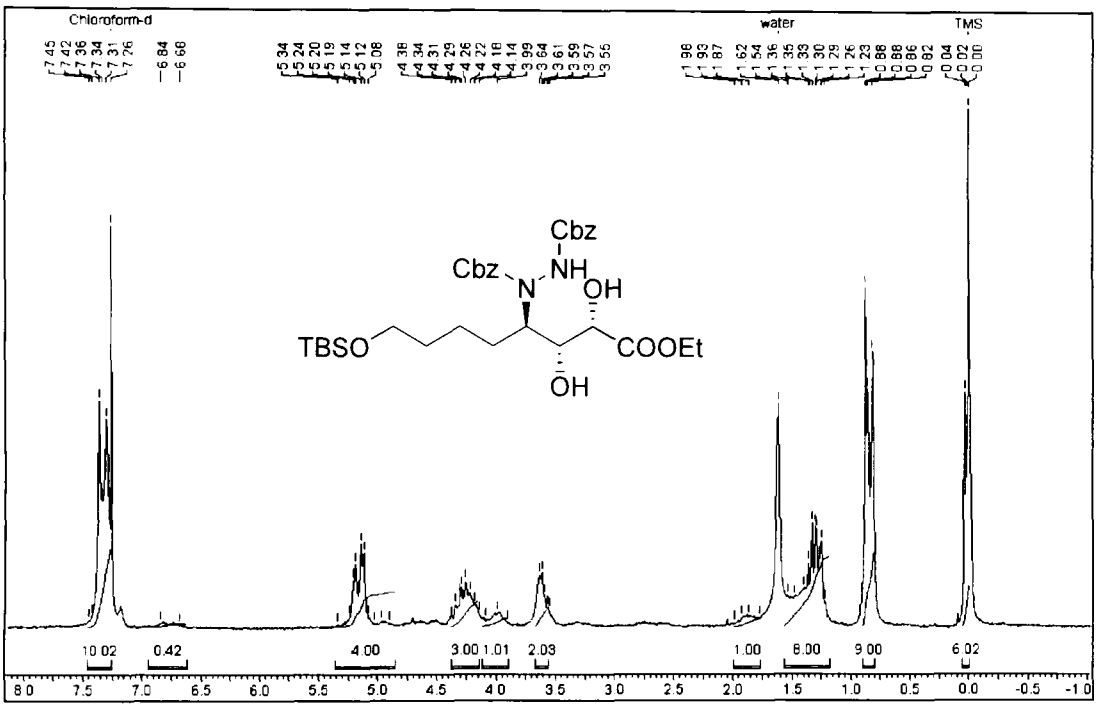
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*R*,3*S*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (53):



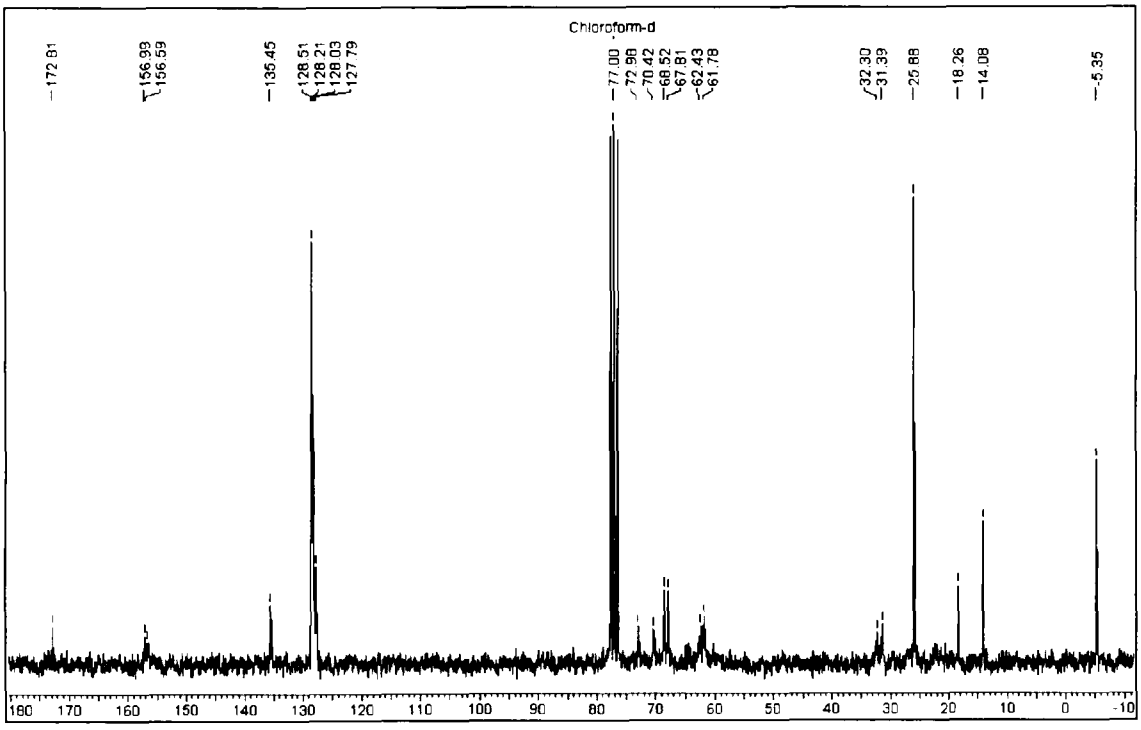
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*R*,3*S*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (53):



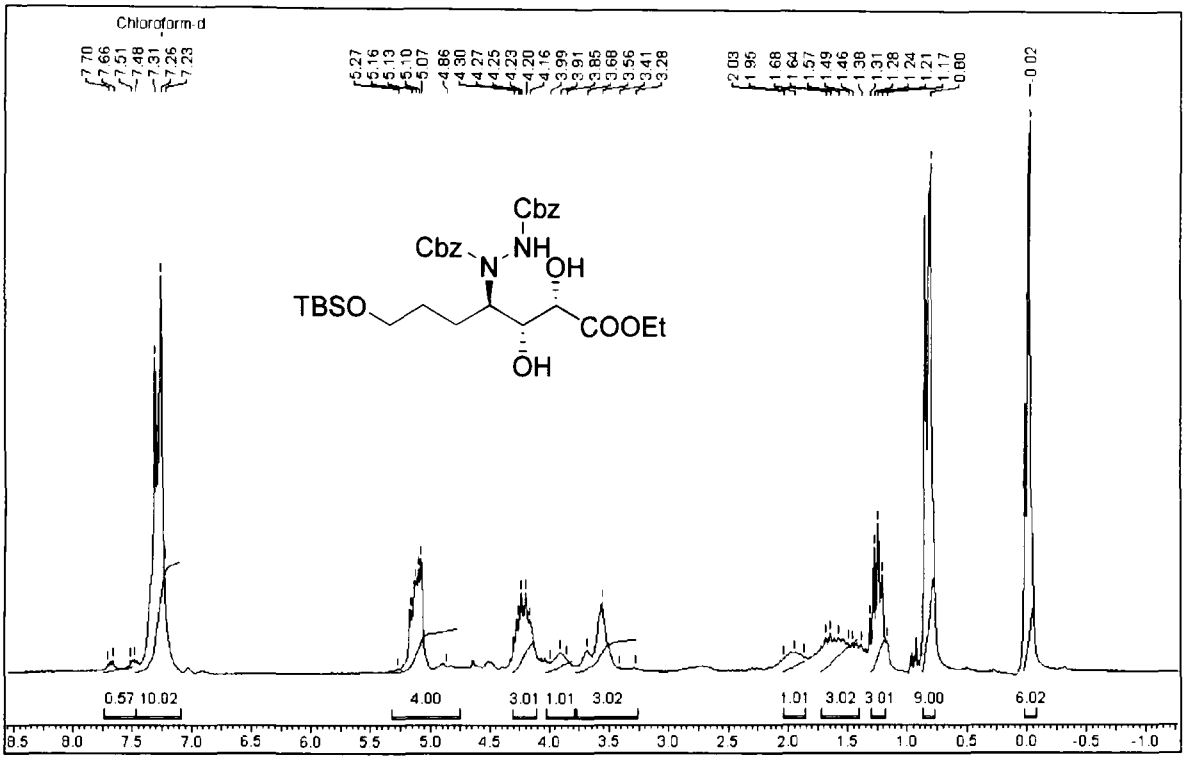
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*S*,3*R*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1- ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (54):



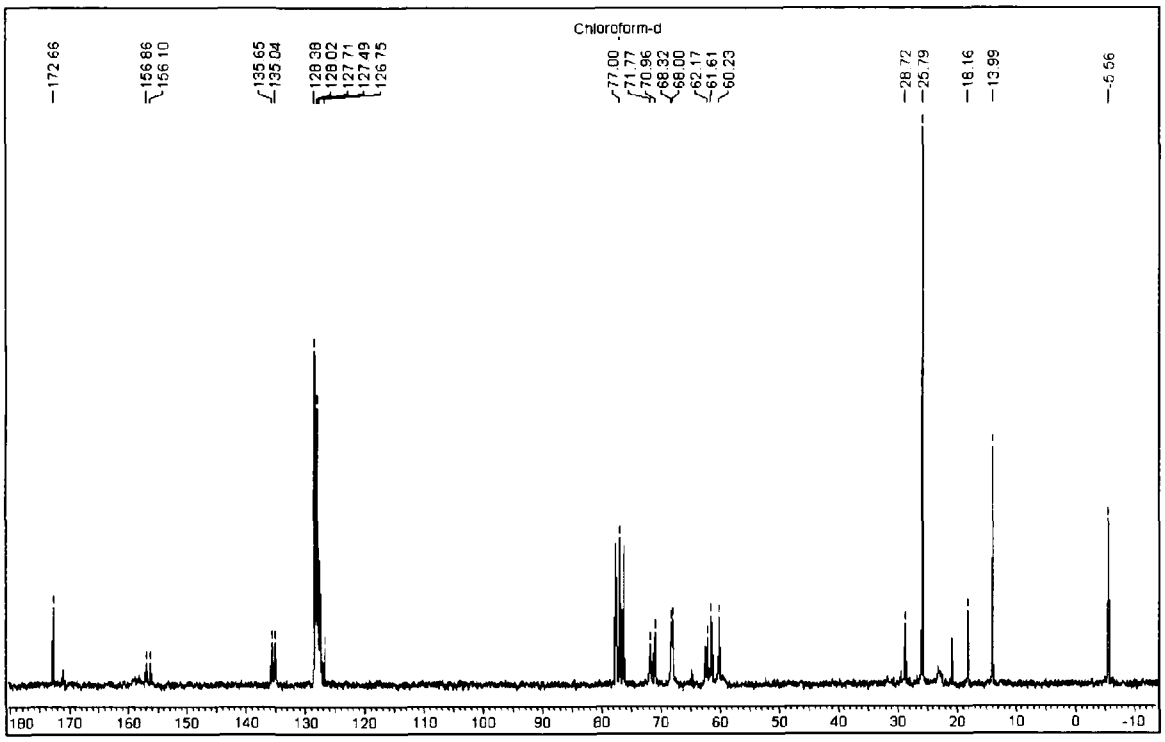
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*S*,3*R*,4*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxooctan-4-yl)hydrazine-1,2-dicarboxylate (54) :



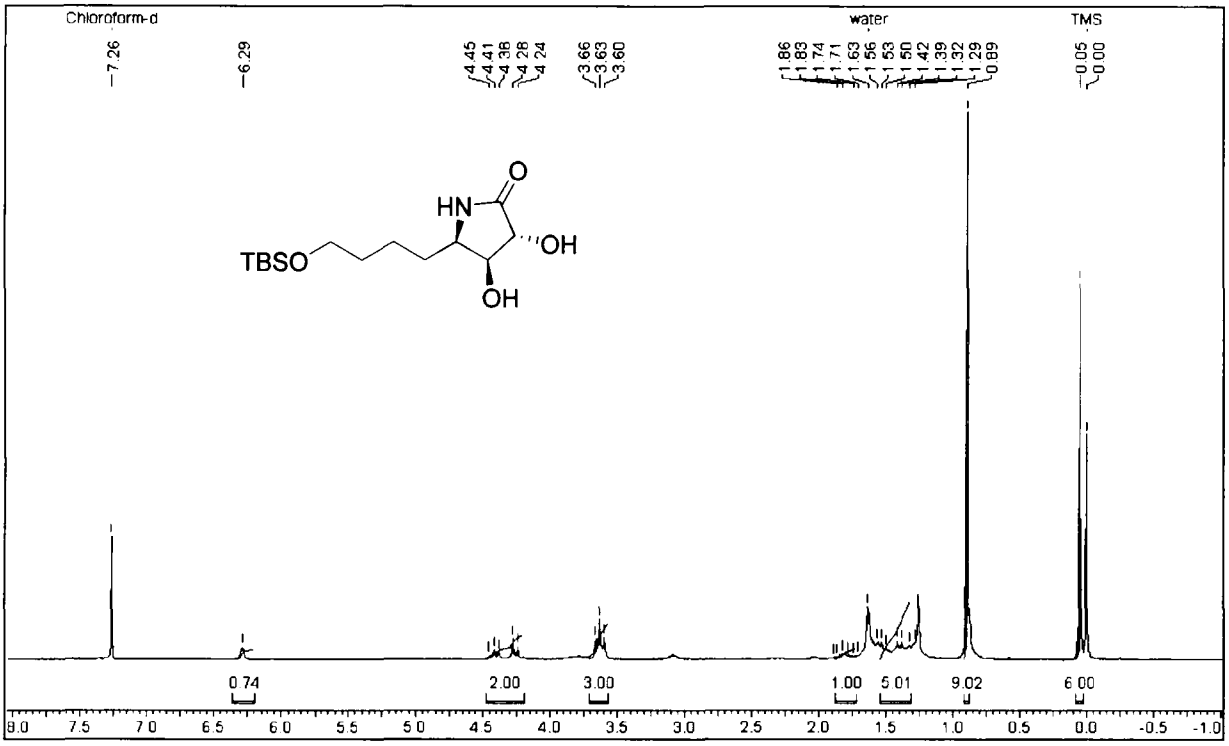
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*S*,3*R*,4*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (60):



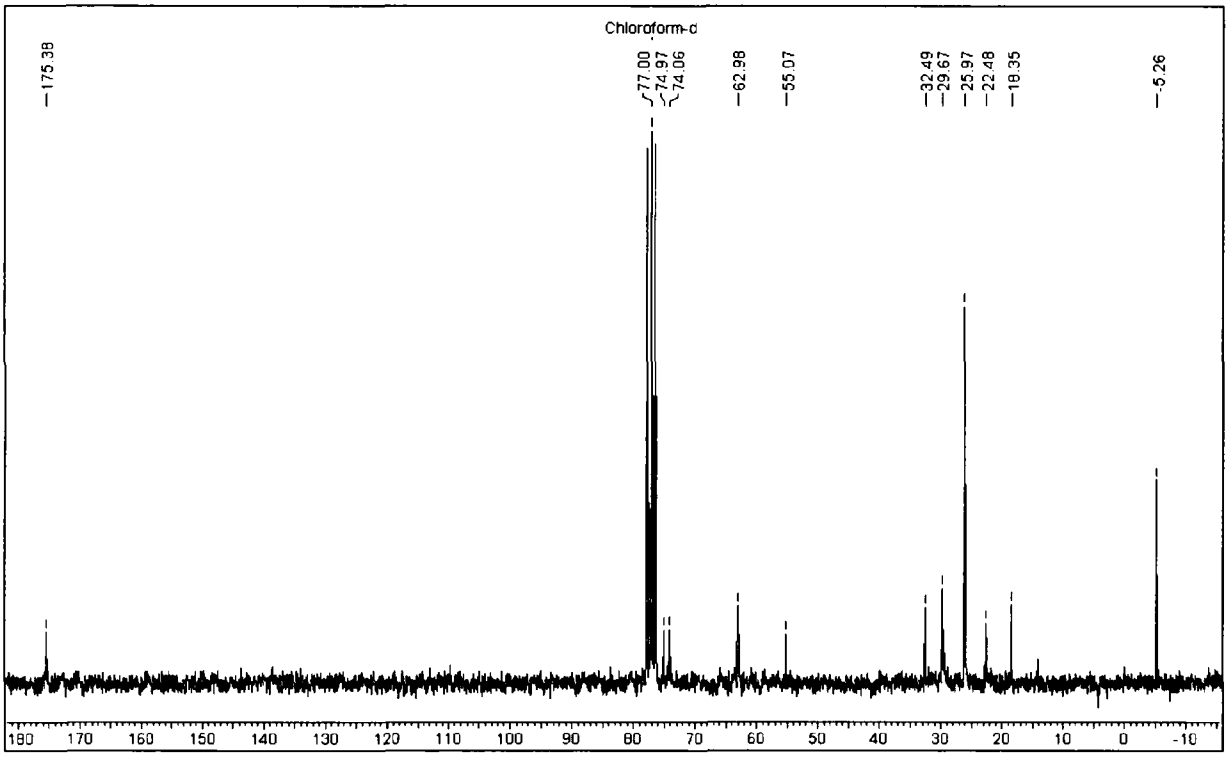
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*S*,3*R*,4*R*)-7-((*tert*-butyldimethylsilyl)oxy)-1-ethoxy-2,3-dihydroxy-1-oxoheptan-4-yl)hydrazine-1,2-dicarboxylate (60):



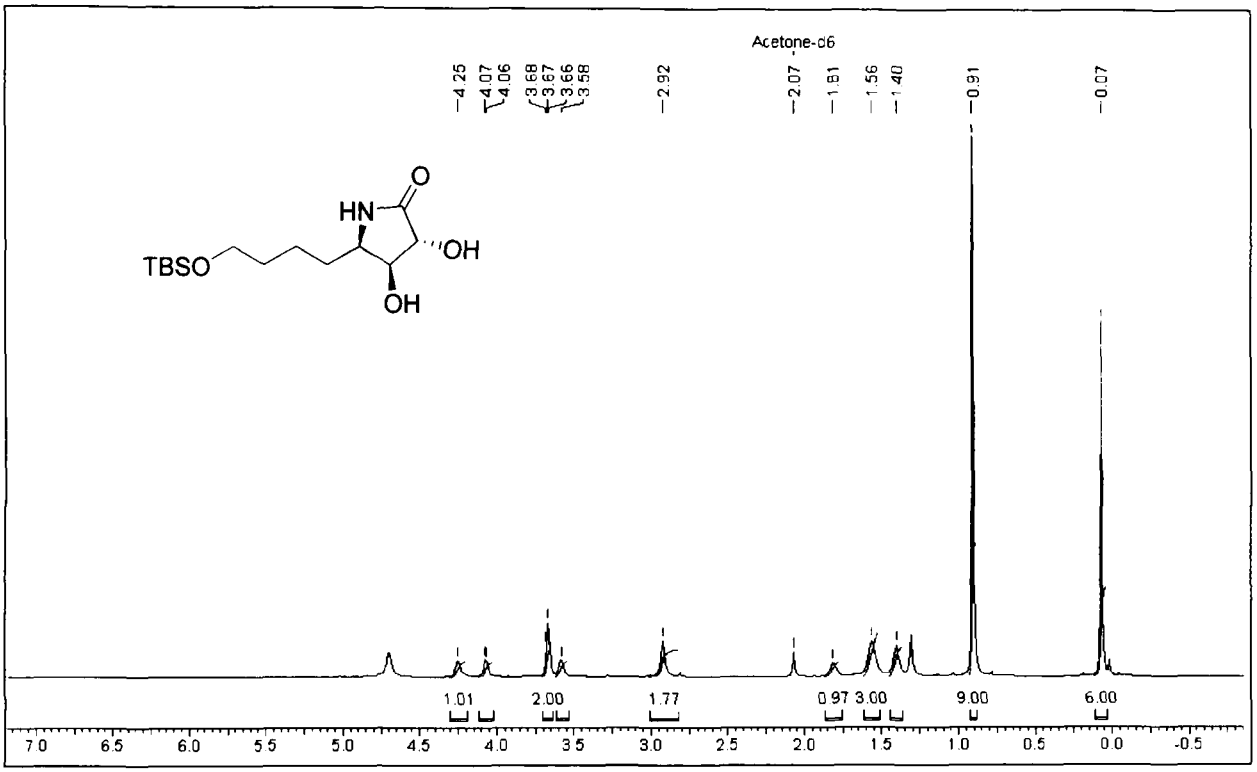
^{1}H NMR ($CDCl_3$, 200 MHz) of (3*R*,4*S*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):



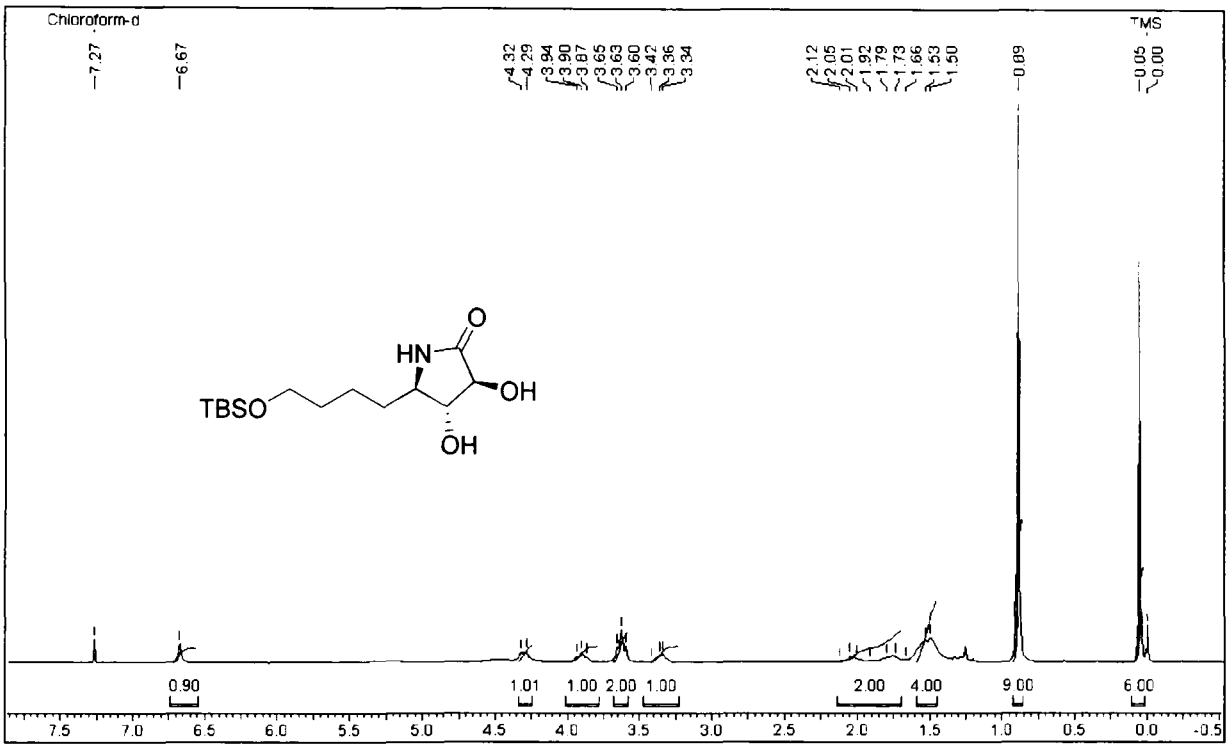
^{13}C NMR ($CDCl_3$, 50 MHz) of (3*R*,4*S*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):



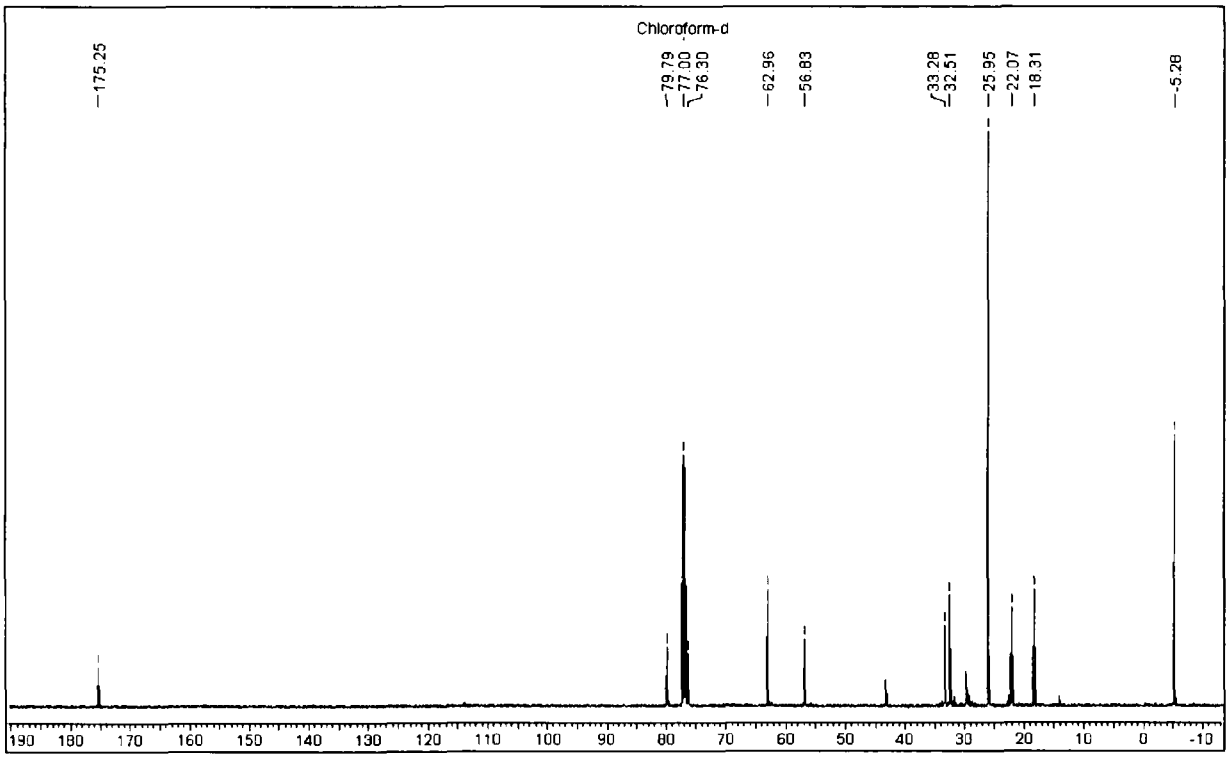
^{1}H NMR in Acetone-d6 of (3*R*,4*S*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (55):



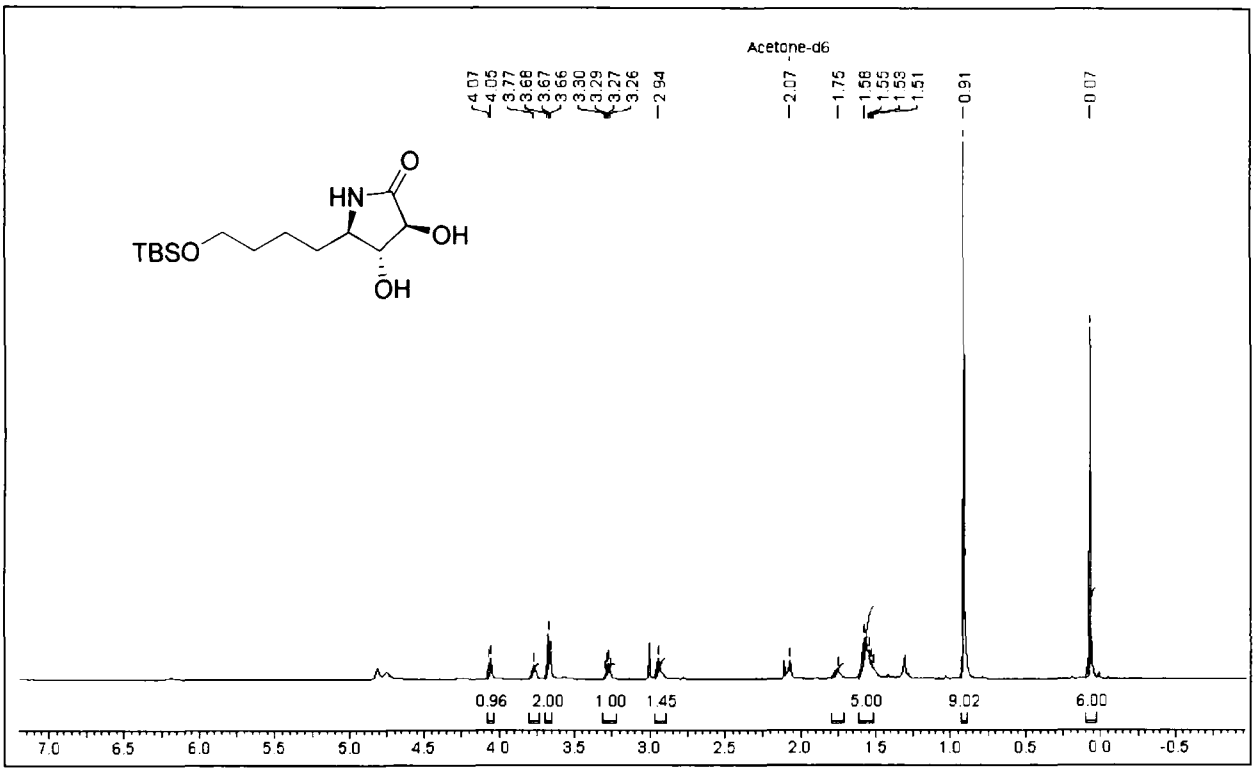
^{1}H NMR ($CDCl_3$, 200 MHz) of (3*S*,4*R*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):



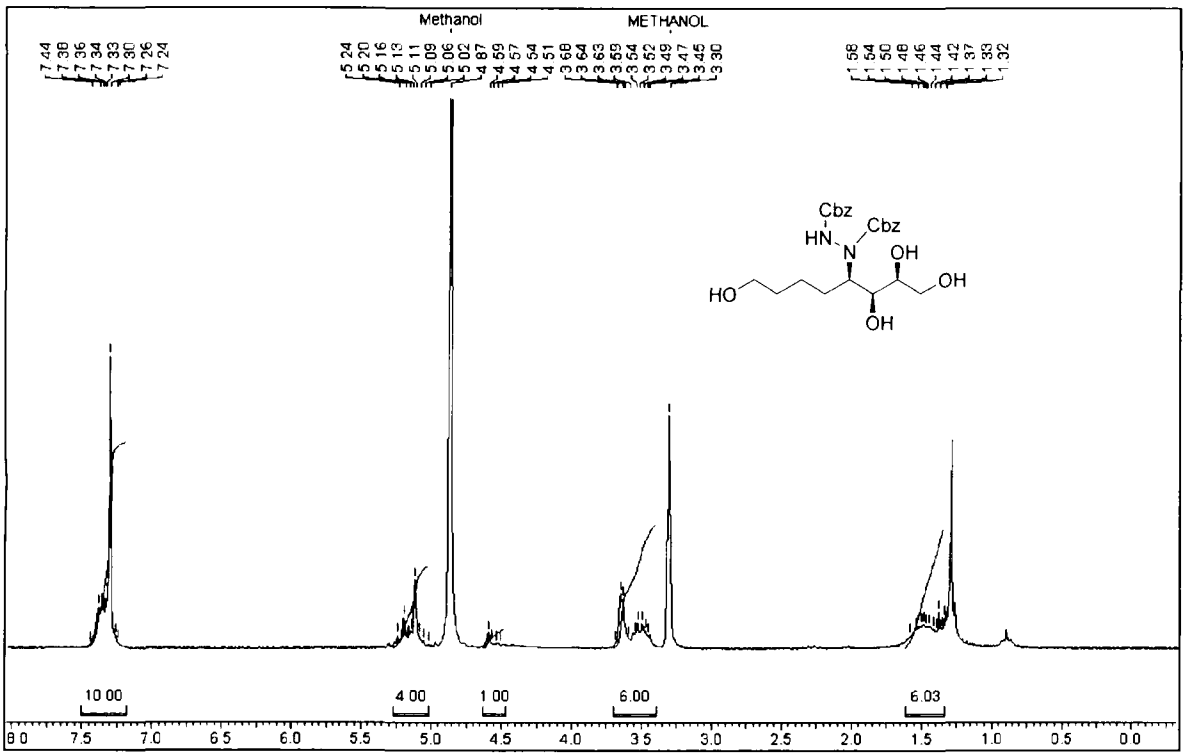
^{13}C NMR ($CDCl_3$, 50 MHz) of (3*S*,4*R*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):



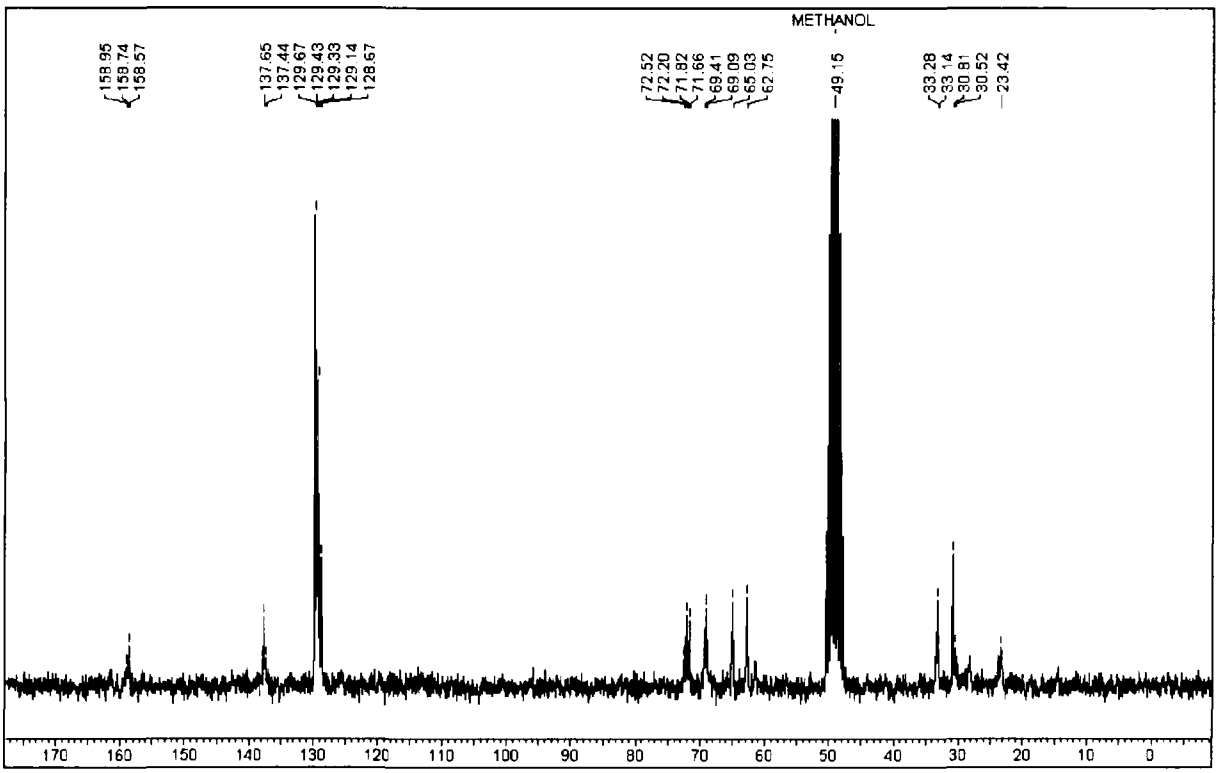
^{1}HNMR in Acetone-d6 of (3*S*,4*R*,5*R*)-5-(4-((*tert*-butyldimethylsilyl)oxy)butyl)-3,4-dihydroxypyrrolidin-2-one (56):



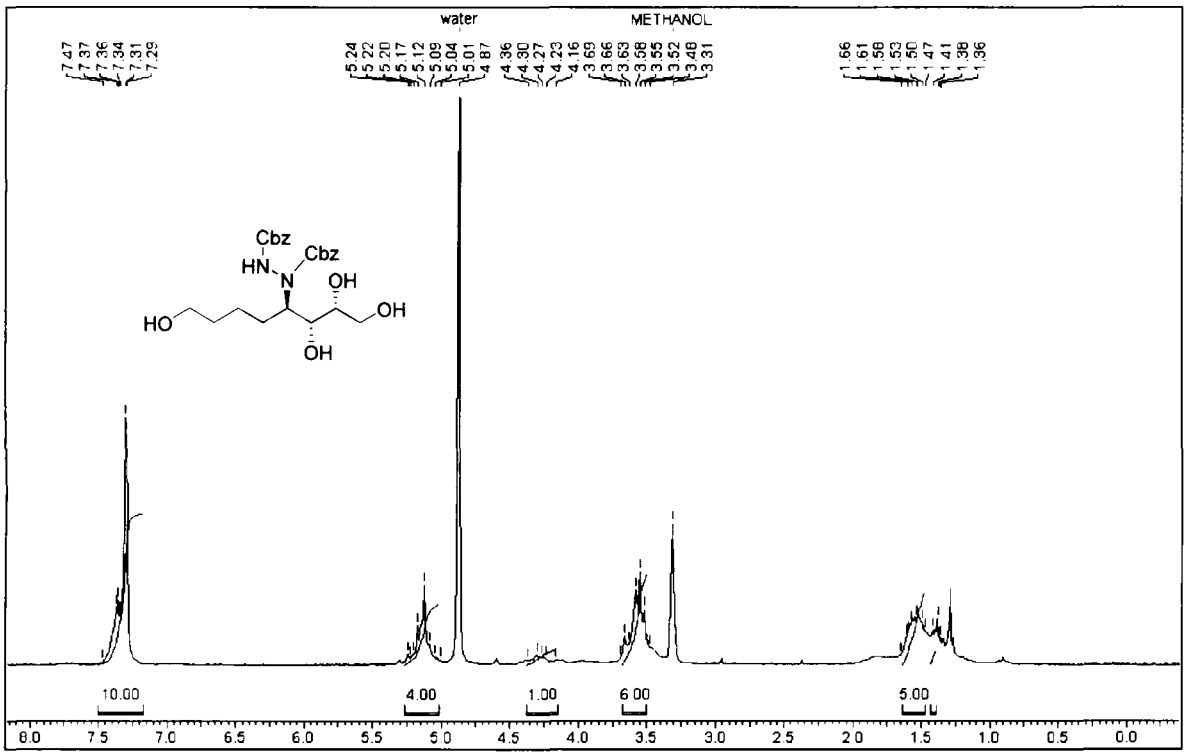
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*S*,3*S*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (57):



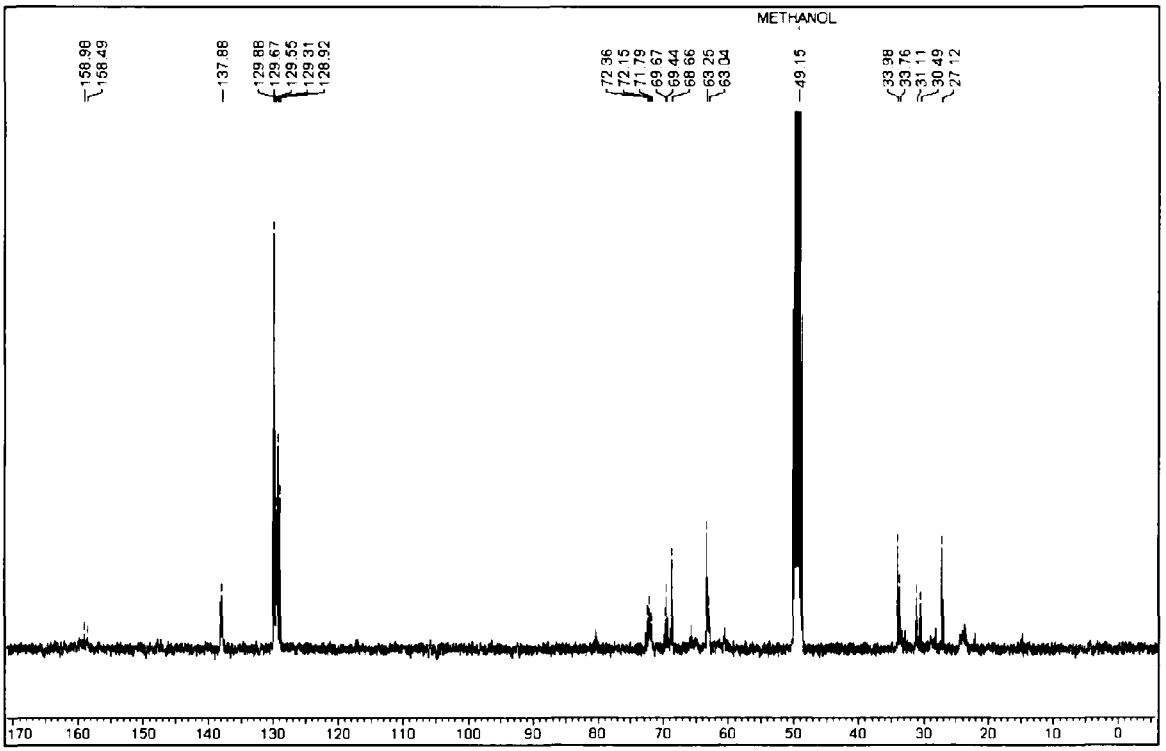
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*S*,3*S*,4*R*)-1,2,3,8-tetrahydroxyoctan 4yl)hydrazine1,2dicarboxylate (57):



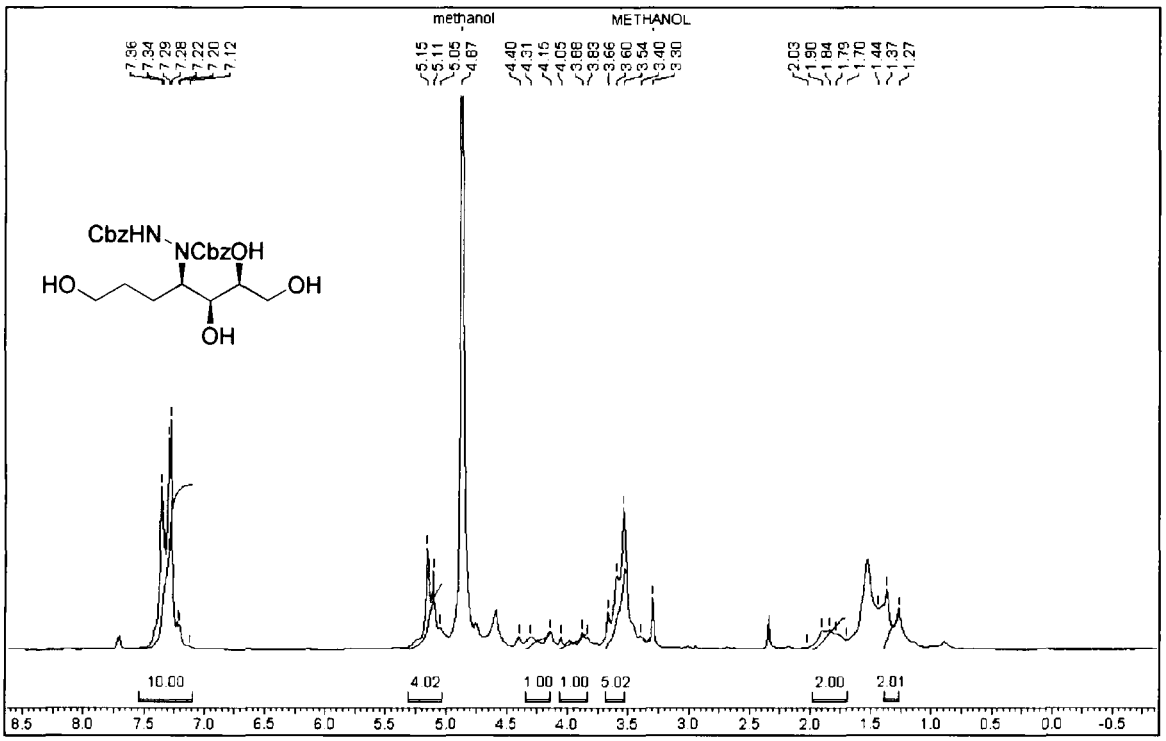
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):



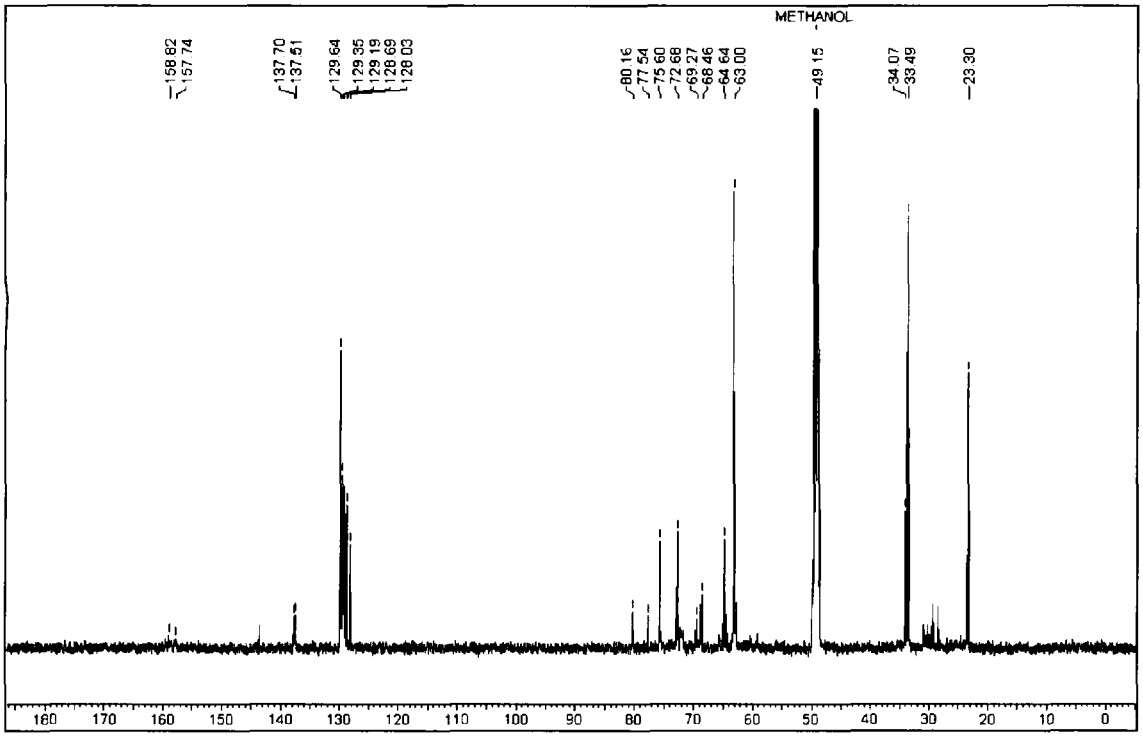
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,8-tetrahydroxyoctan-4-yl)hydrazine-1,2-dicarboxylate (58):



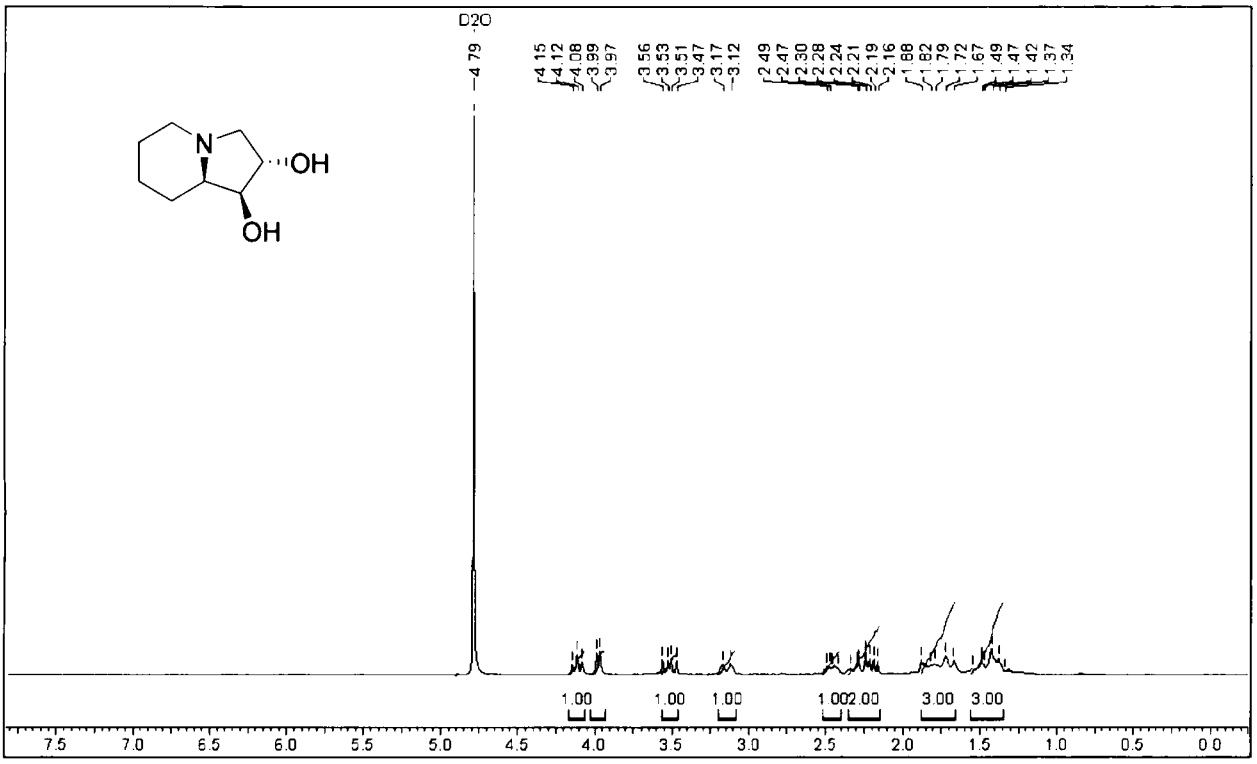
^{1}H NMR ($CDCl_3$, 200 MHz) of Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (61):



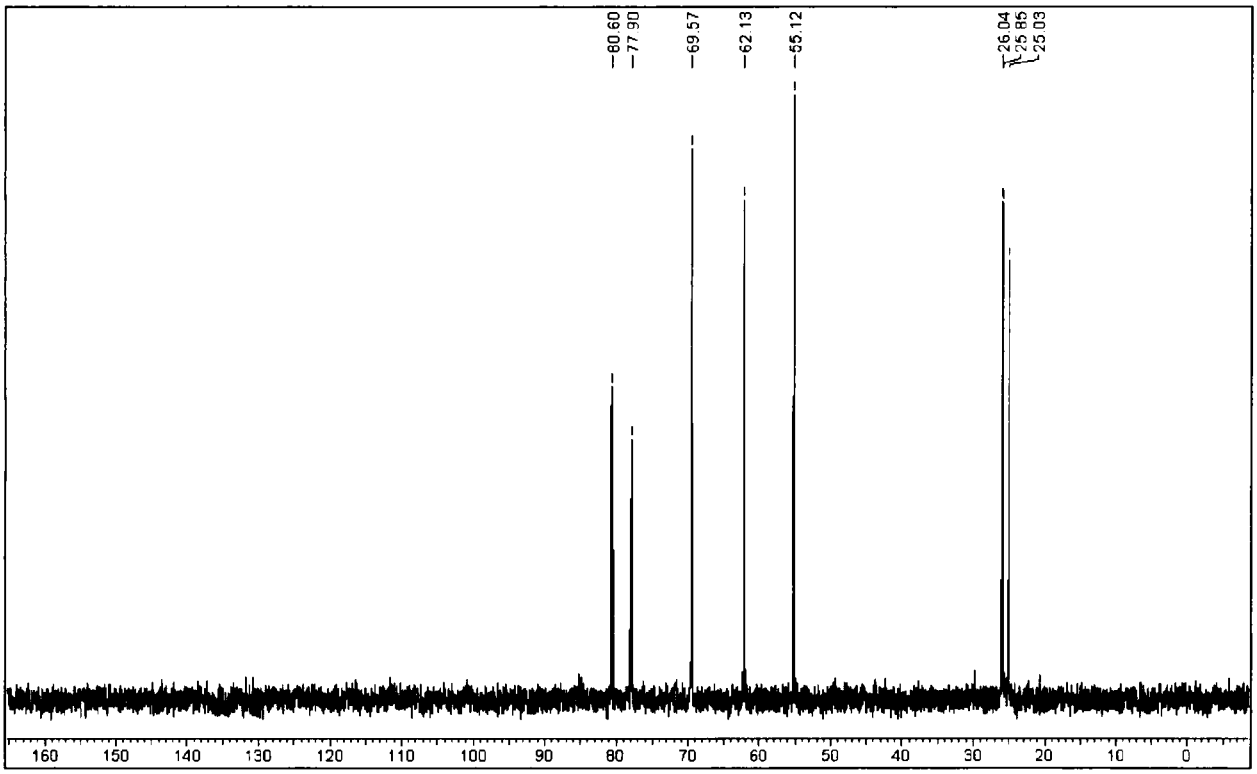
^{13}C NMR ($CDCl_3$, 50 MHz) of Dibenzyl 1-((2*R*,3*R*,4*R*)-1,2,3,7-tetrahydroxyheptan-4-yl)hydrazine-1,2-dicarboxylate (17):



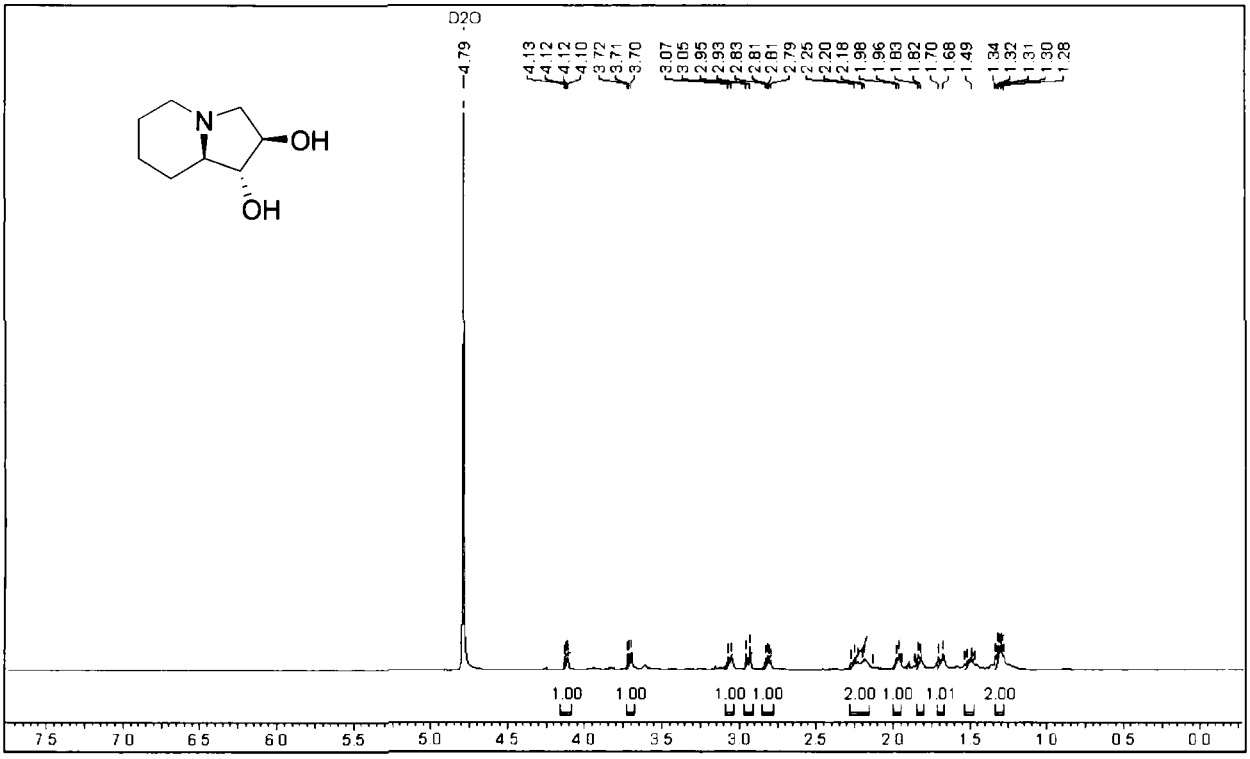
^{1}H NMR ($CDCl_3$, 200 MHz) of (1*S*,2*S*,8a*R*)- octahydroindolizine-1,2-diol (3):



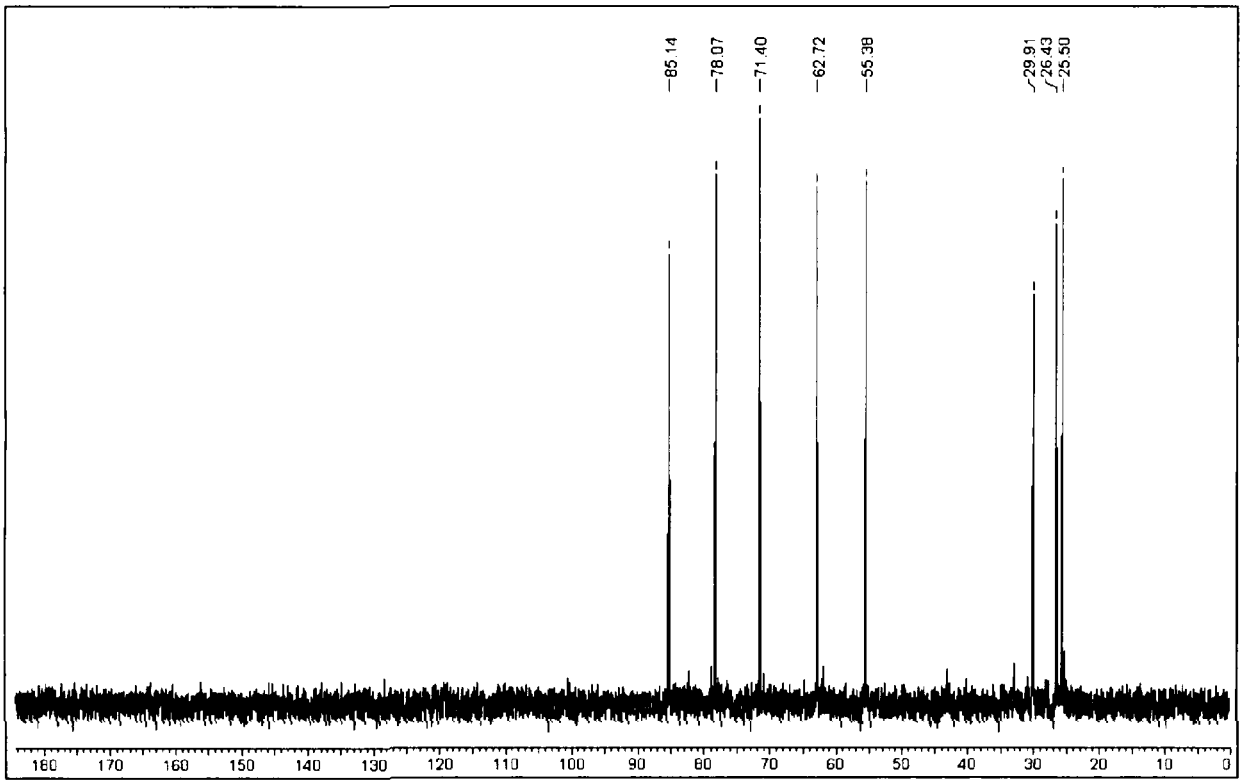
^{13}C NMR ($CDCl_3$, 50 MHz) of (1*S*,2*S*,8a*R*)- octahydroindolizine-1,2-diol (3):



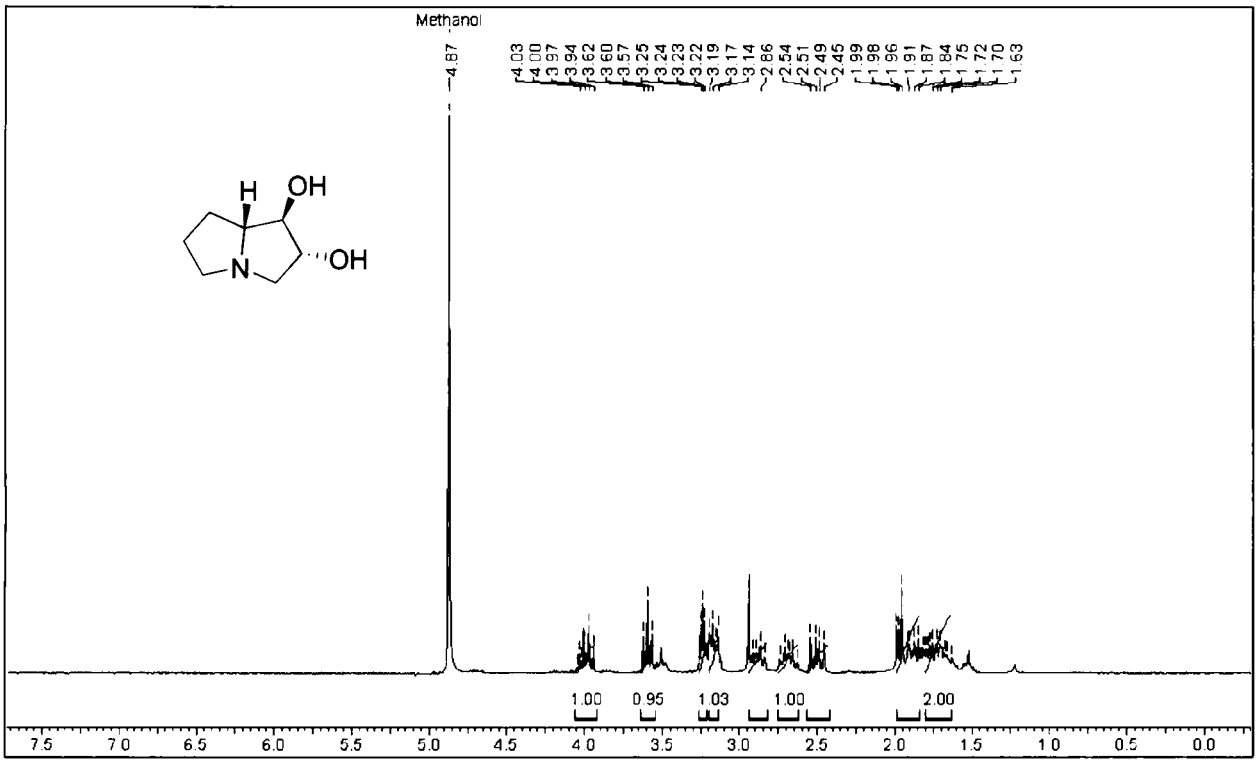
^{1}H NMR ($CDCl_3$, 200 MHz) of (1*R*,2*R*,8a*R*)-octahydroindolizine-1,2-diol (2):



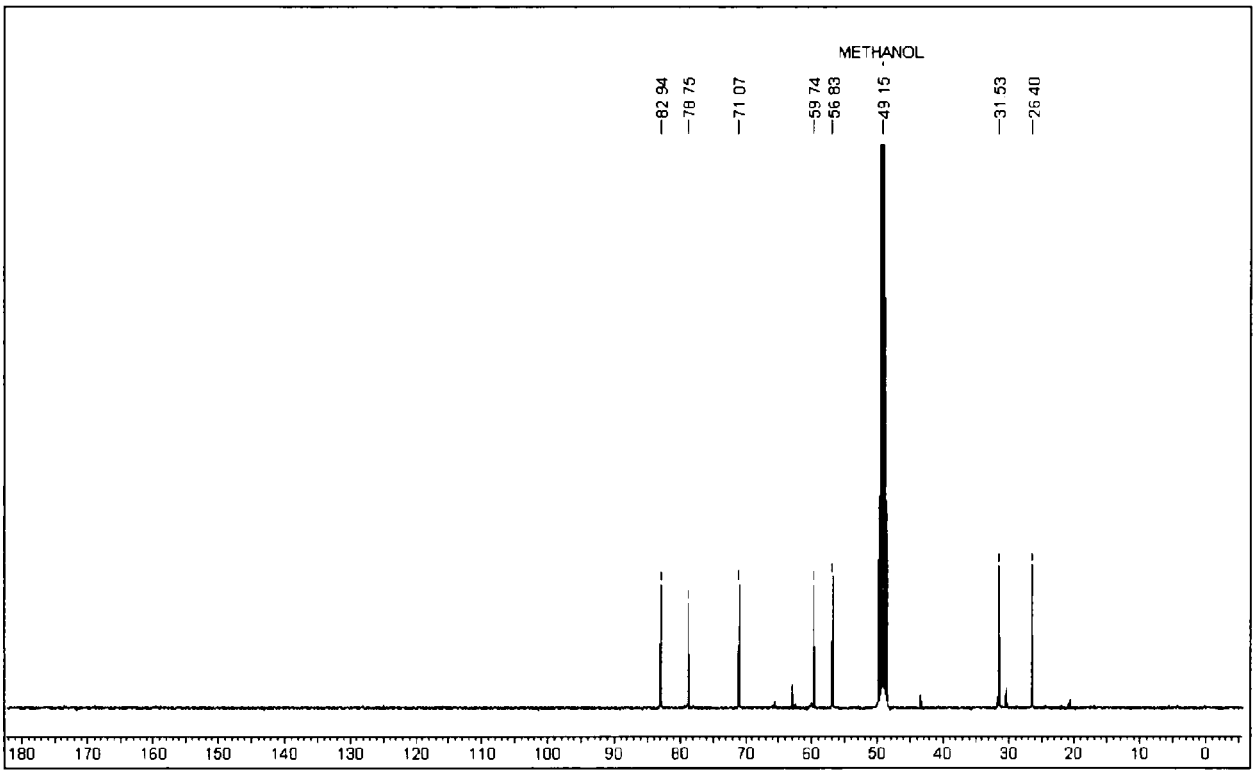
^{13}C NMR ($CDCl_3$, 50 MHz) of (1*R*,2*R*,8a*R*)-octahydroindolizine-1,2-diol (2):



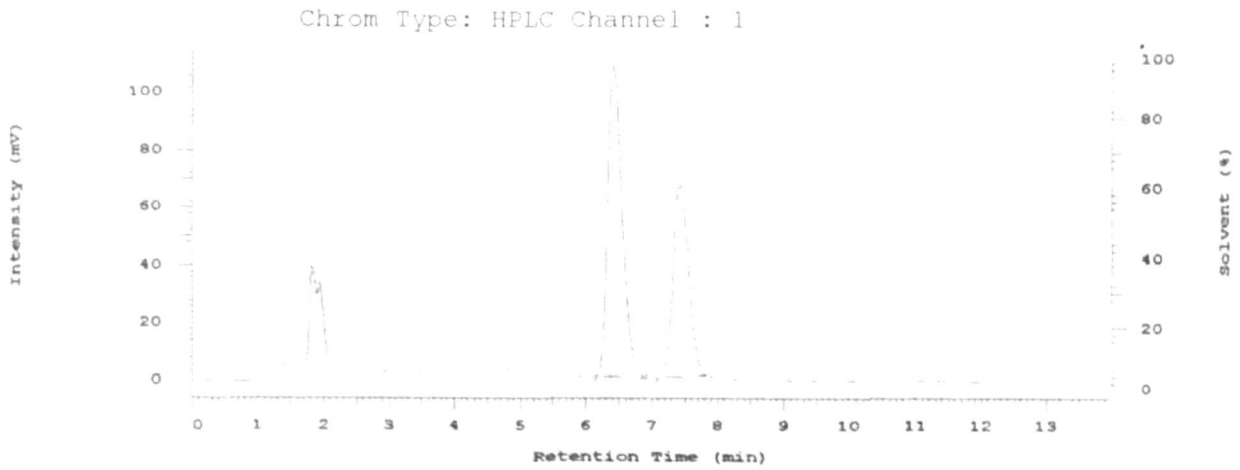
^{1}H NMR ($CDCl_3$, 200 MHz) of (1*R*,2*R*,7a*R*)-hexahydro-1H-pyrrolizine-1,2-diol (4):



^{13}C NMR ($CDCl_3$, 50 MHz) of (1*R*,2*R*,7a*R*)-hexahydro-1H-pyrrolizine-1,2-diol (4):

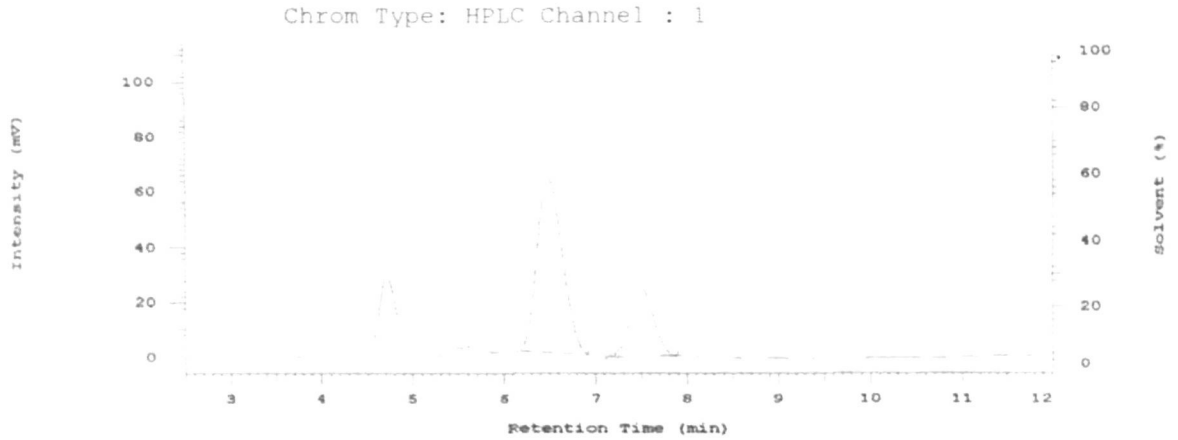


Diastereomeric ratio of compounds 53, 54 and 60



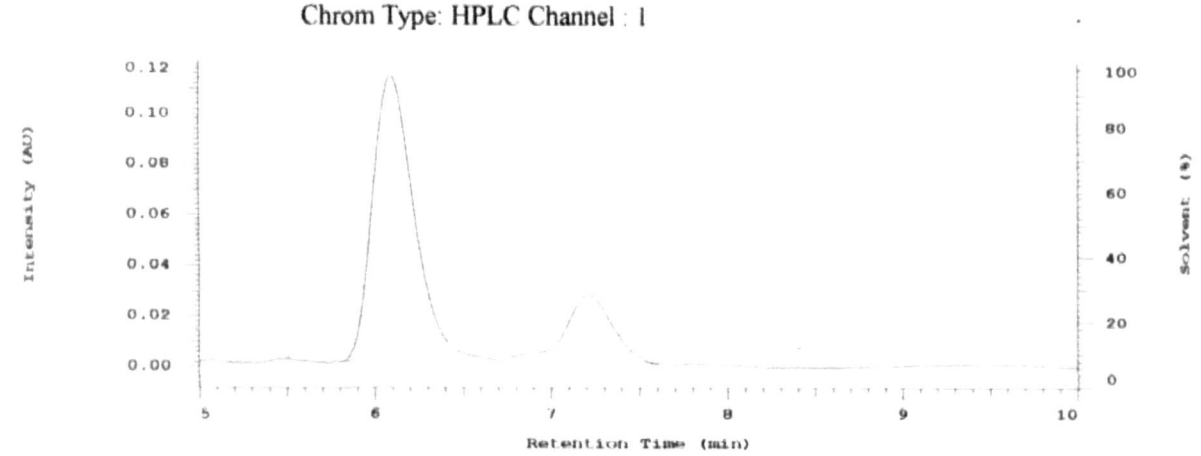
Peak Quantitation: AREA Calculation Method: AREA

No.	RT	Height	Area	Area
1	6.42	108336	1637966	60.016
2	7.43	67091	1091240	39.984
		175427	2729206	100.000

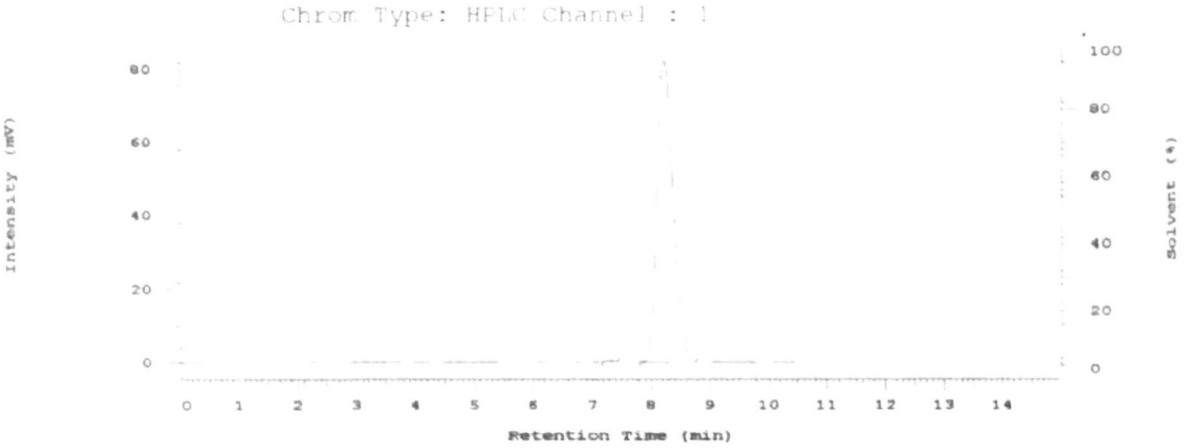


Peak Quantitation: AREA Calculation Method: AREA

No.	RT	Height	Area	Area
1	6.49	63111	1204084	73.668
2	7.50	24267	430392	26.332
		87378	1634476	100.000



No	RT	Height	Area	Area %
1	6.09	56928	950097	77.155
2	7.22	13787	281318	22.845
		70715	1231415	100.000



Peak Quantitation: AREA Calculation Method: AREA

No.	RT	Height	Area	Area
1	7.33	362	3613	0.228
2	8.23	83063	1579306	99.772
		83425	1582919	100.000

3.1.8. References

1. (a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139; (b) A. Mitchenson, A. Nadin, *J. Chem. Soc. Perkin Trans.* 1 **2000**, 2862; (c) D. O. Hagan, *Nat. Prod. Rep.* **1997**, *14*, 637; (d) K. Sakata, K. A. Oki, C.-F. Chang, A. Sakurai, S. Tamura, S. Murakoshi, *Agric. Biol. Chem.* **1978**, *42*, 457; (e) H. Shinozaki, M. Ishida, *Brain Res.* **1985**, *334*, 33.
2. (a) J. R. Liddell, *Nat. Prod. Rep.* **2001**, *18*, 441; (b) J. R. Liddell, *Nat. Prod. Rep.* **2000**, *17*, 455.
3. For reviews, see: (a) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265.
4. I. Pastuszak, R. J. Molyneux, L. F. James, A. D. Elbein, *Biochemistry* **1990**, *29*, 1886.
5. (a) A. Brandi, S. Cicchi, F. M. Cordero, R. Frignoli, A. Goti, S. Picasso, P. Vogel, *J. Org. Chem.* **1995**, *60*, 6806; (b) F. Cardona, A. Goti, S. Picasso, P. Vogel, A. Brandi, *Journal of Carbohydrate Chemistry* **2000**, *19*, 585.
6. (a) H. Yoda, H. Kitayama, T. Katagiri, K. Takabe, *Tetrahedron: Asymmetry* **1993**, *4*, 1455; (b) D. C. Ha, C. S. Yun, Y. Lee, *J. Org. Chem.* **2000**, *65*, 621; (c) H. Yoda, H. Katoh, Y. Ujihara, K. Takabe, *Tetrahedron Lett.* **2001**, *42*, 2509; (d) C. F. Klitzke, R. A. Pilli, *Tetrahedron Lett.* **2001**, *42*, 5605; (e) A. O. H. El-Nezhawy, H. I. El-Diwani, R. R. Schmidt, *Eur. J. Org. Chem.* **2002**, 4137; (f) Y. Ichikawa, T. Ito, T. Nishiyama, M. Isobe, *Chem. Eur. J.* **2005**, *11*, 1949; (g) J. Zeng, Q. Zhang, H.-K. Zhang, A. Chen, *RSC Adv.* **2013**, *3*, 20298; (h) S. Du-a-man, D. Soorukram, C. Kuhakarn, P. Tuchinda, V. Reutrakul, M. Pohmakotr *Eur. J. Org. Chem.* **2014**, 1708.
7. (a) L. F. Cordero, S. Cicchi, A. Goti, A. Brandi, *Tetrahedron Lett.* **1994**, *35*, 949; (b) D. Socha, M. Jurczak, M. Chmielewski, *Carbohydr. Res.* **2001**, *336*, 315; (c) A. E. McCaig, K. P. Meldrum, R. H. Wightman, *Tetrahedron* **1998**, *54*, 9429; (d) F. Cardona, G. Moreno, F. Guarna, P. Vogel, C. Schuetz, P. Merino, A. Goti, *J. Org. Chem.* **2005**, *70*, 6552.

8. (a) H. Yoda, M. Kawauchi, K. Takabe, *Synlett* **1998**, 137; (b) K. L. Chandra, M. Chandrasekhar, V. K. Singh, *J. Org. Chem.* **2002**, *67*, 4630; (c) G. Casiraghi, P. Spanu, G. Rassu, L. Pinna, F. Ulgheri *J. Org. Chem.* **1994**, *59*, 2906; (d) V. D. Chaudhari, K. S. Ajishkumar, D. D. Dhavale, *Tetrahedron* **2006**, *62*, 4349; (e) I. S. Kim, O. P. Zee, Y. H. Jung, *Org. Lett.* **2006**, *8*, 4101; (f) S. R. Angle, D. Bensa, D. S. Belanger, *J. Org. Chem.* **2007**, *72*, 5592; (g) R. Lahiri, H. P. Kokatla, Y. D. Vankar, *Tetrahedron Lett.* **2011**, *52*, 781; (h) A. Kamal, S. R. Vangala, *Tetrahedron* **2011**, *67*, 1341; (i) I. S. Kim, Q. R. Li, G. R. Dong, Y. C. Kim, Y. J. Hong, M. Lee, K. -W. Chi, J. S. Oh, Y. H. Jung, *Eur. J. Org. Chem.* **2010**, 1569. (j) K. S. Ajish Kumar, V. D. Chaudhari, D. D. Dhavale, *Org. Biomol. Chem.* **2008**, *6*, 703; (k) A. A. Ansari, Y. D. Vankar, *RSC Adv.* **2014**, *4*, 12555;(l) M. Morillo, V. Lequart, E. Grand, G. Goethals, A. Usubillaga, P. Villa, P. Martin, Carbohydr. Res. **2001**, *334*, 281.

9. M. K. Gurjar, L. Ghosh, M. Syamala, V. Jayasree, *Tetrahedron Lett.* **1994**, *35*, 8871.

10. (a) S. Nukui, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 398; (b) M. O. Rasmussen, P. Delair, A. E. Greene, *J. Org. Chem.* **2001**, *66*, 5438; (c) S. H. Lim, S. Ma, P. Beak, *J. Org. Chem.* **2001**, *66*, 9056; (d) Z.-H. Feng, W.-S. Zhou, *Tetrahedron Lett.* **2003**, *44*, 497; (e) T. Ayad, Y. Genisson, M. Baltas, *Org. Biomol. Chem.* **2005**, *3*, 2626; (f) S. -W. Liu, H. -C. Hsu, C. -H. Chang, H. -H. T. Tsai, D. -R. Hou, *Eur. J. Org. Chem.* **2010**, 4771; (g) J. Shao, J. -S. Yang, *J. Org. Chem.* **2012**, **77**, 7891; (h) G. Kim, T. Jin, J. Kim, S. Park, K. Lee, S. Kim, I. Myeong, W. Ham, *Tetrahedron: Asymmetry* **2014**, *25*, 87.

11. (a) V. Jha, N. B. Kondekar, P. Kumar, *Org. Lett.* **2010**, *12*, 2762; (b) P. Kumar, N. Dwivedi, *Acc. Chem. Res.* **2013**, *46*, 289; (c) N. B. Kondekar, P. Kumar, *Org. Lett.* **2009**, *11*, 2611; (d) V. Jha, P. Kumar, *RSC Adv.* **2014**, *4*, 3238; (b) V. Jha, P. Kumar, *Synlett* **2014**, *25*, 1089; (c) S. V. Kauloorkar, V. Jha, G. Jogdand, P. Kumar, *Org. Biomol. Chem.* **2014**, *12*, 4454; (d) V. Jha, S. V. Kauloorkar, Pradeep Kumar, *Eur. J. Org. Chem.* **2014**, 4897.

12. B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656.

13. S. P. Kotkar, V. B. Chavan, A. Sudalai, *Org. Lett.* **2007**, *9*, 1001.

14. (a) H. Becker and K. B. Sharpless, *Angew. Chem. Int. Ed.* **1996**, *35*, 448; (b) H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

15. P. Kumar, V. Jha, R. G. Gonnade, *J. Org. Chem.* **2013**, *78*, 11756.

16. Diastereoselectivity were determined using HPLC.

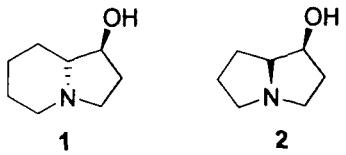
17. (a) T. J. Donohoe, C. J. R Bataille, P. Innocenti, *Org. React.* **2012**, *76*, 1 ; (b) T. J Donohoe, K . Blades, P. R Moore, M. J . Waring, J. J. G. Winter, M . Helliwell, N. J. Newcombe, G. Stemp, *J. Org. Chem.* **2002**, *67*, 7946.

Stereoselective approach to the synthesis of 1-hydroxyindolizidines and pyrrolizidines

3.2.1 Introduction

Biosynthesis of many hydroxylated indolizidine and pyrrolizidine alkaloids reveal the formation of useful intermediates such as D/L-1-hydroxy indolizidines other than amino acids such as pipecolinic acid.[1,2] These compounds were found to be useful precursors for the synthesis of toxic indolizidine and pyrrolizidine alkaloids such as slaframine and swainsonine in the fungus *Rhizoctonia legumniola*.[3] A close study of both the isomers of hydroxyl indolizidines reveled an insight to the biosynthesis of swainsonine. Cytotoxicity and other biological properties have attracted many chemists to take up hydroxyl indolizidines and pyrrolizidines as target compound for synthesis.[4]

Both indolizidines and pyrrolizidines have been molecules of great interest to us as evident from our earlier communications.[2] We have used tools like HKR, proline catalyzed α-aminoxylation as key tools in our previous strategies for the synthesis of molecules like swainsonine, conine and conicine.[3a] We then devised a short and an efficient strategy using proline catalyzed α-amination and Sharpless asymmetric dihydroxylation to achieve the synthesis of lentiginosine and analogues in high enantio- and diastereoselectivity. We have reported the synthesis of core azabicyclic systems and also their dihydroxylated derivatives in our previous communication.[3b] These studies further prompted us to devise a new strategy for the synthesis of 1-hydroxy indolizidines and pyyrolizidines in a high enantio- and diastereomanner.



1 2

Figure 1. Some indolizidine and pyrrolizidine alkaloids

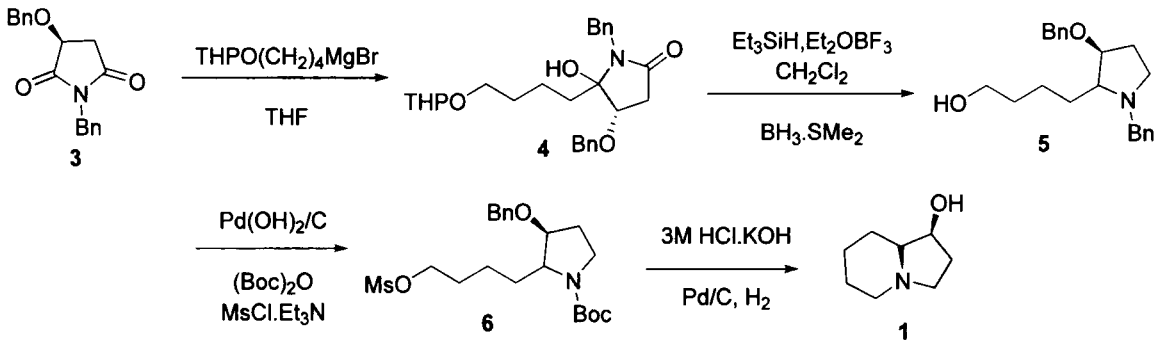
Literature reports as mentioned below show that the azabicylic system can be assembled in numerous ways. However an approach that addresses issues like fewer steps, high yields, good enantio and diastereoselectivity is always a quest and therefore highly desirable.

3.2.2. Review of Literature

Literature reports show that the hydroxylated indolizidine and pyrrolizidine alkaloids can be assembled in numerous ways.[5,6] A detailed report of recent syntheses is described below.

Huang *et al.* (2007)[7o]

Huang and coworkers synthesized the hydroxylated indolizidine starting from maleimide derivative. Grignard reaction of the THP-protected 4-hydroxybutyl magnesium bromide with maleimide derivative **3** at −20°C gave *N,O*-acetal **4** which was then subjected to acidic conditions for 30 min to afford the aza-spiropyran. This aza-spiropyran on reduction with borane-dimethyl sulfide gave pyrrolidine compound **5**. Free alcohol of pyrrolidine **5** was mesylated to get compound **6** which on hydrogenation conditions gave (1*S*,8a*R*)-1-hydroxyindolizidine **1**.

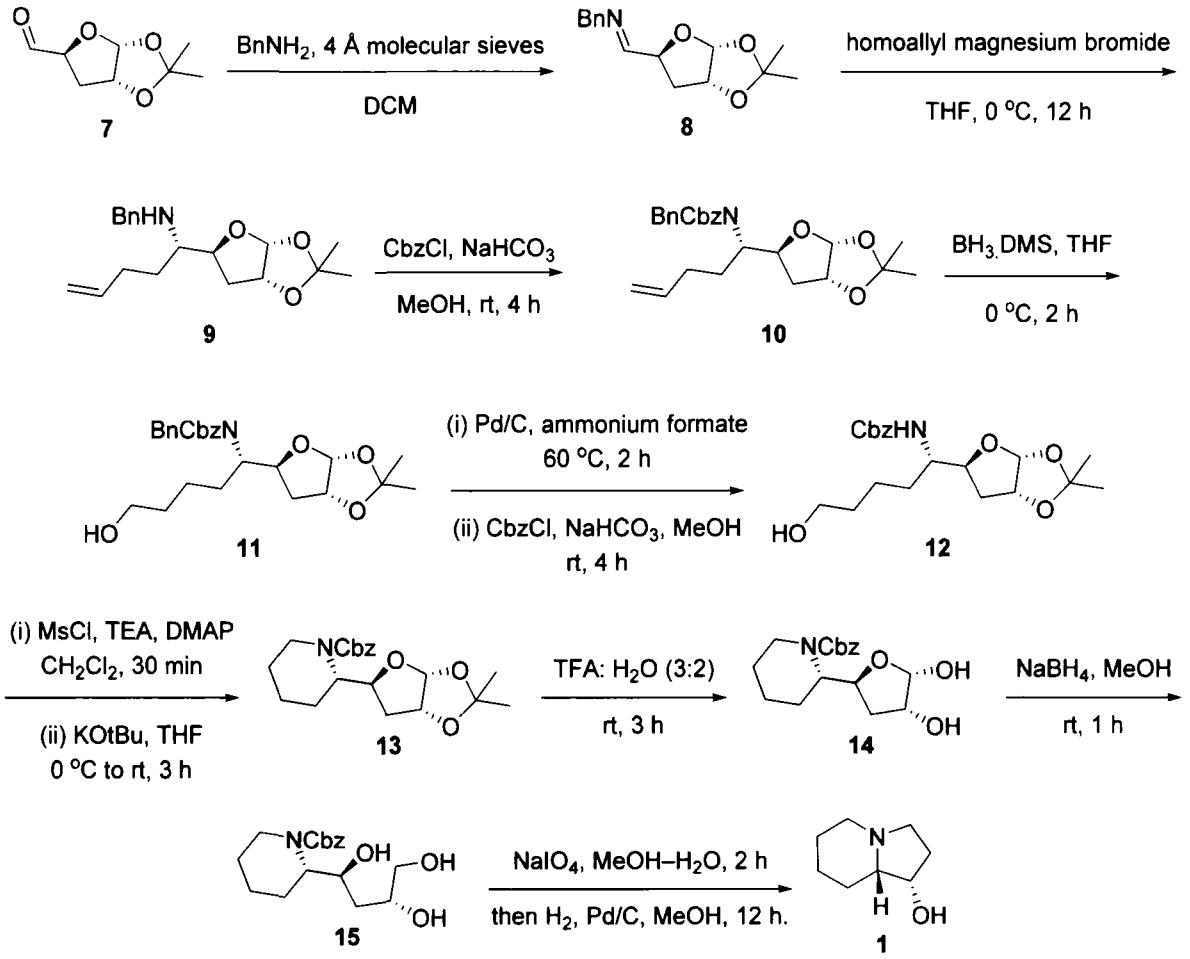


Scheme 1. Synthesis of 1-hydroxyindolizidine (Huang's method)

Chandrasekhar *et al.* (2010)[7n]

Chandrasekhar and coworkers synthesized the hydroxylated indolizidine starting from pyrrolidine aldehyde which in turn was prepared from D-glucose using a known literature procedure. Condensation of aldehyde **7** with benzylamine in the presence of 4 Å molecular sieves afforded chiral imine **8** which on treatment with homoallyl magnesium bromide in

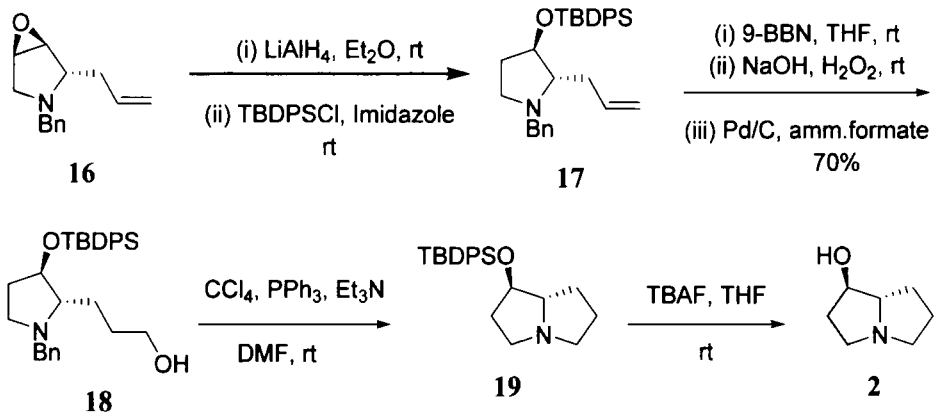
THF at 0 °C gave *syn*-amino olefin **9** as the exclusive isomer. The amino compound **9** was treated with benzyloxy carbonyl chloride to afford compound **10**. Hydroboration of compound **10** with BH_3.DMS gave amino alcohol **11**. Debenzylation of amino alcohol **11** with Pd/C in the presence of ammonium formate gave the free amine, which was immediately protected as the Cbz derivative **12**. Compound **12** was treated with MsCl and Et_3N to get the mesyl derivative, which on cyclization using KO^{t}Bu in THF afforded compound **13**. The acetonide moiety present in compound **13** was removed using TFA–H_2O to give hemiacetal **14** which on treatment with $NaBH_4$ in methanol gave triol **15**. The subsequent oxidative degradation of compound **15** with $NaIO_4$ gave the aldehyde, which was used as such in the next step without any purification. Deprotection of Cbz and simultaneous reductive amino cyclization under Pd/C gave 1-hydroxyindolizidine **1**.



Scheme 2. Synthesis of 1-hydroxyindolizidine (Chandrasekhar's method)

Zapata Machina *et al.* (2015)[8c]

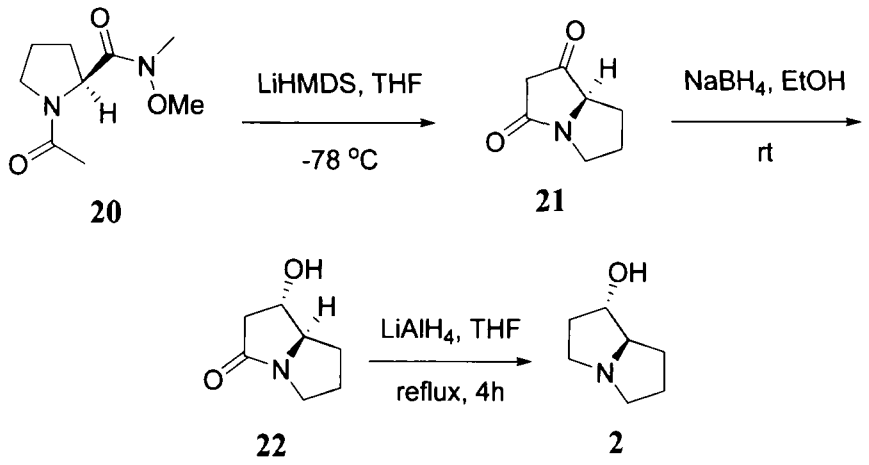
Zapata Machina and co-workers synthesized the hydroxylated pyrrolizidine starting from epoxy-pyrrolidine derivative which in turn was prepared from an epoxy-aldehyde using a known literature procedure. Epoxy-pyrrolidine derivative **16** on reduction with $LiAlH_4$ delivered the alcohol and the secondary hydroxyl group was protected as its t-butyldiphenylsilyl (TBDPS) ether to get compound **17**. Compound **17** on oxidative functionalization of the olefin using hydroboration reaction followed by treatment with peroxide and NaOH afforded the pyrrolidine compound **18**. N-Deprotection under Pd/C-catalyzed hydrogenolysis afforded the deprotected pyrrolidine which on Appel conditions with PPh_3/CCl_4 and Et_3N in DMF gave the pyrrolizidine **19**. Finally deprotection of TBDPS group using TBAF delivered the targeted hydroxylated pyrrolizidine **2**.



Scheme 3. Synthesis of 1-hydroxy pyrrolizidine (Zapata Machina's method)

Murray *et al.* (2007)[8b]

Murray and co-workers synthesized the hydroxylated pyrrolizidine starting from N-methoxy-*N*-methyl amide. Amide **20** upon treatment with LiHMDS was successfully cyclised to ketone **21** which was then reduced with sodium borohydride to give the *exo*-alcohol **22**. Subsequent reductiom under $LiAiH_4$ conditions gave (1S,8aR)-1-hydroxyindolizidine **2**.



Scheme 4. Synthesis of 1-hydroxy pyrrolizidine (Murray's method)

3.2.3. Present work

Objective

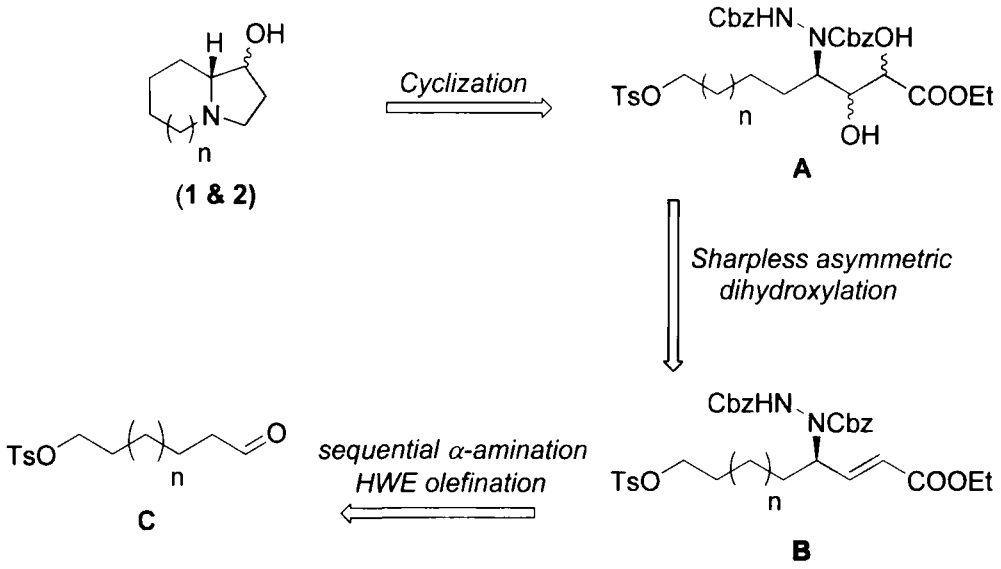
Although the majority of the literature reports have used a chiral pool approach, they prove to be useful protocols for only a limited number of molecules and also involve a large number of synthetic steps. Therefore, a general enantioselective synthetic approach to several azasugars and their unnatural analogues that are amenable to implementation of requisite stereochemical variations and different forms of substitution has become essential.

As a part of our research interest on developing new methodologies and their subsequent application to bioactive compounds, we envisioned that the proline-catalyzed α-amination[7] of aldehydes could easily give us stereocontrolled synthetic access to indolizidine and pyrrolizidine. Since the α-amino aldehydes are prone to racemization, they have been sucessesfully trapped *in situ* by various methods to furnish 1,2-amino alcohol, γ-amino-α,β-unsaturated ester, β-amino alcohol etc.[8]

We chose to trap them by HWE olefination to furnish γ-amino-α,β-unsaturated ester using a mild procedure developed by Sudalai *et al.*[9] It is noteworthy that γ-amino-α,β-unsaturated esters, an allylic amines serve as useful building blocks and can further be elaborated to the synthesis of variety of compounds of biological importance.

3.2.4. Results and Discussion

Our general synthetic strategy is outlined in Scheme 5. The hydroxylated indolizidine **1** and pyrrolizidine alkaloids **2** could be obtained from compound **A**. Compound **A** could be obtained by Sharpless asymmetric dihydroxylation[12] of γ-amino-α,β-unsaturated ester **B**. Ester B could be obtained from aldehyde **C** via organocatalytic α-amination reaction.[11]



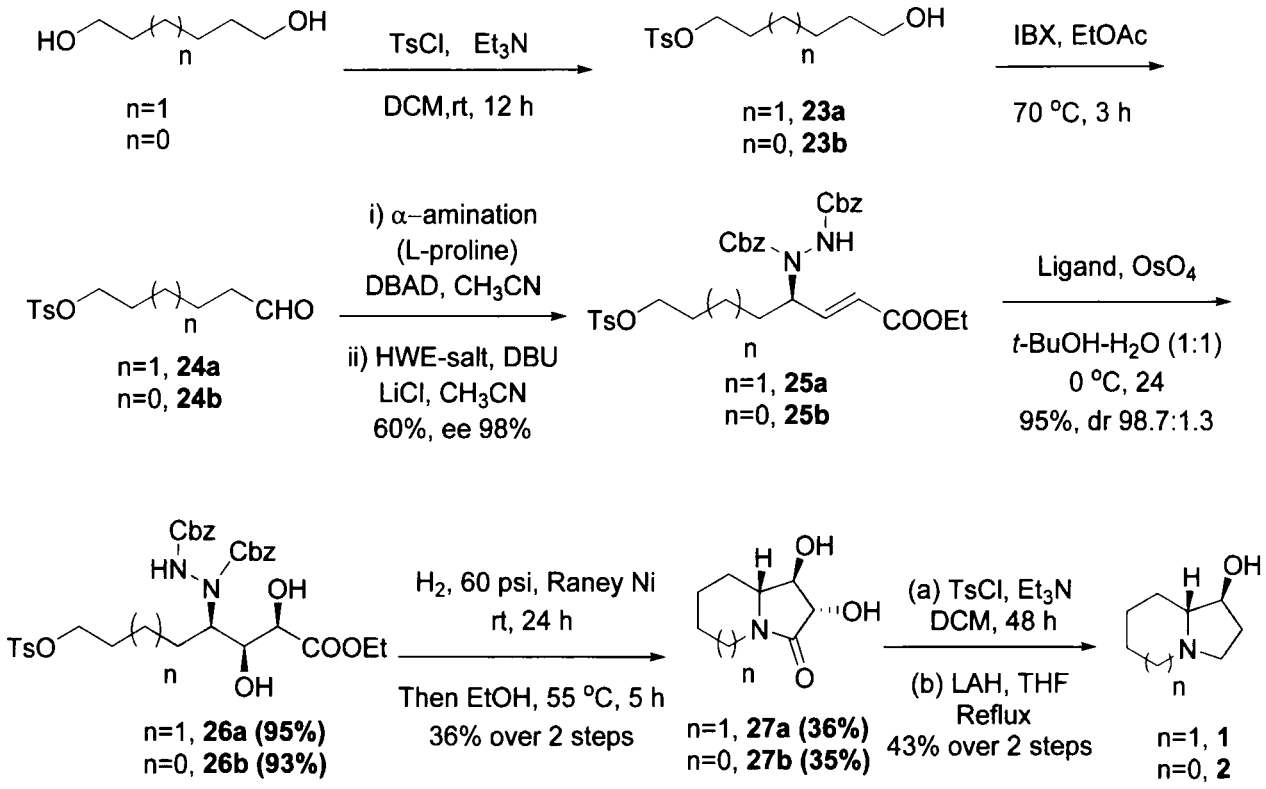
Scheme 5. Retrosynthetic analysis of 1-hydroxy indolizidine and pyrrolizidine alkaloids

Our synthesis started from mono tosylated 1,6-hexane diol **23a**. The choice of tosylation as protecting group was found to be an alternative to our previously reported silyl ethers in order to avoid protection and deprotection steps. Oxidation of the primary alcohol using IBX *in* ethyl acetate gave aldehyde **24a** which was subjected to α-amination reaction as a crude mixture using DBAD as a nitrogen source and L-proline as a catalyst followed by HWE olefination to furnish γ-amino-α,β-unsaturated ester **25a** in 60% yield and 98% enantioselectivity.[14] The ^{1}H NMR spectrum gave olefin protons at δ 6.80 (doublet of doublet) with the coupling constant J = 6.0, 15.2 Hz and δ 6.57 (doublet) with the coupling constant J = 15.2 Hz indicating *trans*-olefin. The α, β-unsaturated hydrazino ester **25a** was then treated with OsO_4 in presence of $(DHQ)_2AQN$ (5 mol %) as a ligand to give syn diastereomer **26a** as the major product in 95% yield.[11] The disappearance of olefinic protons

in the ^{1}H NMR confirmed the formation of the dihydroxylated product which was further confirmed by IR spectroscopy which showed strong absorption at 3743 and 3470 cm^{-1}.

In the dihydroxylation step, although a general behaviour of the ligands for diastereofacial selectivity was studied with respect to the silylated substrate. It was seen that no much difference was observed in the present case although the protecting group was changed. This was first observed on TLC that the ratio of diastereomers remained same which was further confirmed using HPLC where we observed similar results as in the previous case.[3b] Therefore, our concept of hydrogen bonding between OsO_4 and H of NCbz group facilitating *syn* isomer holds good in each case.

With the dihydroxylation product **26a** in hand we proceeded to the cyclisation step where we treated compound **26a** with freshly prepared Raney Ni in methanol with few drops of glacial acetic acid to simultaneously cleave N-N bond and cyclisation to give the aza bicyclic lactam **27a** in 36% yield (over 2 steps). Disappearance of the Cbz proton peaks in the aromatic region ranging from δ 7.49-7.17 confirmed the formation of product. Formation of product was also confirmed using the IR spectroscopy where the ester peak at 1716 cm^{-1} was not observed, instead a new peak at 1690 was observed that corresponds to a 5 membered lactam. The α-hydroxy group of lactam **27a** was then selectively tosylated[13] using tosyl chloride under highly dilute conditons for 48 hrs with triethyl amine as a base in CH_2Cl_2 as a solvent to get monotosylate lactam which without column purification was subjected to $LiAlH_4$ reduction in THF to get (1*S*,8a*R*)-1-hydroxyindolizidine **1** in 43% yield (over 2 steps). Formation of product was also confirmed using the IR spectroscopy due to the absence of lactam peak at 1690 cm^{-1}.



Scheme 6. Synthesis of hydroxylated indolizidine and pyrrolizidine alkaloids

After successful completion of synthesis of 1-hydroxyindolizidine we thought to extrapolate our synthetic strategy to other analogues. Thus, by simply changing the chain length, the synthesis of 1-hydroxy pyrrolizidine **2** was achieved. As illustrated in Scheme 6, synthesis started with mono-tosylated pentane diol **23b** which on IBX oxidation gave aldehyde **24b**, which on sequential α-amination followed by HWE olefination gave the γ-amino-α, β-unsaturated ester **25b** in 60% yield and 98% enantioselectivity.[11] The olefinic compound **25b** was subjected to Sharpless asymmetric dihydroxylation using OsO_4 as an oxidant and $(DHQD)_2AQN$ as a ligand and to get diol **26b**. Diol **26b** was converted to target compound **2** using same set of reactions as described in scheme 6.

3.2.5. Conclusion

In conclusion, we have developed a new protocol employing proline-catalyzed sequential α-amination and Horner–Wadsworth–Emmons olefination approach to the synthesis of 1-

hydroxy indolizidine and pyrrolizidine systems. The present method is easily amenable for the synthesis of a variety of monohydroxy alkaloids.

3.2.6. Experimental section

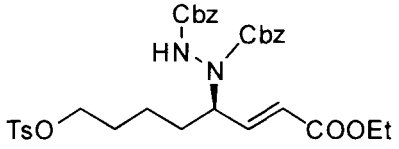
General Procedure for the preparation of aldehydes 24a,b:

To a solution of 1,6-hexanediol (1.0 g, 8.5 mmol) in CH_2Cl_2 (17 mL) was added imidazole (0.58 g, 8.5 mmol) and toluene sulfonyl chloride (1.278 g, 8.5 mmol) at 0 °C and reaction mixture was stirred at room temperature for 12 h. It was quenched with saturated solution of NH_4Cl and extracted with CH_2Cl_2.The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give crude product. Silica gel column chromatography of the crude product using petroleum ether / ethyl acetate (9:1) provided mono tosylated alcohol **23a** as a pale yellow oil.

To a suspension of mono tosylated alcohol **23a** (0.5 g, 2.16 mmol) in ethyl acetate was added IBX (1.21 g, 4.32 mmol) and refluxed (3h) until complete consumption of alcohol. The mixture was cooled to room temperature then filtered through a pad of celite, washing with ethyl acetate. The filtrate was collected and concentrated under reduced pressure to give aldehyde **24a** which was subjected to further reaction without purification.

Using the same procedure as mentioned above, aldehyde **24b** was prepared starting from 1,5-pentanediol .

Dibenzyl (*R*,*E*)-1-(1-ethoxy-1-oxo-8-(tosyloxy)oct-2-en-4-yl)hydrazine-1,2-dicarboxylate (25a):



General procedure for sequential α-amination/ Horner-Wadsworth-Emmons olefination: To a cooled solution of dibenzylazodicarboxylate (DBAD) (0.54 g, 1.81 mmol) and L-proline (0.02 g, 8 mol%) in CH_3CN (34 mL) at 0 °C was added aldehyde **24a** (0.5 g, 2.17 mmol) and the mixture was stirred for 2 h at 0 °C and further for 1 h at 10 °C. This was followed by addition of lithium chloride (0.11 g, 2.7 mmol), triethylphosphonoacetate (0.54

mL, 2.71 mmol) and DBU (0.27 mL, 1.81 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 85:15) of the crude product gave **25a** as a colorless syrupy liquid.

Yield: 0.760 g, 60%

Mol. Formula: $C_{33}H_{38}N_2O_9S$

$[\alpha]_D^{25}$: + 0.35 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 32840, 2296, 1716, 1454, 1238, 1054

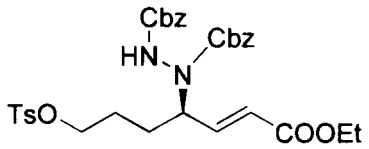
^1H NMR (200 MHz, $CDCl_3$) : δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.34 (s, 12H), 6.80 (dd, *J* = 15.2 Hz, 6.0 Hz, 1H), 6.57 (d, *J* = 15.2 Hz, 1H), 5.17 (s, 4H), 4.23-4.13 (m, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 1.71-1.55 (m, 4H), 1.48-1.38 (m, 2H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 156.5, 156.4, 144.7, 135.5, 129.8, 128.5, 128.4, 128.1, 127.8, 77.0, 70.0, 67.8, 60.6, 30.2, 28.4, 21.9, 21.6, 14.1 ppm.

MS (ESI) : *m/z* 639.22 $(M+H)^+$

HPLC: Kromasil 5-CelluCoat (250 X 4.6cm) (Ethanol: n-Hexane: DEA(1 :99:0.1), flow rate : 1 mL/min 465Psi, λ = 254 nm). Retention time (min):16.625 (major) and 18.150 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 98%.

Dibenzyl (*R*,*E*)-1-(1-ethoxy-1-oxo-7-(tosyloxy)hept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):



Compound **25b** was prepared using the general procedure for sequential α-amination/ Horner-Wadsworth-Emmons olefination starting from aldehyde **24b**.

Yield: 0.724 g, 58%

Mol. Formula: $C_{32}H_{36}N_2O_9S$

$[\alpha]_D^{25}$: + 0.29 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 32844, 2290, 1716, 1546, 1218, 1052

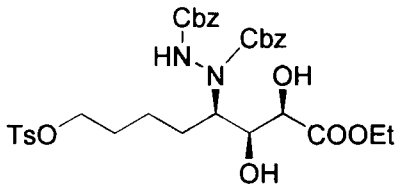
^{1}H NMR (200 MHz, $CDCl_3$) : δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 2.8 Hz, 13H), 6.96 (dd, *J* = 7.1, 15.8 Hz, 1H), 6.00 (d, *J* = 15.8 Hz, 1H), 5.25 (s, 4H), 4.47-3.87 (m, 4H), 2.55 (s, 3H), 1.59 (d, *J* = 6.4 Hz, 2H), 1.49-1.26 (m, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 165.9, 156.6, 155.4, 144.5, 135.4, 132.8, 129.6, 128.3, 128.1, 128.0, 127.9, 127.6, 122.8, 69.9, 68.1, 67.4, 60.4, 30.0, 29.4, 28.2, 21.6, 21.3, 13.9 ppm.

MS (ESI) : *m/z* 647.29 $(M+Na)^+$

HPLC: Kromasil 5-CelluCoat (250 X 4.6cm) (Ethanol: n-Hexane: DEA (1:99:0.1), flow rate : 1 mL/min 465Psi, λ = 254 nm). Retention time (min): 8.82 (major) and 10.09 (minor). The racemic standard was prepared in the same way using *dl*-proline as a catalyst, ee 98%.

Dibenzyl 1-((2*R*,3*S*,4*R*)-1-ethoxy-2,3-dihydroxy-1-oxo-8-(tosyloxy)octan-4-yl)hydrazine-1,2-dicarboxylate (26a):



General procedure for Sharpless asymmetric dihydroxylation: To a mixture of $K_3Fe(CN)_6$ (0.825 g, 2.50 mmol), K_2CO_3 (0.345 g, 2.50 mmol), $(DHQ)_2AQN$ (6.5mg, 1 mol%) in *t*-BuOH/H_2O (1:1, 10 mL) at 0 °C was added osmium tetroxide (0.32 mL, 0.1 M solution in toluene, 0.4 mol%), followed by methane sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the olefin **25a** (0.500 g, 0.79 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (0.5 g). Stirring was continued for additional 15 min and then the solution was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. Silica gel column chromatography purification (R_f = 0.40, EtOAc /petroleum ether, 3:7) of the crude product gave **26a** as a white waxy solid.

Yield: 0.500 g, 95%

Mol. Formula: $C_{33}H_{40}O_{11}N_2S$

$[\alpha]_D^{25}$: + 0.56 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 3743, 3470, 3255, 3031, 2925, 1716, 1683, 1464.

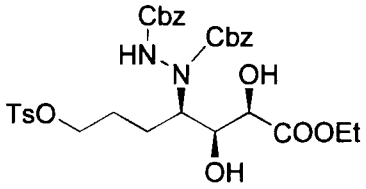
^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.49-7.17 (m, 12H), 5.30-5.02 (m, 4H), 4.92 (brs., 1H), 4.35-4.10 (m, 5H), 4.05-3.89 (m, 2H), 2.43 (s, 3H), 1.97-1.48 (m, 5H), 1.33-1.24 (m, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.0, 172.8, 165.9, 165.8, 156.8, 144.9, 135.6, 133.0, 129.9, 128.6, 128.2, 128.2, 127.9, 77.2, 70.3, 68.6, 67.9, 62.9, 62.8, 61.7, 43.2, 35.0, 33.6, 29.7, 28.6, 21.7, 16.4, 16.3, 14.2, 14.2, 14.1 ppm.

MS (ESI) : *m/z* 655.29 $(M+Na)^+$

HPLC: Kromasil RP-8 (150 X 4.6mm) (methanol : H_2O = 75:25, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 5.87 and 7.51 (dr 98.7:1.3)

Dibenzyl 1-((2*R*,3*S*,4*R*)-1-ethoxy-2,3-dihydroxy-1-oxo-7-(tosyloxy)heptan-4-yl)hydrazine-1,2-dicarboxylate (26b):



Compound **26b** was prepared using the general procedure for Sharpless asymmetric dihydroxylation starting from α,β-unsaturated ester **25b**.

Yield: 0.490 g, 93%

Mol. Formula: $C_{32}H_{38}O_{11}N_2S$

$[\alpha]_D^{25}$: + 0.22 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 3423, 3016, 1732,1545

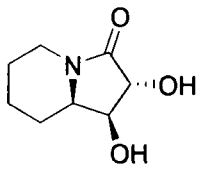
^1H NMR (200 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.46-7.29 (m, 13H), 5.37-5.09 (m, 4H), 4.32-4.13 (m, 6H), 3.12 (s, 3H), 2.45 (s, 3H), 1.38-1.28 (m, 9H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 172.6, 144.8, 129.8, 128.6, 128.1, 127.8, 77.0, 68.5, 62.8, 61.5, 43.2, 35.6, 28.2, 21.5, 14.1 ppm.

MS (ESI) : *m/z* 681.29 $(M+Na)^+$

HPLC: Kromasil RP-8 (150 X 4.6mm) (methanol : H_2O = 75:25, flow rate 1ml/min, (λ = 254 nm). Retention time (min) : 6.41 and 7.48 (dr 95.5:4.5)

(1*S*,2*R*,8a*R*)-1,2-Dihydroxyhexahydroindolizin-3(2*H*)-one (27a):



General procedure of N-N bond cleavage using Raney-Ni: The solution of **27a** (0.5 g, 0.74 mmol) in MeOH (10 mL) and acetic acid (8 drops) was treated with Raney nickel (1.0 g, excess) under H_2 (70 psig) atmosphere for 24 h. The reaction mixture was then filtered over celite and concentrated to give crude amino alcohol which was stirred in EtOH at 55 ^{0}C for 5 h. The reaction mixture was concentrated in vacuo to give crude product. Silica gel column chromatography (petroleum ether: ethyl acetate: 40:60) of the crude product gave lactam **27a** as a colorless liquid.

Yield: 0.045 g, 36%

Mol. Formula: $C_8H_{13}O_3N$

$[\alpha]_D^{25}$: -6.1 (*c* 1.2, MeOH)

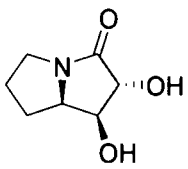
IR ($CHCl_3$, cm^{-1}) : ν^{max} 3280, 2933, 2856, 1690, 1254

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.19-3.95 (m, 3H), 3.72-3.50 (m, 1H), 2.81-2.59 (m, 1H), 1.73 (t, *J* = 14.5 Hz, 2H), 1.57-1.20 (m, 4H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.1, 77.4, 74.4, 60.3, 41.9, 27.0, 26.0, 24.7 ppm.

MS (ESI) : *m/z* 172.20 $(M+H)^+$

(1*S*,2*R*,7a*R*)-1,2-Dihydroxyhexahydro-3*H*-pyrrolizin-3-one (27b):



Compound **27b** was prepared using the general procedure for N-N bond cleavage starting from diol **26b**.

Yield: 0.044 g, 35%

Mol. Formula: $C_7H_{11}NO_3$

$[\alpha]_D^{25}$: -5.83 (*c* 1.0, MeOH)

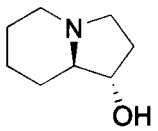
IR ($CHCl_3$, cm^{-1}) : ν^{max} 3352, 2926, 1690, 1462, 1375

^1H NMR (200 MHz, $CDCl_3$) : δ 6.79 (d, *J* = 8.7 Hz, 1 H), 6.21 (dd, *J* = 7.2, 8.5 Hz, 1 H), 6.04 - 5.87 (m, 2 H), 5.61 - 5.46 (m, 2 H), 4.74 - 4.59 (m, 1 H), 4.54 - 4.39 (m, 2 H), 4.09 - 3.89 (m, 1 H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 173.9, 83.3, 80.3, 64.4, 49.1, 43.4, 43.0, 31.1, 26.8

MS (ESI) : *m/z* 158.20 $(M+H)^+$

(1*S*,8a*R*)-Octahydroindolizin-1-ol (1):



General procedure for reduction: To the stirred solution of lactam **27a** (0.04 g, 0.23 mmol) in CH_2Cl_2 (10 mL) was added tosyl chloride (0.044 g, 0.23 mmol) under high dilution conditions and stirred for 48 h under room temperature. After completion of the reaction as observed on TLC the reaction was quenched with water and the organic layer was extracted with CH_2Cl_2 (3 x 20 mL) twice and concentrated in vacuo to give the crude monotosylated product which was further used for subsequent reaction without any purification.

To a stirred suspension of $LiAlH_4$ (0.017 g, 0.46 mmol) in dry THF (1 mL) was added a solution of crude monotosylate product in THF (1 mL), and the mixture was refluxed for 6 h. After being cooled to ambient temperature, the mixture was treated with a saturated aqueous solution of sodium sulfate (2 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography (MeOH: CH_2Cl_2: 2:8) of the crude product gave as a colorless liquid.

Yield: 0.014 g, 43%

Mol. Formula: $C_8H_{15}NO$

$[\alpha]_D^{25}$: -16.2 (*c* 1.0, MeOH)

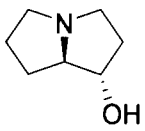
IR ($CHCl_3$, cm^{-1}) : ν^{max} 3420, 3220

^{1}H NMR (500 MHz, CH_3OD) : δ 3.86-3.76 (m, 1H), 3.46 (t, J = 6.6 Hz, 1H), 3.04-2.85 (m, 2H), 2.68-2.55 (m, 1H), 2.45-2.34 (m, 1H), 2.27 (dd, J = 8.1, 10.5 Hz, 1H), 1.83-1.64 (m, 1H), 1.64-1.54 (m, 1H), 1.51-1.38 (m, 2H), 1.28 (t, J = 2.9 Hz, 1H) ppm.

^{13}C NMR (101 MHz, CH_3OD): δ 78.7, 71.1, 59.6, 56.8, 49.2, 43.5, 31.4, 26.3, 24.5 ppm.

MS (ESI) : *m/z* 142.12 $(M+H)^+$

(1*S*,7a*R*)-Hexahydro-1H-pyrrolizin-1-ol (2):



Yield: 0.013 g, 43%

Mol. Formula: $C_7H_{13}NO$

$[\alpha]_D^{25}$: -15.4 (*c* 1.0, MeOH)

IR ($CHCl_3$, cm^{-1}) : ν^{max} 3472, 3150

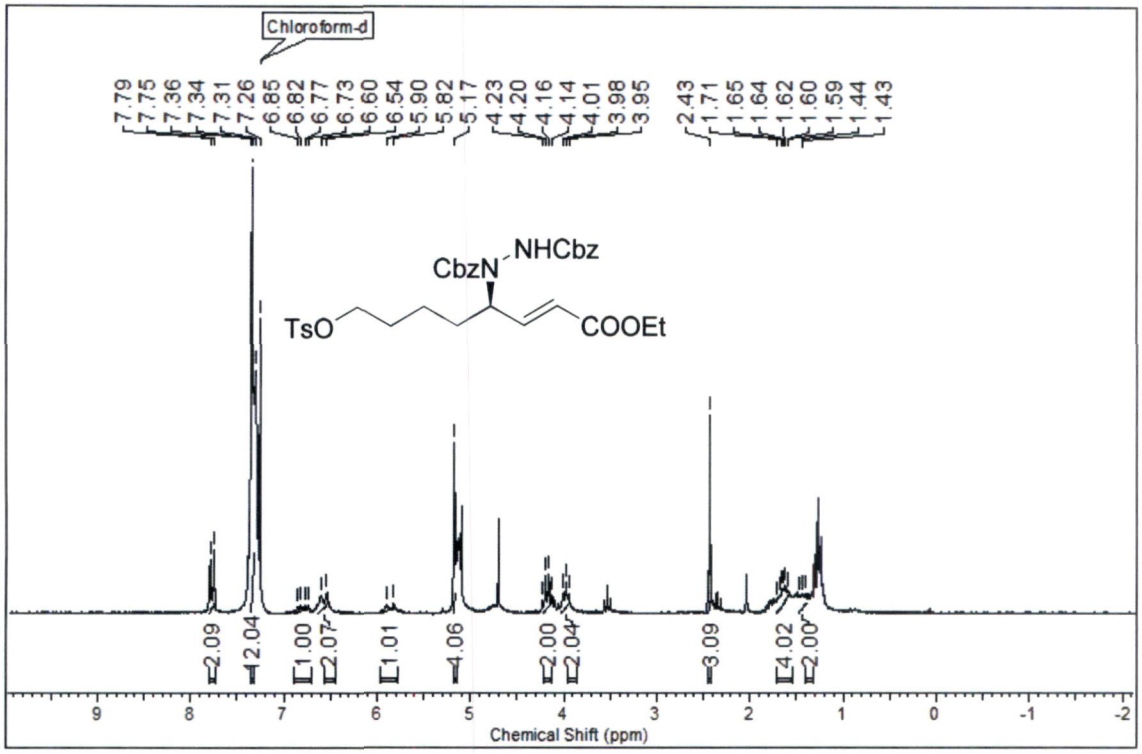
^{1}H NMR (200 MHz, CH_3OD) δ 4.36 (d, J = 8.7 Hz, 1H), 3.78 (dd, J = 7.1, 8.5 Hz, 1H), 3.61-3.45 (m, 2H), 3.16-2.94 (m, 4H), 2.33-1.90 (m, 3H), 1.68-1.40 (m, 1H) ppm.

^{13}C NMR (50 MHz, CH_3OD) : 80.9, 77.6, 60.5, 43.4, 40.8, 31.7, 25.3 ppm.

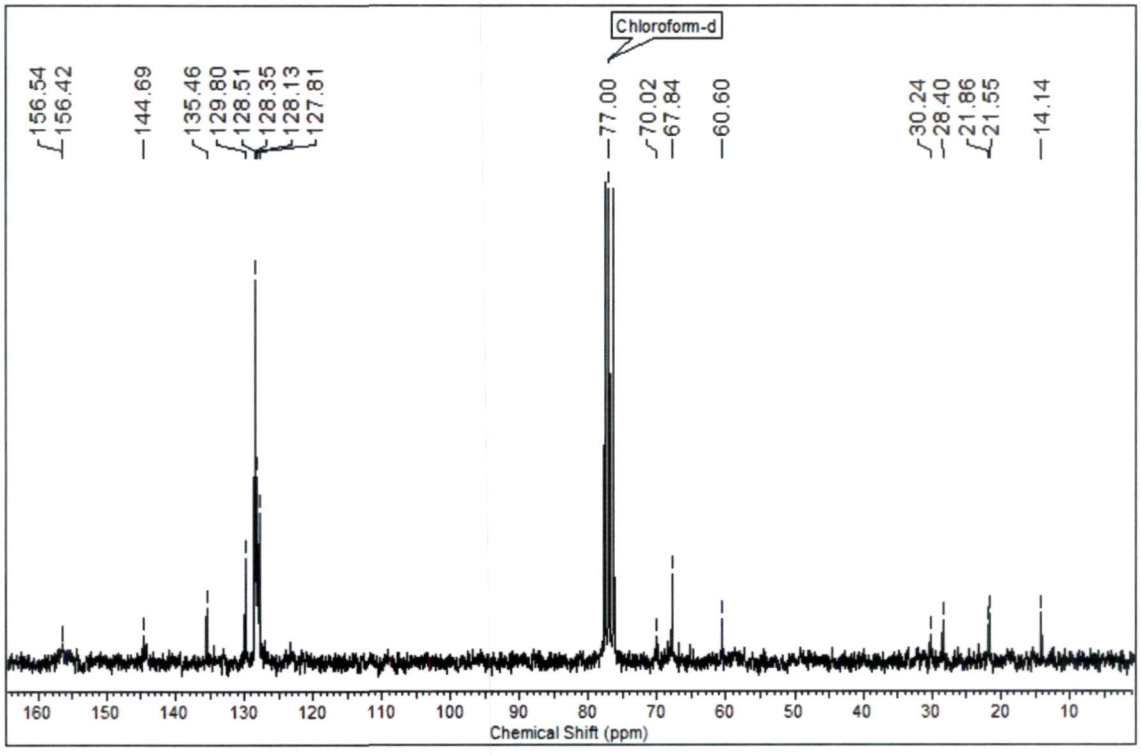
MS (ESI) : *m/z* 128.20 $(M+H)^+$

3.2.7. Spectra

Dibenzyl (*R*,*E*)-1-(1-ethoxy-1-oxo-8-(tosyloxy)oct-2-en-4-yl)hydrazine-1,2-dicarboxylate (25a):

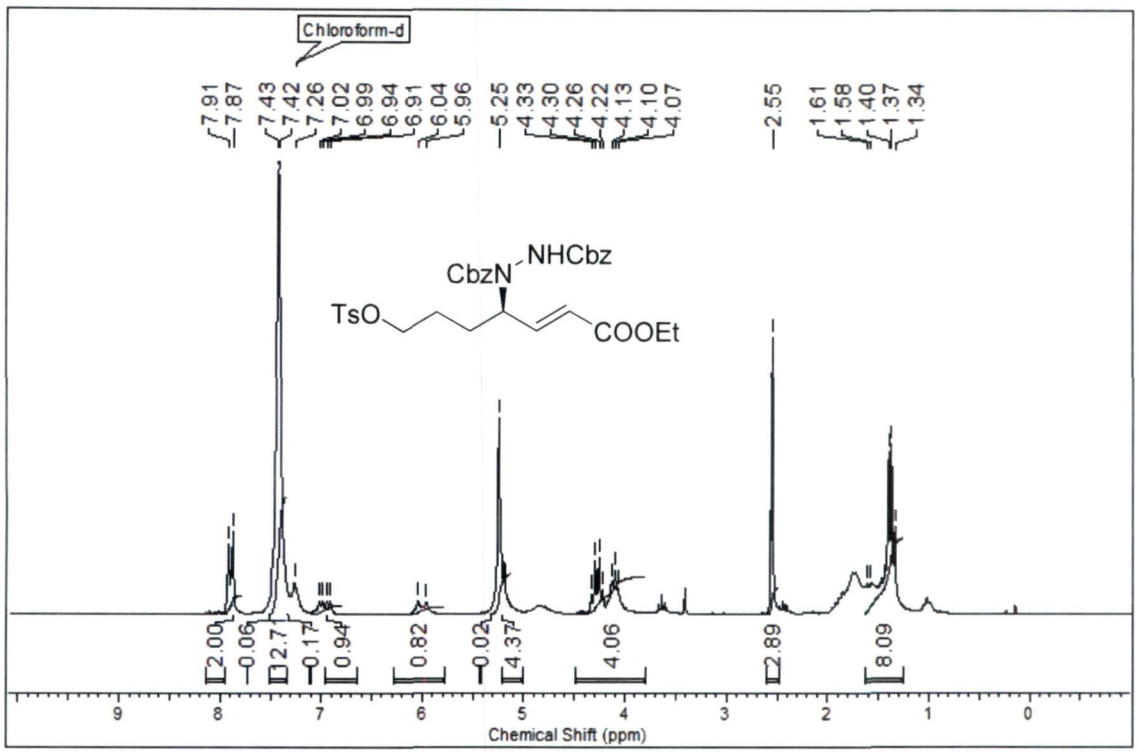


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

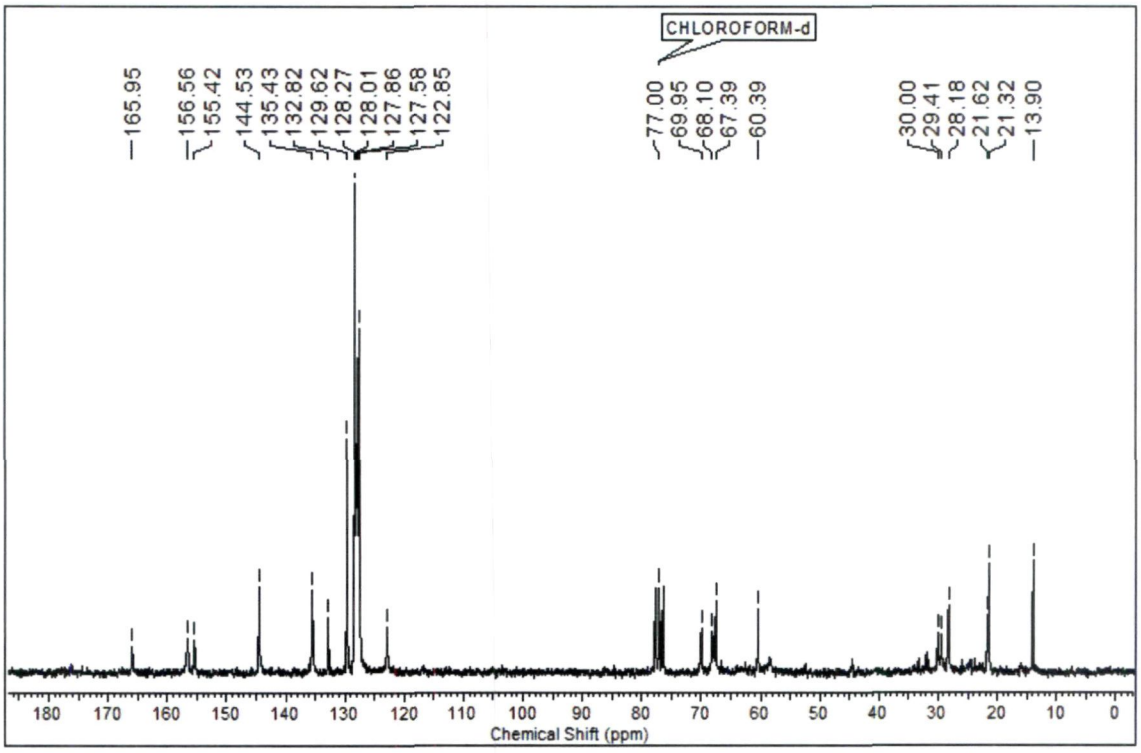


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

Dibenzyl(*R*,*E*)-1-(1-ethoxy-1-oxo-7-(tosyloxy)hept-2-en-4-yl)hydrazine-1,2-dicarboxylate (25b):

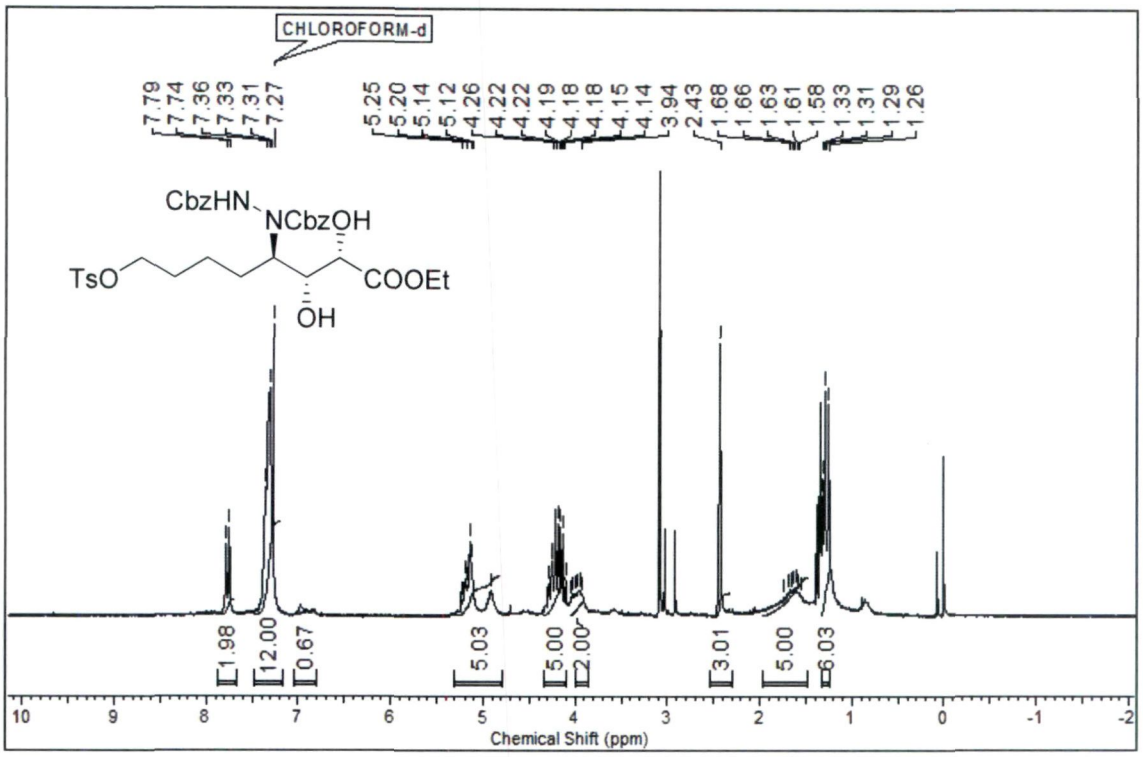


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

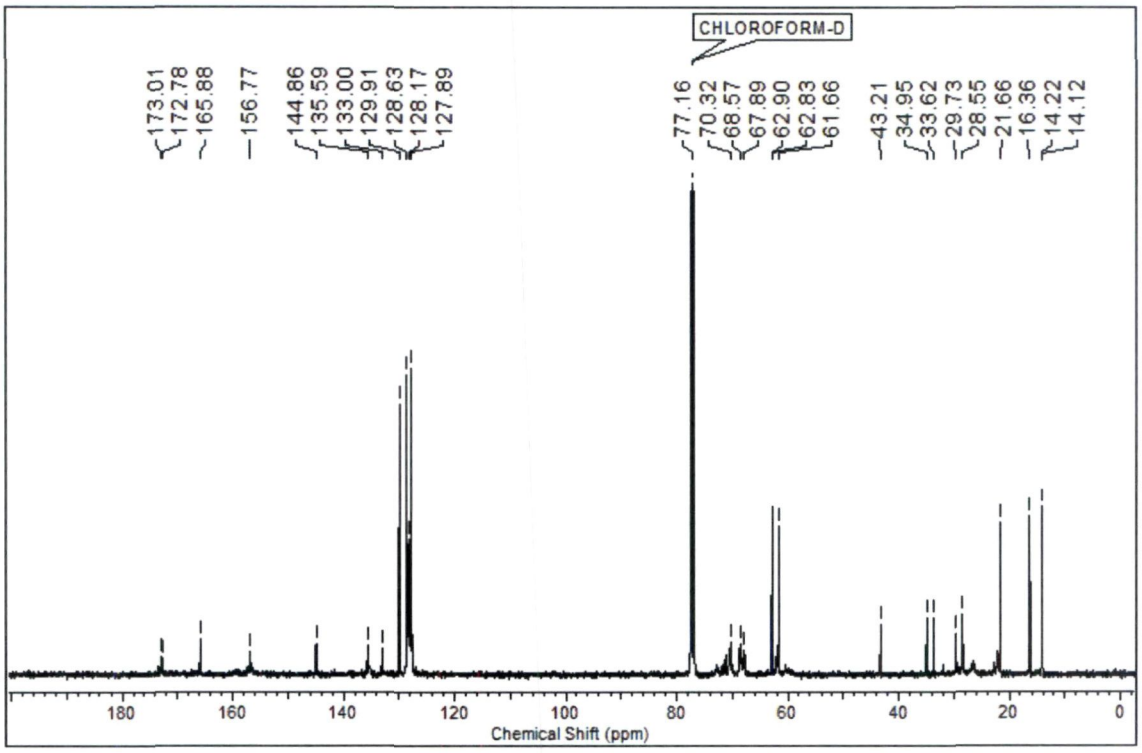


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

Dibenzyl1-((2*R*,3*S*,4*R*)-1-ethoxy-2,3-dihydroxy-1-oxo-8-(tosyloxy)octan-4-yl)hydrazine-1,2-dicarboxylate (26a):

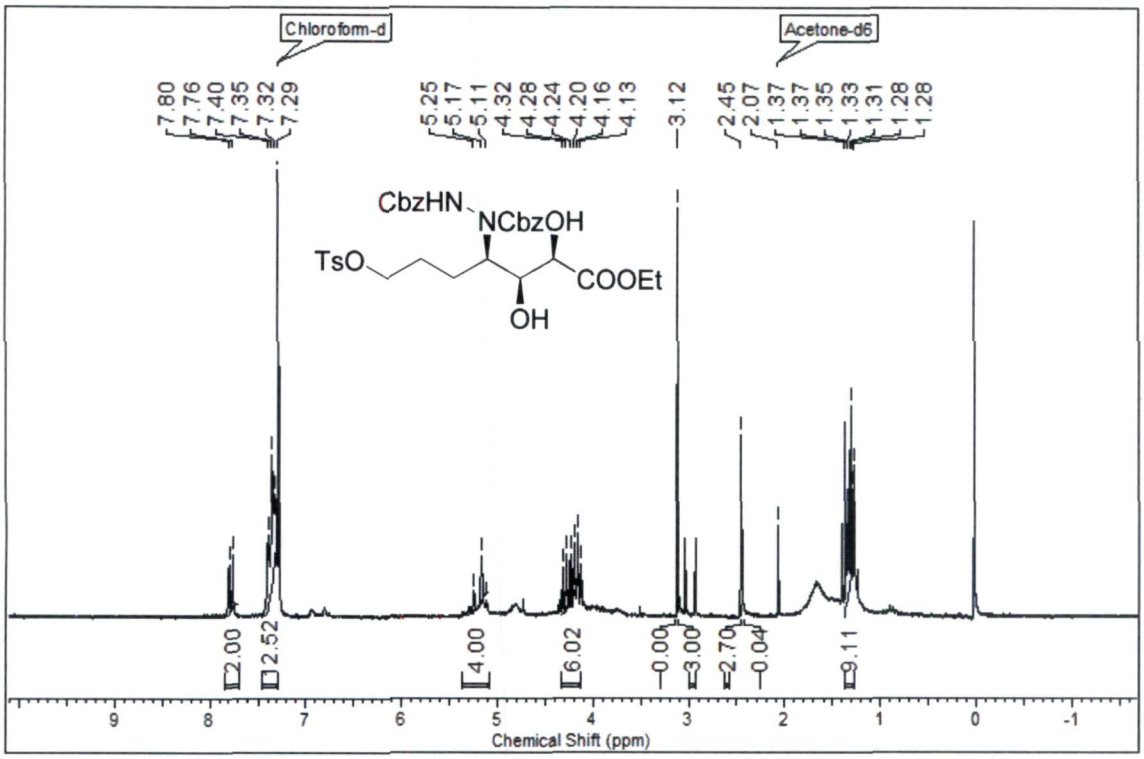


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

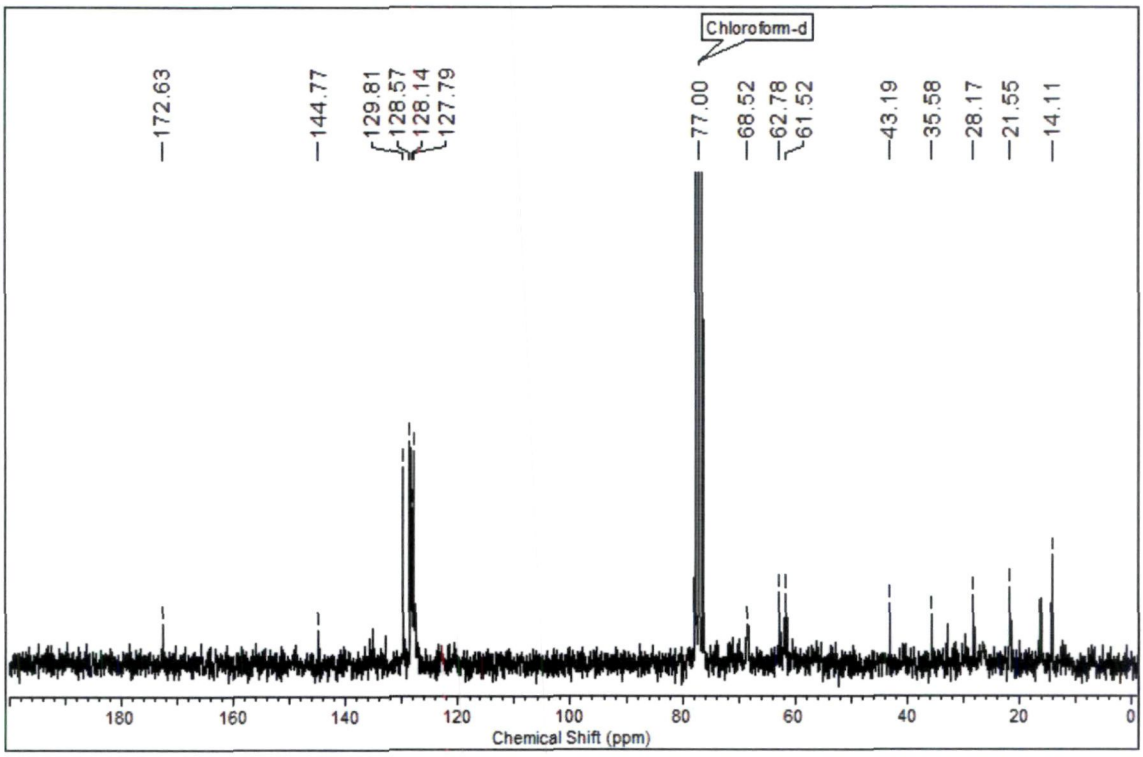


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

Dibenzyl 1-((2*R*,3*S*,4*R*)-1-ethoxy-2,3-dihydroxy-1-oxo-7-(tosyloxy)heptan-4-yl)hydrazine-1,2-dicarboxylate (26b):

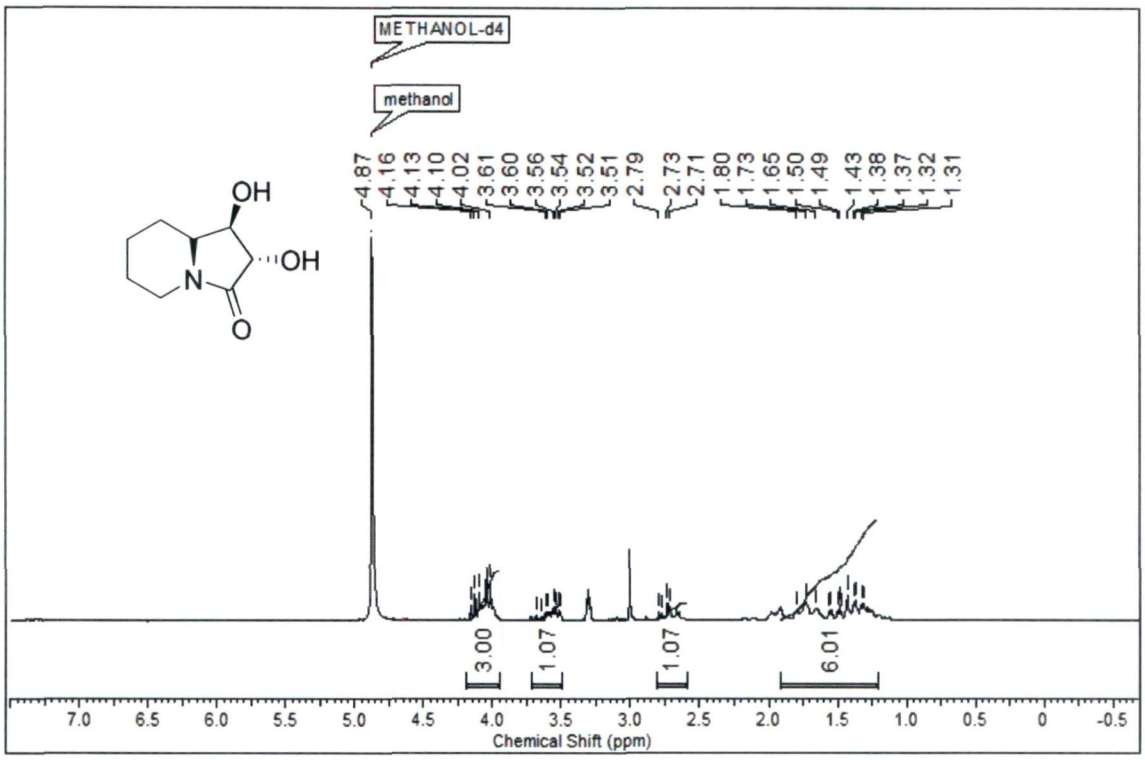


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

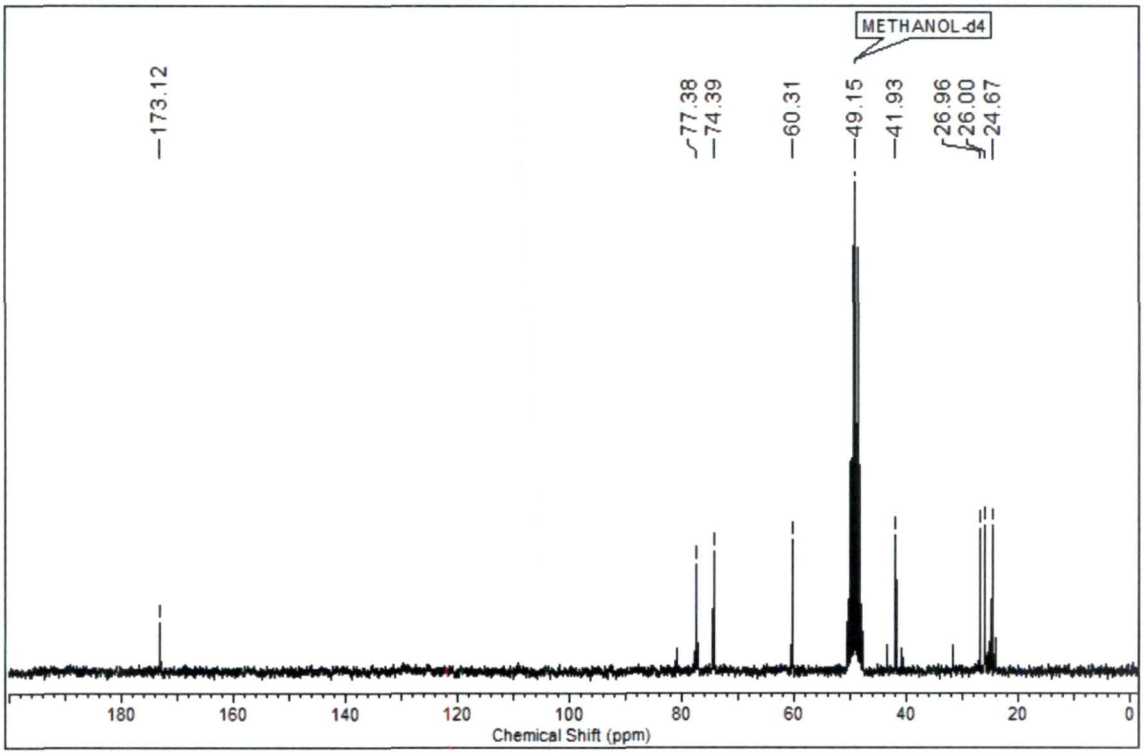


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

(1*S*,2*R*,8a*R*)-1,2-Dihydroxyhexahydroindolizin-3(2*H*)-one (27a):

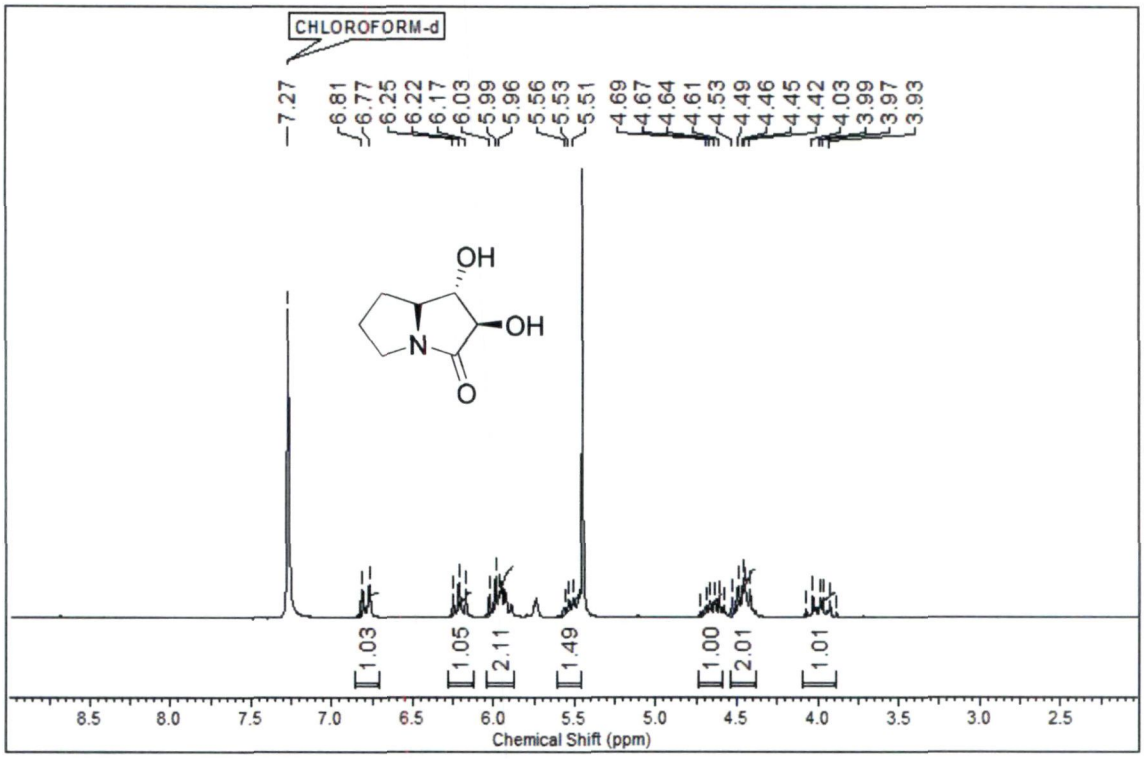


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

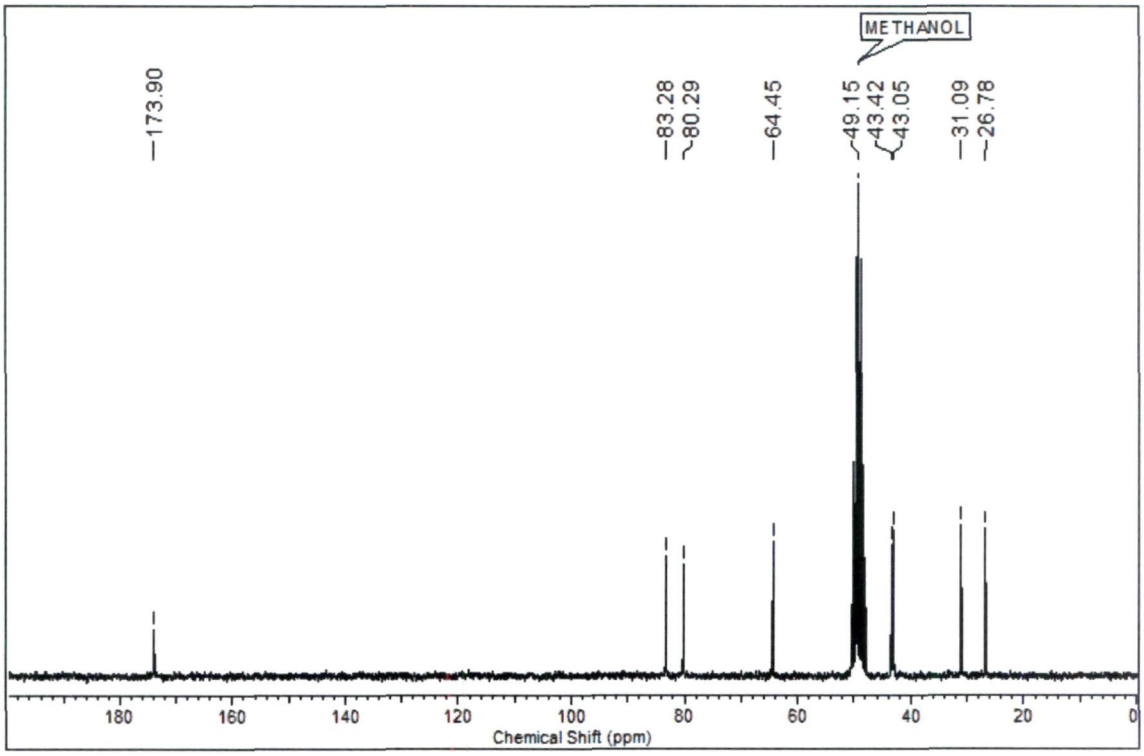


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

(1*S*,2*R*,7a*R*)-1,2-Dihydroxyhexahydro-3H-pyrrolizin-3-one (27b):

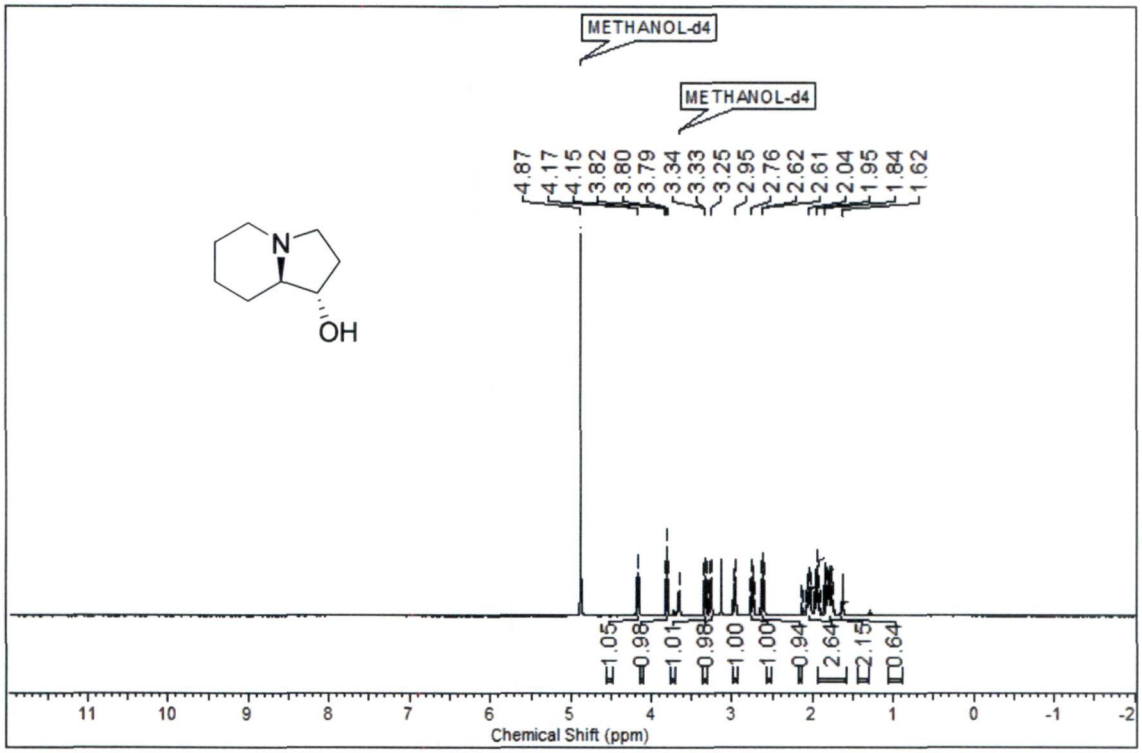


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

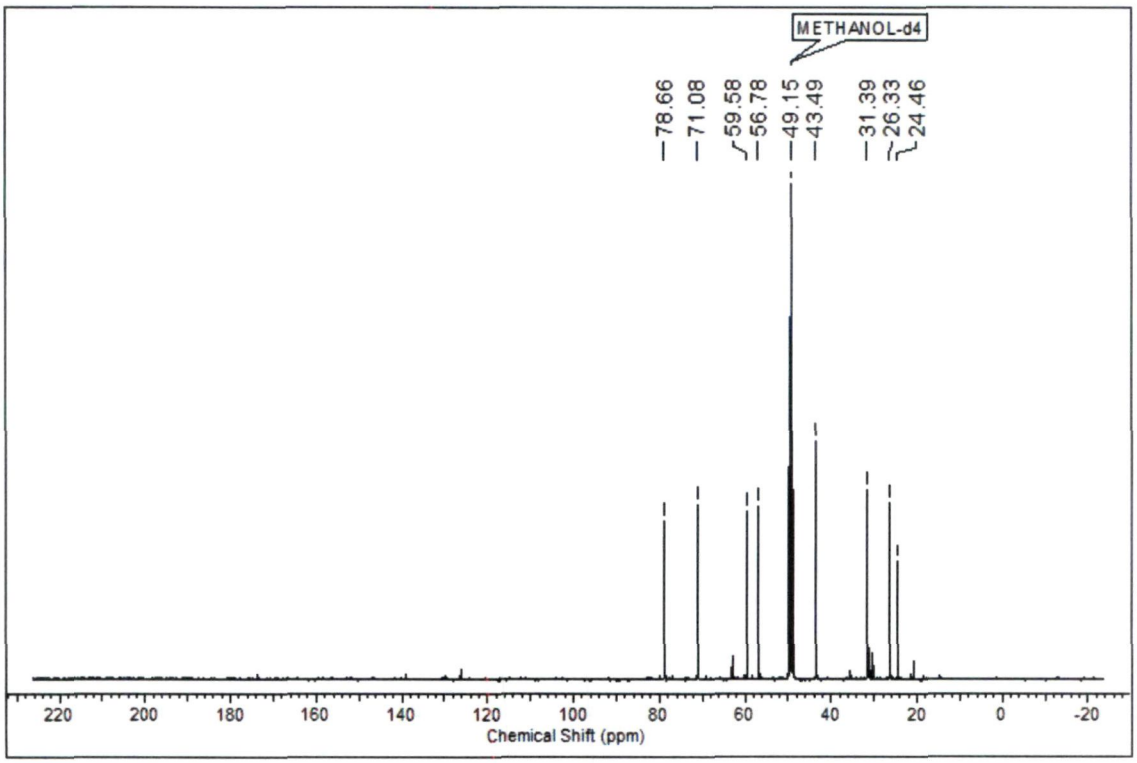


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

(1*S*,8a*R*)-Octahydroindolizin-1-ol (1):

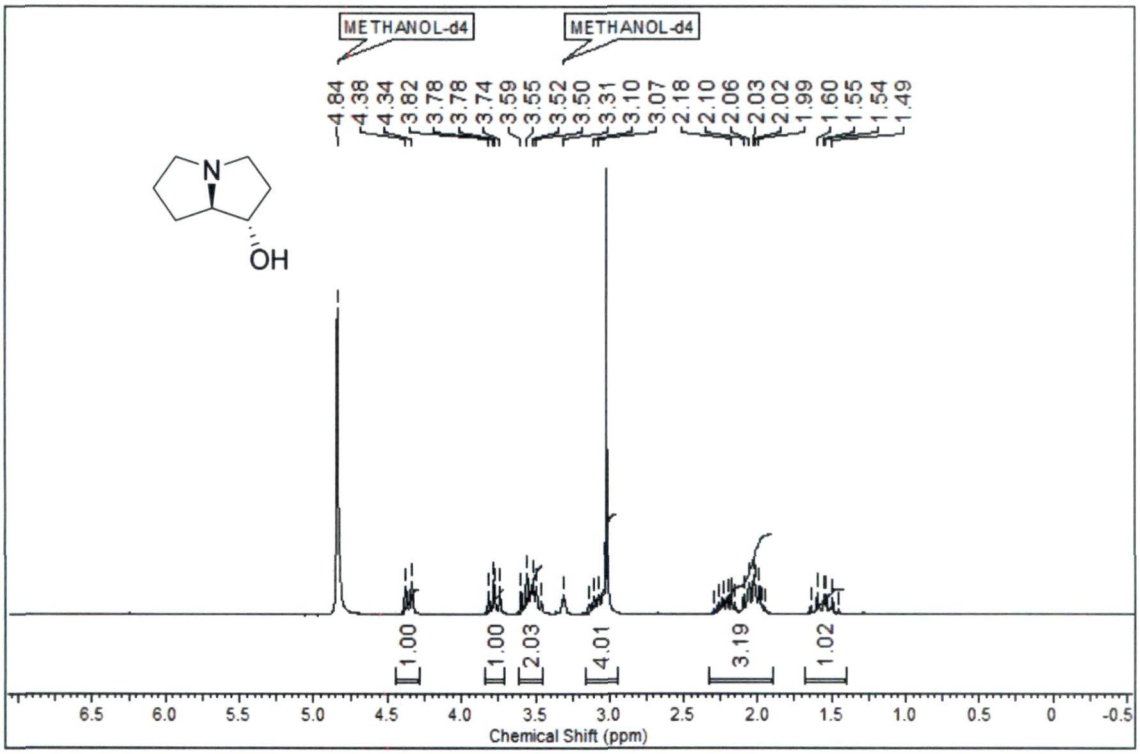


➢ **^{1}H NMR (CH_3OD, 500 MHz)**

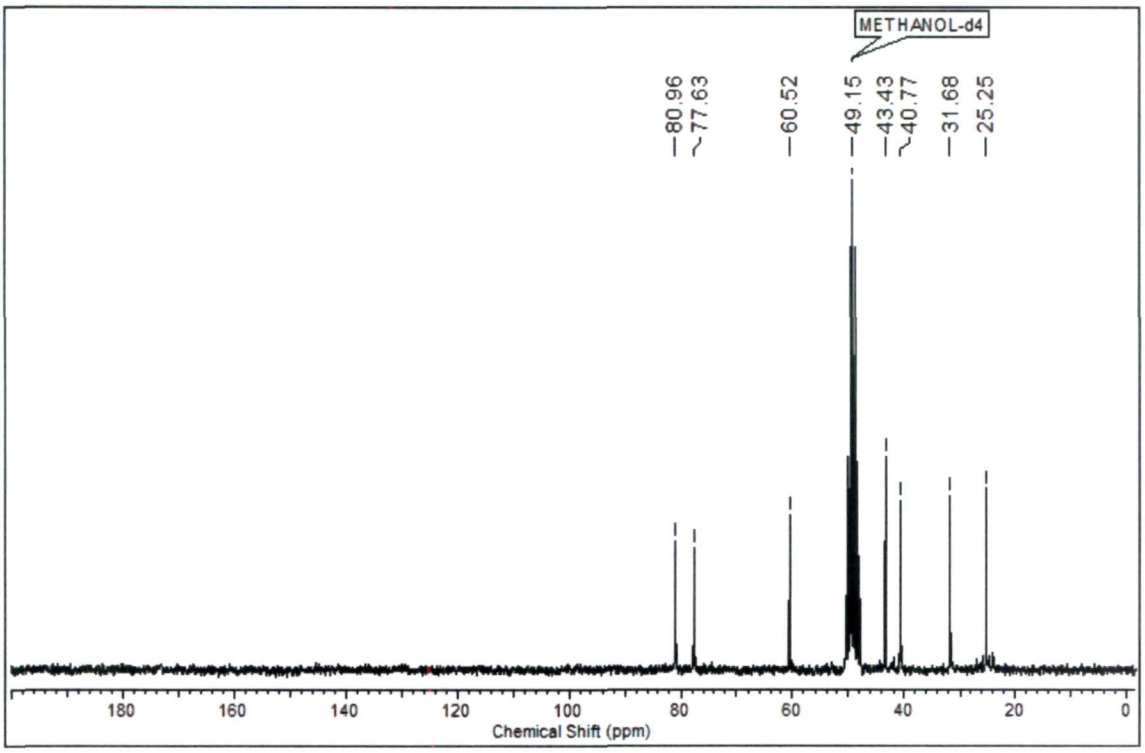


➢ **^{13}C NMR (CH_3OD, 125 MHz)**

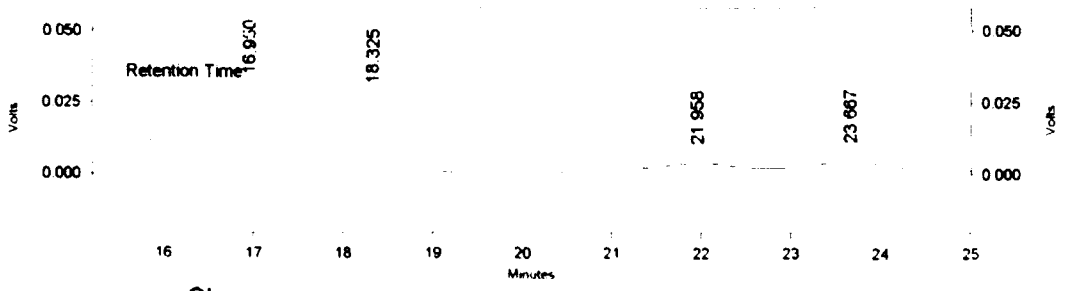
(1*S*,7a*R*)-Hexahydro-1H-pyrrolizin-1-ol (2):

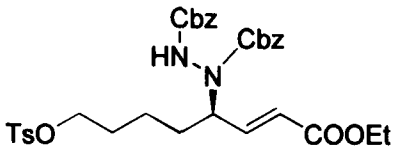


➢ **^{1}H NMR (CH_3OD, 200 MHz)**



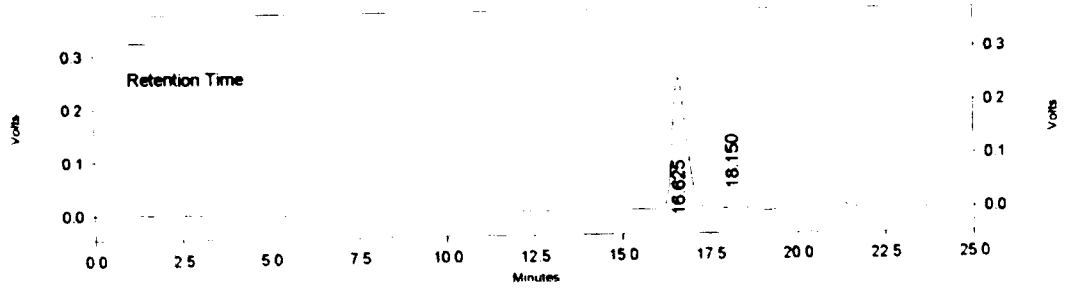
➢ **^{13}C NMR (CH_3OD, 125 MHz)**





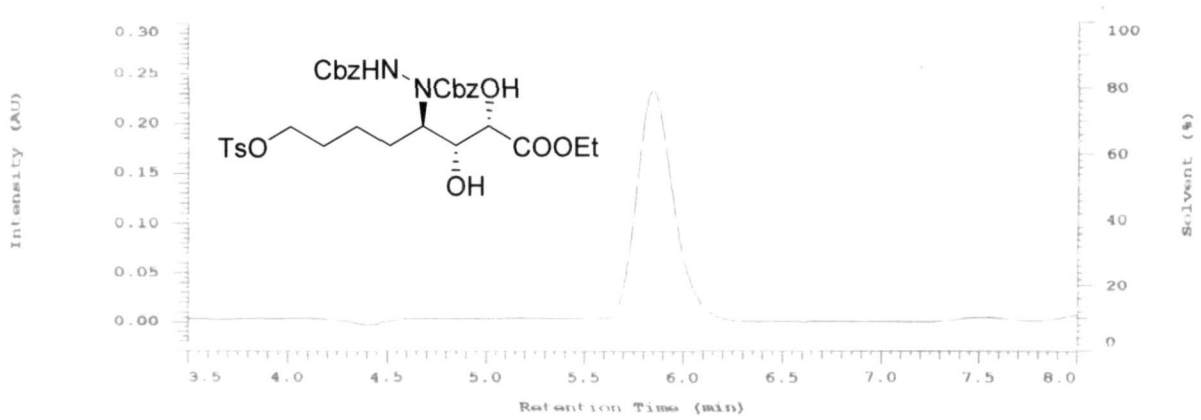
Detector A - 1 (254nm)

Retention Time	C Area	Area %
16.950	572940	45.952
18.325	590504	47.361
21.958	38149	3.060
23.667	45228	3.627
Totals	1246821	100.000

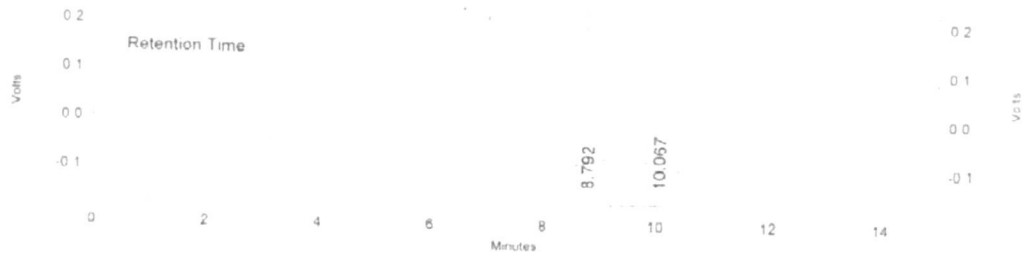


Detector A - 1 (254nm)

Retention Time	C Area	Area %
16.625	4579705	99.483
18.150	23785	0.517
Totals	4603490	100.000

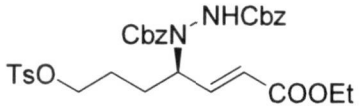


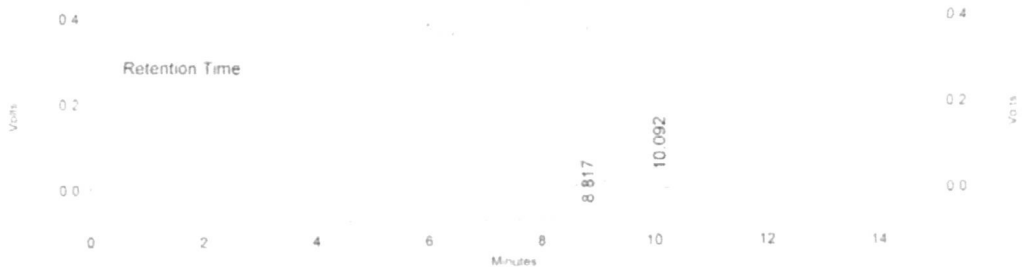
No.	RT	Height	Area	Area %
1	5.85	115115	1488123	98.689
2	7.51	1540	19763	1.311
		116655	1507886	100.000



Detector A - 1 (214nm)

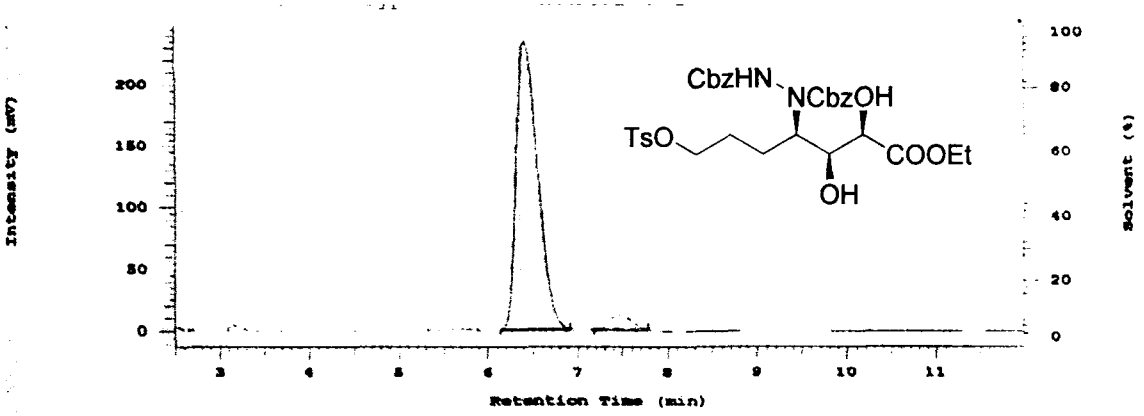
Pk #	Retention Time	Area	Area %
1	8.792	3878568	55.917
2	10.067	3057690	44.083
Totals		6936258	100.000





Detector A - 1 (214nm)

Pk #	Retention Time	Area	Area %
1	8.817	4626206	99.289
2	10.092	33141	0.711
Totals		4659347	100.000



Peak Quantitation: AREA Calculation Method: AREA

No.	RT	Height	Area	Area
1	6.41	235219	3890904	95.306
2	7.48	11768	191646	4.694
		24[illegible]	[illegible]550	100.000

3.2.8. References:

1. (a) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) H. P. Broquist, *Annu. Rev. Nutr.* **1985**, *5*, 391; (c) A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265. (d) J. R. Liddell, *Nat. Prod. Rep.* **2001**, *18*, 441; (e) J. R. Liddell, *Nat. Prod. Rep.* **2000**, *17*, 455.
2. *(a)*V. Jha, P. Kumar, *RSC Adv.* **2014**, *4*, *3238; (b)* V. Jha, P. Kumar, *Synlett* **2014**, *25*, 1089;
3. (a) S. V. Kauloorkar, V. Jha, P. Kumar, *RSC Adv.* **2013**, *3*, 18288.(b) S. V. Kauloorkar, V. Jha, G. jogdand, P. Kumar, *Org. Biomol. Chem.*, **2014**, *12*, 4454.
4. I. A. Kagan, *Front Vet Sci.* **2016**, *3*, 3. and references therein.
5. (a) F. P. Guengerich, J. J. Synder, H. P. Broquist, *Biochemistry* **1973**, *12*, 4264; (b) E. C. Clevenstine, P. Walter, T. M. Harris, H. P. Broquist, *Biochemistry* **1979**, *18*, 3663.
6. (a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139; (b) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191; (c) J. P. Michael, *Nat. Prod. Rep.* **2005**, *22*, 603. and references cited therein.
7. (a) C. M. Harris, T. M. Harris, *Tetrahedron Lett.* **1987**, *28*, 2559; (b) M. P. Sibi, J. W. Christensen, *Tetrahedron Lett.* **1990**, *31*, 5689; (c) T. Shono, N. Kise, T. Tanabe, *J. Org. Chem.* **1988**, *53*, 1364; (d) H. Takahata, Y. Banba, T. Momose, *Tetrahedron: Asymmetry* **1990**, *1*, 763; (e) H. Takahata, T. Takamatsu, T. Yamazaki, *J. Org. Chem.* **1989**, *54*, 4812; (f) H. Takahata, M. Tajima, Y. Banba, T. Momose, *Chem. Pharm. Bull.* **1989**, *37*, 2550; (g) S. Nukui, M. Sodeoka, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 398; (h) D. L. C. Green, J. J. Kiddle, C. M. Thompson, *Tetrahedron* **1995**, *51*, 2865; (i) M. P. Sibi, J. W. Christensen, *J. Org. Chem.* **1999**, *64*, 6434; (j) M. Pourashraf, P. Delair, M. O. Rasmussen, A. E. Greene, *J. Org. Chem.* **2000**, *65*, 6966; (k) R. A. Batey, D. B. MacKay, V. Santhakumar, *J. Am. Chem. Soc.* **1999**, *121*, 5075; (l) A. G. H. Wee, G. –J. Fan, H. M. Bayirinoba, *J. Org. Chem.* **2009**, *74*, 8261; (m) C. F. Klitzke, R. A. Pilli, *Tetrahedron Lett.* **2001**, *42*, 5605; (n) Y. Jagadeesh, B. Chandrasekhar, B. Venkateswara Rao *Tetrahedron:*

Asymmetry **2010**, *21*, 2314; (o) J. -F. Zheng, W. Chen, S. –Y. Huang, J. –L. Ye, P. Huang *Beilstein Journal of Organic Chemistry* **2007**, *3*, 41.

8. (a) T. Shono, N. Kise, T. Tanabe, *J. Org. Chem.* **1988**, *53*, 1364; (b) A. Murray, G. R. Proctor, P. J. Murray, *Tetrahedron* **1996**, *52*, 3757; (c) E. Z. -Machina , T. Castellana, C. B. –Dehouxa, Y. Génisson, *Synthetic Communications* **2015**, 1.
9. (a) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; (b) A. Bogevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jorgensen, *Angew.Chem., Int. Ed.* **2002**, *41*, 1790.
10. (a) A. J. Oelke, S. Kumarn, D. A. Longbottom, S. V. Ley, *Synlett* **2006**, 2548; (b) N. S. Chowdari, D. B. Ramachary, C. F. Barbas III, *Org. Lett.* **2003**, *5*, 1685.
11. S. P. Kotkar, V. B. Chavan, A. Sudalai, *Org. Lett.* **2007**, *9*, 1001.
12. (a) H. Becker and K. B. Sharpless, *Angew. Chem. Int. Ed.* **1996**, *35*, 448; (b) H. C. Kolb, M. S. Van Nieuwenhze and K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
13. P. R. Fleming, K. B. Sharpless *J. Org. Chem.* **1991**,*56*,2869
14. Diastereomeric and enantiomeric excess were determined using HPLC (See experimental section).

Chapter 4

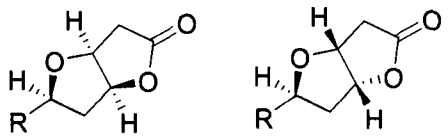
An organocatalytic approach to asymmetric synthesis of Hagen's gland lactones and (-)-Colletallol

A stereocontrolled synthesis of Hagen's gland lactones via iterative proline catalyzed α-aminoxylation and oxa-Michael addition reactions

4.1.1 Introduction

Hagen's glands (**Fig. 1**) earlier known as pygidialglands (located near the abdominal tips) of the braconid wasps, D. Longicaudata (Ashmead), D. Tryoni (Cameron) and Fopius (Biosteres) arisanus, are found to contain fragrance rich lactones. This was first observed by Hagen (1953) and Buckingham (1975) who also put in efforts to study the significance of these secretions in the pest management of fruitfly population control in Hawaii and eastern Queensland, especially against the Queensland fruitfly Bactroceratryoni which is known to be an aggressive pest with a wide host range.[1]

Williams *et al.* suggested the presence of two bicyclic lactones and experimentally characterized these bicyclic lactones by NMR studies using Karplus based calculations.[1c] Kitching *et al.* have determined the absolute stereochemistry of these lactones through synthesis which employs an interesting route that uses 1,3-diol approach followed by $PdCl_2$-catalyzed oxycarbonylation-lactonization reaction.[2a]



1, R = *n*-C_3H_5 **2**, R = *n*-C_3H_5
3, R = *n*-C_5H_{11} **4**, R = *n*-C_5H_{11}

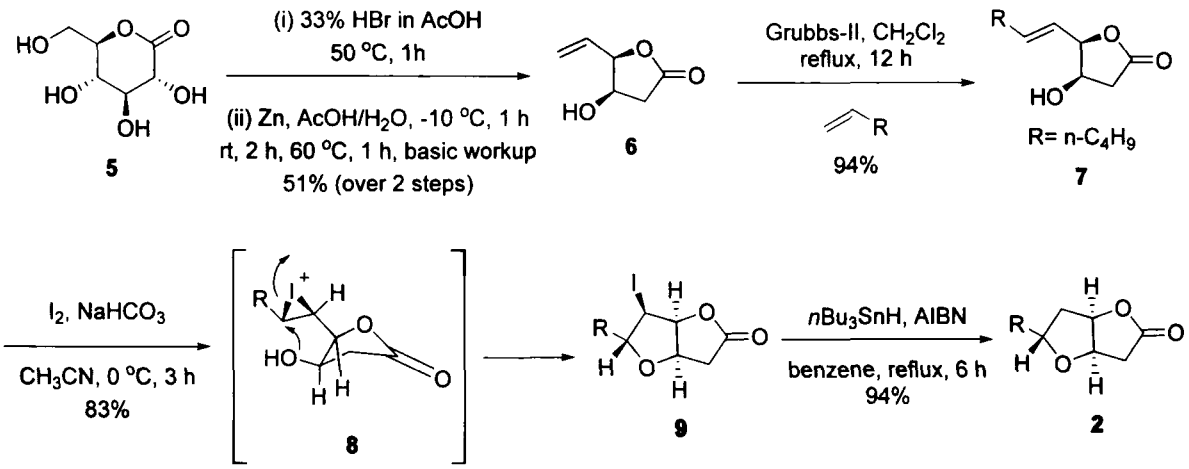
Figure 1. Hagen's gland lactones and their epimers

4.1.2. Review of Literature

Considering their possible role in pest management strategies, several authors have reported the synthesis of these lactones either targeting the natural isomer or its epimer.[3-8] A detailed report of recent syntheses is described below.

Fernandes *et al.* (2012)[7a]

Fernandes and coworkers synthesized the Hagen's gland lactone starting from sugar derivative. D-Glucono-δ-lactone **5** was converted to γ-lactone **6** which on cross metathesis catalyzed by Grubbs second-generation (Grubbs-II) catalyst furnished the lactone **7**. Lactone **7** on iodolactonization followed by cycloetherification gave iodo lactone **9**. This reaction goes via formation of plausible iodonium ion intermediate **8**. Reductive radical-mediated removal of iodine from iodo lactone **9** using n-Bu_3SnH and AIBN provided the Hagen's gland lactone **2**.

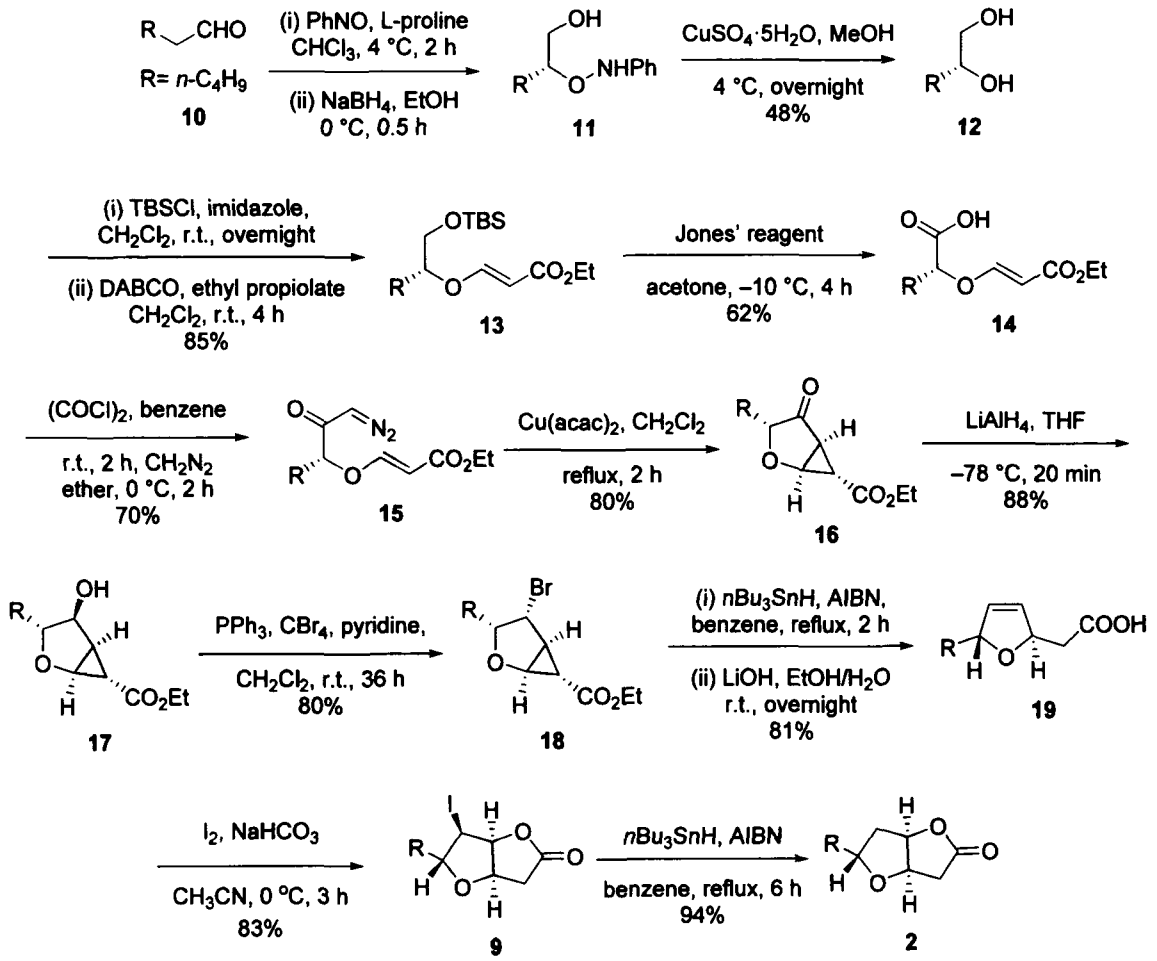


Scheme 1: Synthesis of Hagen's gland lactone (Fernandes method)

Gharpure *et al.* (2011)[8]

Gharpure and coworkers synthesized the Hagen's gland lactone starting from aldehyde hexanal **10** which on enantioselective organocatalytic α-oxyamination in the presence of L-proline followed by reduction gave oxyamino product **11**. Oxyamino compound **11** was treated with $CuSO_4 \cdot 5H_2O$ to obtain diol **12**. Diol **12** on regioselective protection of the

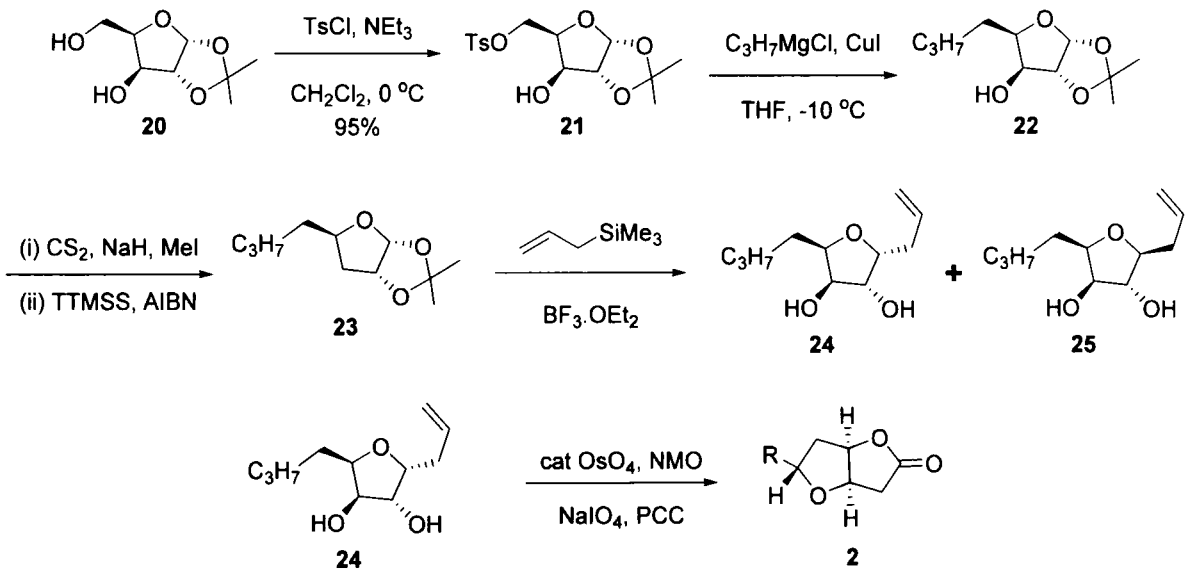
primary hydroxy group followed by reaction with ethyl propiolate furnished vinylogous carbonates **13**. Deprotection of the silyl group and oxidation of the resultant alcohol furnished acid **14**. Reaction of acid **14** with oxalyl chloride followed by treatment with an ethereal solution of diazomethane gave diazo ketones **15**. Decomposition of **15** in the presence of $Cu(acac)_2$ led to donor–acceptor cyclopropane (DAC) **16** through stereo- and regioselective intramolecular cyclopropanation of the vinylogous carbonate moiety. Chemo- and stereoselective reduction of ketones **16** with $LiAlH_4$ in THF at –78 °C furnished alcohol **17** which on Appel reaction condition gave bromo compound **18**. Regioselective cyclopropane ring opening of bromide **18** furnished dihydrofuran derivative **19**. Base-catalyzed hydrolysis of ester **18** followed by iodolactonization of resultant acid **19** yielded iodolactone **9**. Reductive radical-mediated removal of iodine from iodo lactone **9** using n-Bu_3SnH and AIBN provided the Hagen's gland lactone **2**.



Scheme 2: Synthesis of Hagen's gland lactone (Gharpure's method)

Sartillo-Piscil *et al.*(2009)[4]

Sartillo-Piscil and coworkers synthesized the Hagen's gland lactone starting from sugar derivative. Xylofuranose derivative **20** on selective tosylation of the primary hydroxyl group gave tosyl product **21**. The tosyl group of compound **21** was substituted by Grignard reagent in the presence of CuI to get compound **22**. Secondary hydroxyl group of **22** was removed by the use of the Barton–McCombie deoxygenation method affording compound **23**. Compound **23** on C-glycosylation reaction with allyltrimethylsilane gave a distereoisomeric mixture of tetrahydrofurans **24** and **25** in which the 1,4-*trans* stereoisomer **24** was major product. Finally, on sequential dihydroxylation–dehomologation–oxidation procedure, Hagen's gland lactone **2** was obtained.



Scheme 3: Synthesis of Hagen's gland lactone (Sartillo-Piscil's method)

2.1.3. Present work

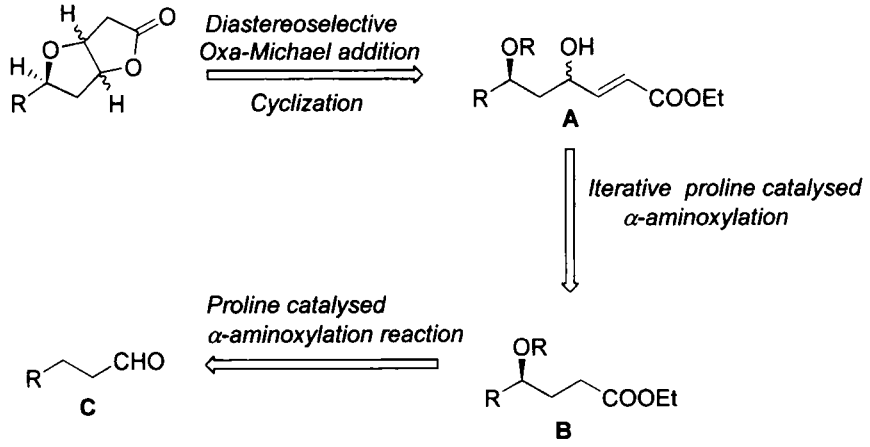
Objective

During last decade, there has been growing interest in the use of small organic molecules to catalyze reactions in a stereoselective manner in organic synthesis. Proline is among the most successful secondary amine based organocatalyst which has been widely employed in several organic transformations.[9]

As a part of our research interest in developing new methodologies and their subsequent application to bioactive compounds, [10] we have recently developed an iterative approach to enantiopure synthesis of *syn* and *anti*-1,3-polyols based on proline catalyzed sequential α-aminoxylation, followed by Horner-Wadsworth- Emmons olefination of aldehydes at ambient temperature.[11a] This method has several advantages over the most widely used method to prepare 1,3-polyols in an iterative fashion. We have earlier reported the synthesis of various lactones using 1,3-polyol approach.[11b,c] However the construction of bridged frameworks containing THF ring systems using the same remains unexplored. We therefore considered application of this methodology along with a highly diastereoselective oxa-Michael addition reaction in the efficient synthesis of substituted tetrahydrofuro[3,2-b]furan-2(3*H*)-one derivatives (Hagen's gland lactones).

4.1.4 Results and discussion

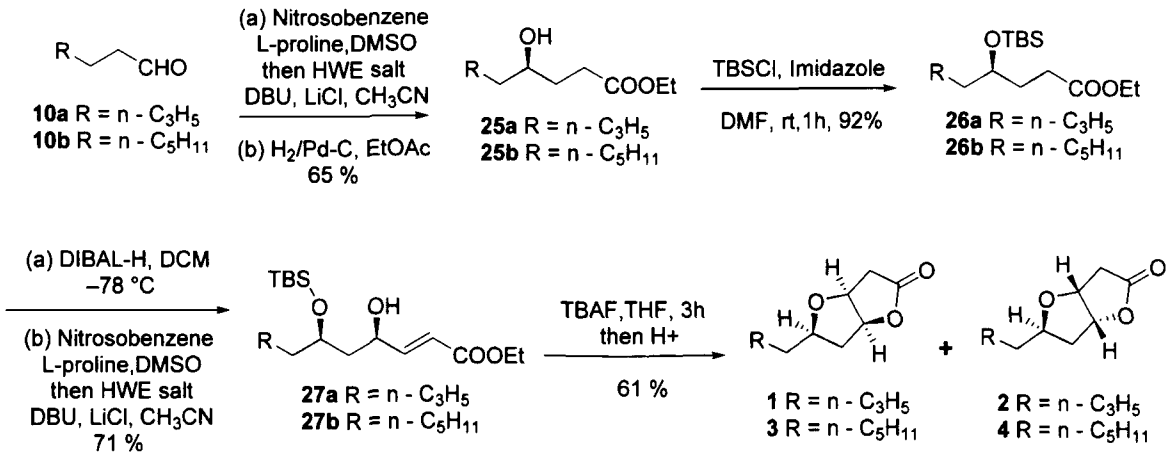
As per the retrosynthetic scheme as delineated in **scheme 4**, the Hagen's gland lactones could be synthesized from the skipped 1,3-diol fragment **A**. We envisioned that **A** could be derived from γ–hydroxy ester moiety **B**, a common intermediate which in turn could be obtained via iterative sequential α-aminoxylation and Horner-Wadsworth-Emmons olefination of aldehyde **C**.



Scheme 4. Retrosynthetic route to the synthesis of Hagen's gland lactones

As shown in **scheme 5**, the synthesis of the target lactones commenced with the commercially available hexanal **10a** which on sequential α-aminoxylation using nitroso

benzene as the oxygen source and L-proline as catalyst and subsequent HWE olefination using triethylphosphonoacetate, followed by hydrogenation using a catalytic amount of Pd/C, furnished the γ–hydroxy ester **25a**. Thus, in two steps and one column purification **25a** was obtained in 65% yield and 94% ee.[11] Protection of the free hydroxyl group as its TBS ether gave **26a** in 92% yield. Disappearance of peak at 3432 cm^{-1} in IR spectrum confirmed the formation of **26a**. The TBS protected hydroxyester **26a** was then reduced using DIBAL-H in toluene (1.0 M) in CH_2Cl_2 as a solvent at -78 °C to furnish an aldehyde. Crude aldehyde was further subjected to α-aminoxylation reaction using L-proline as a catalyst followed by HWE-olefination to yield compound **27a** in good diastereomeric excess (dr ratio 95:5) determined using HPLC.[12] The IR spectrum of **27a** showed the ester carbonyl absorption at 1712 cm^{-1}. With *syn*-1,3-diol **27a** in hand we proceeded to the synthesis of Hagen's gland lactone using oxa-Michael addition which was triggered through the fluoride-mediated cleavage of a silyl protecting group using TBAF in THF followed by lactonisation with catalytic amount of HCl (pH~3 in toluene). At this stage we could observe the formation of two products **1** & **2** (ratio 5:1).[13] The stereochemistry of both the products was confirmed using detailed 1D and 2D-NMR techniques.



Scheme 5. Synthesis of Hagen's gland Lactones

Taking into consideration this observation we considered it worthwhile to study the stereochemistry of both the products which was confirmed using detailed 1D and 2D-NMR techniques.

In NOESY analysis of the compound **1**, proton H_{3a} shows nOe correlation with proton H_{6a} indicating syn stereochemistry at the bridgehead of the substituted tetrahydrofuro[3,2-b]furan-2(3H)-one. H_{3a} also shows nOe correlation with proton H_5, which confirms the *syn* relative stereochemistry between these three protons. Since the methylene protons $H_{6\alpha}$ and $H_{6\beta}$ resonated at different chemical shifts; the above results are also confirmed from the nOe of the $H_{6\alpha}$ and $H_{6\beta}$ with the H_5 and $H_{6\alpha}$. The $H_{6\alpha}$ resonating at δ 2.41 ppm showed nOe correlations with H_5 as well as with $H_{6\alpha}$ confirming the *syn* relative stereochemistry between these three protons. While the other methylene proton ($H_{6\beta}$) does not show nOe correlations either to H_5 or with $H_{6\alpha}$ confirming the *syn* relative stereochemistry between these three protons. While the other methylene proton ($H_{6\beta}$) does not show nOe correlations either to H_5 or with $H_{6\alpha}$ indicating anti relative orientation with the H_5 and $H_{6\alpha}$ (**Figure 2**).

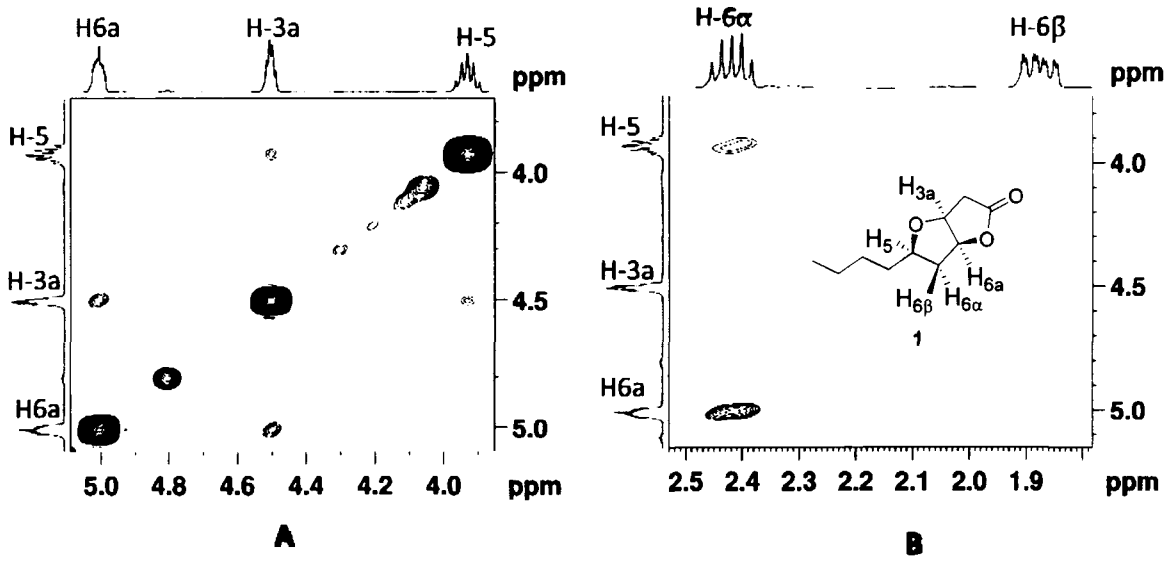


Figure 2: ^{1}H-^{1}H NOESY spectra of the compound **1** (400 MHz, $CDCl_3$, 298 ^{0}K)

Although the spectra of both the compounds **1** & **2** were quite similar, they showed significant differences in the chemical shift values especially of the methine protons. In case of compound **2** among the two methylene groups of the substituted tetrahydrofuro[3.2-b]furan-2(3H)-one, both the methylene show different chemical shifts for the individual proton, the methylene (H_6) resonating at δ2.37 and 1.66 ppm shows

COSY correlation with two methine protons resonating at δ 4.07 and δ 5.11 ppm indicating that this methylene is from the furyl ring.

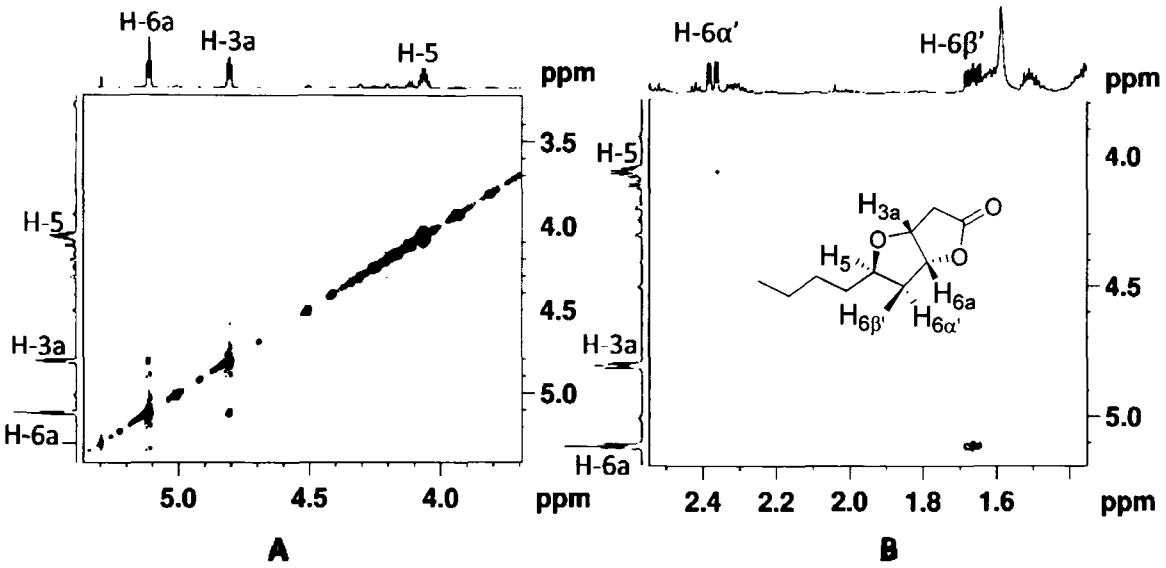


Figure 3: ^{1}H-^{1}H NOESY spectra of the compound **2** (700 MHz, $CDCl_3$, 298 ^{0}K)

As it can be seen from **Figure 3**, the H_5 proton shows nOe correlation with δ 2.37 ppm ($H_{6\alpha'}$) while H_{6a} shows nOe correlation with δ 1.66 ppm ($H_{6\beta'}$). These results show that the H_{6a} and H_5 methine protons show nOe correlation with different protons of the furyl methylene indicating anti relative stereochemistry between H_5 and H_{6a}. In addition, H_{6a} also shows nOe correlation with H_{3a} indicating *syn* stereochemistry at the bridgehead of the substituted tetrahydrofuro[3,2-b]furan-2(3H)-one. The above results are also evaluated from the fact that none of the protons among H_{3a} and H_{6a} shows nOe correlation with H_5 confirming the anti-relative stereochemistry of H_5 with the H_{6a} and H_{3a} as shown in the pictorial representation in **Figure 4**.

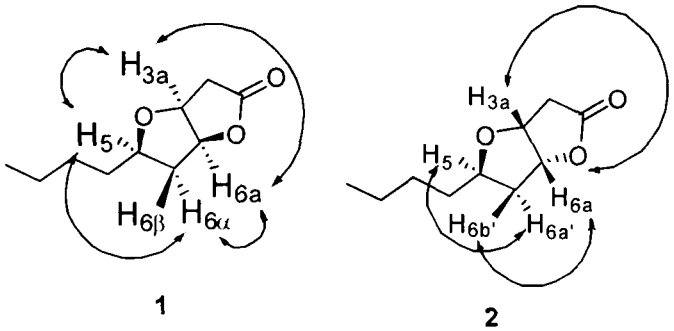
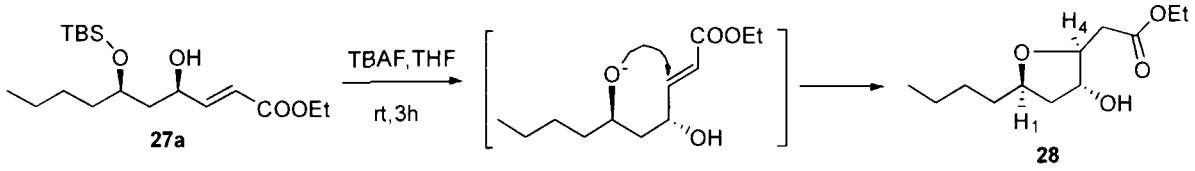


Figure 4: Pictorial representation of both *cis* and *trans* nOe correlations

This result motivated us to study the stereoselection of both oxa-Michael and cyclization reactions very closely. The reproducibility of the strategy and high yielding steps efficiently allowed us to quickly synthesize 1,3-*syn* diol compound **27a** which was subjected to simultaneous desilylation/oxa-Michael reaction. Instead of going further for cyclization at this stage, we quenched the reaction mixture using saturated ammonium chloride solution to get the oxa-Michael product **28** (scheme 3). Preliminary examination using Thin Layer chromatography showed the presence of only one product. ^{1}H and ^{13}C NMR did not show the formation of other diastereomer and revealed that the oxa-Michael addition reaction proceeded in a highly diastereoselective manner. The stereochemistry of compound **28** was confirmed using detailed 1D and 2D NMR techniques.



Scheme 6: Diastereoselective oxa-Michael addition reaction of **27a**

It was observed that in compound **28**, H_4 and H_1 show nOe correlations indicating syn relative stereochemistry[14] while none of them shows nOe correlations with H_3 indicating anti relative stereochemistry with H_3 as shown in **Figure 5**. The relative stereochemistry among H_1 with H_3 was further confirmed by their nOe correlations with methylene protons (H_2 & H_5). It was found that H_1 shows nOe correlations only with H_2 while H_3 shows nOe correlations only with H_5 indicating anti relative stereochemistry between H_1 and H_3 as shown in the pictorial representation in **Figure 7**.

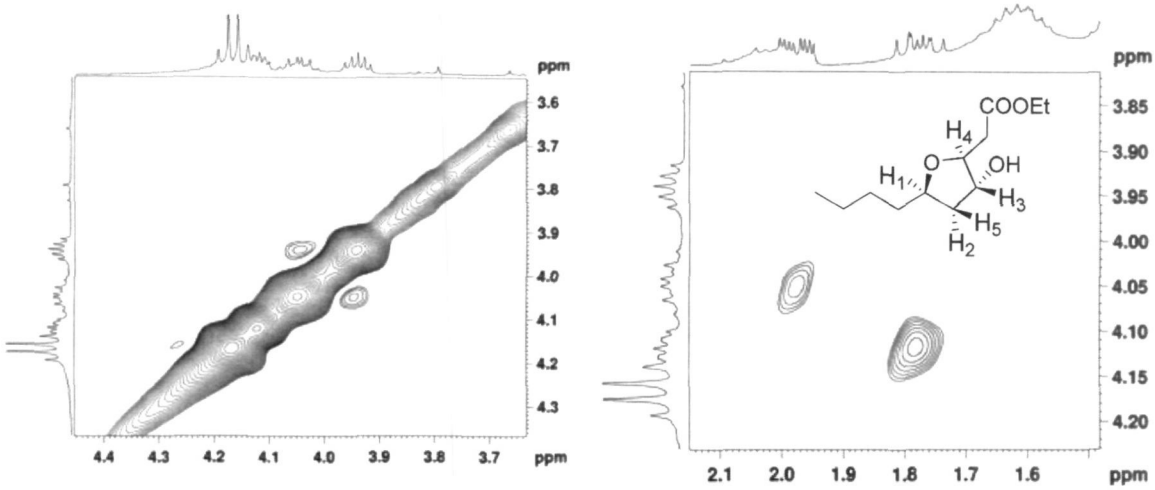
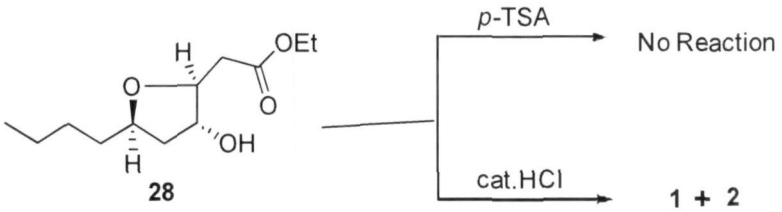


Figure 5: ^{1}H-^{1}H NOESY spectra of the compound **28** (400 MHz, $CDCl_3$, 298 ^{o}K)

To check the feasibility of cyclization of **28** without epimerization, we carried out reaction using *p*-TSA in toluene both at room temperature and under reflux conditions. As anticipated, the cyclization reaction proved to be a total failure as it gave only the starting material back (**scheme 7**). However, when compound **28** was treated with catalytic amount of HCl, it afforded the diastereomeric mixture of bicyclic compounds **1** & **2** in the ratio 5:1 respectively.

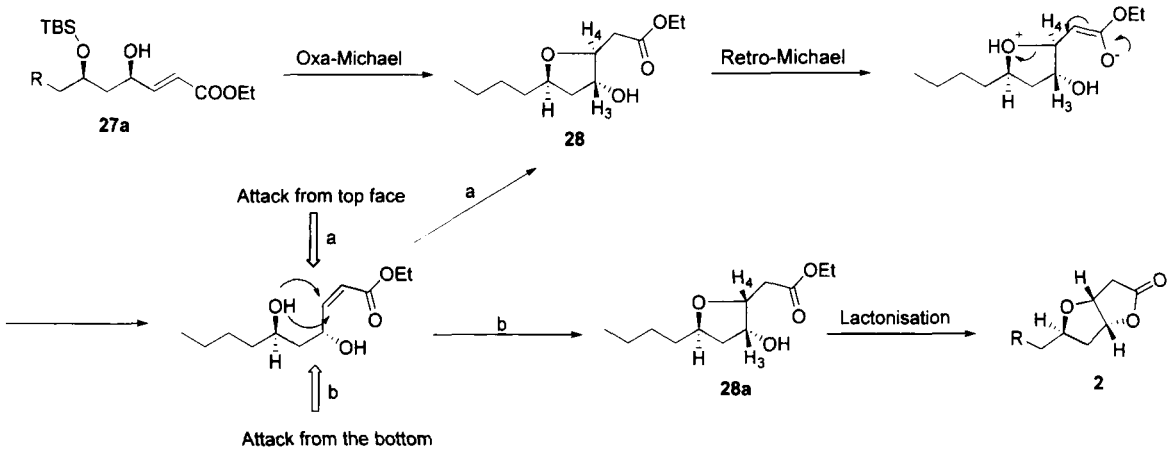


Scheme 7: Lactonization reaction

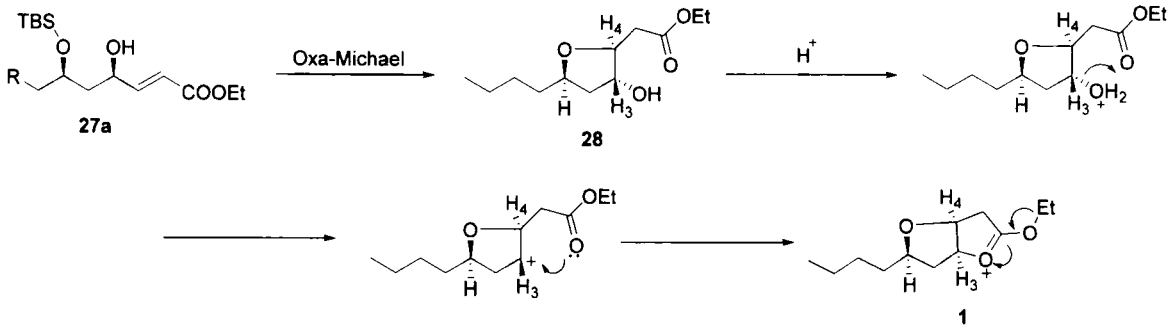
The possible reason for the formation of mixture of diastereomers in the cyclization step could be attributed to the racemization of either of the two protons (H_3 or H_4) in the presence of HCl (P^{H}~3) under reflux conditions, leading to cyclized products **1** & **2** with both the bridged protons *syn* to each other.

The formation of both the products may be explained individually on the basis of the acidic medium present. Compound **2** is found to be a major compound and compound **1** as a minor product in the ratio 5:1 respectively. The major product **2** ie.. epimer of Hagen's gland lactone can be visualized to have formed via a retro-Michael reaction where a consequent ring opening occurs as a result of protonation of the oxygen atom of the THF ring leading to the formation of an open chain product. This open chain product now contains a planar sp^2 olefin where the free hydroxyl group is now free to attack the double bond from either the top of the plane which may give back starting material or may approach from the bottom of the sp^2 plane to give compound **28a** that could easily undergo lactonisation to give **2.**

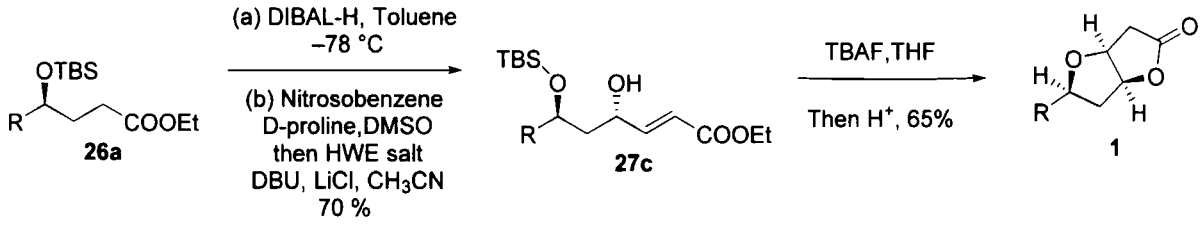
Plausible mechanism for the formation of 2:



Whereas in case of compound **1** the reaction proceeds via a carbocation intermediate that is formed through the protonation of the free hydroxyl group. The carbonyl group of the ester could then approach the carbocation in a way that the cis fusion of the five membered ring is maintained, leading to the formation of **1.** However since compound **1** is obtained as minor product, it can be concluded that the reaction proceeds predominantly via a retro Michael approach **(Scheme 9)**.

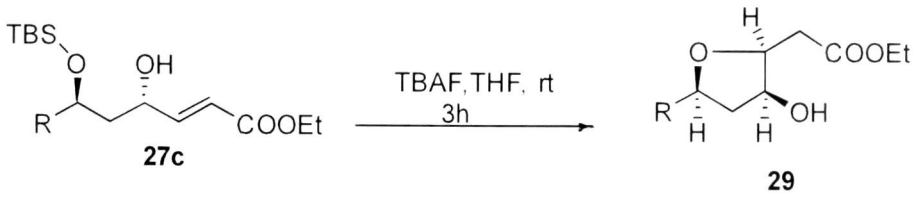


In order to rationalise our findings, we planned to test the devised strategy by synthesizing 1,3-anti diol as an intermediate. For this purpose, we started with previously synthesized protected γ-hydroxy ester **26a** which was reduced using DIBAL-H in toluene at -78 °C to furnish corresponding aldehyde. Crude aldehyde was further subjected to α-aminoxylation/HWE olefination reaction using D-proline as a catalyst to obtain 1,3-anti diol **27c** with an excellent dr ratio (97:3).[13] To test the formation of diastereomeric mixture, one-pot oxa-Michael/ lactonisation was performed on the diol **27c**. In this case we observed the formation of only one product **1** as characterised by ^{13}C NMR which was an entirely different result when compared to the *syn*-diol product (**Scheme 8**).



Scheme 8: Synthesis of epi-Hagen's gland Lactone

This observation was further substantiated and proved by isolating the oxa-Michael adduct **29.** Towards this end, compound **27c** was submitted to a concomitant desilylation/oxa-Michael reaction with TBAF in THF for 3h to get **29** in 85% yield as shown in **scheme 9**. Characterisation of the oxa-Michael adduct **29** was carried out by 1D and 2D NMR techniques. Initially, nOe studies at 400 MHz were a little difficult to decipher as the peaks of both methine and methylene protons resonated at δ 4.04 ppm. However, this issue was resolved by analyzing the spectra at higher field strength (700MHz) which showed a slight difference in chemical shifts for protons H_1 and H_4.



Scheme 9: Synthesis of compound **29**

As shown in **Figure 6**, H_3 proton shows nOe correlation with both methine protons H_1 and H_4 indicating syn stereochemistry among them. The relative stereochemistry was also confirmed with the help of methylene group which shows two different signals for two protons (H_2 and H_5). The H_1 and H_3 methine protons show nOe correlations only with H_2 proton, but it does not show any correlation with H_5 proton indicating all the three methine protons (H_1, H_3 and H_4) being syn to each other as shown in the pictorial representation in **Figure 7**.

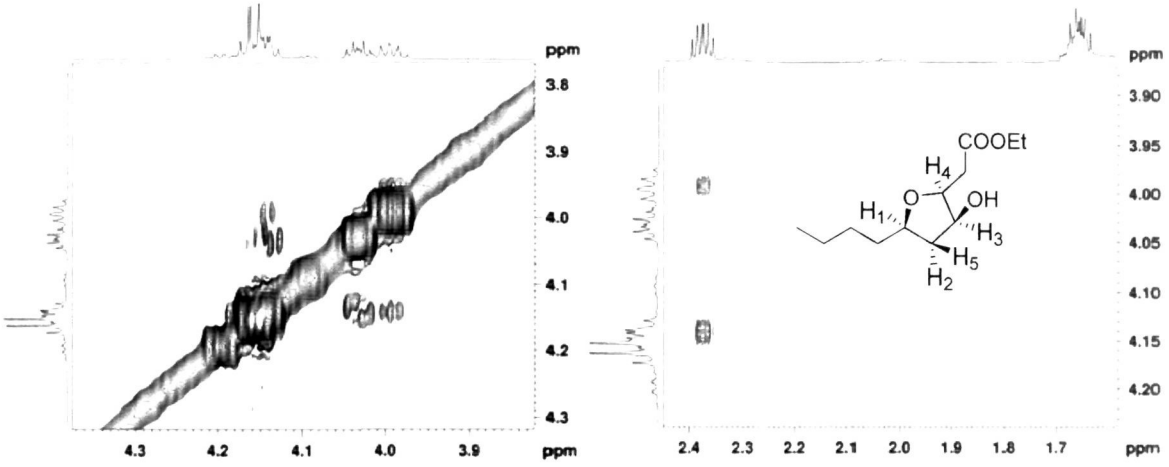
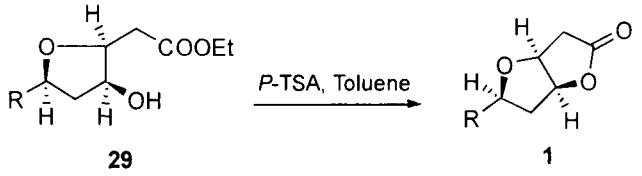


Figure 6: ^1H-^1H NOESY spectra of the compound **29** (700 MHz, $CDCl_3$, 298 ^0K)

After confirming the stereochemistry of compound **29**, it was initially subjected to cyclization using *p*-TSA at rt to give compound **1** as a sole product. Even under reflux conditions, there was no racemisation and reaction led to the only product **1**. We then examined the possibility of racemisation under strong acidic conditions by using conc. HCl both at rt and under reflux conditions. Interestingly, no racemisation was observed and cyclization was smooth leading to the desired product **1** in excellent yield. The

stereochemistry of **1** was confirmed simply by comparing the ^{1}H-NMR and optical rotation (**scheme 10**).



Scheme 10: Lactonization reaction

This could be due to the syn stereochemistry of the intermediate making cyclisation more facile than the racemization. To check the reproducibility and improve the confidence in the stereochemical outcome by the above methods, we thought of extrapolating the strategy to the synthesis of **3** and **4** isolated from *D.krausii*. Both the compound could easily be synthesized as a separable mixture of *cis* and *trans* isomers from the corresponding aldehyde octanal **24b** by subjecting it to similar set of reaction conditions as described in **scheme 5**.

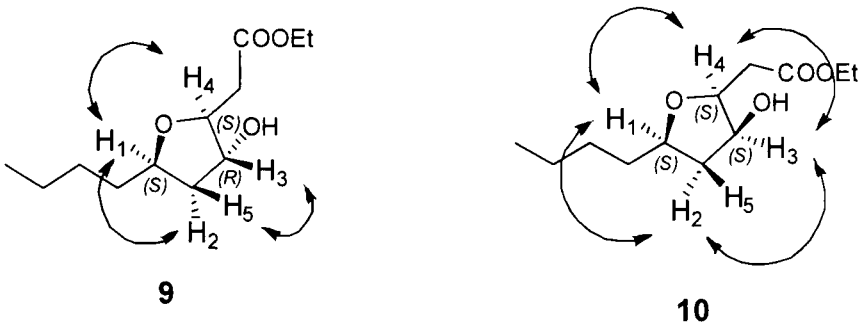


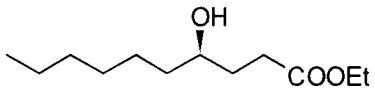
Figure 7: nOe correlations for compounds **9** and **10**

4.1.5 Conclusion

In conclusion, we have developed a new, efficient and organocatalytic protocol to Hagens gland lactones using a proline catalyzed α-aminoxylation and consequent oxa-Michael reaction. Desirable stereocenters can be obtained by using the suitable catalyst and this approach could further be extended to the synthesis of other stereoisomers and synthetic analogues.

4.1.6. Experimental section

Ethyl (*R*)-4-hydroxydecanoate (25b):



General procedure for α-aminoxylation: To a solution of octanal **10b** (2.0 g, 15.62 mmol) and nitroso benzene (1.6 g, 15.62 mmol) in anhydrous DMSO (29 mL) was added L-proline (0.72 g, 6.2 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (6.22mL, 31.25 mmol), DBU (4.29 mL, 31.25 mmol) and LiCl (1.32 g, 31.25 mmol) in CH_3CN (29 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature over 1 h, and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product which was directly subjected to next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. On completion of reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of celite and concentrated in vacuo to give γ-alcohol. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (85:15) as eluent to give ethyl (*R*)-4-hydroxydecanoate **25b** as a colourless liquid.

Yield: 2.19 g, 65%

Mol. Formula: $C_{12}H_{24}O_3$

$[\alpha]_D^{25}$: +1.17 (c 1.5, $CHCl_3$)

IR ($CHCl_3$, cm-1): ν^{max} 3432, 2934, 1718.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.13 (q, J = 7.2 Hz, 2H), 3.67-3.52 (m, 1H), 2.50-2.39 (m, 2H), 1.99-1.61 (m, 4H), 1.56-1.29 (m, 8H), 1.29-1.22 (m, 3H), 0.92 (d, J = 4.8 Hz, 3H) ppm.

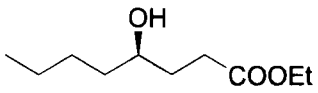
^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 80.9, 71.0, 60.2, 37.4, 32.1, 30.7, 29.5, 25.5, 22.5, 14.0, 13.9 ppm.

MS (ESI): *m/z* 239.12

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{24}O_3Na$ 239.1618: Found 239.1614

HPLC: Kromasil 5–Amycoat (250 X 4.6mm) (2-propanol : petroleum ether = 10:90, flow rate 0.5ml/min, (λ = 220 nm). Retention time (min):78.48 (minor) and 80.70 (major). The racemic standard was prepared in the same way using *dl*-proline as a catalyst. ee>98%.

(*R*)-Ethyl 4-hydroxyoctanoate (25a):



Hexanal **10a** (2.0 g, 20 mmol) was subjected to the above condition to furnish crude product to give (*R*)-ethyl 4-hydroxyoctanoate **25a** as colorless liquid.

Yield: 2.44 g, 65 %

Mol. Formula: $C_{10}H_{20}O_3$

$[\alpha]_D^{25}$: - 0.93 (*c* 2.24, $CHCl_3$)

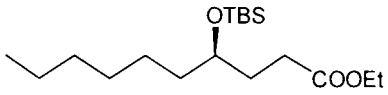
IR ($CHCl_3$, cm^{-1}): ν_{max} 3430, 2934, 1718, 1465, 1177.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86-0.93 (m, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.32-1.36 (m, 3H), 1.41-1.45 (m, 2H), 1.62-1.93 (m, 4H), 2.44 (t, J = 7.2 Hz, 2H), 3.55-3.67 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 13.8, 22.4, 27.5, 30.4, 31.9, 36.9, 60.1, 70.5, 174.0 ppm.

MS (ESI): m/z 211.2468 (M^++Na).

Ethyl (*R*)-4-((tert-butyldimethylsilyl)oxy)decanoate (26b):



General procedure for TBS protection: To an ice-cold stirred solution of **25b** (1.70 g, 7.87 mmol) in DMF (10 mL) were added imidazole (1.00 g, 15.74 mmol) and TBSCl (1.77g, 11.80 mmol) at 0 °C. The resulting mixture was stirred for 1 h at rt before H_2O (20 mL) was added. The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of crude product using petroleum ether: ethyl acetate: (95:05) as eluent gave TBS ether **26b** as a colourless liquid.

Yield: 2.39 g, 92%

Mol. Formula: $C_{18}H_{38}O_3Si$

$[\alpha]_D^{25}$: -7.08 (*c* 1.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 2856, 1726.

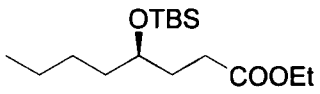
^{1}H NMR (200 MHz, $CDCl_3$): δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.75-3.59 (m, 1H), 2.40-2.29 (m, 2H), 1.82-1.63 (m, 2H), 1.47-1.34 (m, 2H), 1.30-1.22 (m, 11H), 0.88 (m, 12H), 0.04 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 71.2, 60.2, 37.0, 31.8, 31.7, 30.1, 29.5, 25.9, 25.1, 22.6, 18.1, 14.2, 14.1, -4.4, -4.6 ppm.

MS (ESI) : *m/z* 353.20

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{38}O_3NaSi$ 353.2482; Found 353.2472

(*R*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate (25b):



Following the procedure as described above **25b** was obtained from compound (1g, 5.3 mmol) as a crude product which was purified by column chromatography using petroleum ether: EtOAc (95:5) to give (*R*)-ethyl 4-(*tert*-butyldimethylsilyloxy)octanoate **25b** as a colorless liquid.

Yield:1.48 g, 92%

Mol. Formula: $C_{16}H_{34}O_3Si$

$[\alpha]_D^{25}$: + 9.96 (*c* 1.78, $CHCl_3$).

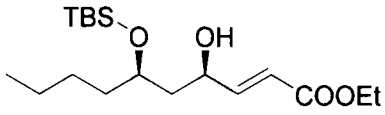
IR ($CHCl_3$, cm^{-1}): ν_{max} 2858, 1726, 1463, 1256.

^{1}H NMR (400 MHz, $CDCl_3$): δ -0.04 (s, 6H), 0.89 (s, 12H), 1.24-1.30 (m, 7H), 1.41-1.46 (m, 2H), 1.65-1.72 (m, 1H), 1.77-1.85 (m, 1H), 2.33-2.38 (m, 2H), 3.66-3.72 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.7, 13.9, 14.0, 17.8, 22.6, 25.7, 27.2, 29.8, 31.5, 36.6, 59.9, 70.9, 173.5 ppm.

MS (ESI): m/z 325.4028 (M^++Na).

Ethyl (4*R*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27a):



General procedure for iterative aminoxylation: To a solution of ethyl ester **26a** (1.0 g, 4.63 mmol) in CH_2Cl_2 (6 mL), was added DIBAL-H (2.5 mL 2.3 M solution in toluene, 5.09 mmol) at -78 °C under argon atmosphere. The reaction was stirred at this temperature for 40 min. Then a solution of tartaric acid (2.5 mL) was added. The resulting mixture was stirred for 15 min and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give aldehyde as a colourless liquid, which was directly used in the next step without further purification. Following the general procedure for α-aminoxylation (L-proline as a catalyst) **27a** was obtained as a crude product (~95% diastereomeric excess) and was purified by flash column chromatography using petroleum ether: ethyl acetate (9:1) to furnish pure diol **27a** as a colorless liquid.

Yield: 0.80 g, 71%

Mol. Formula: $C_{18}H_{36}O_4Si$

$[\alpha]_D^{25}$: -15.76 (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max}3436, 2967, 1218.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92 (dd, J = 4.4, 15.6 Hz, 1H), 6.10 (dd, J= 1.8, 15.6 Hz, 1H), 4.46 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.96 (m, 1H), 1.76-1.50 (m, 4H), 1.27-1.23 (m, 7H), 0.94-0.90 (m, 12H), 0.16-0.08 (m, 6H) ppm.

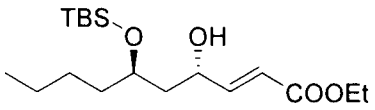
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 149.7, 119.8, 73.3, 70.4, 60.3, 41.9, 37.7, 26.8, 25.8, 22.8, 17.9, 14.2, 14.0, -4.0, -4.8 ppm.

MS (ESI): *m/z* 367.18

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{36}O_4NaSi$ 367.2275; Found 367.2275.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0ml/min, (λ = 210 nm). Retention time (min): 7.31 (major) and 7.89 (minor), (dr 95:5)

Ethyl (4*S*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27c):



Compound **27c** was prepared using the general procedure for iterative aminoxylation starting from ethyl ester **26a** and using D-proline as a catalyst.

Yield: 0.79 g, 70%

Mol. Formula: $C_{18}H_{36}O_4Si$

$[\alpha]_D^{25}$: -7.5 (*c* 0.4, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3430, 2934, 1718

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.92 (dd, J = 4.2, 15.6 Hz, 1H), 6.11 (dd, J = 1.9, 15.5 Hz, 1H), 4.64 (dtd, J = 1.8, 4.2, 8.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.05-3.94 (m, 1H), 1.74-1.65 (m, 2H), 1.29 (t, J = 7.1 Hz, 9H), 0.90 (m, 12H), 0.09 (d, J = 1.4 Hz, 6H) ppm.

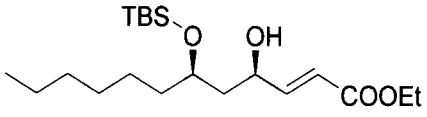
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 150.4, 119.8, 71.5, 68.0, 60.3, 40.5, 35.7, 27.8, 25.8, 22.7, 17.9, 14.2, 14.0, -4.5, -4.8 ppm.

MS (ESI): *m/z* 367.19

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{18}H_{36}O_4NaSi$ 367.2273; Found 367.2275.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0 ml/min,(λ = 210 nm). Retention time (min): 6.91 (major) and 7.43 (minor),dr 3:97

Ethyl (4*R*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (27b):



Compound **27b** was prepared using the general procedure for iterative aminoxylation starting from ethyl ester **26b** and using L-proline as a catalyst.

Yield: 0.80 g, 70%

Mol. Formula: $C_{20}H_{40}O_4Si$

$[\alpha]_D^{25}$: -6.49 (*c* 1.8, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3450, 2920.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.91 (dd, *J* = 4.4, 15.6 Hz, 1H), 6.10 (dd, *J* = 1.9, 15.5 Hz, 1H), 4.24 - 4.09 (m, 2H), 4.07-3.82 (m, 1H), 3.82-3.51 (m, 1H), 1.63-1.52 (m, 4H), 1.27 (d, *J* = 4.5 Hz, 11H), 0.92-0.88 (m, 12H), 0.12 (d, *J* = 2.5 Hz, 6H) ppm.

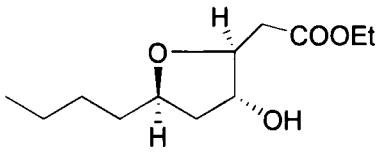
^{13}C NMR (126 MHz, $CDCl_3$): δ 166.7, 149.7, 119.8, 73.3, 70.4, 60.3, 42.0, 38.0, 31.8, 29.4, 25.8, 24.6, 22.5, 17.9, 14.2, 14.0, -4.0,-4.7 ppm.

MS (ESI): *m/z* 395.20

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{20}H_{40}O_4NaSi$ 395.2588; Found 395.2578.

HPLC: Kromasil RP-18 (150 X 4.6mm) (Acetonitrile : H_2O = 90:10), flow rate 1.0 ml/min.(λ = 210 nm). Retention time (min):10.61(major) and 11.61 (minor), dr 96:4.

Ethyl 2-((2*S*,3*R*,5*R*)-5-butyl-3-hydroxytetrahydrofuran-2-yl)acetate (28):



General procedure for oxa Michael addition: The solution of **27a** (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using petroleum ether: ethyl acetate: (8:2) as eluent gave oxa-Michael product **28** as a colorless liquid.

Yield: 0.14 g, 85%

Mol. Formula: $C_{12}H_{22}O_4$

$[\alpha]_D^{25}$: +1.3 (*c* 0.3, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max} 3463, 2931, 1764

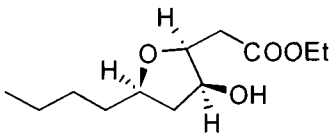
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (d, *J* = 7.0 Hz, 2H), 4.14-4.10 (m, 1H), 4.06 (dd, *J* = 6.1, 9.2 Hz, 1H), 3.95 (td, *J* = 4.6, 9.4 Hz, 1H), 2.80 (dd, *J* = 5.0, 16.3 Hz, 1H), 2.51 (dd, *J* = 9.2, 16.5 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 1H), 2.01-1.96 (m, 1H), 1.82-1.75 (m, 1H), 1.49-1.42 (m, 2H), 1.33-1.26 (m, 6H), 0.91-0.87 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2, 82.3, 78.4, 77.2, 60.9, 40.3, 38.8, 35.2, 28.1, 22.7, 14.1, 14.0 ppm.

MS (ESI): *m/z* 253.12

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{12}H_{22}O_4Na$ 253.1410: Found 253.1411

Ethyl 2-((2*S*,3*S*,5*R*)-5-hexyl-3-hydroxytetrahydrofuran-2-yl)acetate (29):



Compound **29** was prepared using the general procedure for oxa Michael addition starting from ethyl ester **27c**.

Yield: 0.14 g, 85%

Mol. Formula: $C_{12}H_{22}O_4$

$[\alpha]_D^{25}$: -8.4 (*c* 1.0, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν^{max}3463, 2931, 1764

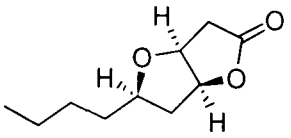
^{1}H NMR (700 MHz, $CDCl_3$): δ 4.13-4.05 (m, 3H), 3.98-3.93 (m, 1H), 3.93-3.88 (m, 1H), 2.66 (dd, *J* = 5.3, 16.3 Hz, 1H), 2.45-2.41 (m, 1H), 2.30 (td, *J* = 6.7, 13.0 Hz, 1H), 1.58 (dd, *J* = 4.9, 7.9 Hz, 1H), 1.44-1.41 (m, 2H), 1.30-1.18 (m, 7H), 0.82-0.78 (m, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 172.4, 79.8, 77.7, 76.8, 60.9, 40.2, 38.6, 35.8, 28.0, 25.7, 22.6, 14.0 ppm.

MS (ESI): *m/z* 253.10

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{12}H_{22}O_4Na$ 253.1410; Found 253.1411

(3a*S*,5*R*,6a*S*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (1):



General procedure for lactonization reaction: The solution of crude **28** (0.1 g, 0.368 mmol) was treated with catalytic amount of dil. HCl (pH~3) in dry toluene. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using pet ether: ethylacetate: (85:15) as eluent afforded **1** as a syrupy liquid.

Yield: 0.047 g, 61%

Mol. Formula: $C_{10}H_{16}O_3$

$[\alpha]_D^{25}$: -53.39 (*c* 0.8, $CHCl_3$)

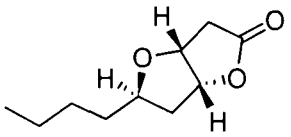
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03-5.00 (m, 1H), 4.53-4.50 (m, 1H), 3.97 - 3.91 (m, 1H), 2.73 (d, *J* = 3.3 Hz, 2H), 2.46 - 2.39 (m, 1H), 1.91-1.86 (m, 1H), 1.70-1.65 (m, 1H), 1.60-1.54 (m, 1H), 1.37-1.30 (m, 4H), 0.92-0.89 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5, 84.7, 80.3, 78.2, 38.3, 36.6, 35.2, 28.2, 22.6, 13.9 ppm.

MS (ESI): *m/z* 207.08

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{10}H_{16}O_3Na$ 207.0991; Found 207.0992

(3a*R*,5*R*,6a*R*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3*H*)-one (2):



Compound **2** was prepared using the general procedure for lactonization reaction starting from ethyl ester **28**.

Yield: 0.009 g, 12.2%

Mol. Formula: $C_{10}H_{16}O_3$

$[\alpha]_D^{25}$: +47.22 (*c* 0.3, $CHCl_3$)

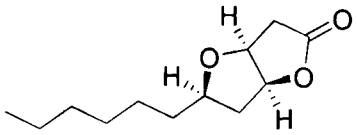
^{1}H NMR (700 MHz, $CDCl_3$): δ 5.12 (t, J = 4.7 Hz, 1H), 4.83-4.79 (m, 1H), 4.07 (dt, J = 6.0, 10.7 Hz, 1H), 2.76 (dd, J = 6.7, 18.7 Hz, 1H), 2.65 (d, J = 18.9 Hz, 1H), 2.38 (dd, J = 4.5, 13.9 Hz, 1H), 1.69-1.65 (m, 1H), 1.56-1.43 (m, 2H), 1.39-1.28 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$): δ 176.0, 84.9, 78.3, 77.3, 38.8, 36.6, 34.4, 28.2, 22.6, 13.9 ppm.

MS (ESI): *m/z* 207.06

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{10}H_{16}O_3Na$ 207.0991: Found 207.0991

(3a*S*,5*R*,6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (3):



General procedure: The solution of **27b** (0.25 g, 0.92 mmol) was treated with TBAF (0.5 mL, 1.8 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt and quenched with saturated ammonium chloride solution (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give a crude product.

The solution of crude product in toluene was treated with catalytic amount of dil. HCl (pH~3) in dry toluene. The reaction mixture was refluxed for 12 h and concentrated under reduced pressure to give a crude product. Silica gel column chromatography of the crude product using pet ether: ethylacetate: (85:15) as eluent afforded **3** as a syrupy liquid.

Yield: 0.046 g, 60%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{25}$: -39.62 (*c* 0.8, $CHCl_3$)

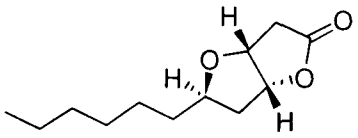
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.01 (ddd, J = 2.3, 4.6, 6.9 Hz, 1 H), 4.53-4.49 (m, 1H), 3.94 (td, J = 7.0, 13.8 Hz, 1H), 2.42 (td, J = 7.2, 14.2 Hz, 2H), 1.89 (ddd, J = 2.3, 7.9, 14.2 Hz, 2H), 1.60-1.50 (m, 4H), 1.37-1.30 (m, 6H), 0.90 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 84.7, 80.4, 78.2, 38.3, 36.4, 35.2, 29.7, 29.6, 28.2, 22.6, 14.0 ppm.

MS (ESI): *m/z* 235.10

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{12}H_{20}O_3Na$ 235.1302: Found 235.1302

(3a*R*,5*R*,6a*R*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (4):



Compound **4** was prepared using the general procedure for oxa Michael addition followed by general procedure for lactonization starting from ethyl ester **27b**.

Yield: 0.009 g, 12%

Mol. Formula: $C_{12}H_{20}O_3$

$[\alpha]_D^{25}$: +42.78 (*c* 0.5, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (t, *J* = 4.8 Hz, 1H), 4.84-4.80 (m, 1H), 4.07 (td, *J* = 5.3, 10.7 Hz, 1H), 2.79-2.68 (m, 2H), 2.39 (dd, *J* = 4.6, 13.7 Hz, 2H), 1.68-1.61 (m, 4H), 1.56-1.50 (m, 2H), 1.34 (dd, *J* = 6.5, 12.2 Hz, 4H), 0.92-0.90 (m, 3H) ppm.

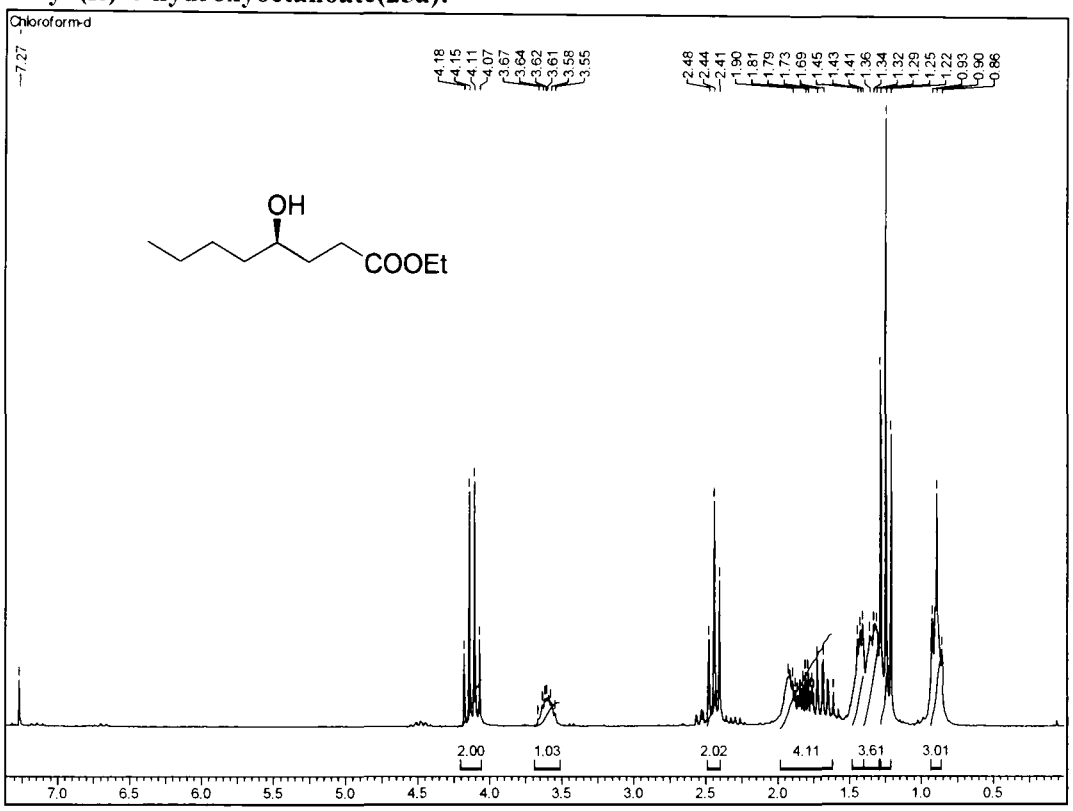
^{13}C NMR (126 MHz, $CDCl_3$): δ 175.5, 84.7, 78.2, 77.3, 38.2, 36.3, 35.2, 31.9, 29.6, 29.3, 22.5, 13.9 ppm.

MS (ESI): *m/z* 235.10

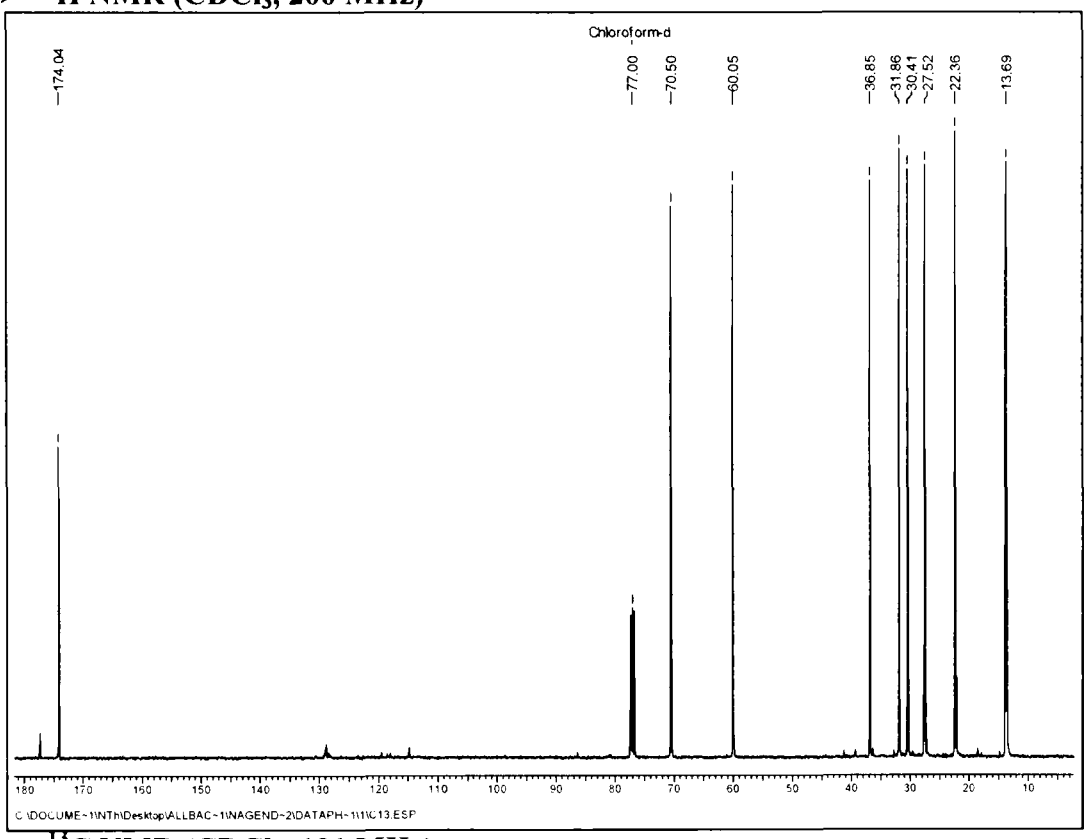
HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{12}H_{20}O_3Na$ 235.1304: Found 235.1305

4.1.7. Spectra

Ethyl (*R*)-4-hydroxyoctanoate(25a):

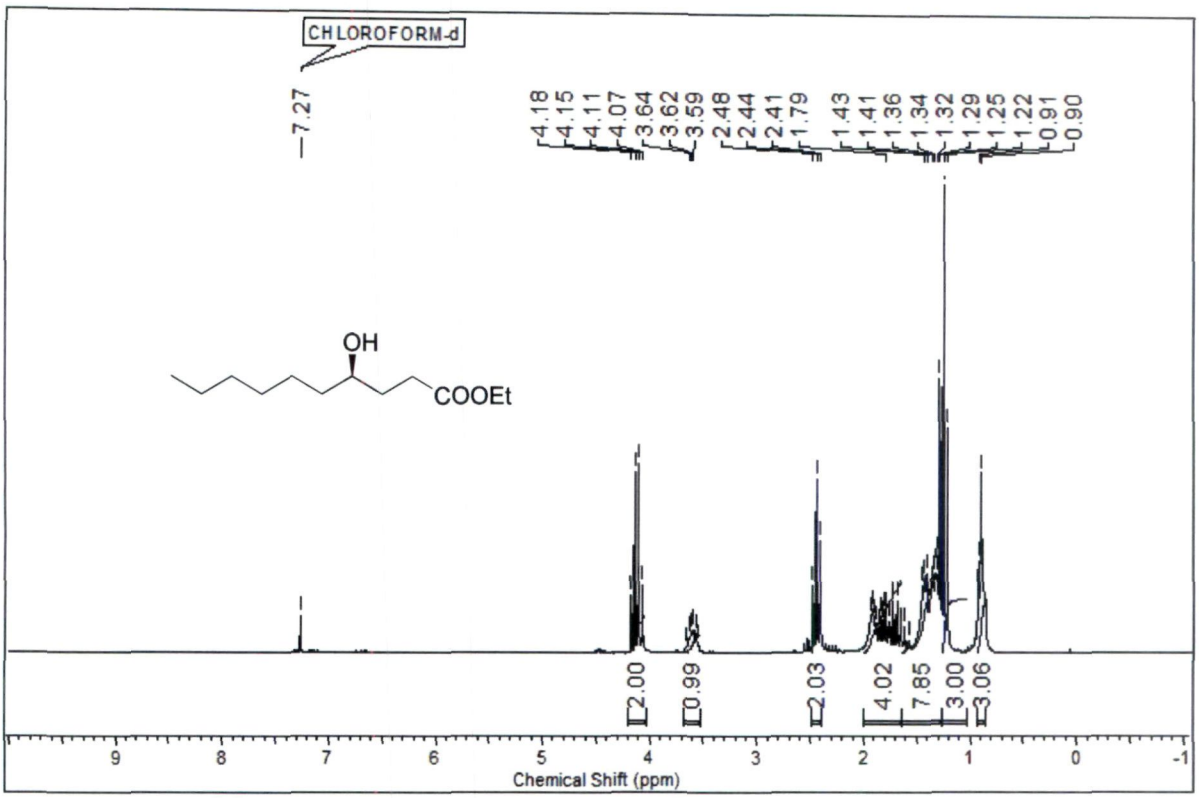


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

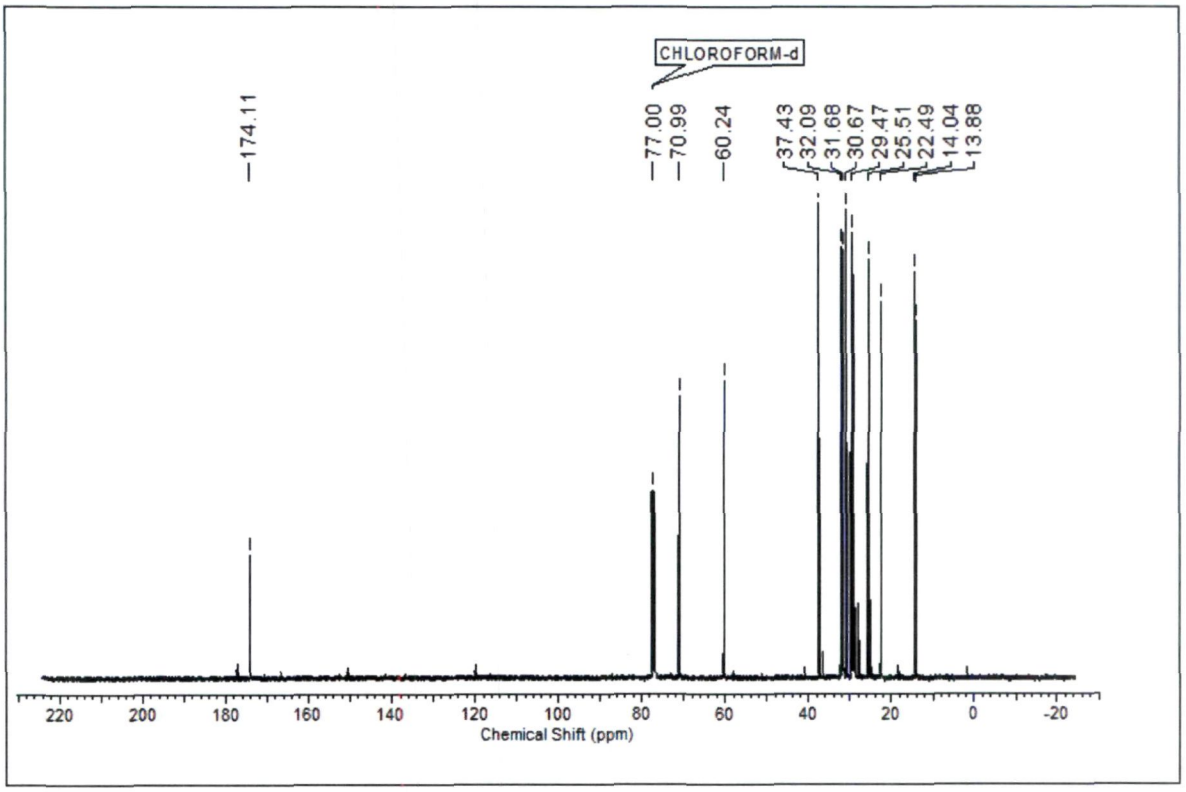


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl (*R*)-4-hydroxydecanoate (25b):



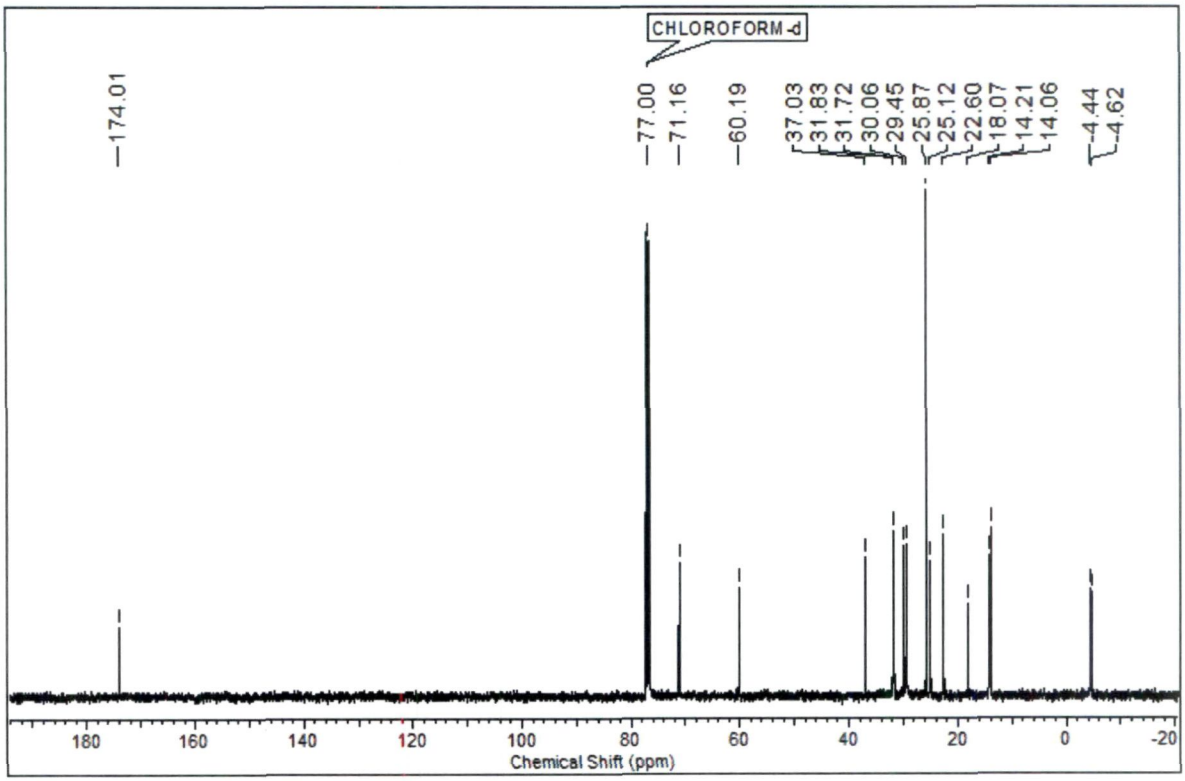
^{1}H NMR ($CDCl_3$, 200 MHz)



- **^{13}C NMR ($CDCl_3$, 101 MHz**

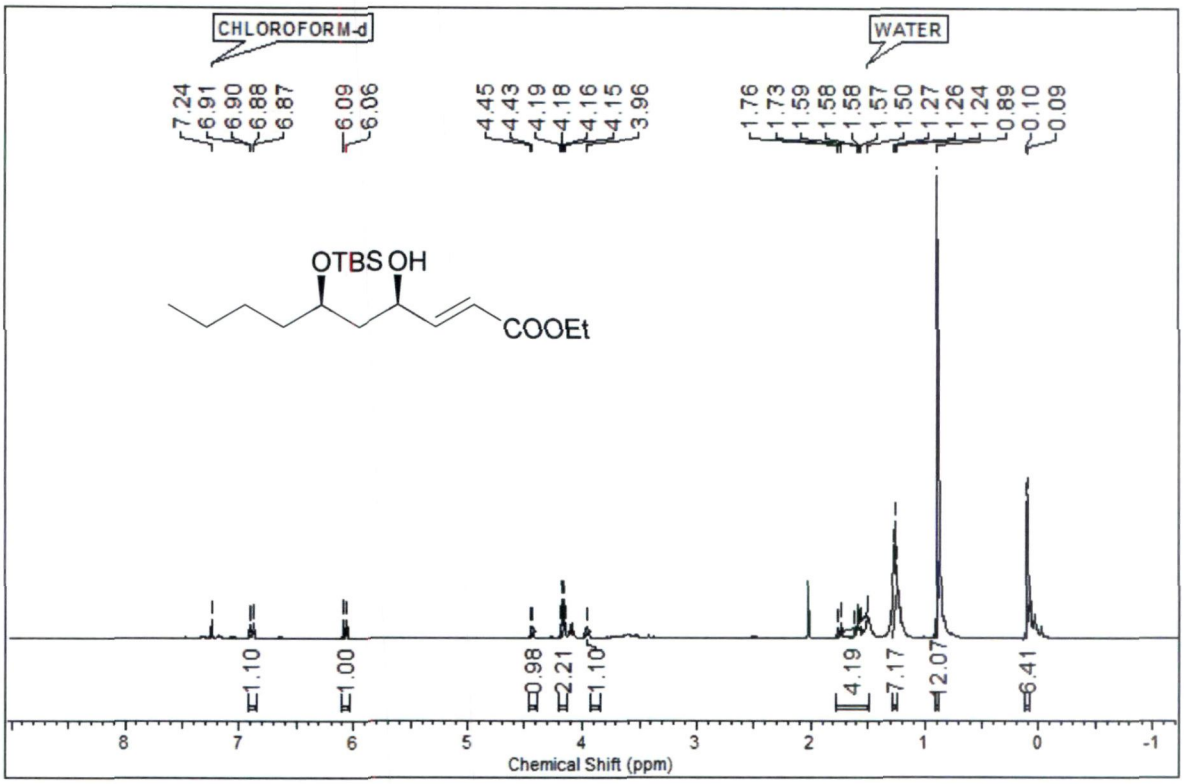
Ethyl (*R*)-4-((tert-butyldimethylsilyl)oxy)decanoate (26b):

➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

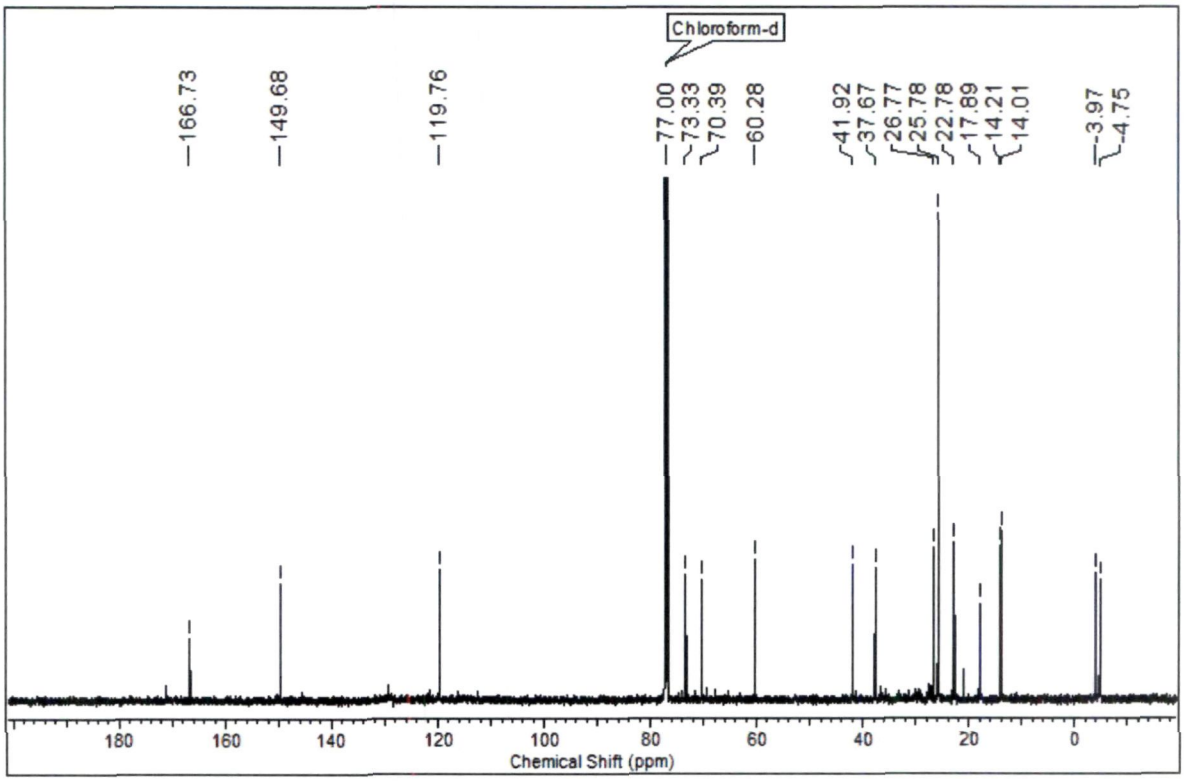


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl (4*R*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27a):

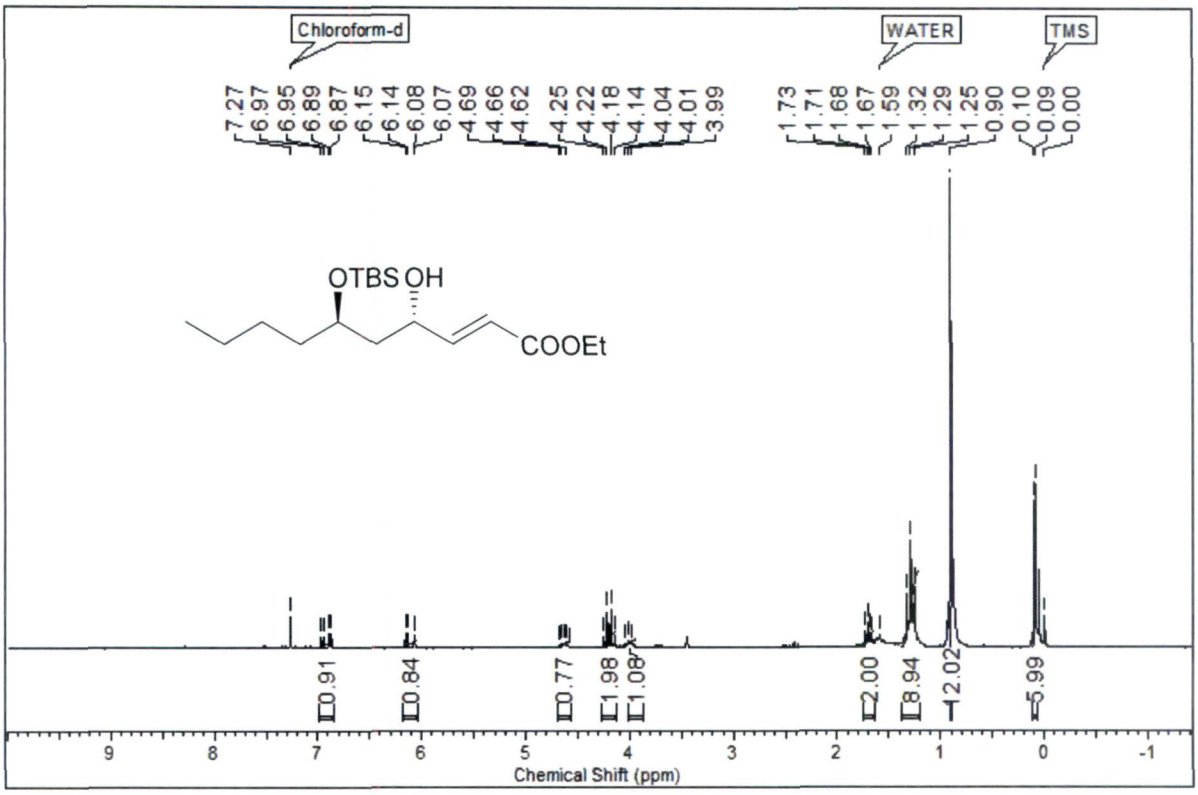


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

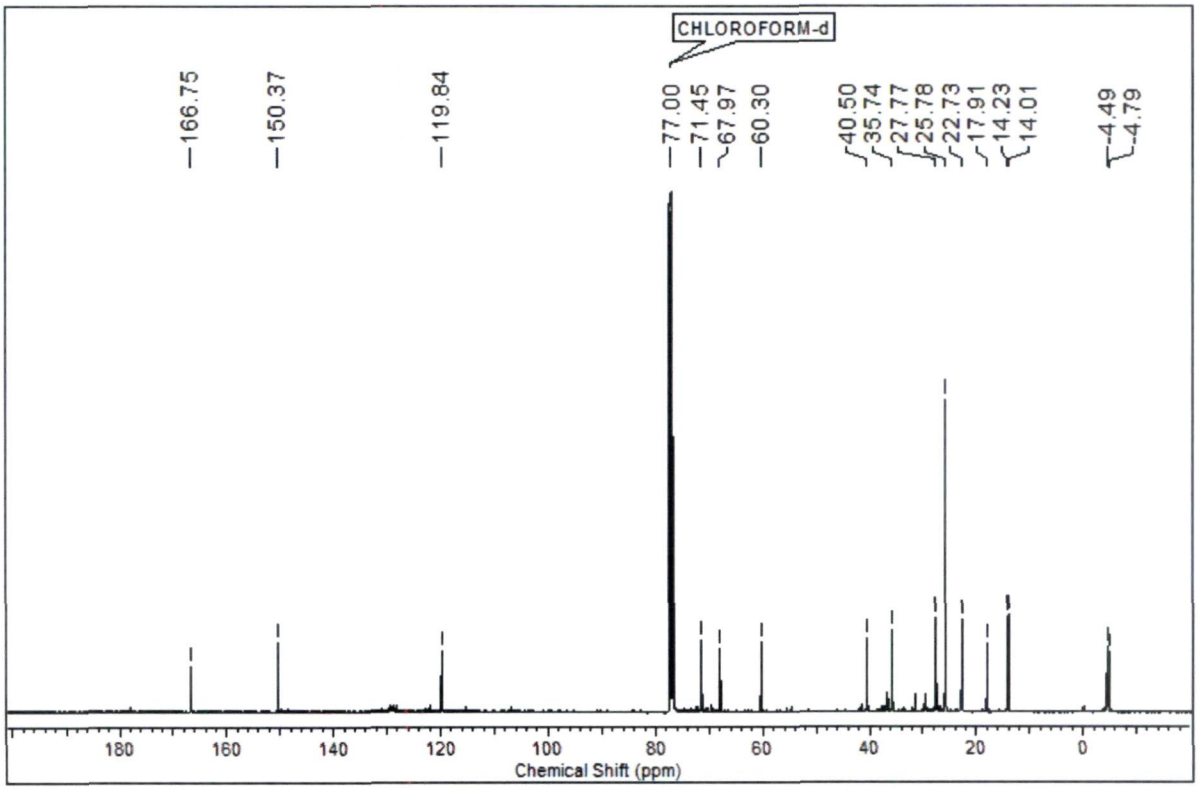


➢ **^{13}C NMR ($CDCl_3$, 126 MHz)**

Ethyl (4*S*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydec-2-enoate (27c):

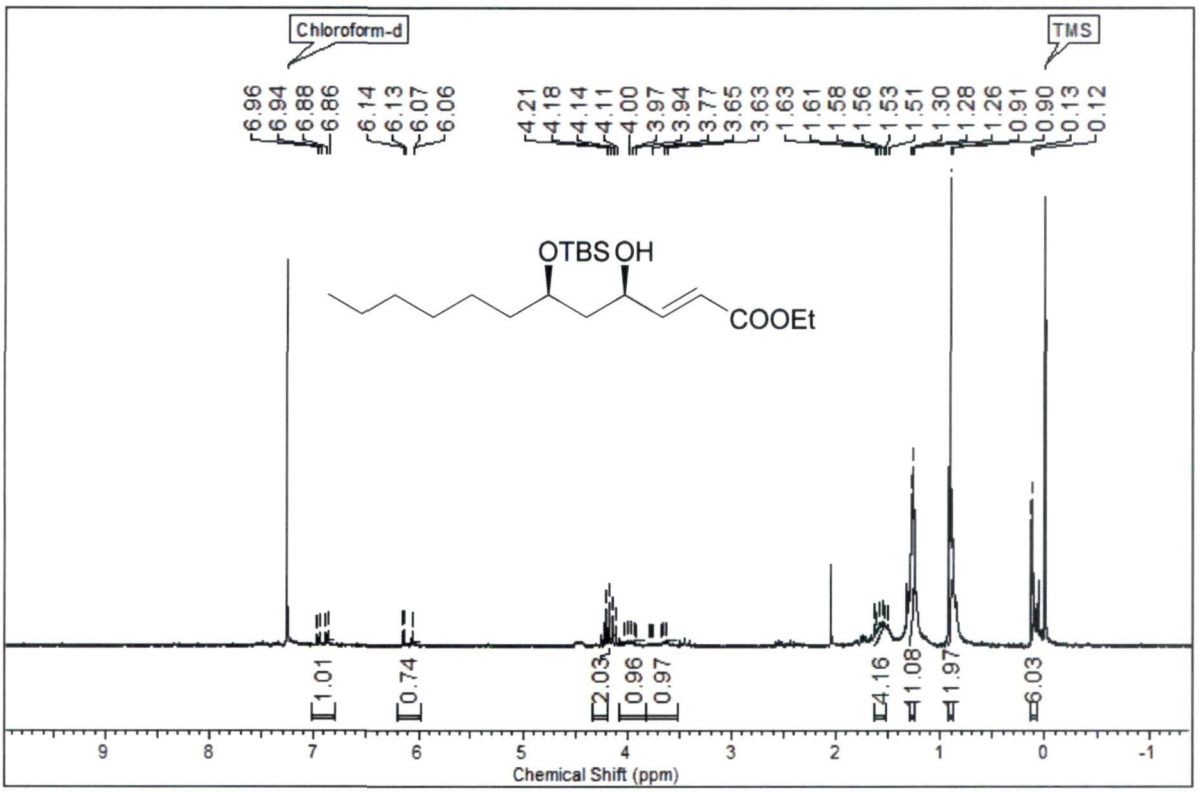


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

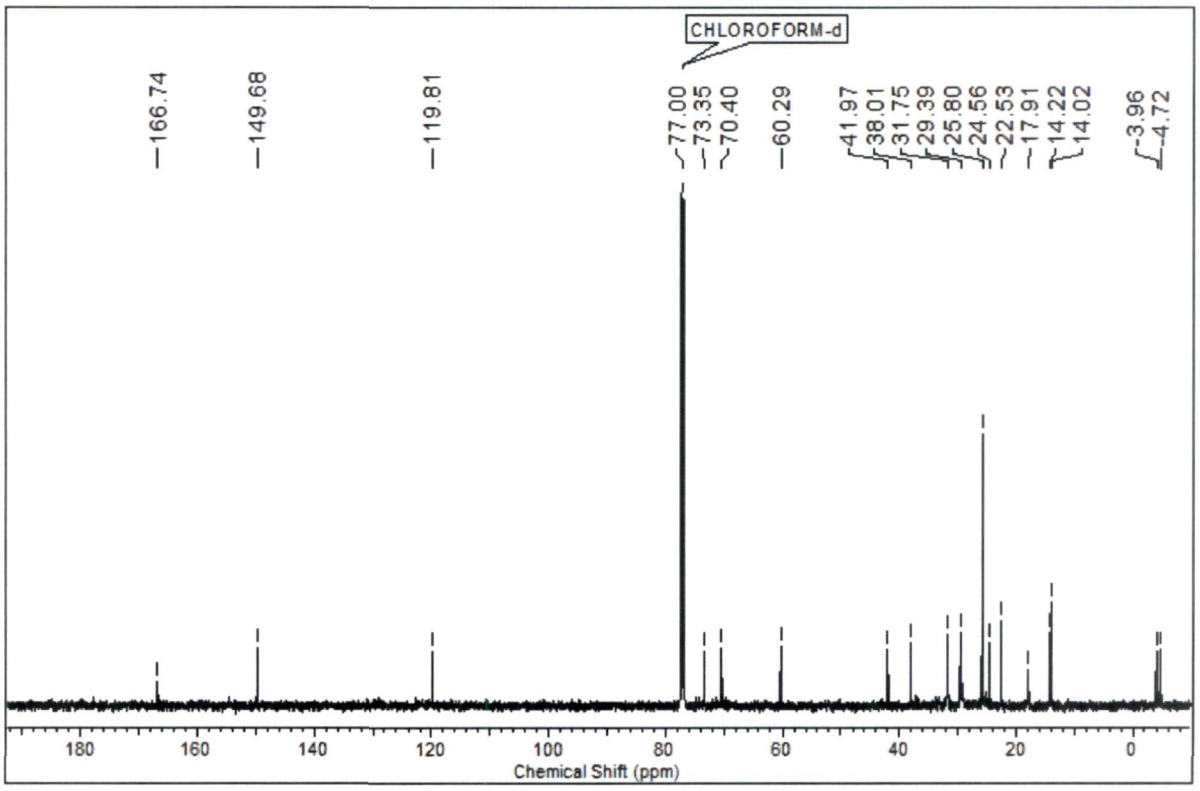


- **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl (4*R*,6*R*,*E*)-6-((tert-butyldimethylsilyl)oxy)-4-hydroxydodec-2-enoate (27b):

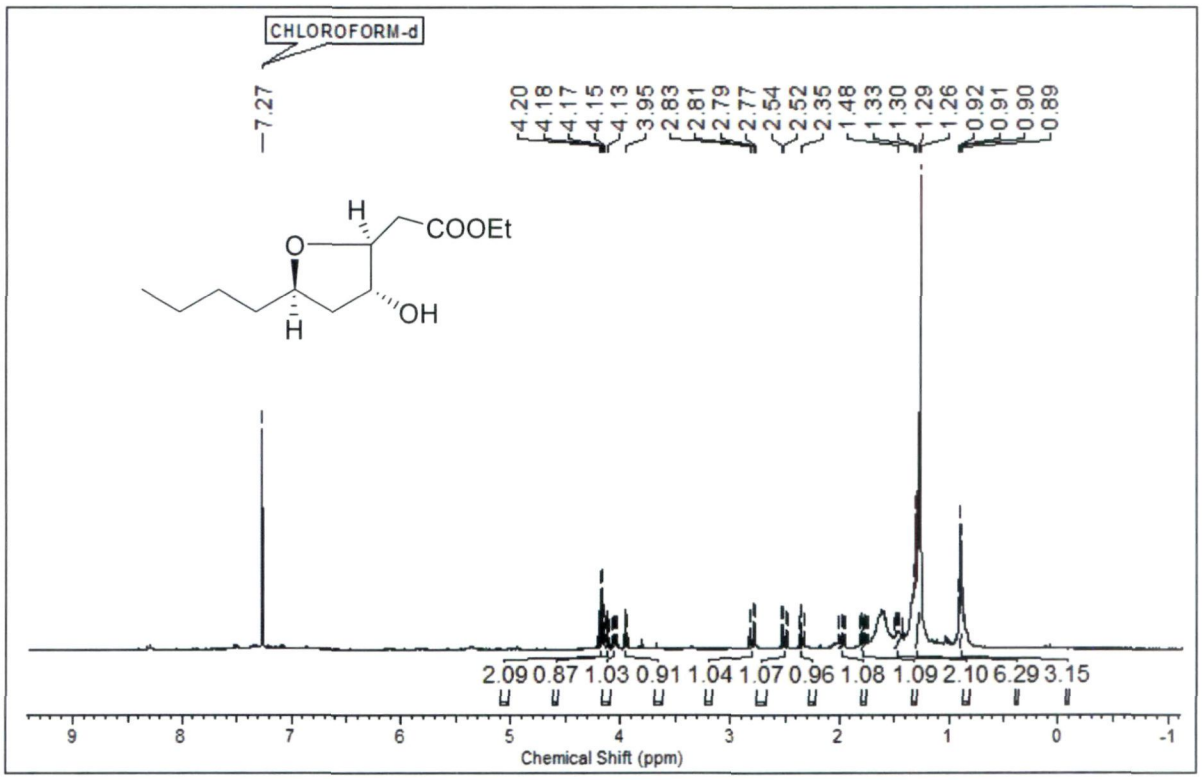


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

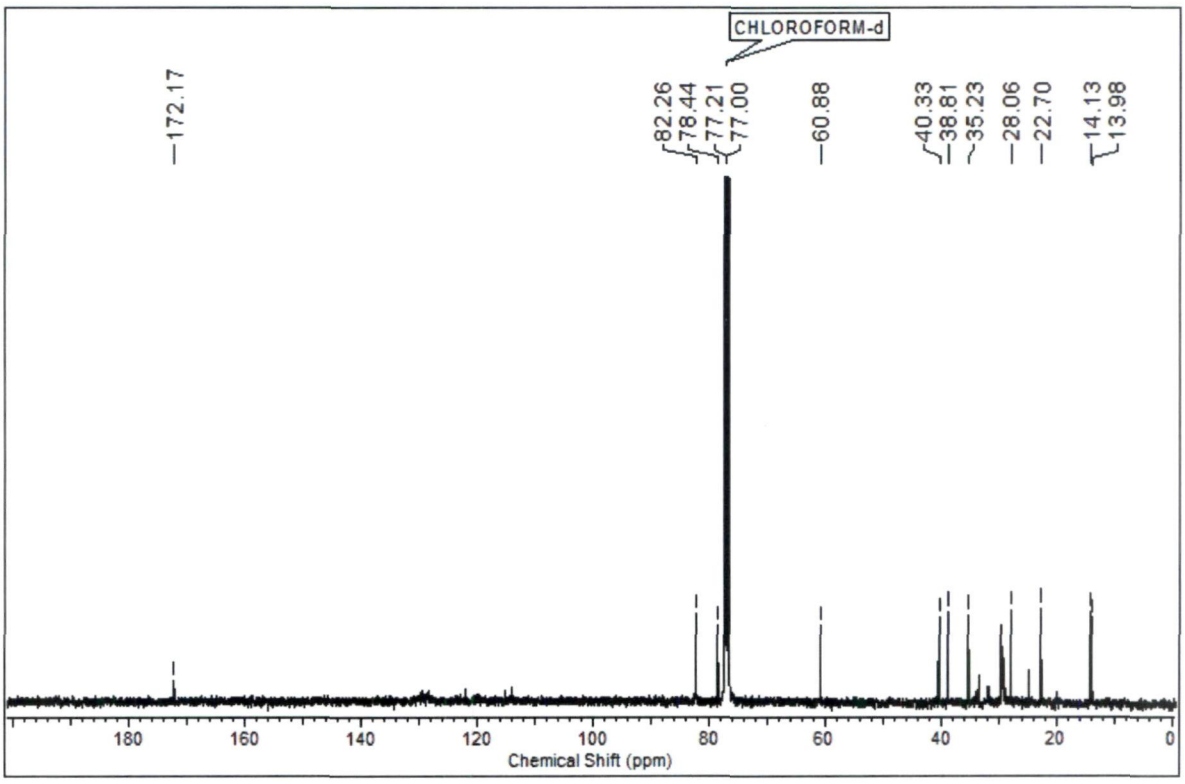


- **^{13}C NMR ($CDCl_3$, 126 MHz)**

Ethyl 2-((2*S*,3*R*,5*R*)-5-butyl-3-hydroxytetrahydrofuran-2-yl)acetate (28):

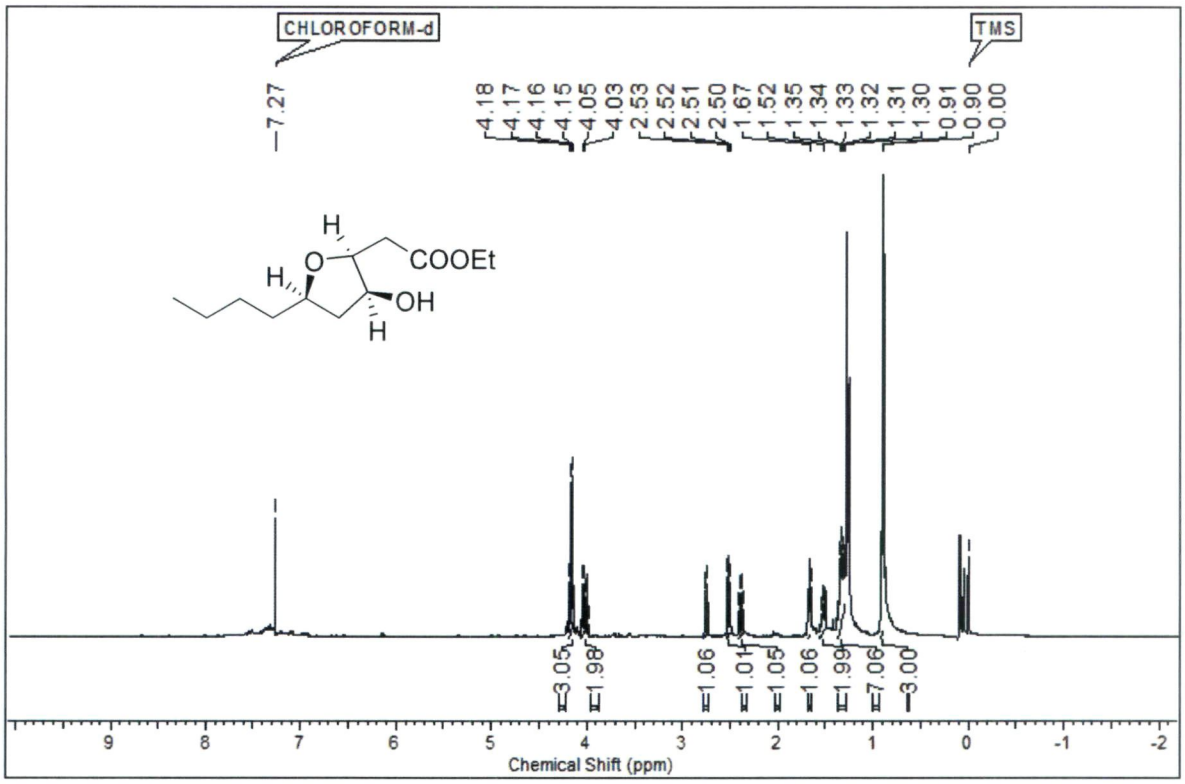


- **^{1}H NMR ($CDCl_3$, 400 MHz)**

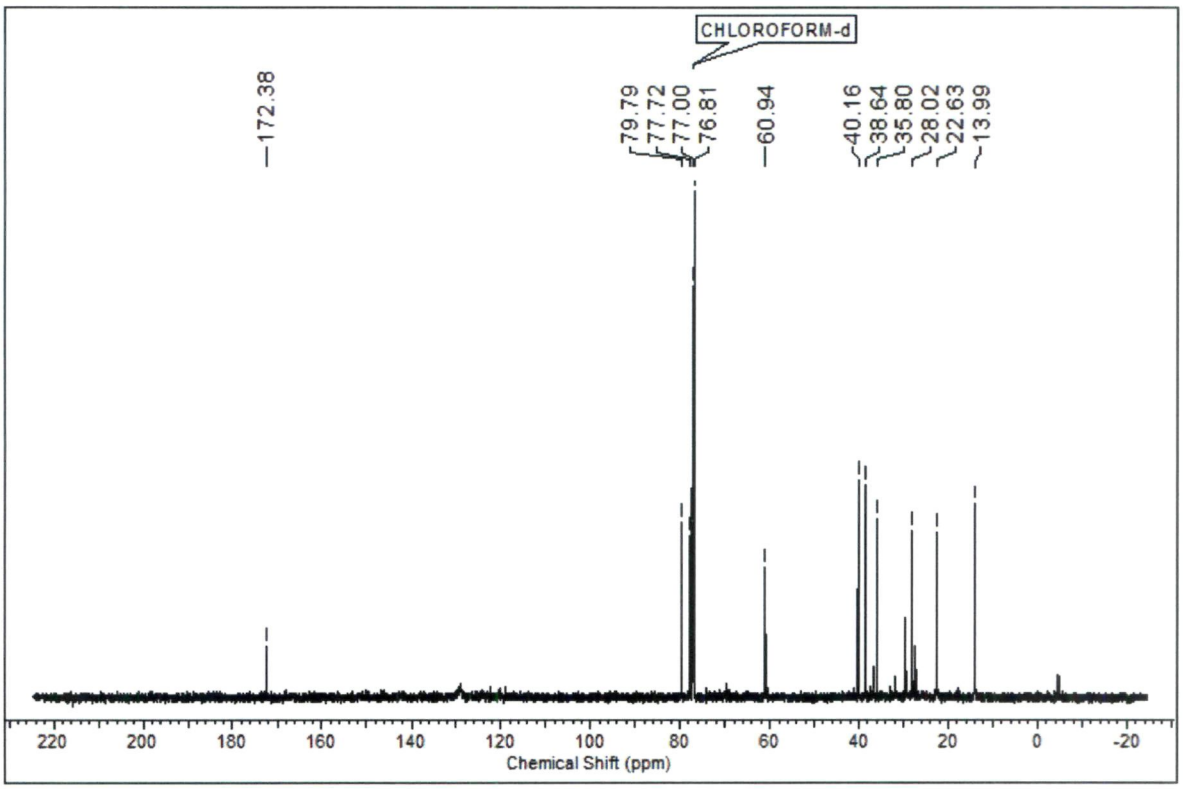


- **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl 2-((2*S*,3*S*,5*R*)-5-hexyl-3-hydroxytetrahydrofuran-2-yl)acetate (10):

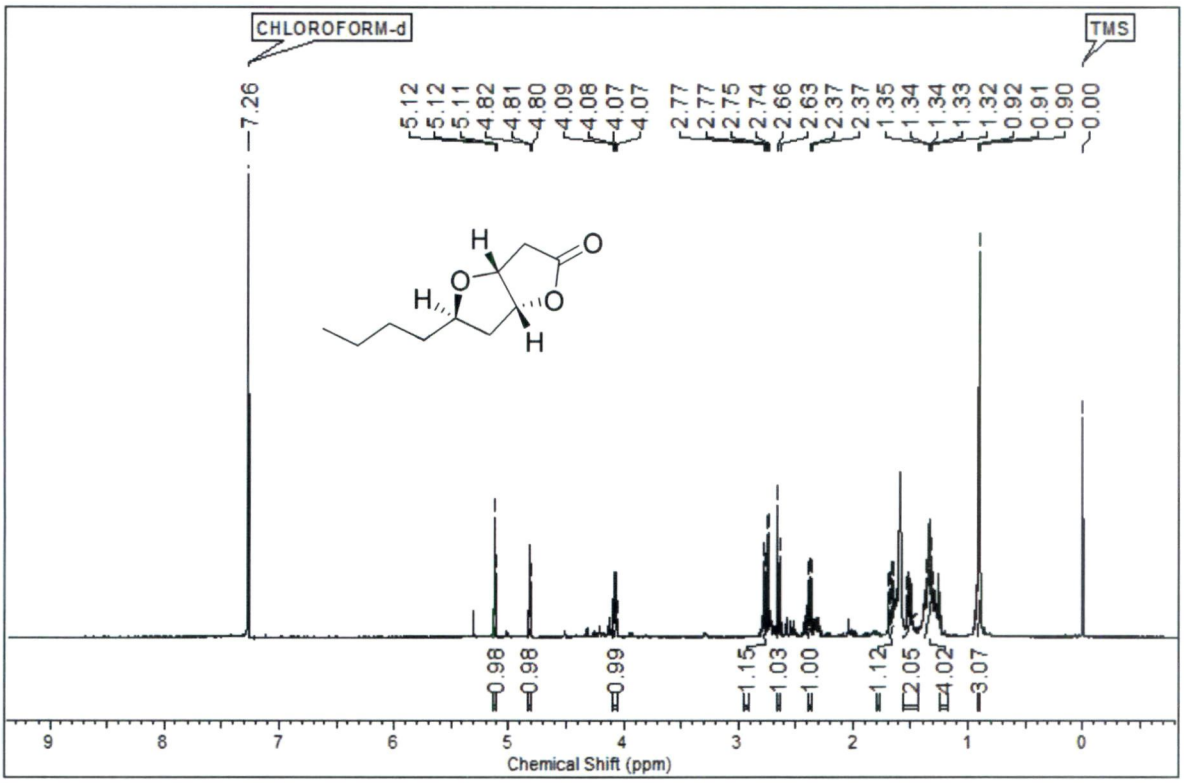


- **^{1}H NMR ($CDCl_3$, 700 MHz)**

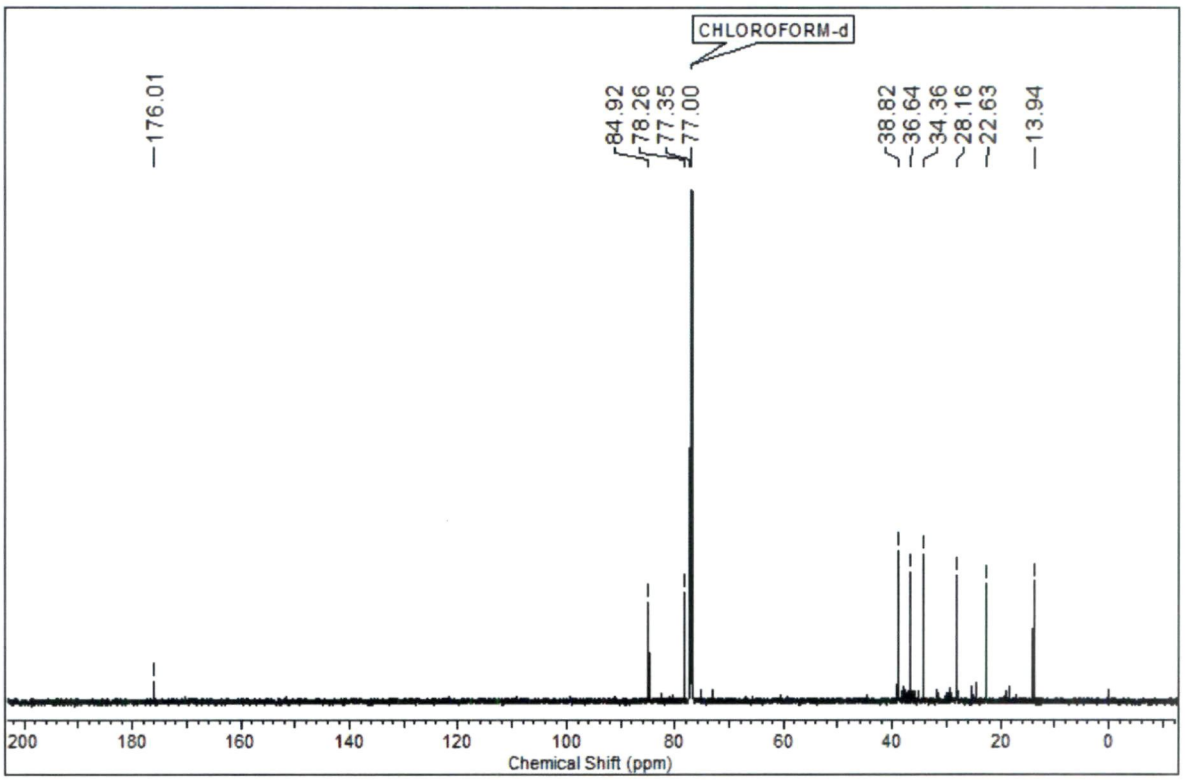


- **^{13}C NMR ($CDCl_3$, 176 MHz)**

(3a*R*,5*R*,6a*R*)-5-Butyltetrahydrofuro[3,2-b]furan-2(3H)-one (2):

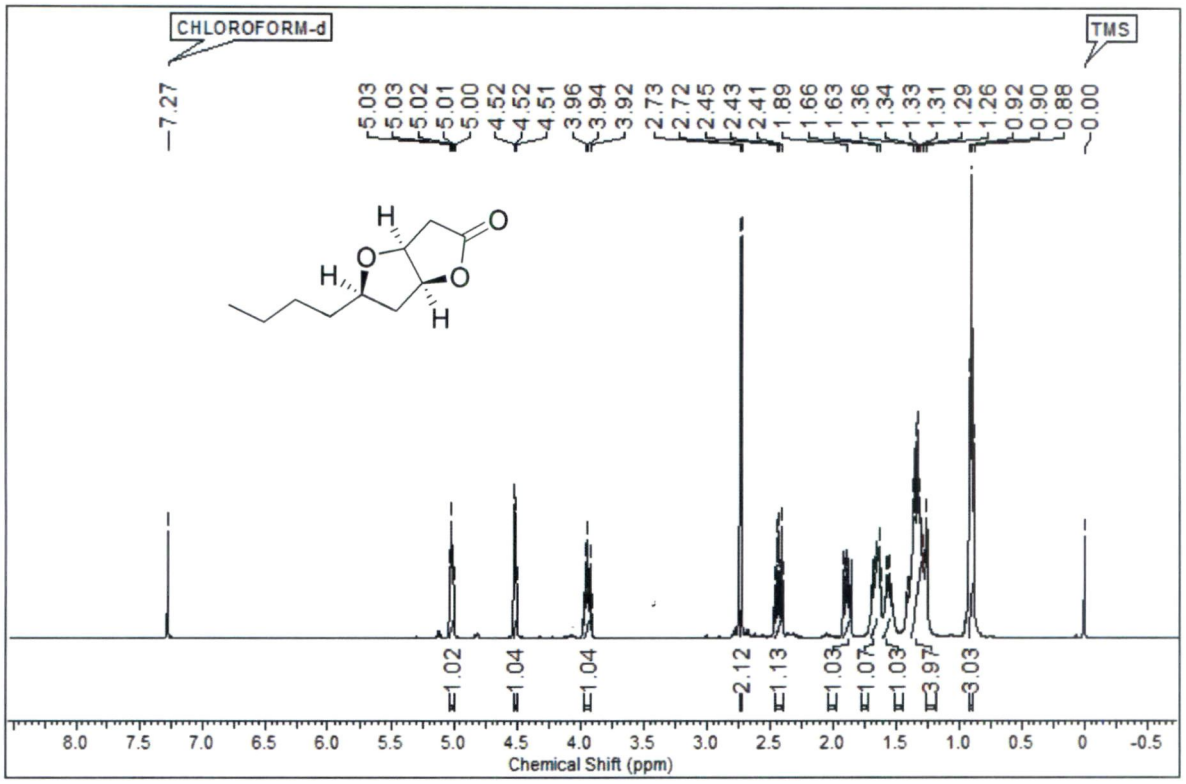


➢ **^{1}H NMR ($CDCl_3$, 700 MHz)**

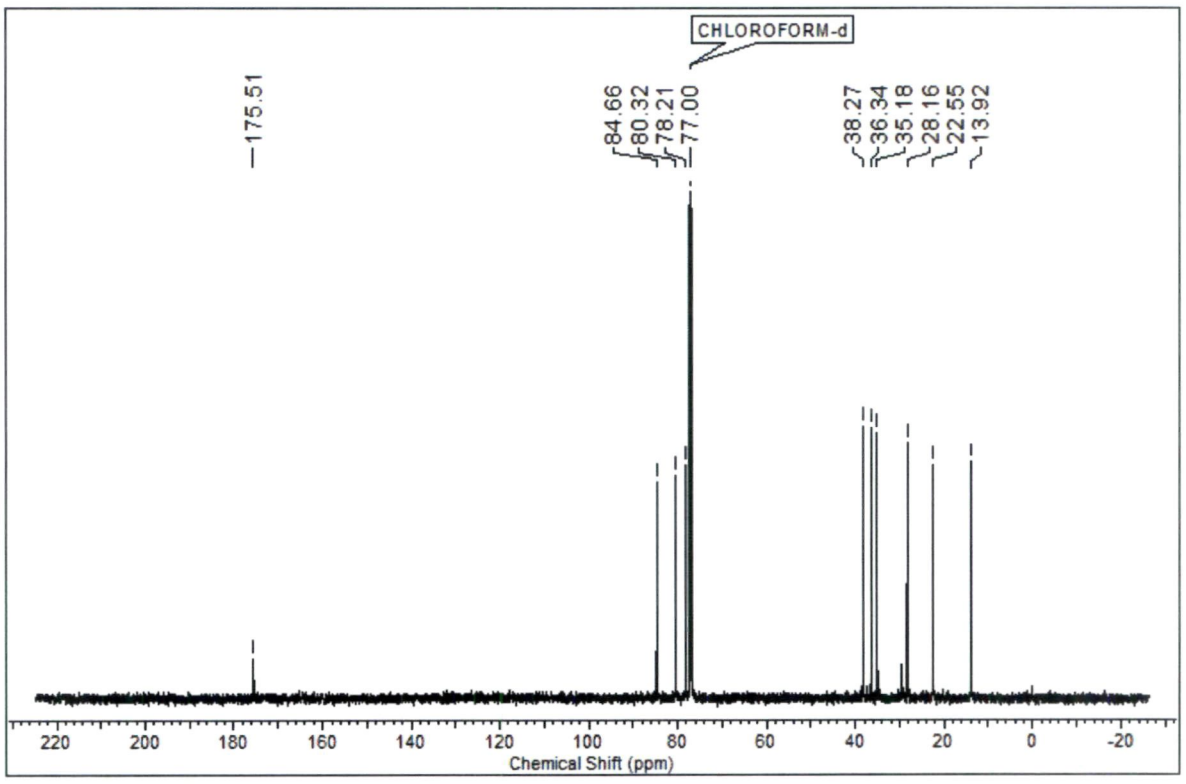


➢ **^{13}C NMR ($CDCl_3$, 176 MHz)**

Ethyl 2-((2*S*,3*S*,5*R*)-5-Butyl-3-hydroxytetrahydrofuran-2-yl)acetate (1):

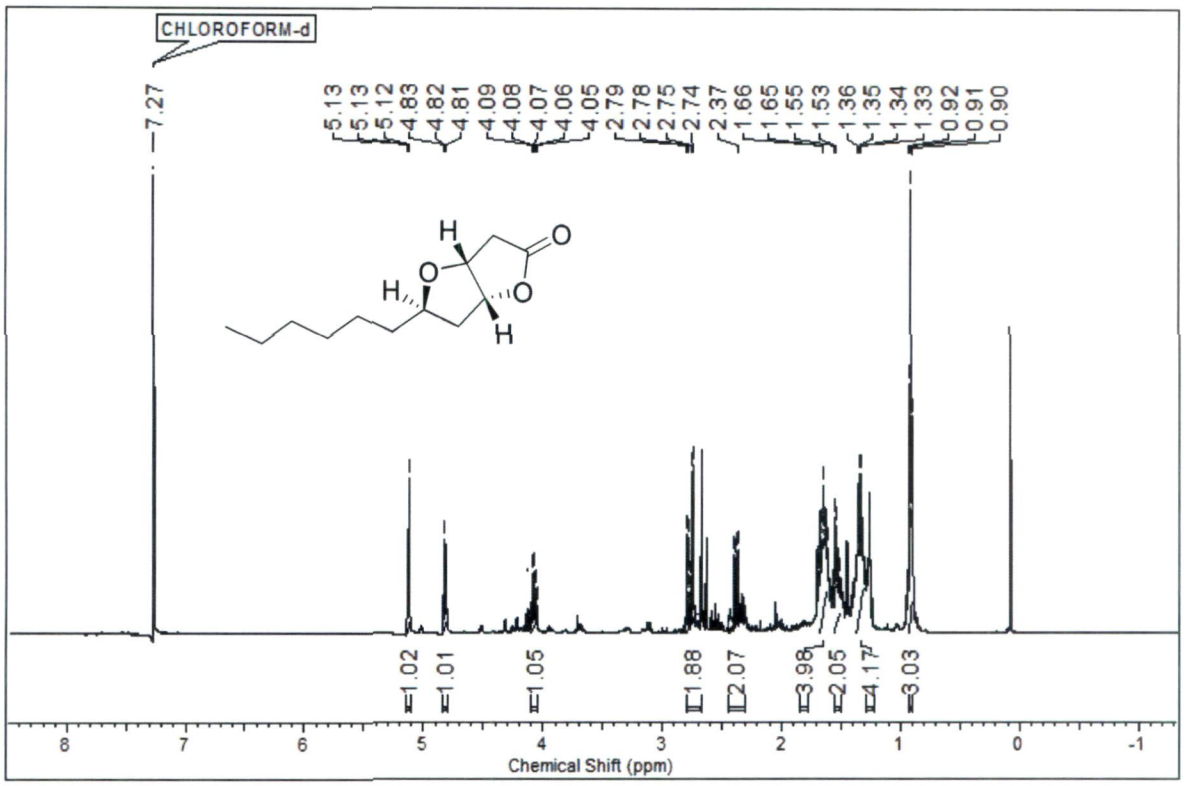


- **^{1}H NMR ($CDCl_3$, 400 MHz)**

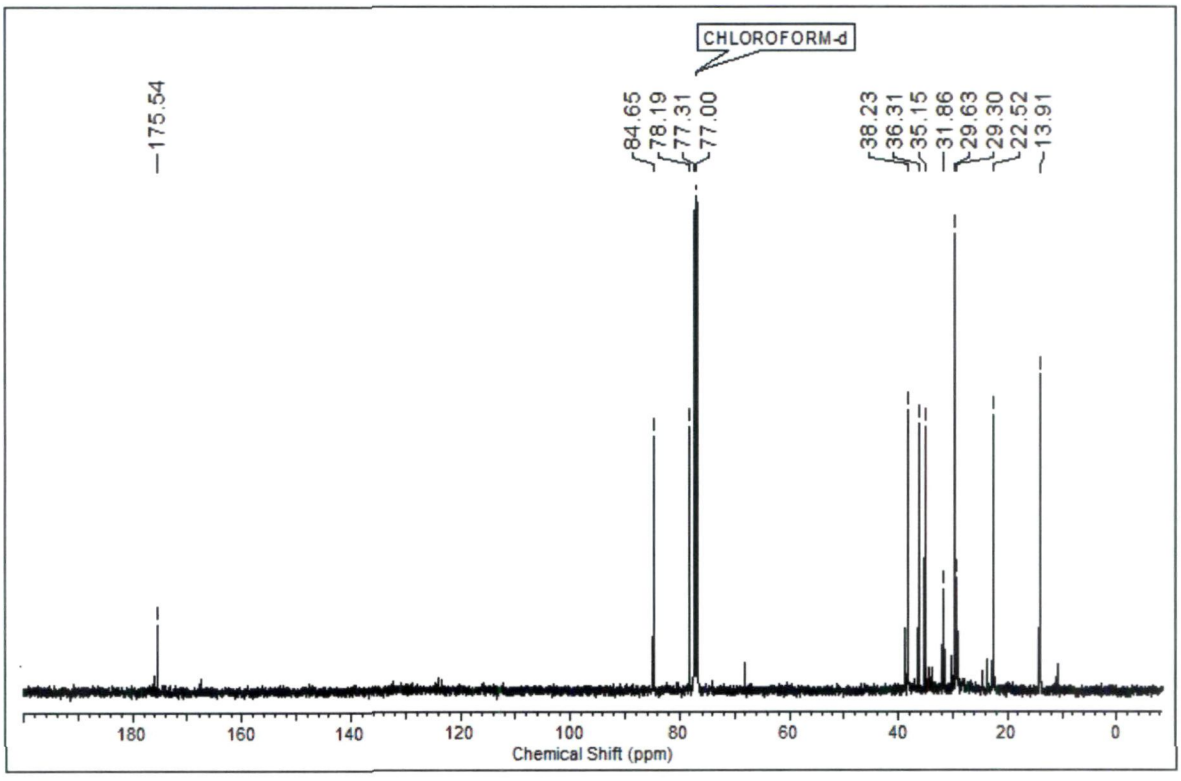


- **^{13}C NMR ($CDCl_3$, 101 MHz)**

(3a*R*,5*R*,6a*R*)5Hexyltetrahydrofuro[3,2b]furan2(3H)one (4):

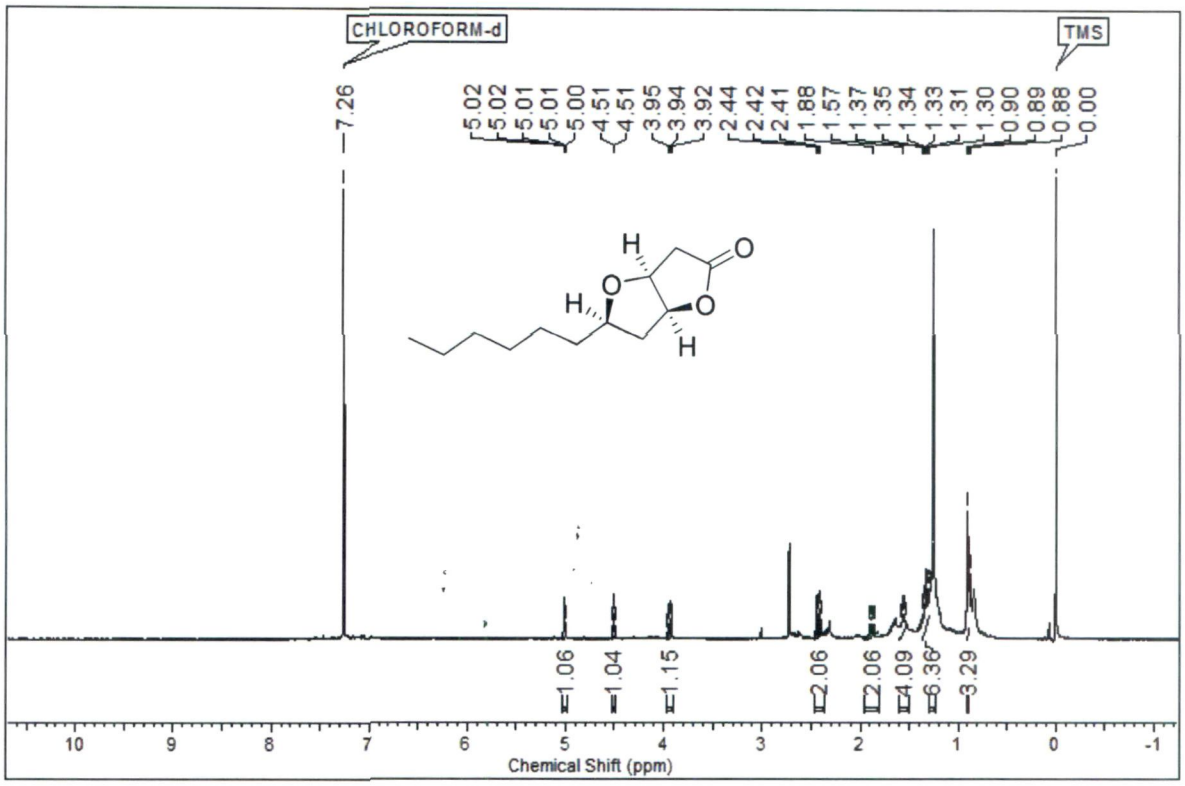


- **^{1}H NMR ($CDCl_3$, 500 MHz)**

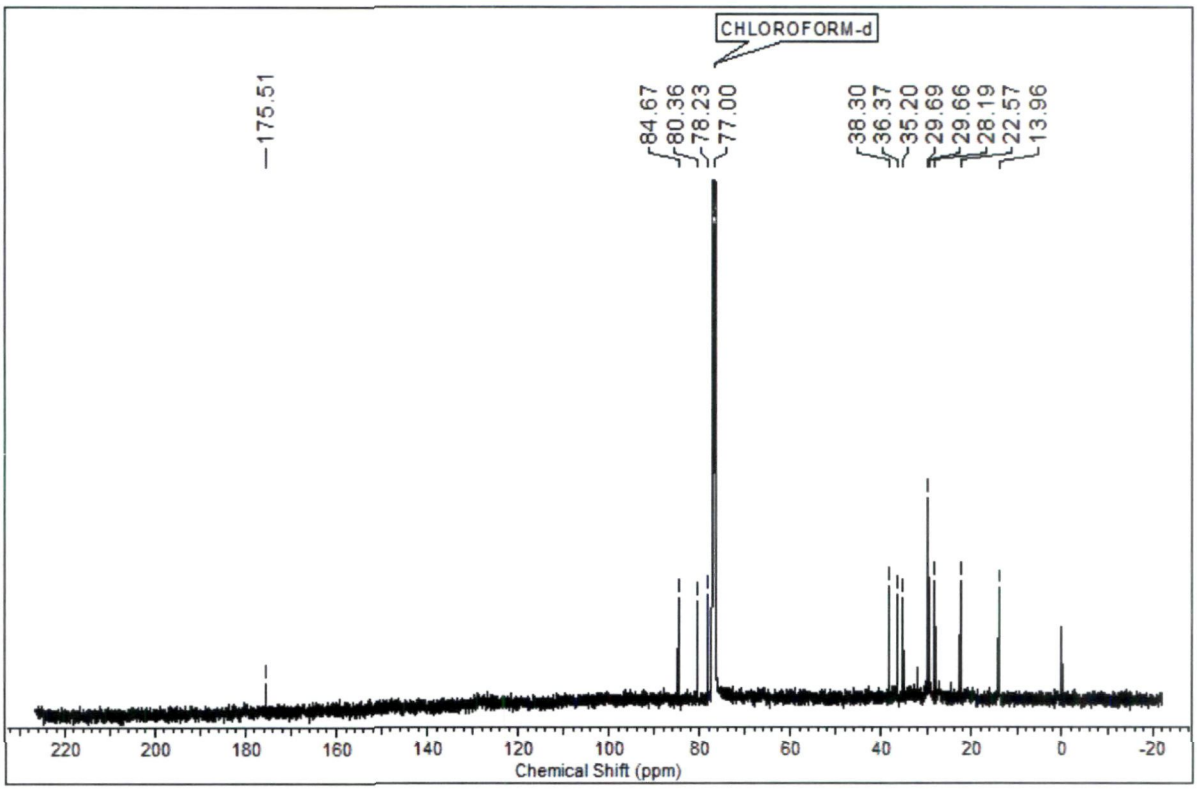


- **^{13}C NMR ($CDCl_3$, 126 MHz)**

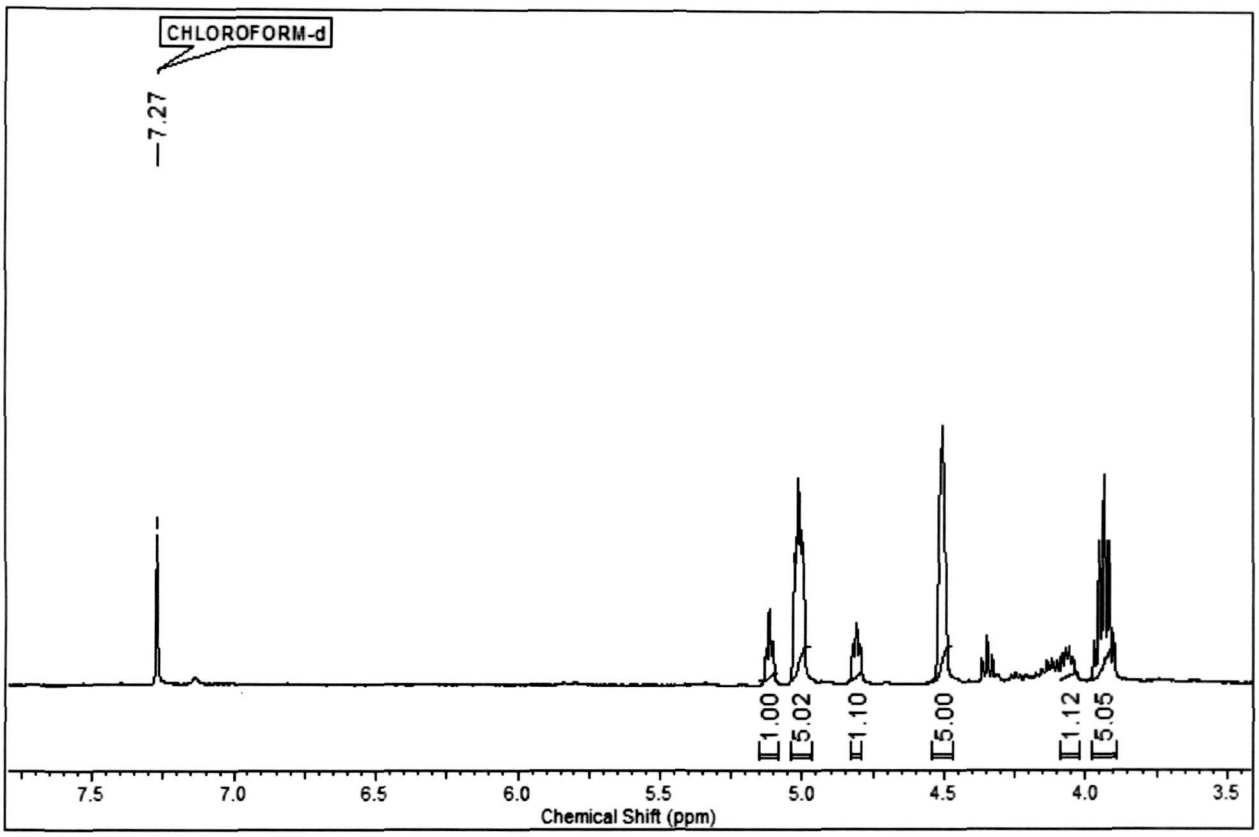
(3a*S*,5*R*,6a*S*)-5-Hexyltetrahydrofuro[3,2-b]furan-2(3H)-one (3):



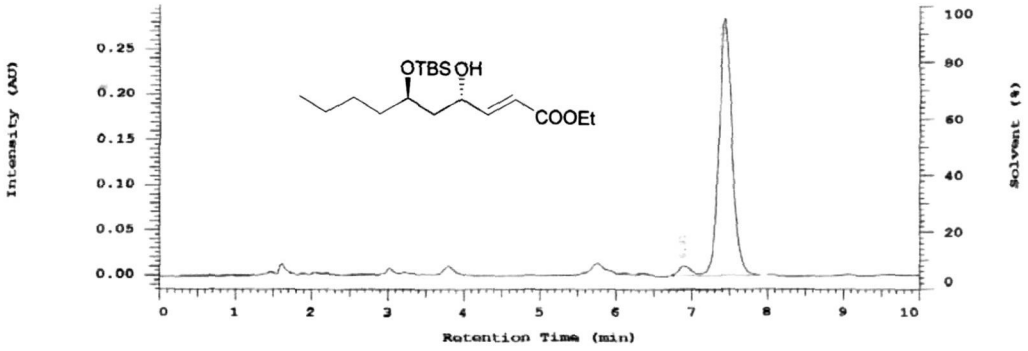
- **^{1}H NMR ($CDCl_3$, 500 MHz)**



- **^{13}C NMR ($CDCl_3$, 126 MHz)**


CHLOROFORM-d
7.27
1.00
5.02
1.10
5.00
1.12
5.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)

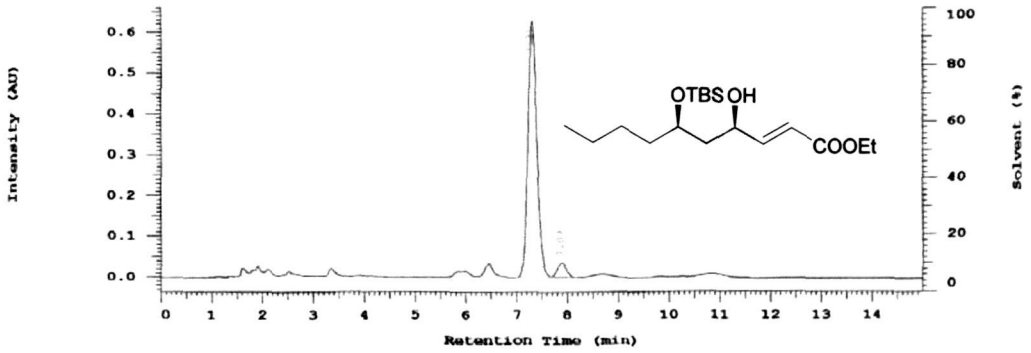
Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	6.91	5404	61375	3.405
2	7.43	142688	1741276	96.595
		148092	1802651	100.000

Peak rejection level: 0

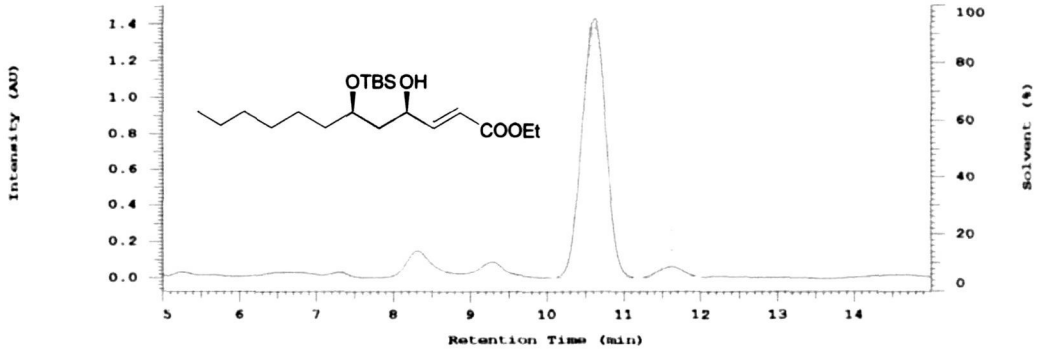
Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	7.31	314879	3882718	94.984
2	7.89	17317	205022	5.016
		332196	4087740	100.000

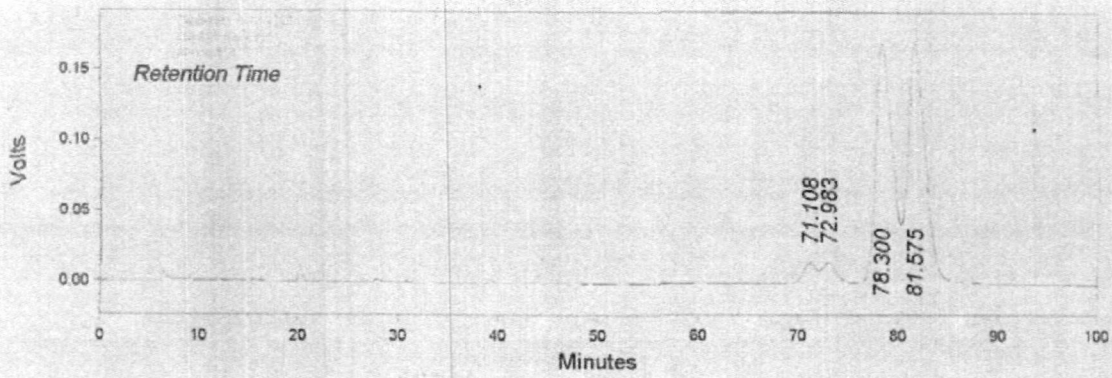
Peak rejection level: 0

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	10.61	715879	15494145	95.984
2	11.61	29299	648225	4.016
		745178	16142370	100.000

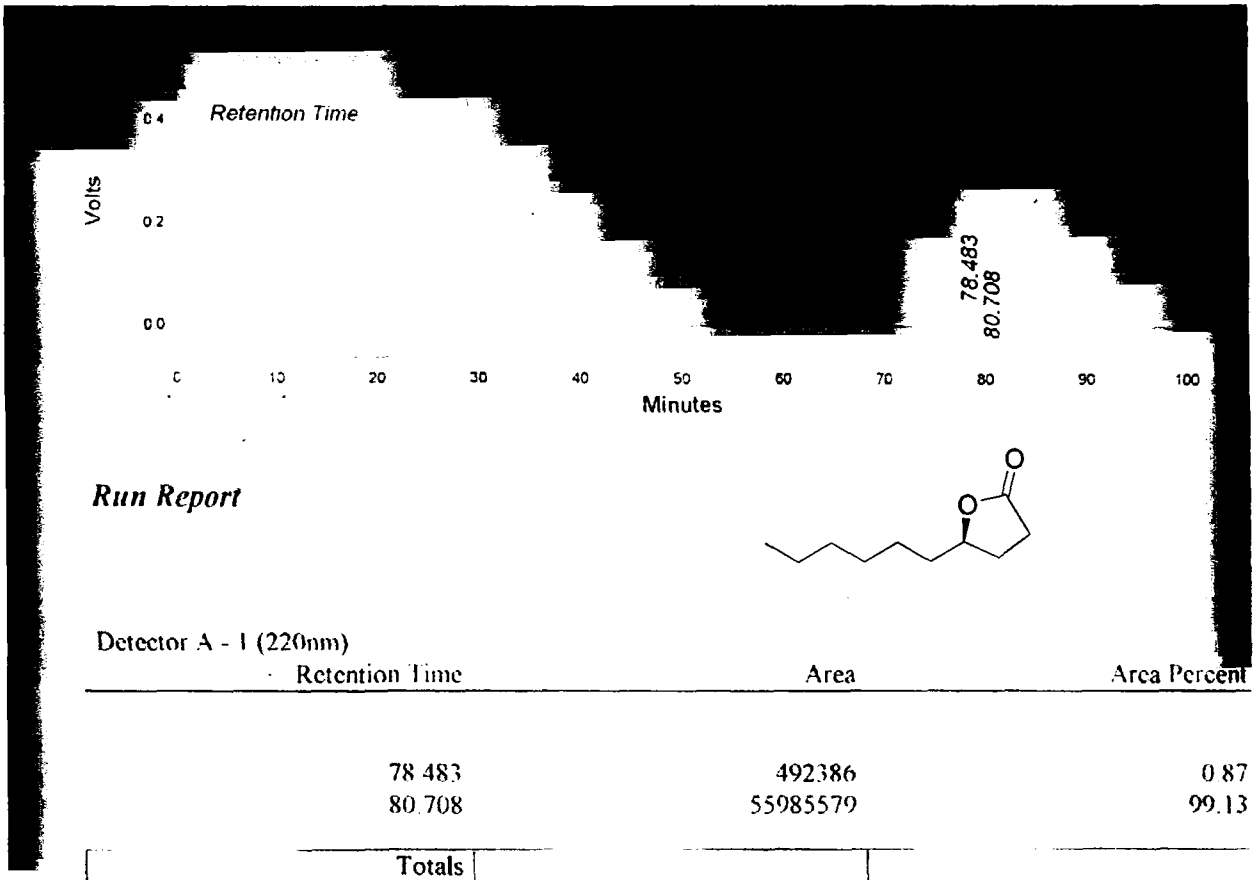
Peak rejection level: 0



Run Report

Detector A - 1 (220nm)

Retention Time	Area	Area Percent
71.108	1256170	2.99
72.983	1371866	3.27
78.300	19033388	45.32
81.575	20338275	48.42
Totals	41999699	100.00



Run Report

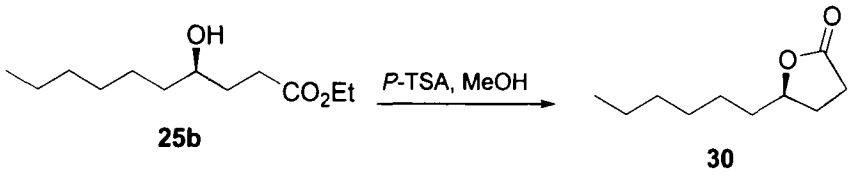
Detector A - 1 (220nm)

Retention Time	Area	Area Percent
78.483	492386	0.87
80.708	55985579	99.13
Totals	56477965	100.00

4.1.8. References

1. (a) K. L. Hagen, *Proc. Hawaii. Entomol. Soc.* **1953**, *15*, 115; (b) G. R. Buckingham, *Ann. Entomol. Soc. Am.* **1968**, *61*, 233; (c) H. J. Williams, M. Wong, R. A. Wharton, S. B. Vinson, *J. Chem. Ecol.* **1988**, *14*, 1727.
2. (a) G. C. Paddon-Jones, C. J. Moore, D. J. Brecknell, W. A. Konig, W. Kitching, *Tetrahedron Lett.* **1997**, *38*, 3479; b) G. C. Paddon-Jones, C. S. P. McErlean, P. P. Hayes, C. J. Moore, W. A. Konig, W. Kitching, *J. Org. Chem.* **2001**, *66*, 7487.
3. a) H. B. Mereyala, R. R. Gadikota, *Chem. Lett.* **1999**, 273; b) H. B. Mereyala, R. R. Gadikota, *Tetrahedron: Asymmetry* **2000**, *11*, 743; c) H. B. Mereyala, R. R. Gadikota, K. S. Sunder, S. Shailaja, *Tetrahedron* **2000**, *56*, 3021.
4. E. Paz-Morales, M. Ruth, F. Sartillo-Piscil, *Carbohydr. Res.* **2009**, *344*, 1123.
5. D. Agrawal, V. Sriramurthy, V. K. Yadav, *Tetrahedron Lett.* **2006**, *47*, 7615.
6. G. Banda, I. E. Chakravarthy, *Tetrahedron: Asymmetry* **2006**, *17*, 1684.
7. a) R. A. Fernandes, K. Pullaiah, *J. Org. Chem.* **2012**, *77*, 9357; b) D. A. Chaudhari, K. Pullaiah, R. A. Fernandes, *Tetrahedron: Asymmetry* **2014**, *25*, 1022.
8. S. J. Gharpure, L. N. Nanda, M. K. Shukla, *Eur. J. Org. Chem.* **2011**, 6632.
9. (a) G. Zhong, *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; (c) D. W. C. MacMillian, *Nature* **2008**, *455*, 304.
10. (a) P. Kumar, V. Jha, R. G. Gonnade, *J. Org. Chem.* **2013**, *78*, 11756; (b) V. Jha, P. Kumar, *RSC Adv.* **2014**, *4*, 3238; (c) V. Jha, P. Kumar, *Synlett* **2014**, *25*, 1089; (d) S. V. Kauloorkar, V. Jha, P. Kumar, *RSC Adv.* **2013**, *3*, 18288; (e) S. V. Kauloorkar, V. Jha, G. Jogdand, P. Kumar, *Org. Biomol. Chem.*, **2014**, *12*, 4454.
11. (a) N. B. Kondekar, P. Kumar, *Org. Lett.* **2009**, *11*, 2611; (b) P. Kumar, N. Dwivedi, *Acc. Chem. Res.* **2013**, *46*, 289 (c) V. Jha, N. B. Kondekar, P. Kumar, *Org. Lett.* **2010**, *12*, 2762.
12. Diastereomeric and enantiomeric excess were determined using HPLC (See experimental section).

    In order to determine the chiral purity of (*R*)-ethyl-4-hydroxydecanoate **25b**, it was converted into lactone **30** on treatment with *p*-TSA in methanol.



25b **30**

13. The ratio of the mixture was determined by ^{1}H-NMR of crude mixture.
14. The protons H1, H2, H3, H4 and H5 were arbitrarily assigned to show the relative *syn* and *anti*-stereochemistry.

Total synthesis of (–)-(6*R*,11*R*,14*S*)-colletallol via proline catalyzed α-aminoxylation and Yamaguchi macrolactonization

4.2.1 Introduction

Macrolides are broadly classified into two categories, first class of compounds having C_2 symmetry in a 16 membered lactone ring and another class of 14-membered unsymmetrical bis-macrolactone to which (-)-colletallol **3,** a macrolide belongs. It was isolated from the plant pathogen *Collectotrichum capsici* along with structurally related macrolides colletol **1,** colletodiol **2** and colletoketol **4** (Fig. 1)[1] More recently, two related 14-membered bis-lactones were isolated from the aerobic fermentation of cultures of *Cytospora sp.* ATCC 20502, these being the structurally isomeric grahamimycin A **4** and grahamimycin A_1 **5**.[2] It was later realized that the structures of colletoketol and grahamimycin A were identical.[3] These macrolactones can result from a biosynthesis *via* the macrodiolide colletotriene **6**.[4] This class of macrolactone has been a synthetic target of considerable interest due to its promising biological activity and unique structure with an array of functionalities.

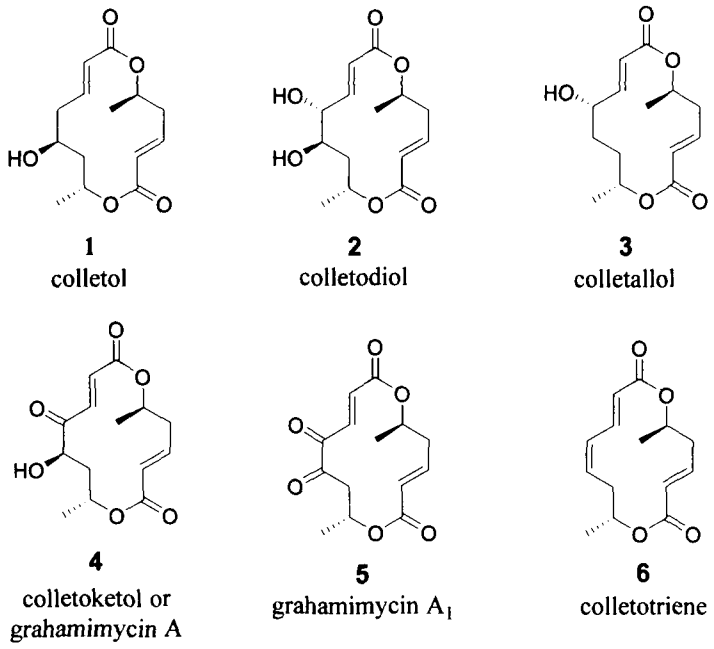


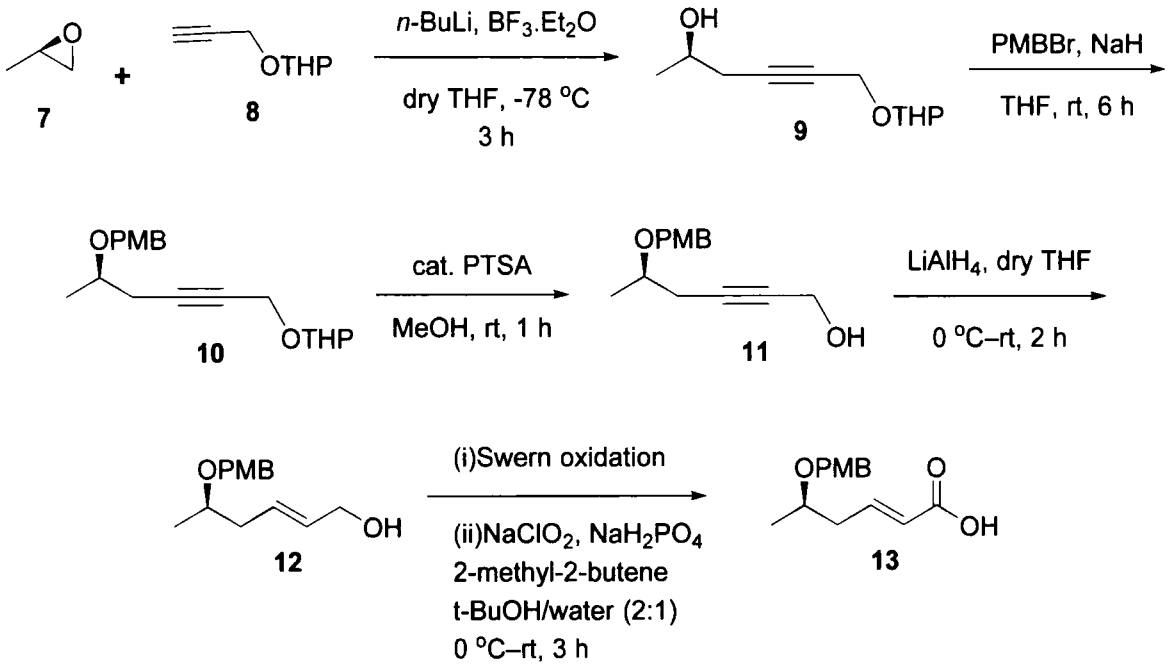
Figure 1. Some 14 membered bis-lactones

4.2.2. Review of Literature

Three synthesis of (–)-colletallol **3** is reported in literature[5] out of which one is racemic synthesis. Synthesis of its 14-epimer is also reported in literature.[6]

Radha Krishna *et al.* (2009)[5a]

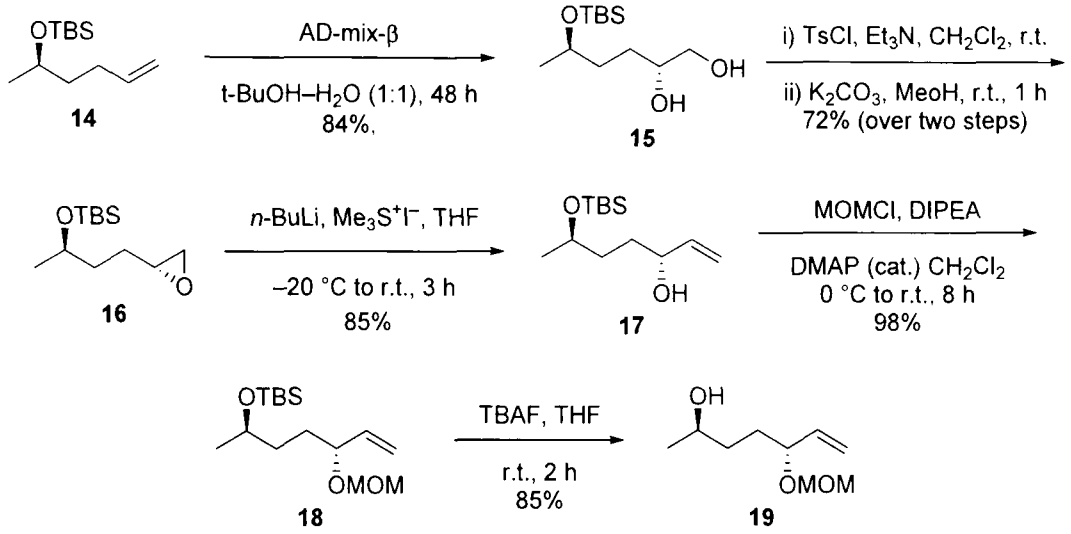
Radha Krishna and co-workers accomplished the enantioselective synthesis of (–)-colletollol **3** starting from epoxide. Chiral propylene oxide **7** was treated with 2-(2-propynyl)tetrahydro-*2H*-pyran **8** in the presence of *n*-BuLi to give alcohol **9** which on treatment with PMBBr afforded protected alcohol **10**. Compound **10** was treated with cat. amount of PTSA to give compound **11** which on reduction with $LiAlH_4$ in THF afforded allylic alcohol **12**. Swern oxidation of allylic alcohol **12** gave the corresponding aldehyde, which on further oxidation with $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene afforded the acid fragment **13**.



Scheme 1: Synthesis of acid fragment

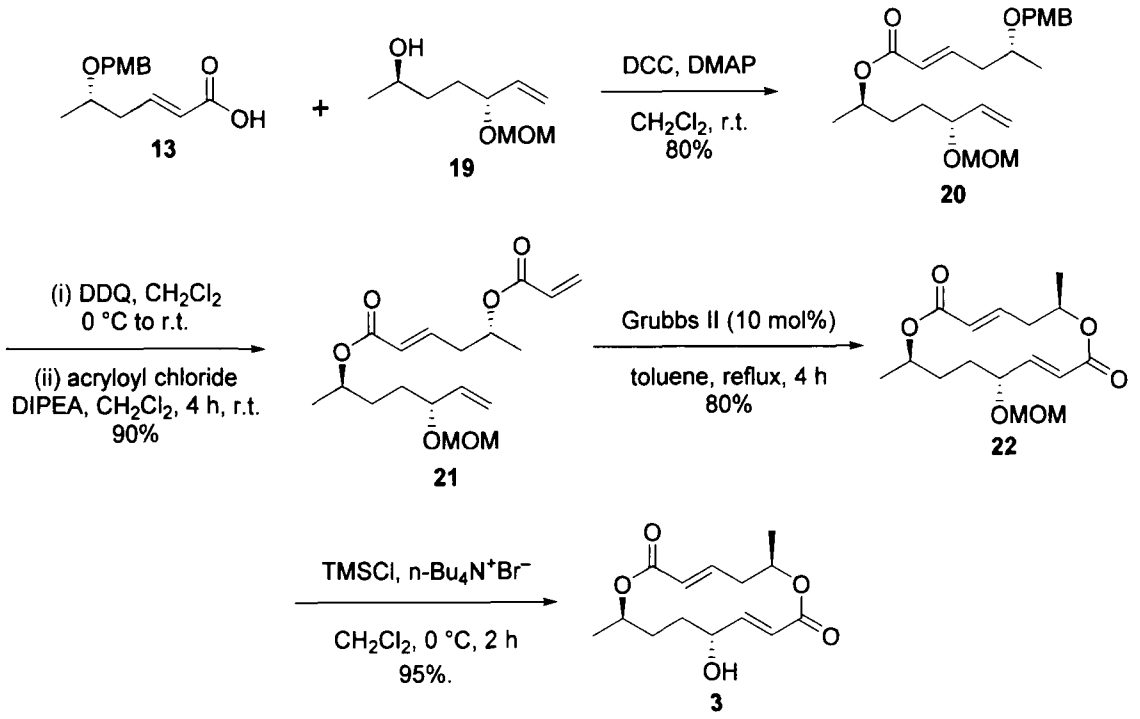
Synthesis of alcohol fragment started with hexenol **14** which on Sharpless asymmetric dihydroxylation gave diol **15**. Diol **15** was converted to epoxide **16** which on ring opening

reaction with trimethylsulfonium iodide gave allylic alcohol **17** which was protected as its MOM ether **18**. TBS deprotection of compound **18** furnished the corresponding alcohol **19**.



Scheme 2: Synthesis of alcohol fragment

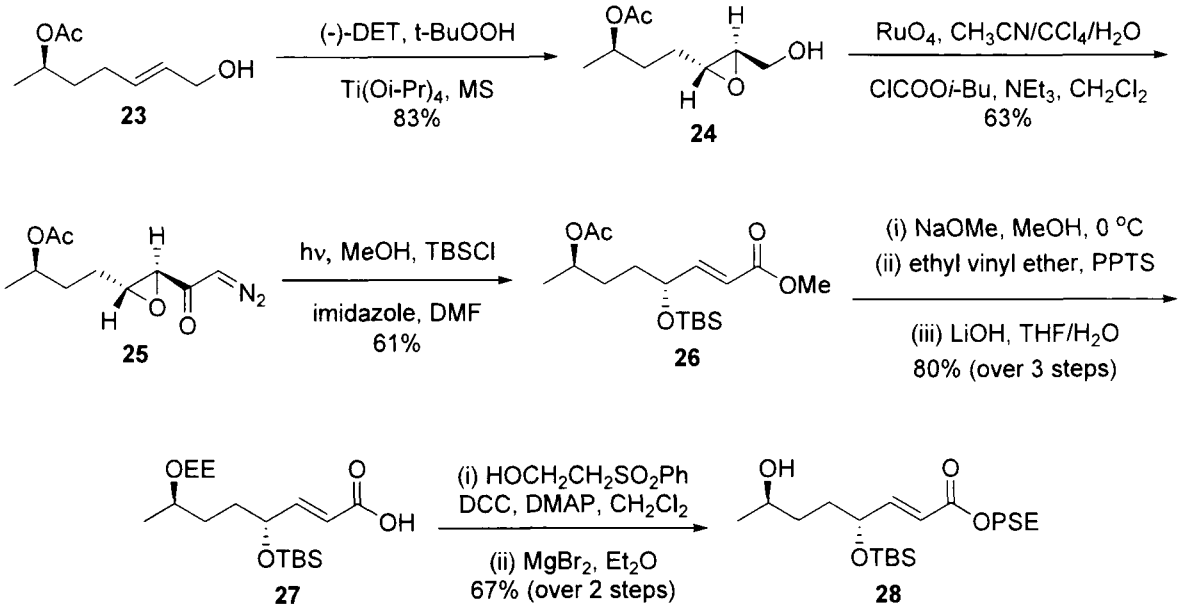
Esterification of acid **13** and alcohol **19** using DCC gave compound **20**. PMB deprotection of compound **20** gave corresponding alcohol which on reaction with acryloyl chloride furnished diester **21**. **21** on ring closing metathesis using Grubbs II afforded diolide **22**. Finally MOM deprotection resulted into target colletallol **3**.



Scheme 3: Completion of synthesis of colletallol

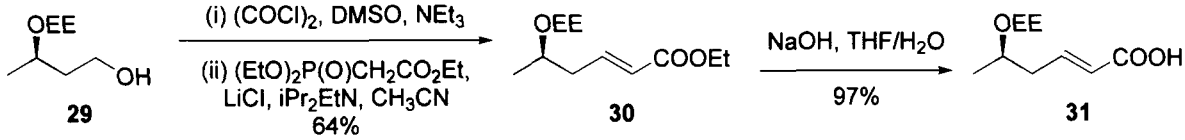
Zwanenburg *et al.* (1991)[5b]

Zwanenburg and co-workers accomplished the enantioselective synthesis of (–)-colletallol **3** starting from allylic alcohol. Asymmetric Sharpless epoxidation of allylic alcohol **23** gave epoxy-alcohol **24**, which was converted into diazoketone **25**. Irradiation of this diazo ketone **25** in methanol, followed by silylation gave compound **26**. Acetate group of silyl compound **26** was replaced with ether protection and ester was hydrolysed to give acid **27**. Carboxylic acid **27** was esterified with phenylsulfonyl ethanol and EE protecting group was removed to provide alcohol **28**.



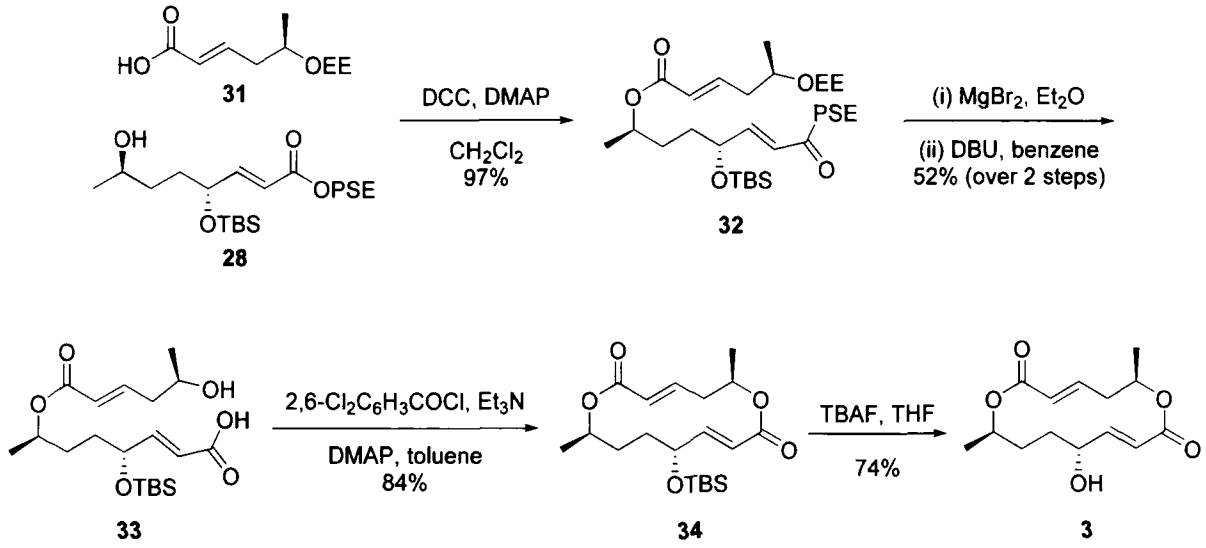
Scheme 4: Synthesis of alcohol fragment

Synthesis of acid fragment started with alcohol **29** which on oxidation and subsequent Wittig-Horner reaction gave ester **30**. Ester **30** on saponification gave acid **31**.



Scheme 5: Synthesis of acid fragment

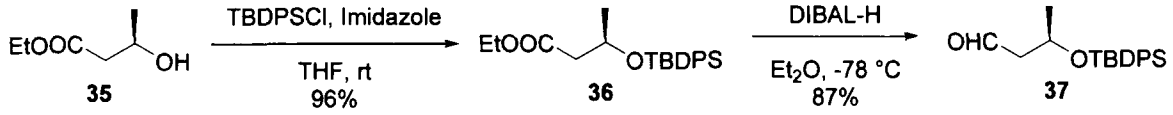
The coupling of acid **31** with the alcohol fragment **28** was successfully accomplished using DCC/DMAP as the condensing agent to get half lactone **32**. The half lactone **32** was converted into seco-colletallol **33** by successive removal of the EE protecting group and hydrolysis of ester group. Seco-colletallol **33** was subjected to macrolactonization using Yamaguchi condition to get lactone **34** which on TBS deprotection gave colletallol **3**.



Scheme 6: Completion of synthesis of colletallol (Zwanenburg's method)

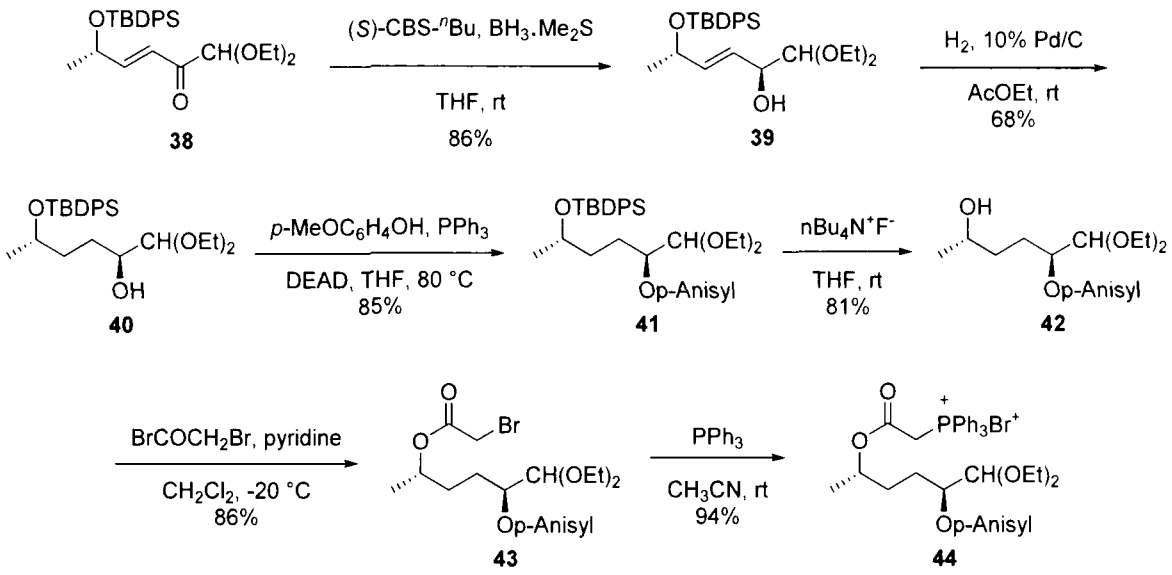
Floc'h *et al.* (1997)[6]

Floc'h and co-workers have synthesized 14-epimer of colletallol starting from hydroxyl butanoate **35**. They used double Wittig reaction to construct the lactone ring. The free hydroxyl group of compound **35** was protected to get compound **36** which was reduced to aldehyde **37** using DIBAL-H at -78 °C.



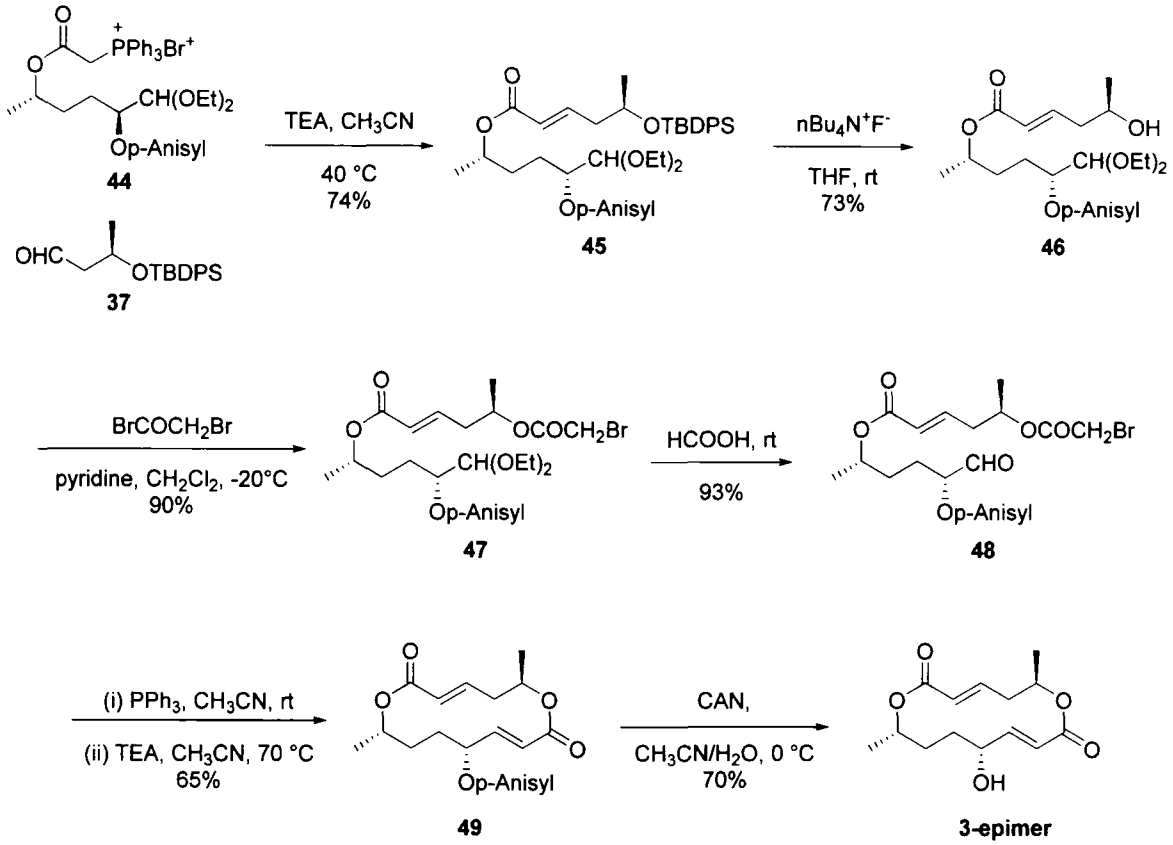
Scheme 7: Synthesis of aldehyde fragment

The enantioselective reduction of enone **38** with CBS reagent afforded the allylic alcohol **39** which on hydrogenation condition gave saturated alcohol **40**. The free hydroxyl group was subjected to Mitsunobu condition to get *p*-anisyl ether **41** via inversion of configuration. Ether **41** on TBDPS deprotection gave alcohol **42**. The alcohol **42** was esterified using bromoacetyl bromide to give the bromo ester **43** which was converted into the phosphonium salt **44** by addition of triphenylphosphine.



Scheme 8: Synthesis of phosphonium salt fragment

The phosphonium salt **44** was treated with 0.8 equiv of TEA to generate *in situ* the corresponding phosphorane which was condensed with 1.5 equiv of the aldehyde **37** in CH_3CN to give (*E*)-enoate **45**. The cleavage of the silyl ether of (*E*)-enoate **45** afforded alcohol **46**. Esterification of alcohol **46** with bromoacetyl bromide afforded ester **47** which on deprotection of the aldehyde function in neat formic acid yielded free aldehyde **48.** The addition of triphenylphosphine to aldehyde **48** generated the phosphonium salt which undergoes Wittig reaction in the presence of large excess of TEA to give Wittig product **49**. Cleavage of the *p*-anisyl ether of Wittig product **48** with CAN afforded the 14-epimer of colletallol.



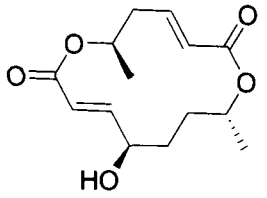
Scheme 9: Synthesis of 14-*epi*-colletallol (Floc'h's method)

4.2.3. Present work

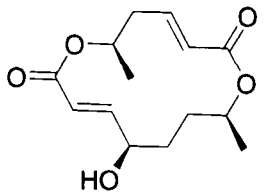
Objective:

The promising biological activity and the unique structure of the 14-membered unsymmetrical diolides make them attractive synthetic target and so far three syntheses of colletallol **(3)** including a racemic synthesis have been reported in the literature. However, the natural (6*R*,11*R*,14*R*) colletalol was found to be inactive, its 14-epimer was found to be a useful target for structure activity studies.

In recent years, there has been growing interest in the use of small organic molecules to catalyze reactions in organic synthesis.[7] As a result, the area of organocatalysis has now emerged as a promising strategy and as an alternative to expensive protein catalysis and toxic metal catalysis,[8] thus becoming a fundamental tool in the catalysis toolbox available for asymmetric synthesis.[9]



(6*R*,11*R*,14*R*)-Colletallol



(6*R*,11*R*,14*S*)-Colletellol

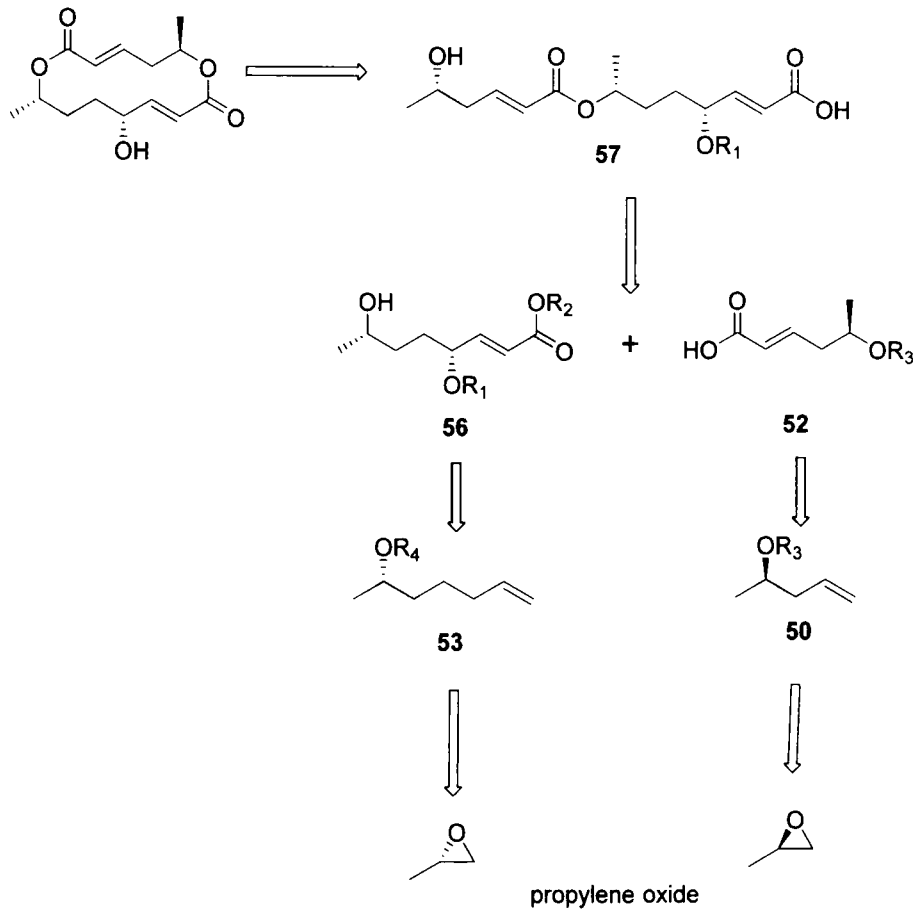
Figure 2. Colletallol and its 14-*S*-epimer

Proline is among the most successful secondary amine based organocatalysts which has been widely employed in the asymmetric aldol, Mannich, Michael addition, and α-functionalization, viz. α-aminoxylation, α-amination, and α-aminoxylation directed tandem reactions, among many others, providing rapid, catalytic, and atom-economical access to enantiomerically pure products.

In continuation of our interest in organocatalysis[10] and asymmetric synthesis of 1,3-polyol[11a] and naturally occurring lactones[11b] we considered undertaking the enantioselective total synthesis of (–)-(6*R*,11*R*,14*S*)-colletallol (**3**-*epimer*), employing sequential α-aminoxylation/HWE olefination catalyzed by proline.

4.2.4. Results and Discussion:

As per the retrosynthetic scheme as delineated in **scheme 10**, colletallol could be synthesized from the acid fragment **52** and alcohol fragment **56** . Both the acid and alcohol fragment could be accessed independently from chiral propylene oxide, a commercially available starting material.

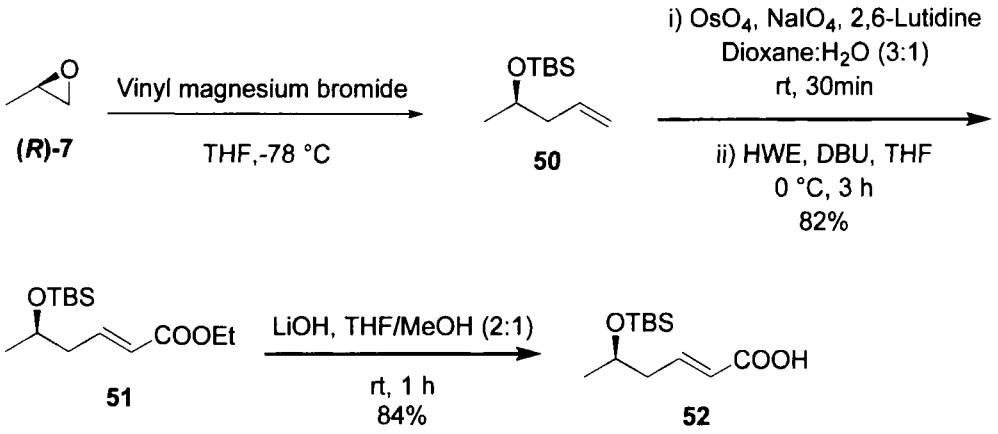


Scheme 10. Retrosynthetic route to colletallol

Synthesis of acid fragment 52

Synthesis of acid fragment started with (*R*)-propylene oxide **7**, which was converted to TBS protected homoallylic alcohol **50** by literature procedure.[12] The olefin of TBS protected homoallylic alcohol **50** was oxidized to aldehyde in the presence of OsO_4 and $NaIO_4$ and the aldehyde without purification was subjected to the HWE olefination reaction with triethylphosphonoacetate in dry THF at 0°C to furnish the *trans*-olefin **51** in 82% (two steps, *E/Z* 99:1) yield. The IR spectrum of **51** showed the ester carbonyl absorption at 1708 cm^{-1} and olefin C=C stretching at 1664 cm^{-1}. The ^1H NMR spectrum gave olefin protons at δ 5.84 (doublet of triplet) with the coupling constant J = 1.34, 15.66 Hz and δ 6.88-7.03 (multiplet) indicating *trans*-olefin. The ester group of *trans*-olefin **51** was hydrolyzed with LiOH to afford the corresponding acid **52** in 84% yield (**scheme 11**).

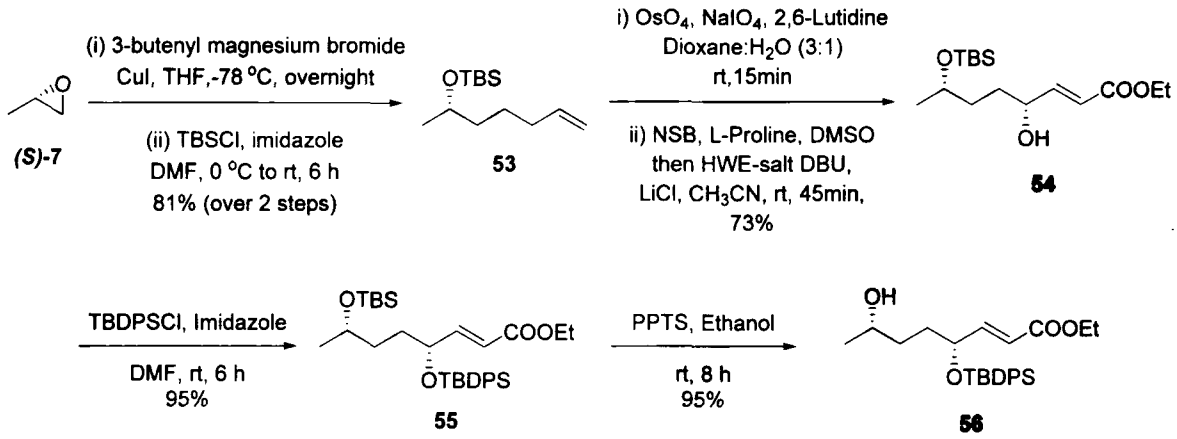
The disappearance of ethyl protons in the range of δ 4.19 as quartet and 1.29 as doublet in ^{1}H NMR spectrum confirmed the formation of the product.



Scheme 11: Synthesis of acid fragment

Synthesis of alcohol fragment 56

Synthesis of alcohol fragment started with (*S*)-propylene oxide **7**. The ring opening of (*S*)-propylene oxide **7** with 3-butenyl magnesium bromide using CuI as a catalyst gave the corresponding alkenol which on protection of free hydroxyl group as TBS ether gave olefin **53**[13] in 81% yield. The olefin **53** was oxidized to aldehyde in the presence of OsO_4 and $NaIO_4$ and the aldehyde was subjected to α-aminoxylation[14] reaction using L-proline as a catalyst followed by HWE-olefination to yield compound **54** in 73% (two steps) yield and good diastereomeric excess (dr ratio 98:2).[15] The IR spectrum of **54** showed the ester carbonyl absorption at 1712 cm^{-1}. The ^{1}H NMR spectrum gave olefin protons at δ 6.94 (doublet of doublet) with the coupling constant J = 4.7, 15.7 Hz, and δ 6.06 (doublet of doublet) with the coupling constant J = 1.8, 15.7 Hz indicating *trans*-olefin. Protection of the free hydroxyl group as its TBDPS ether gave **55** in 95% yield. Disappearance of peak at 3432 cm^{-1} in IR spectrum confirmed the formation of **55**. The TBS group was deprotected using PPTS in ethanol for 8 h to give alcohol **56** in 90% yield. Prolonging the reaction resulted in some deprotection of TBDPS group also. The IR spectra of **56** showed presence of hydroxyl absorption at 3378 cm^{-1}.



Scheme 12: Synthesis of alcohol fragment

Completion of synthesis of colletallol

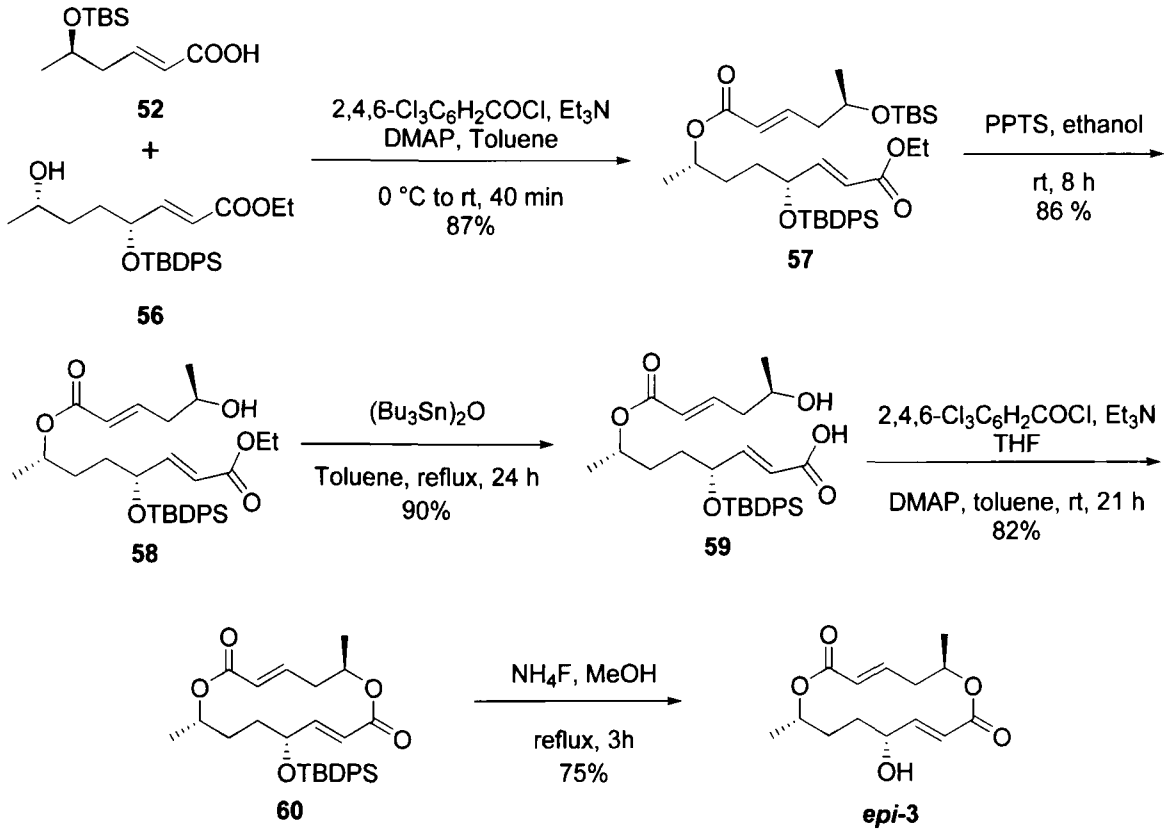
Having obtained both the fragments alcohol **56** and acid **52** in substantial amount we required to couple them and achieve the synthesis of target molecule by synthetic manipulations. Thus. both the fragments were subjected to esterification under different conditions. Our first few attempts using Steglich condition, Shiina condition and Mitsunobu procedures were unsuccessful. We then proceeded with Yamaguchi protocol where after a few optimizations, we could observe the formation of **57** within 40 minutes (87% yield) when the reaction was performed at 0°C (**scheme 13**). The TBS ether of **57** was cleaved by PPTS in EtOH to afford alcohol **58** in 86% yield. The IR spectra of **58** showed presence of hydroxyl absorption at 3370 cm^{-1}. Hydrolysis of ethyl ester **58** to seco acid **59** using LiOH[16] failed inspite of several attempts with different solvent combinations, temperature and equivalents, instead we ended up hydrolyzing the ester and acid fragment. Using DBU in benzene[5b] also gave only a complex reaction mixture. Since basic conditions were not found suitable to our substrate, therefore we considered changing the conditions to neutral medium. Finally the desired *seco*-acid **59** was obtained in 90% yield using bis(tributyltin) oxide[17] in toluene under reflux conditions (**Table 1**). The disappearance of ethyl protons in the range of δ 4.18 as quartet in ^{1}H NMR spectrum confirmed the formation of the product.

Reagent and condition	Solvent	Product
$LiOH.H_2O$ (rt)	THF:MeOH:H_2O 3 : 2 :1	NR*
$LiOH.H_2O$ (rt)	THF:H_2O 1 : 1	NR*
$LiOH.H_2O$ (rt)	MeOH:H_2O 2 : 1	NR*
$LiOH.H_2O$ (reflux)	THF:MeOH:H_2O 3:2:1	NR*
DBU	Benzene	Complex mixture
$(n\text{-}Bu_3Sn)_2O$ (rt)	Toluene	SM recovered
$(n\text{-}Bu_3Sn)_2O$ (2 equiv.) reflux	Toluene	20%
$(n\text{-}Bu_3Sn)_2O$ (5 equiv.) reflux	**Toluene**	**90%**

NR* Hydrolysis of internal ester to give alcohol and acid fragments

Table 1: Optimisation for hydrolysis of **58**

Macrolactonization of *seco*-acid **59** was achieved using Yamaguchi coupling condition to give corresponding macrocycle lactone **60**. From our previous experiences we thought that prolonged reaction times using PPTS would cleave TBDPS but attempts under varied temperature and reaction conditions were unsuccessful. We then chose ammonium fluoride in methanol under reflux conditions to cleave TBDPS which afforded the target molecule *epi*-**3** in 75% yield (**scheme 13**).



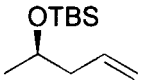
Scheme 13: Completion of synthesis of colletallol

4.2.5. Conclusion

In conclusion, a new and efficient total synthesis of (-)-colletallol (*epi*-3) with high diastereoselectivity has been achieved using proline catalyzed α-aminoxylation and Yamaguchi macrolactonization reactions. The synthetic strategy described here has significant potential as we have achieved overall yield of 22% in 11 linear steps. The method is amenable for further extension to the synthesis of all the isomers of (-)-colletallol and other 14-membered unsymmetrical bis-macrolactones.

4.2.6. Experimental Section

(*R*)-*tert*-Butyldimethyl-(pent-4-en-2-yloxy)-silane (50):



A round bottomed flask was charged with copper (I) iodide (0.76 g, 4 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (5 mL) was added. This suspension was cooled to –20 °C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 60 mL, 60 mmol) was injected to it. A solution of (*R*)-propylene oxide **7** (2.3 g, 4 mmol) in THF (3 mL) was added slowly to the above reagent, and the mixture was stirred at –20 °C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude alcohol product.

To a stirred soluion of crude alcohol in CH_2Cl_2 (10 mL), imidazole (0.425 g, 6 mmol) was added. To this solution *t*-butylchlorodimethyl silane (0.9 g, 6 mmol) was added at 0 °C and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided (*R*)-*tert*-Butyldimethyl-(pent-4-en-2-yloxy)-silane **50** as a colorless liquid.

Yield: 6.08 g, 76%

$[\alpha]_D^{25}$: -11.87 (c 1.00 $CHCl_3$) {lit.[12] $[\alpha]_D^{28}$ –14.46 (*c* = 1.8, $CHCl_3$)}

Mol. Formula: $C_{11}H_{24}OSi$

IR ($CHCl_3$, cm^{-1}): ν_{max} 3088, 2929, 2896, 1642, 1255, 1129

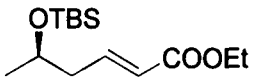
^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.91 (s, 9H), 1.14 (d, *J* = 6.06 Hz, 3H), 2.19 (dq, *J* = 1.01, 5.81, 11.88 Hz, 1H), 3.21-3.37 (m, 1H), 3.92-4.04 (m, 1H), 5.00-5.10 (m, 2H), 5.82 (d, *J* = 8.1 Hz, 1H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ -4.7, -4.5, 18.1, 23.4, 25.9, 44.3, 68.6, 116.5, 135.6 ppm.

Enantiomeric ratio was determined by HPLC analysis: 98% ee

HPLC: Chiralcel OJ-RH (150 X 4.6mm) (MeOH: H_2O = 90:10, flow rate 0.7 ml/min, λ = 254 nm). Retention time (min): 6.31 (major) and 7.48 (minor). The racemic standard was prepared in the same way using racemic propylene oxide, ee 98%.

(*R*,*E*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)hex-2-enoate (51):



To a solution of compound **50** (2 g, 7.34 mmol) in dioxane-water (3:1, 20 mL) were added 2,6-lutidine (1.70 mL, 14.69 mmol), OsO_4 (0.1M solution in toluene, 0.4 mL, 0.20 mmol) and $NaIO_4$ (6.28 g, 29.39 mmol). The reaction was stirred at 25 °C for 30 min. After the reaction was complete, the reaction mixture was passed through a pad of celite. 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 (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To the solution of triethylphosphonoacetate (2.2 mL, 11.01 mmol) and DBU (1.7 mL, 11.01 mmol) in THF, crude aldehyde dissolved in THF was added and the whole mixture was stirred at 0 °C for 3h. It was then quenched with aq. ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude product. It was then concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (94:06) as eluent to afford the (*R*,*E*)-ethyl 5-(*tert*-butyldimethylsilyloxy)hex-2-enoate **51** as a pale yellow liquid.

Yield: 2.24 g, 82%

Mol. Formula: $C_{14}H_{28}O_3Si$

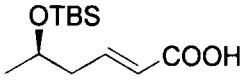
$[\alpha]_D^{25}$: -9.2 (*c* 1, $CHCl_3$){lit.[9a] $[\alpha]_D^{25}$ -9.5 (*c* 1.00, $CHCl_3$)}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 6.88-7.03 (m, 1H), 5.84 (dt, *J* = 1.34, 15.66 Hz, 1H), 4.19 (q, *J* = 7.20 Hz, 2H), 3.85-4.0 (m, 1H), 2.32 (tt, *J* = 1.13, 7.20 Hz, 2H), 1.29 (t, *J* = 7.07 Hz, 3H), 1.17 (d, *J* = 6.06 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 146.0, 123.1, 67.6, 60.1, 42.4, 25.7, 23.7, 18.0, 14.2, -4.9, -4.6 ppm.

MS (ESI): *m/z* 295.20

(*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)hex-2-enoic acid (52):



Procedure for ester hydrolysis:

To the ester **51** (1.4 g, 5.14 mmol) dissolved in THF (10 mL) and MeOH (5 mL) was added $LiOH.H_2O$ (266 mg, 6.49 mmol) and stirred at 0 °C to room temperature for 1 h. The reaction mixture was further diluted with H_2O (5 mL) and stirred for 30 min then concentrated by rotary evaporator to quarter of its volume. The mixture was acidified with 1 M HCl (p^H 3) and the reaction mixture was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (80:20) as eluent to afford (*R*,*E*)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoic acid **52** as a pale yellow liquid.

Yield: 1.05 g, 84%.

Mol. Formula: $C_{12}H_{24}O_3Si$

$[\alpha]_D^{25}$: -7.0 (*c* 1, $CHCl_3$)){lit.[9b] $[\alpha]_D^{25}$ -7.6 (*c* 0.81, $CHCl_3$)}.

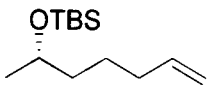
IR ($CHCl_3$, cm^{-1}): ν_{max} 2972, 1717, 1680, 1475, 1449

^{1}H NMR (200 MHz, $CDCl_3$): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.20-6.96 (m, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 3.95 (q, *J* = 6.0 Hz, 1H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 149.0, 122.6, 67.5, 42.5, 25.8, 23.8, 18.0, -4.6, -4.9 ppm.

MS (ESI): *m/z* 267.12. **HRMS (ESI) *m/z*:** [M + Na]+ Calcd for $C_{12}H_{24}O_3SiNa$ 267.1387; Found 267.1385

(*S*)-tert-butyl(hept-6-en-2-yloxy)dimethylsilane (53):



A round bottomed flask was charged with copper (I) iodide (2.63 g, 13.78 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to –78 °C and vigorously stirred, and 3-butenylmagnesium bromide (0.5 M in THF, 42 mL, 20.67 mmol) was injected to it. A solution of (*S*)-propylene oxide **7** (8 g, 13.78 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –78 °C overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the crude alcohol.

To a solution of crude alcohol in DMF (15 ml), imidazole (1.41 g, 20.67 mmol) was added. To this solution *t*-butylchlorodimethyl silane (3.12 g, 31.92 mmol) was added at 0 °C and reaction was stirred at room temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided (*R*)-*tert*-butyl(hept-6-en-2-yloxy)dimethylsilane **53** as a colorless liquid.

Yield: 8.37 g, 81%.

Mol. Formula: $C_{13}H_{28}OSi$

$[\alpha]_D^{25}$: -9.2 (*c* 1, $CHCl_3$){lit.[13] $[\alpha]_D^{25}$ -9.5 (*c* 1.00, $CHCl_3$)}

IR ($CHCl_3$, cm^{-1}): ν_{max} 3090, 2925, 1640, 1261, 1120

^{1}H NMR (200 MHz, $CDCl_3$): δ 5.94 - 5.68 (m, 1 H), 5.09 - 4.89 (m, 2 H), 3.89 - 3.71 (m, 1 H), 2.13 - 1.98 (m, 2 H), 1.55 - 1.35 (m, 4 H), 1.13 (d, J = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H) ppm.

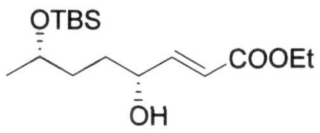
^{13}C NMR (50 MHz, $CDCl_3$): = δ 139.0, 114.3, 68.5, 39.2, 33.8, 25.9, 25.1, 23.8, 18.1, -4.4, -4.7

MS (ESI): *m/z* 251.18

Enantiomeric ratio was determined by HPLC analysis; 98% ee

HPLC: Chiralcel OJ-RH (150 X 4.6mm) (MeOH: H_2O = 90:10, flow rate 0.7 ml/min, λ = 230 nm). Retention time (min): 8.15 (major) and 8.79 (minor). The racemic standard was prepared in the same way using racemic propylene oxide, ee 98%.

Ethyl (4*R*,7*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate (54):



To a solution of compound **53** (2 g, 8.76 mmol) in dioxane-water (3:1, 16 mL) were added 2,6-lutidine (2.0 mL, 17.53 mmol), OsO_4 (0.1 M solution in toluene, 0.4 mL, 0.20 mmol) and $NaIO_4$ (7.53 g, 35.06 mmol). The reaction mixture was stirred at 25 °C for 15 min. After the reaction was complete, water (5 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried (Na_2SO_4) to give crude aldehyde which was used as such for the next step without further purification.

To a solution of above aldehyde and nitroso benzene (0.9 g, 8.76 mmol) in anhydrous DMSO (16 mL) was added L-proline (0.42 g, 3.5 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (3.50 mL, 17.52 mmol), DBU (2.40 mL, 17.52 mmol) and LiCl (0.75 g, 17.52 mmol) in CH_3CN (16 mL) was added quickly (1-2 min) at 0 °C. The resulting mixture was allowed to warm to room temperature for 45 min and quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. This reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5×100 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using petroleum ether: EtOAc (80:20) as eluent to give ethyl-(4*R*,7*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate **54** as a colorless liquid.

Yield: 2.02 g, 73%.

Mol. Formula: $C_{16}H_{32}O_4Si$

$[\alpha]_D^{25}$: -26.7 (*c* 1, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3056, 3019, 2962, 2916, 1712, 1661, 1472, 1463

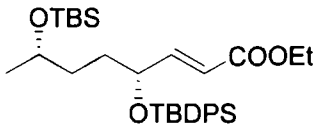
^{1}H NMR (200 MHz, $CDCl_3$): δ 6.94 (dd, J = 4.7, 15.7 Hz, 1H), 6.06 (dd, J = 1.8, 15.7 Hz, 1H), 4.33-4.25 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.00-3.82 (m, 1H), 1.81-1.49 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 150.4, 119.9, 70.9, 68.3, 60.2, 35.2, 32.2, 25.7, 23.0, 18.0, 14.1, -4.6, -4.9 ppm.

MS (ESI): *m/z* 339.18. **HRMS (ESI)** ***m/z***: [M + Na]+ Calcd for $C_{16}H_{32}O_4SiNa$ 339.1962: Found 339.1960

HPLC: Kromasil RP-18 (150 X 4.6mm) (MeOH : H_2O = 75:25), flow rate 1.0 ml/min, (λ = 254 nm). Retention time (min): 5.85 (major) and 7.81 (minor), (dr 98:2)

Ethyl (4*R*,7*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)oct-2-enoate (55):



General procedure for TBDPS protection: To a stirred solution of alcohol **54** (1.5 g, 4.74 mmol) in dry DMF (10 mL) and imidazole (484 mg, 7.12 mmol) at 0 °C was added TBDPSCl (1.96 g, 1.85 mL, 7.12 mmol) dropwise and DMAP (cat.) and the reaction mixture was warmed to rt for 6 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was washed with brine (2 x 40 mL) and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure to give crude product. The crude product was then purified by flash column chromatography using pet ether: EtOAc (98:2) as eluent to give ethyl-(4*R*,7*R*,*E*)-7-((*tert*-butyldimethylsilyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)oct-2-enoate **55** as a colorless liquid.

Yield: 2.50 g, 95%.

Mol. Formula: $C_{32}H_{50}O_4Si_2$

$[\alpha]_D^{25}$: +16.18 (*c* 1.2, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3019, 2962, 2916, 1712, 1661, 1472, 1463

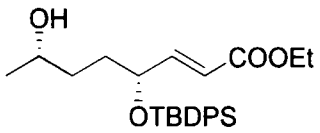
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72-7.61 (m, 4H), 7.45-7.35 (m, 6H), 6.88 (dd, J = 5.2, 15.6 Hz, 1H), 5.92 (dd, J = 1.4, 15.5 Hz, 1H), 4.37 (q, J = 5.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.84-3.59 (m, 1H), 1.34-1.27 (m, 6H), 1.14-1.06 (m, 13H), 0.89 (s, 9H), 0.04 (d, J = 3.5 Hz, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 150.1, 135.8, 133.9, 133.5, 129.7, 127.6, 120.2, 72.4, 68.4, 60.2, 39.5, 36.8, 27.0, 25.9, 23.8, 19.3, 18.1, 14.2, -4.4, -4.7 ppm.

MS (ESI): *m/z* 577.30.

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{32}H_{50}O_4Si_2Na$ 577.3140; Found 577.3137

Ethyl (4*R*,7*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-7-hydroxyoct-2-enoate (56):



General procedure for TBDMS deprotection: To a stirred solution of α,β-unsaturated ester **55** (2.4 g, 4.3 mmol) in ethanol at 0 °C, PPTS (161 mg, 0.65 mmol) was added in portions, and the reaction mixture was warmed to rt, stirred for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (80:20) as eluent to give ethyl (4*R*,7*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-7-hydroxyoct-2-enoate **56** as a colorless liquid

Yield: 1.30 g, 95%

Mol. Formula: $C_{26}H_{36}O_4Si$

$[\alpha]_D^{25}$: +12.42 (*c* 0.85, $CHCl_3$).

IR ($CHCl_3$, cm^{-1}): ν_{max} 3371, 2975, 2932, 1713, 1638, 1583, 1422, 1375, 1227, 1129

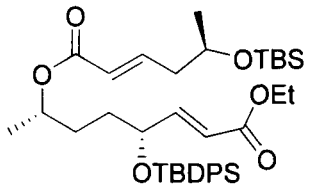
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72-7.61 (m, 4H), 7.45-7.35 (m, 6H), 6.88 (dd, J = 5.2, 15.6 Hz, 1H), 5.92 (dd, J = 1.4, 15.5 Hz, 1H), 4.37 (q, J = 5.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.84-3.59 (m, 1H), 1.31 (t, J = 7.1 Hz, 6H), 1.14-1.06 (m, 13H), 0.89 (s, 9H), 0.04 (d, J = 3.5 Hz, 6H) ppm.

^{13}C NMR (50 MHz, $CDCl_3$): δ 166.6, 150.1, 135.8, 133.9, 133.4, 129.7, 127.6, 120.2, 72.3, 67.9, 60.3, 39.0, 36.7, 27.0, 23.4, 19.3, 14.2 ppm.

MS (ESI): *m/z* 463.21.

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{26}H_{36}O_4SiNa$ 463.2275; Found 463.2271.

Ethyl (4*R*,7*R*,*E*)-7-(((R,E)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy)oct-2-enoate (57):



To a solution of acid **52** (200 mg, 0.82 mmol) in toluene (4mL), was added triethyl amine (0.37 mL, 1.64 mmol) and 2,4,6-trichlorobenzoyl chloride (0.45 mL, 0.98 mmol) under nitrogen atmosphere at 0 °C and the resulting mixture was stirred at room temperature for 30 min. To this, alcohol **56** (240 mg, 0.55 mmol) in toluene (10 mL) and 4-dimethyl aminopyridine (DMAP) (1.0 g, 8.2 mmol) were added successively at 0 °C. Stirring was continued for additional 10 min. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated to afford the crude product which was purified by silica gel column chromatography using pet ether: EtOAc (90:10) as eluent to give ethyl (4*R*,7*R*,*E*)-7-(((*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoyl)oxy)-4-((*tert*-butyldiphenylsilyl)oxy) oct-2-enoate **57** as a colorless syrupy liquid.

Yield: 316 mg, 87%.

Mol. Formula: $C_{38}H_{58}O_6Si_2$

$[\alpha]_D^{25}$: -16.82 (*c* 0.55, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2935, 1716, 1680, 1475, 1320, 1216, 1144, 1110

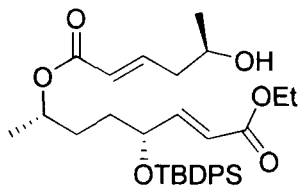
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.61 (m, 4H), 7.43-7.36 (m, 6H), 6.97-6.81 (m, 2H), 5.89 (d, J = 15.7 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 4.91-4.77 (m, 1H), 4.35 (d, J = 5.1 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.97-3.85 (m, 1H), 2.38-2.24 (m, 2 H), 1.32-1.26 (m, 4H), 1.18-1.16 (m, 6H), 1.08 (s, 12H), 0.88 (s, 9H), 0.05 (d, J = 4.6 Hz, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 166.0, 150.0, 145.8, 135.8, 134.8, 133.9, 133.4, 129.8, 127.6, 123.6, 120.2, 72.3, 70.6, 67.6, 60.3, 42.4, 36.6, 35.8, 27.0, 25.8, 23.9, 20.0, 19.3, 14.2, -4.5, -4.8 ppm.

MS (ESI): *m/z* 689.34

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{38}H_{58}O_6Si_2Na$ 689.3269; Found 689.3263

Ethyl (4*R*,7*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoate (58):



To a stirred solution of TBS protected α,β-unsaturated ester **57** (260 mg, 0.39 mmol) in ethanol at 0 °C, PPTS (108 mg, 0.43 mmol) was added in portions, and the reaction mixture was warmed to rt, stirred for 8 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (70:30) as eluent to give ethyl (4*R*,7*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoate **58** as a colorless thick syrupy liquid.

Yield: 185 mg, 86%.

Mol. Formula: $C_{32}H_{44}O_6Si$

$[\alpha]_D^{25}$: -14.87 (*c* 0.6, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2935, 1727, 1690, 1466, 1322, 1216

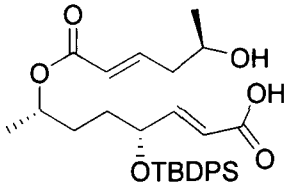
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.58 (m, 4H), 7.46-7.31 (m, 6H), 6.98-6.80 (m, 2H), 5.91 (d, *J* = 5.9 Hz, 1H), 5.87 (d, *J* = 6.1 Hz, 1H), 4.91-4.80 (m, 1H), 4.39-4.31 (m, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 4.03-3.92 (m, 1H), 2.41-2.31 (m, 2H), 1.31-1.24 (m, 9H), 1.19 (d, *J* = 6.1 Hz, 4H), 1.09 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 165.9, 150.0, 144.5, 135.8, 134.0, 133.4, 129.7, 127.6, 124.4, 120.3, 72.3, 70.9, 66.7, 60.3, 41.8, 36.6, 35.8, 27.0, 25.3, 23.9, 23.3, 20.0, 19.3, 14.2 ppm.

MS (ESI): *m/z* 575.22

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{32}H_{44}O_6SiNa$ 575.2799, Found 575.2796

(4*R*,7*R*,*E*)-4-((*tert*-Butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoic acid (59):



To a stirred solution of α,β-unsaturated ester **58** (170 mg, 0.31 mmol) in dry toluene at rt, bis(tributyltin) oxide (0.8 ml, 1.50 mmol) was added drop wise. The reaction mixture was refluxed at 110 °C for 24 h. After completion of reaction, the reaction mixture was cooled to rt evoparated and dissolved in ethyl acetate. The mixture was acidified with 1 M HCl (p^H 5) and was extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with brine (2 x 5 mL) and dried over anhydrous Na_2SO_4, filtered, evaporated and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (50:50) as eluent to afford (4*R*,7*R*,*E*)-4-((*tert*-butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoic acid **59** as a colorless thick syrupy liquid.

Yield: 145 mg, 90%.

Mol. Formula: $C_{30}H_{40}O_6Si$

$[\alpha]_D^{25}$: -19.79 (*c* 1.25, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 3468, 2971, 2832, 1727, 1654, 1589, 1462, 1370, 1108

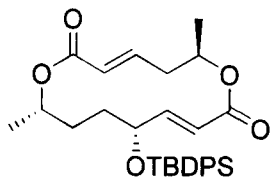
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75-7.55 (m, 4H), 7.51-7.32 (m, 6H), 7.13-6.67 (m, 2H), 6.22-5.69 (m, 2H), 5.00-4.69 (m, 1H), 4.53-4.32 (m, 1H), 4.09-3.92 (m, 1H), 2.40-2.34 (m, 1H), 1.78 (brs., 2H), 1.67-1.35 (m, 6H), 1.34-1.14 (m, 6H), 1.09 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 165.8, 152.3, 144.7, 135.8, 133.6, 133.1, 129.9, 127.7, 124.2, 119.7, 71.8, 70.6, 66.8, 41.8, 33.4, 32.0, 30.0, 27.0, 23.2, 19.8, 19.3 ppm.

MS (ESI): *m/z* 547.21

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{30}H_{40}O_6SiNa$ 547.2486; Found 547.2489

(3*E*,6*R*,9*E*,11*R*,14*S*)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7dioxacyclotetradeca-3,9-diene-2,8-dione (60):



To a solution of *seco*-acid **59** (0.086 g, 0.16 mmol) in THF (2 mL) were added Et_3N (0.726 mL, 0.32 mmol) and 2,4,6-trichlorobenzoyl chloride (1.56 mL, 0.17 mmol) and the reaction mixture was stirred for 6h at room temperature under argon atmosphere and then diluted using dry toluene (20 mL), and added dropwise to a refluxing solution of 4-dimethyl aminopyridine (DMAP) in toluene (100 mL) for over a period of 13h using syringe pump (1.7 mL/h). The reaction mixture was stirred for an additional 8h. After completion of reaction as indicated by TLC, the resulting reaction mixture was cooled, evaporated, dissolved in EtOAc (15 mL), the reaction mixture was washed with saturated aq. $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give crude macrocyclic lactone. Crude macrocyclic lactone was purified by silica gel column chromatography using petroleum ether/EtOAc (90:10) as eluent to afford (3*E*,6*R*,9*E*,11*R*,14*S*)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7dioxacyclotetradeca -3,9-diene-2,8-dione **60** as a colorless thick syrupy liquid.

Yield: 68 mg, 82%.

Mol. Formula: $C_{30}H_{40}O_6Si$

$[\alpha]_D^{25}$: -29.27 (*c* 0.1, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}): ν_{max} 2965, 2811, 1745, 1644, 1575, 1450, 1110

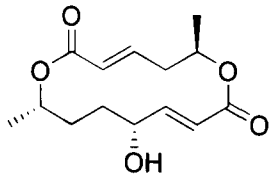
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.65 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.44-7.34 (m, 6H), 6.81-6.69 (m, 2H), 5.74 (d, J = 15.6 Hz, 2H), 5.24-5.17 (m, 1H), 5.13 (dt, J = 2.7, 6.5 Hz, 1H), 4.28 (t, J = 6.8 Hz, 1H), 2.82 (td, J = 6.8, 13.7 Hz, 1 H), 2.33-2.27 (m, 1H), 1.80-1.73 (m, 1H), 1.67-1.61 (m, 1H), 1.55-1.48 (m, 1H), 1.42 (d, J = 6.5 Hz, 3H), 1.35 (dd, J = 6.5, 13.4 Hz, 1H), 1.12 (d, J = 6.5 Hz, 3H), 1.05 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 166.0, 150.0, 142.9, 135.7, 133.8, 133.3, 129.8, 127.6, 125.7, 120.9, 72.0, 70.0, 69.2, 37.3, 30.9, 27.8, 26.9, 20.0, 19.2, 18.7 ppm

MS (ESI): *m/z* 529.20

HRMS (ESI) *m/z*: [M + Na]+ Calcd for $C_{30}H_{38}O_5NaSi$ 529.2381; Found 529.2380

(–)-(6*R*,11*R*,14*S*)-colletallol (*epi*-3):



To a refluxing solution of macrocyclic lactone **60** (12.5 mg, 0.025mmol) in methanol, ammonium fluoride (13.7 mg, 0.37) was added, and the reaction mixture, stirred for 3 h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give crude product. The crude product was then purified by using flash column chromatography using pet ether: EtOAc (70:30) as eluent to give (–)-(6*R*, 11*R*, 14*S*)- colletallol (***epi*-3)** as a solid.

Yield: 4.8 mg, 75%.

Mol. Formula: $C_{14}H_{20}O_5$

$[\alpha]_D^{25}$: -107.5 (*c* 0.4, CH_2Cl_2) {lit.[6] $[\alpha]_D^{25}$ -99.0 (*c* 0.02, CH_2Cl_2)}.

IR ($CHCl_3$, cm^{-1}): ν_{max} 3410, 2940, 1716, 1630, 1347, 1282, 1075

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81-6.66 (m, 2 H), 5.93 (d, *J* = 15.6 Hz, 1 H), 5.77 (d, *J* = 15.6 Hz, 1 H), 5.24 (d, *J* = 5.7 Hz, 1 H), 5.11 (m, 1 H), 4.27 (m, 1H), 2.84-2.75 (m, 1H), 2.33 (dd, *J* = 6.3, 13.2 Hz, 1H), 1.95 (m, 1H), 1.89-1.79 (m, 1H), 1.74-1.60 (m, 2H), 1.41 (d, *J* = 5.7 Hz, 3H), 1.21 (d, *J* = 5.3 Hz, 3H) ppm.

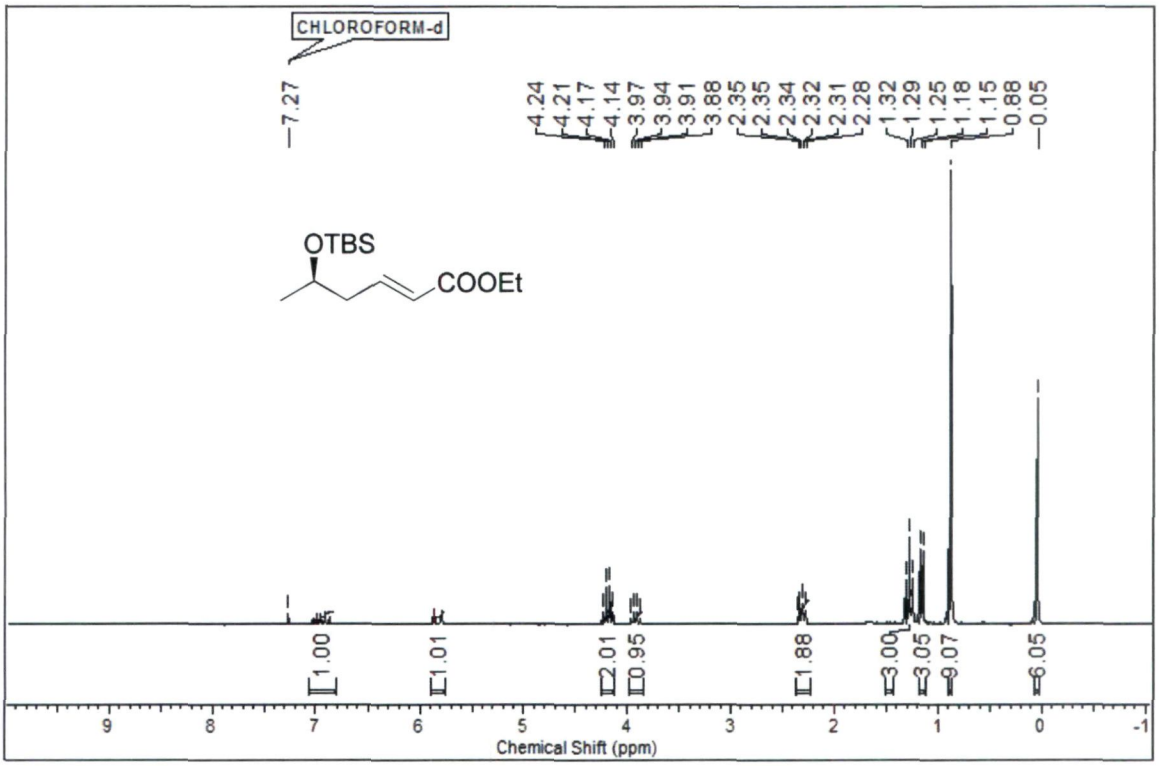
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 165.8, 149.5, 143.0, 125.5, 122.0, 71.2, 70.5, 69.5, 37.6, 31.5, 28.5, 20.2, 19.5 ppm.

MS (ESI): *m/z* 291.12

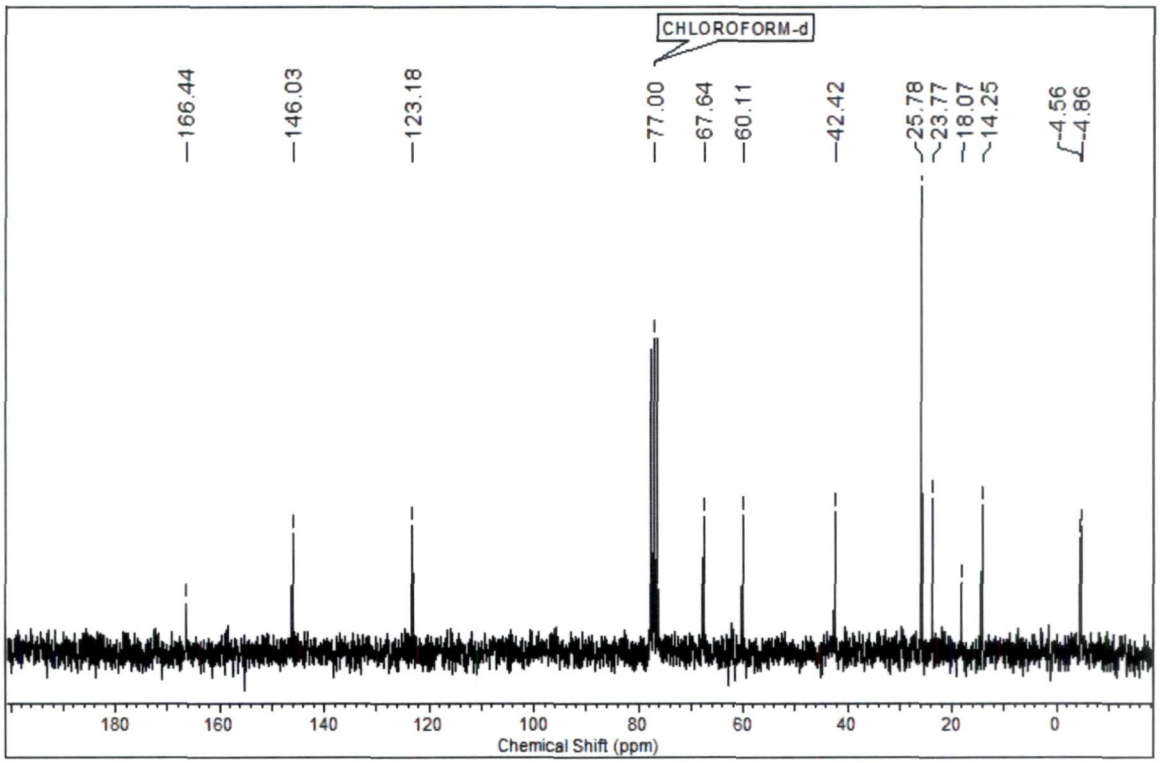
HRMS (ESI) *m/z*: [M + H]+ Calcd for $C_{14}H_{21}O_5$ 269.1384; Found 269.1373

4.2.7. Spectra

Ethyl (*R*,*E*)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoate (51):

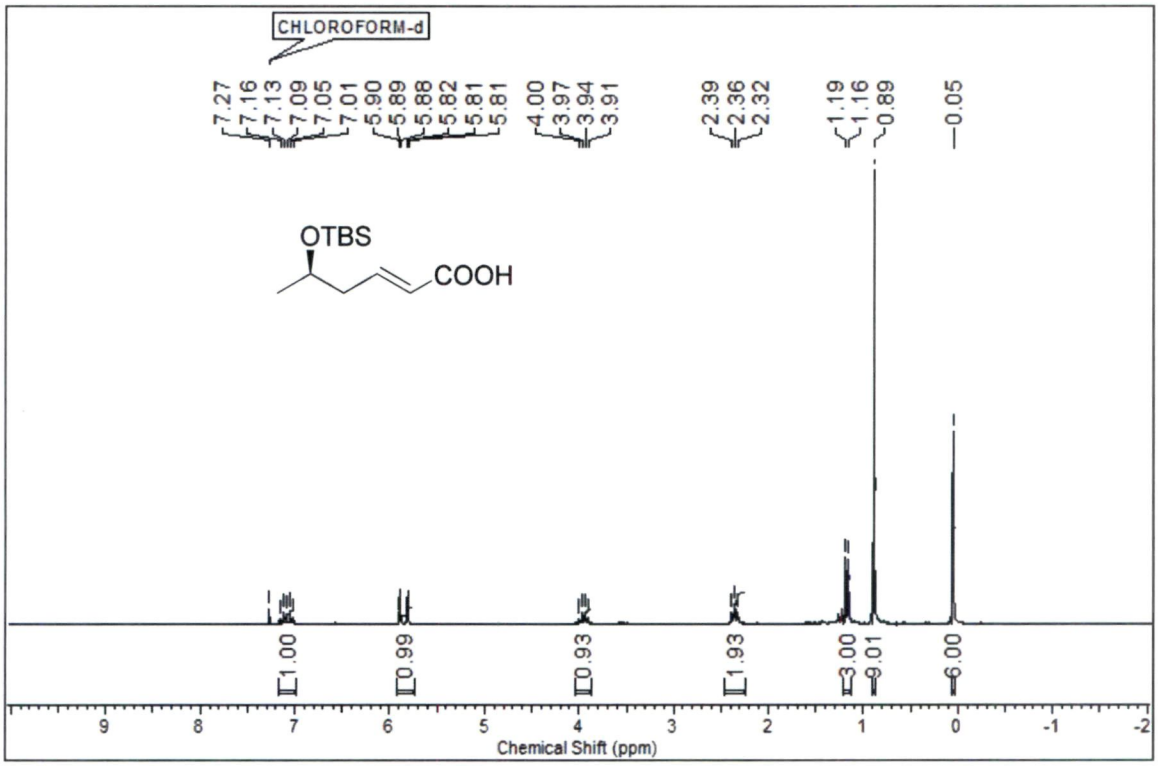


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

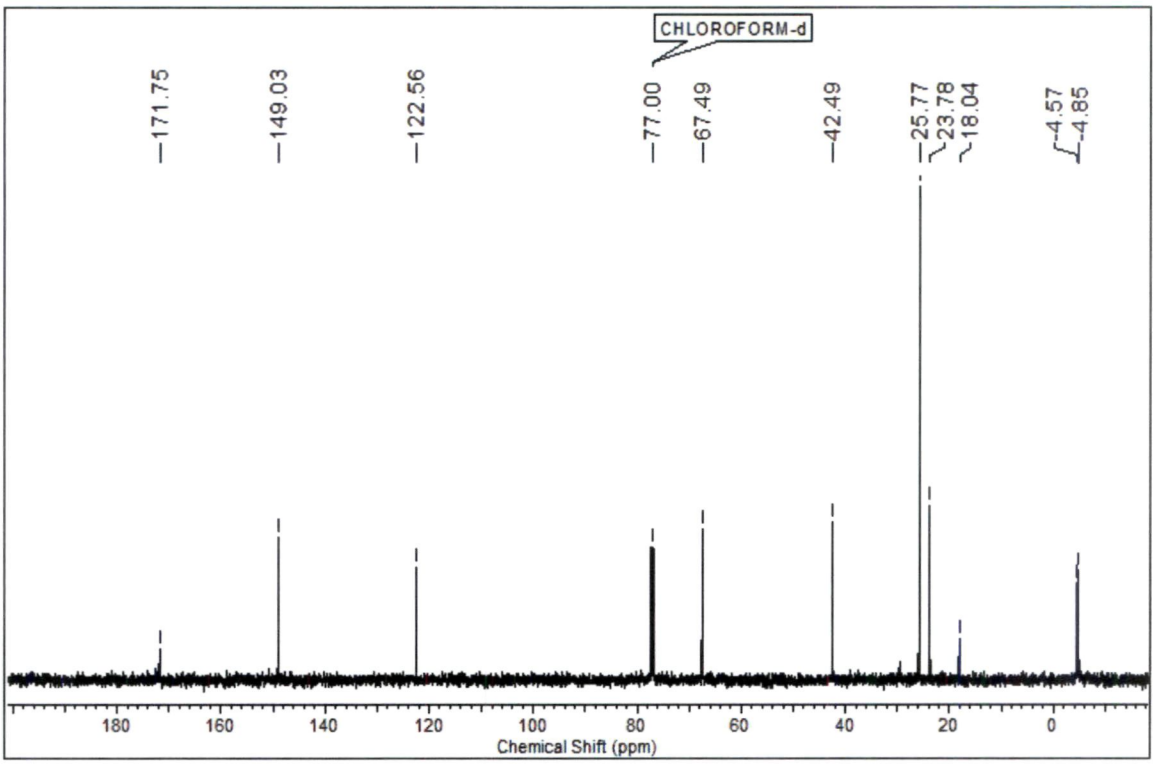


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

(*R*,*E*)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoic acid (52):

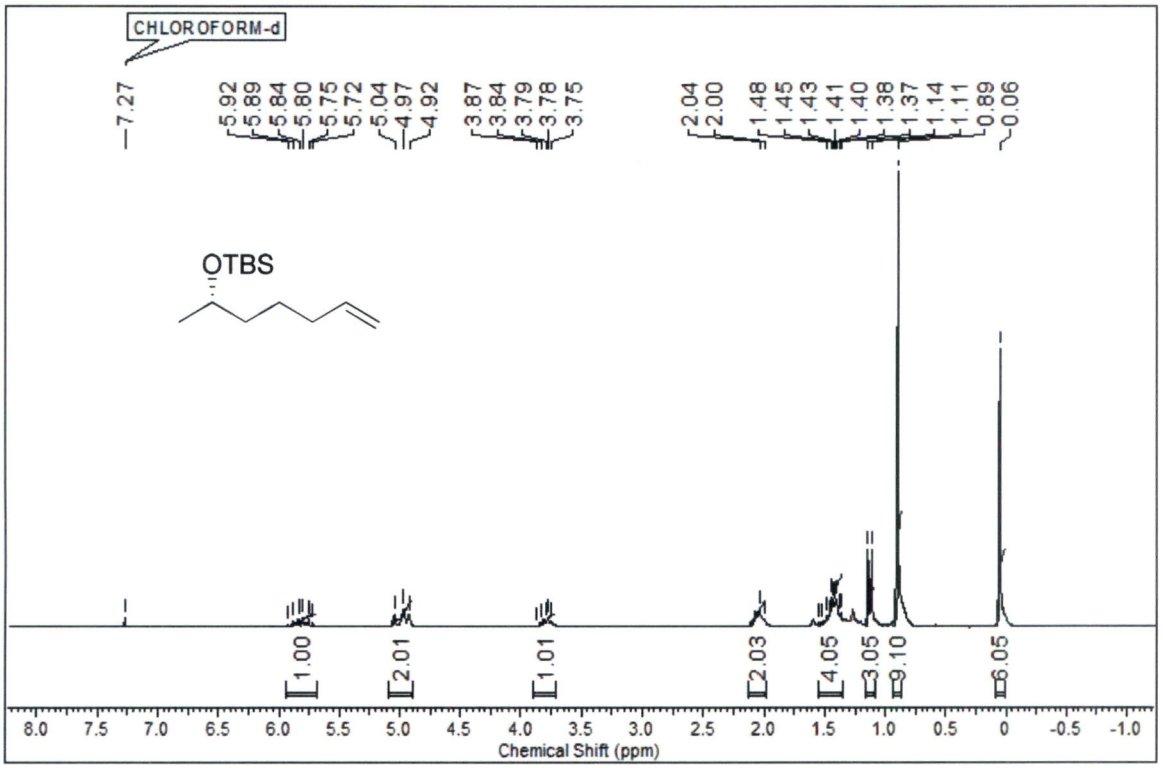


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

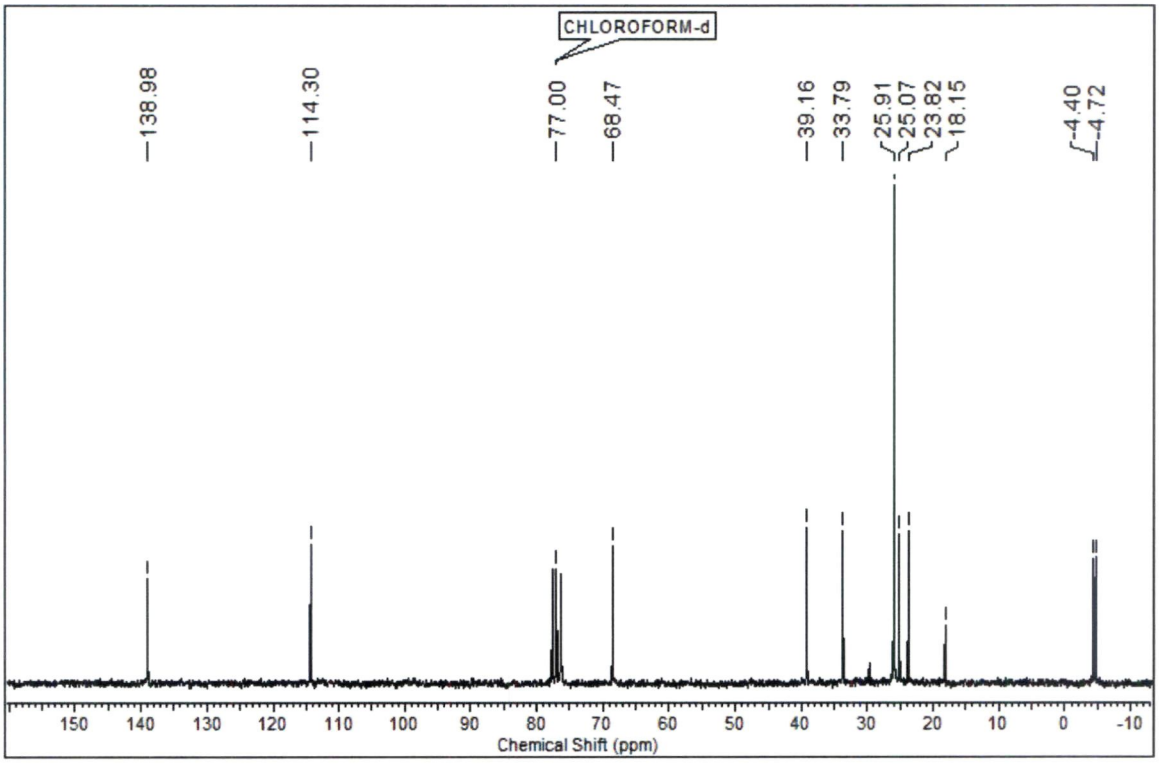


- **^{13}C NMR ($CDCl_3$, 101 MHz)**

(*S*)-tert-butyl(hept-6-en-2-yloxy)dimethylsilane (53):

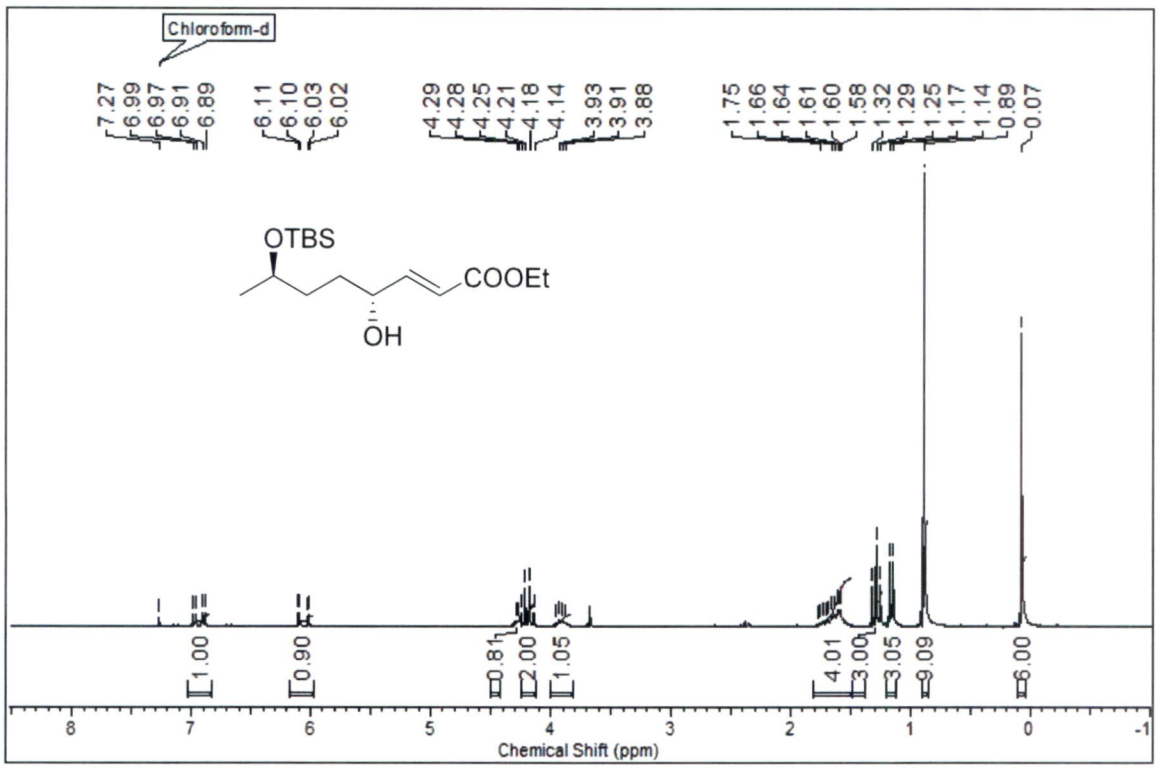


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

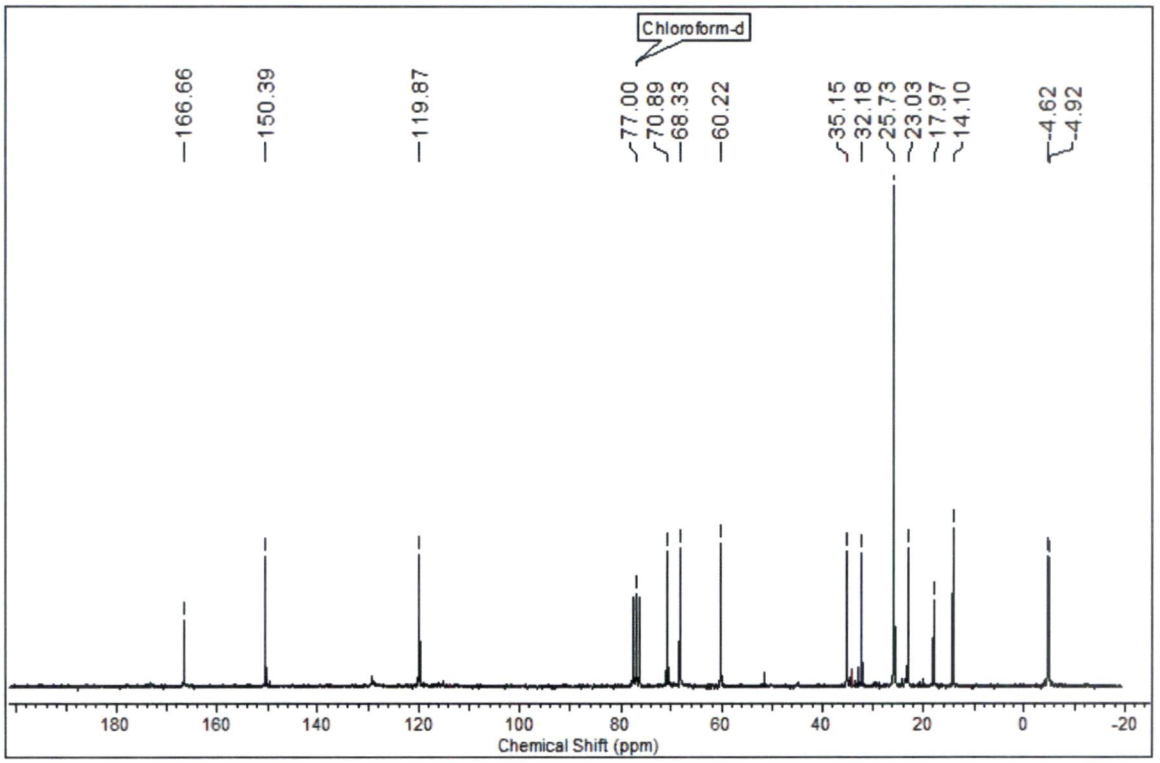


- **^{13}C NMR ($CDCl_3$, 50 MHz)**

Ethyl (4*R*,7*R*,*E*)-7-((tert-butyldimethylsilyl)oxy)-4-hydroxyoct-2-enoate (54):

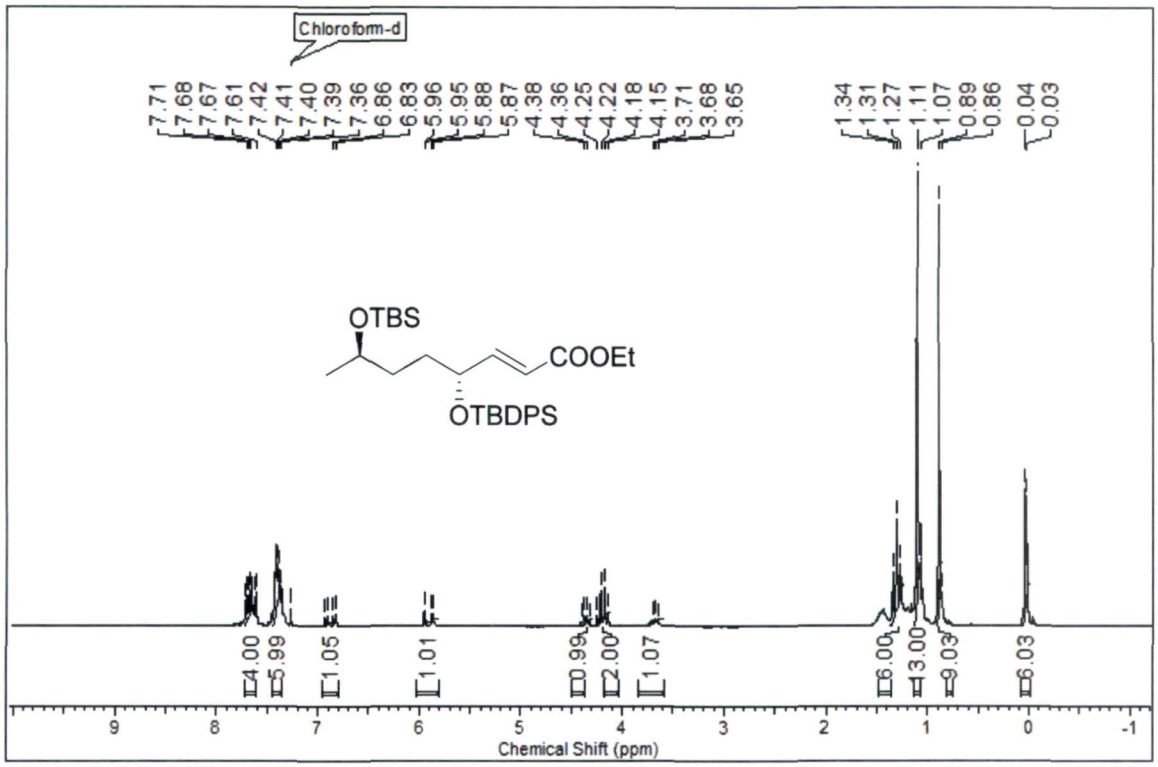


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

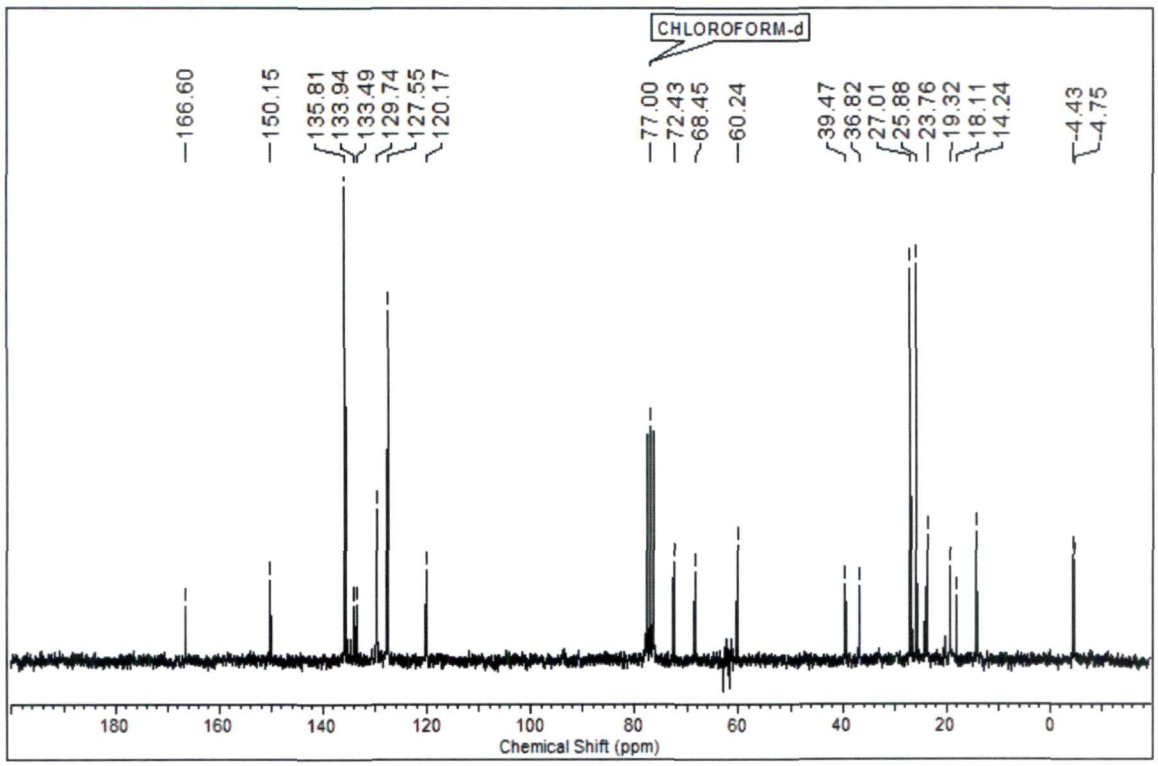


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl (4*R*,7*R*,*E*)-7-((tert-butyldimethylsilyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2-enoate (55):

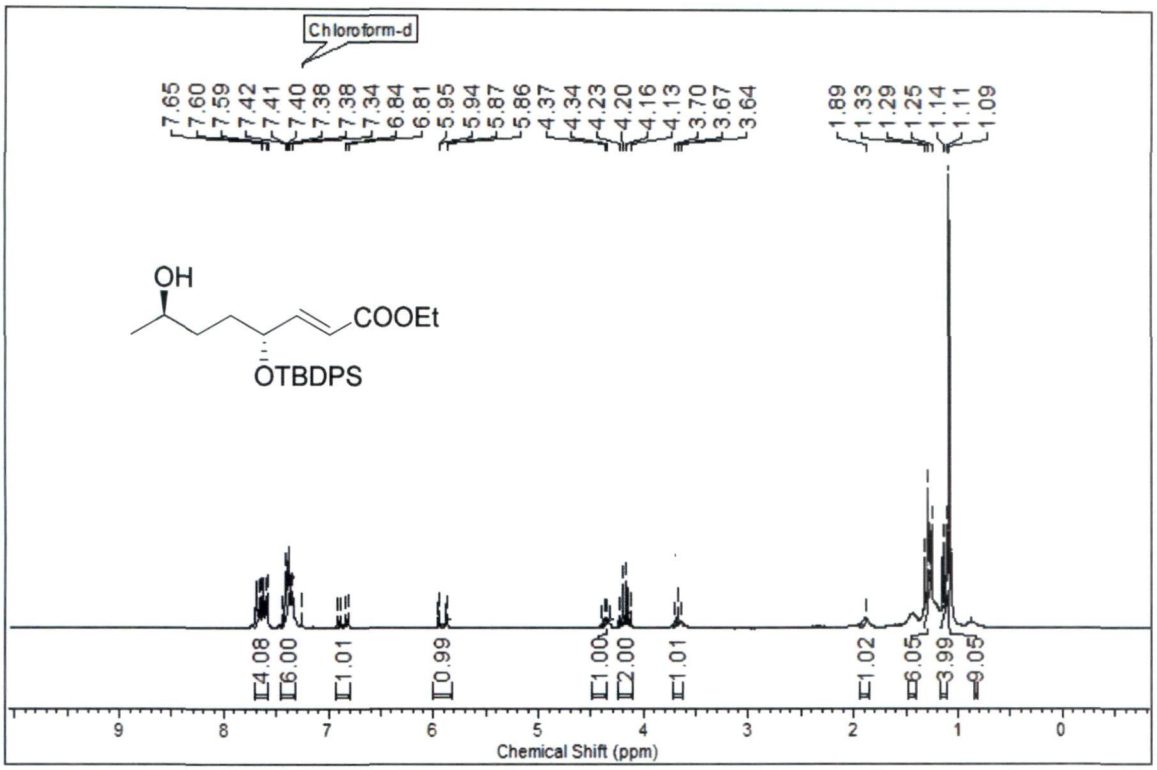


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

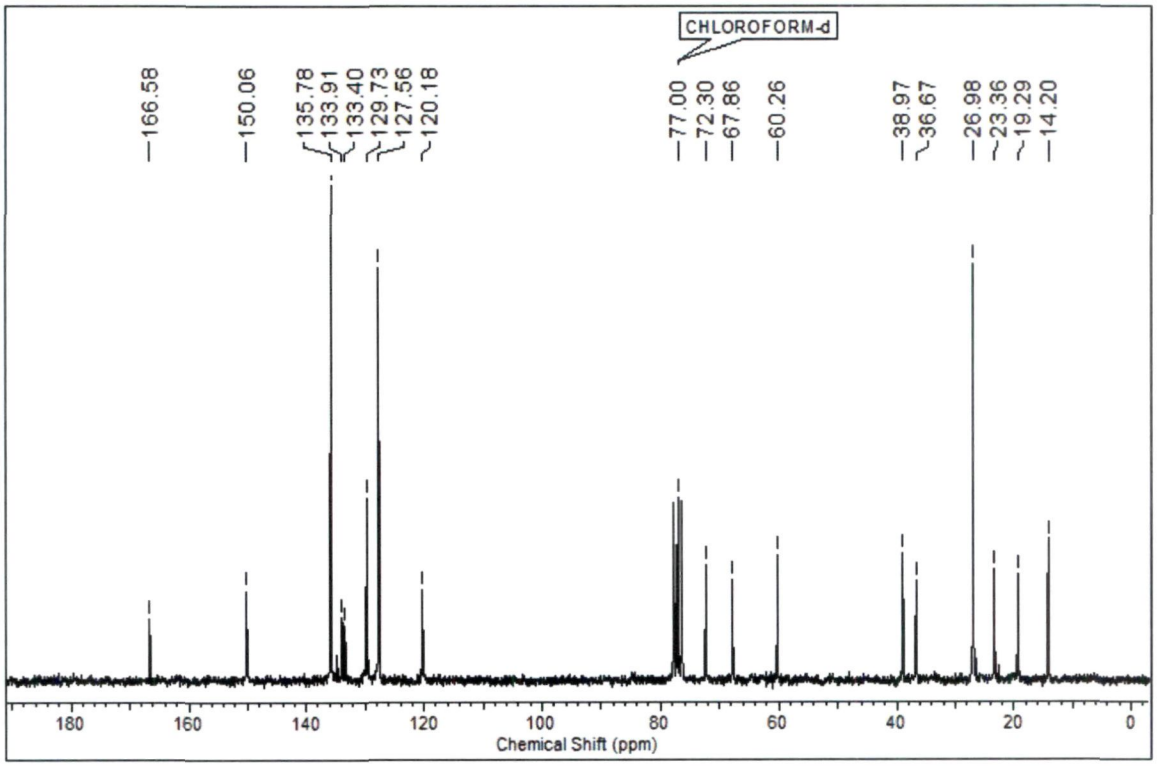


- **^{13}C NMR ($CDCl_3$, 50 MHz)**

Ethyl (4*R*,7*R*,*E*)-4-((tert-butyldiphenylsilyl)oxy)-7-hydroxyoct-2-enoate (56):

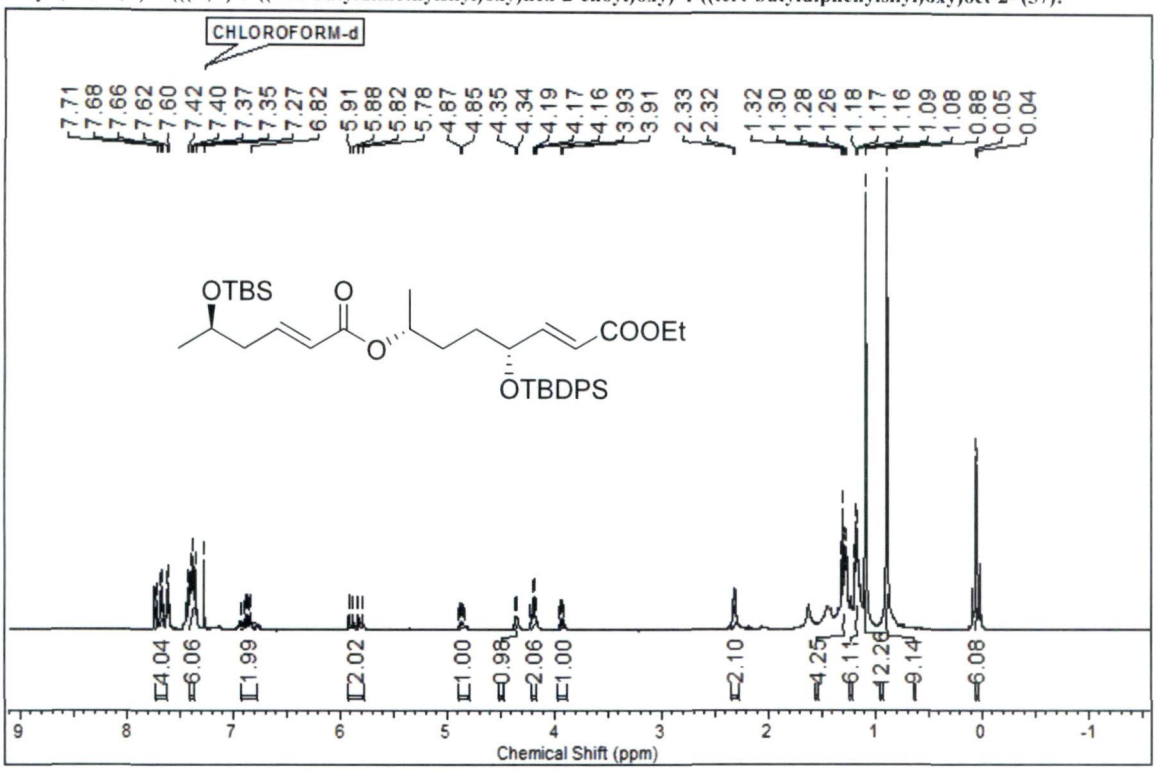


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

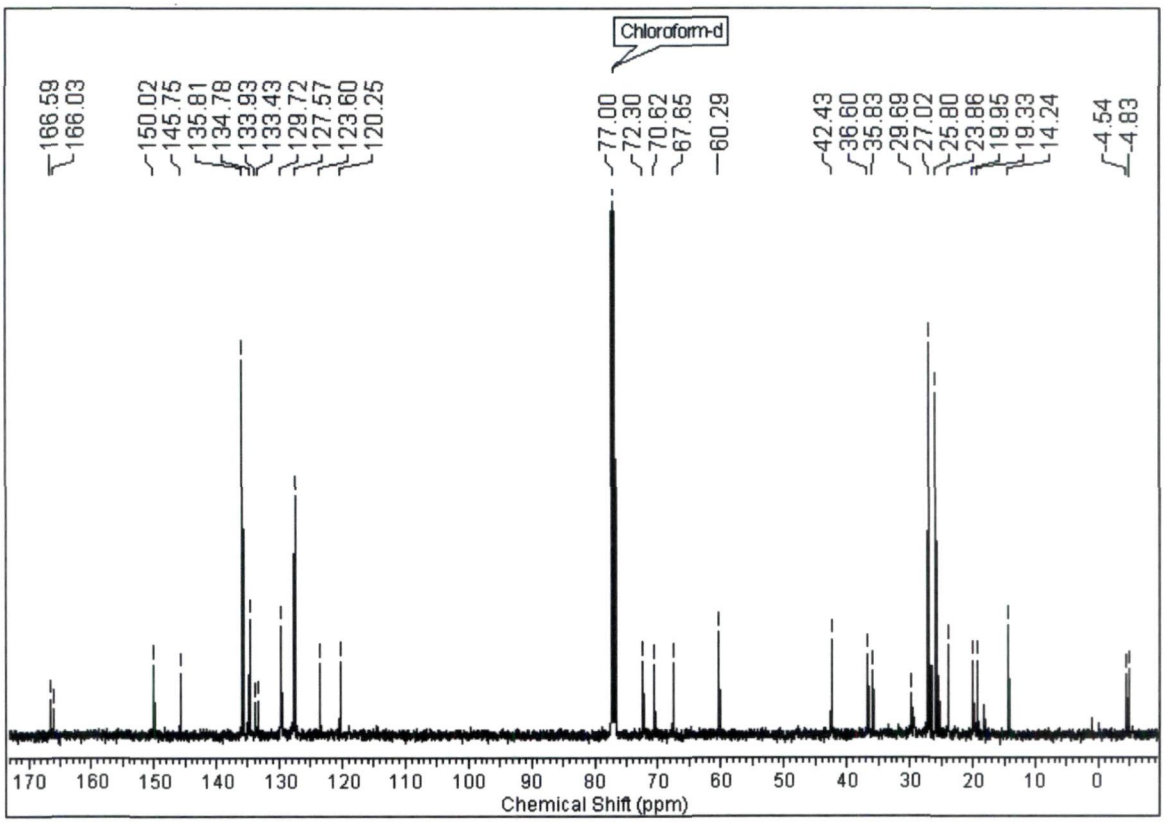


➢ **^{13}C NMR ($CDCl_3$, 50 MHz)**

Ethyl (4*R*,7*R*,*E*)-7-(((*R*,*E*)-5-((tert-butyldimethylsilyl)oxy)hex-2-enoyl)oxy)-4-((tert-butyldiphenylsilyl)oxy)oct-2- (57):

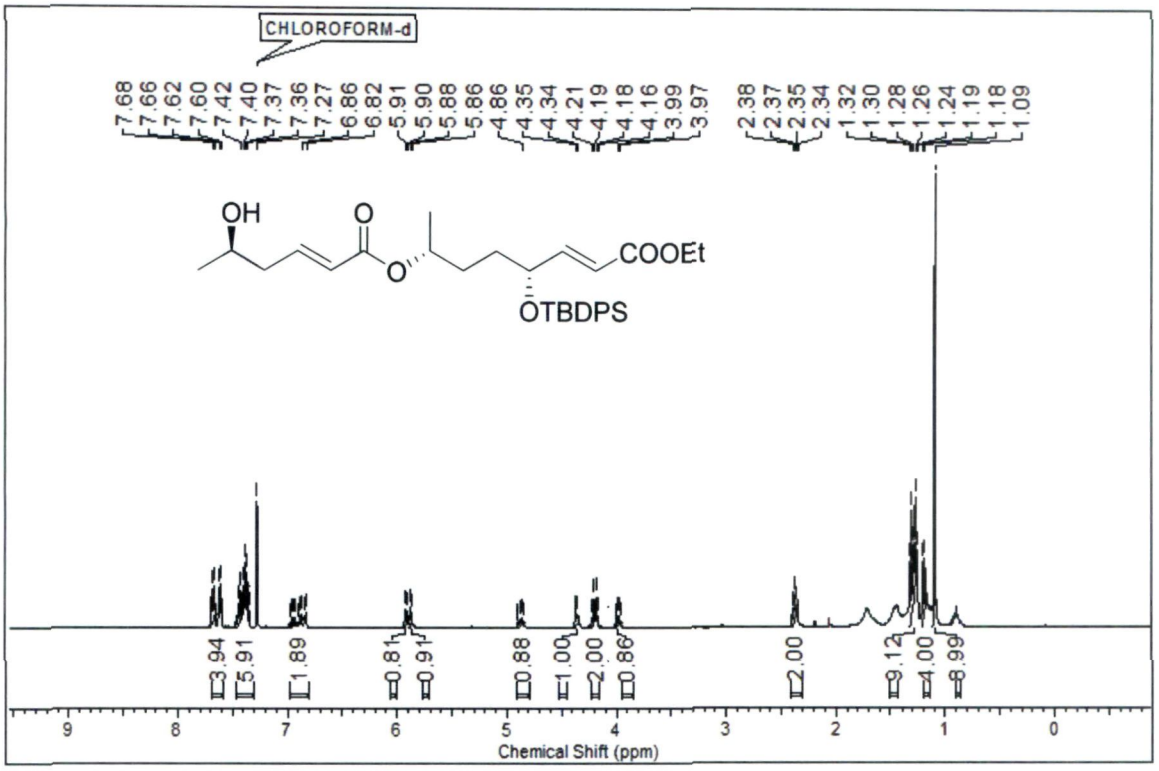


➢ **^{1}H NMR ($CDCl_3$, 400 MHz)**

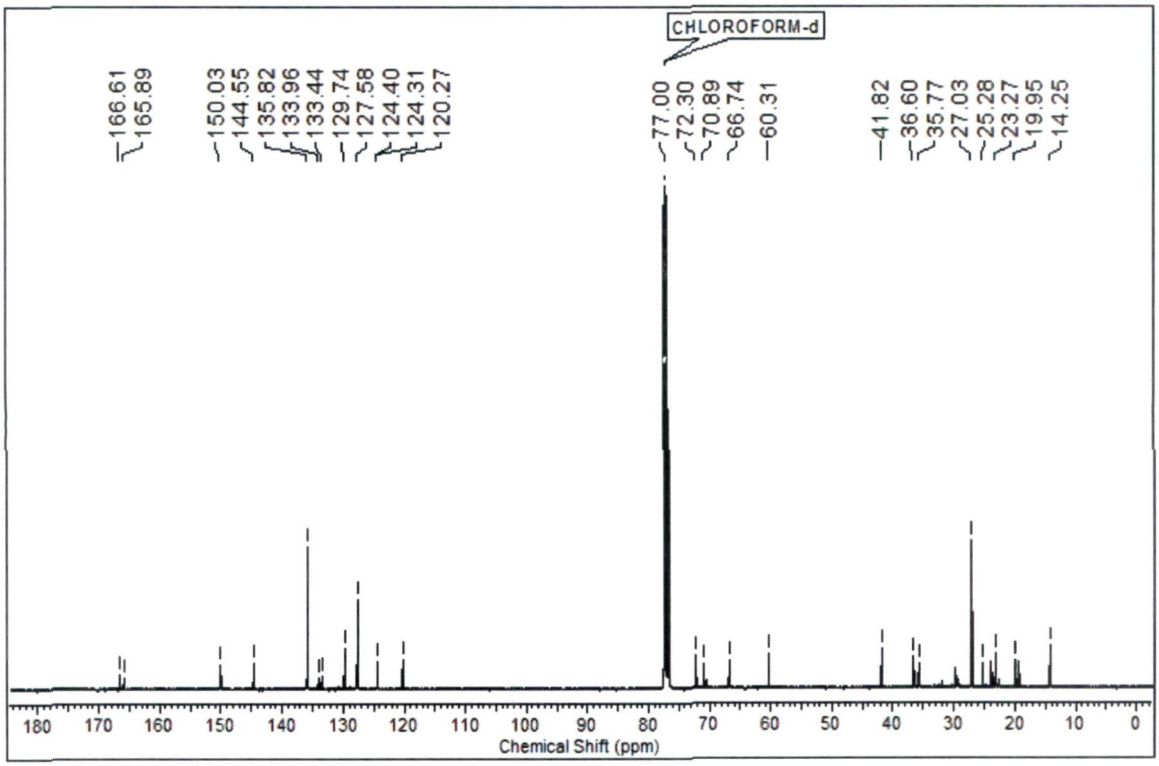


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

Ethyl (4*R*,7*R*,*E*)-4-((tert-butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoate (58):

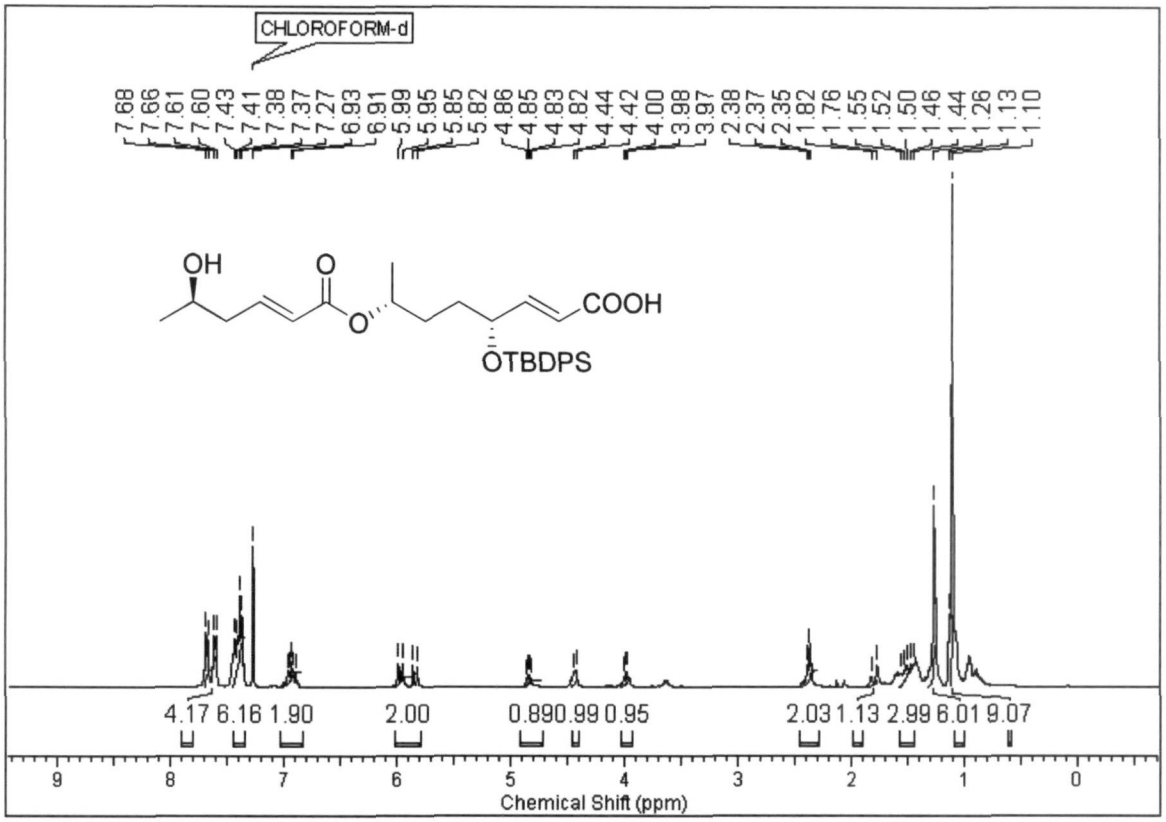


➢ **^{1}H NMR ($CDCl_3$, 400 MHz)**

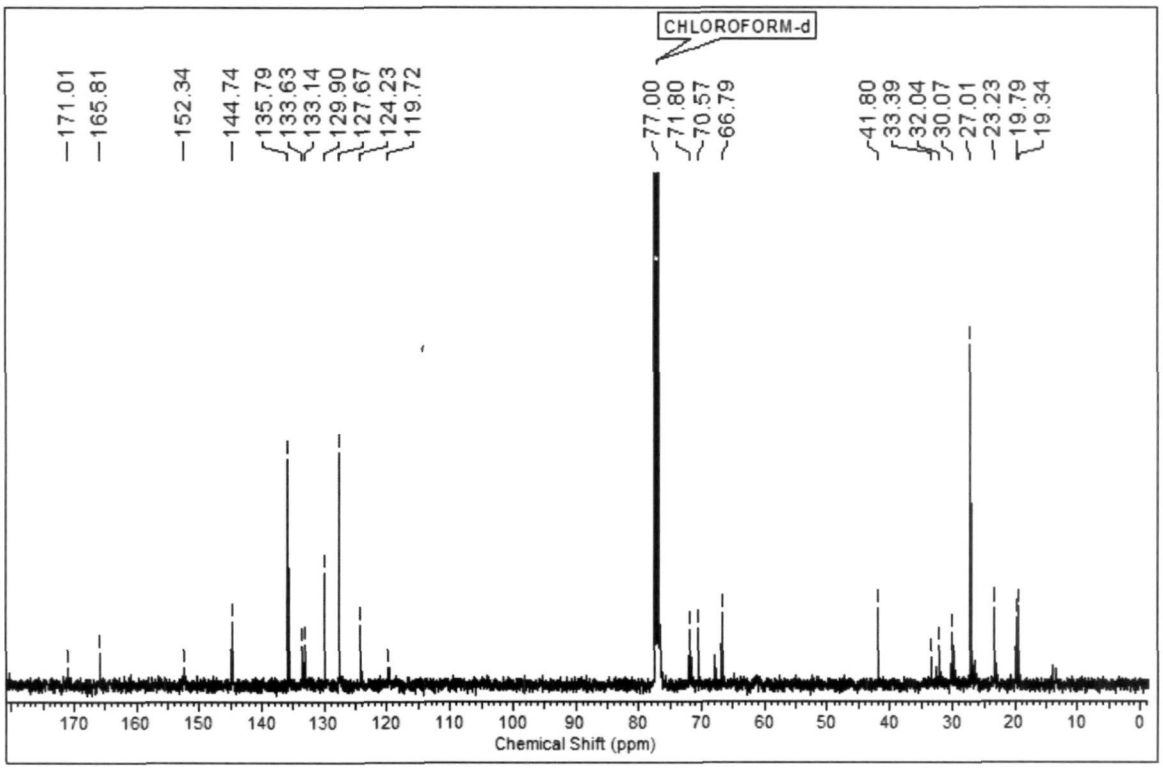


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

(4*R*,7*R*,*E*)-4-((tert-butyldiphenylsilyl)oxy)-7-(((*R*,*E*)-5-hydroxyhex-2-enoyl)oxy)oct-2-enoic acid(59):

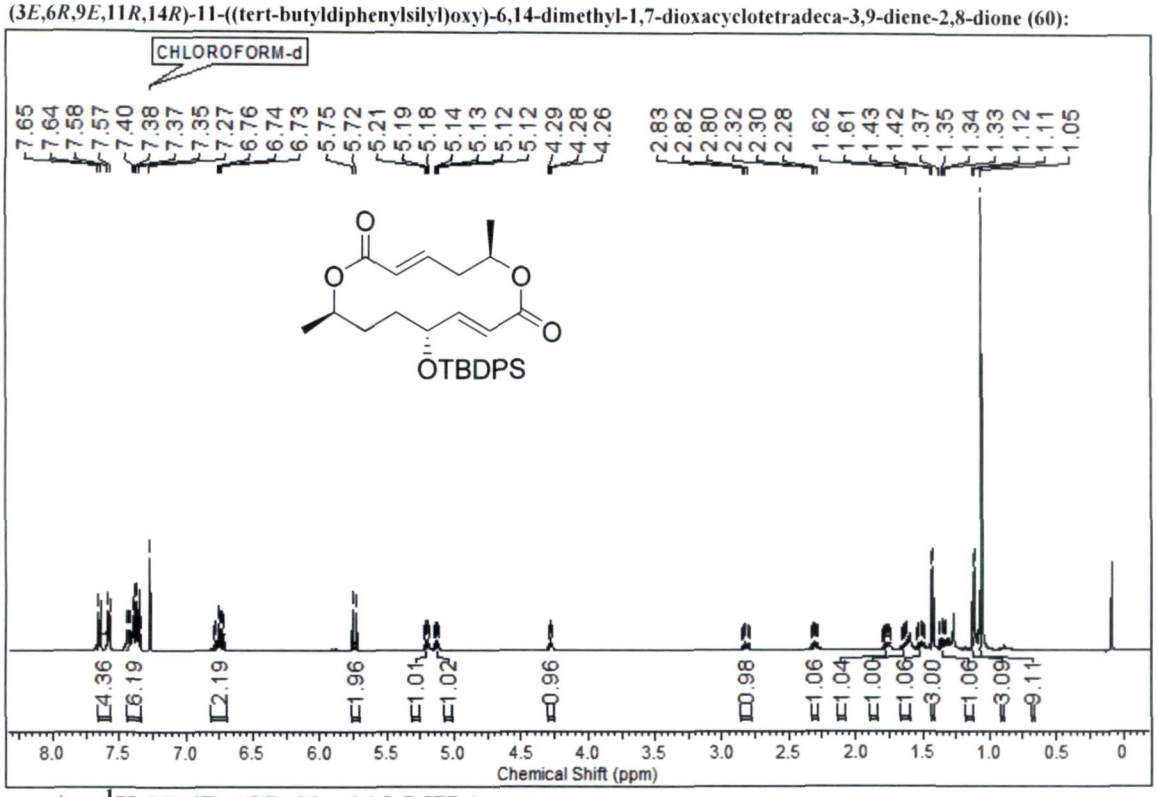


➢ **^{1}H NMR ($CDCl_3$, 200 MHz)**

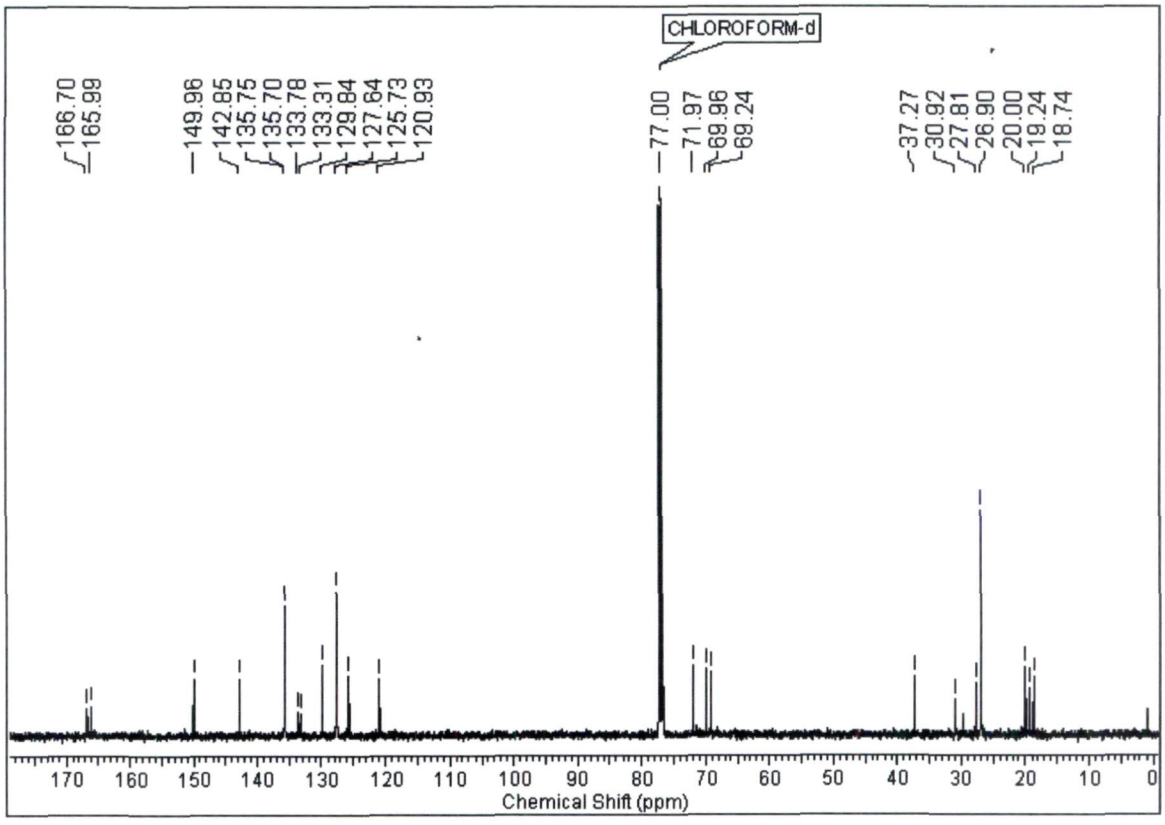


➢ **^{13}C NMR ($CDCl_3$, 101 MHz)**

(3*E*,6*R*,9*E*,11*R*,14*R*)-11-((tert-butyldiphenylsilyl)oxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (60):

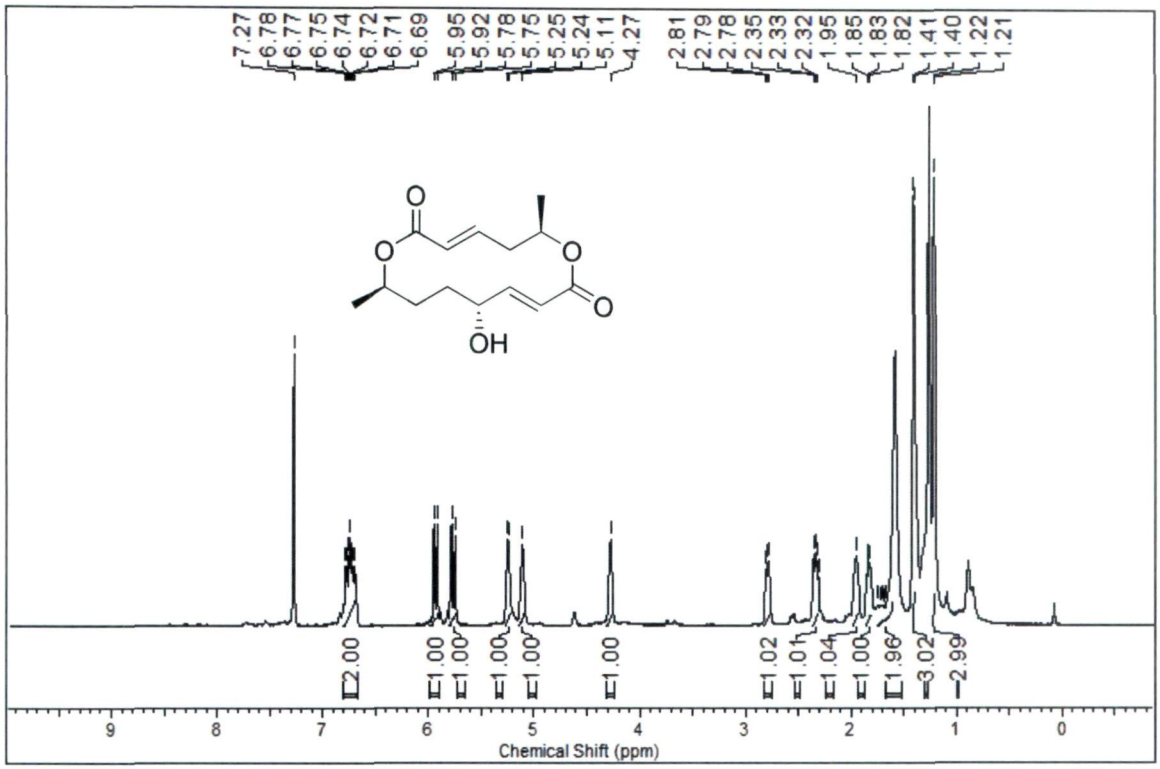


- **^{1}H NMR ($CDCl_3$, 200 MHz)**

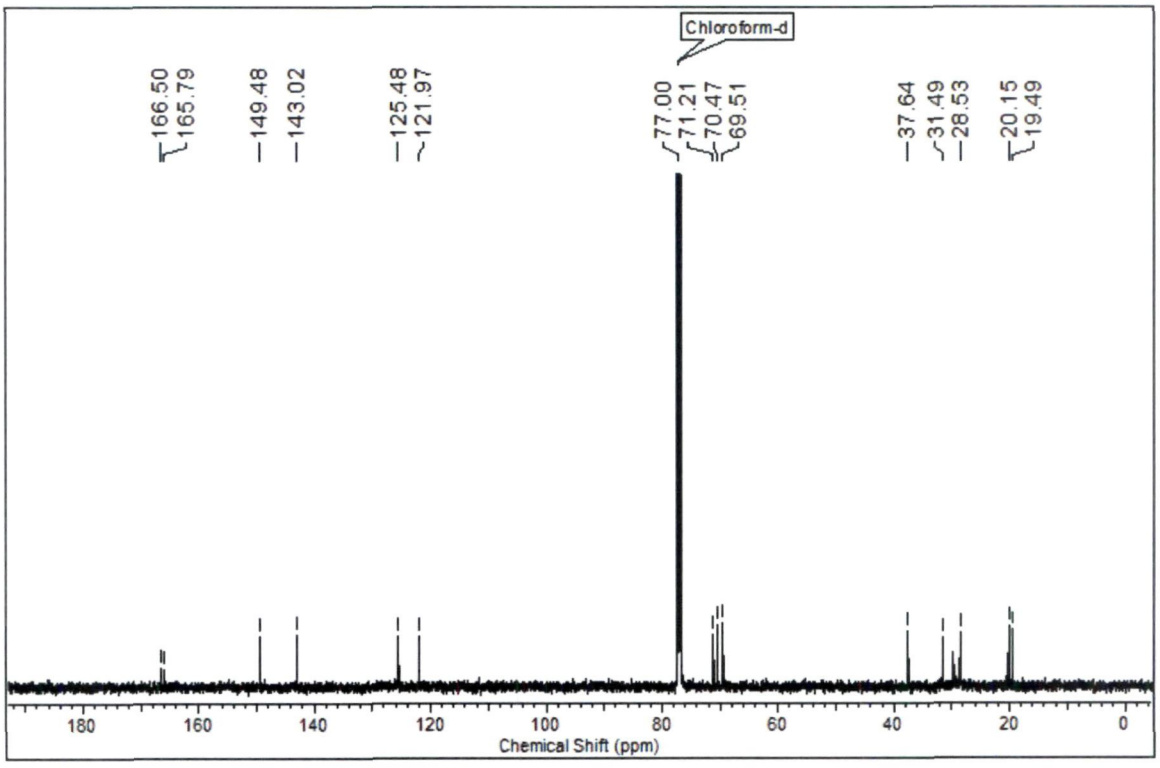


- **^{13}C NMR ($CDCl_3$, 101 MHz)**

(3*E*,6*R*,9*E*,11*R*,14*R*)-11-hydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (*epi*-3):



^{1}H NMR ($CDCl_3$, 500 MHz)



- **^{13}C NMR ($CDCl_3$, 125 MHz)**

D-7000 HPLC System Manager Report

Analyzed: 02/25/16 11:57 AM

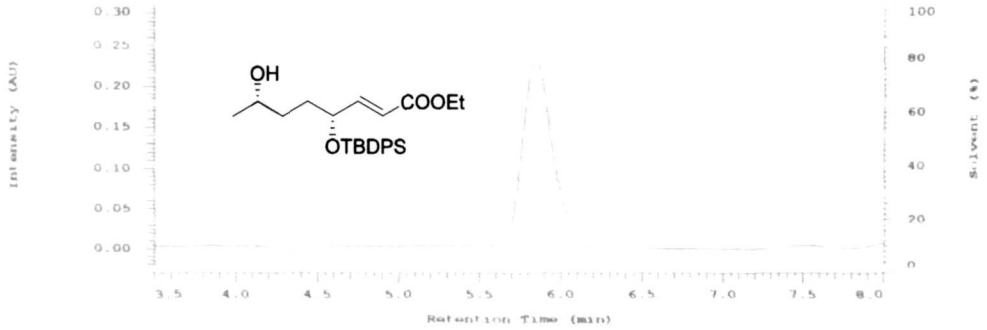
Reported: 03/20/17 02:02 PM
Processed: 03/20/17 02:01 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8823\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Application: HPLC
Sample Name: 14diol -p
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O:(75:25:)

Series:8823
Volume: 10.0 ul

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	5.85	115115	1488123	98.689
2	7.51	1540	19763	1.311
		116655	1507886	100.000

Peak rejection level: 0

Group Leader :-Dr.Tripathi P.K.
COLUMN :Kromasil Rp-8(150 X 4.6mm)
MOBILE PHASE :-MEOH:H2O(75:25)
WAVELENGTH :- 254nm
FLOW RATE :- 1.0ml/min (1680 psi)
SAMPLE CONC :-1mg/1ml Injection vol: 20ul

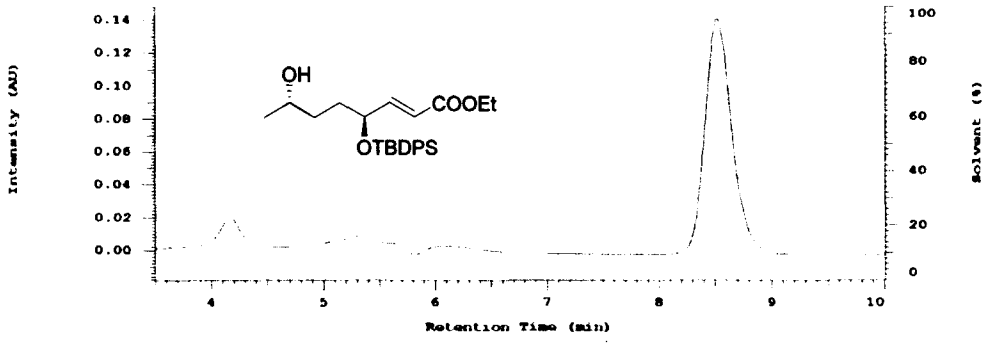
D-7000 HPLC System Manager Report

Analyzed: 02/25/16 11:19 AM
Reported: 05/20/16 11:58 AM
Processed: 05/20/16 11:57 AM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8821\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:8821
Application: HPLC
Volume: 10.0 ul
Sample Name: 14diol
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O:(70:30:)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	6.11	1018	19323	1.653
2	8.52	70705	1149817	98.347
		71723	1169140	100.000

Peak rejection level: 0

```
Group Leader   :-Dr.Tripathi P.K.
COLUMN         :Kromasil RP-8 (150 X 4.6mm)
MOBILE PHASE   :-MEOH:H20(75:25)
WAVELENGTH     :- 254nm
FLOW RATE      :- 1.0 ml/min (1680 psi)
SAMPLE CONC    :-1 mg/1ml Injection vol: 20ul
```

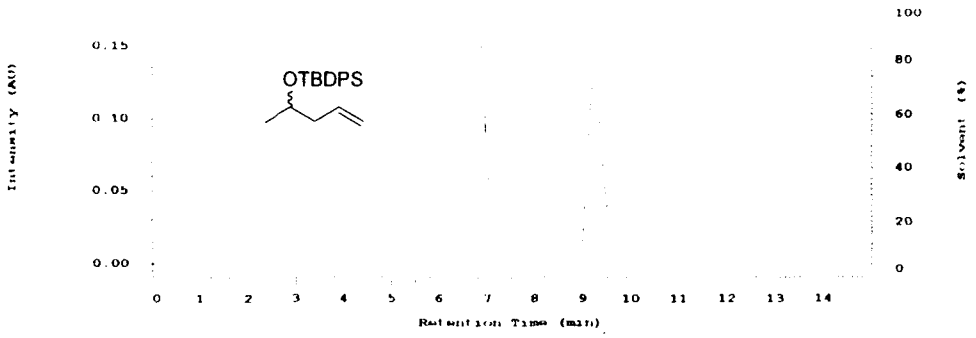
D-7000 HPLC System Manager Report

Analyzed: 05/25/16 11:58 AM
Reported: 05/25/16 12:43 PM
Processed: 05/25/16 12:42 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8914\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:8914
Application: HPLC
Volume: 10.0 ul
Sample Name: SVK-VINYL-RAC
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(90:10)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	6.82	82959	1445474	51.967
2	9.24	61018	1336045	48.033
		143977	2781519	100.000

Peak rejection level: 0

```
Group Leader   :-Dr.Tripathi P.K.
COLUMN         :Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE   :-MEOH:H20(90:10)
WAVELENGTH     :- 254nm
FLOW RATE      :- 0.7 ml/min (740 psi)
SAMPLE CONC    :-1 mg/1ml Injection vol: 2ul
```

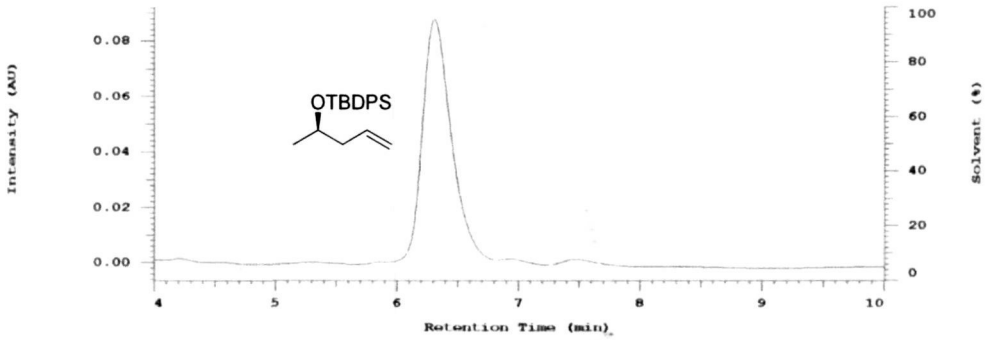
D-7000 HPLC System Manager Report

Analyzed: 05/25/16 01:52 PM
Reported: 05/25/16 03:06 PM
Processed: 05/25/16 03:06 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8919\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:8919
Application: HPLC
Volume: 10.0 ul
Sample Name: SVK-VINYL-CHIRAL
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(90:10)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	6.31	43592	713048	98.374
2	7.48	876	11788	1.626
		44468	724836	100.000

Peak rejection level: 0

```
Group Leader   :-Dr.Tripathi P.K.
COLUMN         :Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE   :-MEOH:H20(90:10)
WAVELENGTH     :- 254nm
FLOW RATE      :- 0.7 ml/min (740 psi)
SAMPLE CONC    :-1 mg/1ml Injection vol: 2ul
```

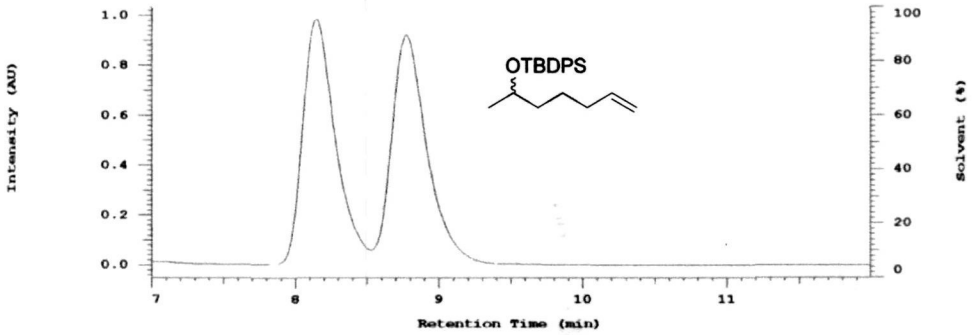
D-7000 HPLC System Manager Report

Analyzed: 05/27/16 01:35 PM
Reported: 05/27/16 02:07 PM
Processed: 05/27/16 02:07 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8930\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:8930
Application: HPLC
Volume: 10.0 ul
Sample Name: SVK-BUTANYL-RAC
Injection from this vial: 1 of 1
Sample Description: ACN:H2O (90:10)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	8.14	490017	7753344	49.671
2	8.77	458354	7855972	50.329
		948371	15609316	100.000

Peak rejection level: 0

```
Group Leader   :-Dr.Tripathi P.K.
COLUMN         :Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE   :-MEOH:H20(90:10)
WAVELENGTH     :- 230nm
FLOW RATE      :- 0.7 ml/min (740 psi)
SAMPLE CONC    :-X mg/1ml Injection vol: 2ul
```

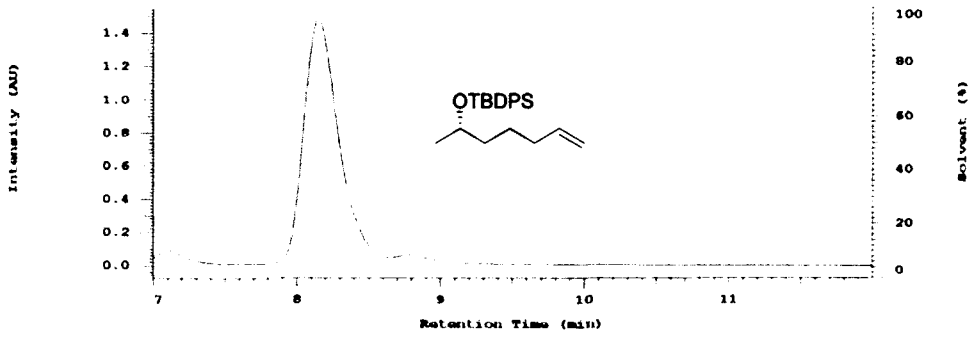
D-7000 HPLC System Manager Report

Analyzed: 05/27/16 01:48 PM
Reported: 05/27/16 02:09 PM
Processed: 05/27/16 02:08 PM

Data Path: C:\WIN32APP\HSM\HPLC\DATA\8931\
Processing Method: SANTOSHH

System(acquisition): Sys 1
Series:8931
Application: HPLC
Volume: 10.0 ul
Sample Name: SVK-BUTANYL-CHIRAL
Injection from this vial: 1 of 1
Sample Description: MEOH:H2O(95:05)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	8.15	732649	12806862	98.749
2	8.79	13131	162284	1.251
		745780	12969146	100.000

Peak rejection level: 0

```
Group Leader   :-Dr.Tripathi P.K.
COLUMN         :Chiralcel OJ-RH (150 X 4.6mm)
MOBILE PHASE   :-MEOH:H20(90:10)
WAVELENGTH     :- 230nm
FLOW RATE      :- 0.7 ml/min (740 psi)
SAMPLE CONC    :-X mg/1ml Injection vol: 2ul
```

4.2.8. References

1. (a) J. MacMillan and R. J. Pryce, *Tetrahedron Lett.* **1968**, *9*, 5497; (b) J. MacMillan and T. J. Simpson, *J. Chem. Soc., Perkin Trans.* 1, **1973**, 1487.
2. S. Gurusiddaiah and R. C. Ronald, *Antimicrob. Agents Chemother.* **1981**, *19*, 153.
3. (a) J. A. O'Neill, T. J. Simpson and C. L. Willis, J. Chem. Soc., *Chem. Commun.* **1993**, 738; (b) G. E. Keck, E. P. Boden and M. R. Wiley, *J. Org. Chem.* **1989**, *54*, 896.
4. D. C. Munoz, S. C. Passey, T. J. Simpson, C. L.Willis, J. B. Campbell, and R. Rosser, *Aust. J. Chem.* **2004**, *57*, 645.
5. (a) P. Radha Krishna, D. V. Ramana and B. K. Reddy, *Synlett* **2009**, *18*, 2924; (b) F. J. Dommerholt, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.* **1991**, *32*, 1495; (c) T. Wakamatsu, S.Yamada, Y. Ozaki and Y. Ban, *Tetrahedron Lett.* **1985**, *26*, 1989.
6. S. J. Amigoni, L. J. Toupet and Y. J. Le Floćh, *J. Org. Chem.* **1997**, *62*, 6374.
7. (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley VCH: Weinheim, 2005. (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
8. P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, **2007**.
9. (a) D. W. C. MacMillian, *Nature* 2008, **455**, 304; (b) V. Jha, N. B. Kondekar and P. Kumar, *Org. Lett.* **2010**, *12*, 2762.
10. P. Kumar and N. Dwivedi, *Acc. Chem. Res.* **2013**, *46*, 289.
11. (a) N. B. Kondekar and P. Kumar, *Org. Lett.* **2009**, *11*, 2611; (b) S. V. Kauloorkar, V. Jha, G. Jogdand and P. Kumar, *RSC Adv.* **2015**, *5*, 61000.
12. (a) P. Gupta and P. Kumar, *Eur. J. Org. Chem.* **2008**, 1995; (b) M. N. Reddy, P. A. Reddy, H. Ather and A. R. Prasad, *Synthesis* **2010**, 1473.
13. A. J. M. Hendrix and M. P. Jennings, *Tetrahedron Letters* **2010**, *51*, 4260.
14. (a) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; (b) P. J. Chua, Tan and G. Zhong, *Green Chem.* **2009**, *11*, 543.
15. Diastereomeric ratio was determined using HPLC.

16. T. J. Hunter and G. A. O'Doherty, *Org. Lett.* **2002**, *4*, 4447.

17. C. J. Salomon, E. G. Mata and O. A. Mascaretti, *J. Org. Chem.* **1994**, *59*, 7259.

Publications

1. Synthesis of indolizidine, pyrrolizidine and quinolizidine ring systems by proline-catalyzed sequential α-amination and HWE olefination of an aldehyde
   Shruti Vandana Kauloorkar, Vishwajeet Jha and Pradeep Kumar
   RSC Adv.2013, 3, 18288.

2. An Organocatalytic approach towards the synthesis of azasugars: A short route to total synthesis of (-)-lentiginosine, epi-(-)-lentiginosine and 1,2-dihydroxypyrrolizidine
   Shruti Vandana Kauloorkar, Vishwajeet Jha and Pradeep Kumar
   Organic Biomolecular Chemistry 2014, 12, 4454.

3. A stereocontrolled synthesis of Hagens gland lactones via iterative proline catalysed a-aminoxylation and oxa-Michael reactions
   Shruti Vandana Kauloorkar, Vishwajeet Jha, G. Jogdand and Pradeep Kumar
   ***RSC Adv.* 2015,5,61000**

4. Total synthesis of (–)-(6*R*,11*R*,14*S*)-colletallol via proline catalyzed α - aminoxylation and Yamaguchi macrolactonization
   Shruti Vandana Kauloorkar and Pradeep Kumar
   RSC Adv. 2016 (accepted) DOI: 10.1039/C6RA08484B

5. Stereoselective organocatalytic approach to 2,6-disubstituted piperidin-3-ol: A concise and protecting group free synthesis of (-)-Deoxoprosopinine and (+)-Deoxoprosophylline
   Vishwajeet Jha, **Shruti Vandana Kauloorkar** and Pradeep Kumar
   ***Eur. J. Org. Chem.* 2014, 4897.**

6. Synthesis of (-)-galantinic acid via iterative hydrolytic kinetic resolution and tethered aminohydroxylation
   Abhishek Dubey, **Shruti Vandana Kauloorkar** and Pradeep Kumar
   ***Tetrahedron* 2010, 66, 3159.**

7. An organocatalytic approach to the synthesis of monohydroxylated izidines using proline catalysed α- amination reaction.
   Shruti Vandana Kauloorkar and Pradeep Kumar
   (Manuscript under preparation)